Sunday, 30 August 2009

UNMET PSYCHOSOCIAL NEEDS IN HEART DISEASE

123 Family member interventions improve their knowledge of heart failure and supportive communication

S.B. Dunbar[1], P.C. Clark[2], R.A. Gary[1], F. Mccarty[3], M. Higgins[1], C.M. Reilly[1], D. Grossniklaus[1], J.M. Robinson[1], A.L. Smith[1]. [1]*Emory University School of Nursing, Atlanta, United States of America;* [2]*Georgia State University School of Nursing, Atlanta, United States of America;* [3]*Georgia State University School of Public Health, Atlanta, United States of America*

Background and Purpose: Although clinical practice guidelines suggest that family members (FM) should be included in heart failure (HF) patient education, little data exist to guide clinical practice. Thus the purpose of this study was to test the effect of education-counseling interventions for FMs on their HF knowledge and perceived supportive communication with HF patients.
Methods: HF patient and FM dyads (113) were randomized to usual care (UC), patient-family education (PFE) or family partnership (FPI) interventions. This report is of FM data only. PFE and FPI were delivered at baseline (BL) and at 2-3 months. PFE was structured patient-family education on diet, meds, and HF patient symptoms. FPI included PFE plus teaching about communication strategies to support the HF patients' autonomy in self care. Variables and measures obtained from FM at BL, immediately after intervention, and at 4 months were HF knowledge (A-HFKQ), perceived autonomy support (AST), and outcome of depressive symptoms (BDI-II)). Data were analyzed with descriptive statistics and repeated measures analysis of variance (RM-ANOVA) and covariance (ANCOVA) to correct for baseline values.
Results: FMs were 19-78 (52.8 + 13) years in age, 81% female, 45% spouses, 57% minorities, 42% working full time. RM-ANOVA revealed that knowledge increased significantly and equivalently immediately post intervention ($p<0.0001$) for the PFE & FPI intervention groups. ANCOVA showed group differences at 4 months ($F=3.52$, $df=2$, $p=0.04$). Post hoc testing showed that FPI, but not PFE, retained HF knowledge significantly better than UC ($p=0.03$). AST analysis revealed significant increases between BL and 4 months in the FPI group compared to the PFE and UC groups ($F=3.55$, $df=2$, $p=0.03$). BDI-II scores did not change differently by group between BL and 4 months.
Conclusions: A family partnership intervention combining HF education and teaching supportive communication strategies to FM was effective in increasing their HF knowledge and improving their perceived support to HF patients. The FPI may have increased the salience of the information to promote greater retention compared to PFE and UC. The lack of differential change in depressive scores indicated the interventions did not increase FM burden in comparison to UC. The influence of FM knowledge and autonomy support on HF patient self care and outcomes should be explored.

124 Exploring the boundaries of heart failure prevention: The Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) study

S. Stewart, M.C. Carrington, G. Lee, G. Jennings on behalf of NIL-CHF Investigators. *Baker IDI Heart and Diabetes Institute, Melbourne, Australia*

Purpose: While there is a plethora of evidence to support multidisciplinary, chronic heart failure (CHF) management programs, there is a paucity of evidence to support programs of care that cost-effectively prevent the development of CHF – even in high risk individuals. The Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) Study is a randomised controlled trial of a hybrid, home and clinic-based, nurse-led multidisciplinary intervention targeting hospitalised patients at risk of developing CHF.
Methods: A minimum of 750 patients aged $>$ 45 years will be exposed to usual post-discharge care or the NIL-CHF intervention. All patients are comprehensively profiled, while intervention patients alone are subject to annual clinical reviews and targeted management. The primary, composite endpoint is all-cause mortality or a chronic heart failure (CHF)-related admission during 3 – 5 year follow-up. Secondary endpoints include progressive cardiac dysfunction (according to pre and post echocardiography subject to blinded adjudication), recurrent hospital stay and quality of life.
Results: To date, a total of 138 patients (71% male and mean age 65$\pm$11 years) have been randomised to either usual care (n = 69) or the NIL-CHF intervention (n = 69). At baseline, the most common antecedents for CHF were hypertension (68%), coronary artery disease (38%) and type 2 diabetes (26%). Baseline echocardiography and imaging has revealed that 56% of patients have some form of (asymptomatic) diastolic dysfunction, 22% left ventricular hypertrophy, 19% mitral valve dysfunction, 11% a left ventricular (LV) ejection fraction $\leq$ 45% indicative of asymptomatic LV systolic dysfunction and 6% clinically significant carotid intimal medial thickness. Of those patients subject to home visits within 7-14 days of hospital discharge, 8% were found to be clinically unstable, 20% required adjustments to their pharmacological/non-pharmacological management and 28% had only reasonable to poor knowledge about their risk profile and danger of future cardiovascular events requiring intervention.
Conclusions: When completed in 2013, the NIL-CHF Study will represent one of the largest cardiac disease management studies of its kind. Early data from the first 138 participants clearly identify the potential to slow the impact and progression of pre-existing heart disease in order to prevent the development of CHF and/or premature mortality in high risk individuals.

125 Determinants of quality of life in cardioverter-defibrillator recipients: a nurse-led study

J.D. Kasprzak, M. Kaczmarek, M. Fiutowski, Z. Bednarkiewicz, T. Wcislo, M. Krzeminska-Pakula. *Medical University of Lodz, Lodz, Poland*

Background: Implantable cardioverter defibrillator (ICD) is increasingly used in the prevention of sudden cardiac death. However, even though this therapy prolongs life, numerous inconveniences may affect resulting quality of life (QoL).
Aim: to define the clinical predictors of post-implantation quality of life in a nurse–conducted questionnaire study.
Methods: We studied a consecutive series of 52 patients (pts; 5 females; median age 62$\pm$15 years) with ICD implanted as secondary (24 pts) and primary (28 pts) prevention of sudden cardiac death. 27% of pts experienced a shock during this time. A specialized nurse contacted the patients on ambulatory basis to evaluate the impact of clinical variables onto the results of custom QoL questionnaire (CQ), in EuroQol EQ-5D with visual analogue scale (VAS) and Beck Hopelessness Scale (HS-20) 22$\pm$15 months after the implantation.
Results: General well-being improved after the implantation in 80% of patients and worsened in only 6%, with change in score 1,1 to 2.6 on a 0-4 scale ($p<0.05$). Unexpectedly, scores obtained from HS-20 revealed that symptoms of probable depression or subdepression occurred at 73% and 25% of pts. 62% pts after the implantation reported less intense somatic symptoms (chest pain) which probably reflects a placebo effect of a complex medical procedure. Patients with ischemic etiology and recipients for primary prevention had slightly lower VAS score ($p=0.022$, $p=0.006$ resp.) without differences in EQ-5D, CQ or HS-20 as compared to those without infarction or those in secondary prevention of cardiac arrest, respectively. Initial heart failure class (at implantation) and current depression status had little relationship with EQ-5D, VAS or CQ results. Recipients experiencing shocks had lower VAS score ($p=0.002$) and EQ-5D score ($p=0.027$) than non-shocked individuals and fear of shock was a unique most prevalent element decreasing QoL. Longer time of follow-up was related to a trend (0.06) for better QoL according to EQ-5D, possibly due to "learning to live with ICD" effect.
Conclusions: Patients with ICD show a marked improvement in self-reported indices of quality of life. Depression is a common and underdiagnosed problem in this population. Experienced or expected shocks represent a major negative factor affecting the quality of life in ICD recipients and longer post-procedural time may alleviate this issue. Our findings indicate that a dedicated nurses may effectively collect psychological surveys, provide additional educational and psychological support and potentially ease the well-being issues which are prevalent after ICD implantation.

126 Comparative prognostic value of the Kansas City cardiomyopathy and the Minnesota living with heart failure questionnaires in chronic heart failure

J.T. Parissis, D. Farmakis, M. Nikolaou, V. Bistola, D. Birmpa, S. Lagou, T. Katsoulas, D. Karatzas, G. Filippatos, D. Kremastinos. *Athens University Hospital Attikon, Athens, Greece*

Background: Self-assessment of health status by questionnaires has been associated with severity and prognosis of chronic heart failure (CHF). We assessed comparatively the predictive value of Kansas City Cardiomyopathy Questionnaires (summary, KCCQ-s and functional, KCCQ-f) and of Minnesota Living with Heart Failure Questionnaire (MLHFQ) in CHF.
Methods: We studied 137 consecutive CHF patients (aged 64$\pm$12 years, mean left ventricular ejection fraction 27$\pm$7%). Besides KCCQ and MLHFQ, plasma B-type natriuretic peptide (BNP), 6-minute walked distance (6MWD), inflammatory markers (IL-6, IL-10, TNF-α) and Zung self-rated depression scale (SDS) were also assessed. Patients were followed for death or cardiovascular hospitalization for 250 days.
Results: During follow-up, 61% of patients experiencing an event; median event-free survival was 120 days. Compared to patients with uneventful course, those having experienced an event had significantly worse KCCQ-s (42.4$\pm$21% vs 28.8$\pm$18%, $p<0.001$) and KCCQ-f (54.4$\pm$20% vs 37.8$\pm$20%, $p<0.001$) scores but similar MLHFQ score (59.5$\pm$22.4 vs 47.6$\pm$30.9, p=NS). Those patients also had lower EF (24$\pm$6 vs 30$\pm$7%, $p<0.001$), higher NYHA class ($p=0.001$), lower 6MWD (256$\pm$193 vs 345$\pm$148 meters, $p<0.05$), higher BNP (976$\pm$910 vs 403$\pm$311 pg/ml, $p<0.001$), higher levels of pro-inflammatory cytokines (IL-6, 13.4$\pm$6.9 vs 7.3$\pm$5.3 pg/ml, $p<0.001$; TNF-α, 42.4$\pm$43 vs 21.2$\pm$33 pg/ml, $p=0.001$), lower levels of the anti-inflammatory cytokine IL-10 (5.8$\pm$3.2 vs 9.3$\pm$4.8 pg/ml, $p<0.05$) and higher frequency of depressive symptoms (72% vs 49%, $p=0.011$). Event-free survival was significantly shorter in patients with KCCQ-s $<$50% (130$\pm$10 vs 205$\pm$15 days, $p=0.0009$) and in those with KCCQ-f $<$50% (113$\pm$10 vs 190$\pm$12 days, $p<0.0001$), but it did not differ significantly between patients in the low and those in the high MLHFQ 50% percentile (118$\pm$15 vs 155$\pm$11 days, log-rank test $p=0.0919$). In multivariate analysis, only LVEF (HR=0.768, 95% CI=0.632-0.933, $p=0.008$) and KCCQ-f ($<$50% vs $\geq$50%, HR=0.113, 95% CI=0.016-0.803, $p=0.029$) remained as significant predictors of survival.

Conclusion: KCCQ seems to be a better predictor of long-term event-free survival than MLHFQ in CHF patients.

127 A comparative study addressing health-related quality of life, symptoms of depression, perceived control and knowledge in patients with heart failure and their partners

S. Agren[1], L. Evangelista[2], A. Stromberg[1]. [1]*Linkoping University Hospital, Linkoping, Sweden;* [2]*UCLA, School of Nursing, Los Angeles, United States of America*

Background: High social support is associated with better outcomes of cardiovascular disease. Therefore partners have a very important role in influencing the well-being of the patient. Hospitalisations are often short and at discharge all responsibility for self-care management is put on the patient and partner. Home care has been shown to give the patients security, freedom and increased awareness of their symptoms. However, many partners felt anxious when being left alone with the responsibility of care. Quality of life (QOL) in partners of patients with CHF has been found to be low and sometimes lower than the QOL of the patients.
The study aims were therefore to 1) describe health-related quality of life (HRQOL), symptoms of depression, perceived control and self-estimated knowledge of patients with chronic heart failure (CHF) and their partners (patient-partner dyads) and 2) compare HRQOL in the partners with an age- and gender matched reference group.
Methods: Data for this descriptive cross sectional study were collected from 135 patient-partner dyads at two hospitals in south-eastern Sweden between January 2005 and September 2008. The inclusion criteria were to be a dyad consisting of a patient diagnosed with heart failure based on the criteria of the ESC heart failure guidelines, in NYHA class II-IV and with a partner living in the same household as the patient. The partner-age and gender matched reference group came from the same region in Sweden. Data were collected by SF-36, Beck Depression Inventory (BDI), Control Attitude Scale (CAS) and Rand knowledge questionnaire. Co-morbidity was measured by Charlson Co-morbidity Index.
Results: Patients had lower scores compared to their partners in all dimensions ($P<0.001$) except in the mental domain of SF-36. Data also showed similar levels of perceived control and self – estimated knowledge between patients and partners, but patients had more depressive symptoms than their partners ($P<0.001$). Mental health scores were lower in partners compared to age and gender-matched references ($P<0.001$); all other HRQOL scores were comparable between the partners and the reference group. Patients Co-morbidity Index was 'moderate' compared with partners who had a 'mild' level ($p = 0.008$). The reference group had a similar level of co-morbidity as the partners.
Conclusion: Being a partner to a patient with heart failure affects the mental health component most. Interventions focusing on support to improve mental health can strengthen the partner and their ability to support the patient.

128 Does telephone follow-up after discharge for acute myocardial infarction reduce anxiety and depression? A randomized controlled trial

T.A. Hanssen[1], J.E. Nordrehaug[1], G.E. Eide[1], I. Bjelland[1], B. Rokne[2]. [1]*Haukeland University Hospital, Bergen, Norway;* [2]*University of Bergen, Bergen, Norway*

Background: Following discharge from hospital for acute myocardial infarction patients many patients experience stress and have unmet information needs. In a context where existing follow-up services are poorly developed, we previously demonstrated that a telephone follow-up intervention after discharge from hospital, showed positive effects after 6 months on the physical dimension of health related quality of life (HRQOL). No long term effects on physical or mental HRQOL were found.
Purpose: To assess whether the telephone follow-up intervention has short- and longterm effects on symptoms of anxiety and depression using the HADS scale 3, 6, 12 and 18 months after discharge. Further to compare patients levels of anxiety and depression to levels in the normal population.
Method: Out of 413 screened patients with a diagnosis of acute myocardial infarction, 288 patients consented to participate, and were randomized to an intervention (n= 156) or a control group (n= 132). The intervention group received weekly telephone follow-up by a nurse the first four weeks after discharge, thereafter in week 6, 8, 12 and 24, in addition to the standard post discharge follow-up of the control group. Endpoint data on the HADS was collected through mailed questionnaires. Reference population data were obtained from the Nord-Trøndelag Health Study (HUNT) 1995-97.
Results: There were no baseline difference between the groups, or any effects of the intervention on the HADS subscales at each of the different measurement points 3, 6, 12 and 18 months after discharge. Analysing both groups together, 20% and 14% of AMI patients reported high levels of anxiety and depressive symptoms at baseline, respectively. Comparing to reference population at baseline AMI patients were more anxious, but not more depressed ($p<0.001$ and $p=0.092$), respectively. After 3–18 months, AMI patients' levels of anxiety and depression were not higher than levels in the reference population.
Conclusion: This study demonstrates that the telephone follow-up intervention had no effects on symptoms of anxiety and depression. However, the potential for improvement was less than anticipated, as patients after 3 months did not have more symptoms of anxiety or depression than the reference population. The results indicate a reduced psychological morbidity among acute myocardial infarction patients compared to levels reported in research a decade ago.

MARKERS AND MAKERS OF CARDIOVASCULAR RISK

129 Is elevated resting heart rate an independent predictor of cardiovascular disease? A report from the National FINRISK Study

M.T. Cooney[1], E. Vartiainen[2], T. Laatikainen[2], A. Juolevi[2], A. Dudina[1], I.M. Graham[1]. [1]*Adelaide and Meath Hospital, Dublin, Ireland;* [2]*National Institute for Health and Welfare, Helsinki, Finland*

Background: Elevated resting heart rate (RHR) is known to be associated with increased risk of cardiovascular disease (CVD). However, there are many inconsistencies including the relationship in healthy women and independence from the effect of physical activity, systolic blood pressure (SBP) and co-morbid conditions.
Objective: To clarify the above inconsistencies in the relationship between RHR and CV risk.
Methods: We examined the relationship between RHR and several endpoints, including CVD, CHD and total mortality and CHD incidence, in the National FINRISK Study, a representative, prospective study of the general population. The analysis includes 14,673 men and 15,478 women, with follow-up of up to 21 years. Cox proportional hazards model was used. All analyses were performed separately in men and women and stratified by year of study and area and adjusted for other risk factors. Those with previous myocardial infarction, angina, heart failure or baseline use of anti-hypertensive medications were excluded.
Results: Elevated RHR was associated with increased risk of CHD, CVD and total mortality and CHD incidence, independently of other CV risk factors including, age, BMI, SBP, smoking, total and HDL cholesterol, diabetes and physical activity. Fully adjusted hazard ratios for RHR > 90bpm compared to < 60 bpm are shown in the table. The relationship remained significant after removal of those with defined co-morbidities, lung disease, cancer and arthritis and after exclusion of events occuring within the first two years of follow-up. Elevated RHR was more strongly related to fatal than non-fatal CHD events.

HRs for RHR >90bpm compared to <60bpm

Endpoint	Men	Women
CHD mortality	2.38 (1.43 to 3.96)	7.63 (1.71 to 34.07)
CVD mortality	1.94 (1.27 to 2.97)	3.07 (1.19 to 7.94)
Total mortality	1.77 (1.38 to 2.26)	1.71 (1.18 to 2.49)
CHD incidence	1.42 (1.02 to 1.99)	1.98 (1.08 to 3.62)

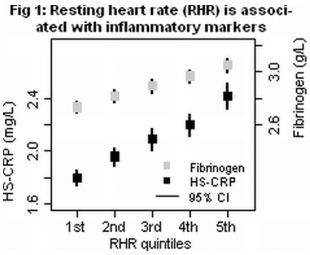
HR: Hazard ratio (fully adjusted); RHR: Resting heart rate; CVD: Cardiovascular disease; CHD: Coronary heart disease.

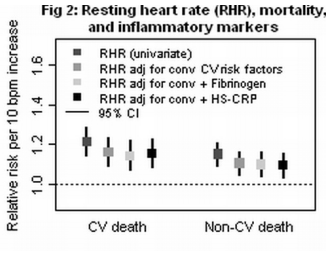
Conclusions: A strong, graded and independent relationship between RHR and CVD has been established. Importantly, this relationship extends to women in the general population. The temporal sequence would be compatible with a causal relationship. The stronger effect on fatal events suggests a possible proarrthymogenic effect of elevated RHR.

130 Resting heart rate remains a risk factor for CardioVascular (CV) and non-CardioVascular (non-CV) mortality in healthy subjects after adjusting for inflammatory markers. The Copenhagen city heart study

M.T. Jensen[1], J.L. Marott[1], G.B. Jensen[2]. [1]*Copenhagen University Hospital, Bispebjerg, Copenhagen, Denmark;* [2]*Copenhagen University Hospital, Hvidovre, Copenhagen, Denmark*

Purpose: Elevated resting heart rate (RHR) is a risk factor for mortality. Fibrinogen and HS-CRP are validated markers of inflammation and are both correlated with CV and non-CV mortality. So far, the association between RHR, inflammation, and mortality in a healthy population is not yet clear.
Methods: Healthy subjects were sampled from the Copenhagen City Heart Study, a prospective study of the general population. Subjects underwent assessment of RHR, conventional CV risk factors including FEV1, and levels of fibrinogen and HS-CRP. The association between CV and non-CV mortality, risk factors, and inflammatory markers was studied in multivariate Cox-models with age as underlying time-scale.
Results: 6752 subjects, 1797 deaths and 16 years of follow-up. A total of 2455 subjects were excluded due to use of heart medication, diabetes, atrial fibrillation or other known CV disease. Levels of fibrinogen and HS-CRP increased significantly with increasing RHR ($p<0.001$). Mean levels of inflammatory markers according to RHR quintiles are shown in Fig 1. The association between RHR and mortality was studied in univariate models, multivariate models including conventional risk factors, and same multivariate models with fibrinogen or HS-CRP (Fig. 2). The relative risk estimates from a 10 bpm increase in RHR were 1.2 for CV mortality (all $p<0.001$) and 1.1 for non-CV mortality (all $p<0.002$) when adjusting for CV risk factors, FEV1, and HS-CRP or fibrinogen.





Conclusion: RHR is associated with levels of inflammatory markers. Elevated RHR remains a risk factor for both CV and non-CV mortality in healthy subjects after adjusting for CV risk factors and markers of inflammation.

131 Increased exercise capacity is associated with lower mortality risk in men 70 years and older

P. Kokkinos[1], J. Myers[2], C. Faselis[1], M. Doumas[1], A. Pittaras[1], A. Manolis[1], J.P. Kokkinos[1], S. Singh[1], R. Fletcher[1]. *[1]Veterans Affairs Medical Center, Washington, United States of America; [2]Veterans Affairs Health Care System, Palo Alto, United States of America*

Purpose: Exercise capacity is inversely related to mortality risk in healthy individuals and those with cardiovascular disease (CVD). This evidence is based largely on middle-aged individuals with little information available for those 70 years and older. Thus, the purpose of this study was to assess the association between exercise capacity and mortality in men 70 years and older.
Methods: We assessed the association between exercise capacity and mortality in male veterans (n=3,041) 70-92 years of age who successfully completed a treadmill exercise test at the Veterans Affairs Medical Centers. We established four fitness categories based on peak metabolic equivalents (METs) achieved. We classified Very-Low-Fit (n=659) those who achieved a peak MET level $\leq$4 METs; Low-Fit (n=1335) those who achieved 4.1-6.0 METs; Moderate-Fit (n=862) those who achieved of 6.1-9.0 METs; and High-Fit (n=185) those with an exercise capacity $>$9 METs. Subjects were followed for all-cause mortality for more than 20 years (mean 6.5$\pm$5.6 years).
Results: There were 1,251 deaths (6.4% annual mortality rate). After adjusting for age, body mass index, CVD risk factors and medications, exercise capacity was a strong predictor of risk for mortality. The adjusted risk was reduced by 10% for every 1-MET increase in exercise capacity (hazard ratio= 0.90; CI: 0.87-0.92; p$<$0.001). Compared to those who achieved $\leq$4 METs, the mortality risk was 26% lower for those with an exercise capacity 4.1-6.0 METs (hazard ratio= 0.74; CI: 0.65-0.85; p$<$0.001), 46% lower for those who achieved 6.1-9 METs (hazard ratio=0.54; CI:0.46-0.63; p$<$0.001) and 54% lower for those achieving $>$9 METs (hazard ratio= 0.46; CI: 0.34-0.61; p$<$0.001).
Conclusions: Exercise capacity is a strong predictor of all-cause mortality in men $\geq$70 years old. The relationship was inverse, graded and similar to that observed in middle-aged and younger individuals. Our findings suggest that increased exercise capacity attenuates mortality risk at any age.

132 Adipokines and coronary heart disease - results from the MONICA/KORA Augsburg case-cohort study, 1984-2002

M. Karakas[1], A. Zierer[2], C. Herder[3], J. Baumert[2], C. Meisinger[2], W. Koenig[1], B. Thorand[2]. *[1]Universitaetsklinikum Ulm, Ulm, Germany; [2]Helmholtz Zentrum München, Institute of Epidemiology, Neuherberg, Germany; [3]German Diabetes Center, Institute for Clinical Diabetology, Heinrich Heine University, Düsseldorf, Germany*

Purpose: Adiponectin and leptin are both protein hormones secreted by adipose tissue. Despite modulating a number of metabolic processes linked to atherosclerosis, including glucose regulation, insulin sensitivity, hematopoiesis, fatty acid catabolism and angiogenesis, their potential association with coronary heart disease (CHD) is still a matter of controversy.
Methods: We conducted a population-based case-cohort study using data from the MONICA/KORA Augsburg studies. Serum levels of adipokines were measured in 333 case subjects with incident CHD and 1,728 non-case subjects selected from a source population of 9,300 middle-aged men and women. The mean follow-up time was 10.8$\pm$4.6 years. In extension to previous studies we also sought to analyze the combined effect of leptin and adiponectin using the leptin/adiponectin ratio, since this ratio has previously been suggested to be a better indicator of atherosclerosis complications than the single adipokines.
Results: Baseline concentrations were significantly lower in cases compared to noncases (p$\leq$0.001 for both adipokines). After adjustment for various confounding factors, including age, sex, BMI, lifestyle factors, systolic blood pressure, ratio of total cholesterol/HDL-cholesterol, parental history of CHD, inflammatory markers and markers of endothelial dysfunction, the hazard ratios (HRs) and 95% confidence intervals (CIs) comparing tertile extremes were 0.79 (95% CI 0.53-1.17) for leptin (top vs bottom tertile) and 1.14 (95% CI 0.81-1.61) for adiponectin (bottom vs top tertile), respectively. Furthermore, the ratio of leptin/adiponectin also showed no association with CHD (HR 1.01 (95% CI 0.68-1.51)).
Conclusions: The present report is the largest single study so far on leptin and adiponectin levels and incident CHD. In contrast to fairly strong associations previously reported, our findings indicate no association between leptin, adiponectin and their ratio with the risk of CHD after adjustment for potential confounders.

133 Respective contribution of carotid intima-media thickness and plaques to incident coronary heart disease in community-dwelling elderly. The three-city study

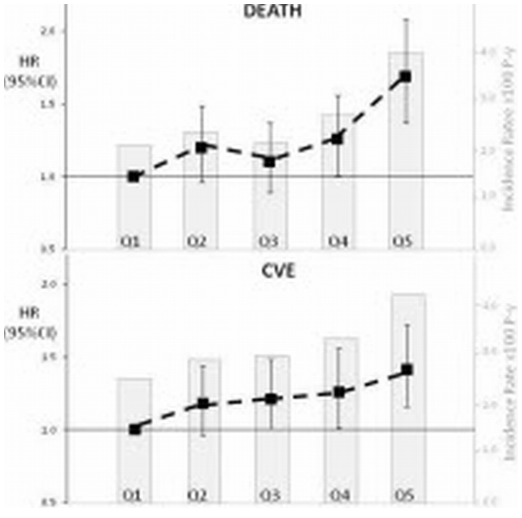
M. Plichart[1], M. Zureik[2], J. Gariepy[3], J.F. Dartigues[4], X. Jouven[1], K. Ritchie[5], C. Tzourio[6], P. Ducimetiere[1], J.P. Empana[1]. *[1]Inserm, U970 - Cardiovascular Epidemiology and Sudden Death, Paris, France; [2]Inserm, U700, Paris, France; [3]AP-HP - Hopital Broussais, Paris, France; [4]Inserm, U897, University V Segalen Bordeaux 2, Bordeaux, France; [5]Inserm, E0361, Montpellier, France; [6]Inserm, U708, Paris, France*

Objective: To explore the association of common carotid artery IMT (CCA-IMT) and carotid plaques (CP) with incident coronary heart disease (CHD) among the participants of the Three-City Study, a French population-based cohort study.
Methods: Between 1999 and 2001, 6631 participants (61% of women) aged 65-85 years underwent a bilateral ultrasound examination of carotid arteries involving the scanning of CCAs, the carotid bifurcations and the origin of the internal carotid arteries. Mean IMT was measured at the CCA at site free of any discrete plaque and the presence of plaque was assessed at any of the 3 sites. The study population included the 5895 subjects who were free of prevalent CHD. The hazard ratios (HR) of CIMT and CP with incident CHD events were estimated by Cox proportional hazard model.
Results: The mean level of cardiovascular risk factors was higher in subjects with CP and increased gradually with increasing CCA-IMT. After a median follow-up of 5.4 years, 223 incident CHD events occurred. After adjustment for established cardiovascular risk factors, CCA-IMT (highest ($\geq$0.81 mm) vs. lowest quintile ($\leq$0.61 mm)) was not associated with CHD risk (HR=0.8, 95% CI: 0.5-1.2) whereas subjects with CP had a nearly a two-fold increased risk (HR=1.8, 95% CI: 1.3-2.4) compared to those without CP. When both CCA-IMT and CP were in the same model, CP remained significantly associated with CHD risk. Finally, adding CP to a model based on traditional risk factors improved significantly the model discrimination as measured by the Harrell's c-index (0.748 to 0.762; p$<$0.001 after 1000 bootstrap replications)
Conclusion: In community-dwelling elderly, the presence of CP but not CCA-IMT was predictive of CHD events. Furthermore, screening for CP may improve the identification of those subjects at increased risk of CHD who may benefit from more aggressive primary prevention.

134 Uric acid: an underestimated cardiovascular risk factor

G. Levantesi[1], R.M. Marfisi[1], M.G. Franzosi[2], A.P. Maggioni[3], G.L. Nicolosi[4], C. Schweiger[5], M.G. Silletta[1], L. Tavazzi[6], G. Tognoni[1], R. Marchioli[1] on behalf of GISSI Prevenzione Investigators. *[1]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [2]The Mario Negri Institute for Pharmacological Research, Milan, Italy; [3]Associazione Nazionale Medici Cardiologi Ospedalieri Research Centre, Florence, Italy; [4]Azienda Ospedaliera S Maria Angeli, Pordenone, Italy; [5]Ospedale Civile, Passirana Di Rho, Italy; [6]Villa Maria Cecilia Ospedale, Cotignola, Italy*

Aims: To determine the relation between uric acid (UA) levels and risk for total mortality and cardiovascular events among patients surviving a myocardial infarction (MI).
Methods: Prospectively ascertained information among 10,994 patients enrolled in the GISSI-Prevenzione trial was used. UA serum level assessed at baseline



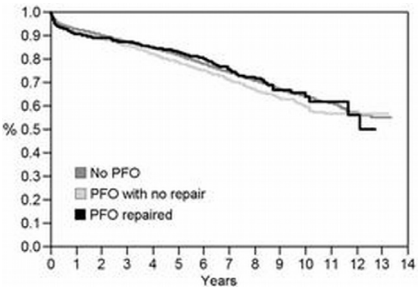
was categorized in quintiles, as <4.5 (Q1), 4.6 to 5.2 (Q2), 5.3 to 6.0 (Q3), 6.1 to 6.8 (Q4) and >6.8 (Q5)mg/dL. Outcome measures were the incidence of all-cause death and cardiovascular events (CVE- defined as cardiovascular death (CVD) or non-fatal myocardial infarction (nfMI) or non-fatal stroke (nfS)). Multivariable analysis adjusted for potential confounding factors (age, gender, hypertension, diabetes mellitus, electrical instability, left ventricular ejection fraction, NYHA class, creatinine, hematocrit, body mass index and medications) was used to estimate the relative risks (HR) of outcome measures across categories of UA.
Results: During 37,301 person-years of follow-up, 999 subjects deceased and 1,148 CVE (659 CVD, 450 nfMI, 117 nfS) occurred. The multivariable analysis showed a statistically significant association between high UA serum levels and both total mortality and CVE (Figure 1).
For death [RR, P value]: Q1 [reference category,1.00]; Q2 [1.20, 0.114]; Q3 [1.10, 0.375]; Q4 [1.26, 0.042]; Q5 [1.69, <0.0001].
For CVE [RR, P value]: Q1 [reference category,1.00]; Q2 [1.18, 0.121]; Q3 [1.21, 0.055]; Q4 [1.26, 0.025]; Q5 [1.41, 0.001].
Conclusions: UA serum levels increase the risk of death and CVE in post-MI patients, thus suggesting that a simple measure of serum UA might increase the possibilities to correctly estimate the real global cardiovascular risk of patient with ischemic heart disease.

STROKE: CURRENT CHALLENGES AND EMERGING THERAPIES

147 Impact of incidentally discovered patent foramen ovale and its operative repair on long-term survival

S.A. Hart, D. Allen, A. Qureshi, G. Pettersson, R.A. Krasuski. *Cleveland Clinic, Cleveland, United States of America*

Background: Patent foramen ovale (PFO) has been postulated to adversely impact long-term survival, and the proper approach to the incidentally discovered PFO at the time of cardiothoracic surgery is uncertain.
Methods: We reviewed the intraoperative transesophageal echocardiograms of 13261 patients with no prior diagnosis of atrial septal defect or PFO undergoing cardiothoracic surgery between 1995 and 2006 at a large academic medical center. The social security death index was utilized to assess all cause mortality in the 12293 patients (93%) with valid social security numbers.
Results: The mean age of the cohort was 63.1±13.4 years and 65.3% were male. PFO was discovered in 2144 patients (17.4%) and surgical closure was performed in 612 (28.5%). Patients undergoing closure were younger (61.0±13.9 vs. 64.5±13.1, p<0.001) and had higher frequency of prior stroke (12.6% vs. 7.6%, p<0.001) and atrial fibrillation (12.9% vs. 9.7%, p=0.03). Death occurred in 3276 patients (26.6%) over a median follow-up time of 6.1 years (range <0.1 to 13.3 years). Kaplan Meier analysis demonstrated that PFO closure improved survival to the level of patients without PFO after approximately 3 years (Figure), p=0.02. A proportional hazards model, however, demonstrated that after adjustment for confounders, patients without PFO, patients with PFO that went unrepaired and patients with PFO that was surgically repaired exhibited similar long-term survivals.



Conclusions: Surgical intervention on incidentally discovered PFO at the time of cardiothoracic surgery does not appear to impact long-term survival.

148 Natriuretic peptide testing for long-term risk assessment following acute ischemic stroke

J.K. Jensen[1], J.L. Januzzi[2], D. Atar[3], S.R. Kristensen[4], H. Mickley[1]. *[1]Department of Cardiology, Odense University Hospital, Odense, Denmark; [2]Cardiology Division, Massachusetts General Hospital, Boston, United States of America; [3]Division of Cardiology, Aker University Hospital, University of Oslo, Norway, Oslo, Norway; [4]Department of Clinical Biochemistry, Center of Cardiovascular Research, Aalborg, Denmark*

Background: The acute-phase levels of B-type natriuretic peptide and the N-terminal fragment of the BNP prohormone (NT-proBNP) have been associated with mortality when measured in patients with an ischemic stroke, whereas the longer-term value of NT-proBNP for chronic prognostication following ischemic stroke are limited.
Methods: Two hundred and sixteen patients (mean age, 67±13) with acute ischemic stroke were seen 6 months after index event. All patients underwent a structured interview and measurements of plasma NT-proBNP. Follow-uped was 45 months, with all-cause mortality as the clinical end point.
Results: The median NT-proBNP concentration for the whole group of patients was 147 pg/mL (10th to 90th percentile, 37 to 869 pg/ml). At follow-up 45 patients (21%) had died. NT-proBNP concentrations were significantly higher in decedents (308 pg/ml (10th to 90th percentile, 74 to 2279 pg/ml)) than in the 171 survivors (132 pg/ml (10th to 90th percentile, 35 to 570 pg/ml); P<0.001). Patients with NT-proBNP ≤147 pg/ml had a significantly improved survival rate on univariate analysis (Figure 1) (Log rank, P<0.001). In multivariate analysis after adjustment for age, stroke severity, heart- and renal failure, levels of NT-proBNP were an independent predictor of mortality later than 6 months after stroke (adjusted hazard ratio, 1.5; 95% CI, 1.1 to 1.9; P=0.005).

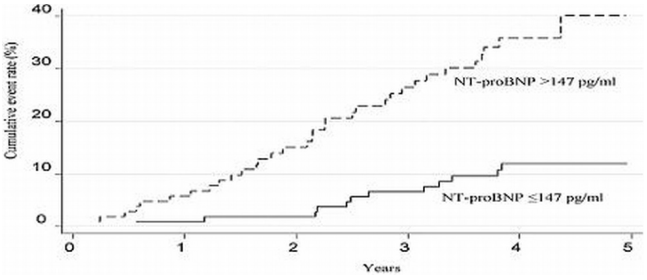


Figure 1

Conclusion: NT-proBNP concentrations measured during the stable phase after acute ischemic stroke are strongly predictive of long-term mortality.

149 Bleeding history and stroke subtypes, a cohort study of 105 043 patients reported to the Swedish Stroke Register (Riks-Stroke)

S. Aasberg[1], K.M. Henriksson[2], B. Farahmand[3], A. Terent[1]. *[1]Uppsala University Hospital, Uppsala, Sweden; [2]Department of Laboratory Medicine, Lund University, Lund, Sweden; [3]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*

Purpose: This study investigates frequency of bleeding events (BE) among patients who later suffered a hemorrhagic (HS) or ischemic stroke (IS). The aim was to increase our understanding of the bleeding patterns in stroke patients.
Methods: A cohort of 105043 patients was identified in the Swedish Stroke Register (RS) between 2001 and 2005. BEs occurring before stroke were traced back to 1987 (the entire observation period) by cross-linking RS with the Swedish Hospital Discharge Register. The bleeding diagnoses were further organized in anatomical subgroups. The frequency of BEs before stroke were related to age at stroke onset, time span between BE and stroke onset and stroke subtype. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression models.
Results: During the most recent 5 years before stroke, BE that was severe enough to require hospitalisation occurred in 7763 (9%) of IS and 1460 (12%) of HS patients (OR 0.74, 0.70-0.79). The corresponding figures for the entire observation period, 1987-2005, were 23 191 (27%) and 3 586 (29%) respectively (OR 0.90, 0.87-0.94). The most numerous BE in both subtypes of stroke (9% in HS versus 10% in IS) was gastrointestinal bleedings followed by bleeding in the respiratory tract (8% in HS versus 9% in IS). The third most common BE in HS, intracranial bleedings, were less frequent in IS (8% in HS versus 2% in IS). The frequency of BE increased by 3.7% per year (p<0.001) for IS patients <60 years of age, and by 1.5% per year (p<0.001) for patients ≥60 years of age. No increase was found in these age groups (p=0.55, p=0.07 respectively) among HS patients.
Conclusions: This study shows that bleeding events are common before stroke. The bleeding pattern differs between stroke subtypes, being more common, more recent and less correlated to age among patients with hemorrhagic stroke.

150 Temporal trends in hospitalisation for stroke recurrence following incident hospitalisation for stroke

S.C. Inglis[1], J.D. Lewsey[1], P. Jhund[1], M. Gillies[1], P. Langhorne[1], M. Walters[1], A. Briggs[1], J. Chalmers[2], J.J.V. Mcmurray[1], K. Macintyre[1]. *[1]University of Glasgow, Glasgow, United Kingdom; [2]Information Services Division, NHS Scotland, Edinburgh, United Kingdom*

Purpose: To examine temporal trends in hospitalisation of stroke recurrence following incident hospitalisation for stroke in Scotland during 1986-2005.
Methods: Using routinely linked data from the Scottish Morbidity Record, all first hospitalizations in Scotland during the period 1996-2005 where a stroke was coded in the principal diagnostic position (ICD 9 430, 431, 433, 434, 436; ICD 10 I60, I61, I63, I64) at discharge were identified. Unadjusted survival analysis of time to first hospitalisation for recurrent stroke was undertaken using the cu-

mulative incidence method which takes into account the competing risk of death. Regression on cumulative incidence functions was used to model in men and women separately the temporal trends of first recurrent stroke with adjustment for age, deprivation and comorbidity. We tested whether temporal trends were modified by age by including interaction terms to our models.
Results: There were 157,639 incident hospitalisations for stroke in Scotland between 1986 and 2005, 70,726 (45%) in men. 13,835 (10.8%) patients had a recurrent hospitalisation for stroke within five years of their incident hospitalisation during 1986-2001. For men, the hazard ratio (HR) comparing the risk of recurrent stroke in 2001 compared to 1986 was 0.73 95% CI (0.65, 0.82) and this effect was not modified by age. The results for women aged between 55 and 74 years were comparable to those for men (e.g. 65-74 years HR = 0.65 (0.54, 0.77)). However, no significant reduction in risk of recurrent stroke was observed for women aged under 55 years or 75 years and over.
Conclusions: Approximately 11 in 100 patients who had an incident hospitalisation of stroke in Scotland went on to have a recurrent stroke hospitalisation within 5 years. Over the study period there was a reduction in the risk of recurrent stroke in all men and for women aged between 55-74 years.

151 Efficacy of tirofiban in reducing short-term and long-term neurologic deficit in patients with ischaemic stroke. A double-blind, randomized trial of intravenous tirofiban versus aspirin

G. Torgano, C. Mandelli, B. Zecca, A. Maestroni, P. Rossi, D. Manganaro, C. Casiraghi, M. Cazzaniga, V. Monzani. *Ospedale Maggiore Policlinico, Milan, Italy*

Background: Thrombolysis with alteplase is presently the only approved therapy for ischaemic stroke, but for safety concerns it is administrable only within 3 hours; beyond this time the choice of treatment is limited to endovascular treatment, reserved to specialised centers, and antiplatelet drugs, mainly aspirin, whose efficacy in early administration has scarcely been evaluated. We tested the efficacy of tirofiban, a short half-life GP-IIb/IIIa inhibitor, administered within 6 hours from stroke onset.
Methods: One hundred and fifty patients were randomly assigned to treatment with tirofiban or ASA, both given with a three-days regimen in a double-blind fashion. Major inclusion criteria were basal NIHSS score between 5 and 25, clinical onset within 6 hours, absence of haemorrhage at basal CT scan. Primary outcome variables were the proportion of patients with a NIHSS score reduction $\geq$4 points after three days, and proportion of patients with a modified Rankin scale score $\leq$1 at 3 months.
Results: The trial was planned with 300 patients (150 for each treatment arm), but interrupted at interim analysis due to the absence of a superiority of tirofiban over ASA. Clinical basal caracteristics were similar in the two treatment groups. Short–term neurological improvement was observed in 56% of the patients in each group; at late follow-up, minimal or absent disability (mRS score 0-1) was seen in 45% of the patients in the tirofiban group and 53% in the ASA group; these differences were not significant. Three-months mortality was the same in both groups (10.6%); rate of any type of intracranial haemorrhage and of symptomatic haemorrhage was 9 vs 11% and 1% vs 5%, respectively.
Conclusion: Despite the trial was formally negative in the pre-planned hypothesis, the interesting finding is that, overall, antiplatelet drugs could be safe and effective when used in the first hours of cerebral ischaemia.

152 Plasma homocysteine level predicts stroke recurrence and all-cause mortality

W. Zhang[1], K. Sun[1], J. Chen[1], D. Wang[2], Q. Qin[3], A. Ma[4], Y. Liao[5], R. Hui[1]. *[1]Fuwai Hospital and Cardiovascular Institute, Beijing, China, People's Republic of; [2]Tongji Hospital, Huazhong University of Science and Technology, Wuhan City, China, People's Republic of; [3]Tianjin Cardiovascular Institute, Tianjin, China, People's Republic of; [4]First Hospital of Xi'an JiaoTong University, Xi'an City, China, People's Republic of; [5]Union Hospital, Huazhong University of Science and Technology, Wuhan City, China, People's Republic of*

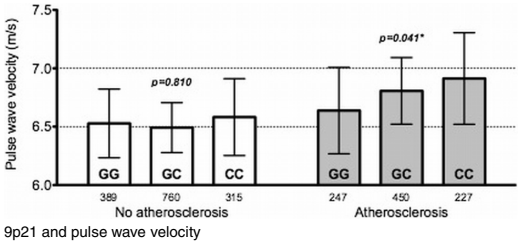
Objective: Plasma homocysteine concentration has been associated with the risk of stroke, but its relevance to stroke recurrence remains unclear. We investigated the relation between homocysteine and stroke recurrence in a Chinese population.
Methods: A total of 1,823 patients with stroke 35 to 74 years of age (1158 men and 976 women) were recruited in the Multicenter Chinese Stroke Study during 2000-2001 and prospectively followed up for a median 4.5 years. Plasma homocysteine at baseline was determined and methylenetetrahydrofolate reductase (MTHFR) variant C677T was genotyped.
Results: During the follow-up, 347 recurrent strokes and 323 deaths from all causes were documented. After adjustment for age, gender, and other cardiovascular risk factors, elevated homocysteine concentration was associated with increased risk of 1.74-fold for stroke recurrence (relative risk [RR] 1.74, 95% CI 1.3-2.3; P for trend $<$ 0.0001) and 1.75-fold for mortality (RR 1.75, 95% CI 1.3-2.4; P for trend $<$ 0.0001) in comparison of the highest to lowest category. Further analyses showed that plasma homocysteine in the highest category was positively associated with cardiovascular death (RR 1.88, 95%CI 1.2-2.7; P for trend=0.006), but not with non-cardiovascular death (RR 1.14, 95%CI 0.7-1.9; P for trend=0.59). Spline regression analyses demonstrated a threshold level of homocysteine for stroke recurrence. By dichotomizing homocysteine concentration, the RR was 1.31 (95% CI 1.10-1.61; P = 0.016) for stroke recurrence and 1.47 (95% CI 1.15-1.88; P $<$ 0.0001) for mortality in patients with homocysteine concentration $\geq$ 16 μmol/L relative to those with $<$ 16 μmol/L. No significant association was found between MTHFR 677TT genotype and stroke recurrence or mortality. In addition, stratified analysis showed that the positive association between homocysteine and stroke recurrence or mortality was not substantially modified by variant C677T.
Conclusions: Our findings suggest that elevated homocysteine concentration is associated with increased risk of stroke recurrence and mortality in the patients with stroke.

PERIPHERAL ARTERIAL DISEASE: FROM PATHOPHYSIOLOGY TO PROGNOSIS

153 The 9p21 locus and arterial stiffening in the general population: results from ASKLEPIOS

E. Rietzschel[1], I. Buysschaert[2], T. De Meyer[1], G. De Backer[1], S. Bekaert[1], D. De Bacquer[1], T.C. Gillebert[1], P. Segers[1], D. Lambrechts[2], M.L. De Buyzere[1] on behalf of the ASKLEPIOS investigators. *[1]University of Ghent, Ghent, Belgium; [2]Catholic University of Leuven (KULeuven), Leuven, Belgium*

Background: Carotid-femoral pulse wave velocity (PWV) is a well validated marker of arterial stiffness and of subsequent cardiovascular outcome measures. It is unknown whether genetic variants on the 9p21 locus, which confer a major risk for atherosclerotic cardiovascular morbidity and mortality, are related to arterial stiffness in the general population.
Methods: The prospective Asklepios study is a random sample (n=2524 apparently healthy volunteers) from the Belgian general population, free from overt cardiovascular disease. The subjects were extensively screened, including genotyping of the rs1333049 variation on 9p21 and screening for subclinical atherosclerotic lesions in the carotid and femoral arteries. PWV was measured using Doppler echography in the femoral and carotid arteries.
Results: In a multivariable analysis, adjusting for age, smoking, systolic blood pressure, heart rate, total and HDL-cholesterol, obesity, glycemia, high-sensitive c-reactive protein, physical activity, fruit and vegetable intake, educational achievement and drug therapies (lipid-lowering, antihypertensive), the rs1333049 at-risk C-allele was significantly and independently associated with PWV (F=4.6; p=0.032). Per C-allelle, PWV increased by 0.074 (95%CI: 0.007 – 0.142) m/s. In post-hoc analyses, the association between rs1333049 and PWV was restricted to subjects with detectable atherosclerosis (intima-media thickening and/or plaque). In subjects with atherosclerosis PWV increases by 0.126 – 0.226 m/s per copy of the at-risk C-allele of rs13333049.



9p21 and pulse wave velocity

Interpretation: These are the first results linking the 9p21 locus to arterial stiffness in a random population sample. 9p21 impacts arterial stiffness through shared pathways with atherosclerosis.

154 Are levels of the complex between activated protein C and the protein C inhibitor useful for prediction of clinical events in patients with peripheral arterial disease?

A. Gottsater, D. Blomstrand, T. Kolbel, B. Lindblad. *Malmo University Hospital, Malmo, Sweden*

Purpose: The complex between activated protein C (APC) and the protein C inhibitor (PCI) reflects thrombin generation and activation of coagulation, and has been shown to be elevated in atherosclerotic disorders. The aim of this study was to evaluate if increased levels of the APC-PCI complex in peripheral arterial disease (PAD) are related to prognosis in terms of death or future vascular events.
Methods: In a prospective, longitudinal study performed at a Vascular Centre, APC-PCI complex levels were analyzed in 286 consecutive patients hospitalized for PAD. Patients with warfarin treatment (n=35) less than 4 weeks prior to APC-PCI sampling were excluded from analysis, as warfarin affects APC-PCI complex levels. APC-PCI complex levels were compared to 42 healthy controls (median age 74 years). Medical records of all 251 remaining patients (median age 72

[25th–75th percentile 65–80] years, 126 men and 125 women, 116 with intermittent claudication and 135 with critical limb ischaemia) were searched for vascular events such as hospitalization due to atherosclerotic disease, operative or endovascular recanalization of peripheral arteries, transtibial or transfemoral amputation due to PAD, acute coronary syndrome, stroke or death.
Results: Median duration of follow up was 15 months (25th to 75th percentile 11–22 months). APC-PCI complex levels were higher in PAD patients than in controls ($P<0.0001$) but were not increased in the 124 (49%) patients experiencing events during follow up (0.25 [25th–75th percentile 0.19–0.33] μg/L) versus in those without events (0.23 [0.18–0.33] μg/L; P=0.5209) or in the 39 (16%) patients dying during follow-up (0.26 [0.20–0.36] μg/L) versus in survivors (0.24 [0.18–0.32] μg/L; P=0.2269). Independent predictors of future events in logistic regression analysis were low b-hemoglobin (P=0.0020), high b-leukocyte count (P=0.0090) and history of a previous vascular event (P=0.0036). Higher age (P=0.0418) and p-creatinine (P=0.0426) were independent predictors of death.
Conclusion: In our study high APC-PCI complex levels did not predict clinical outcome in PAD patients. We conclude that the impact of a prethrombotic state with increased thrombin generation and activation of coagulation, as reflected in increased APC-PCI levels, on prognosis and severity of peripheral atherosclerotic disease is not clarified and has to be further investigated.

155 Hemorheological profile in peripheral arterial disease patients

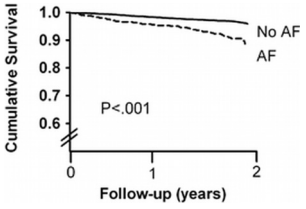
F. Sofi, F. Cesari, L. Mannini, G. Pratesi, R. Pulli, C. Pratesi, R. Abbate, G.F. Gensini. *University of Florence, Florence, Italy*

Introduction: Peripheral arterial disease (PAD), defined as a chronic obstruction of the arteries supplying the lower extremities, is a common manifestation of systemic atherosclerosis. Recently, many advances in the understanding of the development of such vascular disease have been reported, and a number of novel risk factors have been described. Hyperviscosity, due to alterations of blood cells and plasma components, may play a role in the pathogenesis of the disease. Aim of this study was to evaluate the possible association between hemorheological variables and PAD.
Material and Methods: The hemorheologic variables [whole blood viscosity (WBV), erythrocyte deformability index (DI), plasma viscosity (PLV), fibrinogen] were analyzed in 90 patients (median age: 73, range 31-87 years; 70 M, 20 F) and in 180 healthy subjects comparable for age and gender (median age: 70, range: 35-89 years; 140 M, 40 F). WBV and PLV were measured using a Rotational Viscosimeter (Contraves, Switzerland), whereas DI was measured by a microcomputer-assisted filtrometer (Myrenne, Germany).
Results: EF and PLV, but not WBV at 0.512 s^{-1} and 94.5 s^{-1} shear rates were found to be significantly different in patients as compared to healthy subjects. In order to investigate the possible association between these parameters and the disease we divided the study population into tertiles of their distribution among the healthy control group. At the univariate analysis, we found a significant association between the highest tertiles of PLV (2nd tertile: OR 3.61, 95%CI 1.32-9.86, p=0.01; 3rd tertile: OR 12.1, 95%CI 4.88-29.88, $p<0.0001$), and DI (2nd tertile: OR 0.48, 95%CI 0.25-0.89, p=0.02; 3rd tertile: OR 0.49, 95%CI 0.26-0.93, p=0.03) and the disease.
After adjustment for multiple potential confounders, at a multivariate analysis, the highest tertiles of PLV (OR 9.64, 95%CI 3.62-25.72; $p<0.0001$), and DI (OR 0.49, 95%CI 0.25-0.99; p=0.04) remained to be significantly associated with the disease, as compared to the lowest tertiles.
Conclusions: Our data indicate that an alteration of hemorheologic parameters, namely PLV and DI, may modulate the susceptibility to PAD. Hemorheological profile in PAD patients could allow to identify patients who might benefit from hemodilution.

156 Prognosis of atrial fibrillation in patients with peripheral arterial disease: data from the Reduction of Atherothrombosis for Continued Health (REACH) registry

T.A. Winkel[1], S.E. Hoeks[1], T. Limbourg[2], U. Zeymer[2], I. Baumgartner[3], D.L. Bhatt[4], P.G. Steg[5], S. Goto[6], D. Poldermans[1]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [3]Universitaet Spital Bern, Bern, Switzerland; [4]Cleveland Clinic, Cleveland, United States of America; [5]Bichat-Claude Bernard Hospital (AP-HP), Paris, France; [6]Tokai University, Kanagawa, Japan*

Background: Atrial fibrillation (AF) is a significant risk factor for cardiocerebrovascular mortality. The prevalence and prognosis of AF in patients with peripheral arterial disease (PAD) is unclear. The aim of this study is to evaluate the prognostic implication of AF in patients with PAD.
Methods: The international Reduction of Atherothrombosis for Continued Health (REACH) Registry included more than 21.000 outpatients in Europe with established coronary artery disease (CAD), cardiovascular disease (CVD), PAD, and/or ≥ 3 risk factors. Of these, 3753 patients had symptomatic PAD. Cardiovascular risk factors and medication use were determined at baseline. Endpoint of this study was cardio-cerebrovascular mortality during 2 years of follow-up. Cox regression analysis adjusted for age, gender and other risk factors (congestive heart failure, coronary artery revascularization, myocardial infarction, hypertension, stroke, and diabetes) was used.
Results: Of 3753 patients with PAD, 392 (10%) were known with AF. Patients with AF were older and had a higher prevalence of CVD, stroke, diabetes and hypertension. Long term cardio-cerebrovascular mortality occurred in 5.6% of PAD patients with AF compared to 1.6% in those without AF ($p<0.001$). Multivariable analyses showed AF to be an independent predictor of late cardio-cerebrovascular mortality (HR 1.6; 95% CI 1.05-2.4).



Conclusions: Atrial fibrillation is common in peripheral arterial disease patients and independently associated with a worse outcome.

157 Impaired walking distance is a strong prognostic indicator on long-term outcome in both patients with impaired and normal ABI

I.I. De Liefde[1], S.E. Hoeks[2], Y.R.B.M. Van Gestel[1], J. Klein[1], J.J. Bax[3], H.J.M. Verhagen[4], R.T. Van Domburg[2], D. Poldermans[4]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]Cardiology, Erasmus MC, Rotterdam, Netherlands; [3]Leiden University Medical Center, Leiden, Netherlands; [4]Vascular Surgery, Erasmus MC, Rotterdam, Netherlands*

Purpose: In contrast to the ankle brachial index (ABI), the clinical value of walking distance is still unclear. Therefore, we investigated the predictive value of walking distance on long-term outcome in patients with normal and impaired ABI.
Methods: 2191 patients, referred for a single-stage exercise treadmill walking test to diagnose or evaluate peripheral artery disease, were enrolled in an observational study. Patients were divided in normal ABI (≥ 0.90) or impaired ABI (<0.90). The total walking distance was divided into quartiles for each patient group (no, mild, moderate or severe).
Results: The mean follow-up was 5 years. In patients with normal ABI, severe impaired total walking distance was associated with higher mortality risk (table). In patient with impaired ABI, all total walking distance quartiles were associated with an increased mortality (table). Furthermore, comparable results were observed between all total walking distance quartiles, cardiac death and major adverse cerebrovascular and cardiac events.

Mortality risk on total walking distance

Total walking distance	Model I (HR, 95%CI)	Model II (HR, 95% CI)
Patients with normal ABI		
I no impairment	reference	reference
II mild impairment	1.70 (0.74-3.89)	1.70 (0.73-3.98)
III moderate impairment	1.52 (0.69-3.39)	1.57 (0.70-3.54)
IV severe impairment	2.72 (1.24-5.98)	2.60 (1.16-5.78)
Patients with impaired ABI		
I no impairment	reference	reference
II mild impairment	1.33 (1.00-1.76)	1.26 (0.95-1.67
III moderate impairment	1.62 (1.21-2.16)	1.52 (1.13-2.05)
IV severe impairment	1.83 (1.38-2.44)	1.69 (1.21-2.27)

Model I = age, gender. Model II = Model I, current smoking, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, resting systolic blood pressure, exercise ankle brachial index (ABI).

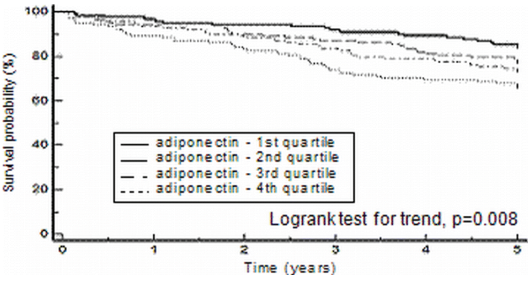
Conclusions: Our study showed that walking impairment is a strong independent prognostic indicator of long-term outcome in patients with impaired and normal ABI, which should be a warning sign to physicians to monitor these patients carefully and provide them optimal treatment.

158 Adiponectin predicts 5-year all cause in patients with symptomatic peripheral arterial disease: Results from the Linz Peripheral Arterial Disease (LIPAD) study

B. Dieplinger[1], A. Gegenhuber[2], W. Poelz[3], M. Haltmayer[1], T. Mueller[1]. *[1]Konvent Hospital Barmherzige Brueder Linz, Linz, Austria; [2]Krankenhaus Bad Ischl, Bad Ischl, Austria; [3]University of Linz, Linz, Austria*

Background: We have previously demonstrated that adiponectin is associated with amino terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with peripheral artery disease (PAD). Furthermore, we have shown that NT-proBNP is a strong predictor of mortality in these patients. The aim of this study was therefore to evaluate the value of adiponectin as long-term prognostic marker in patients with PAD.
Methods: We measured adiponectin serum concentrations in 487 consecutive patients with symptomatic PAD attending a tertiary care hospital. The endpoint

was defined as all-cause mortality, and the study participants were followed up for 5 years.
Results: Of the 487 patients enrolled, 114 died and 373 survived during follow up. The median adiponectin concentration was significant higher among decedents than survivors (11.3 vs. 9.1 mg/L; p<0.001). Cox proportional-hazards regression analyses revealed that increasing baseline adiponectin concentrations were associated with 5-year mortality in patients with symptomatic PAD (risk ratio 1.44, 95% CI 1.26-1.66; p <0.001 per 1 standard deviation increase). The predictive value of increasing adiponectin remained significant (risk ratio 1.24, 95% CI 1.02-1.45; p=0.029) after adjustment for age, sex, body mass index, estimated glomerular filtration rate, clinical stage of PAD, cardiovascular comorbidity, the presence of symptomatic heart failure, and other potential confounders. However, after additional adjustment for NT-proBNP, adiponectin did not remain an independent predictor.



Kaplan-Meier plot

Conclusions: Increased serum concentrations of adiponectin predicted 5-year all cause mortality in patients with symptomatic PAD independent of clinical and biochemical confounders. Only after adjustment for NT-proBNP, adiponectin lost its independent predictive value.

UNDER PRESSURE – TARGET ORGAN DAMAGE IN HYPERTENSION

159 Is it necessary to perform echocardiography in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study?

E. Gerdts[1], P.M. Okin[2], K. Wachtell[3], K. Boman[4], M.S. Nieminen[5], R.B. Devereux[2]. *[1]University of Bergen and Haukeland University Hospital, Bergen, Norway; [2]Weill Cornell Medical Centre, New York, United States of America; [3]Rigshospitalet, Copenhagen, Denmark; [4]Skelefteaa Hospital and Umeaa University, Skelefteaa, Sweden; [5]Helsinki University Central Hospital, Helsinki, Finland*

Background: Characteristics of hypertensive patients with left ventricular hypertrophy (LVH) diagnosed by electrocardiogram (ECG), echocardiogram (echo) or both are uncertain.
Methods: Baseline clinical, ECG and echo data and occurrence of the prespecified composite primary study end-point (cardiovascular death, stroke and myocardial infarction) and hospitalized heart failure (a secondary endpoint) during 4.8 years randomized losartan- or atenolol-based treatment were recorded in 832 hypertensive patients aged 55-80 (mean 66) years in the LIFE echocardiography substudy. LVH was diagnosed by ECG Sokolow Lyon and Cornell product criteria and as LV mass/body surface area >116 g/m^2 in men and >104 g/m^2 in women.
Results: 156 patients had LVH only on ECG, 143 only on echo and 533 had LVH on both ECG and echo. Compared to patients with ECG LVH alone, patients with both ECG and echo LVH were older, more obese, had higher systolic blood pressure and included more women and patients with history of ischemic heart disease, and fewer African Americans (all p<0.05). Patients with combined ECG and echo LVH had larger echo left atrial diameter, higher end-systolic wall stress, lower LV ejection fraction and stress-corrected midwall shortening, and included more patients with aortic valve regurgitation. Incidence of the primary study endpoint did not differ among groups with echo and/or ECG LVH during 4.8 years follow-up, while incidence of hospitalized heart failure was 3.5 times higher in patients with both ECG and echo LVH (p<0.05). In Cox regression analysis, baseline combined ECG and echo LVH predicted hospitalization for heart failure [HR 3.46 (95% CI 1.20-10.01), p=0.022] independent of gender, study treatment and time-varying systolic blood pressure.
Conclusion: Performing echocardiography in hypertensive patients with ECG LVH helps identify patients with lower LV systolic function and higher risk for hospitalized heart failure.

160 White-coat hypertension as a risk factor for developing left ventricular hypertrophy. The harvest study

L. Mos[1], P. Visentin[2], F. Dorigatti[2], M. Santonastaso[3], A. Bortolazzi[4], S. Cozzio[5], P. Bratti[2], F. Saladini[2], D. D'Este[6], P. Palatini[2]. *[1]Town Hospital, San Daniele Del Friuli, Italy; [2]University, Padova, Italy; [3]Town Hospital, Vittorio Veneto, Italy; [4]Town Hospital, Rovigo, Italy; [5]Town Hospital, Trento, Italy; [6]Town Hospital, Mirano, Italy*

Purpose: White-coat hypertension (WCH) is considered a benign clinical condition, but recent longitudinal studies indicate that patients with WCH may be at increased risk of events. No study reported on the risk of left ventricular hypertrophy (LVH) in this hypertension category.
Methods: Four-hundred and seventy never-treated young adults (330 men) with a mean age of 33.8±8.5 years (range, 18 to 45 years), who were screened for stage 1 hypertension on at least two occasions, were enrolled. Patients were seen every six months for clinic blood pressure and global risk assessment to determine which subjects developed hypertension needing drug therapy (HT). Echocardiographic left ventricular mass and 24h ambulatory blood pressure (ABP) were measured at entry, every 5 years, and/or at the time of HT development before starting treatment. Echocardiograms were sent to the reading Center. Subjects were divided according to whether they had WCH (n=184) or sustained hypertension (SH, n=286) at baseline. ABP and left ventricular mass measured at baseline and at the end of follow-up were used for analysis. To account for the regression to the mean effect in WCH patients, ABP measured after 3 months was also used for analysis. LVH was defined as a left ventricular mass ≥50 g/m$^{2.7}$ in men and ≥47 g/m$^{2.7}$ in women.
Results: During a 8.5 year follow-up, similar percents of subjects developed LVH (WCH, 8.2% vs SH, 6.3%, p=n.s.). Left ventricular mass increased by 1.8±6.4 g/m$^{2.7}$ in WCH and by 0.7±6.9 g/m$^{2.7}$ in SH (p adjusted for age, sex, body mass index, baseline left ventricular mass, and time = n.s.). ABP from baseline to study-end rose by 7.9±10.8/5.6±7.2 mmHg in WCH and by 1.2±10.9/1.9±7.9 mmHg in SH (adjusted p for WCH vs SH <0.000). WCH had a greater increase in ABP than SH also from the 3-month to the study-end measurement (+6.2±9.7/4.3±8.2 vs 2.4±12.3/2.8±8.6 mmHg, p=0.009 for systolic blood pressure, and p=0.02 for diastolic blood pressure). When data were adjusted also for baseline ABP, no significant difference emerged between WCH and SH for all comparisons. In the fully adjusted model, a significant difference in body weight change over the 8.5 year period was found between WCH (+3.5±7.2 kg) and SH (+1.8±6.6 kg, p=0.027).
Conclusions: A greater increase in ABP and body weight and a similar susceptibility to develop LVH was observed in WCH compared to SH, suggesting that WCH should not be regarded as a benign condition. This implies an increased risk of cardiovascular events and prompts for a more tight clinical control along with target organ surveillance in WCH subjects.

161 Regional myocardial performance in hypertensive heart disease

D. Foell, M. Markl, E. Schilli, F. Staehle, J. Hennig, C.H. Bode, B. Jung. *Universitaetsklinikum Freiburg, Freiburg im Breisgau, Germany*

Purpose: Hypertensive heart disease leads to diastolic and subtle systolic dysfunction. MR Tissue Phase Mapping (TPM) allows a segmental analysis of all myocardial velocities with high temporal resolution. Our aim was to analyze regional LV motion in 18 patients with hypertensive heart disease.
Methods: We acquired 3 short axis slices in 18 patients with LV hypertrophy and arterial hypertension (wall thickness >12mm, mean: 53.3 years), and 20 healthy

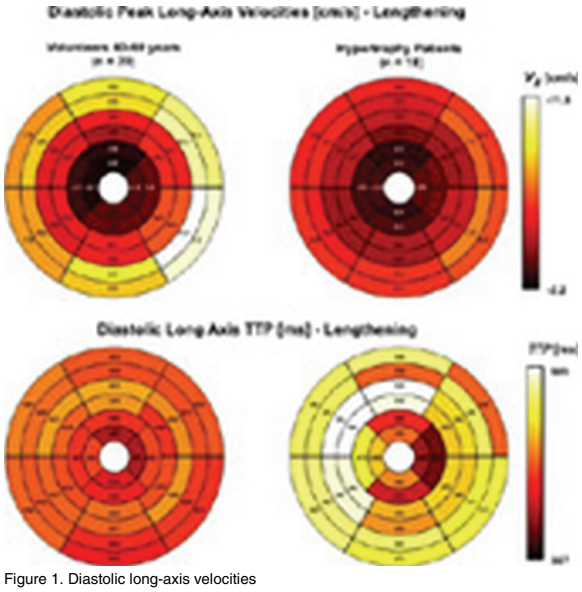


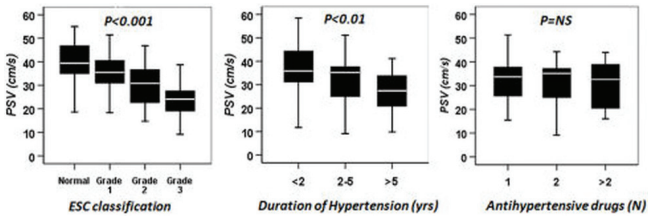
Figure 1. Diastolic long-axis velocities

age-matched controls (mean: 51.3years) with a gradient echo sequence (TR=6.9 ms; temp. resolution 13.8ms; 1.3×1.3mm; venc =15cm/s resp. 25cm/s). For group comparisons a 16 segment model, including endo- and epicardial regions was used. Peak and time to peak (TTP) radial, rotational and long-axis velocities were derived from velocity time courses of each segment.
Results: Patients revealed reduced and delayed mean diastolic peak velocities ($p<0.05$). Diastolic radial velocities were delayed in most segments, whereas the timing of long-axis peak velocities was more heterogeneous in basal, midventricular and septal regions compared to the controls. TTP radial and long-axis velocities showed an altered distribution, e.g. the apico-basal gradient of TTP diastolic radial velocities was absent in inferior and septal regions of patients. For diastolic long-axis velocities, TTP and peak velocities showed an increased asynchrony in the patients (fig. 1). In systole, long-axis velocities were increased in anteroseptal, reduced in inferolateral regions, and enhanced in the septum of the patients.
Conclusion: Magnitude, timing and distribution of systolic and diastolic segmental myocardial velocities were strongly altered in patients with hypertensive heart disease. New imaging methods as TPM may help to improve the understanding of the complex segmental LV motion.

162 Penile vasculature: an organ target in essential hypertensive men

C. Vlachopoulos, N. Ioakeimidis, K. Rokkas, D. Terentes-Printzios, A. Bratsas, K. Baou, P. Pietri, G. Lazaros, A. Askitis, C. Stefanadis.
Hippokration General Hospital of Athens, Athens, Greece

Purpose: Hypertension is the most common comorbidity in patients with erectile dysfunction (ED). The aim of this study was to evaluate the effect of hypertension and antihypertensive medication on penile vascular function.
Methods: 96 hypertensive and 41 age-matched normotesive men with ED (mean age 56±7 yrs) were submitted to penile color duplex Doppler ultrasonography. Lower penile Doppler velocities indicate impaired arterial function and increased cardiovascular risk.
Results: Severe penile arterial insufficiency (SAI) was found in 36 of 96 (37.5%) hypertensive men and in 7 of 41 (17%) normotensive subjects (χ^2=3.28, P < 0.05). Severity of hypertension was significantly associated with penile vascular damage in our study population according to ESH-ESC guidelines (left figure, $P<0.001$ by ANCOCA, post hoc $P<0.05$ for comparing Grade 3 with Grade 2 hypertension patients and Grade 2 with Grade 1 hypertension patients). Duration of hypertension also affected severity of ED as shown in the middle figure ($P<0.01$ by ANCOVA, post hoc $P<0.01$ for comparing men with long-standing hypertension with men with duration less than 3 years). Treated hypertensive patients had significantly lower Doppler velocities as compared to untreated men ($P<0.05$), however the number of antihypertensive drugs did not affect ED severity (P =NS, right figure).



Hypertension and penile vascular damage

Conclusions: Severity and duration of hypertension and antihypertensive medication are unfavorably correlated with penile Doppler velocities and extent of ED. This finding provides further insights into the pathophysiology of ED in hypertensive men and may have implications for the cardiovascular risk in these patients.

163 Carotid intima-media thickness correlates closer with central than brachial pulse pressure

P. Jankowski[1], Y. Jin[2], K. Stolarz-Skrzypek[1], L. Thijs[2], W. Wojciechowska[1], T. Kuznetsova[2], T. Richart[2], T. Grodzicki[1], J.A. Staessen[2], K. Kawecka-Jaszcz[1]. *[1]Jagiellonian University Medical College, 1st Department of Cardiology and Hypertension, Krakow, Poland; [2]Studies Coordinating Centre, Div. of Hypertension and Cardiovascular Rehabilitation, Univ. of Leuven, Leuven, Belgium*

Purpose: We compared the independent correlations of IMT with central and peripheral blood pressure components.
Methods: Carotid intima-media thickness (IMT) and brachial (cuff) as well as central (assessed noninvasively by applanation tonometry) blood pressure were measured in 560 subjects (mean age: 46.8±16.3 year; 280 women, 280 men) who were randomly recruited from populations living in defined geographical areas in northern Belgium and southern Poland. We used single and multiple linear regression. We compared correlations by calculation of z- statistics within a single sample.
Results: IMT correlated significantly with central and brachial systolic, diastolic, mean and pulse pressures (table). IMT correlated closer with central systolic, mean, and pulse pressures than with the brachial counterparts ($p<0.001$; table). After adjustment for sex, age, country, and body mass index, IMT remained significantly correlated with central pulse pressure. In addition, IMT correlated closer with central than brachial pulse pressure, both before ($p<0.05$; table) and after further adjustments for heart rate, smoking, blood glucose, serum creatinine, total-to-HDL cholesterol ratio and antihypertensive treatment (p=0.005).

IMT - blood pressure relation

Blood pressure component	Univariable r ± SE, p value	Multivariable* β ± SE, p value
Central systolic	0.428±0.038†, p<0.001	0.0797±0.0442, p=0.07
Brachial systolic	0.344±0.040, p<0.001	0.0578±0.0396, p=0.15
Central diastolic	0.222±0.041, p<0.001	-0.0047±0.0388, p=0.90
Brachial diastolic	0.222±0.041, p<0.001	-0.0092±0.0387, p=0.81
Central mean	0.345±0.040†, p<0.001	0.0371±0.0415, p=0.37
Brachial mean	0.309±0.041, p<0.001	0.0248±0.0403, p=0.54
Central pulse	0.413±0.039†, p<0.001	0.1068±0.0430‡, p=0.01
Brachial pulse	0.276±0.041, p<0.001	0.0689±0.0365, p=0.06

*Adjusted for country, sex, age and body mass index. †$p < 0.001$ vs brachial pressure, ‡$p < 0.05$ vs brachial pressure.

Conclusion: The multivariable-adjusted correlation with IMT is stronger for central than peripheral pulse pressure.

164 Excessive inotropic response during exercise as a marker of cardiovascular stiffening in newly diagnosed essential hypertension

D. Tsiachris, C. Tsioufis, D. Syrseloudis, D. Soulis, T. Papaioannou, A. Mazaraki, V. Tzamou, I. Andrikou, I. Vlasseros, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: Exaggerated blood pressure response during exercise (EBPR) is associated with high risk for worsening hypertension, while arterial stiffness and left ventricular (LV) diastolic dysfunction have both been related with adverse cardiovascular outcomes. We investigated the relationship between these parameters in the early stages of essential hypertension (EH).
Methods: 222 untreated non-diabetics (152 males, mean age 54 years) with stage I – II EH underwent treadmill exercise testing and were classified as hypertensives with EBPR (n=75) based on the systolic blood pressure (BP) elevation ≥210mmHg for men and ≥190mmHg for women, at peak exercise. The remaining patients were classified as normal inotropic responders (n=147). In all subjects of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP), while LV diastolic function was estimated by pulsed Tissue Doppler Imaging (TDI), averaging diastolic mitral annular velocities (Em, Am) from 4 separate sites of measurement.
Results: Hypertensives with EBPR compared to normal inotropic responders had increased office systolic BP (154±16 vs 149.3±16 mmHg, p=0.043) and PP (57±14 vs 51.5±13 mmHg, p=0.003), 24-hour systolic BP (137.4±10 vs 134±9 mmHg, p=0.013) and PP (52.6±8 vs 49±7 mmHg, p=0.001), while there was no difference in terms of age, sex and body mass index. Hypertensives with EBPR exhibited also greater relative wall thickness (0.47±0.06 vs 0.44±0.07, p=0.014) while they did not differ compared to those without EBPR with respect to LV mass index and transmitral flow Doppler parameters (p=NS for all). Hypertensives with EBPR compared to those without exhibited significantly lower values of Em (8.5±2.5 vs 9.4±2.9 cm/s, p=0.046) as well as greater E/Em (9.45±3.1 vs 8.35±3.3, p=0.034) and PWV (9.1±1.6 vs 8.5±1.3, p=0.007). Exercise capacity was also significantly deteriorated in hypertensives with EBPR based on the lower values of achieved METs (9.95±2.3 vs 11±2.3, p=0.003). Peak systolic BP at exercise was correlated with 24-hour systolic BP (r=0.240, $p<0.001$), 24-hour PP (r=0.218, p=0.001), PWV (r=0.152, p=0.046) and E/Em (r=0.150, p=0.049). By applying a logistic regression analysis, it was revealed that the only independent predictor of EBPR was PWV (OR=1.31, p=0.047).
Conclusions: The excessive inotropic response during treadmill exercise testing constitutes a sign of cardiovascular stiffening in the setting of newly diagnosed EH. This interrelationship may further elucidate the prognostic role of the abnormal systolic BP elevation at peak exercise.

PROGNOSIS IN HYPERTENSION

165 Exercise capacity status has a strong association with long term mortality risk in both young and older pre-hypertensive men

A. Pittaras[1], J. Myers[2], A.J. Manolis[3], M. Doumas[4], M. Kallistratos[3], A. Giannakopoulos[3], C. Faselis[4], P. Narayan[4], S. Singh[4], P.F. Kokkinos[4]. *[1]Mediton Medical Center, Athens, Greece; [2]VAMC, Palo Alto, United States of America; [3]Asclepion Voulas Hospital, Athens, Greece; [4]VA & Georgetown University Medical Centers, Washington Dc, United States of America*

Purpose: Epidemiologic evidence supports an inverse and strong association between fitness status, and mortality in healthy individuals. Pre-hypertensive individuals are at increased risk for cardiovascular events compared to those with nor-

mal blood pressure. However, there is no information on the association between exercise capacity and mortality in pre-hypertensive men or those with normal and high-normal blood pressure. Additionally there is limited data about differences between young and older men.
Methods: We assessed the association between peak exercise capacity (METs) and all-cause mortality in pre-hypertensive men (n=4,735; age=56±12). We established four fitness categories based on the MET level achieved. Those who achieved <5 METs (n=674); 5–7 METs (n=1,170); 7.1 to 10 METs (1,784); and > 10 METs (n= n=1,107). There were 943 deaths over 22 years of follow-up (mean=8.0±5.5).
Results: After adjusting for age, BMI, diabetes and dyslipidemia, exercise capacity was the strongest predictor of risk for mortality. The adjusted risk was reduced by 14% for every 1-MET increase in exercise capacity (Hazard Ratio= 0.86; CI: 0.84 – 0.88; p<0.001).The mortality risk reduction per 1MET increase in exercise capacity was 18% lower for those <60yrs (HR=0.82; CI:0.79-0.86;p<0.001) and 11% lower for those >60yrs (HR=0.89; CI:0.86-0.92;p<0.001). When compared to those who achieved 5 METs, the mortality risk in those who achieved 5.1–7 METs was 25% lower (hazard ratio= 0.75; CI: 0.64 – 0.87; p<0.001); 60% lower for those who achieved 7.1–10 METs (hazard ratio= 0.40; CI: 0.33– 0.48; p<0.001), and 75% lower for those achieving >10 METs (Hazard Ratio= 0.25; CI: 0.19 – 0.33; p<0.001). According to ESC/ESH classification, comparisons between those with normal and high-normal BP, revealed that mortality rate was similar (HR=0.87; CI:0.83-1.1; p=0.74).
Conclusions: The association between exercise capacity and mortality in pre-hypertensive individuals was strong, inverse and graded. The mortality risk was lowered by 14% for each 1-MET increase in exercise capacity (18% for those <60yrs, and 11% for those >60yrs). Similar mortality risk reduction was also observed in men with normal and high-normal BP. The overall reduction in mortality was 25% to 75% for those with an exercise capacity of >7 METs compared to those who achieved <5 METs.

166 Treated hypertensives with normal standard echocardiography at rest have marked left ventricular dysfunction on exercise

Y.T. Tan[1], E. Lee[2], F. Wenzelburger[1], G. Heatlie[2], M. Frenneaux[1], J.E. Sanderson[1]. *[1]University of Birmingham, Birmingham, United Kingdom; [2]University of North Staffordshire, Stoke-On-Trent, United Kingdom*

Background: The mainstay of treatment for hypertension has been to control blood pressure (BP). Despite well-controlled BP, many patients complain of exertional dyspnoea. These patients frequently have normal echocardiographic findings on conventional scans. Little is known about their cardiac function on exercise.
Methods: Symptomatic hypertensive patients with well-controlled BP on medication and normal baseline echocardiography underwent cardiopulmonary exercise testing to determine their peak oxygen consumption, VO2max, followed by rest and submaxinal supine exercise echocardiography (standard, tissue Doppler and speckle tracking).
Results: 30 treated hypertensive patients with exertional dysnoea (18 female; mean age 71±8 years) and 22 age-matched healthy controls (16 female; 70±6 years) had rest and exercise images of sufficient quality for analysis. Both groups had comparable echocardiographic findings at rest apart from reduced global longitudinal strain (-19.0±2.4% vs. -20.9±3.1%, p=0.031). On exercise, patients had significantly reduced long axis function (Sm 6.12±1.07cm/s vs. 7.77±0.95cm/s, p<0.001; Em 6.74±1.34 vs. 8.48±1.19cm/s, p=0.001; Longitudinal strain -21.2±3.8% vs. -23.8±2.6%, p=0.020)and apical rotation (13.1±4.6° vs. 17.0±3.4°, p=0.013) in systole, delayed untwisting (20.4±7.6° vs. 30.6±7.8°, p=0.001)and reduced suction (47.2±9.7m/s vs. 63.3±12.3 m/s, p<0.001) in diastole in addition to significantly lower overall left ventricular systolic reserve (0.97±1.34 vs. 2.32±1.24, p=0.001)associated with significantly reduced VO2max (18.0±4.0 ml/min/kg vs. 29.0±5.6 ml/min/kg, p<0.001).
Conclusion: Despite apparently treated and well controlled BP, patients with exercise limitation have widespread systolic and diastolic LV dysfunction which is only apparent on exercise. Controlling BP alone might not prevent the progression of hypertensive heart disease.

167 Impaired orthostatic response predicts mortality and coronary events in middle-aged individuals

A. Fedorowski, L. Stavenow, B. Hedblad, O. Melander. *Malmo University Hospital, Malmo, Sweden*

Purpose: Determinants and prognostic aspects of orthostatic hypotension (OH) remain largely unexplored in general population. The main reason is predominantly asymptomatic character of disorder due to protective action of cerebral autoregulation, which often results in underdiagnosing of OH.
Methods: The prospective data of the Swedish "Malmö Preventive Project" cohort (n=33,346, 67.3% men, mean age 45.7±7.4 years, mean follow – up 22.7±6.0 years), including baseline supine and standing blood pressure (BP) measurements, were analyzed. Predictive power of impaired orthostatic response in regard to incident coronary events (CEs), stroke and all-cause mortality was determined as a dichotomous variable (by international OH criteria), and separately for systolic (SBP) and diastolic blood pressure (DBP) response with different threshold limits, and additionally as a continuous variable (Δ mmHg), in crude and adjusted Cox regression models (including demographic covariates and conventional risk factors).
Results: OH was found in 6.2% of study participants and was significantly associated with age, female gender, diabetes, increased SBP, antihypertensive treatment, low BMI and current smoking. OH positive individuals had an increased mortality risk both in crude (Hazard ratio (HR): 1.7, 95%CI 1.5-1.8, P<0.001) and fully adjusted model (HR: 1.2, 95%CI 1.1-1.3, P<0.0001), and increased CE risk in corresponding models (HR: 1.6, 95%CI 1.4-1.8, P<0.0001, and 1.2, 95%CI 1.0-1.3, P=0.007, respectively). Stroke was predicted by OH only in crude model. After adjustment, mortality risk was more than twice higher in those aged<42 yrs, whereas both mortality and CE risk were distinctly increased in those with SBP fall ≥30mmHg (HR: 1.6, 95%CI 1.3-1.9, P<0.0001, and 1.6, 95%CI 1.2-2.1, P=0.001) and DBP fall ≥15 mmHg (HR: 1.4, 95%CI 1.1-1.9, P=0.024 and 1.7, 95%CI 1.1-2.5, P=0.01). In parallel, impaired DBP response as a continuous variable demonstrated greater impact than impaired SBP response (per mmHg) on CE incidence.
Conclusions: OH can be detected in approximately 6% of middle – aged individuals, and its frequency increases with such comorbidities as hypertension or diabetes. Presence of OH moderately increases mortality and CE risk, independently of traditional risk factors. This relation is mediated by both impaired systolic and diastolic BP response but the latter seems to influence coronary circulation in higher grade.

168 Relationship of morning blood pressure surge with cardiovascular events and total mortality in a general population

M. Bombelli[1], E. Toso[2], F. Ganz[2], D. Fodri[1], V. Galbiati[3], G. Seravalle[4], R. Facchetti[2], G. Grassi[1], R. Sega[3], G. Mancia[1]. *[1]Ospedale San Gerardo, Monza, Italy; [2]Universita di Milano-Bicocca, Milan, Italy; [3]Ospedale di Vimercate, Vimercate, Italy; [4]Ospedale San Luca (Istituto Auxiologico Italiano), Milan, Italy*

Purpose: Cardiovascular (CV) events have their greatest prevalence in the morning period and are believed to be associated with and depending on morning surge in blood pressure (BP). Direct evidence is limited, however.
Methods: In 2011 subjects of the PAMELA study (Pressioni Arteriose Monitorate e Loro Associazioni) randomly selected to be representative of the general population of Monza (MI, Italy) for gender and age decades (25-74 ys), we performed 24 hour ambulatory blood pressure (24h BP) by a validated oscillometric device, set to obtain automatic measurements every 20 minutes. The morning BP surge (MBPS) was calculated as the average of the systolic (S) BP readings of the 2 hours after awake minus the average of the lowest SBP readings, the SBP reading immediately preceding and the one immediately following, during the night time. Spectral analysis of BP profile was performed to identify the main cyclic components of SBP variability (1° and 2° cyclic components of variability, respectively day night and post prandial variability), and residual, non-cyclic variability. Subjects were followed for an average of 148 months, during which CV events (fatal and non fatal) and all-cause deaths were recorded.
Results: MBPS was significantly correlated (p<0.0001) with several other 24h BP variables, i.e. 24h mean SBP, day-night SBP difference and other cyclic and non-cyclic components of SBP variability, the correlation coefficients ranging from 0.24 to 0.47 (r values). During the follow up there were 231 all cause deaths and 178 CV events. MBPS showed a significant predictive relationship with the incidence of all cause death (p<0.001), and with the incidence of CV events (p<0.01). The significant relationship with all cause death and CV events, however, disappeared after adjustment for potential confounders such as age and other 24h BP variables. Similar findings were obtained when another method to calculate the morning BP surge, such as the post and preawake BP difference, was used.
Conclusions: In the PAMELA population, MBPS reflects overall BP variability phenomena and does not appear to be an independent predictor of CV or all cause death risk.

169 Influence of blood pressure and blood pressure change on the risk of congestive heart failure in the elderly

D. Conen[1], C.U. Chae[2], J.M. Guralnik[3], R.J. Glynn[4]. *[1]University Hospital Basel, Basel, Switzerland; [2]Massachusetts General Hospital, Boston, United States of America; [3]National Institute on Aging, Bethesda, United States of America; [4]Brigham and Women's Hospital, Boston, United States of America*

Background: While hypertension has been consistently associated with incident congestive heart failure (CHF), much less is known about the effect of blood pressure (BP) change over time. We therefore assessed the association of BP change with subsequent risk of incident CHF.
Methods: 4655 participants ≥65 years old from the prospective Established Populations for Epidemiologic Studies of the Elderly program who were alive and free of CHF after 6 years of follow-up were included. BP change was defined according to BP difference between study entry and 6 years of follow-up. We hypothesized that high systolic BP and a low diastolic BP (suggesting aortic stiffness) would be associated with incident CHF. Therefore, a BP threshold of 160 mmHg for systolic and 70 mmHg for diastolic BP was pre-specified to define sustained high BP,

sustained low BP, BP progression and BP regression. The primary endpoint was incident CHF subsequent to the 6-year examination.
Results: During 4.3 years of follow-up after the 6-year examination, 642 events occurred. The hazard ratio (HR) (95% confidence interval (CI)) for baseline systolic BP ≥160 compared to <120 mmHg at baseline was 1.39 (1.04-1.86). Conversely, the lowest diastolic BP category at baseline was associated with an increased risk of incident CHF (HR (95% CI) <70 mmHg versus 70-79 mmHg 1.42 (1.18-1.71)). Baseline systolic and diastolic BP were better predictors of incident CHF than pulse pressure. With regard to BP change over time, the HRs (95% CI) for incident CHF associated with sustained high systolic BP ≥160 mmHg and systolic BP progression were 1.35 (0.97-1.89) and 1.45 (1.14-1.85), respectively. Conversely, significant associations were found in those with sustained low diastolic BP <70 mmHg or diastolic BP regression (HR (95% CI) 1.42 (1.11-1.83) and 1.45 (1.19-1.76), respectively).
Conclusion: While elevated systolic BP and systolic BP progression were strong predictors of CHF in the elderly, inverse associations were found with regard to diastolic BP. Systolic and diastolic BP alone were better predictors of CHF than pulse pressure.

170 Predictors of progression from prehypertension to hypertension in Japanese men

M. Odaira, H. Tomiyama, C. Matsumoto, M. Yoshida, J. Yamada, K. Shiina, A. Yamashina. *Tokyo Medical University, Tokyo, Japan*

Objective: This 3-year prospective study in middle-aged Japanese men with pre-hypertension examined the usefulness of the plasma levels of C-reactive protein (CRP) and that brachial-ankle pulse wave velocity (baPWV) as predictors of the development to hypertension as compared with other previously proposed markers, such as the age, initial blood pressure, heart rate, obesity, smoking and alcohol intake.
Methods and Results: Among 777 men with pre-hypertension (42±8 years old), hypertension developed in 58 men during the observation period. Significant elevation of blood pressure during this 3-year follow-up was not observed in some, but not all, subjects. Univariate linear regression analysis demonstrated that baPWV, body mass index (BMI), age and alcohol intake, but not plasma levels of CRP, heart rate and smoking, on the first examination were significant variables related to the changes in systolic blood pressure from the first examination to the second examination. Multivariate linear regression analysis confirmed that baPWV and BMI were significant independent variables related to the changes in systolic blood pressure. The logistic regression analysis demonstrated that baPWV >13.5 m/sec {adjusted odds ratio = 3.32 (1.79 – 6.15)} and BMI >25.0 {adjusted odds ratio = 2.27 (1.25 – 4.13)} were significant predictors of future hypertension independent of blood pressure on the first examination.
Conclusion: This 3-year prospective study suggested that the baPWV and BMI, but not plasma CRP levels, are independent markers to identify middle-aged Japanese men with pre-hypertension at high risk for hypertension.

CARDIAC RESYNCHRONISATION THERAPY: EXPLORING NEW INDICATIONS

233 Incidence and prognostic impact of spontaneous conversion to sinus rhythm in patients with permanent atrial fibrillation treated with cardiac resynchronization devices

C. Leclercq[1], M. Gasparini[2], A. Arshad[3], A. Rozier[1], G. Kamath[3], P. Galimbert[2], C. Daubert[1], C. Klersy[3], J.S. Steinberg[3]. *[1]CHU de Rennes - Hopital de Pontchaillou, Rennes, France; [2]Instituto Clinico Humanitas, Milano, Italy; [3]St Luke's Roosevelt Hospital, New York, United States of America*

Introduction: Anecdotal reports of spontaneous resumption to stable sinus rhythm (SR) of heart failure (HF) patients with permanent atrial fibrillation (PeAF) after cardiac resynchronization therapy (CRT) have been reported. If this incidence is appreciable, additional interventions may be indicated such as placement of an atrial lead. A comprehensive multicenter review of our experience was therefore performed.
Methods: We retrospectively reviewed patients with PeAF who received CRT devices; standard CRT indications were applied. PeAF was defined as AF present for more than 1 year refractory to any rhythm control efforts. Rhythm was sampled at each follow-up visit, generally every 6 months.
Results: In total, 345 patients with PeAF were implanted with CRT devices (CRT-D 48%); mean age was 70±9 yrs and mostly male gender (83%). Ischemic HF was present in 154 patients (45%). Mean NYHA class was 3,1±0,5, 6MWT distance 308±113 meters, QRS 156±39 ms, LVEF 28±7%, and LVEDD 65±9 mm. PeAF had been present for 2,1±1.6 years. Over a follow-up of 29±24 months, 34 (9,9%) patients spontaneously reverted to stable (> 3 months) SR. Most SR resumptions occurred within the 1st year after CRT (28/34, 82%), but also occured even after 5 years (2/34). Mortality rate was 20,4 for PeAF compared to 2,5 per 100 patients-year for SR resumption (Log Rank p=0.004, see figure) (HR= 0.13, 95% CI 0.031-0.512, p< 0.0001).
Conclusion: Spontaneous resumption to SR in HF patients with PeAF treated with CRT was observed in roughly 10% of cases, generally within 1 year from implant. SR resumption was associated with a significant 87% reduction of total mortality. Identification of predictors for return of SR may be useful to guide routine atrial lead placement in some patients.

234 Why the patients with permanent atrial fibrillation indicated to CRT have worse prognosis comparing to the patients with sinus rhythm ?

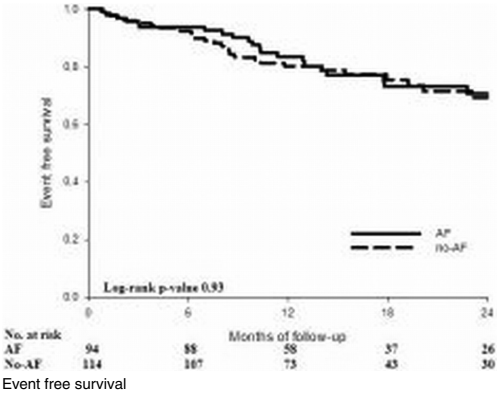
M. Taborsky, P. Neuzil, E. Mandysova, E. Vait. *Na Homolce Hospital, Prague, Czech Republic*

Objectives: Cardiac resynchronization therapy (CRT) has become a standard treatment in patients with refractory heart failure, depressed left ventricle ejection fraction (EF), and ventricular dyssynchrony.
Methods: 1721 consecutive patients were included in a single center register after implantation of CRT –P or –D between 1999-2007. We retrospectively analysed the impact of persistent AF (group I) at the time of implantation on clinical improvement (worse = 0, no change = 1, much better = 3 points) compared with patients in SR (group II) during the continuous follow-up. The aspect of re-establishing SR or need for AVN-ablation in group I was examined. AVN-ablation was recommended in patients with < 90% cummulative ventricular pacing 3 month after CRT implant.
Results: 372 patients (22%) presented with persistent AF (group I) and 1349 with SR (group II) before CRT. Group I differed significantly from group II in age (73±6 vs. 66±8 y: p<0.05) gender (Male 82% vs. 72%: p<0.05) LA diameter (53±6 vs. 45±6 mm: p<0.05), and lenght of clinically documented severe heart failure before CRT implant (17±6 vs.9±5 month: p< 0.05). No significant differences were observed regarding NYHA (3.2±0.5 vs. 3.0±0.4), LV EF (23±8 vs. 25±8%), LVEDD (66±7 vs. 64±11mm), BNP (1212±871 vs. 965±772 pg/ml), QRS with (166±42 vs.157±32 ms) and substrate (CAD 62 vs. 57%). During long-term FU (4.6±1.7 years) clinical improvement was similar in group I and II (2.4±0.7 vs. 2.5±0.5), but there was higher mortality in group I (62/372 – 17% vs. 121/1352 – 9%: p <0.01. 42/372 (11%) in group I presented with sinus rhythm 1 year after CRT implant and 221/372 (59%) were indicated for AVN-ablation because of biventricular pacing less than 90%.
Conclusions: Patient with heart failure, ventricular dyssynchrony and permanent AF had a comparable clinical and objective improvements with CRT as those in SR. Restoration of SR in patients with persistent AF and decrease in mitral regurgitation might be one of the mechanisms of reverse LV remodeling. Nevertheless mortality in patients with severe heart failure and chronic AF supported by the fact of late indication to CRT remained to be higher comparing to patients with sinus rhythm.

235 Atrial fibrillation does not influence long-term response to cardiac resynchronization therapy

S. Buck, A.H. Maass, B.A. Schoonderwoord, D.J. Van Veldhuisen, I.C. Van Gelder. *University Medical Center Groningen, Groningen, Netherlands*

Purpose: Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure and sinus rhythm, but its value in atrial fibrillation (AF) is still controversial. Our aim was to investigate the influence of AF on short and long term response and prognosis in patients treated with CRT.
Methods: Consecutive patients in whom CRT was implanted were included disregarding the atrial rhythm. AF was defined as either current or earlier AF, response to CRT as a decrease in left ventricular end-systolic volume (LVESV) > 10% after 6 months follow up. Echocardiography was repeated at 1 year, and 2 years after implantation.
Results: We included 214 patients, 94 (44%) were known with AF (42 current and 52 earlier). The other 120 (56%) patients had no (history of) AF. Mean follow-up was 27±15 months. AV node ablation was performed only if pharmacological rate control therapy, assessed < 2 months after implant, failed (n = 8 patients). Echocardiographic response was comparable between patients with and without AF (66%, 73% and 65% versus 64%, 71% and 63%, all not significantly different).



Event free survival

The incidence of the composite end point (death, heart transplantation or hospitalization for heart failure) was 27 (29%) in AF patients versus 39 (33%) in no-AF patients (p=0.55). Cumulative event rates of the primary end point were similar between AF and no-AF patients. (Figure)
Conclusion: Response and prognosis is similar in AF and sinus rhythm patients treated with CRT.

236 Expedited management of patients with acute atrial fibrillation and mild structural heart disease in the emergency department

A. Conti, B. Del Taglia, Y. Mariannini, C. Puggioni, B. Paladini, G. Pepe, S. Vanni, S. Magazzini, M. Zanobetti, S. Grifoni. *Emergency Medicine and Chest Pain Unit, Careggi University Hospital, Florence, Italy*

Background: In the primary care setting patients (pts) presenting with acute atrial fibrillation (AF) represent one third of hospital admissions for cardiac dysrhythmia. In these pts, hypertensive, valvular, ischemic, and other types of structural heart disease underlie most cases of AF. This study aims to evaluate the safety and effectiveness of rhythm control in pts with AF and mild structural heart disease as far as in solitary atrial fibrillation by intravenous Flecainide or Propafenone or Amiodarone.
Methods: Prospective, open label, cohort study, enrolling consecutive pts presenting with documented AF lasting ≤48 hours, from 2006 to 2008 years.
Patients received i.v. Flecainide or Propafenone or Amiodarone on presentation and eventually after 6 hours. Primary endpoint was rhythm control achieved within 6 hours. Secondary endpoints included rhythm control, time to rhythm control, side drug effects achieved within 24 hours.
Results: 2.019 pts with AF were considered. Of these, 1.641 were excluded from the study because of evidence of severe comorbidity (n=1176), or less than 18 years old (n=29). Out of the remaining 814 pts, 436 (53.6%) were excluded because of AF lasting >48 hours. Thus, the study population consisted in 378 pts with AF lasting ≤48 hours. Thirty-seven pts (10%) recovered sinus rhythm before therapy was given. Results of the remaining 341 pts are reported in the Table. Rhythm control was achieved in 87% of pts overall, within 24 hours, without significant differences among groups, including side drug effects.

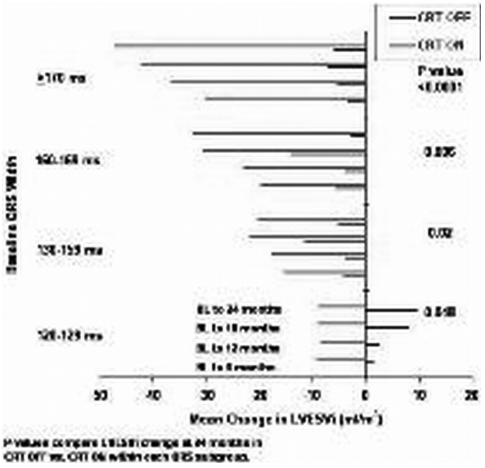
	Flecainiden n=43 (13%)	Propafenonen n=187 (55%)	Amiodaronen n=111 (32%)
Rhythm control within 6 hours, %*	72	55	30
Rhythm control within 24 hours, %	93	86	87
Time to rhythm control (minutes)*, mean±SD	178±227	292±285	472±269
Length of in-hospital stay, (hours)°, mean±SD	8.9±10,3	11,0±13,8	26,1±22,4

Conclusions: Within 6 hours Flecainide and Propafenone achieve rhythm control in a higher proportion of pts as compared with Amiodarone; however within the 24-hour management no differences were seen among groups.

237 Relationship of QRS duration to reverse remodeling with CRT in mild heart failure over 2 years. Results from the European cohort of the REVERSE trial

M. Gold[1], C. Linde[2], I. Lozano[3], J.C. Daubert[4], W.T. Abraham[5]. *[1]Medical University of South Carolina, Charleston, United States of America; [2]Karolinska University Hospital, Stockholm, Swaziland; [3]Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]CHU de Rennes - Hopital de Pontchaillou, Rennes, France; [5]The Ohio State University, Ohio, United States of America*

Background: Cardiac Resynchronization Therapy (CRT) is well established therapy for advanced systolic heart failure (HF) patients (pts) with QRS prolongation. The role of mechanical dyssynchrony to predict reverse remodeling with CRT is controversial. Less is known about the influence of electrical dyssynchrony on remodeling. Accordingly, we evaluated the relationship between QRS width and changes in left ventricular (LV) dimensions in pts with mild HF over 24 months.
Methods: Pts in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial have NYHA I or II HF, QRS-duration ≥ 120 ms and LVEF ≤ 40%. LV end systolic volume index (LVESVi) was measured by core labs. Baseline QRS width was divided into quartiles for analysis. European pts in the trial were randomized for 24 months to CRT ON or OFF and are the basis for this study.
Results: There were 262 pts randomized, 180 to CRT ON and 82 to CRT OFF. LVESVi decreased more during 24 months among CRT ON than CRT OFF pts (-27.5±31.8 vs -2.7±25.8 ml/m^2, p<0.0001). Multivariate analysis showed that QRS duration and time were predictors of the magnitude of remodeling (see graph). The response to CRT was larger as QRS duration increased. However, 24-month LVESVi changes compared with baseline were still statistically significant within each QRS width quartile. The response among CRT ON pts improved from 6 to 12 months (mean change -4.2±16.6, p=0.003), and 12 to 18 months (-4.6±13.0, p<0.0001), but no significant change was observed from 18 to 24 months (-0.3±16.0, p=0.81).
Conclusions: QRS width is an independent and strong predictor of reverse remodeling with CRT, indicating that electrical dyssynchrony is important for the response to CRT in mild HF.

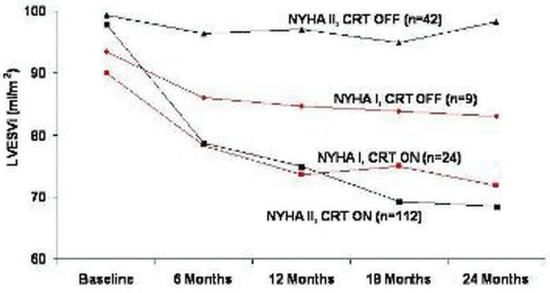


Abstract 237 – Figure 1. LVESVi in relation to baseline QRS

238 CRT in mild heart failure: Differences in outcomes between NYHA Class I and II patients over 24 month of CRT. Results from the European cohort of the REVERSE Trial

C. Linde[1], R. Leman[2], J.C. Daubert[3], W.T. Abraham[4], M.R. Gold[2]. *[1]Karolinska University Hospital, Stockholm, Sweden; [2]Medical University of South Carolina, Charleston, United States of America; [3]CHU de Rennes - Hopital de Pontchaillou, Rennes, France; [4]The Ohio State University, Ohio, United States of America*

Background: The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial is the first prospective randomized double-blind parallel trial that demonstrated that Cardiac Resynchronization Therapy (CRT) plus optimal medical therapy (CRT ON) compared to CRT OFF could slow disease progression and reverse LV remodeling in patients (pts) with NYHA I-II HF, QRS ≥ 120 ms and LV ejection fraction ≤ 40%. The results over 24 months of CRT in the European cohort in relation to baseline NYHA class are reported here.
Methods: 262 pts were randomized in 35 centres in Europe and followed for 24 months. At baseline, the mean LVEF was 28.0±6.8%, LVESVi was 95.8±33.9 ml/m^2, and QRS width was 156 + 23 ms.
Results: Of 262 pts, 218 were in NYHA class II (83%, 69 CRT OFF, 149 CRT ON) and 44 pts in NYHA I (17%, 13 CRT OFF, 31 CRT ON). The mean LVESVi (figure) and LVEF improved significantly by CRT from baseline to 24 months in NYHA II patients (p<0.0001 and p=0.01 respectively). While randomization (CRT ON) was a significant factor (p=0.006) for improvement in LVESVi, neither NYHA (p=0.88) nor the interaction of NYHA and randomization (p=0.11) independently influenced change in LVESVi from baseline to 24 months. In NYHA II pts 8.1% in CRT ON pts were hospitalized for heart failure vs. 21.7% in CRT OFF (p=0.004) while no significant difference was found in the NYHA I group (p=0.37).



LVESVi over 24 months in NYHA I and II

Conclusions: The 24 months results of the European patients in REVERSE indicate that CRT reverses remodeling and reduces the need for heart failure hospitalization in NYHA II patients. The sample size for NYHA class I pts was too low to yield conclusive results.

NEW INSIGHTS INTO THE MECHANISMS OF HEART FAILURE

239 Cachexia in cancer and heart failure development

J. Springer[1], A. Hartmann[1], S. Palus[1], A. Grzesiak[2], E. Kaschina[2], S. Von Haehling[1], J.M. Argiles[3], S.D. Anker[1]. *[1]Charite - Campus Virchow-Klinikum, Berlin, Germany; [2]Charite - Campus Mitte, Humboldt-Universitaet, Berlin, Germany; [3]Universitat de Barcelona, Barcelona, Spain*

Cachexia is a common co-morbidity in patients with cancer. These patients also develop shortness of breath of unknown reason. Whether cancer cachexia can cause heart failure is not known.

Methods: Wistar rats (weight approx. 200g) were inoculated intra-peritoneally with AH-130 cells or saline (sham). High resolution echocardiography and hemodynamic assessment was performed before inoculation (only echo) and on day 7 or 11 of the 16-day protocol. Weight and body composition (NMR-scan) were assessed on day 0 and day 7 or 16 after sacrifice (without tumour).

Results: Rats with cancer reached a cachectic state on day 7 (5% weight loss, $p<0.0001$ vs sham), which fits the clinical consensus definition of cachexia. Animals lost only fat mass at this stage and cardiac function was similar in sham and tumour animals, with the exception of LVmass. With progressing disease and cachexia deterioration, cardiac function became severely impaired (Table). At the end of the study, animals displayed severe cachexia (152±2g vs sham: 263±4g, $p<0.0001$). Cancer rats lost fat (-12.4±0.4g vs sham 9.1±0.9g, $p<0.0001$) and lean tissue (-39.8±1.6g vs sham 41.7±2.1g, $p<0.0001$).

	Tumor			Sham		
	day 0	day 7	day 11	day 0	day 7	day 11
n	78	10	78	16	5	16
LVEF (%)	76±1	74±2	52±2***	72±2	77±2	73±2
FS (%)	50±1	43±2	31±2***	482	47±2	52±2
LVEDD (mm)	6.23±0.06	6.52±0.16	5.71±0.11***	6.22±0.13	6.49±0.28	6.39±0.08
LVSV (μL)	190±5	146±18	105±6***	177±13	175±13	196±10
LVmss (mg)	518±12	496±18**	428±11***	537±33	601±15	626±35
LVEDP (mmHg)		14.2±2.7	1.5±1.6 (7)		10.8±4.2	10.4±3.4 (8)
LVESD (mmHg)		117.1±4.5	82.9±6.2*		110.3±10.8	110.8±6.4

LV: left ventricular, EF: ejection fraction, FS: fractional shortening, EDD: enddiastolic diameter, SV: stroke volume, EDP: enddiasolic pressure, ESP endsystolic pressure. *p>0.05, **p<0.01, ***p<0.001 tumour vs sham (t-test) on respective days.

Conclusion: Cancer cachexia causes severe impairment of cardiac function. The nature of these impairments is comparable to processes in chronic heart failure. Consequently, heart failure therapies may be beneficial in this clinical setting.

240 Aldosterone escape is associated with insulin resistance in patients with heart failure- findings in the ALiskiren Observation of heart Failure Treatment trial (ALOFT)

I.K. Tsorlalis[1], E.M. Freel[1], J.D. Lewsey[2], R. Latini[3], A.P. Maggioni[4], B. Pitt[5], S.D. Solomon[6], A. Verma[6], J.M.C. Connell[1], J.J.V. Mcmurray[1] on behalf of The ALOFT investigators. *[1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [2]Department of Public Health and Health Policy, University of Glasgow, Glasgow, United Kingdom; [3]The Mario Negri Institute for Pharmacological Research, Milan, Italy; [4]Associazione Nazionale Medici Cardiologi Ospedalieri, Florence, Italy; [5]University of Michigan Medical School, Ann Arbor, United States of America; [6]Brigham and Women's Hospital, Boston, United States of America*

Purpose: Aldosterone levels 'escape' in up to 50% of heart failure patients despite therapy. In hypertensive subjects, aldosterone excess is associated with insulin resistance which may contribute to adverse cardiovascular outcome in that condition. The relationship between aldosterone status and insulin resistance is not known in heart failure (HF) and was explored in a cohort of patients with stable HF.

Methods: 302 patients with New York Heart Association class II-IV HF treated with an ACE inhibitor or angiotensin receptor blocker >4 weeks and a beta-blocker were randomized in the ALiskiren Observation of heart Failure Treatment trial (ALOFT). This is analysis of the 113 non-diabetic patients in ALOFT with baseline measurements of both plasma and urinary aldosterone who were not taking a mineralcorticoid receptor antagonist. Fasting plasma insulin and glucose levels were also analysed at baseline and insulin/glucose ratios (IGR) and Homeostatic Mode Assessment-Insulin Resistance (HOMA-IR) calculated. "Aldosterone escape" was defined as either plasma aldosterone level >144pg/ml or urinary aldosterone excretion > 12micrograms/24hours. We compared the indices of insulin resistance in patients with and without aldosterone escape.

Table 1. Differences of fasting insulin, insulin/glucose ratio and HOMA-IR between aldosterone-escape and no aldosterone-escape groups (Mann-Whitney test)

	Aldosterone-escape (n=38)	No aldosterone-escape (n=75)	P-value
Fasting insulin (pmol/l)	94	58	0.0765
Insulin/glucose ratio	17	10	0.0876
HOMA-IR	3.1	2.0	0.0154

Results: 38/113 (34%) of patients demonstrated aldosterone escape. Patients with aldosterone escape had significantly higher HOMA-IR and increased fasting insulin and IGR compared to patients without aldosterone escape (Table 1).

Conclusions: Aldosterone escape is associated with insulin resistance in HF. Insulin resistance may represent and additional mechanism contributing to the adverse clinical outcomes associated with aldosterone escape in HF. Conversely, RAAS activation may partly explain the high prevalence of dysglycaemia in HF.

241 The novel biomarker Red cell Distribution Width (RDW) has incremental prognostic value, in addition to B-type natriuretic peptide (BNP), in patients with acute decompensated heart failure

C.E. Jackson[1], V. Bezlyak[2], I.K. Tsorlalis[1], J.R. Dalzell[1], R.C. Myles[1], R. Spooner[3], I. Ford[2], M.C. Petrie[4], S.M. Cobbe[1], J.J.V. Mcmurray[1]. *[1]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [2]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom; [3]Dept. of Biochemistry, Gartnavel General Hospital, Glasgow, United Kingdom; [4]Scottish National Advanced Heart Failure Unit, Golden Jubilee National Hospital, Clydebank, Glasgow, United Kingdom*

Purpose: Red cell Distribution Width (RDW) is a measure of the variation of red blood cell width and is routinely measured in a full blood count (FBC). This biomarker recently emerged as an unexpected and powerful predictor of prognosis in patients with chronic ambulatory heart failure (HF), although its additive value to BNP was not assessed. We examined the prognostic utility of RDW in patients with acute decompensated HF in conjunction with other haematological variables and BNP.

Methods: To be eligible, patients had to have typical clinical findings of HF and BNP>100pg/ml. Exploratory data revealed BNP was positively skewed and was analysed as log [BNP] in a continuous fashion. The prognostic importance of total white cell count (WCC), haemoglobin and lymphocytes, in addition to RDW, was analysed in univariate Cox proportional hazard models and then together in a multivariable model including log [BNP], age and sex.

Results: 707 consecutive patients admitted to two city hospitals between December 2006 and July 2008 were recruited into this study and followed for a median of 421 (range 208-792) days. 212 deaths occurred. Univariate analysis demonstrated lower levels of haemoglobin and lymphocytes and raised RDW to be predictive of adverse outcome with higher levels of WCC showing a trend towards statistical significance. In the multivariable model; RDW, log[BNP], age and WCC remained independent predictors of mortality.

Multivariable Analysis

Parameter	Hazard Ratio	95% Confidence Interval	p-Value
Age	1.025	1.011-1.040	0.00068
Sex	1.147	0.868-1.515	0.33
Log [BNP]	1.536	1.322-1.785	<0.0001
Lymphocytes	0.896	0.787-1.021	0.1
RDW	1.062	1.012-1.113	0.014
Haemoglobin	0.958	0.897-1.023	0.2
WCC	1.042	1.006-1.080	0.023

Conclusion: This study shows that the routinely measured biomarker RDW adds independent predictive information to that obtained using BNP, the most powerful known prognostic marker in HF. RDW is not a surrogate for anaemia and the biological basis for this finding, now shown in both acute and chronic HF, merits further investigation.

242 Vitamin D deficiency is common in patients with chronic heart failure and relates to the severity of the condition

K. Witte, R.C. Cubbon, C.P. Gale, M.B. Kahn, A. Rajwani, L.C. Falk, M.T. Kearney. *University of Leeds, Leeds, United Kingdom*

Chronic heart failure (CHF) is a syndrome of exercise intolerance in the presence of left ventricular dysfunction. A further feature is deficiency of essential micronutrients. Vitamin D deficiency leads to impaired skeletal and cardiac muscle and immune function, hence deficiency might also be an aetiological factor. We examined the prevalence of vitamin D deficiency in CHF patients and whether vitamin D levels were related to CHF severity.

Methods: Serum 25(OH)D3 and parathyroid hormone (PTH) levels were measured in 160 stable CHF patients, (115 men), mean age 69 (12) years. CHF was defined as current or previous symptoms of fatigue or breathlessness and left ventricular ejection fraction (LVEF) <45%. Patients taking vitamin D supplementation were excluded from the analysis. Patients with levels of vitamin D levels <75nmol/L were defined as having hypovitaminosis D.

Results: Mean LVEF was 32 (9)% and patients were taking appropriate medical therapy (80% on beta-blockers, 90% ACE inhibitors). Calcium levels were normal (2.32 (0.1) mmol/L). Mean vitamin D level was 32 (18) nmol/L and mean PTH levels were 11 (8) pmol/L. These variables were inversely related (r=0.25; p=0.05). Only seven patients had sufficient vitamin D. Patients with NYHA class 3 and 4 symptoms had lower vitamin D levels than patients with less symptomatic heart failure (p=0.04). There was an inverse relationship between furosemide dose and vitamin D (r=0.22; p=0.02) and a direct relationship between exercise capacity

as measured by peak oxygen consumption and vitamin D (r=0.48; p=0.04). Patients taking spironolactone had lower levels than those not taking this agent (25.8 (13.8) v 43.1 (22.6); p=0.002). There was no relationship between vitamin D and age, left ventricular function, calcium, creatinine or CRP, and no differences between those patients taking and those not taking beta-blockers and angiotensin-converting enzyme inhibitors. There was also an indirect relationship between TNF-alpha levels and vitamin D (r=0.62; p=0.05)

Conclusions: CHF patients are frequently deficient of vitamin D, related to the severity of the condition. Whether vitamin D deficiency contributes to CHF or is merely a result of lifestyle constraints in these patients requires further investigation with a randomised, placebo-controlled trial of high dose vitamin D supplementation.

243 Increased levels of cytokines, vasoactive peptides, and growth factors in alveolar macrophages in heart failure

C.P. Dahl, L.I.B. Sikkeland, A.K. Andreassen, E. Gude, L. Gullestad, J. Kongerud, P. Aukrust, E. Oie. *University of Oslo, Oslo, Norway*

Purpose: Pathophysiologic interactions between the heart and the lungs in heart failure (HF) are well recognised. Increased circulating levels of vasoactive peptides and cytokines known to be synthesised in the heart in HF may directly affect the lungs and potentially also vice versa. The purpose of the present study was to investigate whether expression of different factors known to be increased in the myocardium and/or the circulation in HF is also increased in alveolar macrophages in HF.

Methods: Twenty-two non-smoking HF patients (NYHA functional class II-IV) and 16 healthy controls were included in the study. Lung function and diffusion capacity were investigated by spirometry and DLCO, respectively. Induced sputum was performed after inhalation of hypertonic saline, and alveolar macrophages were isolated from the sputum by use of magnetic microbeads. Gene expression was examined in alveolar macrophages and in peripheral blood by real-time RT-PCR.

Results: Lung function and diffusion capacity were reduced in HF patients compared to controls with significantly lower FVC (88±4 vs. 112±3% of predicted value), FEV1 (84±4 vs. 104±3% of predicted value), and DLCO (69±4 vs. 101±3% of predicted value) ($P<0.05$ for all). Real-time RT-PCR demonstrated increased mRNA levels of several important cytokines, chemokines, vasoactive peptides, and growth factors in alveolar macrophages from HF patients compared to controls ($P<0.05$): endothelin-1 (1.8-fold), adrenomedullin (10-fold), TNFα (2.3-fold), IL-1β (3.9-fold), IL-6 (12-fold), MCP-1 (2.2-fold), IL-8 (4.2-fold), activin A (10.5-fold), and CTGF (3.2-fold). MIP-1α mRNA levels were not altered in HF. A similar increase in mRNA levels was not found in peripheral blood, indicating that the increase in gene expression is taking place in the lungs and is not a result of induction in monocytes in the circulation before entering the pulmonary compartment. mRNA levels of adrenomedullin, IL-6, MCP-1, IL-8, and CTGF in alveolar macrophages from HF patients displayed a negative correlation to left ventricular ejection fraction ($P<0.05$).

Conclusions: Several important cytokines, chemokines, vasoactive peptides, and growth factors are induced in alveolar macrophages in human HF. Further studies should clarify whether this induction affects pulmonary remodelling and whether the increased synthesis of these factors is reflected by increased release to the circulation and thus potentially may affect the failing myocardium.

244 Statin treatment further deteriorates systolic function in doxorubicine treated mice

H. Kilter, J.C. Reil, D. Steffen, M. Boehm. *Universitaetsklinikum der Saarlandes, Homburg, Germany*

Anthracyclines are highly efficious antineoplastic agents commonly used in the treatment of hematopoetic and solid tumors in children and adults. However, the use of anthracyclines is limited by its cardiotoxic adverse effects and a considerable risk to induce heart failure. It has been suggested that anthracycline induced cardiotoxicity may be reduced by cotreatment with high concentrations of statins. However, functional data are limited and the effects of low and pharmacological more relevant statin-concentrations are still unclear.

C57/Bl6 mice were treated with the anthtracycline doxorubicin (2x10 mg/kg, day 0 and day 6) alone or in combination with atorvastatin (2mg/kg once a day, started 3 days before first injection of doxorubicin). The cardiac phenotype was characterized after 21 days. Cotreatment of the mice with atorvastatin had no effect on survival (49% vs. 47%, n.s.) of the animals neither on apoptosis (16.7% vs. 14.3%, n.s.) nor fibrosis (3.03 vs. 3.06%) of the hearts. Furthermore, atorvastatin did not inhibit the slight increase in myocardial NADPH-oxidase activity (1.35±0.09 vs. 1.42±0.07, n.s.) or aconitase-activity (1.28±0.02 vs. 1.32±0.03, n.s.). However, vascular superoxide release was significantly inhibited by cotreatment with atorvastatin (3.85±0.45 vs. 1.40±0.10 relative fluorescence per mg aorta, $p<0.05$), demonstrating the efficiency of the treatment. Atorvastatin alone had no adverse effect compared to control animals.

Hemodynamic measurements were conducted using isolated working heart preparations (preload 10 mmHg, afterload 60 mmHg, heart rate 400 bpm). Hearts from doxorubicin treated mice showed a significant increase in the enddiastolic pressure volume relationship characterized by its stiffness constant β (0.15±0.02 vs. 0.08±0.01, $p<0.01$) and a significant impairment of the endsystolic-pressure volume relationship Ees (3.40±0.20 vs. 4.62±0.38, $p<0.05$) and ejection fraction (38.7±1.5% vs. 60.1±4.1%, $p<0.001$) compared to controls. Interestingly, hearts from mice cotreated with atorvastatin demontrated a further and significant reduction in systolic function compared to hearts from animals treated with doxorubicine alone (Ees 2.34±0.25 vs. 3.40±0.20, $p<0.01$).

In conclusion, low-dose atorvastatin does not protect from doxorubicine induced cardiotoxicity, but further deteriorates the systolic performance of the heart.

SYNCOPE AND IMPLANTABLE LOOP RECORDERS: GOOD VALUE FOR MONEY?

245 REVISE (Reveal in the Investigation of Syncope and Epilepsy) study

S. Petkar[1], P. Iddon[2], W. Bell[1], N. Rice[3], D. Mckee[3], N. Curtis[3], P. Cooper[4], A. Fitzpatrick[1]. *[1]Manchester Heart Centre, Manchester Royal Infirmary, Manchester, United Kingdom; [2]Manchester Primary Care Trust, Manchester, United Kingdom; [3]Manchester Royal Infirmary, Manchester, United Kingdom; [4]Greater Manchester Centre for Neurosciences, Hope Hospital, Salford, United Kingdom*

Background: Published retrospective and prospective studies suggest that ~1 in 4 patients with 'epilepsy' are misdiagnosed, based on clinical review and tilt testing. The common alternative diagnosis in these patients is convulsive syncope. Also, some patients with epilepsy can have bradyarrhythmias and arrhythmias are a postulated mechanism for Sudden Unexpected Death in Epilepsy.

Methods: Prospective study in patients, who on neurological review, were considered to have a misdiagnosis of epilepsy or those in whom the diagnosis of epilepsy was in doubt. Inclusion criteria were as follows: (a) ≥3 episodes of transient loss of consciousness in the last 12 months AND a normal, equivocal or non diagnostic 12 lead ECG, echocardiogram, 24 hour ECG, standard unprovoked EEG and brain CT/MRI. After recruitment, all patients underwent a loop recorder implantation (ILR) (Reveal, Medtronic Inc). and tilt table testing. Follow-up was every 3 months till at least 1 year after ILR implantation.

Aim: (a) To determine the incidence of misdiagnosis of epilepsy as determined by ILR and

(b) the value of tilt testing in this group of patients.

Results: 108 patients screened, 32 found suitable for inclusion into the study, 21/32 (67.7%) females, mean age: 38.2±16.8 (median: 36.5, range: 17-79 years). Mean duration of follow-up after ILR: 6±5 months (median: 4, range: 1-18 months). ECG-symptom correlation by ILR achieved in: 19/32 (59.4%). Findings of ILR: asystole: 5/19 (26.3%), muscle artefacts suggestive of tonic-clonic seizures: 3/19 (15.8%) and normal sinus rhythm: 11/19 (57.9%). Four of five (80%) patients with asystole underwent permanent pacemaker implantation (PPM), 2/4 (50%) subsequently asymptomatic. Tilt table positive in: 4/32 (12.5%), three of four (75%) had ECG-symptom correlation on ILR, which showed normal sinus rhythm.

Conclusion: First prospective study to show, by means of ILR, a high incidence of asystole in patients misdiagnosed with epilepsy or where the diagnosis of epilepsy was in doubt. The likely diagnosis in these patients is convulsive syncope. No correlation between results of tilt testing and ILR. Also, shows the usefulness of the ILR in diagnosis of typical epilepsy by the pattern of muscle artefcats.

246 Implantable loop recorders in diagnostics of recurrent syncope in children with apparently normal heart

M. Shkolnikova, S. Termosesov, E. Polyakova, R. Garipov, Y.A. Volkova, I. Ilich on behalf of Russian Federal Center fo Children's Arrhythmia. *Moscow Institute For Paediatry&Surgery, Moscow, Russian Federation*

Syncope is a common symptom in children with apparently normal heart. The diagnosis is often not evidence based in spite of careful analysis of personal and family history, physical examination, ECG, stress test, Holter monitoring, echocardiogram, and even tilt-test. Moreover character of syncope can vary in one and the same child. Therefore, more sophisticated methods for the differential diagnostics are needed especially to avoid risks associated with arrhythmogenic syncope. The study evaluates the diagnostic yield of implantable loop recorders (ILR) for identification of mechanisms of unexplained syncope in children.

Methods: ILR was implanted in 58 patients (33 boys and 25 girls) with unexplained recurrent syncope. The patients were aged 2.5 to 17 years. The mean at implantation was 12.8 years. Incidence of syncope varied from one time in a week to one time in a year. Of the 58 ILR devices, 5 were Reveal, 11 were Reveal plus, and 42 were Reveal XT 9529. The mean follow-up was 11.6±8.82 month.

Results: 7 ILRs were removed with no syncope registered. Symptoms recurred in 20 pts within one day to 16 months after the implantation (mean = 6.5 months). 30 ILRs are still in situ since the syncope have not recurred during 10 to 14 months. Complication (erosion) requiring removal of the device occurred in one patient 3 y.o. The final symptom recurrence with observation period not less than 16 months was 74%. Among them the symptom-rhythm correlation analysis did not detect arrhythmia in 55% (11 of 20): two ILRs were removed and another 9 remain in situ. Arrhythmia yield was 45% (9 of 20). The reported pre-implantation incidence of syncope in patients without arrhythmia was higher than among those with arrhythmia (13.4 vs. 1.9 per year). After the implantation, the

arrhythmia-related syncope manifested two-fold quicker than vasovagal syncope: once in 6.5 months vs. once in 15 months, respectively. Of the 9 pts with arrhythmia, 8 had asystole lasting 3 to 30 s (in 2 cases caused by AV block). These patients were treated with pacemakers; no syncope have been observed afterwards. One patient experienced paroxysmal SVT at syncope with heart rate of 200 bpm.
Conclusion: ILR implantation is efficient and secure method for diagnostics of unexplained syncope. After a 16-month or longer follow-up, cause of the symptom was identified in 74% of cases. 45% of the reveal-confirmed syncope were caused by arrhythmia (mostly bradicardia). Lower post-implantation recurrence of vasovagal syncope agrees with other studies and is comparable to the 'cure' observed with placebo drugs for syncope.

247 Holter monitoring in syncope: good diagnostic yield in octogenarians

M. Kuhne, B. Schaer, C. Sticherling, S. Osswald. *University Hospital Basel, Basel, Switzerland*

Background: The diagnostic yield of 24-hour Holter monitoring for the evaluation of syncope has been reported to be low and more patients are evaluated using prolonged monitoring strategies. However, the value of Holter monitoring in very elderly patients has not been systematically studied. Aim of this analysis was to determine the diagnostic value of Holter monitoring in octogenarians presenting with syncope.
Methods: In patients age 80 or older, Holter studies performed for the evaluation of syncope were reviewed. A study was considered diagnostic if the arrhythmia was found to explain syncope (AV block (at least second-degree Mobitz type II), sinus pauses >3 seconds, atrial fibrillation with severe bradycardia or tachycardia >175 beats per minute) and if there was a correlation of symptoms and the arrhythmia. A comparison was made using a younger control group (age<80).
Results: Holter studies were reviewed in 311 consecutive patients (age 84.8±3.9). There was no age difference (p=0.23) between female patients (n=199, age 85.0±4.0) and male patients (n=112, age 84.5±3.5). Forty-one studies (13.2%) were considered to explain syncope as defined above.The detected arrhythmias were AV block (n=12), sinus node dysfunction (n=10), binodal disease (n=2), atrial fibrillation with slow or rapid ventricular response (n=16) and ventricular tachycardia (n=1). Thirty-two patients (10.3%) received a pacemaker because of the results of Holter monitoring. In the remaining 9 patients (2.9%) the exam resulted in changes of medical therapy. Holter monitoring was diagnostic for syncope in 16% in patients with structural heart disease, in 18% in male subjects and patients with depressed ejection fraction, and in 20% in patients above age 90. The diagnostic yield of 13.2% was significantly higher compared to 5.8% in a younger control group (mean age 72±15) of 515 consecutive patients (p<0.001).
Conclusion: In contrast to younger patients, the yield of 24-hour Holter monitoring in octogenarians is relatively good (13.2%) even when applying strict diagnostic criteria, and the exam results in important decisions in patient management. Its value is especially good in male patients, in the presence of structural heart disease or depressed left ventricular function, and reaches 20% in patients above age 90.

248 Living with the Sleuth: patient experience of a second generation remotely monitored implantable loop recorder

P.S.G. Hong, J. Hunt, R.A. Veasey, S. Shubber, U. Shanker, S.S. Furniss, G.W. Lloyd, N.R. Patel, A.N. Sulke. *Eastbourne District General Hospital, Eastbourne, United Kingdom*

Introduction: The Sleuth ILR uses wireless & Bluetooth technology. Device & hand-held memory is 43 mins & 10.5 hrs respectively. Remote monitoring allows the receipt of daily trending ECG data (4 hourly) from the patient via their modem. Patient activated & auto-triggered events are uploaded immediately, preventing loss or over-writing of data, effectively allowing continuous ECG monitoring for the lifetime of the device (est. 2yrs). We evaluated the first 120 Sleuth patients in Europe.
Methods: 120 patients with ≥ 2 unexplained syncopal episodes in 2 years were inducted into the EaSyAS II study & received the Sleuth ILR. Implants were undertaken by cardiologists & ER physicians. All implants were undertaken as day cases & patients given verbal & written instructions regarding use of the activator & modem set-up. Minimum follow up is 12 months. All patients completed a questionnaire evaluating all aspects of the ILR system (Figure 1).
Results: 47 pts (39.1%) were male. Age 72.03±16.39 years. Mean syncopal episodes was 7.31±10.79. 42 pts (35%) had injuries secondary to syncope. No major implant complications occurred. 17 Pts (14.7%) required a further home visit for set-up assistance. 23 Pts (19.2%) required phone assistance. 1 patient had the ILR explanted at 7 months due to study intolerence (not device). Cumulative duration of use (all patients) is 30,685 days (Mean 262.26±145.94 days). Mean time to syncope diagnosis was 61.7 days in the first 50 pts. No episodes were lost.
Conclusions: The Sleuth system is safe & easy to implant by both ER & cardiac physicians & is well tolerated by most patients. The remote monitoring system requires clinician support for set up in a small minority of cases. Almost all patients found this ILR to be entirely compatible with normal daily living.

How much discomfort did you experience during the procedure? [Pt No (%)]

None	Mild	Moderate	Severe
48 (45.5%)	28 (27.3%)	14 (13.6%)	14 (13.6%)

How much discomfort did you experience after the procedure when you got home?

None	Mild	Moderate	Severe
42 (40.9%)	47 (45.5%)	14 (13.6%)	0 (0%)

	YES	NO
Did you find the base station (phone connection) difficult to set up at home?	14 (13.6%)	89 (86.4%)
Have the instructions on how to use the Sleuth system (written & verbal) been easy to understand?	98 (95.2%)	5 (4.8%)
Have you found it easy to live with the Sleuth device?	98 (95.2%)	5 (4.8%)
Have you found it easy to use and carry the activator during everyday life?	98 (95.2%)	5 (4.8%)

Figure 1. Patient Experience Survery

249 Early use of implantable loop recorders in the assessment of patients presenting to secondary care with syncope or severe palpitations with pre-syncope

A. Bajpai, D. Eruchie, K.N. Asrress, A. Yavari, D. Cotterill, K. Dickinson, E.T. McWilliams, D.M. Walker. *Conquest Hospital NHS Trust, Hastings, United Kingdom*

Introduction: Implantable loop recorders (ILRs) in patients with syncope are often reserved for those who have had extensive prior investigations, including multiple ambulatory ECG recordings, tilt-testing (TT), and electrophysiological studies (EPS). In district hospitals TT & EPS are less readily available. We used ILRs earlier in the algorithm including use in severe but infrequent palpitations with pre-syncope.
Methods: Indications, time to diagnosis, diagnostic yield & therapeutic decision were analysed in those who received ILRs between March 2004 & January 2009. Separate data from all TT during this period was also studied for indications and diagnostic yield.
Results: Total of 103 patients received an ILR during this period. Follow-up data of ≥6 months was available in 83%. Mean age 64±20.3 yrs (range 17-93; 56% female). Indications for ILR were syncope (82%), severe pre-syncope (6%) & palpitations with pre-syncope (12%). All had previous 24 hr and patient activated recordings. A prior TT was performed in 32%.
Symptom-ECG correlation (SEC) was established in 54%, while no dysrhythmias were detected in 46%. Amongst those with SEC, diagnosis was asystole >3sec in 35%, high grade AV block in 7%, bradycardia <30 bpm in 7%, VT in 9%, paroxysmal AF in 11%, and SVT in 27%.
Mean time delay from 1st clinic review to ILR was 180±293 days. This was much longer in those who underwent TT (32%) or EPS (4%) prior to ILR (n=22, 484±104 days) vs those who received an ILR early after clinic review (n=81, 87 days ±28; p=0.001). Mean duration from ILR to specific diagnosis was similar in both groups (183±78 days vs 172±22 days; p = 0.6). This is clinically relevant as TT was non-contributory in majority of cases with only 2% revealing a cardio-inhibitory (CI) and 6% a vaso-depressor (VD) response.
46% of patients with diagnosis were given permanent pacemaker, 8% had ICDs, 21% had ablation & remaining 25% were managed medically.
Device was explanted in 84%. Average implant duration was 224±28 days in patients with positive diagnosis vs 667±92 days in those with no SEC (p = 0.001). 302 TT were performed during this period for syncope (72%) and presyncope (23%). Only 10% (n=31) of TT were conclusive for CI or VD syncope. 27% had normal test; 63% were inconclusive with minor changes and no significant symptoms.
Conclusion: Our data show high diagnostic yield from early use of ILRs in this cohort. Diagnostic yield from TT per se appears to be low. Early use of ILR in secondary care setting is likely to be cost effective by reducing unnecessary low yield investigations and the time delay to definitive treatment.

250 Prodrome in syncope: A predictor of cause?

P.S.G. Hong, R.A. Veasey, J. Hunt, A. Nahhas, M. Fonseka, C. Athlumudali, S.S. Furniss, G.W. Lloyd, N.R. Patel, A.N. Sulke. *Eastbourne District General Hospital, Eastbourne, United Kingdom*

Introduction: It is postulated that vasodepressor syncope is preceded by prodrome (light-headedness,nausea, sweating) as opposed to cardiogenic syncope which typically occurs without warning. We sought to validate this hypothesis.
Methods: 246 patients (146 female,mean 70.2 yrs) with ≥2 episodes of syncope within 2 yrs were enrolled on the Eastbourne Syncope Assessment Study II. 120 pts received the Sleuth implantable loop recorder (ILR).Following a syncopal event, patient activation of the ILR immediately uploads the corresponding ECG tracings to a monitoring centre. Results are analysed immediately & the Dr notified within hours. We obtained a detailed history of all syncope episodes within hours of the event, enabling highly accurate recollection of preceding symptoms & correlation with corresponding ECG tracings.
Results: In 52 (28.8%) pts the cause of syncope had been diagnosed (via ILR & tilt testing). In 25 pts (48.1%) the diagnosis was vasovagal syncope (VVS cohort).15 pts (29.4%) had significant bradycardia, heart block or pauses (cardiac cohort).

In the VVS cohort 13 (52%) pts reported no prodromal symptoms.All 13 subsequently had presyncope at tilt testing.3 (25%) pts with prodrome histories had syncopal events without warning on tilting. Mean time of symptom onset to syncope was 108.6s (±101.8). Most common symptoms:dizziness/light headedness. 14 pts in the cardiac cohort had Sleuths in situ. 7 pts had concurrent tilt testing.7 (46.6%) pts experienced prodromal symptoms. Most common:nausea/lightheadedness.

Table 1. Diagnostic characteristics of cardiac syncope cohort

Diagnosis (ISSUE/VASIS Classification)	No. of Patients	Auto/Manual Activation	Pts with Prodromal Symptoms
Type 2B Cardioinhibitory	6	Manual	3
Type 1A Sinus Pauses	4	Manual (1 Auto)	2
2:1 AV Block	2	Manual	1
Mobitz Type 1 (Wenckebach)	1	Manual	0
Type 1 Mixed	1	Manual	1
3rd Degree Heart Block	1	Non-Sleuth	0

Conclusion: Although a clinical history is important for syncope assessment, prodrome is not a consistent feature of VVS & frequently accompanies cardiac syncope. The use of ILRs has an important role in the assessment of syncope with & without prodrome. Remote monitoring of syncope prevents loss of data & provides excellent symptom correlation.

OUT OF HOSPITAL CARDIAC ARREST: THE FIGHT GOES ON

251 Temporal improvement in survival from out of hospital cardiac arrest - The Dublin cardiac arrest registry

R. Margey, L. Browne, E. Murphy, H.A. Mccann, G. Blake, N.G. Mahon, J. Galvin, D. Sugrue. *Mater Misericordiae University Hospital, Dublin, Ireland*

Introduction: Survival from cardiac arrest remains poor, estimated at 3-5%. We aimed to assess the impact of improved pre-hospital care on survival from out-of-hospital cardiac arrest (OOHCA) in an urban centre.
Methods: We established a prospective cardiac arrest registry from January 2003. Multi-source information was used to identify cases following the introduction of community education and CPR programmes from 2003 and dispatcher directed CPR, ACLS directed, AED supported resuscitation and a chest pain/suspected AMI protocol from 2004. We estimated survival from cardiac arrest overall, from asystole/PEA arrest, and from VF.
Results: A total of 961 cardiac arrests occurred. 70% were male. Median age was 64 y.o., with an age range of 16- 99 years. 16.7% of the victims had a documented cardiac history or reported chest pain prior to collapse. 72% occurred at home. Survival of initial resuscitation from VF improved dramatically, from 16% in 2003, to 83% in 2008. Survival to discharge from VF improved from 8.3% to 40.5%. Survival to discharge from Asystole/PEA arrest remains poor, annual survival rate of 0%- 0.45%. Overall survival to discharge has improved from 2.6% to 11.25% year 2008. The majority (42/52) of survivors were neurologically intact, with only 5 in persistent vegetative state. Collapse in a public venue with an AED was associated with a significantly improved survival 56% vs' 9%, $p<0.0001$.

Outcome: Out-of-Hospital Cardiac Arrest

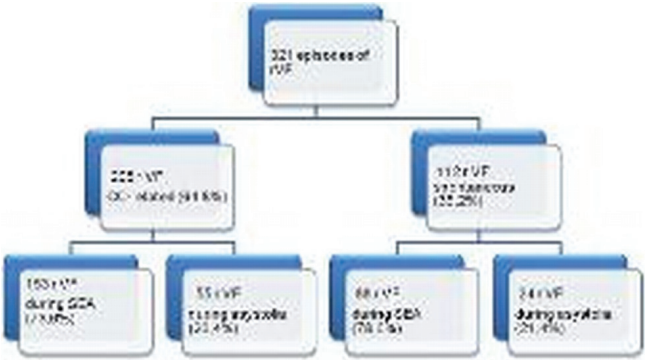
	2003 (n=194)	2004 (n=199)	2005 (n=135)	2006 (n=136)	2007 (n=136)	2008 (n=151)
Adj Incidence per 100,000	127	125.3	116.5	101.8	105.8	88.8
Adj Mortality per 100,000	111	112.9	77	75.3	79.4	78.8
Case Fatality Rate %	97.6	96.7	97.9	95.3	93.8	88.7
Male incidence per 100,000	159.7	174	111.6	126.8	106.8	110.4
Survival to discharge from VF	8.3%	14.3%	10.3%	16.6%	24.4%	40.5%
Overall survival to hospital discharge	2.6%	3.5%	2.9%	5.9%	7.5%	11.25%

Conclusions: Targeted interventions to improve management of OOHCA can result in dramatic improvements in survival, especially from VF.

252 Ventricular fibrillation may be provoked by chest compression during post-shock organized rhythms in out-of-hospital cardiac arrest

D. Aschieri[1], V. Pelizzoni[1], S. Ferraro[1], A.M. Andreoli[1], A. Capucci[2]. *[1]U.O. Cardiologia, Ospedale G.da Saliceto, Piacenza, Piacenza, Italy; [2]Clinica Cardiologica,Università degli Studi di Ancona, Ancona, Italy*

Recurrence of ventricular fibrillation (VF) following defibrillation is a frequent event described during resuscitation attempt. The aim of this study was to evaluated the relationship between chest compression and induction of recurrent VF (rVF) after the first successful shock.
Methods: This is a retrospective study of out-of-hospital cardiac arrest recorded in the city of Piacenza, Italy where a lay responders project of early defibrillation called "Progetto Vita" was organized. rVF were identified by analyzing the available ECGs from the automated external defibrillators. Successful shock was defined as cases in which VF was interrupted for at least 5 seconds. Rhythms after shocks were categorized as 1) asystolia (amplitude $< 100\ \mu V$) and 2) spontaneous electrical activity (SEA), when ventricular or atrial activity were present in the 5 seconds post shock. Chest compression was assessed for association with rVF during either asystole or spontaneous electrical activity.
Results: 160 consecutive pts with available and good quality ECG were considered for the analysis of rVF. 102/160 pts had rVF (63,75%). The total rVF were 321. 208/321 rVF (64.8%) were related to chest compression and 112/321 (35.2%) were spontaneous (R/T phenomenon). Before chest compression-rVF a spontaneous electrical activity was present in 153/208 episodes (73,6%) while asystolia was present in only 55/208 episodes (26.4%).



Conclusions: The potential benefit of chest compression, in term of oxygen supply, can be blunted by the reinduction of VF, a frequente event that occurred in 63,75% of pts analyzed. After shock the restoration of a spontaneous electrical rhythm should delay chest compression.

253 A logistic regression model to predict the occurrence of ventricular fibrillation in out of hospital cardiac arrest

A. Hamilton[1], K.J. Cairns[2], A.A.J. Adgey[1], F. Kee[2]. *[1]Royal Victoria Hospital, Belfast, Belfast, United Kingdom; [2]Queen's University, Belfast, United Kingdom*

Background: The Emergency Medical Services (EMS) in the UK have a target to respond to 75% of life threatening emergencies within 8 minutes. The presence of ventricular fibrillation following OHCA is generally assumed to follow a linear decline with time such that survival declines by 10% per minute delay from collapse to defibrillation. We established robust data collection techniques using multiple source surveillance to establish the baseline response to OHCA before and after the addition of lay first responder defibrillation. The objective of this study was to develop a model to predict the probability a patient is in ventricular fibrillation (VF) on EMS arrival as a function of the call-to-response interval (CRI), for cases of witnessed OHCA.
Methods: Logistic regression analysis was performed on a series of OHCA from the NIPAD trial region containing a population of 285,347 individuals with 29,585 emergency "999" ambulance calls across a 115-week period (January 2004 – April 2006). The main outcome measure was whether the initial cardiac rhythm was VF for witnessed arrests. Patient age, gender, initiation of CPR by bystanders, CRI, location of arrest and interaction terms were considered.
Results: There were 609 OHCA attended by the Northern Ireland Ambulance Service, of which 200 OHCA cases were witnessed. Witnessed OHCA accounted for only 32.8% of all OHCA. In those cases of unwitnessed OHCA 24/409 = 5.9% were in VF compared to 71/200 = 35.5% of witnessed OHCA in VF. Logistic regression analysis suggested that reduced call to response interval (P=0.002), patient age <55 years (P=0.016), location of arrest not at home (P=0.026), and initiation of cardiopulmonary resuscitation (CPR) by bystanders (P=0.041) were significantly associated with the rhythm of VF on EMS arrival. Gender, geographical region and interaction terms were not significant ($P>0.25$). A predictive model was produced to quantify the effect of the call to response interval in minutes. Probability of VF given a witnessed OHCA = $1/(1 + \exp(-0.601 + 0.149 \times \text{CRI}))$ where $\exp \approx 2.718$. Using this equation at one minute post witnessed OHCA the probability of being in VF is 61%, at five minutes the probability is 46.4% and at eight minutes is 35.6%.
Conclusion: The simplified model suggests that there is an upper limit for the incidence of VF in OHCA of 64.5% at the moment of collapse. Conversely without an increase in the level of bystander CPR the percentage probability of being in VF following a witnessed OHCA in Northern Ireland is 35.6% at the Ambulance Service 8 minute response target.

254 Efficacy of biphasic 150j and 200j shocks in out-of-hospital ventricular fibrillation

D. Mueller, G. Moehl, J. Breckwoldt, H.-R. Arntz. *Charite - Campus Benjamin Franklin, Berlin, Germany*

The survival of out-of-hospital sudden cardiac death (SCD) above alldepends on the rhythm initially detected, ventricular fibrillation (VF) havingthe best prognosis. The optimal time point of delivering electricalcountershocks, the discharge characteristic, and the optimal energy in patients (pts) with a prolonged down time (i.e. the typical patients cared for by theEMS) is under discussion.

Methods: We analyzed the data of the Berlin two-tiered EMS, the firsttier performing BLS including the application of electrical countershocks usingautomated external defibrillators (AED, Physiocontrol, LP500). The AED wererandomly (and blinded for the users) programmed to deliver biphasic 150J, 150Jwith the two first shocks, followed by 360J shocks for each consecutive shock (A), or 200J, 200J, followed by 360J each (B) if appropriate. Information onheart rhythm, defibrillation data, and voice recordings stored in the deviceswere reviewed manually. BLS was performed according to the 2005 ERC guidelines.

Results: Throughout 1 year the data of 465 resuscitations were analyzed.Of them 205 pts had VF and received at least one shock. Group A: n=105, 68±15 years, 72%male. VF was terminated by the first shock in 37% (shock impedance 72±24W): Asystole (ASYS) 24%, coordinated rhythm (CR) 27%. Group B: n=55, 65±16 years, 81%male. VF terminated in 53% (shock impedance 78±22W): ASYS 25%, CR42%. Efficacy for the first shock was significantly higher in group B (p=0.03).The higher success rate was gained by more CR in group B but not by a higheramount of ASYS. Every pt received in median 2 shocks (1-3 shocks) in bothgroups. 50% vs. 45% survived to hospital admission (A vs. B, p=n.s.). Theduration of resuscitation until arrival of an emergency physician was equal inboth groups (7.4±2.3min).

Conclusion: Biphasic countershocks of 200J showed to have asignificantly higher probability to terminate out-of-hospital VF than biphasic150J shocks into CR. In contrast to previous studies with monophasic shocks theamount of ASYS did not increase at the higher energy level. Whether the highersuccess translates into increased survival to hospital discharge has to beinvestigated in a larger trial.

255 Sport-related sudden cardiac death in the community. Time for action

E. Marijon[1], M. Tafflet[1], F. Tchatchum[1], F. Dumas[1], N. Benameur[2], S. Narcisse[3], J.F. Toussaint[4], J.P. Empana[1], X. Jouven[1]. *[1]INSERM 970 Unit, Paris, France; [2]SAMU de Lille-59, Lille, France; [3]SAMU d'Orléans-45, Orléans, France; [4]IRMES, Institut de Recherche Médicale et d'Epidémiologie du Sport, INSEP, Paris, France*

Purpose: The association between physical activity and sudden cardiac death (SCD) is well established. However, previous studies have focused on sport-related SCD in competitive athletes and few have looked at sport-related SCD in the general community.

Methods: This prospective study started in May 2005 and has been progressively extended to 70 out of 95 departmental French districts. Cases of SCD occurring during or immediately after sports activity were obtained from emergency medical services (SAMU), firefighting units as well as from accounts in the news media.

Results: Until January 2008, 404 unselected sports-related SCDs were included. The mean age was 47.2±15.5 years, with a predominance of men (94.1%). Known coronary risk factors or underlying heart disease were present in 28.4%. SCD occurred predominantly in the 3 most frequently practiced sports ie. cycling (32.9%), running (21.7%) and soccer (11.8%). Intense physical activity was reported in 40.0% of deaths, whereas light and moderate activities in 6.6% and 53.4%, respectively. Most of sport-related SCD occurred in public sports areas (72.5%). Shockable rhythm was present in 65% of cases. External cardiac massage was initiated by bystander in only 40% of cases. The proportion of patients admitted to hospital increased from 10%, when no resuscitation was initiated, to 40% when a bystander performed cardiac massage.

Conclusion: The majority of sport-related SCD occurs in public areas with a consequent number of witnesses. However, our data demonstrated that in practice only half of them begin resuscitation maneuvers. Educational programs and larger deployments of external defibrillators in sports areas are primordial to reduce sport-related SCD burden.

256 Early defibrillation in out-of-hospital cardiac arrest: ten years experience of the Italian project Piacenza-Progetto Vita

D. Aschieri[1], V. Pelizzoni[1], S. Ferraro[1], A. Rosi[1], M.S. Pisati[1], E. Bonibaldoni[1], M. Arvedi[1], A. Capucci[2]. *[1]U.O. Cardiologia, Ospedale G.da Saliceto, Piacenza, Piacenza, Italy; [2]Clinica Cardiologica,Università degli Studi di Ancona, Ancona, Italy*

This is a retrospective study of out-of-hospital cardiac arrest in the project of early defibrillation "Progetto Vita" (PV). PV lay responders were trained only to use AEDs while Emergency Medical System (EMS) performed BLS. With "blue code" EMS activate the ambulance together with the PV-AED.

The aim of this study was to determine survival rate in this particular setting of early defibrillation program.

Methods: Survival rate was recorded dividing patients (pts) firstly treated by PV or by EMS. Number of "blue code" was recorded and related to survival rate.

Results: 1956 cardiac arrest were recorded. VF was in 294/1956 pts (15,03%). 78/294 pts survived (26,53%). Survival rate was higher in group treated by PV than in group treated by EMS (Table 1). Total survival rate in the integrated system remains low: 78/1956 = 3,9%. Survival rate was strictly related to "Blu code" activation as demonstrate in figure 1.

Table 1

	Integrated system	EMS intervention	PV intervention	P value
Sudden cardiac arrest	1956			
VF at arrive	294/1956 (15.03%)	160/294 (54.4%)	131/294 (44.5%)	
Survival rate from VF	78/294 (26.53%)	30/160 (18.75%)	48/131 (36.6%)	P<0,05
Defibrillation time	6.30±2.1 min	7.20±2.30 min	5.40±1.10 min	P<0.05

VF = ventricular fibrillation; EMS = Emergency medical system; PV = Progetto Vita volunteers.

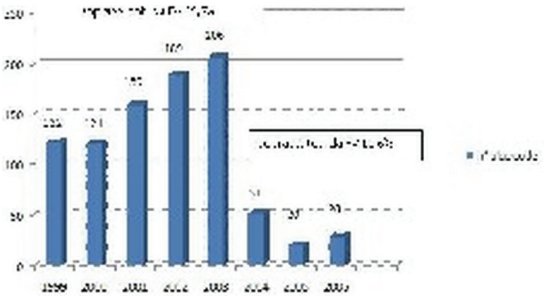


Figure 1. Blue code activation along years

Conclusions: Lay responders trained to only defibrillate saved up to 36,6% of VF cardiac arrest pts, more than twice compared to EMS because of their earlier arrival. The results are better when the blue code is activated.

UPDATE ON BIOMARKERS IN ACUTE CARDIAC CARE

282 Diagnostic and prognostic value of high sensitive troponin T in patients with acute coronary syndromes

M. Weber, H. Moellmann, H. Nef, S. Mayer, C. Liebetrau, M. Woelken, C. Hamm. *Kerckhoff Klinik GmbH, Bad Nauheim, Germany*

Background: Cardiac troponins are the gold standard for diagnosis and risk stratification of patients with ACS. As a threshold for troponins, the serum concentration which is identical to the 99th percentile of a healthy population has been defined. However, this threshold has to measurable with sufficient analytical precision, which has been defined as coefficient of variation (CV) below 10%. In the past, commercially available troponin assays were not able to measure a troponin concentration at the 99th percentile with sufficient precision, in fact the lowest concentration that be could measured with a CV<10% was about 1.4 to 4.4 fold higher. With the introduction of newly developed highsensitive troponin assays it will be possible to measure troponin concentrations at the 99th percentile with the required precision. The aim of the present study is to evaluate the diagnostic and prognostic value of a new high sensitive troponin T assay in comparison to the established troponin T assay.

Methods and results: From April 2003 until April 2005 all consecutive patients (n=1023, 30% females, median age 65 years) admitted because of an ACS within the last 48 hours were included. The final diagnosis was myocardial infarction in 857 (84%) patients. Clinical follow up after 6 months was available. During this period 72 (7.0%) patients died.

Conventional troponin T (TnT) was measured on admission and at day 1 (Elecsys®, Roche, Germany). A TnT > 0.03 ng/ml was considered positive. High sensitive troponin T (hsTnT) was measured on admission (Elecsys®, Roche, Germany). For this assay, a threshold of 0.012 ng/ml, which is the 99th percentile and identical with the 10% CV, has been applied.

On admission 694 (68%) of the patients were TnT positive, yielding a sensitivity of 81% for the diagnosis of MI. In comparison, 879 (86%) of the patients were hsTnT positive on admission yielding a sensitivity of 96%. The AUC of the ROC curves for TnT and hsTnT for the diagnosis of MI were comparable (0.929 for TnT and 0.954 for hsTnT). Among the 329 patients who were TnT negative on admission, in 133 patients MI could have been diagnosed correctly by hsTnT (sensitivity of 82%, specificity of 67%). In a multivariate Cox regression model, hsTnT was an independent predictor for mortality. In this model, conventional TnT lost its predictive value.

Conclusion: A new high sensitive troponin T assay enables early diagnosis of MI with a higher sensitivity as conventional troponin assays. Furthermore, hsTnT levels provide stronger prognostic information for mortality within 6 months as conventional TnT levels.

283 Mid Regional pro-Adrenomedullin shows additional prognostic value when used in combination with N terminal Pro B-type Natriuretic Peptide in patients with non ST elevation myocardial infarction

O.S. Dhillon, S.Q. Khan, N. Mohammed, I.B. Squire, J.E. Davies, L.L. Ng. *University of Leicester, Leicester, United Kingdom*

Purpose: To assess the prognostic value of admission MRproADM levels in unselected patients' with non ST elevation myocardial infarction (NSTEMI) for all cause mortality and readmission with heart failure (HF) both as a primary composite end point and separately as secondary end points and then compare it to the well established N terminal Pro B-type Natriuretic Peptide (NTproBNP) to evaluate its clinical utility as a risk marker.
Methods: In this single centre prospective study plasma MRproADM was measured within 36 hours of symptoms and NTproBNP within 3 to 5 days in 684 patients (469 men, median age 70.0±12.6 years) patients with NSTE-ACS.
Results: During follow up 532[150 -1059] median[range] days 113 (16.5%) patients died and 63 (9.2%) readmitted with HF. MRproADM was increased in patients with death or HF over the event free (median [range] 1.16 nmol/L [0.35-6.95] vs. 0.70 nmol/L [0.25-6.66]. Multivariate cox regression modelling adjusted for important clinical and biochemical factors revealed both logMRproADM and NTproBNP as independent predictors of the composite end point (HR [95% Confidence Interval] 7.08 [3.08-16.26] and HR 2.15 [1.51-3.05] respectively both $p<0.001$) along with age (HR 1.02 p=0.011). Receiver Operator Characteristic curve analysis C-statistic 0.77 for MRproADM and 0.79 for NTproBNP and 0.80 for both biomarkers combined. Findings were similar for death and HF as individual end points.
Comparison of the primary composite end point rates according to tertiles of A-MRproADM and NTproBNP were evaluated. The combined use of A-MRproADM and NTproBNP levels allows improved risk stratification especially at detecting those at highest risk in each tertile of NTproBNP (Log Rank test 17.93, 16.36 and 15.43 pooled comparison for 1st, 2nd and 3rd tertiles respectively all at $p<0.001$). Those with the highest levels of each biomarker were at the most risk represented by a relative risk of death or HF of 17.33 (OR 38.32) when compared to those in the lowest tertile of each biomarker.
Conclusions: MRproADM level is a strong prognostic marker in NSTE-ACS patients and improves risk stratification over use of NTproBNP alone and may represent an important clinical tool and neurohormonal pathway.

284 Prognostic value of pentaxin3 in patients with chest pain

K. Inoue[1], S. Suwa[2], S. Okazaki[1], S. Ito[2], M. Kawamura[2], I. Okai[1], M. Sumiyoshi[1], T. Kodama[3], H. Daida[4]. *[1]Juntendo Univ.Nerima Hospital, Tokyo, Japan; [2]Juntendo Univ. Shizuoka Hospital, Shizuoka, Japan; [3]RCAST, Univ of Tokyo, Tokyo, Japan; [4]Juntendo Univ.School of Medicine, Tokyo, Japan*

Introduction: Pentraxin3 (PTX3) is a newly identified member of the pentraxin family that belongs C-reactive protein (CRP). Recently we reported the levels of plasma PTX3 were increased in patients with unstable angina pectoris. Unlike CRP, plasma PTX3 is produced by the major cell types involved in atherosclerotic lesions in response to inflammatory stimuli. But the role in long-term prediction of clinical outcome is unknown. In this study, we tested the hypothesis that plasma PTX3 levels serve as a novel predictive marker compare to other cardiovascular markers of cardiovascular event in patients with chest discomfort.
Material and Methods: We assessed the value of plasma PTX3 as a risk predictor of cardiovascular events in 269 patients (average age 68.2±12.5 years; 211 men and 58 women) presenting to the emergency department with chest pain. We also examined for N-Terminal Pro-B-Type Natriuretic Peptide (NT-pro BNP), CRP, Myeloperoxide (MPO), white blood cell (WBC) and CPK.
Results: Final diagnoses included acute coronary syndrome in 66.5%, pulmonary embolism in 3.0%, effort angina pectoris in 3.0%, aortic dissection in 2.6%, or vasospastic angina pectoris in 1.5%, and atypical chest pain in 9.3%. Thirty four patients suffered severe congestive heart failure (CHF) required intra aortic balloon pumping (IABP) treatment or an intubation. During the median follow-up period of 14 months, 24 patients were dead. Multiple logistic regression analysis demonstrated that PTX3 and NT-pro BNP were significantly and independently predicted severe CHF or cardiac death (PTX3: odds ratio [OR] 1.61; 95% confidence interval [CI] 1.03 to 2.50; p = 0.036; and, NT-pro BNP: OR 1.37; 95% CI 1.07 to 1.76; p =0.012).
Conclusion: In a patient population consisting of 269 subjects with a chest pain, plasma PTX3 predicts prognostic information mostly.

285 Copeptin for prediction of outcome in patients with cardiogenic shock

B. Meyer[1], P. Wexberg[1], J. Struck[2], A. Bergmann[2], N.G. Morgenthaler[2], G. Heinz[1], R. Pacher[1], M. Huelsmann[1]. *[1]Medical University of Vienna, Vienna, Austria; [2]B.R.A.H.M.S. AG, Hennigsdorf, Germany*

Purpose: Arginine vasopressin (AVP) is significantly increased in acute hemodynamic instability. As a stress hormone, AVP is released in response to osmotic and hemodynamic changes in order to maintain fluid volume and vascular tone. Copeptin is a stable fragment of pre-pro-vasopressin which is synthesised and released in equimolar quantities as AVP. Unlike AVP copeptin is highly stable ex vivo and thus used for analysis. We assessed the hypothesis, that an elevation of copeptin serves as a predictor of adverse outcome in patients with cardiogenic shock.
Methods: The study was performed as a prospective observational trial at the Intensive Care Unit (ICU). In an 18 months study period, we included consecutive patients with diagnosis of cardiogenic shock on ICU admission. Baseline demographics were recorded in all patients and blood samples for determination of routine laboratory tests and NT-pro-BNP and copeptin plasma levels were obtained in all patients on admission. Copeptin was assessed using an immunoassay in the chemiluminescence/coated tube format. Age, gender, presence of acute renal failure, mechanical ventilation, NT-pro-BNP and copeptin were analysed for prediction of ICU survival.
Results: We included a total of 91 consecutive patients (66 male [72%], age 66.5±11.4 years) presenting with cardiogenic shock. All patients were on intravenous inotropic support, 19 patients (21%) were treated with an intraaortic balloon counterpulsation, 8 patients (8%) were on extracorporeal membrane oxygenation and 1 patient (1%) was on novacor support. A total of 56 patients (62%) survived and 35 patients (38%) died. Copeptin plasma levels were significantly higher in ICU non-survivors than in ICU survivors (164.4±117.8 vs 248.2±256.6 pg/ml, p=0.034). Using a logistic regression model, copeptin was the best predictor of ICU survival with only NT-pro-BNP providing independent additional information (copeptin odds ratio 1.002; p=0.001 and NT-pro-BNP odds ratio 1.001; p=0.05).
Conclusions: An elevation of copeptin, a fragment of pro-vasopressin, is an independent predictor of adverse outcome in patients with cardiogenic shock. Whether vasopressin antagonism provides a therapeutic option in these patients remains to be studied.

286 A new high-sensitive cardiac troponin I assay allows identification of the vast majority of patients with acute coronary syndromes

B. Lindahl[1], S. James[2], N. Johnston[2], P. Venge[3]. *[1]Uppsala University Hospital, Uppsala, Sweden; [2]Dept of Cardiology, University Hospital, Uppsala, Sweden; [3]Dept of Clinical Chemistry, University Hospital, Uppsala, Sweden*

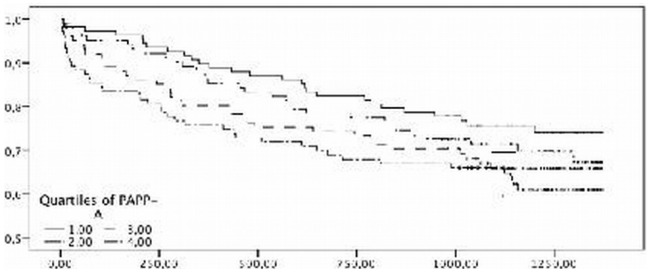
Purpose: Cardiac troponins (Tn) are the preferred markers for diagnosis of acute myocardial infarction (AMI). However, with the current tn assays most healthy individuals and a large proportion of patients with Acute Coronary Syndromes (ACS) have undetectable levels of Tn. Therefore, measurement of Tn has not so far been useful for identification or exclusion of ACS. The aim of the present study was to evaluate whether it is possible to discriminate between healthy and ACS individuals based on measurement of troponin I (TnI) with a new high-sensitive assay.
Methods: TnI levels were measured with a new prototype high-sensitive cardiac tnI assay from Beckman Coulter in EDTA-plasma in 542 healthy subjects (mean age 60 y, 39% women) and in serum from 1503 randomly selected patients) included in the GUSTO-IV trial, in which patients with symptoms and signs of nonST-elevation ACS were included (mean age 65 y, 38% women, mean delay from onset of chest pain 9 h, 28% had undetectable troponin T (<0.01 μg/L)).
Results: The new high-sensitive TnI assay allowed measurement of TnI levels in >95% of the healthy subjects, with a median level of 0.0032 μg/L. The TnI levels at 10% CV were 0.0033 μg/L. The 99th percentile was found at 0.017 μg/L. ROC analyzes showed an AUC of 0.942 (95% CI 0.931-0.952), and that the optimal cut-off for separation of the two groups was 0.0064 μg/L, giving a sensitivity and specificity of 85 and 90%, respectively, for detection of ACS. 13.3% of the GUSTO-IV population had levels below 0.0064 μg/L. Cardiac events (AMI/death) at 30 days had occurred in 2.0% and 8.6% of those in the GUSTO-IV population with levels below and above 0.0064 μg/L, respectively. The corresponding figures were 4.1% and 9.2% for those with levels below and above the 99th percentile cut-off (0.017 μg/L), respectively.
Conclusions: Measurement of TnI with a high-sensitive assay might be useful for early diagnosis of ACS, but requires a lower cut-off level than for diagnosis of AMI. Further studies should evaluate whether serial sampling, taking also dynamic changes in the low range in consideration, would further improve the identification of patients with ACS.

287 Pregnancy associated plasma protein A, a marker for outcome in patients with low-risk acute coronary syndrome

K.K. Iversen[1], M. Dalsgaard[1], A. Teisner[2], B. Teisner[3], P. Grande[4], H. Nielsen[2], P. Clemmesen[4]. *[1]Hilleroed Hospital, Copenhagen, Denmark; [2]Copenhagen University Hospital, Bispebjerg, Copenhagen, Denmark; [3]Odense University Hospital, Odense, Denmark; [4]Rigshospitalet (The Heart Centre), Copenhagen, Denmark*

Purpose: Patients admitted with Non ST-segment elevation acute coronary syndrome (NSTE-ACS) with normal electrocardiogram and normal biomarkers have in general a good prognosis and are categorised as low-risk. Some of these patients might still have vulnerable plaques in the coronary arteries. A marker for the vulnerable plaque could identify patients who potentially would benefit from inten-

sive treatment and surveillance. The purpose of the present study was to investigate the prognostic impact of Pregnancy Associated Plasma Protein-A (PAPP-A) in patients admitted with low-risk NSTE-ACS.
Methods: Consecutive patients admitted with low-risk NSTE-ACS were evaluated with serial measurements of PAPP-A. The incidence of mortality and non-fatal myocardial infarction was prospectively registered.
Results: Serial samples were drawn from 415 patients with low-risk NSTE-ACS. Median age was 67 years (range: 20-92 years) and 43% were women. The risk of death or nonfatal myocardial infarction after 3 months was 15% in the highest quartile of circulating PAPP-A compared to 3% in the lowest quartile (RR 3.7, $p<0.01$). After 1 year the risk was 24% and 10% respectively (RR 2.4, p=0.01). Corresponding numbers for mortality was 11% in the highest quartile compared to 1% in the lowest quartile after 3 month (RR 11.9, $p<0.01$), and 14% and 6% (RR 2.4, p=0.05) after 1 year. In multivariate analyses including known risk factors PAPP-A independently predicted risk for death and non-fatal myocardial infarction (HR 1.01 (per mIU/l), 95% c.i. 1.00-1.02, p=0.02). Kaplan Meyer plot of the risk for death or non fatal myocardial infarction is shown in the figure.



Conclusion: In patients admitted with low-risk NSTE-ACS, PAPP-A identifies patients in high risk for death and non-fatal myocardial infarction.

ADVANCES IN CARDIOPULMONARY RESUSCITATION

288 Outcome of mild induced hypothermia after out-of-hospital sudden cardiac arrest in non-selected patients

U. Pittl, D. Lehmann, S. Erbs, E. Grebe, S. Gielen, G. Schuler, H. Thiele. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Background and Purpose: Sudden cardiac arrest (SCA) remains one of the major leading causes of death. Cognitive deficits are common in survivors of SCA. Post-resuscitative mild induced hypothermia (MIH) lowers mortality and reduces neurologic damage after cardiac arrest. We evaluated the efficacy and side effects of therapeutic hypothermia in an unselected group of patients after SCA.
Methods: 100 consecutive patients with restoration of spontaneous circulation (ROSC) after resuscitation due to out-of-hospital SCA, admitted to our intensive care unit, underwent MIH. Hypothermia was induced by infusion of cold saline and whole-body-cooling methods (invasive or non-invasive). The core body temperature was operated at 32 to 34°C over a period of 24 hours followed by active rewarming. Neurological status was evaluated at hospital discharge using the Pittsburgh Cerebral Performance Category (CPC).
Results: Overall, 100 patients (mean age 64±14 years, 80% male) were included with a "no- or low-flow" duration of 30 min (SCA to ROSC). The APACHE II-Score at admission was 26.0±4.9. Left ventricular ejection fraction was 35.0±13.6%. SCA was bystander-witnessed in 86%. In 55% resuscitation was initiated before arriving of emergency services. Because 61% of all patients were firstly admitted to a non-tertiary center, the time from ROSC to target temperature was 455±654 min. Survival rate at discharge was 64%. Thirty-six percent of all patients presented in good neurologic functional status (CPC 1-2). Infectious complications were observed in 74% of our non-selected patients, mostly nosocomial pneumonia (80%), with 13 patients developing a severe sepsis (13%) and a sepsis-related mortality of 38% (5 of 13 patients). Antibiotic prophylaxis was not given in any patient. Fifty-one percent of all patients suffered renal failure with a necessity of dialysis in 39%.
Conclusions: Neurologic outcome after out-of-hospital sudden cardiac arrest remains poor. Treating non-selected patients successfully resuscitated with mild induced hypothermia is proven effective and safe. However, the high rate of complications compared to other published studies may be a result of our real-world scenario including older patients with more comorbidities that is associated with multiple secondary infectious complications. Furthermore, the different definitions of complications might have an impact.

289 Electrocardiographic disturbances induced by mild therapeutic hypothermia after cardiac arrest

P. Salinas Sanguino, E. Lopez De Sa, A. Viana-Tejedor, L. Pena-Conde, E. Armada, J.R. Rey-Blas, S. Garcia-Blas, D. Iglesias, M.C. Monedero, J.L. Lopez-Sendon. *Hospital Universitario La Paz, Madrid, Spain*

Purpose: Several electrocardiographic (ECG) changes and arrhythmias have been described in accidental deep hypothermia; however few data have been published about changes in mild therapeutic hypothermia (MTH).
Methods: Prospectively we collected data from all cardiac arrest patients admitted to the Coronary Care Unit (CCU) from 2006 to 2009. All patients underwent MTH (32° - 34° C), by intravenous cold fluid or with an intravascular cooling system. ECGs were recorded at admission (A), peak MHT (B), and after rewarming (C). ECG telemetry was recorded and analyzed by CCU staff for rhythm disturbances. ECGs were blinded and analyzed by two independent cardiologists.The variables studied were: rhythm, RR, PR, QT and corrected QT (QTc, Bazett) intervals; QRS duration as well as ST segment displacement and T wave amplitude in leads II, v2 and v5.
Results: Our population was 45 patients. Main results are shown in Table 1. No significant changes were found between initial and final ECGs, except for QTc that lengthened. No difference was found in ST segment or T waves. The ECG changes were more pronounced in those patients that reached lower temperature. No clinical consequences were attributed to this changes although we had no long QT related cardiac arrest patients. 9 patients (20%) developed Osborn J waves during hypothermia. Non-sustained ventricular tachycardia was detected in 8 (17.88%) patients. 4 patients (8.89%) had reversible rhythm changes during MHT: 3 patients in sinus rhythm had atrial fibrillation (AF) and 1 patient in AF had a rapid idioventricular rhythm. Sinus bradycardia transiently appeared in 9 patients (20%). Non-reversible rhythm changes were not considered in this study.

Table 1. Changes in ECG intervals

	Admission (A)	Peak MHT (B)	After MHT (C)	p for difference (A to B)	p for difference (B to C)	p for difference (A to C)
RR interval (ms)	657,7 (179)	843,8 (221)	662,2 (116)	0,0001	<0,0001	0,86
PR interval (ms)	172,2 (45)	181,5 (40)	162,5 (38)	0,15	0,003	0,14
QRS duration (ms)	108,0 (23)	119,5 (40)	102,9 (24)	0,03	0,0009	0,10
QTc interval (ms)	440,7 (52)	496,9 (97)	464,3 (80)	0,0005	0,03	0,04

Data are means, standard deviation (in brackets) and p for difference.

Conclusions: PR, RR,QT and QTc intervals, as well as QRS duration are prolonged during MHT, and changes revert with rewarming. Most frequent arrhythmia was sinus bradycardia. ECG changes are similar to those described previously in deep accidental hypothermia.

290 In vivo systemic effects of catheter based selective unilateral profound cerebral hypothermia

D. Meerkin[1], S.P. Lownie[2], C.J. Prestigiacomo[3], R.J. Solar[4]. [1]*Shaare Zedek Medical Center, Jerusalem, Israel;* [2]*London Health Sciences Centre, London, Ontario, Canada;* [3]*Neurological Institute of New Jersey, Newark, United States of America;* [4]*ThermapeutiX, San Diego, United States of America*

Background: Mild hypothermia has been shown to improve outcome in comatose survivors after resuscitation from out-of-hospital cardiac arrest. It has been suggested that induction of deep hypothermia before reperfusion may further improve outcome. Current techniques involve total body cooling, with the limitations of rapidity and depth of cooling due to systemic, predominantly cardiac, adverse effects. We studied a novel catheter-based system designed to rapidly and selectively cool the brain while maintaining systemic temperature within normal range. The unique design incorporates a counter current flow to insulate the normothermic systemic blood from the cooled blood perfusing the brain.
Methods: A transfemoral approach was employed in 12 swine (65-72kg). Using standard radiological techniques, the multilumen catheter was positioned to isolate the right or left common carotid artery. The outer lumen was positioned in the aortic arch. Blood was withdrawn from the aorta via one lumen, cooled extra corporeally, and reperfused through a second lumen into the carotid artery. Outflow blood was cooled to 5-20°C, and reperfused at rates of 80-250 ml/min for 30-180 minutes. Temperature was measured in bilateral frontal lobes, nasopharynx, ear, esophagus and descending aorta.
Results: Unilateral hemicranial and hemicerebral cooling to 15°C was achieved. Only limited associated systemic cooling was noted. Initial cooling rates of 1.8°C/min were attained, and were dependant on inflow rate and temperature. No adverse events occurred. Contralateral hemispheric cerebral temperature closely followed systemic temperature. Passive rewarming did not result in rebound hyperthermia.
Conclusion: This catheter-based system demonstrated feasibility in providing rapid, selective deep cerebral hypothermia, and may offer an improved method for neuroprotection during cardiac arrest and other ischemic injury.

291 Therapeutic hypothermia improves myocardial function and stabilizes the hemodynamic situation in patients after cardiac arrest

C. Jacobshagen, A. Pax, S. Schmidt-Schweda, B.W. Unsoeld, T. Seidler, G. Hasenfuss, L.S. Maier. *Department of Cardiology, Georg-August-University Goettingen, Goettingen, Germany*

Post-cardiac arrest myocardial dysfunction is a common phenomenon after return of spontaneous circulation (ROSC) and contributes to hemodynamic instability and low survival rates after cardiac arrest. Mild hypothermia (32-34°C) for 12-24 hours after ROSC is the only therapy applied in the post-cardiac arrest setting that has been shown to significantly improve neurologic recovery and survival rates. In the present study we investigate the influence of therapeutic hypothermia on hemodynamic parameters in resuscitated patients and on contractility of human failing myocardium.

We retrospectively analyzed the data from 52 patients (age 61.3±2.3 years) during the post-resuscitative hypothermia period. The initial ejection fraction was 35.8±2.2% indicating a significantly impaired left ventricular function. The target temperature of 32-34°C was achieved after 4.1±0.5 h. During this time, the positive inotropic stimulation with epinephrine could be reduced from 7.89±2.83 μg/min (at admission to the ICU) to 4.76±2.87 μg/min (34°C) and 2.18±0.98 μg/min (33°C). The dobutamine dose could also be reduced, whereas the infusion rate of norepinephrine was slightly increased. The mean arterial blood pressure (MAP) remained stable at 85.4±4.0 mmHg (initially), 80.1±2.6 mmHg (34°C) and 78.1±2.3 mmHg (33°C). The mean heart rate decreased from 93.4±3.9 bpm (initial) to 77.4±4.6 bpm (34°C) and 71.1±4.1 bpm (33°C).

To investigate the particular impact of hypothermia on myocardial function, we treated isolated ventricular muscle strips from explanted failing human hearts with hypothermia and analyzed the contractile function. With decreasing temperature the contractility significantly increased to a maximum of 167.51±22.95% at 27° C (n=16, $P < 0.05$). A subgroup analysis showed a particularly enhanced effect on myocardium from patients with dilative cardiomyopathy (208.62±40.14%, n=7, $P < 0.05$). Inhibiting the sarcoplasmic reticulum Ca^{2+} release by ryanodine did not significantly reduce the positive inotropic effect of hypothermia (a linear regression analysis demonstrated a high correlation of force development with and without ryanodine, r=0.75). Furthermore, hypothermia reduced cardiac relaxation parameters, indicating an increased Ca^{2+}-sensitivity as mechanism for the positive inotropic effect of hypothermia.

In conclusion, therapeutic hypothermia stabilizes the hemodynamic function in patients after cardiac arrest. Mechanistically, we demonstrate that hypothermia improves contractility in failing human myocardium by increasing Ca^{2+}-sensitivity.

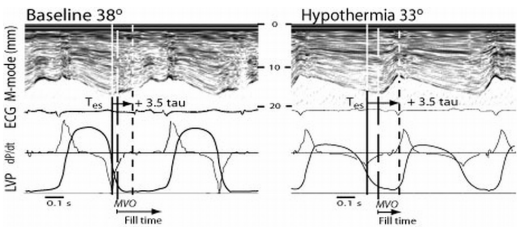
292 Moderate hypothermia induces severe diastolic changes in a porcine model

A. Espinoza[1], V. Kerans[1], A. Opdahl[1], P.S. Halvorsen[1], H. Skulstad[1], L. Hoff[2], J.F. Bugge[1], T. Edvardsen[1]. *[1]Rikshospitalet University Hospital, Oslo, Norway; [2]Vestfold University College, Horten, Norway*

Purpose: Hypothermia is used in patients after cardiac arrest for neuroprotection. The associated cardiac effects in diastole are not well described. We have studied the effects of hypothermia on left ventricular (LV) diastolic function in a porcine model.

Methods: 6 anesthetized pigs were cooled from 38° to 33°C. Using micromanometer we measured LV pressure and the time constant (tau) of LV isovolumic pressure decay. Systolic duration was calculated from R on ECG to time of dP/dtmin (Tes). Isovolumic relaxation (IVR) was calculated from Tes to mitral valve opening (MVO), and filling time from MVO to R on ECG. Duration of the relaxation was calculated from Tes as 3.5 times tau. LV volume was measured by echocardiography. Registrations (mean ± SEM) were made during atrial pacing at 100 beats/min.

Results: Systolic duration increased (P=0.01) while stroke volume decreased from 48±1 to 40±2 ml, P=0.01. This was accompanied by a marked decrease in diastolic duration (285±30 to 185±6ms, P=0.01), also shown by M-mode (Figure). IVR increased (41±3 to 91±8 ms, P=0.02) and filling time decreased from 226±9 to 87±9ms (P=0.01). Tau increased from 30±2 to 54±3ms (P=0.01). Relaxation time increased as fraction of diastolic duration from 0.4±0.1 to 1.1±0.1 (P=0.01), indicating that relaxation was not completed before next systole. LV EDP was unchanged while EDV decreased from 72±3 to 63±2 ml, P=0.04.



Conclusions: Moderate hypothermia induced a significant decrease in diastolic filling time and prolonged relaxation. The shift in end-diastolic pressure-volume relation is consistent with a stiffer myocardium due to incomplete relaxation. These findings suggest that diastolic dysfunction may be an important contributor to reduced stroke volume during hypothermia.

293 Randomized comparison of percutaneous left ventricular assist device with open chest cardiac massage and surgical left ventricular assist device in ischemic cardiac arrest

V. Tuseth[1], R.J. Pettersen[1], K. Grong[2], T. Wentzel-Larsen[3], R. Haaverstad[2], R. Fannelop[2], J.E. Nordrehaug[1]. *[1]Haukeland University Hospital, Dept of Heart Disease, Bergen, Norway; [2]Department of Surgical Sciences, University of Bergen, Bergen, Norway; [3]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway*

Purpose: A percutaneous left ventricular assist device (LVAD) may maintain blood flow to vital organs and prevent myocardial and cerebral ischemia during cardiac arrest and may be useful by supplementing chest compressions during treatment of patients with cardiac arrest in the catheterization laboratory. We compared a percutaneous LVAD, with open chest cardiac compressions (OCCM), and with a surgical LVAD during ischemic cardiac arrest in a randomized experimental model.

Methods: Transit-time flowmetry probes were placed around the pulmonary artery (Cardiac Output) and both carotid arteries (CA). Myocardial ischemia was induced by coronary ligature and ventricular fibrillation (VF) was induced by diathermia. Perfusion was measured by microspheres. Defibrillation was attempted after 20 minutes of VF.

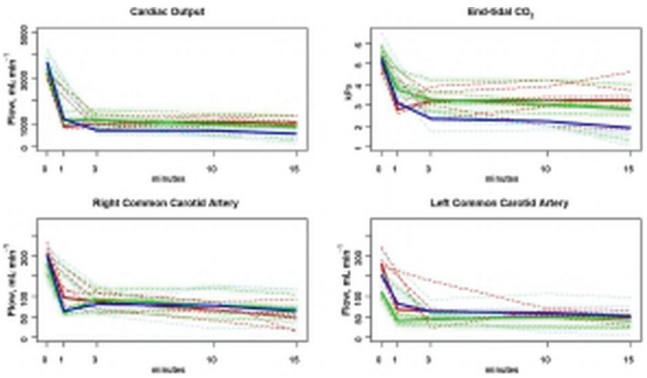
Results: After 3 minutes of VF, Cardiac Output in the OCCM group was 1129mL/min vs. 1169 mL/min in the percutaneous LVAD- and 570 mL/min in the surgical LVAD group ($P < 0.05$ for surgical LVAD vs. others).

Right common carotid artery flow was 86mL/min for OCCM, 98 mL/min for percutaneous- and 79 mL/min for surgical LVAD (P=NS).

End-tidal CO2 was 3.3 kPa in OCCM, 3.2 kPa in percutaneous-, and 2.3 kPa in surgical LVAD ($P < 0.05$ for surgical LVAD vs. others).

Epicardial perfusion was 0.33 mL/g/min for OCCM vs 0.62 mL/g/min for both LVADs ($P < 0.05$ LVADs vs. OCCM).

Return of spontaneous circulation after defibrillation at 20 minutes was not different between groups (P=0.27).



Cardiac Output, et CO2 and carotid flow

Conclusion: A percutaneous LVAD can achieve hemodynamics comparable to open chest cardiac massage during cardiac arrest in an experimental model.

MITRAL REGURGITATION: WHAT'S NEW?

335 Myocardial systolic velocities and deformation assessed by speckle tracking for the early detection of cardiac dysfunction in asymptomatic patients with severe primary mitral regurgitation

M. Florescu[1], D. Benea[2], R. Sisu[1], O. Enescu[1], L.S. Magda[1], G. Cerin[2], M. Diena[2], M. Cinteza[3], D. Vinereanu[3]. *[1]University Emergency Hospital, Bucharest, Romania; [2]San Gaudenzio Clinic, Novara, Italy; [3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

In asymptomatic patients with severe primary mitral regurgitation (PMR), early detection of LV dysfunction indicates the optimal timing of mitral valve surgery. Ejection fraction (EF) and end-systolic diameter (ESD) are the most widely used indices to demonstrate LV dysfunction. However, normal EF or ESD can mask LV impairment. We hypothesized that changes in myocardial velocities, strain and strain rate might represent an early marker of subclinical LV dysfunction, and can predict postoperative LV function.

Methods: We studied 28 asymptomatic patients (59±13 yrs) with severe PMR, EF>60% and ESD<45 mm (group I), and 10 age-matched healthy subjects (group II). All underwent conventional echo and tissue velocity imaging to assess LV geometry, EF, and long-axis systolic function (from mean 6 basal segments

velocities – STVI); 2D speckle tracking was used to assess radial strain (rS) and strain rate (rSR), and longitudinal strain (LS) and strain rate (LSR). Group I was evaluated preoperatively and 14 days after successful mitral valve repair, and was divided into 2 subgroups: IA, with a postoperative EF reduction >10% (13 patients), and IB, with an EF reduction <10% (15 patients).
Results: Although there were no differences in preoperative EF or ESD between groups, STVI, radial as well as longitudinal systolic S and SR were significantly decreased in patients from group I (table). Despite subgroups IA and IB had similar preoperative LV mass index, diameters, volumes, and EF, IA had significantly lower STVI, rS, and LS (7.39±0.90 vs. 10.80±1.50 cm/s; 37.4±2.5% vs. 41.7±2.4; and –16.1±4.2% vs. -21.7±2.1%, respectively, all $p<0.001$) than IB. Multiple stepwise regression analysis showed that STVI, and the combination of STVI and LS, represent the main independent predictors for a postoperative EF reduction >10% (R^2=0.52, and R^2=0.70, respectively, both $p<0.001$).

LV function in patients with PMR

Group	EF (%)	ESD (mm)	STVI (cm/s)	rS (%)	rSR (1/s)	LS (%)	LSR (1/s)
I	63.5±2.8	39.7±4.5	9.23±2.10	39.9±3.2	1.9±0.2	-19.4±4.4	-1.2±0.4
II	62.5±1.3	43.8±7.0	12.80±0.20	48.8±5.7	2.5±0.8	-22.8±2.4	-1.8±0.6
p	0.39	0.56	0.0001	0.001	0.005	0.02	0.002

Conclusion: Myocardial long-axis systolic velocities and LV deformation assessed by speckle tracking can detect subclinical LV dysfunction, and predict impaired postoperative LV function, in asymptomatic patients with severe PMR.

336 Prospective validation of the prognostic usefulness of BNP in asymptomatic patients with chronic severe mitral regurgitation

R. Pizarro, P. Oberti, A. Arias, M. Falconi, F. Achilli, J. Krauss, A. Cagide, O. Bazzino. *Italian Hospital of Buenos Aires, Buenos Aires, Argentina*

Background: Early and timely valve surgery could be convenient in selected patients with chronic severe mitral regurgitation (MR) who are free of heart failure or left ventricular dysfunction. However, there are not strong criteria available to identify patients that could benefit from that strategy. Assessment of brain natriuretic peptide (BNP) has been studied in patients with left ventricular dysfunction. However, the clinical relevance in asymptomatic patients with preserved left ventricular function is unclear.
Objective: The purpose of the study was to determine the independent and additive prognostic value of BNP, in two samples of patients presenting with severe asymptomatic MR without alterations of left ventricular systolic function.
Methods: We prospectively evaluated 269 consecutive patients with severe asymptomatic organic MR and left ventricular ejection fraction (EF) over 60%. The first 167 consecutive patients served as the derivation cohort and the following 102 patients served as a validation cohort. BNP was measured at entry and annually thereafter. The combined end point was the occurrence of either symptoms of congestive heart failure, left ventricular dysfunction (EF below 60%) or death at follow-up.
Results: The end point was reached in thirty five (21%) patients of the derivation set and in twenty one patients (20.6%) of the validation cohort. Receiver-operating characteristics curve yielded an optimal cut-off point of 105 pg/ml of BNP that was able to discriminate patients at higher risk in both cohorts (76% vs 5.4% in the derivation set and 66% vs 4% in the validation set). By Kaplan-Meier analysis, patients with BNP values over 105 pg/ml were at high risk of adverse outcome in the derivation set (log- rank 16.2, adjusted hazard ratio 5.6; 95% CI: 2.9-10.6, $p<0.001$), and in the validation set (log- rank 13.2, adjusted hazard ratio 4.7; 95% CI: 2.4-11.3, $p<0.001$). In both the derivation and validation sets, BNP increased significantly the area under the ROC curve of the predictive model, and was the strongest independent predictor by multivariable analysis.
Conclusion: Among patients with severe asymptomatic organic mitral regurgitation BNP ≥105 pg/ml discriminates a subgroup of patients at high risk. Because of its incremental prognostic value, BNP assessment should be considered in clinical routine for risk stratification in this group of patients.

337 Prognostic impact of pulmonary arterial hypertension in patients with severe mitral regurgitation due to flail leflets: a multicenter long-term international study

F. Bursi[1], F. Grigioni[2], A. Barbieri[1], C. Tribouilloy[3], J.F. Avierinos[4], A. Branzi[2], M.G. Modena[1], M. Enriquez-Sarano[5] on behalf of MIDA Investigators. *[1]Ospedale Policlinico, Modena, Italy; [2]S. Orsola Hospital Cardiology Department, Bologna, Italy; [3]University of Amiens, Amiens, France; [4]University of Marseille, Marseille, France; [5]Mayo Clinic and Foundation, Rochester, Mn, United States of America*

Objectives: Knowledge of pulmonary arterial hypertension (PAH) complicating degenerative mitral regurgitation (MR) relies on single-center studies enrolling small sample size with varying degree of regurgitation. We investigated in a large and homogenous cohort predictors and prognostic implications of PAH complicating MR.
Methods: The MIDA is a registry assembled by merging a series of institutional databases. The registry includes consecutive patients with a diagnosis of severe MR due to flail leaflets from tertiary centers in Europe and USA. Specific criteria for the present analysis were: 1) presence of tricuspid regurgitation allowing measurement of pulmonary artery systolic pressure (PASP) by Doppler Echocardiography; 2) absence of hypoxemic pulmonary disorders.
Results: The inclusion/exclusion criteria were fulfilled by 437 patients (age 67±11; 66% males; LVEF 64±10; NYHA III-IV 35%). At multivariable analysis age (adjusted HR [95% CI] 1.05 [1.03-1.08], $p<0.0001$) and larger LA size (adjusted HR [95% CI] 1.06 [1.03-1.09], $p<0.0001$) were independently associated with presence of PAH (defined as PASP≥50 mmHg). Mean follow-up was 4.8±2.8 years (101 deaths). On multivariable analysis, after adjustment for age, gender, NYHA Class, LVEF and atrial fibrillation, PAH retained an independent prognostic significance under non-surgical management (adjusted HR 2.64 [1.25 – 5.57] P=0.011). Mitral valve surgery at any time was beneficial (adjusted RR 0.23 [0.14-0.37] P<0.001), but PAH retained negative prognostic significance from surgery (adjusted HR 1.95 [1.23-2.98] P=0.002). Post operative survival at 5 years was better in patients without PAH (90±2 vs 80±5%; P=0.009).
Conclusions: PAH is as serious complication of MR. MV surgery should be considered before the occurrence of PAH.

338 Functional mitral regurgitation as a predictor of atrial fibrillation following acute myocardial infarction

F. Bahouth, D. Mutlak, S. Dabbah, H. Hammerman, Y. Agmon, D. Aronson. *Rambam Health Care Campus, Haifa, Israel*

Background: The role of factors that increase left atrial pressure or cause an acute left atrial dilatation is frequently emphasized in the pathogenesis of atrial fibrillation (AF) in patients (pts) with acute myocardial infarction (AMI). Functional (ischemic) mitral regurgitation (FMR) occurring after AMI may promote AF. However, there is no information concerning the role of FMR in the development of new-onset AF in pts with AMI.
Methods: We performed a post hoc analysis of 1714 pts admitted with AMI and enrolled in a prospective study on the clinical outcomes of FMR. Pts with known AF were excluded. FMR was classified using echocardiography into 3 groups: 1) none, 2) mild or mild-moderate, 3) moderate to severe. The relationship between FMR and new-onset AF occurring at any time during hospital course was examined using multivariable logistic regression, adjusting for age, gender, hypertension, diabetes, anterior location of infarction, ST-elevation infarction, Killip class, coronary revascularization, and left ventricular ejection fraction (LVEF).
Results: Mild or mild-moderate FMR was present in 655 pts (38.2%) and moderate to severe FMR in 124 pts (7.2%). AF developed in 34 (3.7%), 65 (9.9%), and 21 (15.7%) of pts with no FMR, mild or mild-moderate FMR, and moderate to severe FMR, respectively (P trend < 0.0001). In a multivariable logistic regression, both mild or mild-moderate and moderate to severe FMR were strong independent predictors of AF (Table). There was a significant interaction between LVEF and FMR such that mild or mild-moderate FMR was predictive for AF only in patients with reduced LVEF.

Independent predictors of new-onset AF

Variable	Odds Ratio	95% CI	P value
Age > 65 years	2.5	1.6-3.8	<0.0001
Ejection fraction < 45%	1.6	1.1-2.4	0.01
No/trivial FMR	1.0 (Referent)	–	–
Mild or mild-moderate FMR	2.2	1.4-3.5	0.003
Moderate to Severe FMR	3.1	1.7-5.7	0.002

Conclusions: There is a graded independent association between the severity of FMR and development of AF in pts with AMI. Concomitant FMR may be an important determinant of new-onset AF in pts with acute MI.

339 Matrix metalloproteinase-1 mitral expression and -1607 1g/2g gene promoter polymorphism in patients with mitral chordae tendinae rupture

T.H. Lin, S.F. Yang, C.C. Chiu, Y.T. Lee, H.M. Su, W.C. Voon, W.T. Lai, S.H. Sheu. *Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*

Background: Understanding the pathogenesis of chordae tendinae rupture (CTR), a progressive disease eventually resulting in the need for mitral valve (MV) surgey, is important in further identification of risk factors for early intervention. We previously found the association between CTR and hypertension. Matrix metalloproteinase-1 (MMP1) expression increases under left ventricular (LV) pressure overload and triggers the signal cascade instigating cardiac fibrosis possibly predisposing to CTR. Therefore, we investigate the association between MMP1 mitral expression, MMP1 -1607 1G/2G polymorphism and CTR.
Method: Using the cross-sectional study in a tertiary medical center in Taiwan, 185 patients (group A) receiving MV replacement were enrolled and classified into 64 patients with CTR and 121 without CTR. Expression of MV MMP1, assessed on a semi-quantitative scale (0 to 3), was determined by immunohistochemical staining using antibodies against MMP1. We further recruited 227 subjects (group B, 75 CTR and 152 controls) for genetic association study. The gene polymorphisms were analyzed by the polymerase chain reaction.
Result: The group A CTR patients have more male sex ($p = 0.005$), shorter duration from onset of symptom to surgery ($p < 0.001$), higher prevalence of hypertension and coronary artery disease (both $p \leq 0.028$), lower prevalence of

rheumatic heart disease (RHD, $p < 0.001$), larger LV end-diastolic dimension (LVEDD, $p < 0.001$), smaller left atrium dimension ($p = 0.016$) and higher expression of MV MMP1 ($p < 0.001$) than those without CTR. Using binary logistic regression analysis, the variation in CTR group was found to be independently explained by MMP1 ($p = 0.029$, OR = 1.51, CI = 1.04-2.19), hypertension ($p = 0.028$, OR = 2.38, CI = 1.10-5.14), history of RHD ($p = 0.030$, OR = 0.22, CI = 0.05-0.71), disease duration ($p = 0.039$, OR = 0.99, CI = 0.98-1.00) and LVEDD ($p < 0.001$, OR = 1.09, CI = 1.04-1.15). CTR patients in group B are older ($p = 0.014$) and have larger LVEDD ($p = 0.002$) than the control group. The MMP1 -1607 1G allele increased in patients with CTR ($p = 0.014$). The odds ratio (OR) for the 1G/1G genotype to the 2G/2G genotype was 3.22 ($p = 0.007$). Univariate and logistic regression analysis showed the independent association of MMP1 -1607 polymorphisms with CTR ($p = 0.014$ and 0.044, respectively).
Conclusion: MMP1 mitral expression and -1607 1G/2G polymorphism were associated with CTR in this study. Because it was observed independently of other baseline characteristics, we think that the MMP1 may play a role in the individuals' susceptibility toCTR.

340 Hybrid approach for patients with mitral valve disease and coronary artery disease: a pilot study on the association of minimally invasive video- assisted mitral valve surgery and PCI

C. Trana[1], F. Mangiacapra[1], A. Ntalianis[1], J. Bartunek[1], F. Van Praet[2], F. Casselman[2], E. Barbato[1], H. Vanermen[2], B. De Bruyne[1]. *[1]Cardiovascular Center OLV Hospital, Aalst, Belgium; [2]OLV Hospital, Department of Cardiovascular Surgery, Aalst, Belgium*

Background: We sought to assess the long term clinical outcome of patients with combined mitral valve disease and coronary artery disease in whom an intentional combination of minimally invasive video – assisted mitral valve surgery and PCI was performed.
Methods: Between January 2004 and May 2008, the upfront strategy of combining Port Access mitral valve surgery and PCI was applied in 23 patients (21 patients with mitral regurgitation and 2 patients with mitral stenosis). Three patients had had prior cardiac surgery. Stents were implanted in the LAD (8 patients), LCX (3 patients), RCA (11 patients) and in the saphenus graft to RCA (1 patient). Eleven patients underwent mitral valve repair with mitral annuloplasty, 6 patients underwent only mitral annuloplasty and 6 patients received a mitral prosthesis (4 biological and 2 mechanical).
Results: The PCI was performed in 14 patients prior to mitral valve surgery (8.9±3.6 weeks) and in the other 9 patients the PCI was performed after mitral valve surgery (22±34 days). There were no PCI-related complications. In one patient PCI of another artery needed to be done 9 months after the mitral procedure. All the surgical procedures were fully endoscopic, and resulted in a competent mitral valve. Mean clinical follow-up was 23± 17 months. One patient died from cerebral metastasis and bleeding 2 years after treatment. NYHA class and CCS class were respectively 2.4±0.8 and 1.8±1.2 before, and 1±1.1 and 0.3±0.9 at follow up. On echocardiography, mitral valve function was satisfactory in all patients. Due to recurrent chest pain, one patient had a control coronary angiogram which did not show any restenosis.
Conclusions: For selected patients with mitral valve disease and coronary artery disease, the intentional combination of minimally invasive mitral valve surgery and PCI is a reasonable alternative to conventional surgery and avoids sternotomy.

THERAPEUTIC INTERVENTIONS AND OUTCOMES IN CARDIOMYOPATHIES

341 Bromocriptine promotes recovery of cardiac function and survival in patients with PPCM: first randomized study

K. Sliwa[1], K. Tibazarwa[1], L. Blauwet[2], E. Libhaber[1], J.P. Smedema[3], A. Becker[1], D. Hilfiker-Kleiner[4] on behalf of Soweto Cardiovascular Research Unit. *[1]Department of Cardiology, Chris Hani Baragwanath Hospital Soweto, University of the Witwatersrand, Johannesburg, South Africa; [2]Department of Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota, USA, Rochester, United States of America; [3]Netcare N1 City Hospital, Cape Town, South Africa; [4]Medizinische Hochschule Hannover, Department of Cardiology and Angiology, Hannover, Germany*

Background: Peripartum cardiomyopathy (PPCM) has a high mortality rate (9-30%). We demonstrated that mice with a cardiac specific knockout for the signal transducer and activator of transcription-3 (STAT-3) develop PPCM. Treatment with bromocriptine (BR), a dopamine-D2 receptor antagonist that inhibits prolactin secretion, prevented PPCM in these mice. A few case reports in humans suggest that BR has beneficial effects in PPCM patients.
Aim: To assess the efficacy of BR on the clinical parameters and recovery of left ventricular (LV) function in symptomatic patients with newly diagnosed PPCM presenting within the first month after childbirth.
Methods: This was a prospective single centre randomized study of women with newly diagnosed PPCM receiving standard care including ACE-inhibitor, beta-blocker, and diuretic (PPCM-Std, n=10) versus standard care plus BR 2.5 mg bid for 6 weeks (PPCM-BR, n=10). The 6 month outcome of their offspring (n=21) was also studied, as mothers receiving BR could not breastfeed. Clinical assessment, echocardiography and prolactin measureent were done at baseline and 6 months post diagnosis.
Results: There was no significant difference in baseline characteristics between the two study groups. PPCM-BR patients had significant recovery of LV systolic function (p=0.006), reduction of mitral regurgitation, and improvement in parameters of LV diastolic function compared to PPCM-Std patients (Table). Four patients in the PPCM-Std group died versus 1 patient in the PPCM-BR group. There was no significant difference between prolactin levels in the two groups either at baseline or at 6 months. No thromboembolic events were reported. There was no difference in outcome between the children of PPCM-BR vs PPCM-Std patients.

Table 1

	PPCM-BR*		PPCM-Std*		p value†
	Baseline	6 months	Baseline	6 months*	
EF, %	28±9	58±11	28±9	26±11	0.006
Mitral ERO, cm^2	0.45±0.13	0.11±0.03	0.44±0.18	0.34±0.18	0.02
TDI E' medial, m/sec	7.0±1.3	12.4±2.4	6.5±1.1	7.3±2.5	0.04
TDI E' lateral, m/sec	7.2±1.1	12.4±2.5	6.6±1.0	7.3±2.5	0.02

*Value = mean ± 1 SD. †Comparing PPCM-BR to PPCM-Std.

Conclusions: The addition of bromocriptine to standard heart failure therapy improved LV systolic and diastolic function as well as survival in patients with newly diagnosed PPCM. No detrimental effect on the children that could not be breastfed was observed in this cohort.

342 Survival of 644 consecutive patients with severe HOCM after transcoronary ablation of septal hypertrophy (TASH). A single centre experience

T. Lawrenz, C. Leuner, M. Bartelsmeier, M. Schloesser, F. Lieder, C. Stellbrink, H. Kuhn. *Stadt Kliniken Bielefeld, Bielefeld, Germany*

Background: Catheter-based treatment of patients with hypertrophic obstructive cardiomyopathy (HOCM) by alcohol ablation (transcoronary ablation of septal hypertrophy, TASH) leads to symptomatic and hemodynamic improvement. The prognosis after TASH has only been reported in small series of patients so far.
Methods: All patients who underwent TASH at our institution between 1995 and 2005 were included in the follow-up study (n=644, age: 58±15 years). The first 329 patients were contacted by telefone call and in the remaining 315 patients we retrospectively assessed the survival using the latest hospital stay at our clinic.
Results: We were able to complete a 99.2% follow-up (mean follow-up time 1.4 years). 33 patients (5%) had died. Annual all cause mortality was 3.2%, total in-hospital mortality 1.2% in all patients (8 of 644 patients, 6 of them with severe comorbidity) and 0.4% in low risk patients. Annual cardiac mortality after hospital discharge was 0.7% (6 patients, all with sudden death). In the first series of patients who were treated between 1995 and 2001 the in-hospital mortality was higher (6/329 = 1.8%) compared to the patients treated after 2001 with an in-hospital mortality of only 0.6% (2/315). Independent predictors of death were age, atrial fibrillation and an ethanol dosage used for TASH > 2.0 ml.
Conclusion: These data represent the largest available database on survival after alcohol septal ablation of HOCM from a single centre. The in-hospital mortality has become very low with increasing experience. Mainly the reduction of the ethanol dosage below 2.0 ml appears to be important to improve the safety of the procedure in the acute phase and during follow-up. Prognosis after TASH is excellent and comparable to patients with HNCM. Longer follow-up time would be desirable for definite evaluation of this relatively new therapeutic option in the management of HOCM.

343 Enzyme replacement therapy delays the onset of cardiac involvement in Fabry disease

V. Serra, L. Perez De Isla, A. Calli, J. Paniagua, V. Valverde, A. Ribera, J. Herrera, J. Zamorano. *Hospital Clinico San Carlos, Madrid, Spain*

Cardiac involvement, including progressive cardiomyopathy, is very common sign in Fabry disease and is a leading cause of premature mortality. We sought to determine if tissue Doppler imaging (TDI) could identify Fabry disease patients at risk for the development of cardiomyopathy and if enzyme replacement therapy with agalsidase alpha might slow or prevent the progression of cardiac involvement.
Methods: Fabry disease patients were enrolled in this prospective, observational study. Echocardiography was performed at baseline and periodically throughout the study to determine left ventricular mass (LVM) and TDI velocities. A single investigator blinded to both the type of assessment (baseline or follow-up) and enzyme replacement status of the patient, evaluated all echocardiograms.
Results: Seventy-six patients (26 male, 50 females) were enrolled in the study. Twenty men and 13 women were treated with agalsidase alpha during the study. At baseline, increasing interventricular septum thickness was significantly associated with decreasing TDI velocities. Twenty-nine older than 18 years old patients (23 females) had no evidence of cardiac involvement at baseline (normal LVM and normal TDI velocities). In this cohort, 80% (16 out of 20) of patients not on ERT progressed to demonstrating an abnormal TDI velocity during follow-up,

whereas only 33% (3 out of 9) of patients on ERT progressed to TDI abnormalities (P=0.031).
Conclusions: In Fabry disease, reduced TDI velocity is the initial sign of cardiac involvement which occurs before the development of cardiac hypertrophy. Enzyme replacement therapy with agalsidase alpha delays the onset of cardiac involvement and should be considered at an earlier stage of the disease, even in the absence of left ventricular hypertrophy.

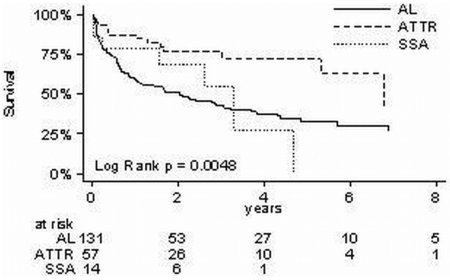
344 The systemic cardiac amyloidoses: disease profiles and clinical courses of the three main etiologic forms

C.C. Quarta[1], L. Riva[1], S. Perlini[2], S. Longhi[1], P. Ciliberti[1], M.L. Fonte[2], G. Galati[1], E. Biagini[1], G.P. Merlini[2], C. Rapezzi[1]. [1]*Azienda Ospedaliera S. Orsola Malpighi, Bologna, Italy;* [2]*Istituto S.Matteo, Pavia, Italy*

Purpose: Systemic cardiac amyloidosis (CA) is often considered a single entity. We assessed diagnostic/clinical profiles in primary (AL), hereditary transthyretin-related (ATTR) and systemic senile amyloidosis (SSA).
Methods: We conducted a retrospective multicenter cohort study of 233 patients with clear-cut etiological diagnosis of CA based on data pooled from two large Italian centers. In addition to diagnostic ECG and echocardiographic findings, hemodynamic data were available from one of the two centers.
Results: The table summarizes baseline characteristics. The figure reports survival in terms of freedom from major cardiac events (MACE). AL patients showed greater hemodynamic impairment. ATTR and SSA patients had better outcomes than AL patients.

Baseline instrumental characteristics

	AL (n=157)	ATTR (n=61)	SSA (n=15)	P value
Low QRS voltage, n/N (%)	88/146 (60)	15/60 (25)	6 (40)	0.0001
Left bundle branch block, n/N (%)	6/146 (4)	4/60 (7)	6 (40)	0.0001
Voltage/mass ratio	0.9±0.5	1.1±0.5	1.97±0.5	0.0001
Diastolic interventricular septum thickness (mm)	15.8±2.8	16.6±3.8	19.7±4.1	0.0001
LV ejection fraction (%)	52.5±13.1	58±13	44.2±15.4	0.0001
Mean RA pressure (mm Hg)	9.3±5.6 (n=43)	6.3±5.3 (n=38)	6.3±4.4 (n=12)	0.006
Mean PCWP (mm Hg)	18.2±8.3 (n=43)	13±7.9 (n=38)	16.2±6.5 (n=12)	0.006
Cardiac index (L/min/m^2)	2.5±0.7 (n=43)	2.7±0.6 (n=38)	2.3±0.4 (n=12)	0.03



Freedom from MACE by subtype

Conclusions: AL, ATTR and SSA should be considered three different cardiac diseases, characterized by different pathophysiological substrates and courses.

345 Clinical outcome in patients with hypertrophic cardiomyopathy and implantable cardioverter defibrillator therapy

C. Schukro, R. Rosenhek, T. Pezawas, G. Stix, J. Kastner, M. Wolzt, H. Schmidinger. *Medical University of Vienna, Vienna, Austria*

Purpose: Hypertrophic cardiomyopathy (HCM) is associated with an increased risk of sudden cardiac death (SCD) or syncope caused by ventricular tachyarrhythmia. Thus, implantable cardioverter defibrillators (ICD) became the main therapeutic option for high risk patients with HCM. The purpose was to investigate the outcome of ICD therapy in this collective.
Methods: We followed overall 264 patients with HCM during the last 18 years. In this collective, 28 patients (17 male (60%); age at implantation: 41.6±16.0 years; 15 with outflow tract obstruction (53%); 10 with atrial fibrillation or atrial flutter (36%)) were treated with an ICD for at least one major risk factor: SCD survival, documented ventricular tachycardia (VT), unexplained syncope, or family history of SCD. In case of severe left ventricular hypertrophy (thickness of septal wall >30mm), patients initially were treated with percutaneous alcohol septal ablation. Previous to availability of guidelines, electrophysiological studies were performed for risk stratification in 9 patients.
Results: Indications for ICD implantation were SCD survival (50%), documented VT (18%), family history (14%), inducible VT (11%), and syncope (7%). Mean ICD follow-up period was 62.3±55.8 months. Appropriate defibrillation was documented in 2 patients (7%), and appropriate anti-tachycardic pacing (ATP) in 3 further patients (11%). There was no predominant risk factor for ventricular tachyarrhythmia, and no difference was found between obstructive and non-obstructive HCM. Inappropriate shocks were found in 8 patients (29%), two of them also had inappropriate ATP. Causes of inappropriate ICD therapies were atrial fibrillation (62.5%), T-wave oversensing (25%), and lead dysfunction (12.5%). Finally, all-cause mortality was 14%: causes of death were acute heart failure in 2 patients, as well as stroke and hospital-acquired pneumonia in one patient, respectively.
Conclusions: Patients with HCM do benefit from ICD implantation, but less frequently than anticipated. The problem of inappropriate ICD therapies with further risk for arrhythmia induction is still of major concern, with atrial fibrillation being the major cause.

346 Clinical management and therapeutic strategies in patients with tako- tsubo- cardiomyopathy: results of the German tako- tsubo registry

B. Schneider[1], A. Athanasiadis[2], W. Pistner[3], R. Schamberger[4], W. Toepel[5], R. Schoeller[6], U. Gottwald[7], B. Gerecke[8], J. Schwab[9], U. Sechtem[2]. [1]*Klinik fuer Kardiologie, Sana Kliniken, Luebeck, Germany;* [2]*Abteilung fuer Kardiologie und Pulmologie, Robert Bosch Krankenhaus, Stuttgart, Germany;* [3]*Medizinische Klinik I, Klinikum Aschaffenburg, Aschaffenburg, Germany;* [4]*Herz- und Gefäßklinik, Bad Neustadt/Saale, Germany;* [5]*Klinikum Idar- Oberstein, Idar- Oberstein, Germany;* [6]*DRK Kliniken Berlin Westend, Berlin, Germany;* [7]*Allgemeines Krankenhaus Celle, Celle, Germany;* [8]*Klinikum der Stadt Wolfsburg, Wolfsburg, Germany;* [9]*Klinikum Nuernberg Sued, Nuernberg, Germany*

Background: Tako-tsubo cardiomyopathy (TTC) has increasingly been recognized all over the world. Most studies, however, comprise relatively few patients. A TTC registry has, therefore, been initiated in Germany by the ALKK. So far no trial data are available to guide the treatment of TTC patients.
This study evaluated clinical management and therapeutic strategies in patients of the German TTC registry.
Methods: Until November 2008, 297 patients from 37 hospitals were included according to the following criteria: 1) acute chest symptoms, 2) ischemic ECG changes, 3) reversible left ventricular akinesia not corresponding to a single coronary artery territory, 4) absence of significant coronary artery stenoses. Clinical management and acute as well as long-term treatment was assessed.
Results: Of 297 TTC patients (age 68±12 years), 269 were female (91%), 28 male (9%). Main symptoms were angina (72%), dyspnea (16%), and syncope (3%), 2% of patients were resuscitated or in cardiogenic shock. A triggering event preceding TTC onset was present in 77% (emotional stress 36%, physical stress 31%, both 10%). Patients were admitted to the hospital by an emergency team with physician (44%), general practioner (24%), ambulance without physician (13%) or by directly contacting the emergency room (12%). In 6% TTC developed during hospitalization for another disease. The initial clinical diagnosis was ST-elevation myocardial infarction (48%), non-ST-elevation myocardial infarction (39%) or pulmonary embolism (1%); 12% were admitted with other diagnoses. Time from symptom onset to hospital admission was 6.5±6.8 hours (STEMI 6.4±6.7, NSTEMI 7.1±7 hours). Concordant with the diagnosis of an acute coronary syndrome, 69% of patients were transferred to the intensive care unit. The acute medication could be evaluated in 162 patients and included heparin (91%), aspirin (90%, combined with clopidogrel in 38%), beta-blocker (61%), nitroglycerine (46%), ACE-inhibitor (34%) and diuretics (30%). Catecholamines or an intraaortic balloon pump were necessary in 5% and 1% of patients, respectively. The medication at discharge was known in 191 patients and included aspirin or clopidogrel (70%), beta-blocker (74%), ACE-Inhibitor (77%) and calcium-antagonist (19%). Nine patients (3%) died during the acute course, 8 had a recurrence during f/u.
Conclusion: In this large registry, 87% of TTC patients get an initial diagnosis of an acute coronary syndrome. They are treated accordingly by monitoring in the intensive care unit, cardiac catheterisation and medications corresponding to the guidelines for STEMI and NSTEMI.

MOLECULAR AND CELLULAR DRIVERS OF ATHEROSCLEROTIC PLAQUE REMODELLING

377 Deficient phosphorylation of p27 in serine 10 is associated with human atherosclerosis and aggravates disease progression in hypercholesterolemic mice

J.J. Fuster[1], H. Gonzalez-Navarro[1], A. Vinue[1], M.A. Ibanez[1], K.I. Nakayama[2], K. Nakayama[3], C. Rodriguez[4], J. Martinez-Gonzalez[4], V. Andres[1]. [1]*Instituto de Biomedicina de Valencia (CSIC), Valencia, Spain;* [2]*Medical Institute of Bioregulation - Kyushu University, Fukuoka, Japan;* [3]*Tohoku University Graduate School of Medicine, Miyagi, Japan;* [4]*Centro de Investigación Cardiovascular (CSIC-ICCC), Barcelona, Spain*

Background and purpose: The tumor suppressor p27 protects against atherosclerosis in the mouse, however the molecular mechanisms regulating its function in the arterial wall remain poorly characterized. It is well established that p27 protein levels are mostly regulated by post-translational modifications which modulate its degradation via the ubiquitin-proteasome pathway. Phosphorylation of p27 at Serine 10 (S10) modulates these processes in different tissues. In this

study, we investigated the role of p27-S10 phosphorylation on p27 stability in the arterial wall and atherosclerosis development.
Methods: Human arterial specimens were analyzed by Western blot. We generated apoE-null mice harboring a non-phosphorylatable S10A mutation in p27 (apoE-/-p27S10A) and apoE-/- controls to analyze atherosclerosis development and lesion characteristics, including macrophage, vascular smooth muscle cell (VSMC) and collagen content, and cell proliferation. Peritoneal and bone marrow-derived macrophages (BMDM) were obtained to analyze acetylated LDL uptake, foam cell formation and cytokine production.
Results: Immunoblot analysis demonstrates markedly lower levels of phospho-S10-p27 in human atherosclerotic coronary arteries versus non-atherosclerotic internal mammary arteries. Consistently, apoE-/-p27S10A mice have reduced levels of p27 in the aorta and accelerated atherosclerosis compared to apoE-/- controls, both when fed standard chow or high-fat diet, without affecting neointimal macrophage, VSMC or collagen content. Strikingly, similar arterial cell proliferation is observed in advanced atheromas of both groups of mice. We also find that apoE-/-p27S10A mice have a higher percentage of foam cells in peritoneal macrophage populations in vivo, and this correlates with increased acetylated-LDL uptake in vitro. Additionally, apoE-/-p27S10A BMDM exhibit increased LPS-induced expression of the proatherogenic cytokine MCP1.
Conclusions: Defective phosphorylation of p27 in S10 is associated with human atherosclerosis and accelerates disease progression in hypercholesterolemic apoE-/- mice, thus highlighting an atheroprotective role of phospho-S10-p27. This antiatherogenic action, which does not correlate with reduced arterial cell proliferation in advanced atheromas, might be related to a novel function of p27 as a key regulator of macrophage function and foam cell formation.

378 Endogenous SIRT1 protects against atherosclerosis by decreasing macrophage infiltration and foam cell formation

M.A.S. Stein[1], C. Lohmann[1], N. Schaefer[1], L. Rohrer[2], A. Breitenstein[1], J. Boren[3], F.C. Tanner[1], T.F. Luescher[1], C.M. Matter[1]. *[1]Inst. of Physiology, University of Zurich-Irchel, Zurich, Switzerland; [2]University Hospital Zurich, Zurich, Switzerland; [3]Sahlgrenska University Hospital, Gothenburg, Sweden*

Background: Atherosclerosis is a chronic inflammatory disease evolving from activated endothelial cells recruiting monocytes that infiltrate the arterial wall as proinflammatory macrophages. Upon uptake of oxidized low-density lipoproteins (oxLDL) via scavenger receptors such as lectin-like oxLDL receptor-1 (Lox-1), they become foam cells, thereby promoting plaque growth. SIRT1 is a class III deacetylase that mediates the effects of caloric restriction on lifespan and metabolic pathways. The role of endogenous SIRT1 on atherosclerosis remains unknown.
Methods: We compared 20-week old ApoE-/- SIRT1+/+ with ApoE-/- SIRT1+/- mice that were kept on a high-cholesterol diet for 12 weeks. Immunohistochemical analyses were done to quantify lipid content and the expression of inflammatory molecules in aortic plaques. Total plasma cholesterol and lipid subfractions were quantified. Peritoneal-elicited macrophages were used for in vitro foam cell studies. In addition, human aortic endothelial cells (HAECs) and RAW macrophages were treated with the SIRT1 inhibitor splitomicin to verify our in vivo findings.
Results: We show that decreased endogenous SIRT1 expression enhances plaque formation. We observed no difference in total cholesterol and its subfractions between ApoE-/- SIRT1+/+ and ApoE-/- SIRT1+/-. Furthermore, ApoE-/- SIRT1+/- have more macrophages and T cells in their plaques than ApoE-/- SIRT1+/+ mice, as well as a higher expression of the inflammatory molecules ICAM-1, VCAM-1 and P-Selectin. Moreover, peritoneal-elicited macrophages from heterozygous mice accumulate increased modified low-density lipoproteins. In vitro, we show that these SIRT1-dependent effects are mediated via NF-κB inhibition: in HAECs SIRT1 inhibits NF-κB activity and diminishes expression of adhesion molecules; in macrophages the inhibitory effect reduces expression of Lox-1.
Conclusions: Our in vivo and in vitro findings show protective effects of SIRT1 on atherosclerotic plaque formation. Given the availability of specific SIRT1-activating drugs, pharmacological activation of SIRT1 may become an attractive anti-atherogenic strategy.

379 Toll-like receptor-2 mediates inflammation and matrix degradation in human atherosclerosis

C. Monaco, S.M. Gregan, T.J. Navin, B.M.J. Foxwell, A.H. Davies, M. Feldmann. *Imperial College London, London, United Kingdom*

Purpose: Toll-like receptors (TLRs), key players in innate immunity, are upregulated in atherosclerotic lesions but their functional role in human atherosclerosis is unknown. We explored the effects of blocking TLR-2, -4 and myeloid differentiation factor 88 (MyD88), a signaling adaptor shared by most TLRs and interleukin-1 receptor (IL-1R), in an in vitro model of human atherosclerosis.
Methods: Carotid endarterectomies were obtained from patients with symptomatic carotid disease. Cells were isolated via enzymatic tissue dissociation and immediately cultured. This complex mixture represented by macrophages, lymphocytes and smooth muscle cells, displays production of pro-inflammatory cytokines, chemokines and matrix metalloproteinases in the absence of extrinsic stimuli. Adenoviral gene transfer was used to target intracellular signaling adaptors MyD88 and Trif-related adaptor molecule (TRAM), while commercially available neutralising antibodies were used for blocking TLR-2 and TLR-4.
Results: Overexpression of a dominant-negative form of MyD88 in atheroma cell cultures through adenoviral gene transfer (AdMyd88DN) decreased the production of monocyte chemotactic protein-1 (MCP-1/CCL2; P=0.015), IL-8/CXCL8 (P=0.002), IL-6 (P=0.001), matrix metalloproteinase-1 (MMP-1; P=0.016), and MMP-3 (P=0.0001), as well as nuclear factor kappaB (NFkappaB) activation (P=0.0001). IL-1R antagonist, TLR-4 blocking antibodies, or overexpression of a dominant negative form of the TLR-4 signaling adaptor TRAM reduced NFkappaB activity, but did not have a broad impact on the production of the mediators studied. In contrast, TLR-2 neutralizing antibodies inhibited NFkappaB activation (P=0.025), and significantly reduced MCP-1/CCL2 (P=0.0001), IL-8/CXCL8 (P=0.007), IL-6 (P=0.0001), and MMP-1, -2, -3, -9 production (P=0.0001).
Conclusions: Our data indicate that TLR-2 signaling through MyD88, but not IL-1 nor TLR-4, mediates inflammation and matrix degradation in human atherosclerosis. TLR-2 blockade may represent a therapeutic strategy for atherosclerosis and its complications.

380 Bone marrow derived progenitor cells in murine atherosclerotic calcification

C. Heeger, E.M. Ehlers, Z. Aherrahrou, J. Erdmann, H. Schunkert, L.C. Doehring. *University of Luebeck, Medical Clinic II, Luebeck, Germany*

Objective: Recent studies demonstrate that vascular calcification is not a passive precipitation but rather an actively regulated process, similar to embryonic osteogenesis. In this process chondrocyte metaplasia, performed by chondrocyte-like cells, plays a decisive role. These cells present a morphological similarity to chondrocytes and the ability to express cartilage typical proteins such as collagen-II. The origin of these cells has remained unknown. Three hypotheses have been postulated: local pericytes from the tunica adventitia, VSMC from the tunica media or progenitor cells derived from bone marrow.
Material and Methods: Sublethally irradiated C57BL/6 LDLr-/- mice received bone marrow from ROSA-26 mice, which ubiquitously express the bacterial enzyme β-galactosidase. This enzyme marks bone marrow derived cells. Mice were fed a high-fat diet and aortic freeze thaw injury of the infrarenal aorta was performed to induce selective vascular calcification. 1, 3, 14 and 56 days after injury, infrarenal and aorta ascendens specimens were examined employing histological (Oil-Red O and calcein) and immunhistological (β-galactosidase-/MOMA-II-collagen-II double marking) methods. Sections were analyzed by using fluorescence confocal laser-scanning microscopy.
Results: Early plaques of both infrarenal and aorta ascendens displayed a homogenous structure with 88.57% (±6.88%) macrophages (Moma-II) and 83.13% (±7.05%) β-galactosidase positive cells without evidence of collagen-II. 56 days after freeze-thaw injury both infrarenal and aorta ascendens specimens (n=7) displayed distinct intimal atherosclerotic calcification. Advanced plaques yielded a narrow luminal zone with concentrated cell numbers (22.70 per 10000μm^2 (±4.09%) containing collagen-II (44.10% (±6.20%)), Moma-II (12.24% (±6.41%)) and β-galactosidase (63.33% (±11.30%)) positive cells. 87.4% (±3.3%) of the chondrocyte-like cells were co-stained positive for β-galactosidase. The chimera-analysis revealed a mean of 88.0% (±1.4%) of β-galactosidase positive cells in blood specimens.
Conclusions: Here we present evidence that chondrocyte-like cells in atherosclerotic intimal calcification emerge in more advanced plaques. They originate from bone marrow while migrating actively into the calcifying plaque.

381 A subset of non-foam macrophages expressing myeloid-related protein 8 and 14 is associated with rupture-prone plaque phenotype

G.M. Ionita, A. Vink, P. Van Der Kraak, P. Van Den Borne, G. Pasterkamp, D.P.V. De Kleijn. *University Medical Center Utrecht, Utrecht, Netherlands*

Purpose: The presence of macrophages in atherosclerotic plaques has been documented for a long time. The concept of distinct morphological and functional subpopulations of plaque macrophages, however, is just emerging. Previous studies showed a gradual change in macrophage phenotypic expression pattern, which coincides with different stages of atherosclerosis. Myeloid related protein (MRP) 8 and 14 are expressed by subset of blood monocytes and macrophages in different tissues, including atherosclerotic plaques. However, the relation between Mrp-macrophage subset and plaque phenotype is unknown. For this, we assessed expression of Mrp-macrophage subset in a large number (90) of human carotid plaques.
Methods: A set of 90 human carotid endarterectomy specimens was used for immunohistological analysis. Phenotype of each plaque was assessed and recorded as stable or rupture-prone. Consecutive sections of the 90 carotid plaques were stained for CD68 (a pan-macrophage marker), Mrp-8 and Mrp-14. The CD68 staining and the Mrp-8 staining were quantified using image-analyzing software and reported as a ratio between the percentage of Mrp-8 positive area and the percentage of non-foam CD68 area.
Results: Macrophage staining of Mrp-8 and Mrp-14 was detected in a subset

of non-foam CD68-positive macrophages. We selected only the non-foam CD68-positive macrophage areas for quantitative analysis; areas rich in macrophage foam cells were excluded from the analysis. Within non-foam CD68-positive macrophage areas, the percentage of Mrp-8 positive macrophages is significantly higher in rupture-prone (n=57, mean 33.5±3.7%) than in stable lesions (n=33, mean 9.5±3.5%) ($p<0.001$). Concomitant, the Mrp-8 macrophage subset associates with characteristics of rupture-prone plaques: larger lipid core ($p<0.001$), less collagen amount (p=0.041) and less smooth muscle cells (p=0.004). Interestingly, Mrp-8 macrophage subset showed a positive correlation with interleukin (IL)-8 plaque levels (p=0.012); Mrp-8 and Mrp-14 are known stimuli for IL-8 production in the lung, therefore amplifying inflammation.

Conclusions: We show that Mrp-8 and Mrp-14 are expressed by subset of plaque macrophages without a foamy-phenotype. Moreover, this macrophage subset expressing Mrp-8 and Mrp-14 is strongly associated with histological characteristics of rupture-prone plaques. The association of Mrp-8 and -14 subset with high levels of IL-8 suggests a role for this subset in amplifying inflammation in plaque.

382 Progenitor cell mobilization is FGF-2 dependant and results in the activation of osteoclasts

M. Steinmetz[1], B. Pelster[1], V. Fontaine[2], J.F. Arnal[2], G. Nickenig[1], N. Werner[1]. *[1]Universitaetsklinikum Bonn, Bonn, Germany; [2]CHU de Toulouse - Hopital de Rangueil, Toulouse, France*

Background: Fibroblast growth factor-2 (FGF2) regulates proliferation of bone marrow (BM) stromal cells and has pro-angiogenic effects regulating endothelial cell growth, migration, and reendothelialization. We have previously demonstrated that estrogen-mediated endothelial progenitor cell (EPC) mobilization from BM into peripheral blood is inhibited in FGF2 knock-out (-/-) mice indicating a central role of medullary FGF2 in progenitor cell mobilization. Here we determine the underlying molecular mechanisms of FGF2-dependent statin-mediated progenitor cell mobilization.

Methods and Results: To determine the molecular mechanisms of FGF2-mediated progenitor cell mobilization, FGF2-/- and wild type (wt) mice were treated with the HMG-CoA reductase-inhibitor atorvastatin (10mg/kg body weight s.c. per day) and placebo. In contrast to wt mice, the number of Sca1/flk-1 positive EPC in peripheral blood (flow cytometry) of atorvastatin treated FGF2-/- mice did not increase. This was due to an accumulation of Sca1/flk-1 positive cells within the BM. Inhibition of EPC mobilization in FGF2-/- mice was associated with a delay in reendothelialization in a mouse model of a focal endothelial cell denudation and a severe reduction in neoangiogenesis despite statin treatment. BM transplantation experiments demonstrated that reconstitution of FGF2-/- mice with wt stem cells completely restored statin-mediated EPC mobilization while wt mice reconstituted with FGF2-/- stem cells developed a severe mobilization defect associated with an impaired endothelial dependent vasorelaxation (organ chamber) and enhanced neointima formation. In wt mice, statin treatment was associated with an increased number of activated osteoclasts compared to placebo treated mice which are known to play a pivotal role in stem cell mobilization. Treatment with osteoclast-activating RANKL induced an effective mobilization of Sca1/flk1 and Sca1/CD117 positive progenitor cells and enhanced the number of early outgrowth EPC.

Conclusion: Medullary FGF2 is essential in the statin-mediated mobilization of EPC from BM into peripheral blood while it seems not to influence EPC proliferation. The severe mobilization defect in FGF2-/- mice is associated with a significant impairment of vascular endothelial function and repair which underlines the importance of EPC in endothelial cell regeneration. First results indicate that a reduction in the number and activation status of osteoclasts may account for the impairment in EPC mobilization.

STRESS AT THE SURFACE: RISK FACTORS FOR ENDOTHELIAL DYSFUNCTION

384 Genetic deletion of JunD enhances age-related endothelial dysfunction

E. Osto[1], G. Coppolino[1], B. Mateescu[2], A. Akhmedov[1], T. Malinski[3], R. Kubant[3], F. Mechta-Grigoriou[2], C. Matter[1], T.F. Luescher[1], F. Cosentino[1]. *[1]Department of Cardiology, University Hospital and Cardiovascular Research, Institute of Physiology, Zürich, Switzerland; [2]Institut Curie, 26 Rue d'Ulm, Paris, France and Inserm U830, Stress and Cancer, Paris, France; [3]Department of Biochemistry, Ohio University, Athens,Ohio, United States of America*

Purpose: Enhanced production of reactive oxygen species (ROS) is the major determinant of age-related endothelial dysfunction. JunD, a member of the AP-1 family of transcription factors, regulates genes involved in antioxidant defense. The present study was design to investigate whether JunD deficient mice (JunD-/-) are more prone to age-related endothelial dysfunction in comparison to age-matched wild type (WT) mice.

Methods: Thoracic aortic rings from young (3 months old), middle aged (6 months old) and old (22 months old) male JunD-/- and WT mice were suspended for isometric tension recording. Endothelium-dependent relaxation to acetylcholine (Ach, 10^{-9}–10^{-6} mol/L)) was assessed after submaximal contraction with norepinephrine (10^{-6} mol/L). Calcium ionophore stimulated nitric oxide (NO), superoxide anion (O2-) and peroxynitrite (ONOO-) were measured with electrochemical nanosensors placed near the surface (5±2 μm) of a single endothelial cell.

Results: The age-associated impairment of endothelium-dependent relaxations to acetylcholine (Ach, 10-9-10-6 mol/L) was significantly enhanced in JunD-/- as compared to age-matched WT. Maximal relaxations were 55±5 vs 78±4% at 6 months and 39±3 vs 50±2% at 22 months for JunD-/- and WT mice, respectively (n=6-8, $p<0.05$ vs age-matched group). Endothelium-independent relaxations to sodium nitroprusside (10-10-10-5 mol/L) did not differ in JunD-/- and WT of different age groups (n=6-8, p=NS). Age-induced decrease of NO production was higher in JunD-/- as compared with WT (475±32 vs 350±28 nmol/L and 358±26 vs 220±23 nmol/L for 6 and 22 months old WT and JunD-/-, respectively; n=3-5, $p<0.05$ vs age-matched group). Accordingly, O2- and ONOO- generation increased with age in WT and more significantly in JunD-/- mice (O2-, 67±6 vs 103±8 nmol/L and 116±9 vs 210±16 nmol/L; ONOO-, 224±17 vs 319±22 nmol/L and 313±21 vs 492±29 nmol/L for 6 and 22 months old WT and JunD-/-, respectively; n= 3-5, $p<0.05$ vs age-matched group). Furthermore, the blunted relaxations to Ach observed in JunD-/- mice were restored by free radical scavengers superoxide dismutase (SOD) (150 U/ml) and catalase (1200 U/ml).

Conclusion: Our results show that JunD protects against vascular oxidative stress providing new insights into the pathophysiology of age-associated endothelial dysfunction.

385 Guanylyl cyclase activation using HMR1766 improves endothelial function and reduces platelet activation in congestive heart failure

A. Schaefer, D. Fraccarollo, G. Ertl, J. Bauersachs. *University of Wuerzburg, Wuerzburg, Germany*

Background: Endothelial dysfunction and platelet activation are part of the cardiovascular phenotype of severe congestive heart failure (CHF). An association between reduced endothelium-dependent NO-bioavailability and platelet activation has been described in experimental CHF.

We investigated, whether chronic activation of soluble guanylyl cyclase using HMR1766 increases vascular NO-bioavailability and reduces platelet activation in experimental CHF.

Methods and results: Chronic myocardial infarction was induced in male Wistar rats by coronary ligation. Rats were randomised to placebo or HMR1766 (10mg/kg twice daily). After 10 weeks, haemodynamics were measured and endothelial function was assessed in organ bath studies. Only animals were included in the CHF groups, when left-ventricular infarct size was >45% and left-ventricular end-diastolic pressure was >15 mmHg. Endothelium-dependent, acetylcholine-induced and NO-mediated relaxation of the aorta was significantly attenuated in CHF-Placebo compared to Sham-operated rats (Rmax: Sham 83.9±1.4%, CHF-Placebo 56.9±5.9%, $p<0.01$) and markedly improved in CHF-HMR1766 (Rmax 75.4±4.6% $p<0.01$ vs. CHF-Placebo). Basal NO-bioavailability in vivo was determined by the extent of phosphorylation of vasodilator-stimulated phosphoprotein (VASP) in platelets from whole blood fixed in formaldehyde immediately following collection. Platelet in vivo-VASP phosphorylation was attenuated in CHF-Placebo compared to Sham animals (mean fluorescence intensity: Sham 16.4±1.0%, CHF-Placebo 13.4±0.3%, $p<0.05$), and normalised by HMR1766 treatment (17.1±1.2% $p<0.05$ vs. CHF-Placebo). Activation of circulating platelets was determined measuring P-selectin surface-expression on platelets by flow-cytometry. P-selectin surface-expression was significantly increased in CHF-Placebo (mean fluorescence intensity: Sham 14.2±0.4%, CHF-Placebo 16.0±0.4%, $p<0.05$) and reduced following treatment with HMR1766 (14.5±0.3% $p<0.05$ vs. CHF-Placebo).

Conclusion: Chronic guanylyl cyclase activation using HMR1766 significantly improved endothelial function, enhanced systemic NO-bioavailability and reduced platelet activation in CHF rats.

386 Relationship of resistin levels with urinary albumin excretion in essential hypertensive subjects: introducing a novel index of diffuse vascular damage

C. Tsioufis, M. Selima, K. Dimitriadis, D. Tsiachris, E. Andrikou, A. Gennadi, A. Miliou, A. Kasiakogias, C. Stefanadis. *First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece*

Purpose: Evidence suggests that resistin, a recently described hormone, is associated with the atherosclerotic process, while urinary albumin excretion constitutes a marker of vascular dysfunction and increased cardiovascular risk. In this study we investigated the relationships of urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR) with resistin in essential hypertensive subjects.

Methods: Our population consisted of 80 newly diagnosed untreated non-diabetic females with stage I to II essential hypertension [mean age=54 years, office blood pressure (BP)= 159/101]. According to the ACR values determined as the mean of two non-consecutive morning spot urine samples, the study population was divided into microalbuminurics (n=22) (mean ACR=30-300 mg/g) and normoalbuminurics (n=58) (mean ACR<30 mg/g). Moreover, in all patients a ve-

nous blood sampling was performed for estimation of metabolic profile and resistin concentrations.
Results: Microalbuminurics compared to normoalbuminurics had higher 24-h systolic BP (140±7 vs 133±11 mmHg, p<0.05), while did not differ regarding age, smoking status and metabolic profile (p=NS for all). Furthermore, microalbuminurics compared to normoalbuminurics exhibited higher resistin levels (8.45±5.37 vs 4.4±1.37 ng/ml). In the total population, resistin exhibited a positive association with body mass index (r=0.369, p=0.001), 24-h systolic BP (r=0.244, p<0.05) and ACR (r=0.544, p<0.0001. Multiple regression analysis revealed that resistin (b=0.868, p<0.0001), 24-h diastolic BP (b=0.173, p<0.05), waist to hip ratio (b=0.514, p<0.0001), body mass index (b=0.516, p<0.0001) and age (b=0.263, p=0.008) were independent predictors of ACR. By analysis of covariance it was revealed that resistin values were significantly different between microalbuminurics and normoalbuminurics after adjustment for confounders (p<0.05).
Conclusions: Microalbuminuria in essential hypertension is accompanied by increased resistin levels, confirming the integrative role of urinary albumin excretion in the estimation of vascular status. Moreover, these findings suggest that resistin and ACR are interrelated and contribute in tandem to the progression of the hypertensive atherosclerotic disease.

387 Mechanisms leading to impaired endothelial-protective properties of high density lipoprotein (HDL) in patients with stable coronary disease and an acute coronary syndrome: Role of paraoxonase activity

C. Besler, K. Heinrich, K. Yonekawa, C. Doerries, E. Holy, C. Manes, F.C. Tanner, A. Von Eckardstein, T.F. Luscher, U. Landmesser. *University Hospital Zurich, Zurich, Switzerland*

Background: HDL is intensely evaluated as a potential novel therapeutic target in patients with stable coronary disease (sCAD) or an acute coronary syndrome (ACS). However, recent results suggest that HDL from these patients loses endothelial-protective effects, such as stimulation of endothelial nitric oxide (NO) production. In the present study we have therefore examined mechanisms leading to impaired endothelial-protective effects of HDL in CAD patients.
Methods: HDL was isolated from patients with sCAD or ACS and healthy subjects (HS; n=20-25) by sequential ultracentrifugation. HDL's effect on endothelial signaling pathways leading to endothelial NO synthase (eNOS) activation were examined, i.e. Akt and eNOS Ser1177-phosphorylation and eNOS Thr495-dephosphorylation. Endothelial cell superoxide (O2-) production in response to HDL was analysed by electron spin resonance spectroscopy. HDL's PON activity and content were measured. The impact of specific PON inhibition by hydroxyquinoline on HDL's endothelial effects, i.e. stimulation of NO production and NO-dependent vasodilation, O2- production and anti-inflammatory properties, were characterized.
Results: HDL from HS stimulated Akt and eNOS Ser1177-phosphorylation and a rapid eNOS Thr495-dephosphorylation, whereas HDL from sCAD and ACS patients had no such effects. Endothelial O2- production was not increased by HDL from sCAD and ACS patients, suggesting that HDL in CAD patients does not increase NO inactivation by O2-.
PON activity was reduced, whereas PON1 content was increased in HDL from sCAD and ACS patients as compared to HS, suggesting marked PON inactivation in CAD patients. PON inhibition in HDL from HS impaired the capacity to promote Akt and eNOS Ser1177-phosphorylation or eNOS Thr495-dephosphorylation. PON inhibition impaired stimulation of endothelial NO production and NO-dependent vasodilation by HDL from HS. Notably, both eNOS siRNA knockdown and PON inhibition also reversed HDL's beneficial effects on endothelial inflammatory activation.
Conclusion: The present study demonstrates for the first time that the impaired capacity of HDL from patients with CAD to exert beneficial endothelial effects relates, at least in part, to a loss of the capacity to stimulate signaling events leading to eNOS activation, and is not due to increased NO inactivation by O2-. Our findings suggest that inactivation of HDL-associated PON is a major mechanism leading to the loss of HDL's endothelial protective effects in CAD patients. These findings may have important implications for the understanding of HDL dysfunction and development of novel HDL-targeted therapies.

388 Identification of miRNAs responsive to the glucose stress

F. Patella[1], A. Mercatanti[2], L. Pitto[2], G. Rainaldi[2]. *[1]Scuola Superiore Sant'Anna, Pisa, Italy; [2]CNR Istituto di Fisiologia Clinica, Pisa, Italy*

It is already known that high glucose concentration in culture medium affects the angiogenic properties of HUVEC. A current concept is that the RNA interference plays a role in angiogenesis. Mediators of RNA interference are miRNAs, a class of endogenous 22-25nt single-stranded RNA molecules that regulate gene expression post-transcriptionally.
Purpose: To investigate whether miRNAs are involved in the glucose-induced metabolic stress.
Methods: We cultured HUVEC in 30mM glucose-containing medium for three days. At day 3, the fraction of BrdU-incorporating cells, tube formation (Fig. 1b-1c) and cell motility, peculiar of the angiogenic response, were measured. At molecular level, the miRNA expression profiles of HUVEC after 3 days growth in medium containing 5 mM (G-5) or 30mM (G-30) glucose was determined.
Results: Following the glucose stress, tube formation (Fig. 1d), cell proliferation and cell motility were reduced. The miRNA microarray analysis revealed that 13 miRNAs were over-expressed and 1 miRNA was under-expressed in G-30 cells. Among over-expressed miRNAs a subset of miRNAs was selected and demonstrated to form a regulatory circuitry (Fig. 1a). The transfection of these miRNAs in exponentially growing HUVEC reduced the tube number similarly to high glucose (Fig. 1d).

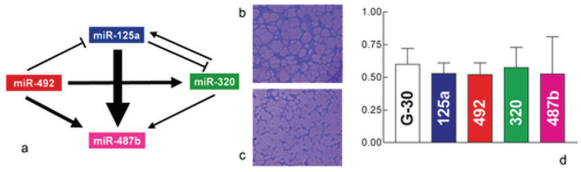


Figure 1

Conclusion: This work demonstrates that high glucose modifies the miRNA expression profiles of HUVEC and that miRNAs identified as glucose responsive belongs to the same regulatory circuitry. In addition to that, it has been found the transfection of each glucose-responsive miRNA is able to reduce the tube formation ability of HUVEC similarly to G-30. We speculate that the dysregulation of glucose-responsive miRNAs is sensed by cells as a signal to activate the same gene expression network activated by high glucose alone.

389 Systemic endothelial dysfunction in normotensive offspring of preeclampsia

S.F. Rimoldi[1], C. Sartori[2], S. Garcin[2], M. Villena[3], U. Scherrer[2], Y. Allemann[1]. *[1]Swiss Cardiovascular Center Bern, University Hospital Bern, Bern, Switzerland; [2]Department of Internal Medicine, CHUV, Lausanne, Switzerland; [3]Instituto Bolivano de Biologia de Altura, La Paz, Bolivia*

Objectives: Epidemiological studies suggest that adverse events in utero are associated with cardiovascular disease in adulthood, but the mechanisms are not known. Hypoxia associated with high-altitude exposure may facilitate the detection of vascular dysfunction. Recently, it has been suggested that offspring of mothers having suffered from preeclampsia are predisposed to hypertension, but the underlying mechanism is not clear. We hypothesized that young normotensive offspring of preeclampsia display systemic vascular dysfunction, and speculated that high-altitude exposure may facilitate the detection of this problem.
Methods: We, therefore, assessed endothelium-dependent (flow-mediated vasodilation, FMD) and -independent (glycerin trinitrate, 250 μg) vasodilation, vascular stiffness (pulse wave velocity, PWV), and central arterial blood pressure (applanation tonometry) in 15 healthy normotensive offspring of preeclampsia (mean±SD age, 14±7 y) who were born at term, and 16 matched control subjects. All subjects were born and permanently living at high altitude (3600 m).
Results: The major new finding was that young, normotensive offspring of preeclampsia displayed systemic endothelial dysfunction, as evidenced by a roughly 25 percent smaller FMD (6.4±1.0 vs. 8.1±1.3%, P=0.0007) than in controls. In contrast, arterial stiffness (PWV, 7.8±1.0 vs. 8.0±1.6 m/s) and endothelium-independent vasodilation (16.4±2.7 vs. 15.8±3.6%) were comparable in offspring of preeclampsia and controls. The endothelial dysfunction in the offspring of preeclampsia was not related to a difference in the central arterial blood pressure (systolic 97±7 vs. 96±8, diastolic 76±7 vs. 74±5 mm Hg, offspring vs. controls) or arterial oxygen saturation (91.6±2.1 vs. 90.5±2.0%).
Conclusions: We provide the very first evidence that endothelial function in young normotensive offspring of preeclampsia is abnormal, whereas arterial stiffness and endothelium-independent vasodilation are still normal. We speculate that as in other populations at risk, endothelial dysfunction represents a very early step in the development of arterial hypertension and cardiovascular disease later in life. To detect this early vascular dysfunction, the measurement of FMD is more sensitive than the assessment of PWV.

MOLECULAR IMAGING: FROM BENCH TO BEDSIDE

390 Large vessel inflammation detected by 11C-PK 11195 PET/CT

F. Pugliese[1], F. Lamare[1], J.C. Mason[2], R. Hinz[3], A. Kinderlerer[2], M. Pickering[2], O.E. Rimoldi[1], P.G. Camici[1]. *[1]MRC Clinical Sciences Centre, Imperial College London, London, United Kingdom; [2]Imperial College London, London, United Kingdom; [3]The University of Manchester, Manchester, United Kingdom*

Purpose: To image arterial inflammation using PET/CT with 11C-PK 11195 which binds to the peripheral benzodiazepine receptor highly expressed in macrophages infiltrating the vessel wall.
Methods: 11C-PK 11195 uptake in the ascending aorta and arch was measured in 11 patients (aged 51±16 years, 10 females) with systemic lupus erythematosus

(n=7), Takaysu's arteritis (n=2) or giant cell arteritis (n=2). 11C-PK 11195 (6.85 MBq/kg) was injected and a 60 min PET dynamic emission acquired in list mode followed by CT angiography. OSEM-reconstructed PET images were inspected for 11C-PK 11195 uptake. To quantify tracer uptake in the vessel wall, regions of interest (ROI) were drawn on cross sections of the ascending aorta and arch and average count densities and time activity curves (TAC) were computed.
Results: Eight patients were on steroids and long term anti-inflammatory drugs and had normal C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white cell count (WCC). At PET imaging, these patients demonstrated no uptake of 11C-PK 11195 in the aorta. In the remaining 3 patients, ESR was increased (range 21-52 mm/h) (active disease) and 2 patients also had high WCC (18,000/L and 11,000/L, respectively) while CRP was increased in 1 patient (35 mg/L). In these patients, 11C-PK 11195 uptake was visually detected and the TAC in the aortic wall peaked at 106±65.2 kilo-count per second (kcps) (Figure). In patients with inactive disease, the corresponding value was 42.1±16.2 kcps. In one patient suffering from giant cell arteritis, temporal biopsy confirmed active granulomatous vasculitis with macrophage infiltration.

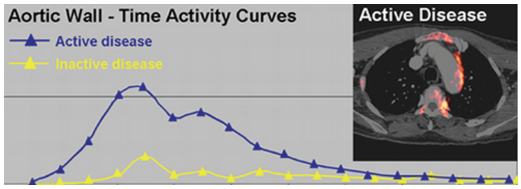


Figure 1

Conclusions: Imaging of macrophage infiltration in large arteries using 11C-PK 11195 PET/CT is clinically feasible. This ligand can be used as a marker of inflammation in large vessels.

391 Detection of inflammatory activity in patients with takayasu's arteritis by Positron Emission Tomography (PET)

E. Alexanderson, A. Ricalde, M.E. Soto, J.M. Ochoa, A. Meave, P. Reyes. *Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico*

Background: Takayasu's arteritis (TA) is a chronic inflammatory disease. Established diagnostic criteria have high sensitivity and specificity, however detection of inflammatory activity (IA) remains a diagnostic challenge because 40% of active patients with no clinical criteria of IA (CCA) are active in histopathologic studies. With 18F-FDG PET it is possible to detect IA in large vessels, so it might be helpful to detect IA in a more specific way and in the follow up of the treatment.
Methods: 35 patients with TA were enrolled. Clinical evaluation of IA using actual criteria was done, 5 or more points were considered as active. PET FDG uptake was analyzed using the standard uptake value (SUV) defined as a tissue activity concentration divided by the total activity injected per body weight. SUV <1.2 was considered as inactive while higher values were considered as active. Active patients received specific treatment. Follow up was done by a second clinical and PET assessment applying the IA criteria at different times (3rd, 6th or 9th month). Correlation between CCA and PET was evaluated. Correlation between both forms of analysis of IA was analyzed.
Results: 34 female and 1 male with mean age 31±11 were studied, 15 had clinical and PET criteria (SUV >1.2) for IA, 1 patient had CCA but no PET criteria and 9 had PET criteria but no CCA. The last 10 patients were negative in CCA and PET. Correlation between PET and CCA decreases during the follow up due to negativity in the clinical criteria meanwhile PET remained positive (table 1).

Table 1. Correlation between PET and CCA

	PIA in PET & CCA	PIA in PET & NIA in CCA	NIA in PET &PIA in CCA	NIA in PET & CCA	Correlation
Basal	33%	28%	6%	33%	0.66
3rd month	33%	67%	0%	0.0%	0.33
6th month	13%	50%	0%	38%	0.50
9th month	0.0%	64%	7%	29%	0.29
Means	20%	52%	3%	25%	0.45

PIA, Positive inflammatory activity; NIA, negative inflammatory activity.

Conclusions: 18F-FDG PET detects inflammatory activity in patients who appear to be clinically inactive. Findings in PET seem to correlate with the findings of pathologic studies reported in literature. Probably PET could identify activity even in patients that do not fulfill CCA, therefore PET could help to establish the adequate time that treatment should be given.

392 Peri-coronary adipose tissue inflammation affects coronary atherosclerosis in patients with stable angina

T. Mazurek, M. Kobylecka, J. Kochman, K. Filipiak, L. Krolicki, G. Opolski on behalf of WG23 - Pathogenesis of Atherosclerosis. *Medical University of Warsaw, Warsaw, Poland*

Background: Extravascular expression of inflammatory mediators may adversely influence coronary lesion formation and plaque stability through outside-to-inside signaling. It has been also shown, that maximal standardized uptake value (SUV) of fluorodeoxyglucose (FDG) detected by positron emission tomography is proportional to macrophage density. Accordingly, we examined peri-coronary adipose tissue (PAT) inflammatory activity using FDG-PET/CT in patients with stable coronary artery disease (CAD) and in controls.
Methods: 12 consecutive, non-diabetic patients with angiographicaly confirmed CAD underwent FDG-PET/CT. SUV was measured in subcutaneous fat (SC), visceral thoracic fat (VS), epicardial fat over right ventricle (EPI), and in fat surrounding three main coronary arteries on the sections corresponding to proximal segments (RCA, LCX, LAD, respectively). Similar measurements of SUV were taken in a group of healthy volunteers matched for age and BMI (n=10). In the group of CAD patients, associations of SUV with gender, age, body mass index (BMI), serum glucose, were further analyzed. Extent of CAD was determined measuring % stenosis using QCA in segments corresponding to PET/CT sections.
Results: The SUV surrounding all three main coronary arteries (PAT SUV) in CAD patients was significantly greater than SUV in other fat locations for both CAD patients and controls (SC: 0.21; VS: 0.40; EPI: 0.39; RCA SUV: 0.65; LCX SUV: 0.90; LAD SUV: 0.87; $p<0.001$).
When divided into CAD vs. control, PAT SUV was significantly greater in CAD patients than in the control group (RCA SUV: 0.86 vs 0.50; $p<0.005$; LCX SUV: 1.34 vs 0.58, $p<0.005$, LAD SUV: 1.23 vs 0.59, $p<0.005$, respectively), while there was no significant difference in SUV in other fat locations. PAT SUV was not related to gender, age, BMI, or serum glucose. Finally, PAT SUV was positively related to % stenosis of respective coronary artery (RCA: 0.82; $p<0.001$; LCX 0.60; $p<0.005$; LAD 0.50; $p< 0.05$, respectively).
Conclusions: 1. Inflammatory activity of peri-coronary adipose tissue reflected by SUV is greater than in subcutaneous, visceral thoracic, or epicardial tissue; 2. SUV in PAT is higher in CAD patients, than in non-CAD controls; 3. PAT SUV correlates with the extent of the disease. In conclusion, the greater pro-inflammatory activity of PAT in patients with CAD compared to healthy controls may contribute to plaque formation, vessel narrowing and plaque rupture, supporting the hypothesis of the outside-to-inside signaling;

393 Molecular Imaging of neoangiogenesis within atherosclerotic plaque with radiolabeled single chain VEGF and RGD peptides

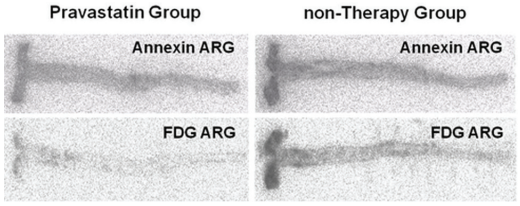
S. Ohshima[1], N. Tahara[1], S. Fujimoto[1], S. Tsimikas[2], F.D. Kolodgie[3], R. Virmani[3], J.M. Backer[4], F.G. Blankenberg[5], A. Petrov[1], J. Narula[1]. *[1]University of California, Irvine, Irvine, United States of America; [2]University of California, San Diego, La Jolla, United States of America; [3]CVPath, Gaithersburg, United States of America; [4]SibTech, Inc., Brookfield, United States of America; [5]Stanford University, Stanford, United States of America*

Purpose: Neointimal neovascularization within atherosclerotic plaque contributes to RBC leak, hemorrhage, expansion of necrotic core, and hence plaque vulnerability. Increased expressions of VEGF, VEGF receptor, and $\alpha v\beta 3$ integrins in neoangiogenic vasculature are closely associated with neoangiogenic process. We used 99mTc – labeled single chained VEGF (VegF) and RGD imaging peptide direct against $\alpha v\beta 3$ integrin (RIP) for noninvasive imaging of neoangiogenesis in experimentally induced aortic atherosclerotic lesion.
Methods: 14 NZW rabbits and 2 Watanabe heritable hyperlipidemic (WHHL) rabbits were used for non invasive imaging with VegF, and 17 NZW rabbits with RGD. In VegF group, 5 NZW rabbits had balloon-dedndothelialized (B) atherosclerotic lesions in abdominal aorta followed by 4mo high fat, high cholesterol (CD) diet (VegF-B-Chol), 6 non-dedendothelialized NZW rabits with 1year CD diet (VegF-CD), and 3 unmanipulated with normal diet (ND) used as control (VegF-ND). WHHL rabbits received CD for 2 years (VegF-WHHL). Similarly, in RIP group, 6 had B lesions and received CD (RIP-B-CD), 6 unmanipulated with CD (RIP-CD), and 5 unmanipulated with normal diet (RIP-con). Four hours after intravenous administration of VegF and RIP, micro SPECT-CT imaging was performed for evaluation of in vivo tracer uptake in abdominal atherosclerotic lesion. After in vivo imaging, aortas were explanted for ex vivo imaging and gamma counted for determination of % injected dose per gram (%ID/g), followed by histopathologic characterization.
Results: The uptake in abdominal aorta was clearly visualized non-invasively in all VegF-B-CD and RGD-B-CD rabbits. The %ID/g of VegF in VegF-B-CD rabbits (0.045±0.019%) was siginificantly higher than VegF-WHHL (0.027±0.011%), VegF-CD (0.016±0.010%) and VegF-con (0.009±0.003%). The %ID/g of RIP in RIP-B-CD rabbits (0.066±0.029%) was siginificantly higher than RIP-CD (0.030±0.010%) and RIP-con (0.027±0.010%).
Conclusions: This study demonstrated a feasibility for non-invasive molecular imaging of neoangiogenesis within atherosclerotic plaque using VegF and RIP.

394 The feasibility of Tc-99m Annexin A5 to evaluate the anti-atherosclerotic therapy by HMG-CoA reductase inhibitor pravastatin in cholesterol-fed rabbits: comparative study with F18-FDG

T. Doue[1], K. Ohtsuki[2], M. Ueda[3], K. Ogawa[4], A. Azuma[5], H. Saji[6], H.W. Strauss[7], H. Matsubara[8]. *[1]Meiji University of Integrative Medicine, Nantan, Japan; [2]Kameoka Hospital, Kameoka, Japan; [3]Kyoto University Hospital, Kyoto, Japan; [4]Kanazawa University, Kanazawa, Japan; [5]Yokaichi National Hospital, Shiga, Japan; [6]Kyoto University, Kyoto, Japan; [7]Sloan-kettering cancer research center, New York, United States of America; [8]Kyoto Prefectural University of Medicine, Kyoto, Japan*

Purpose: This study assessed the feasibility of Tc-99m Annexin A5 (Tc-An) to evaluate the anti-atherosclerotic therapy and compared the ability of Tc-An with that of F18-FDG (FDG) in cholesterol-fed rabbits.
Methods: Ten rabbits were maintained on a high-cholesterol diet [non-Therapy (nT) group, 1 died] and the other ten on both a high-cholesterol diet and pravastatin (P group) for 8 weeks. Ten rabbits (nT=5, P=5) were injected with Tc-An, while 9 rabbits (nT=4, P=5) with FDG. At 1 hr after the injection, ascending thoracic aorta (ATA), descending thoracic aorta (DTA) and abdominal aorta (AA) were removed for autoradiography, radioactivity-assay, and comparison between autoradiograhy and histology.
Results: In nT group, both Tc-An and FDG accumulated intensely in plaque lesions of ATA and moderately in lesions of DTA and AA. In P group, faint accumulation of Tc-An and FDG were shown in ATA, and plaque lesions could hardly be observed in DTA and AA (Figure). The photostimulated luminescence (PSL/mm^2) and radioactivity in lesions of ATA, and comparison of PSL/mm^2 with stained cell density were shown in table.



	Tc-99m AnV (left nT, right P group)		F18-FDG (left nT, right P group)	
PSL/mm^2 (Autoradiography)	33.0±5.6	7.6±0.7*	24.5±3.0	3.4±0.4*
Radioactivity PSL/mm^2 vs cell count in histology	3.92±0.52 ×10^5	1.77±0.27×10^5** R=0.673#	7.08±1.32 ×10^3	1.01±0.35×10^3* R=0.82#

*p<0.0001 vs non-treated, **p=0.0009 vs non-treated, #p<0.0001.

Conclusion: Tc-An may have an ability to evaluate the reduction of atherosclerotic lesions by pravastatin, which might be comparable to that of FDG.

395 Thermal heterogeneity in atherosclerotic vascular disease. An experimental study with microwave thermography

K. Toutouzas[1], A. Synetos[1], M. Drakopoulou[1], E. Tsiamis[1], A. Karanasos[1], A. Michelongona[1], H. Grassos[2], E. Stefanadi[1], C. Stefanadis[1]. *[1]Hippokration General Hospital of Athens, Athens, Greece; [2]West Attica's Prefecture General Hospital "Agia Varvara", Athens, Greece*

Purpose: Intravascular thermography (IVT) is the only method currently available, which can be used to measure heat generation from atheromatic plaques indicating local inflammation. Thermal heterogeneity of the atheromatic plaque has been correlated with mophological characteristics of the culprit lesion in patients with coronary artery disease. Microwave radiometry (MR) is a new noninvasive method. We investigated whether thermal heterogeneity measured by MR is corellated with IVT findings in an experimental model of atherosclerotic disease.
Method: Microwave radiometry (RTM-01-RES system) was applied noninvasively in 15 atherosclerotic segments of the aorta (3 segments, 5cm long in 5 rabbits) that were clearly separated from each other, as well as in 15 control segments. Microwave radiometry measures natural electromagnetic radiation from the internal tissues at microwave frequencies. The intensity of the radiation is proportional to the temperature of tissue; therefore, MR allows measuring of the internal temperature of tissue. The system consists of an internal temperature sensor with the antenna, a skin temperature sensor and the data processing unit. The accuracy of measuring the internal temperature of the device is ±0.2°C and the depth of temperature detection is 1-7 cm depending on the water content of the body. Thereafter, IVT was performed in the same segments. For both techniques temperature difference (ΔT) was calculated by subtracting the mean temperature of proximal healthy vessel wall from the maximal temperature of each segment.
Results: Thermal heterogeneity was detected by both methods in the rabbits with the high atherogenic diet. Microwave radiometry detected that ΔT of the atherosclerotic aortas was significantly higher compared to the ΔT of the controls (0.78±0.27°C versus 0.24±0.11°C, p<0.001). These findings were confirmed by the measurements acquired by IVT. Mean temperature difference was 0.07±0.01°C for the atherosclerotic aortas versus 0.02±0.01°C, (p<0.001) for the control group.The segments that had the highest ΔT were those that were recognized in angiography as having significant atheromatosis.
Conclusion: Microwave radiometry is the first non-invasive method for detection of local inflammatory activation in arterial segments in an experimental model. Further studies in humans should be performed for the evaluation of this method.

NOVEL APPROACHES IN NUCLEAR IMAGING

396 Long-term prognostic value of coronary flow reserve assessed with 13N-Ammonia PET

B.A. Herzog, L. Husmann, R.R. Buechel, I. Valenta, O. Gaemperli, I.A. Burger, P.T. Siegrist, C.A. Wyss, P.A. Kaufmann. *University Hospital Zurich, Zurich, Switzerland*

Purpose: To assess the predictive value of myocardial perfusion imaging with 13N-ammonia positron emission tomography (PET) and coronary flow reserve (CFR) on long-term prognosis in patients with suspected myocardial ischemia.
Methods: Perfusion and CFR was assessed in 256 patients using PET and 13N-ammonia. Follow-up was obtained successfully in 245 (96%) patients. Sixteen early revascularized patients were excluded. Finally 229 patients were assigned to normal versus abnormal perfusion or normal versus abnormal CFR (<2.0). Major adverse cardiac events (MACE; cardiac death, non-fatal myocardial infarction, late revascularization or hospitalization for cardiac reasons) were assessed using the Kaplan-Meier method. Cox proportional hazard regression was used to identify independent predictors for cardiac events.
Results: During a mean follow-up of 5.4±2.2 years 78 patients had at least one cardiac event including 29 cardiac deaths. Abnormal perfusion (n=130) was associated with a significantly higher incidence of MACE (P<0.001) and cardiac death (P<0.05). In patients with normal perfusion abnormal CFR was independently associated with a higher annual event rate over 3 years compared to normal CFR for MACE (1.3% versus 4.9%; P<0.05) and cardiac death (0.3% versus 2.9%; P<0.05). In abnormal perfusion predictive value of CFR was maintained to the end of follow-up.
Conclusions: Perfusion findings in 13N-ammonia PET and CFR are strong outcome predictors. CFR allows further risk stratification, suggesting a warranty period of 3 years if associated with normal perfusion.

397 Impact of ischemia, hibernation and scar on mortality in patients undergoing PET perfusion/viability studies

D. Verhaert, Y.M. Smyth, V. Menon, R. Brunken, A. Bhargava, P. Houghtaling, M. Cerqueira, W.A. Jaber. *Cleveland Clinic, Cleveland, United States of America*

Background: Assessing ischemia and viability by positron emission tomography with Rubidium and F-18-fluorodeoxyglucose (R/FDG PET) has been shown to identify patients who may benefit from revascularization. We sought to define prognostic determinants provided by an R/FDG PET study in a large group of consecutive patients undergoing this test.
Methods: Survival and freedom from heart transplantation were analyzed in 720 consecutive patients (70% male, mean age 62 years) referred to our center for an R/FDG PET study between March 2006 and October 2007. Patients were classified into 5 groups according to the result of their study: normal (n=178), ischemic (n=108), hibernation (n=49), scar (n=146) or mixture (all possible combinations of ischemia, scar and hibernation; n=239). The burden of ischemia, hibernation and scar was prospectively scored using the 17-segment model. The prognostic value of these scores was assessed along with revascularization data and other potential clinical predictors in a univariable and multivariable Cox proportional hazards model.
Results: During a mean follow-up of 600 days, 113 patients died and 9 underwent heart transplantation. R/FDG PET-derived ejection fraction (EF), scar burden and the amount of hibernation were the most powerful predictors of outcome (Table I), whereas ischemia in this population was not predictive even by univariable analysis (p=0.95).
Kaplan-Meier survival analysis showed better survival in patients without scar or hibernation.

Table I

Variable	Hazard Ratio	95% HR CL	Chi-Square	p-value
R/FDG PET derived EF	0.97	0.95 - 0.98	17.0	<0.0001
≥3 segments with scar	2.18	1.48 - 3.21	15.6	<0.0001
≥3 segments with hibernation	1.92	1.25 - 2.95	8.84	0.003
CABG after PET	0.59	0.36 - 0.99	3.97	0.046
Age	1.01	1.00 - 1.03	3.42	0.064
PCI after PET	0.97	0.61 - 1.55	0.01	0.91

95% HR CL = 95% Hazard Ratio confidence limits.

Conclusion: Poor left ventricular EF and large areas of scar or hibernation on Rubidium/FDG PET are associated with worse outcomes. Coronary artery bypass surgery but not percutaneous intervention appear to offer protection.

398 Phase 1 human safety, dosimetry, biodistribution, and rest-stress myocardial imaging characteristics of the new F-18 labeled BMS747158 myocardial perfusion PET tracer

J. Maddahi[1], F. Bengel[2], S. Huang[1], J. Czernin[1], J. Case[3], C. Schiepers[1], H. Schelbert[1], Q. Zhu[4], J. Lazewatsky[4], M. Phelps[1]. [1]*David Geffen School of Medicine at UCLA, Los Angeles, United States of America;* [2]*Johns Hopkins University, Baltimore, United States of America;* [3]*Mid America Heart Institute, Kansas City, United States of America;* [4]*Lantheus Medical Imaging, Billerica, United States of America*

Background: F-18 labeled BMS747158 is a novel myocardial perfusion imaging PET tracer that targets mitochondrial complex 1. In Phase 1 studies, human safety, dosimetry, biodistribution, and myocardial imaging characteristics of this tracer were evaluated.
Methods: 25 normal subjects were enrolled in 2 trials:13 subjects received 222 MBq intravenously at rest only and 12 more subjects received 94 MBq at rest and, on a second day, 124 MBq at peak pharmacologic coronary vasodilation with adenosine (Adeno, n=6) or at peak treadmill exercise (n=6). Physical examination, laboratory values, vital signs, ECG, and EEG were monitored pre- and post-injection. Myocardial (Myo), liver, blood pool and lung Standardized Uptake Values (SUV) were determined from sequential PET images over time. Mean dose for various organs and mean effective dose (in mSv/MBq) were estimated.
Results: There were no adverse events related to the tracer. The highest-dose organs were kidneys at rest and heart with Adeno and exercise. Mean effective dose was 0.019 at rest and with Adeno and 0.015 with exercise, all within the clinically acceptable range. Myo SUV's remained high and myo was viasualized clearly throughout the imaging time. Myo SUV was lower with exercise most likely due to higher skeletal muscle uptake. Myo/liver was highest with exercise, followed by Adeno and rest (Table). Myo/blood and Myo/lung were high and rapidly improved with time.

	10 mins	30 mins	60 mins	90 mins	149 mins
Rest Myo SUV	3.9±0.9	4.2±1.1	4.5±1.2	4.3±1.3	4.1±1.4
Rest Myo/liver	1.0±0.3	0.9±0.2	1.1±0.2	1.4±0.2	2.1±0.3
Adeno Myo SUV	10.5±1.5	10.8±2.1	10.3±2.1	9.6±2.1	8.4±2.1
Adeno Myo/liver	1.9±0.6	2.0±0.5	2.2±0.5	2.6±0.5	3.8±1.0
Exercise Myo SUV	6.2±2.1	5.5±1.0	5.1±0.9	4.9±0.9	4.5±0.8
Exercise Myo/liver	28.0±33.6	5.6±1.0	5.6±1.3	5.8±1.5	5.5±1.5

Conclusions: F-18 labeled BMS747158 appears to be clinically safe, has good dosimetry and myocardial imaging characteristics. This tracer has a unique potential for rest-stress myocardial perfusion PET imaging

399 Low-dose fast hybrid cardiac imaging: a breakthrough in non-invasive assessment of ischemic coronary artery disease

B.A. Herzog, L. Husmann, R.R. Buechel, I.A. Burger, O. Gaemperli, I. Valenta, C.A. Wyss, U. Landmesser, P.A. Kaufmann. *University Hospital Zurich, Zurich, Switzerland*

Purpose: To validate a new hybrid imaging method with low radiation dose for rapid non-invasive comprehensive assessment of ischemic coronary artery disease (CAD) combining prospective ECG-triggered CT coronary angiography (CTCA) and low-dose single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI).
Methods: Forty patients referred for elective invasive coronary angiography (CA) due to suspected CAD were prospectively enrolled to undergo a low-dose CTCA and a stress only SPECT-MPI scan administering half of the standard low-dose stress 99mTc-tetrofosmin activity. The latter was acquired immediately after adenosine stress (omitting the standard 45-90 min waiting time) and reconstructed with a new dedicated iterative algorithm for low count imaging. Decisions towards conservative management versus revascularization strategy based on hybrid imaging were compared to the decisions taken by the interventional operator in the catheterization laboratory based on CA. The latter served as standard of reference.
Results: For predicting coronary revascularization sensitivity, specificity, positive and negative predictive value and accuracy for hybrid imaging was 100%, 96.0%, 100%, 93.8% and 97.5%. The estimated mean effective radiation doses was significantly lower for hybrid imaging than for invasive CA (4.4±1.0mSv; 8.7±4.2mSv; $P<0.001$). Total protocol time was below 60min, comparing favourably to standard SPECT protocols.
Conclusions: Rapid cardiac hybrid imaging allows accurate prediction of invasive CA findings and of treatment decision despite minimized radiation dose.

400 The correlation between the Duke coronary artery disease prognostic index and stress myocardial SPECT

C. Shiba, T. Chikamori, H. Tanaka, Y. Igarashi, S. Hida, Y. Usui, T. Hatano, K. Hirose, Y. Ohtaki, A. Yamashina. *Tokyo Medical University, Tokyo, Japan*

Backgound: Although the Duke coronary artery disease (CAD) prognostic index derived from coronary angiogram has recently been implemented in the risk stratification, the relation between this index and stress SPECT is seldom evaluated.
Methods: Database of 620 patients with suspected or known CAD who underwent both stress SPECT and coronary angiography was evaluated. Coronary angiogram was evaluated by both conventional AHA criteria and the Duke scoring system. Stress myocardial SPECT was evaluated by a 20-segment model, and a summed stress score (SSS) and summed difference score (SDS) were calculated. The high-risk SPECT was defined as SSS>13 and/or SDS>8.
Results: The SSS and SDS correlated well with the Duke CAD prognostic index (r=0.462; $p<0.0001$ and r=0.334; $p<0.0001$) and the number of diseased vessels (r=0.419; $p<0.0001$, and r=0.281; $p<0.0001$). Left main (LM) or 3-vessel CAD were observed in 134 patients, whereas 168 patients were regarded as at high risk according to the Duke index. The high-risk SPECT showed 73% sensitivity and 64% specificity (chi-square=71.3) for detecting the high-risk subset of the Duke index and 69% sensitivity and 61% specificity (chi-square=37.5) for LM or 3-vessel CAD. When combined with non-perfusion parameters such as lung uptake of radiotracers and transient ischemic dilation, the multivariate analysis revealed that the combination of the high-risk SPECT and transient ischemic dilation best identified the high-risk Duke sebset (76% sensitivity, 63% specificity; $p<0.0001$, chi-square=123.6) and LM or 3-vessel CAD (72% sensitivity, 60% specificity; $p<0.0001$, chi-square=69.9)
Conclusion: The Duke CAD prognostic index correlates well with the findings of stress SPECT, and appears more applicable in clinical settings as compared with conventional AHA criteria.

401 Infarct size in primary angioplasty without on-site cardiac surgical backup versus transferal to a tertiary center: a single photon emission computed tomography study

V.A. Umans[1], P. Knaapen[2], M. De Mulder[1], F. Van Der Zant[1], J.H. Cornel[1]. [1]*Medical Center Alkmaar, Alkmaar, Netherlands;* [2]*VU University Medical Center, Amsterdam, Netherlands*

Background: Primary percutaneous coronary intervention (PCI) performed in large community hospitals without cardiac surgery back-up facilities (off-site) reduces door-to-balloon time compared with emergency transferal to tertiary interventional centers (on-site). The present study was performed to explore whether off-site PCI for acute myocardial infarction results in reduced infarct size.
Methods: 128 patients with acute ST-segment elevation myocardial infarction were randomly assigned to undergo primary PCI at the off-site center (n=68) or to transferal to an on-site center (n=60). Three days after PCI, 99mTc-sestamibi SPECT was performed to estimate infarct size.
Results: Off-site PCI significantly reduced door-to-balloon time compared with on-site PCI (94±54 versus 125±59 min, respectively, $p<0.01$), although symptoms-to-treatment time was only insignificantly reduced (257±211 versus 286±146 min, respectively, p=0.39). Infarct size was comparable between treatment centers (16±15 versus 14±12%, respectively p=0.35). Multivariate analysis revealed that TIMI 0/1 flow grade at initial coronary angiography (OR 3.125, 95% CI 1.17–8.33, p=0.023), anterior wall localization of the myocardial infarction (OR 3.44, 95% CI 1.38–8.55, $p<0.01$), and development of pathological Q-waves (OR 5.07, 95% CI 2.10–12.25, $p<0.01$) were independent predictors of an infarct size > 12%.
Conclusions: Off-site PCI reduces door-to-balloon time compared with transferal to a remote on-site interventional center but does not reduce infarct size. Instead, pre-PCI TIMI 0/1 flow, anterior wall infarct localization, and development of Q-waves are more important predictors of infarct size.

POSTER SESSION 1

MODERATED POSTERS 1
SPECIAL ELECTROPHYSIOLOGIC ACTIONS OF ANTIARRHYTHMIC AGENTS

P402 A unique modification of spiral wave reentry by bepridil: relating to ion channel blocking action and inhibition of calmodulin

H. Takanari[1], Y. Takemoto[1], S. Kato[1], Y.S. Ishiguro[1], M. Harada[1], Y. Okuno[1], H. Honjo[1], I. Sakuma[2], K. Kamiya[1], I. Kodama[1]. [1]*RIEM, Nagoya University, Nagoya, Japan;* [2]*Graduate School of Engineering, University of Tokyo, Tokyo, Japan*

Background: Spiral wave (SW) reentry is a major cause of cardiac tachyarrhythmias. Recent clinical studies suggest the efficacy of bepridil against atrial fibrillation and some kinds of ventricular arrhythmias. Bepridil has multiple molecular targets. Bepridil blocks ICa,L, IKr, IKs in low concentration and INa in high concentration. It is also reported that bepridil inhibit the calcium handling protein, calmodulin. But its antiarrhythmic mechanism still remains unclear. We hypothesize that bepridil destabilizes of SW dynamics through ion channel blocking action and inhibition of calmodulin.
Methods: Optical action potential signals were recorded from 2D ventricular myocardial layer of Langendorff-perfused rabbit hearts. Action potential duration

(APD) and conduction velocity (CV) were compared under constant pacing (at basic cycle length ranged from 150 to 800 ms). We also delivered subthreshold stimulus (STS) and the attenuation of membrane response to STS was calculated as space constant, index of intercellular electrical coupling. Ventricular tachycardia (VT) was induced by burst pacing and SW dynamics were assessed.
Results: Bepridil (1 μM) significantly prolonged APD (by 4.6%), increased CV (by 5.8%), and increased space constant (by 18.9%) (n=5). VTs induced in the presence of bepridil terminated earlier than those in control (VT lasting more than 100 seconds: 15/19 for control vs. 3/28 for bepridil). SWs induced in control hearts regularly circulated around the stable functional block line (FBL), whereas those with bepridil were characterized by long irregular FBLs and decremental conduction near the rotation center, resulting in drastic drift of reentrant circuit and its annihilation by collision with unexcitable anatomical boundaries.
Conclusion: Bepridil promotes early termination of SWs through increase in dynamic instability around the center of SWs. Such unique modification of SWs by bepridil in association with prolongation of APD and increase of intercellular electrical coupling may underlie its potent therapeutic potential against reentrant arrhythmias.

P403 Adenosine-resistance in patients receiving amiodaron

S. Nedios, M. Tang, G. Ye, J.-H. Gerds-Li, E. Fleck, C. Kriatselis.
Deutsches Herzzentrum Berlin, Berlin, Germany

Introduction: Adenosine is a substance with many applications in cardiology. It facilitates the differential diagnosis and therapy of paroxysmal supraventricular tachycardias, can be used for thalium-stress test and mediates preconditioning in myocardial ischemia.
Recently, a new imaging approach is used in pulmonary vein isolation (PVI) procedures: a rotational angiography (RTA) of the left atrium is performed after direct contrast-medium injection in the left atrium and during an adenosine-induced ventricular asystole. Three dimensional reconstruction of the left atrium and the pulmonary veins (PV) can be performed by a special software. We studied the effect of adenosine on the av nodal conduction in patients taking amiodaron vs patients taking no amiodarone (control group).
Methods: Fifty patients with indication for PVI were included in the study. A RTA was performed after an bolus adenosine dosis i.v.:30mg for <70kg Body Weight (BW), 40mg>70kg BW, on average 0,47 mg/kg. After the end of RTA right ventricular pacing was applied, until spontaneous recovery of the AV node conduction. We defined as length of the asystole, the time distance (in sec) between the last QRS complex and the first spontaneous QRS complex, after recovery of the av nodal conduction.
Results: There was generally a positive, but not linear correlation between adenosine dose and asystole duration. In the group of patients under amiodarone (n=16, adenosin 0,45 mg/kg KG) and in comparison with the control group without amiodarone (n=34, adenosin 0,47 mg/kg KG), there was a significantly shorter asystole (amiodaron-group 17,4±13,1 sec vs. control group 31,1±17,1 sec; p<0,001). There was no significant difference between the other subgroups of control group (i.e. patients without any av nodal affecting drugs and patients taking one or more av nodal blocking drugs).
Conclusion: Patients receiving amiodaron are characterized by adenosine resistance. The mechanism of this phaenomenon is not clear. It should be taken into consideration though, when adenosine is applied in patients with amiodarone therapy, for diagnostic or therapeutic purposes.

P404 Preferential use-dependent block of cardiac late sodium current by ranolazine

S. Rajamani[1], N. El-Bizri[1], J. Shryock[1], J. Makielski[2], L. Belardinelli[1].
[1]CV Therapeutics Inc, Palo Alto, United States of America; [2]University of Wisconsin-Madison, Madison, United States of America

The gain-of-function SCN5A type 3 long QT syndrome mutation, R1623Q, has been shown to generate enhanced late Na^+ current (INa). Ranolazine, an anti-ischemic agent, has been shown to preferentially block late INa than peak INa. However, it is not known if ranolazine block of late INa is use-dependent (UDB). To test this, ranolazine block of both peak and late INa was investigated using wild-type (WT) and R1623Q channels stably transfected in HEK293 cells. Tonic (0.1 Hz) and UDB (1, 2 and 5 Hz) of peak (WT and R1623Q) and late (R1623Q) INa were measured by whole-cell patch-clamp technique using 40 pulses of 50 msec in duration to -20 mV. Tonic and UDB of R1623Q late INa was measured as mean INa between 46 and 48 msec. The potencies of ranolazine to block WT and R1623Q are shown in the table. Effects of ranolazine on voltage-dependent activation and inactivation were measured for WT and R1623Q. Ranolazine (10 μM) caused a hyperpolarizing shift of the inactivation without affecting activation for WT and R1623Q, suggesting interaction of the drug with the inactivated states of channels. Recovery from inactivation (peak and late INa) was determined with a 1-sec conditioning pulse to -20 mV, followed by a 24 (peak INa) or 50msec (late INa) step to – 20 mV at variable recovery intervals. For recovery from inactivation of peak INa, ranolazine (30μM, n=4) caused a significant ($p<0.05$) slowing of the slow time constants of both channels. For recovery from inactivation of late INa in R1623Q, ranolazine (30 μM, n=4) caused a significant ($p<0.05$) change in the fraction of fast (from 0.49 to 0.28) and slow (from 0.44 to 0.59) components and the slow time constant (from 306 to 835msec, $p<0.05$). These results show that late INa is subject to UDB in the presence of ranolazine caused by slow recovery, and that UDB of late INa by ranolazine is 36 to 80 times that of UDB for peak INa.

Stimulating Frequency	IC_{50} values (μM)			Potency Ratio A÷C
	WT	R1623Q		
	Peak I_{Na} (A)	Peak I_{Na} (B)	Late I_{Na} (C)	
0.1 Hz	427±35	95±2	7.5±0.1	56.9
1 Hz	259±3	77±10	7.3±1.0	35.5
2 Hz	157±3	37±7	2.2±0.2	71.4
5 Hz	154±18	25±2	1.9±.01	81.0

P405 Electrophysiological effects of the potassium channel opener nicorandil in transgenic rabbits with long QT-syndrome 1

M. Brunner[1], J. Biermann[1], K. Wu[1], S. Asbach[1], M. Hartmann[1], G. Koren[2], X. Peng[3], C. Bode[1], M. Zehender[1]. *[1]Universitaetsklinikum Freiburg, Freiburg im Breisgau, Germany; [2]Brown University, Providence, United States of America; [3]Penn State University, Hershey, United States of America*

Introduction: Transgenic rabbits expressing pore mutants of the human gene KCNQ1 (KvLQT1-Y315S) display a Long QT-Syndrome 1 (LQT1) phenotype. We hypothesized that nicorandil, an opener of ATP-sensitive potassium channels, would hasten cardiac repolarization and shorten the action potential duration (APD75 and APD90) in LQT1.
Methods: Transgenic LQT1 New Zealand White rabbits (n=10-11) were compared to littermate controls (LMC, n=9-10). In vivo electrophysiological studies were performed using a 4F catheter in the right atrium and ventricle at baseline, after 200 mg/kg nicorandil (N) i.v. and during combined infusion of nicorandil and the β-agonist isoproterenol (NI). In vitro six simultaneous epicardial monophasic action potentials were recorded from Langendorff-perfused hearts, at baseline, during perfusion with N (20 mmol/l) and during combined infusion of NI.
Results: The ventricular effective refractory period (VERP at 240 ms ± SEM) at the base of the heart was prolonged in LQT1 compared with LMCs (LQT1_baseline 172.8±5.9 vs. LMC 151.6±2.8, $p<0.01$). NI, not N alone, decreased VERP at the base in LMC but not in LQT1 (LQT1_NI 171.8±6.5, LMC_NI 138.2±4.9). Sinus node recovery time was not influenced by N, but significantly decreased by NI in LQT1 and LMC, AV-Wenckebach cycle length was significantly shortened by NI only in LMC. The in vitro APD75 and APD90 of LQT1 were prolonged compared to LMC (e.g. APD75/APD90 at 210bpm: LMC_baseline 97.8±2.2/114.6±3.5, LQT1_baseline 109.1±2.1/131.1±3.4, $p<0.05$). N significantly decreased APD75 and APD90 in LQT1 and LMC at all stimulated heart rates (e.g. APD75/APD90 at 210 bpm: LMC_N 82.3±2.5/105.2±3.2; LQT1_N 88.4±1.8/107.4±2.0). After adding N the APD75 were still shorter in LMC, but the APD90 were no longer different between LMC and LQT1. Dispersion of repolarization, defined as the difference between shortest and longest of APD75 or of APD90, respectively at the six locations, was heart rate dependently decreased after N in LQT1 (at 210/240/270 bpm: 29.0±2.7, 26.4±2.9, 21.4±3.7 and 26.5±2.4, 22.9±1.8, 18.9±2.1, ANOVA $p<0.01$).
Conclusions: In conclusion, we demonstrated that N shortens the APD75 and APD90 in LQT1 and LMC significantly in vitro. After adding N the APD90 but not APD75, was no longer different between LMC and LQT1. Additionally, dispersion of repolarization of LQT1 was decreased by N with increasing heart rates.

P406 Cardioprotective effects of CYP-dependent omega-3 fatty acid metabolites

R. Fischer[1], C. Schmidt[2], M. Marcovic[2], G. Wallukat[2], M. Rothe[2], F.C. Luft[2], D. Muller[2], W.H. Schunck[2]. *[1]Charite - Campus Virchow-Klinikum, Berlin, Germany; [2]Max-Delbrueck-Centrum fuer Molekulare Medizin, Berlin, Germany*

Purpose: Fish oil omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) protect against arrhythmia and sudden cardiac death by so far largely unknown mechanisms. We found that EPA and DHA are efficiently epoxidized by various arachidonic acid (AA) metabolizing cytochrome P450 (CYP) isoforms to novel metabolites such as 17,18-epoxyeicosatetraenoic acid (17,18-EETeTr) and 19,20-epoxydocosapentaenoic acid (19,20-EDP). The present study was aimed at analyzing the in vivo formation of these metabolites and their potential role in mediating the cardioprotective and antiarrhythmic effects of diets rich in EPA and DHA.
Methods and Results: Double transgenic rats (dTGR) expressing the human renin and angiotensinogen genes develop severe angiotensin II-induced hypertension and end-organ damage and die suddenly. Nutritional supplementation with EPA- and DHA-ethylesters (2.5% Omacor oil in the pellet chow) resulted in a strong decrease of arrhythmia inducibility and sudden cardiac death. Moreover, EPA/DHA-feeding significantly decreased cardiac fibrosis, inflammatory cell infiltration and connexin (Cx)43 gap junction dyslocalisation. In contrast, cardiac hypertrophy and ANP-levels were not improved. The diet strongly influenced the cardiac CYP-eicosanoid profile as revealed by determining the levels of epoxides derived from AA (epoxyeicosatrienoic acids, EETs), EPA (EETeTrs) and DHA (EDPs) using liquid chromatography- tandem mass spectrometry. Upon EPA/DHA-feeding, the EET:EETeTr:EDP-ratio was shifted from 81:0.5:18.5 (nor-

mal chow poor in omega-3 fatty acids) to 39:14:47. Under these conditions, 17,18-EETeTr and 19,20-EDP were among the main endogenous epoxy-metabolites produced in the heart. Both metabolites mimicked the effects of EPA and DHA on isolated neonatal rat cardiomyocytes already at nanomolar concentrations: they reduced the spontaneous beating rate and prevented calcium-overload of theses cells.
Conclusion: EPA and DHA efficiently compete with AA for the conversion by CYP enzymes under in vitro and in vivo conditions. The resulting formation of 17,18-EETeTr and 19,20-EDP may contribute to the anti-arrhythmic effect of diets rich in omega-3 fatty acids. The mechanism may involve prevention of Ca-overload and Cx43 gap junction remodeling.

P407 Preoperative HMG-CoA reductase inhibitors and atrial fibrillation in patients undergoing CABG: a prospective randomised trial

G. Melina, E. Angeloni, G. Di Nucci, U. Benedetto, B. Fiorani, G. Sclafani, C. Comito, E. Tonelli, S. Refice, R. Sinatra. *Azienda Ospedaliera Sant'Andrea, Rome, Italy*

Purpose: To investigate whether preoperative HMG-CoA reductase inhibitors (statins) therapy reduce the incidence of atrial fibrillation following coronary artery bypass grafting (CABG).
Methods: Prospective randomised trial of 632 patients undergoing isolated CABG between January 2006 and December 2008. Patients with no history of AF were randomly assgned to receive either preoperative atorvastatin 40 mg daily (N=315) or placebo (N=317). A multivariate analysis including both preoperative, intraoperative and postoperative variables was conducted to find the best predictor of postoperative AF.
Results: Mean number of coronary arteries bypassed was 2.8±0.8 and 2.7±0.9, in statin versus control group, respectively (p=ns). The overall incidence of new-onset postoperative AF was 31.6% (200/632) without statistical difference between groups (94/315, 29.8%, versus 106/317, 33.4%, in statin and control group, respectively, p=ns). At multivariate analysis, statin therapy failed to show any beneficial effect on the incidence of new-onset AF (OR 1.06, 95% CI 0.81-1.46; p=ns). Hypertension (OR 2.91, 95% CI 1.08-7.2; p=0.034), preoperative medication with β-blockers (OR 0.61, 95% CI 0.38-0.93; p=0.033) and off-pump CABG (OR 0.44, 95% CI 0.21-0.93; p=0.033) were independently related to postoperative AF.
Conclusions: This prospective randomised trial shows that preoperative HMG-CoA reductase inhibitors therapy did not reduce the incidence of postoperative AF in patients undergoing CABG. Factors related to the occurence of post-CABG AF were hypertension and lack of preoperative β-blockers. In addition, patients who underwent off-pump CABG showed a significantly lower rate of postoperative AF.

P408 Effects of bepridil on stretch-induced arrhythmia in isolated chick ventricles

G. Iribe, H. Jin, K. Naruse. *Cardiovascular Physiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceuti, Okayama, Japan*

Purpose: It is well known that mechanical stimulus modulates electrophysiological properties of the heart. For instance, commotio cordis (fatal arrhythmia caused by a blunt precordial impact without structural damage) has been reported since 130 years ago. Bepridil is anti-arrhythmic drug with multiple pharmacological effects including inhibition of Na^+, K^+, and Ca^{2+} current. In this study, we investigated the effects of bepridil on diastolic left ventricular stretch-induced arrhythmia (SIA) in isolated chick ventricles.
Methods: Two week old chick heart was excised and Langendorff-perfused. A thin latex balloon was inserted into left ventricle (LV), and LV volume (LVV) was precisely regulated by computer-controlled rapid stepping motor. Initial LVV (Vi) was adjusted to set diastolic LV pressure (LVP) at 10 mmHg. After obtaining a stable and regular beating, a trapezoidal pulse (40 ms upstroke, 10 ms plateau, 40 ms downstroke) of LVV change (ΔV) was applied during diastolic phase to stretch LV wall. The ΔV was set to 20 (small), 40 (middle), and 60 (large) % of Vi, and probabilities of SIA calculated from 10 to 20 stretches were recorded, respectively.
Results: As the ΔV was increased, the probability of SIA increased (3.8±1.9, 24.0±4.8, and 81.5±11.9% for small, middle, and large ΔV, respectively, mean±SEM). The probability was significantly reduced by 1 μM bepridil with middle ΔV (26.7±6.7 to 11.5±0.4%, mean±SEM), while it did not affect probability with large ΔV. We have previously reported that a splicing variant of Ca^{2+}-regulated K^+ channels (SAKCA), cloned from cultured chick embryonic ventricular myocytes and human cDNA library, have stretch-sensitivity. We hypothesized that bepridil might affect SAKCA to modulate probability of SIA. To test this hypothesis, we examined the effects of bepridil on single SAKCA channel activity with inside-out configuration of the patch-clamp technique. Bepridil reduced open probability of the channel in a dose-dependent manner.
Conclusions: The present results suggest that bepridil reduces probability of SIA possibly via SAKCA-mediated mechanism in chick ventricle. Due to the multiple effects of bepridil on electrophysiology, involvement of the mechanisms mediated by other channels remains to be studied.

P409 Electrophysiological evaluation of novel blockers of If current

M. Del Lungo[1], M. Melchiorre[2], L. Sartiani[1], M. Biel[3], A. Varro[4], M.N. Romanelli[2], E. Cerbai[1]. *[1]CIMMBA, University of Florence, Florence, Italy; [2]Department of Pharmaceutical Sciences, University of Florence, Florence, Italy; [3]Department of Pharmacy and Pharmacology, University of Munich, Munich, Germany; [4]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary*

Purpose: In the sino-atrial node (SAN), a major role in the initiation and autonomic control of rhythm generation is played by f-current, a mixed sodium-potassium inward current activated upon hyperpolarization and directly modulated by cyclic nucleotides. If current is encoded by Hyperpolarization-activated Cyclic Nucleotide-gated sodium-potassium channel family genes (HCN1-4). In physiological condition HCN expression is functionally relevant in the SAN region and in other parts of the conduction system. f- current becomes upregulated in many cardiac disease at ventricular level contributing to the increased propensity for cardiac arrhythmias. Thus, selective f-channel blockers have a potential for therapeutic use as bradycardic and antiarrhythmic agents. Zatebradine and ivabradine act as f-channel blockers but both of them blocking the neuronal HCN isoforms. From this, the necessity to develop new compounds selective for the channel isoform typical of mammal SAN, HCN4.
Material and Methods: On the basis of zatebradine structure different analogues (C1-C5) were synthesized and were tested on HEK293 cells expressing mHCN1, mHCN2 and hHCN4 and on SAN cells of guinea-pig and rabbit by patch clamp tecnique.
Results: The compounds used for this study were tested for the first time on HEK293 cells expressing HCN1, HCN2 and HCN4 isoforms of f-channel and their activity was compared with that of ivabradine. All compounds (C1-C5) at the concentration of 10 μM, produced a reduction of maximal f-current amplitude, elicited by a step to -120 mV, although with different potency and selectivity as shown by their EC50 values. C1 and C4 were more potent on HCN1 (2.31±0.4 and 0.60±0.07 μM respectively) and C2 displayed a major activity on HCN4 (5.19±0.6 μM). C3 was more effective on HCN1 and HCN4 and C5, the enantiomer of C4, had a low activity on all isoforms. Current-voltage curves revealed that the effect of all compounds, including ivabradine, was concentration-dependent, did not reverse upon drug removal and did not change current properties. Data obtained in SAN cells suggest that the effects on native f-current resemble those obtained on HCN4 isoform, in line with the hypothesis that HCN4 represent a major contributor in SAN cells.
Conclusions: These findings indicate that the interaction with the different channel isoforms seems to have different structural requirements. Work is underway to clarify the structural requirements to improve the selectivity and to better characterize the pharmacological profile of these substances.

MODERATED POSTERS 2
HEART FAILURE: BENCH TO BEDSIDE

P411 Alpha-adrenergic stimulation decreases myocardial stiffness: a novel PKC mediated-effect

A.P. Fontes-Sousa, L. Lopes-Conceicao, N.S. Pereira-Goncalves, V.F. Monteiro-Cardoso, C. Bras-Silva, A.F. Leite-Moreira. *Faculdade Medicina do Porto, Porto, Portugal*

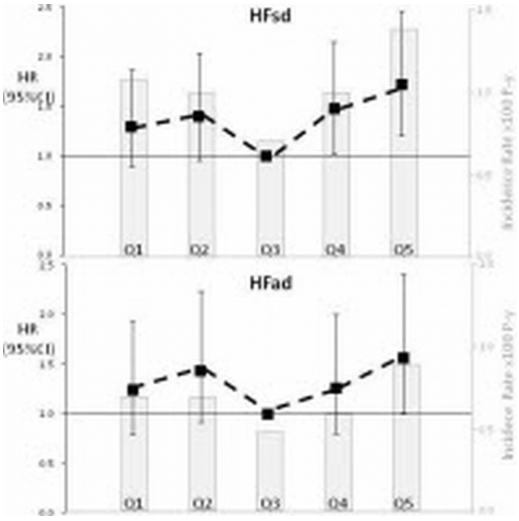
Purpose: Alpha1-adrenoceptor (AR) stimulation has an important role in the regulation of mammalian cardiac function under physiological and pathophysiological conditions. Recently, we have demonstrated that phenylephrine (PE), an alpha1-AR agonist acutely increases myocardial distensibility both in healthy animals and in the model of doxorubicin-induced heart failure. In the current study, we investigated the role of different signalling pathways involved in this effect.
Methods: The effects of the addition of increasing doses of PE (3.10-7-10-4M) were studied in papillary muscles (Krebs-Ringer: 1,8mM CaCl2, 35°C) of normal white New-Zealand rabbits with (i) intact endocardial endothelium (control group; n=12), (ii) damaged endocardial endothelium (EE) (n=7), or in the presence of (iii) NO synthase inhibitor, NG-Nitro-L-Arginine (L-NNA; 10-5 M; n=10), (iv) indomethacin (INDO, cyclooxygenase inhibitor; 10-5M; n=7), (v) prazosin (PRZ, alpha1- adrenergic antagonist; 10-6M; n=8), or (vi) PKC inhibitor, chelerythrine (CHE; 10-5M; n=13). Passive length-tension relations were constructed before and after a single concentration of PE (10-4M; n=7). Reported parameters include: active tension (AT; mN/mm^2), maximum velocities of tension rise and tension decline (dT/dtmax e dT/dtmin, respectively; $mN/mm^2/s$), passive tension (PT; mN/mm^2) and muscle length (L; L/Lmax). Only significant results are given, expressed as % change from baseline.
Results: PE induced concentration-dependent positive inotropic and lusitropic effects, with a maximal effect at 10-6M, promoting an increase of 138.3±22.8% AT, 149.7±26.3% dT/dtmax, and 117.4±21.6% dT/dtmin, effects that were abolished in the presence of PRZ. PE (10-4M) also promoted a significant increase of the muscular length of 1.012±0.002 L/Lmax, which corresponds to a 28±5% decrease of PT and represents a significant decrease of myocardial stiffness, also evident in the down and rightward shift of the passive length-tension relation. This latter effect was abolished in the presence of PKC inhibitor.
Conclusions: The present study demonstrated that PE promotes a decrease of

myocardial stiffness, modulated by the activation of PKC. These findings reinforce the importance of alpha1-adrenergic stimulation in the regulation of myocardial function, including diastolic function, which highlights its role as a potential powerful regulator of cardiac filling.

P412 A novel risk factor for heart failure development: uric acid

G. Levantesi[1], R.M. Marfisi[1], M.G. Franzosi[2], A.P. Maggioni[3], G.L. Nicolosi[4], C. Schweiger[5], M.G. Silletta[1], L. Tavazzi[6], G. Tognoni[1], R. Marchioli[1] on behalf of GISSI Prevenzione Investigators. *[1]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [2]The Mario Negri Institute for Pharmacological Research, Milan, Italy; [3]Associazione Nazionale Medici Cardiologi Ospedalieri Research Centre, Florence, Italy; [4]Azienda Ospedaliera S Maria Angeli, Pordenone, Italy; [5]Ospedale Civile, Passirana Di Rho, Italy; [6]Villa Maria Cecilia Ospedale, Cotignola, Italy*

Aims: To evaluate the relation between uric acid (UA) levels and risk for heart failure (HF) development among patients surviving a myocardial infarction (MI) without signs or symptoms of HF.
Methods: Prospectively ascertained information among 9199 patients free from HF at baseline, enrolled in the GISSI-Prevenzione trial was used. UA serum level was categorized in quintiles, as <4.5 (Q1), 4.6 to 5.2 (Q2), 5.3 to 6.0 (Q3), 6.1 to 6.8 (Q4) and >6.8 mg/dL (Q5). Outcome measures were the incidence of HFsd (defined as development of signs/symptoms of HF or occurrence of death for HF) and HFad (defined as occurrence of hospital admission or death for HF). Multivariable analysis adjusted for potential confounding factors was used to estimate the relative risks (HR) of outcome measures across categories of UA.
Results: During 31.635 person-years of follow-up, 328 HFsd and 222 HFad occurred. The multivariable analysis showed a statistically significant association between high UA serum levels and both HFsd and HFsa (Figure 1).
For HFsd [RR, P value]: Q1 [1.29, 0.173]; Q2 [1.40, 0.084]; Q3 [1.00, reference category]; Q4 [1.48, 0.042]; Q5 [1.72, 0.003].
For HFsa [RR, P value]: Q1 [1.24, 0.345]; Q2 [1.43, 0.119]; Q3 [1.00, reference category]; Q4 [1.26, 0.321]; Q5 [1.56, 0.044].



Conclusions: Our data suggest that the relationship between UA serum levels and risk of HF in post-MI patients is "U-shaped", the risk of HF development being significantly increased in patients with UA serum levels above 6.0 mg/dL.

P413 The degree of lung fluid accumulation is different between preserved and reduced systolic function in patients with acute heart failure

A. Nakagawa, G. Hamano, T. Taniguchi, Y. Utsunomiya, M. Koide, M. Yamato, N. Sasaki, K. Hirooka, Y. Koretsune, Y. Yasumura. *National Hospital Organization Osaka National Hospital, Osaka, Japan*

Objectives: Recently two types of lung fluid accumulation in patients with acute heart failure (AHF) were proposed; one is gradual fluid accumulation as in the case with systolic heart failure (SHF) and another is rapid central volume shift with diastolic heart failure (DHF). The degree of lung fluid accumulation is supposed to be different in patients with AHF between reduced and preserved systolic function.
Methods: Sixty-one patients with AHF (NYHA class III or IV) were enrolled. Patients with acute coronary syndrome and mitral regurgitation as a main cause of AHF were excluded. Blood pressure (BP) on admission was recorded. After initial treatment, BNP levels and LV end-diastolic dimension (Dd), fractional shortening (FS), transtricuspid pressure gradient (TRPG) by echocardiography were measured. Patients with FS$>$0.22 were defined as DHF, FS$<$0.22 as SHF. The amount of thoracic fluid content (TFC) was measured by using BioZ impedance cardiography. Decrease in body weight (dBW) during hospitalization were determined. TFC of 14 patients without heart failure were measured for control.
Results: Twenty-one patients (34%) were DHF. Although the ratio of NYHA class IV (62 vs 68%) and TRPG (38$\pm$7 vs 43$\pm$13mmHg) were not different between DHF (Dd=49$\pm$5mm, FS=0.29$\pm$0.06) and SHF (Dd=62$\pm$7mm, FS=0.14$\pm$0.04), BNP level was lower in DHF (774$\pm$978 vs 1609$\pm$1519pg/ml, $p<0.05$). dBW (4.1$\pm$2.1 vs 6.6$\pm$4.5kg, $p<0.05$) was smaller and the increase in TFC on admission (40$\pm$6 vs 51$\pm$9, $p<0.01$, control value=32$\pm$5/kOhm) was lower in DHF than in SHF. TFC correlated with BNP (r=0.501, $p<0.0001$). BP on admission was higher in DHF than in SHF (172$\pm$34 vs 140$\pm$36mmHg, $p<0.01$).
Conclusions: The small increase in TFC with high BP on admission in DHF supports the concept that the main mechanism of DHF is acute vascular failure, which precipitates the lung congestion.

P414 Diastolic asynchrony in heart failure: which patients?

D.C. Cozma, C. Mornos, L. Petrescu, D. Lighezan, D. Gaita, S.I. Dragulescu. *Institute of Cardiovascular Medicine, Timisoara, Romania*

Diastolic asynchrony is less studied and understood. Despite multiple echocardiographic approaches to evaluate diastolic function and mechanical dyssynchrony there is lack of information concerning the importance of diastolic asynchrony in soubgroups of population. The purpose of this study was to determine the occurrence of diastolic dyssynchrony in three different groups of patients (pts): dilated cardiomyopathy (DCM), coronary artery disease (CAD) and pts without structural heart disease and normal ejection fraction but with "pure" diastolic heart failure (DHF).
Methods: Pts with heart failure were included. Diastolic dyssynchrony were assessed by TDI. and defined using currently accepted parameters used to indicate left ventricular asynchrony. A cutoff value of 40 ms was accepted to define timing for asybchrony. Criteria for diastolic heart failure (DHF) included clinical symptoms and signs, supporting laboratory tests, a typical clinical response to treatment with diuretics and echocardiographic conventional validated parameters.
Results: A total of 212 pts (56$\pm$18 years) were included and divided in 3 groups: group DHF (96 pts, aged 53.5$\pm$15 years), DCM (57 pts, aged 56.5$\pm$16 years) and CAD (59 pts, aged 59$\pm$14 years). The NYHA class distribution was: class II, 81%; class III, 19%; and class IV, 0%. Diastolic asynchrony was present in 29 pts (30,2%). In CAD group pts had left end diastolic diameter $<$6.0 cm and EF$>$40%; 38 pts of these CAD group had myocardial infarction. In this group diastolic asynchrony was found in 30 pts (51%). Finally in DCM group, ventricular either systolic or diastolic asynchrony was found in 42 pts (73.7%), and diastolic asynchrony in 39 pts (69%). Regional ventricular delayed activation results in an uncoordinated and prolonged ventricular contraction with lengthening of the isovolumetric contraction and relaxation time and decrease of the time available for filling and ejection wich may explain higher incidence of asynchrony in this population. Mean septal to lateral E' TDI timing was significantly higher in patients with CAD (51$\pm$24 ms) and DCM (64$\pm$29 ms) than in pts with DHF (30$\pm$18 ms), $p<0.0001$.
Conclusions: Diastolic asynchrony is usually present in patients with dilated cardiomyopathy and ischemic heart disease and of less incidence and importance in patients without structural heart disease even if diastolic heart failure is present. Diastolic asynchrony does not apear to have essential implications in the mechanism of diastolic heart failure with structural normal heart.

P415 Paracrine effects of stem cells on cardiac remodelling in placebo-controlled clinical trial involving patients with congestive heart failure

E.Z. Golukhova, L.A. Bockeria, T.T. Kakuchaya, M.V. Eremeeva, N.A. Chigogidze, I.P. Aslanidi, T.G. Nikitina, I.V. Shurupova, R.A. Serov, A.V. Svobodov on behalf of Bakoulev Scientific Center for Cardiovascular Surgery RAMS. *Bakoulev Scientific Center for Cardiovascular Surgery RAMS, Moscow, Russian Federation*

Purpose of our study included assessment of paracrine effects of stem cell (SC) therapy on cardiac remodelling processes in patients with congestive heart failure (CHF) of different origin.
Methods: Overall 53 patients with CHF were enrolled in our study. Patients were divided into groups according to the SC/placebo (NaCl solution) delivery method: selectively percutaneously intracoronary or transendocardially into the regions of interest and transepicardially during open heart surgery based on the non-invasive/invasive methods of investigation. We applied autologous bone-marrow stem (BMS) cell progenitors CD133+ in the treatment of patients with CHF due to advanced coronary artery disease [CAD] (n=27) and non-ischemic dilative cardiomyopathy patients (NICMP; n=26).
Results: Single isolated SC therapy with autologous CD133+ progenitors at average dosage 2mln, performed transendocardially, resulted in the significant reduction of left ventricular (LV) end-diastolic volume with moderate increase of ejection fraction in short-term follow-up (3-6 months) in patients with CHF due to CAD in comparison to placebo group. Alongside during this period was observed moderate reduction of perfusion defects in SC "treated" regions with viable my-

ocardium according to single photon emission computed tomography. These positive changes eliminated in 1 year follow-up. Other main LV remodeling indexes such as myocardial mass and left atrial volume did not change in 3-6 months follow-up. In NICMP patients we observed no changes in any of the LV remodeling indexes.
In order to evaluate biochemical processes and paracrine effects of stem cells we performed enzyme-linked immunoelectrodiffusion assay of patients plasma samples for VEGF, bFGF, angiogenin, angiopoetins-1,2, MMP-9, PlGF, endostatin, TNF-α, SDF-1α and NT-proBNP levels before and after elective SC therapy. In NICMP patients at 14 days after single isolated transendocardial SC delivery we noted significant increase of SC homing factor SDF-1α plasma concentration, whereas in patients with ischemic CHF - significant decrease of PlGF (placenta growth factor) concentration in comparison with placebo group. There were no changes in plasma NT-proBNP levels in both groups. These alterations meant that SC paracrine effects exerted transiently in ischemic scarred, but viable myocardium and did not exert in non-ischemic dilated myocardium.
Conclusions: Isolated transendocardial delivery of BMS progenitors CD133+ at average dosage 2mln may have some positive effects if it is used in combination with gene therapy and repeated in 6 months in patients with CHF secondary to CAD.

P416 Myocardial inflammation and non-ischaemic heart failure - is there a role for C-reactive protein?

O. Zimmermann, M. Bienek-Ziolkowski, B. Wolf, M. Vetter, R. Baur, V. Mailander, V. Hombach, J. Torzewski. *Universitaetsklinikum Ulm, Ulm, Germany*

Purpose: Whereas C-reactive protein (CRP) is acknowledged as a cardiovascular risk marker, there is ongoing discussion about its role as a risk factor. Previous studies focused on the effects of CRP on ischaemic heart failure and atherosclerosis. In this study we investigated distribution of CRP, the Terminal Complement Complex (C5b-9) and macrophages (CD68) in the myocardium of patients suffering from non-ischaemic heart failure and their implication on clinical parameters.
Methods: Endomyocardial biopsies were taken from 66 patients suffering from dilated cardiomyopathy (DCM). Biopsies were analysed by immunohistochemical and immunofluorescent staining for CRP, C5b-9 and CD68. For co-localisation of these molecules additionally confocal laser scanning microscopy was performed. Viral DNA/RNA for adeno-, enterovirus, Parvovirus B19 and Human Herpes Virus 6 was detected by PCR and Southern Blot analysis. Myocardial biopsy findings were correlated with plasma level of hsCRP and NT-proBNP as well as echocardiography, exercise test and NYHA class.
Results: In 18 (27%) patients a positive staining for CRP and in 57 (86%) patients a positive staining for C5b-9 was detected. All patients showed myocardial infiltration with macrophages with an average of 39 cells/mm^2. CRP, C5b-9 and CD68 co-localised within the myocardium. No correlation was observed for inflammatory proteins and plasma level of hsCRP, NT-proBNP and clinical parameters.
Conclusions: This study shows for the first time that CRP is frequently present in the myocardium of patients suffering from DCM and co-localises with C5b-9 and macrophages. CRP may contribute to myocardial damage in DCM via activation of the complement system and chemotaxis of macrophages.

P417 Obstructive ventilatory disorder in heart failure: is it really COPD?

S. Brenner[1], G. Gueder[1], K. Froehlich[1], G. Gelbrich[2], R. Jahns[1], B. Jany[3], G. Ertl[1], S. Stoerk[1], C.E. Angermann[1] on behalf of the INH Study Group of the German Competence Network Heart Failure. *[1]Medizinische Klinik I, Kardiologie, Klinikum der Universität Würzburg, Wuerzburg, Germany; [2]Koordinationszentrum für Klinische Studien Leipzig, Universität Leipzig, Leipzig, Germany; [3]Missionsärztliche Klinik, Wuerzburg, Germany*

Purpose: Compared with the general population, the prevalence of obstructive ventilatory disorders (OVD) is increased among patients with heart failure (HF). According to literature OVD is associated with adverse prognosis. We aimed to characterise OVD in patients with chronic systolic HF and to search for possible determinants.
Patients: We studied pulmonary function by spirometry in 556 patients who presented at our outpatient clinics 6 months after hospitalisation for systolic heart failure (left ventricular ejection fraction (LVEF) ≤40%). A diagnosis of OVD was assumed if the ratio of forced expiratory volume in 1 second and forced vital capacity was <0.7. Quality of life was assessed by the SF-36 questionnaire.
Results: In 86 patients (15.5%) spirometry indicated OVD. In patients with and without OVD, age (66±11 vs. 65±12 yr; p=0.888), LVEF (42±1 vs. 42±11; p=0.932) gender (78 vs. 75% men; p=0.524) and New York Heart Association class (NYHA I-IV: 17/51/30/1% vs. 24/55/20/0.9%; p=0.176) were not statistically different.
However patients with OVD had a lower SF-36 score (47±28 vs. 58±31; p=0.005) and a higher leucocyte count (8.6±2.8 vs. 7.6±2.6×1000/mm^3; p=0.003). Furthermore, levels of residual lung volume (RLV), intrathoracic gas volume (ITGV) and total resistance (TR) were elevated (all p<0.001) in this subgroup. 42% of the patients with OVD had a history of 'COPD' or 'asthma' and were treated accordingly. 38% of the patients with OVD had never smoked. Among never-smokers, peripheral edema as an indicator of fluid retention and possible trigger of pulmonary obstruction was present in 31% of the patients with OVD versus only 16% of the patients without OVD (p=0.05). Never-smokers with OVD had further higher values (% of expected) for RLV and TR compared with never-smokers without OVD (median RLV: 122 (interquartile range, IQR 109-152) vs. 102 (IQR 86-123) and TR: 169 (IQR 118-218) vs. 86 (IQR 62-115) %; p<0.001 for both).
Conclusions: In patients with HF, OVD is common and associated with worse quality of life and increased systemic inflammation. The degree of obstruction appears only partially explained by a history of smoking or fluid retention. This suggests other, hitherto ill-defined pathophysiological mechanisms leading to OVD.

P418 Adiponectin levels is strongly associated with NT-Brain Natriuretic Peptide levels, LV diameters and ejection fraction in patients with heart failure

U.O. Turk[1], E. Alioglu[1], B. Kirilmaz[2], G.S. Tamer[3], I. Tengiz[1], N. Tuzun[1], E. Ercan[2]. *[1]Central Hospital, Izmir, Turkey; [2]Canakkale Onsekiz Mart University, Canakkale, Turkey; [3]Kocaeli University Microbiology and Clinical Microbiology Dept., Kocaeli, Turkey*

Background: NT-Brain Natriuretic Peptide (NT-BNP) has been shown to be an accurate diagnostic marker in patients with heart failure (HF). Adiponectin levels increased in HF but its diagnostic value is still uncertain in these patients. The study was designed to investigate the possible association of these markers in patients with newly dignosed HF.
Methods: 57 recently diagnosed untreated systolic HF patients (LVEF<%35) and 20 age, sex and body mass index matched controls enrolled into the study. Physical and echocardiographic examinations were performed and serum adiponectin (ng/L), NT-BNP (pg/ml), tumor necrosis factor alpha levels were measured.
Results: Correlation analysis showed positive assocication among adiponectin and NT-BNP levels, (r=0.448;p<0.001), LV end-diastolic (r=0.291; p<0.01) and end-sistolic (r=0.424; p<0.001) diameters. Furthermore significant negative correlation was found between the LVEF (r=-0.466; p<0.001). At a cut-off 8.79 ng/L our study revealed a sensitivity of 86% and a specificity of 65% for predicting the presence of HF (Figure).

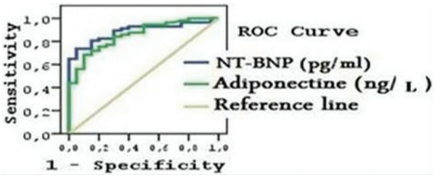


Figure 1

Conclusion: Adiponectin levels may have high diagnostic accuracy in patient with HF.

ASSESSING RISK IN ACUTE CORONARY SYNDROMES: FROM BIOMARKERS TO IMAGING

P420 Low-density lipoprotein cholesterol paradox in patients with acute myocardial infarction

J.H. Lee[1], S.C. Chae[1], M.H. Jeong[2], Y.J. Kim[3], K.S. Kim[4], S.H. Hur[5], I.W. Seong[6], T.J. Hong[7], M.C. Cho[8], C.J. Kim[9] on behalf of Korea Acute Myocardial Infarction Registry Investigators. *[1]Kyungpook National University Hospital, Daegu, Korea, Republic of; [2]Chonnam National University Hospital, Gwangju, Korea, Republic of; [3]Yeungnam University Hospital, Daegu, Korea, Republic of; [4]Daegu Catholic University Hospital, Daegu, Korea, Republic of; [5]Keimyung University Dongsan Medical Center, Daegu, Korea, Republic of; [6]Chungnam National University Hospital, Daejeon, Korea, Republic of; [7]Pusan National University Hospital, Pusan, Korea, Republic of; [8]Chungbuk National University Hospital, Cheongju, Korea, Republic of; [9]The Catholic University Hospital, Seoul, Korea, Republic of*

Purpose: Little is known about the prognosis of acute myocardial infarction (AMI) patients with very low low-density lipoprotein (LDL) cholesterol levels at baseline.
Methods: Between November 2005 and January 2008, 7002 patients (5039 males; mean age=64.2±12.5 year-old) were included in the Korean AMI Registry. Lipid levels were obtained within the first 24 hours of admission. Patients receiving lipid-lowering medications were excluded. Patients were categorized into 10 groups according to the baseline LDL cholesterol levels Results: Overall, 6-month mortality was 5.1%. The 6-month mortality was the highest in 1st decile group (9.0%), and then it was gradually decreased, showing the lowest in 6th decile group (2.3%). Then a gradual increase was observed with a peak in 10th decile group (5.6%)(Figure). The prescription rate of lipid-lowering therapy was significantly lower, and N-terminal pro-B type natriuretic peptide levels (NT-proBNP) were significantly higher in 1st decile group. The LDL cholesterol levels were significantly higher in men, and in patients with hypertension, diabetes, and higher Killp class, whereas significantly lower in patients with ST elevation MI and multivessel disease. It was positively correlated with body mass index, systolic blood

pressure, high-sensitivity C-reactive protein levels, and total cholesterol and high-density lipoprotein cholesterol levels, and negatively correlated with age, serum glucose levels, serum creatinine levels, and NT-proBNP levels.

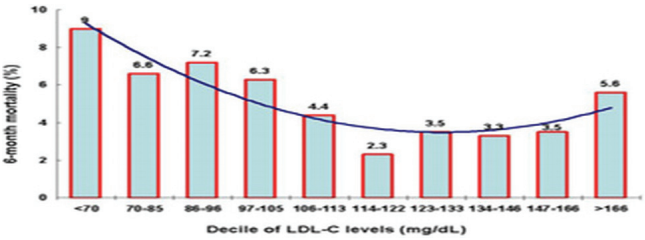


Figure 1. Six-month mortality

Conclusions: The 6-month mortality is the highest in AMI patients with very low baseline LDL cholesterol level. Various clinical situations affect LDL cholesterol level; therefore, further studies are needed to validate the conventional theme in the AMI; "the lower, the better".

P421 Predictors of left ventricular dysfunction in patients admitted with a first acute coronary syndrome

A.T. Timoteo, A. Lousinha, A. Toste, R. Ramos, J.A. Oliveira, M.L. Ferreira, R.C. Ferreira. *Hospital Santa Marta, Lisbon, Portugal*

Introduction: Ischemic cardiomiopathy is the most important etiology of heart failure in developed countries. An early identification of the factors that could lead to left ventricular dysfunction after an acute coronary syndrome (ACS) and an early treatment is essential to improve the prevalence of heart failure.
Objectives: To evaluate the predictors of left ventricular dysfunction in patients (P) admitted with an acute coronary syndrome.
Methods: P admitted with a first ACS in our department since January 2005 were included in the present study. Data was obtained from an internal registry of ACS. Left ventricular function was evaluated in all P by ventriculography or by echocardiography before discharge and we defined left ventricular dysfunction as an ejection fraction $\leq$ 35%.
Results: We included 842 P, 69% males, mean age of 64$\pm$13 years. There was left ventricular dysfunction in 7% of the patients. This group had more diabetics (34 vs. 23%, p=0.049), presented more frequently in Killip class $\geq$2 (42 vs. 10%, p<0.001), with left bundle branch block (LBBB) (11 vs. 2%, p<0.001) and atrial fibrillation (18 vs. 5%, p<0.001). They received less coronary angioplasty (69 vs. 81%, p=0.027) and had higher blood glucose on admission (219$\pm$130 vs. 164$\pm$77 mg/dl, p=0.002), lower creatinine clearance (71$\pm$36 vs. 83$\pm$38 ml/min/1.73m^2, p=0.01) and higher GRACE risk score (184$\pm$49 vs. 146$\pm$33, p<0.001). There were no differences for previous medication, risk factors for coronary artery disease and presentation as ST-segment elevation myocardial infarction. In-hospital mortality (32 vs. 5%), at 30 days (34 vs. 7%) and at first year (34 vs. 7%) was also higher (p<0.001). Independent predictors of left ventricular dysfunction were arterial hypertension (OR 0.39, 95% CI 0.21-0.71, p=0.002), a heart rate > 80 bpm (OR 2.35, 95% CI 1.27-4.33, p=0.006), signs of heart failure on admission (OR 4.28, 95% CI 2.26-8.09, p<0.001), presence of LBBB (OR 4.63, 95% CI 1.49 – 14.35, p=0.008) and atrial fibrillation (OR 2.55, 95% CI 1.11 – 5.88, p=0.027).
Conclusions: In a population admitted with a first acute coronary syndrome, an early identification of predictors for left ventricular dysfunction (hypertension, heart rate > 80 bpm, signs of heart failure, LBBB and atrial fibrillation) should determine an aggressive management to reduce the incidence of left ventricular dysfunction.

P422 Adiponectin as a predictor of left ventricular remodeling after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

K. Piestrzeniewicz, K. Luczak, J. Drozdz. *Medical Univercity, Lodz, Poland*

Background: Left ventricular remodeling (LVR) – an increase in LV end-diastolic volume index $\geq$20% is a consequence of myocardial infarction (MI). The aim of the study was to assess the association between LVR and adiponectin, that has been shown to protect against myocardial ischemia-reperfusion injury.
Methods: In 75 patients echocardiographic examination was performed one year after ST-segment elevation MI, successfully treated with primary percutaneous coronary intervention (pPCI). Two groups of patients were analyzed: with LVR - n=15 and without LVR - n=60.
Results: The predictors of LVR were: anterior myocardial infraction, glucose at admission, baseline C-reactive protein, adiponectin, and echocardiographic parameters: LV end-diastolic and end-systolic volume indexes, ejection fraction <40% and LV wall motion score index (WMSI) at discharge. On multivariable regression analysis lower adiponectin level (OR=0.67, 95%CI 0.49 to 0.91, p<0.05) and higher WMSI (OR=20.14, 95%CI 2.62 to 154.82, p<0.01) were the only independent negative predictors of LVR. The optimal cut-off for adiponectin for predicting LVR was $\leq$4.7μg/ml (sensitivity – 73%, specificity – 85%) and this level 15.5-fold increased the risk of LV remodeling (95% CI 4.05-59.87, p=0.0001).
Conclusion: Baseline low adiponectin concentration, along with WMSI, can be considered as a predictor of the LVR one year after MI and pPCI.

P423 Short and long-term prognostic value of hemoglobin on admission: STE vs NSTE acute coronary syndromes

F. Vagnarelli, L. Cinti, F. Semprini, S. Nanni, A. Branzi, G. Melandri. *Univ. di Bologna - Istituto di Cardiology, Bologna, Italy*

Introduction: We have previously shown that the hemoglobin level (HB) on admission affects the short term prognosis of acute coronary syndromes (ACS). There are few data on its impact in the long-term, differentiating the ST-elevation (STE) vs non-ST elevation (NSTE) ACS.
Purpose: to evaluate whether HB level on admission impacts differently the short and long-term outcome of patient with STE vs NSTE in the real world of an ACS-registry.
Methods: 2046 patients whose final diagnosis of ACS (including STE and NSTE) was confirmed by clinical audit were admitted in 2004-2005 years. 1 year follow up was completed in 1984 patients (96,9%), among whom the HB on admission was available in 1950. The whole population was divided into 3 groups according to Hb on admission: < 10, 10-12 and > 12 mg/dl. 30-day and 1-year mortality were compared for each Hb group between STE vs NSTE groups. We further compared the outcome of STE and NSTE according to the HB level.
Results: 841 had STE and 1109 had NSTE. A decrease in the HB level negatively affected both the 30-day and 1-year mortality in both STE and NSTE patients (p < 0.0001) (table). The higher 30-day mortality in STE vs NSTE groups was observed in all HB categories. Similarly, the catch-up of NSTE 1-year mortality compared to that observed in STE was independent of HB level.

Follow up according to HB in STE/NSTE

	HB < 10	HB 10-12	HB > 12	All	P
30-day mortality					
STE-ACS	16/49 (32.6%)	32/166 (19.2%)	50/626 (7.9%)	98/841 (11.6%)	0.0001
NSTE-ACS	16/97 (16.4%)	31/248 (12.5%)	37/764 (4.8)	84/1109 (7.5%)	0.0001
	P=0.044	P=0.082	P=0.022	P=0.003	
1-year mortality					
STE-ACS	23/49 (46.9%)	54/166 (32.5%)	101/626 (16.1%)	178/841 (21.1%)	0.0001
NSTE-ACS	38/97 (39.1%)	84/248 (33.8%)	102/764 (13.3%)	224/1109 (20.1%)	0.0001
	P=0.471	P=0.859	P=0.166	P=0.641	

HB: hemoglobin on admission (mg/dl). STE/NSTE-ACS: ST segment elevation/non-ST-segment elevation acute coronary syndromes.

Conclusions: we observed a significant adverse effect of a low HB level on 1-year mortality of ACS. The HB level on admission had a similar impact on short and long-term mortality of STE and NSTE ACS.

P424 Short and long-term prognostic value of glomerular filtration rate: STE vs NSTE acute coronary syndromes

F. Vagnarelli, L. Cinti, F. Semprini, S. Nanni, A. Branzi, G. Melandri. *Univ. di Bologna - Istituto di Cardiology, Bologna, Italy*

Introduction: glomerular filtration rate (GFR) affects the short-term prognosis of acute coronary syndromes (ACS). There are few data on its effects in the long run, differentiating the ST (STE) vs non-ST elevation (NSTE) categories.
Purpose: to evaluate whether GFR has a different impact on the short and long-term outcome of patients with STE and NSTE in the real world of an ACS-registry.
Methods: 2046 patients with a final diagnosis of ACS confirmed by clinical audit were admitted in the 2004-2005 years. 1-year follow up was completed in 1984 patients (96,9%): in 1965 of these, GFR on admission (MDRD formula) was available. The population was divided into 3 groups according to GFR on admission: <30, 30-59 and $\geq$60 ml/min/1.73 mq. 30-day and 1-year mortality were compared for each GFR group both in the STE and NSTE cohort.
Results: 849 had STE and 1116 had NSTE. Both in STE and NSTE 30-day and 1 year mortality were inversely related to GFR (p<0.0001). 30-day mortality was higher in STE than NSTE (12.1 vs 7.8%, P=0.0001) whereas 1-year mortality was similar (21.7 vs 20.5%, P=0.917). When GFR was >60, there were no diferrence in short and long term mortality between STE and NSTE. Otherwise, when GFR was 30-59 or <30 ml/min/1.73 mq, STE patients had a greater 30-day and 1-year mortaliity than NSTE (table).

Follow-up according to GFR in STE/NSTE

	GFR < 30	GFR 30–59	GFR $\geq$ 60	All	P
30-day mortality					
STE-ACS	25/54 (46.2%)	47/257 (18.2%)	31/538 (5.7%)	103/849 (12.1%)	0.0001
NSTE-ACS	33/174 (18.9%)	36/389 (9.2%)	19/553 (3.4%)	88/1116 (7.8%)	0.0001
	P = 0.0001	P = 0.001	P = 0.091	P = 0.0001	
1-year mortality					
STE-ACS	40/54 (74.0%)	91/257 (35.4%)	54/538 (10.0%)	185/849 (21.7%)	0.0001
NSTE-ACS	80/174 (45.9%)	90/389 (23.1%)	59/553 (10.6%)	229/1116 (20.5%)	0.0001
	P = 0.0001	P = 0.0001	P = 0.808	P = 0.917	

GFR: glomerular filtration rate on admission (ml/min/1.73 mq); STE-ACS/NSTE-ACS: ST-segment elevation/non-ST-segment elevation acute coronary syndromes.

Conclusions: GFR has a greater impact on both short and long-term mortality in STE compared with NSTE patients when it is below 60 ml/min/1.73 mq.

P425 Admission blood glucose level as a long term risk factor in patients after acute myocardial infarction in dependence of presence diabetes mellitus

R. Adamkova[1], S. Janousek[1], A. Tomasek[1], J. Tumova[2], Z. Cermakova[2], J. Spinar[1]. *[1]University Hospital Brno, Department of Cardiology, Brno, Czech Republic; [2]University Hospital Brno, Department of Clinical Biochemistry, Brno, Czech Republic*

Background: High admission blood glucose levels (BGL) in patients with acute disease like acute myocardial infarction (AMI) are common and associated with an increased risk of death in subjects with and without known diabetes mellitus (DM).
Aim: To estimate the predictive value of admission BGL in AMI for fourth year prognosis in patients without previously diagnosed DM.
Methods and study group: The prognosis of all 873 consecutive patients (608 without and 265 with known diabetes) admitted to our coronary care unit in years 2003 and 2004 with diasnosis of AMI were follow-up during 4 years. Patients were divided into 4 groups. In the A group were patients without known DM and with admission BGL less than 7.8 mmol/l, in the B group were patients without known DM and with admission BGL 7.8 – 11.1 mmol/l, in the C group were patients without known DM and with admission BGL 11.1 mmoł or higher and in the D group were patients with known DM.
Results: Mortality is in tab. below.
The long-term mortality statistically significantly grow with level of BGL (group A vs. B P<0.001; group A vs. C P<0.001; group A vs. D P<0.001; group B vs. C P=0.01; group B vs. D P=0.02; groups A+B vs. C+D P<0.001; groups A+B vs. C P<0.001). The difference in 4-years mortality in group C and D was not statistically significant (P=0.4).

Group/Mortality	In-hospital	30 days	1 year	2 years	3 years	4 years
A 329 patients (37.7%)	4.9%(16)	6.4%(21)	10.6%(35)	12.2%(40)	13.1%(43)	16.1%(53)
B 210 patients (24.0%)	7.6%(16)	10%(21)	16.7%(35)	19%(40)	23.3%(49)	29.0%(61)
C 69 patients (7.9%)	24.6%(17)	26.1%(18)	37.7%(26)	42%(29)	43.5%(30)	44.9%(31)
D 265 patients (30.4%)	11.7%(31)	15.8%(42)	23.8%(63)	32.8%(87)	37.7%(100)	39.6%(105)

Conclusions: The admission BGL in AMI is an independent predictor of long-term mortality in patients without known DM. Subjects without DM and with admission BGL 11.1 mmol/l or higher after AMI had mortality rates similar to them with established DM. Admission BGL could help to identify patients at high long-term mortality risk. It could be particularly valuable in nondiabetics.

P426 Searching for the best outcome predictor post myocardial infarction: kidney function or blood glucose?

S. Monteiro, R. Teixeira, C. Lourenco, R. Batista, E. Jorge, F. Saraiva, N. Antonio, P. Monteiro, M. Freitas, L. Providencia. *University Hospital, Coimbra, Portugal*

Introduction: Renal dysfunction in acute myocardial infarction (AMI) is a predictor of morbidity and mortality. Recently, hyperglycaemia during hospitalization has also been considered an important marker of poor prognosis in this population.
Aim: To compare the predictive value of creatinine clearance (CrCl) with metabolic markers on AMI patients' prognosis and to identify independent predictors of in-hospital and 1-year major acute cardiac events (MACE) and mortality.
Population and methods: 767 consecutive AMI patients. Glycaemia (GLY) variation was defined as the difference between admission and lowest GLY and GLY normalization as the difference between admission and first fasting GLY. Patients were followed for 1 year.
Results: After multivariate analysis, age, necrosis markers, haemoglobin, admission and variation GLY were independent predictors of in-hospital mortality, while age, previous diabetes, necrosis markers and ejection fraction (EF) were predictors of 1-year mortality. In-hospital MACE were predicted by EF, angioplasty (PCI) and admission, variation and normalization GLY; age, previous diabetes, EF, PCI, admission and variation GLY predicted 1-year MACE.

In-hospital MACE	OR	p
LVEF ≤ 46,5	2,957	0,002
PCI	0,283	0,002
Admission on GLY [114,141[vs < 114	3,623	0,112
Admission on GLY [141,195[vs < 114	10,221	0,002
Admission on GLY ≥ vs < 114	4,619	0,056
Variation GLY [23,49[vs < 23	2,217	0,199
Variation GLY [29,93[vs < 23	4,922	0,006
Variation GLY $\|_{geq}$ 93 vs < 23	1,547 7 0.504	
Normalization GLY [23,49[vs < 23	3,460	0,035
Normalization GLY [29,93[vs < 23	2,324	0,164
Normalization GLY ≥ vs < 23	2,303	0,173
CrCl [44,63[vs < 44	0,571	0,303
CrCl [63,87[vs < 44	1,215	0,677
CrCl ≥ 87 vs < 44	1,191	0,716

We then compared the predictive value of each metabolic marker and CrCl in this population. The receiver-operator curves showed that all parameters were equally predictive of both short and long-term MACE and mortality.
Conclusion: In this population, metabolic markers were as predictive of outcome as ClCr, a well recognized and strong prognosis determinant post-AMI. This fact, never before described, underlies the importance of metabolic abnormalities and its control in these patients outcome.

P427 Predictors of 30-day stent thrombosis after primary percutaneous coronary intervention

I. Mrdovic, L. Savic, M. Asanin, J. Perunicic, R. Lasica, J. Marinkovic, Z. Vasiljevic, M. Ostojic on behalf of RISK-PCI. *Clinical Center of Serbia, Beograd, Serbia*

Purpose: Stent thrombosis (STH) following primary percutaneous coronary intervention (PPCI) has been associated with an adverse outcome after acute ST elevation myocardial infarction (STEMI). The aim of the present study was to identify predictors of 30-day STH after PPCI.
Methods: PPCI was performed via the femoral approach. Loading doses of aspirin (300 mg) and clopidogrel (600 mg) were administrated before PPCI. STH has been confirmed angiographicaly during the index hospitalization and/or 30-day follow-up. Various clinical, laboratory, angiographic and procedural variables (identified in the univariable analysis) were tested in the multivariable logistic regression model for the prediction of 30-day STH. The cut-off values were identified using ROC analysis.
Results: From February 2006 to June 2008, 1166 patients with STEMI enrolled in the RISK-PCI trial were treated with PPCI. STH was confirmed in 48 (4.1%) patients. 5 patients (0.4%) had acute STH and 43 (3.7%) had subacute STH. Patients with STH had higher in-hospital mortality (OR 3.5, CI 1.4-8.6, p=0.004), and higher 30-day mortality (OR 16.1, CI 4.5-57.2, p<0.001). The independent predictors of 30-day STH were: postprocedural TIMI flow <3 (OR 9.1, CI 2.5-32.6), discontinuation of dual antiplatelet therapy (OR 6.9, CI 1.7-27.7), LV ejection fraction < 45% (OR 3.0, CI 1,4-6.2), infarct-related artery (IRA) thrombus at presentation (OR 2.3, CI 1.1-5.1), and IRA stent diameter (OR 0.3, CI 0.1-0.8).
Conclusions: Postprocedural TIMI flow <3, discontinuation of dual antiplatelet therapy, LV ejection fraction < 45%, IRA thrombus burden and IRA stent diameter were independent predictors of 30-day STH following PPCI.

P428 Post acute myocardial infarction outcome: admission glycaemia says it all

S. Monteiro, R. Batista, C. Lourenco, R. Teixeira, E. Jorge, N. Antonio, F. Saraiva, P. Monteiro, M. Freitas, L. Providencia. *University Hospital, Coimbra, Portugal*

Introduction: Hyperglycaemia during acute myocardial infarction (AMI) is associated with bad prognosis. There are several parameters to access glucose metabolic control in these patients. Is there one which is clearly better?
Aim: To compare the impact of admission glycaemia (GLY) and fast normalization of GLY on AMI patients' prognosis and to identify independent predictors of mortality post-AMI.
Population and methods: 639 consecutive AMI patients with hyperglycaemia on admission were included. Population was first divided in 4 groups, according to the quartiles of admission GLY (Q1 <5.83, Q2 5.83-7.44, Q3 7.44-10.33, Q4 ≥10.33 mmol/l). A second analysis was made, considering patients with (n=288) and without (n=351) normalization of GLY levels (< 100 mg/dl) during the first 24h after admission. Patients were followed during 1-year.
Results: After multivariate regression analysis, admission GLY≥5.83 mmol/l (OR 8,91; IC 1,20-66,30), non-normalized GLY (OR 3.13; IC 1,27-7,67); age ≥ 72 years (OR 3,58; IC 1,79-7,20), Killip class > 1 (OR 3,49; IC 1,87-6,52) and Troponin I ≥ 6.0 ng/ml (OR 2,68; IC 1,28-5,58) were independent predictors of in-hospital mortality.
In-hospital and 1-year mortality was significantly higher in higher admission GLY quartiles, while patients with normalization of GLY had lower in-hospital mortality (3.8% vs 8.3%; p= 0.021), without differences in 1-year mortality.

	Mortality	Total population (%)				p
		A	B	C	D	
Admission glycaemia	In hospital	0.7	5.2	5.5	7.6	0.001
	1 year	5.9	10.2	13.2	16.3	0.002
Normalization glycaemia	In hospital	3.8 vs 8.3				0.021
	1 year	13.2 vs 15.9				0.39

Conclusion: In our AMI population, admission GLY is a short and long-term bad prognosis marker, while the fast normalization of GLY levels has a good prognosis impact only during hospitalization. These data suggest that AG is a more complete mortality predictor than normalization of GLY.

P429 Serial haemoglobin measures after acute coronary syndrome: a strong, simple and independent predictor of cardiovascular outcomes

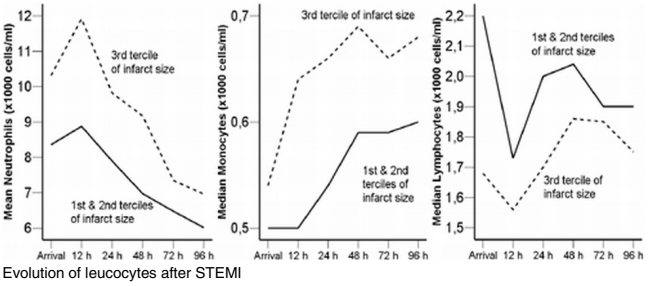
D.S.C. Ang, M.P.C. Kao, C.C. Lang, A.D. Struthers. *University of Dundee, Dundee, United Kingdom*

Introduction: Baseline anaemia in patients with acute coronary syndrome (ACS) is an independent predictor of adverse clinical outcomes. However, little is known about serial haemoglobin measures after an ACS event and its impact on prognosis in this patient population. We sought to determine the prevalence and prognostic impact of anaemia (based on WHO criteria) at baseline and at 7 weeks follow-up in consecutive ACS patients.
Methods: Haemoglobin levels were measured in 448 consecutive patients presenting with ACS and at 7 weeks out patient follow-up. Main outcome measure was either the occurrence of death or acute myocardial infarction (AMI) over a median duration of 2.5 years (range 1-50 months).
Results: Of the 448 patients, 120 patients presented with ST elevation MI (27%). During follow-up there were 117 deaths or AMI. The prevalence of anaemia on admission was 20% and this figure increased to 40% at 7 weeks follow-up. Adjusting for a variety of baseline, clinical, laboratory and echocardiogaphic variables (LV systolic dysfunction), the presence of anaemia was strongly associated with subsequent deaths or AMI when measured on admission [adjusted RR 1.73 (95% CI, 1.13-2.66)] and also at 7 weeks post ACS [adjusted RR 1.67 (95% CI, 1.04-2.69)]. Patients with persistent anaemia at 7 weeks were at an increased risk of death or AMI compared to those with persistently normal haemoglobin [unadjusted RR 3.58 (95% CI, 2.04-6.29)].
Conclusion: In ACS, the prevalence of anaemia increases substantially at 7 weeks follow-up (40%) when compared to admission haemoglobin levels. Both the presence of anaemia at baseline and at follow-up independently predicts long-term adverse clinical outcomes. Furthermore our study suggests that the trend of haemoglobin post ACS is a more important predictor of adverse prognosis compared to a one off low haemoglobin level at baseline.

P430 White blood cell subtypes after STEMI - temporal evolution and association with CMR-derived infarct size

O. Husser[1], V. Bodi[1], J. Sanchis[1], J. Nunez[1], L. Mainar[1], E. Rumiz[1], M.P. Lopez-Lereu[2], J.V. Monmeneu[2], F.J. Chorro[1], A. Llacer[1].
[1]*Hospital Clinico Universitario, Valencia, Spain;* [2]*ERESA, Valencia, Spain*

Background: Data on the temporal evolution of white blood cell subtypes after ST-elevation myocardial infarction (STEMI) as well as their association with cardiovascular magnetic resonance (CMR)-derived infarct size is scarce.
Methods: We analyzed 152 patients with a first STEMI receiving reperfusion within 12 hours of symptom onset. Using CMR at 9±6 days, infarct size was defined as the percentage of left ventricular mass showing delayed enhancement. Total leucocyte and separately neutrophil, lymphocyte and monocyte counts (x1000 cells/ml) were measured upon arrival and at 12, 24, 48, 72 and 96 hours.
Results: Neutrophils boosted and progressively normalized. Monocytes steadily increased, while lymphocytes diminished. Patients in the third tertile (T3) of infarct size compared to patients in the lower tertiles (T1 and T2), showed a boost of neutrophils at 12 hours (T3: 12.3±4.8 vs. T1: 8.7±2.8 and T2: 9.2±3.3, $p<0.001$ and p=0.001) and a steady increase in monocyte count with the most significant difference at 24 hours (T3: 0.65 [0.50-0.91] vs. T1: 0.55 [0.44-0.69] and T2: 0.54 [0.41-0.78], Kruskal Wallis Test p=0.038). In a linear logistic regression, adjusted for baseline and angiographic parameters, neutrophil count at 12 hours independently related to infarct size (Beta 0.221, p=0.003).



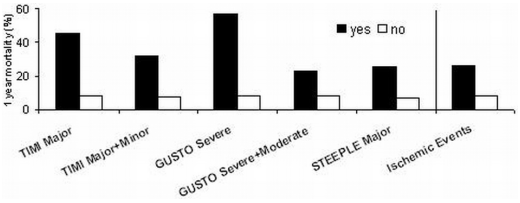
Evolution of leucocytes after STEMI

Conclusions: After STEMI, distinctive patterns of the temporal evolution of white blood cell subtypes occur according to infarct size. Patients with larger infarcts display a neutrophil peak at 12 hours and increasing monocyte count over time. Neutrophil count at 12 hours after revascularization independently relates to CMR-derived infarct size.

P431 Incidence, type and prognostic impact of bleeding complications with radial primary PCI of STEMI: The pitie-salpetriere experience

O. Barthelemy, J. Silvain, A. Bellemain-Appaix, F. Beygui, J.P. Collet, R. Choussat, N. Vignolles, G. Montalescot. *Pitie-Salpetriere Hospital (AP-HP), Paris, France*

Aim: We evaluated the rates, types and prognosis impact of bleeding complications in all-comers presenting with STEMI treated with aggressive antithrombotic treatment and radial access for primary PCI.
Methods: Consecutive STEMI patients (n=695) were evaluated for bleeding complications using a web-based registry (e-PARIS). In-hospital bleedings were adjudicated using various definitions (TIMI, GUSTO, STEEPLE). In-hospital ischemic events were the composite of MI, stroke and recurrent ischemia leading to urgent revascularization.
Results: Mean age was 63±14 years, 531 (76.4%) were male, 142 (20.4%) diabetic. In this non-selected, high risk population, 5.2% had cardiogenic choc on admission, 3.7% had pre-hospital cardiac arrest, 49.4% had multivessel disease. Radial access (88%) was used as often as possible as well as abciximab (82%). The loading dose of clopidogrel ranged from 300 to 900mg. Pre-hospital fibrinolysis was used in 5.9%. Cardiac assist devices (IABP, ECMO, Tandem Heart) all requiring a femoral access, were used in 7.5% of patients. In-hospital death rate was 5.3%. In-hospital bleeding rates varied widely according to the definitions used: 1.6%, 1.0%, 4.2%, 4.7% and 7.5% with TIMI Major, GUSTO Severe, TIMI Major & Minor, GUSTO Severe & Moderate or STEEPLE Major, respectively. One year mortality according to bleeding or ischemic events are shown in the figure. The most frequent TIMI Major Bleeding (MB) complications were gastrointestinal (GI) (44%) and assistance device related (33%) MB.



In Hospital Bleeding or Ischemic events

Conclusions: Although bleeding rates vary a lot with the definitions used, major or minor bleedings strongly relate to 1-yr mortality after primary PCI and weigh at least as much as recurrent ischemic complications. The most frequent MB with radial primary PCI is GI bleeding.

P432 Prognostic relevance and magnetic resonance imaging findings in aborted myocardial infarction after primary angioplasty

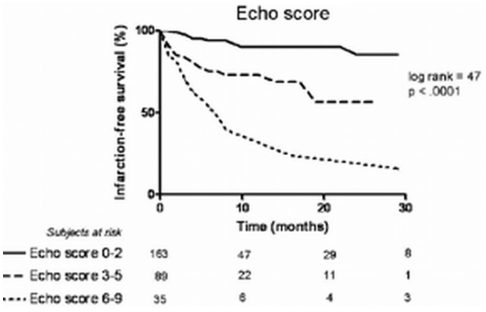
I. Eitel, S. Desch, G. Fuernau, M. Sareban, M. Gutberlet, G. Schuler, H. Thiele. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Purpose: Aborted MI is defined by major (≥50%) ST-segment resolution and a lack of subsequent cardiac enzyme rise ≥2 the upper normal limit. This ultimate myocardial salvage has been observed in approximately 15% of thrombolytic treated patients. Primary angioplasty is also presumed to lead to abortion of infarction, but this has not been studied systematically. The aim was to study the incidence, patient characteristics, prognostic relevance and magnetic resonance imaging (MRI) findings in patients with aborted myocardial infarction (MI) after primary angioplasty.
Methods: We examined 420 consecutive ST-elevation myocardial infarction (STEMI) patients undergoing primary angioplasty within 12 hours after symptom onset. Aborted MI was defined as maximal creatine kinase ≤2 upper limit of normal coupled with typical evolutionary ECG changes. All patients underwent MRI within 1-4 days.
Results: Of the 420 STEMI patients 58 (14%) fulfilled aborted MI criteria. As compared with true MI, patients with aborted MI had a significant lower infarct size, shorter pain-to-balloon time and better left ventricular ejection fraction ($p<0.001$ for all, respectively). Aborted MI patients had a 6-month mortality of 1.7%, significantly less than the 8.3% of true MI patients (p=0.001). In aborted MI patients, MRI detected no myocardial scar in 23 (57%), and a transmural or non-transmural scar in 31 patients (43%).
Conclusions: Aborted MI has a prevalence of 14% after primary angioplasty similar to the rate observed after fibrinolysis. MRI can further distinguish between true aborted MI with absence of myocardial scar and small scar formations. The proven prognostic relevance of aborted MI makes it a meaningful endpoint and therapeutic target in future studies.

P433 The prognostic value of an echographic risk score in acute coronary syndromes: comparison with the TIMI and the GRACE risk score

G. Bedetti[1], L. Gargani[2], R. Sicari[2], M.L. Gianfaldoni[3], S. Molinaro[2], E. Picano[2]. *[1]Ospedale Civile di Imola, Imola, Italy; [2]CNR Istituto di Fisiologia Clinica, Pisa, Italy; [3]Ospedale Civile, Empoli, Italy*

Background: Risk stratification in patients with acute coronary syndromes (ACS) is quintessential to identify high risk patients, whose prognosis is achieved today by clinical models, "blind" to the prognostic support of imaging methods. Aim: To assess the relative value of simple resting cardiac-chest sonography in predicting the intra- and extra-hospital risk of death or myocardial infarction.
Methods: We enrolled 287 consecutive in-patients (197 males, age 71±13 yrs) admitted for ACS. On admission, all received a clinical score with GRACE (Global Registry in Acute Coronary Events) and TIMI (Thrombolysis In Myocardial Infarction) and, within 1 to 12 hours, a comprehensive cardiac-chest ultrasound scan (each parameter scored from 0= normal to 3= severely abnormal).
Results: Median follow-up was 5 months (interquartile range, 1-10). Patients with intra- and extra-hospital hard events (n=56) could be separated from patients without events (n=231) on the basis of GRACE, TIMI and by several echo parameters. Of the 7 echo variables significant to univariate analysis, stepwise interactive analysis selected only 3: ejection fraction, Ultrasound Lung Comets (ULC, an echographic index of extravascular lung water) and TAPSE (tricuspid annular plane systolic excursion). Echo score (from 0= normal to 9= severe abnormalities in EF, ULC and TAPSE) effectively stratified patients (see figure), even better (HR 3.03, 95% C.I. 2.14-4.22, p<.00001) than TIMI (HR 1.91, 95% C.I. 1.38-2.64, p<0.0001), and GRACE risk scores (HR 2.81, 95% C.I. 1.71-4.61, p<0.0001).



Conclusion: In ACS, an effective risk stratification can be achieved with simple cardiac and chest ultrasound imaging parameters, comparable or even superior to clinical risk scores.

P434 Presentation and outcome of patients with acute coronary syndromes in Europe 2006-2008: lessons from the Euro Heart Survey ACS registry

A.K. Gitt[1], M. Gierlotka[2], M. Tubaro[3], M. Hochadel[1], W. Wojakowski[4], M. Tendera[4], H. Katus[5], H. Bueno[6], F. Schiele[7], J.P.P. Bassand[7] on behalf of ACS-Registry. *[1]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [2]Slaskie Centrum Chorob Serca, Zabrze, Poland; [3]Ospedale San Filippo Neri, Rome, Italy; [4]Slaski Uniwersytet Medyczny w Katowicach, Katowice, Poland; [5]Universitaetsklinikum Heidelberg, Heidelberg, Germany; [6]Hospital General Universitario Gregorio Maranon, Madrid, Spain; [7]CHU de Besancon - Hopital Jean Minjoz, Besancon, France*

Background: New guidelines for the management of ACS with and without ST-elevation were published by the ESC in 2006 and 2008. Little is known about the current treatment and outcome of patients with ACS in Europe in clinical practice.
Methods: Between Oct 2006 and Oct 2008, consecutive patients with ACS were enrolled into the ACS-Registry of the Euro Heart Survey Programme to document treatment and hospital complications in STEMI, NSTEMI and unstable angina (UA).
Results: Of 21,582 patients with ACS, 40.5% presented with STEMI, 35.1% with NSTEMI and 24.4% with UA. As in previous ACS registries, patients with NSTEMI and UA were older and had a higher prevalence of concomitant diseases. Acute reperfusion for STEMI was provided to 81.2% with primary PCI for the majority of patients. Patients with NSTEMI received early invasive treatment in 48.3%, patients with UA in 34.7%. Hospital mortality was 7.4% vs 4.8% vs 1.1% for STEMI, NSTEMI and UA respectively.
Conclusion: More patients with STEMI then ever reported before in Europe did receive acute reperfusion, primary PCI being the predominant treatment as recommended by the guidelines. Early invasive strategy was applied to about half of the NSTEMI patients. Hospital mortality was lowest in UA and highest in STEMI.

	STEMI/LBB n=8,854	NSTEMI n=7,688	Unstable Angina n=5,330	p-value
Age [years]	67	74	69	< 0.01
Female Gender	28.6%	35.1%	38.7%	<0.01
Prior MI	15.2%	28.6%	31.5%	<0.01
Prior PCI	8.3%	15.5%	21.0%	<0.01
Prior Bypass	2.2%	7.0%	6.7%	<0.01
Prior Stroke	5.2%	7.7%	4.7%	<0.01
Diabetes mellitus	21.8%	31.1%	28.0%	<0.01
Renal Failure	4.1%	10.0%	5.3%	<0.01
Fibrinolysis	25.1%	n.a.	n.a.	<0.01
Primary/Early PCI	56.1%	48.3%	34.7%	<0.01
GP IIb/IIIa	32.3%	18.9%	3.6%	<0.01
ASA	95.6%	93.9%	92.4%	<0.01
Clopidogrel	86.3%	84.3%	75.3%	<0.01
Hospital Mortality	7.4%	4.8%	1.1%	<0.01

P435 Persistent high levels of circulating whole blood tissue factor procoagulant activity in diabetic patients with acute coronary syndromes

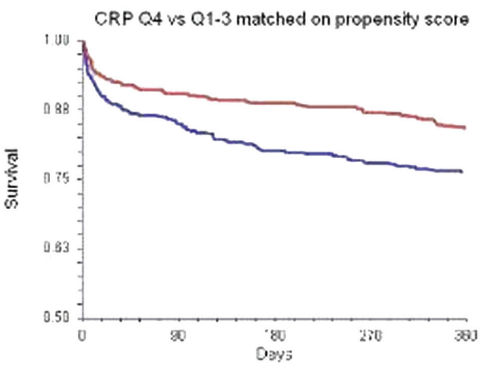
E. Guasch[1], X. Bosch[1], R. Hernandez[2], F. Verbal[1], M. Heras[1], E. Borquez[1], A. Galan[2], G. Escolar[2]. *[1]Cardiology Department, Thorax Institute, Hospital Clinic, Barcelona, Spain; [2]Hemotherapy and Hemostasis Department, Hospital Clinic, Barcelona, Spain*

Background: Diabetic (DM) patients (pts) with an Acute Coronary Syndrome (ACS) are at high risk of acute and recurrent events. Tissue factor (TF) is the principal initiator of blood coagulation and the determination of its circulating levels could be clinically useful in managing these pts.
Purpose: To examine serial levels of whole blood TF procoagulant activity in pts with an ACS with and without DM.
Methods: 70 pts with an ACS had blood sampling at admission and at 3 months, and underwent a Glucose Tolerance Test (GTT) after hospital discharge.Eighteen pts had a normal response (NL), 14 had impared glucose tolerance (IGT) and 38 were DM or had a DM response. All patients were treated from admission with aspirin and clopidogrel.
Results: At admission, plasma glycemia was lower in NL and IGT pts than in DM pts (125±39, 122±33, and 192±79 mg/dl; p<0.001), and directedly correlated with TF levels (44±51, 36±40, and 116±141 pg/ml respectively; p=0.001). Fibrinogen levels were similar in all groups (4±1.2, 3.9±0.7 and 3.8±1,3), as were the levels of F VIIa (3.6±0.6, 3.9±0.5 and 3.9±0.5) and of F XIIa (1.9±1, 1.8±0.6 and 1.6±0.9). At 3-month follow-up, TF levels remained significantly lower (p<0.05) in NL (75±67) and in IGT pts (19±17) than in DM pts (93±160).
Conclusion: Diabetic pts with ACS and acute hyperglycemia at admission have high levels of circulating TF that remain high 3 months after the acute event indicating the presence of a persistent procoagulant state that may predispose these pts to recurrent events.

P436 Prognostic impact on one-year survival of simple routine laboratory measurements at the acute stage of MI: the FAST-MI registry

J. Ferrieres[1], V. Bataille[1], B. Maillier[2], L. Ledain[3], P. Bonnet[4], G. Mulak[5], B. Pace[5], J.P. Cambou[5], T. Simon[6], N. Danchin[7] on behalf of FAST-MI invetigators. *[1]CHU de Toulouse - Hopital de Rangueil, Toulouse, France; [2]CHG, Troyes, France; [3]CHG, La Rochelle, France; [4]CHG, Le Havre, France; [5]Société Francaise de Cardiologie, Paris, France; [6]AP-HP - Hopital St Antoine, Paris, France; [7]European Hospital George Pompidou (AP-HP), Paris, France*

Background: The prognostic information yielded by routinely assessed inflammatory markers and blood cell counts is debated. Methods & results: We assessed correlations between mortality and casual measurements of CRP, WBC and hemoglobin at entry in 3059 consecutive patients admitted for AMI included in the nationwide French FAST-MI registry. In univariate analyses, all 3 parameters were strongly related to 1-year mortality (Table). Using x-variate Cox analysis including age, previous history, co-morbidities, GRACE score, sex and type of AMI, Q4 of CRP (>21 mg/L) (OR: 1.62, 95%CI: 1.17-1.24, p=0.003), of WBC (>12400/μL) (OR: 1.46; 95%CI: 1.06-2.02; p=0.02) and Q1 of Hb (<12.5 g/dL) (OR: 1.42; 95%CI: 1.03-1.95; p=0.033) were all independent correlates of 1-year



One-year survival

Univariate analyses: 1-year death rate

	Quartile1	Quartile 2	Quartile 3	Quartile 4	P value
CRP	7.3%	6.8%	11.4%	28.4%	<0.001
WBC	10.6%	10.5%	13.9%	17.7%	<0.001
Hb	27.0%	12.0%	8.7%	6.3%	<0.001

mortality. Propensity score matching for upper quartile of CRP showed significantly lower survival for Q4 patients (76% v 84%, p=0.003)(Figure). When the analyses were repeated on hospital survivors only, also including discharge medications, both Q4 of CRP (OR: 2.12; 95%CI: 1.44-3.13, p<0.001), and Q1 of Hb (OR: 1.51; 95%CI: 1.01-2.27, p=0.045) were independent correlates of 1-year death.

Conclusion: Simple laboratory measurements at entry are independent predictors of one-year mortality in patients with AMI.

P437 Heart rate is a predictor of left ventricular remodeling in patients with acute myocardial infarction

S. Okino, S. Fukuzawa, J. Sugioka, A. Ikeda, J. Maekawa, S. Ichikawa, T. Uchiyama, M. Inagaki. *Funabashi Municipal Medical Center, Funabashi, Japan*

Objectives: Heart rate (HR) has been shown as a predictor of major cardiovascular events in patients with coronary heart disease. We evaluated the relation between HR and left ventricular (LV) remodeling, which is detectable as LV dilatation and reduced LV function on echocardiograms, in patients with acute myocardial infarction.

Methods: We examined 198 patients with acute myocardial infarction undergoing primary angioplasty. Electrocardiograms and echocardiograms were assessed at the admission (Ad) and six months follow-up (FU). Ad-HR and FU-HR were classified according to larger tertile (82 and 68 beat per minute, respectively). LV enlargement at FU was defined as indexed end-systolic volume (LVESVI) >32 mL/m^2. Reduced LV function at FU was defined as ejection fraction (LVEF) <45%.

Results: LV enlargement was seen in 13.1% of patients and reduced LV function was seen in 16.7% of them at 6 months. Patients with Ad-HR >82 (n=64) had larger LVESVI (24.8±12.7 vs. 19.2±10.1 mL/m^2, p=0.002) and lower LVEF (51.2±11.2 vs. 55.7±9.4%, p=0.006). Patients with FU-HR >68 (n=63) had larger LVESVI (26.3±15.2 vs. 18.5±7.8 mL/m^2, p<0.001) and lower LVEF (49.3±11.7 vs. 56.6±8.5%, p<0.001). Among patients with admission HR <82, patients with FU-HR >68 (n=33) had larger LVESVI (24.4±15.6 vs. 17.5±6.8 mL/m^2, p=0.019) and lower LVEF (50.5±11.2 vs. 57.4±8.0%, p=0.002). Beta-antagonists were more administered to patients with FU-HR ≤68 than to those with FU-HR >68 (46.0% vs. 65.2%, p=0.011). By the multivariable logistic analysis, higher FU-HR was a predictor of larger LVESVI (odds ratio 1.085, 95% confidence interval 1.040 to 1.133, p<0.001) and lower LVEF (odds ratio 1.058, 95% confidence interval 1.016 to 1.102, p=0.006).

Conclusion: Admission HR and FU-HR were related with LV remodeling. Furthermore, even in the patients with lower admission HR, higher FU-HR was associated with LV remodeling. FU-HR was an independent predictor of larger LVESVI and lower LVEF.

P438 Brain natriuretic peptide and glycated haemoglobin A1c as predictors of mortality and new ischemic events after acute coronary syndrome

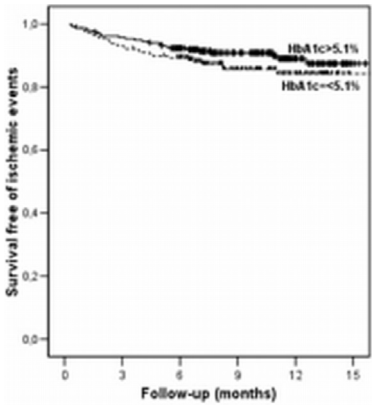
A. Garcia-Alvarez, A. Sionis, F. Bisbal, P. Ramos, M. Farrero, X. Bosch, M. Heras. *Hospital Clinico Universidad de Barcelona, Barcelona, Spain*

Purpose: To identify the best prognostic factors for mortality or new ischemic events during and after hospital admission with acute coronary syndrome (ACS).

Methods: A total of 855 consecutive patients admitted to a tertiary hospital from January 2006-2009 with ST-segment elevation acute myocardial infarction (STEMI), non ST-segment elevation acute myocardial infarction (NSTEMI) or unstable angina were prospectively included. Clinical, hemodinamic and serum analysis data were registered on admission. Information from revascularization procedures and systolic function was also recorded. Median follow-up was 10 months. Primary end-point was mortality or new ischemic events (STEMI, NSTEMI or refractory angina).

Results: Admission plasma glucose, haemoglobin, brain natriuretic peptide (BNP), creatinin, leucocytes and Killip's class were associated to re-infarction or mortality during admission. Logistic multivariate analysis showed BNP (median 84; interquartile range 158 pg/ml) as the best independent predictor for re-infarction or death during admission (OR 1.002; 95% CI 1.001 to 1.003). Age, haemoglobin, creatinin, Killip's class, left ventricular ejection fraction (LVEF), and glycated haemoglobin A1c (HbA1c) were associated to mortality or new ischemic events on follow-up. Multivariate Cox regression analysis showed HbA1c as the best independent prognostic factor for mortality or new ischemic events at follow-up independently of previous diabetes history (HR 1.22; 95% CI 1.03 to 1.45). Figure shows survival free of ischemic events according to HbA1c serum level (≤ or > median value).

Conclusion: BNP and HbA1c give essential prognostic information about the risk for death and new ischemic events on admission and mid-term follow-up after ACS.



Abstract 438 – Figure 1. HbA1c & survival free of ischemic events

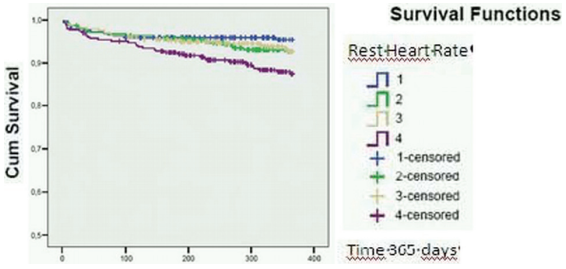
P439 Heart rate at admission independently predicts outcome in acute coronary syndrome patients

N. Antonio, C. Lourenco, R. Teixeira, R. Baptista, E. Jorge, M.F. Saraiva, P. Lazaro, P. Monteiro, M. Freitas, L.A. Providencia. *Coimbra University Hospital and Medical School, Coimbra, Portugal*

Purpose: To assess the impact of baseline heart rate (HR) in 1-year mortality of acute coronary syndrome (ACS) patients.

Population and methods: Retrospective analysis of 1367 consecutive patients in sinus rhythm admitted for ACS and followed for 1-year. Population was stratified by quartiles of resting HR at admission: Q1, 60-69 bpm; Q2, 70-75 bpm; Q3, 76-83 bpm; Q4, 84-100 bpm.

Results: Female gender (Q1:27%, Q2:29%, Q3:27%, Q4:36%, p=0.045), hypertension (Q1:72%, Q2:67%, Q3:72%, Q4:77%, p=0.031), hyperlipidemia (Q1:74%, Q2:66%, Q3:74, Q4:77, p=0.014), diabetes (Q1:27, Q2:28, Q3:30, Q4:35, p=0.046) and previous stroke (Q1:5.6%, Q2:3.9%, Q3:4.1%, Q4:9.0%, p=0.012) were more common in higher quartiles of HR; while pre-treatment with aspirin (Q1:48%, Q2:48%, Q3: 39%, Q4:34% p=0.007) and beta-blockers (Q1:32%, Q2:29%, Q3:24%, Q4:15%, p<0.001) decreased with increasing HR. Patients in Q4 had significantly lower ejection fraction (Q1:54.1±9.4%, Q2:52.6±10.1%, Q3:51.7±10.4%, Q4:49.3±11.0%,<0.001). Patients in higher quartiles had more ST elevation myocardial infarction and higher peak troponin I (Q1:29.9±42.5, Q2:30.2±59.1, Q3:40.3±61.0, Q4: 47.3±35.4, p=0.013), but were less submitted to an invasive strategy (Q1:72%, Q2:75, Q3:74, Q4:64, p=0.010). Patients in Q4 showed significantly worse 1-year survival. Moreover, in logistic regression analysis, HR>82 bpm was an independent predictor of 1-year mortality (OR:1.8; 95%CI:1.2-2.8), as were ejection fraction<50%, age >70 and Killip class >1 at admission, while previous beta-blocker use showed a protector effect.



Conclusions: High resting HR at admission is a simple measurement with important prognostic implications that should no longer be neglected in risk flow-charts in ACS patients.

P440 Major adverse cardiac events in patients with glucose metabolism disturbances, ICA, GADA autoantibodies after myocardial infarction - three years follow-up

T. Zielinska[1], A. Zielinska-Meus[2], J. Kowalczyk[1], R. Lenarczyk[1], M. Swierad[1], O. Kowalski[1], K. Oleszczyk[2], Z. Kalarus[1]. *[1]Department of Cardiology, Congenital Heart Diseases and Electrotherapy Medical University of Silesia, Zabrze, Poland; [2]Upper Silesian Rehabilitation Center "Repty" Department of Cardiac Rehabilitation, Tarnowskie Gory, Poland*

Purpose: The aim of this study was to assess the influence of glucose metabolism disturbances on incidence of major adverse cardiac events (MACE): death, myocardial infarct, PCI, CABG, stroke in patients (pts) after myocardial infarction treated by invasive methods - three years follow-up.

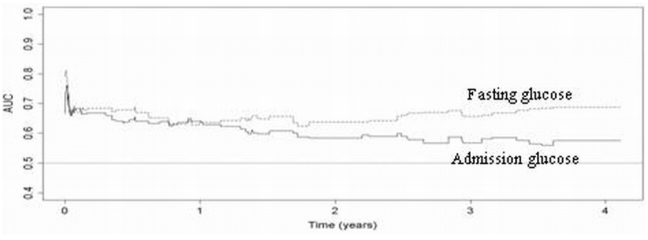
Methods: 257 consecutive pts admitted with acute myocardial infarction treated by invasive methods were examined. The OGTT (oral glucose tolerance test) was

carried out in pts without diabetic diagnosis in fifth day of hospitalization. ICA (islet cell antibodies) and GADA (glutamic acid decarboxylase autontibodies) were determined in diabetic pts to find out LADA (Latent Autoimmune Diabetes in Adults). Examined population was divided on two groups: group with glucose metabolism disturbances (GMD) and normal glucose metabolism (NGM). Incidence of MACE was compared in those two groups. In GDM the incidences of MACE were compared in subgroups with diabetes type 2 and LADA.
Results: Glucose metabolism disturbances were found in 60% subjects: diabetes type 2 was diagnosed in 18% pts, LADA in 9% pts, pre-diabetic state in 33% pts. MACE were observed in 60% of examined population, but in 75% of diabetic pts. The risk of death in GMD was significantly higher than NGM, RR 3,34 95% CI (0,99-11,27) p<0,001. In GMD incidence of MACE also occurred more often, RR 1,37 95% CI (1,01-1,86) p<0,04, especially in diabetic pts OR 4,53 95% CI (2,61-8,17) p<0,001. The risk of reinfarct caused by reoclusion of the same artery was also higher in diabetic pts, RR 1,38 95%CI (0,93-2,05) p<0,06. Positive GADA was independent strong predictor of MACE OR 6,91 95% CI (2,35-20,3) p<0,001 (multiple logistic regression analysis).
Conclusions: Glucose metabolism disturbances were strong predictors of risk of death after myocardial infarction. The higher risk of MACE occurred in all patients with glucose abnormalities, and increased in diabetic patients, particularly with LADA.

P441 Shape and time-course prognostic value of admission and fasting glucose in diabetic and non-diabetic patients with acute coronary syndrome

A.B. Cid Alvarez[1], F. Gude[2], J.M. Garcia-Acuna[1], E. Gonzalez Babarro[1], C. Cadarso Suarez[3], M.X. Rodriguez-Alvarez[3], R. Trillo Nouche[1], J. Garcia Seara[1], A. Varela-Roman[1], J.R. Gonzalez-Juanatey[1]. *[1]Department of Cardiology, Hospital Clinico Universitario, Santiago De Compostela, Spain; [2]Department of Clinical Epidemiology, Hospital Clinico Universitario, Santiago De Compostela, Spain; [3]Department of Statistics and Operations Research, University of Santiago de Compostela, Santiago De Compostela, Spain*

Purpose: In patients with ACS, increased plasma glucose levels are associated with worse outcome. The prognostic value of the fasting glucose (FG) relative to that admission glucose (AG) remains unclear. We aimed to ascertain and compare the predictive ability of AG and FG for short- and long-term mortality in patients with acute coronary syndrome (ACS), with or without diabetes mellitus.
Methods: The study involved 811 consecutive patients who were admitted in our center with a diagnosis of ACS. Patients were classified as having diabetes and the primary study outcome measure was 4-year all cause mortality. Due to the non linear effect of the glucose values on mortality, for the statistical analysis smoothing was introduced in the models by using natural cubic splines.
Results: The primary endpoint was observed in 151 patients (16,8%). The FG and the AG levels were higher in deceased (p<0,001) We found a clear U-shaped relationship between fasting glucose values and mortality rates in non diabetic patients, this relationship persist after multivariate adjustment (lowest hazard rates in 110 mg/dl; for 74 mg/dl HR 2,55 (CI 1,07-6,04); for 252 HR 9,17 (CI 4,11-20,43)). The ROC prediction models over time show that the prognostic power in non diabetic patients, is similar for both AG and FG up to one year follow-up, after one year FG presents AUC values around 0.7, while AUC of AG decreases (p <0.05) (See Picture).



Comparison FG/AG in non diabetic group

Conclusions: Admission and fasting plasma glucose are a strong predictors of mortality after ACS. In non diabetic patients the association with the mortality risk is similar for both, AG and FG, in the early post ACS period; but the FG is better predictor of long term mortality. There was a U-shaped relationship between FG values and mortality rates in the non diabetic population.

P442 Repolarization duration as a prognostic marker of cardiac death in patients with anterior myocardial infarction treated with primary PCI- results of prospective 36 months follow-up

K. Szydlo, K. Wita, M. Trusz-Gluza, Z. Tabor. *I Department of Cardiology, Medical University of Silesia, Katowice, Poland*

Prolonged, diurnal analysis of QT interval, as well early and late phase of it, often fails in patients with acute myocardial infarction (AMI) because of dynamic ST-T segment changes. The purpose of this study was to analyze prospectively if repolarization measured in one hour period, may be a predictor of cardiac death in patients with anterior AMI treated with primary PCI.
Methods: The study population consisted of 115 patients with first anterior MI (87 males, age: 58±11 years, LVEF: 41±7%) treated with primary PCI of left anterior descending coronary artery. All subjects were observed prospectively during 36 months follow-up. Holter recordings were performed in the 5th day of AMI. Repolarization parameters: QT, QTpeak and TpeakTend were assessed from 1 hour (between 1-4 a.m.) in which ST-T segment facilitated automatic beat-to-beat analysis of more than 95% of the recording. Bazzet'z formula was used for heart rate correction.
Results: During 36 moths follow-up 10 cardiac deaths occurred (CD) and 105 subjects were alive: age- 63±13 vs. 58±11 years, p=0.22 and LVEF: 35±7% vs. 41±7%, p=0.01; respectively. Both QTc and TpeakTendc were longer in CD group: 457±30 ms vs. 436±26 ms, p=0.03 and 111±18 ms vs. 94±17 ms, p=0.034; respectively. QTpeakc did not differentiate both groups: 346±31 ms vs. 342±29 ms, p=0.76. Predictive values of QTc and TpeakTendc were calculated with Receiver Operating Characteristics analysis (table).

Predictive values of QTc and TpeakTendc

Cut-off value	QTc = 470 ms	TpeakTendc = 111 ms
Sensitivity	30%	60%
Specificity	91.5%	86%
Positive predictive value	25%	28.5%
Negative predictive value	93%	95.7%

Conclusions: Greater heterogeneity of the spatial and temporal repolarization processes are prognostic markers of cardiac death in patients after acute anterior infarction with high specificity and negative predictive values. One hour of analysis seems to be sufficient for risk stratification of these patients.

P443 Predictors of 30-day major adverse cardiovascular events after primary percutaneous coronary intervention in patients pretreated with 600 mg clopidogrel

I. Mrdovic[1], L. Savic[1], M. Asanin[1], J. Perunicic[1], R. Lasica[1], J. Marinkovic[2], Z. Vasiljevic[3], M. Ostojic[3] on behalf of RISK-PCI. *[1]Clinical Center of Serbia, Beograd, Serbia; [2]Institute for statistics, Beograd, Serbia; [3]Cinical Center of Serbia, Beograd, Serbia*

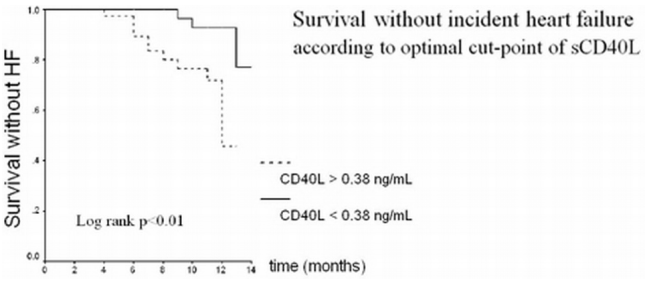
Purpose: There is a lack of data regarding predictors of major adverse cardiovascular events (MACE) following primary percutaneous coronary intervention (pPCI) in patients pretreated with 600 mg clopidogrel. We sought to identify risk factors for 30-day MACE after pPCI.
Methods: The RISK-PCI study cohort, included 1166 consecutive STEMI patients undergoing pPCI after pretreatment with 300 mg aspirin and 600 mg clopidogrel. The primary composite end points of the trial (cMACE) comprise 30-day death, nonfatal reinfarction, ischemic stroke and target vessel revascularization. A logistic regression model, using clinical, procedural and angiographic parameters available at the time of intervention, was developed to predict 30 day cMACE after pPCI. ROC analysis was used to identify cut-of values. Results cMACE occurred in 123/1166 (10.5%) patients during the 30-day follow-up. Univariable analysis identified clinical, procedural and angiographic differences between groups with and without cMACE. Multivariable regression analysis and ROC analysis showed following independent predictors of 30-day cMACE: prior PCI (HR 6.15), number of stents implanted per patients >3 (HR 4.42), hypotension at admission (HR 2.41), LV EF < 45% (HR 1.83), anterior STEMI (HR 1.79), creatinine clearance < 60 ml/min (HR 1.77) and IRA thrombus present (HR 1.73). Conclusions In RISK-PCI patients, 30-day cMACE can be predicted using clinical (previous PCI, hypotension, anterior STEMI, creatinine clearence, EF), procedural (number of stents implanted) and angiographic (IRA thrombus) data available at the time of intervention.

P444 Prognostic value of sCD40 Ligand in outpatients after acute myocardial infarction

M. Radosavljevic Radovanovic[1], Z. Vasiljevic[1], N. Radovanovic[1], P. Mitrovic[1], J. Marinkovic[2], S. Stankovic[3], L. Savic[1], B. Stefanovic[1], G. Krljanac[1], R. Lasica[1]. *[1]Institute of Cardiovascular Disease, Clinical Center of Serbia, Belgrade, Serbia; [2]Institute of statistics, Medical School, Belgrade, Serbia; [3]Institute of medical biochemistry, Belgrade, Serbia*

Purpose: Based on its role in inflammation, matrix degradation and platelet activation we hypothesized that sCD40 ligand could aid in risk prediction of outpatients after acute myocardial infarction (AMI).
Methods: Blood was drawn in the morning from 100 randomly selected stable patients who were younger then 70 years and without any systemic,malignant or hepatic disease, 6 months after AMI. We measured plasma levels of sCD40L, NT pro-BNP and hsCRP according to standard methods and manufactor's advice. Patients were followed-up for 14 months for new coronary events (NCE) and incident heart failure (HF).
Results: According to multivariate Cox regression analysis, which included all conventional risk factors as well as novel biomarkers, sCD40L was a significant

predictor of incident HF (OR 3.92, 95%CI 0.98 to15.81; p=0.04), together with NT pro-BNP (OR 7.43, 95%CI 1.49 to 36.89; p=0.01) and hyperglycaemia (OR 4.92, 95%CI 1.25 to 19.43; p=0.02). As assesed by ROC analysis, the optimal cut-point of sCD40L for the prediction of incident HF was 0.38 ng/mL, with sensitivity of 81% and specificity of 60%. As presented in Figure, cumulative survival free of heart failure in patients with CD40L>0.38 ng/mL was significantly lower than in patients with sCD40L<0.38 ng/mL (Log rank p=0.001). On the other side, sCD40L was not a significant predictor of NCE. Another interesting finding was a high correlation between ln CD40L and ln NT pro-BNP (r=0.75, p=0.001).



Survival without incident HF

Conclusion: In our study sCD40L was an independent predictor of new-onset heart failure in stable outpatients after acute myocardial infarction. The optimal cut-off value was 0,38 ng/mL. New coronary events were not predicted by sCD40L level. There was a strong correlation between sCD40L and NT pro-BNP.

P445 Matrix metalloproteinase-2 predicts cardiac mortality and heart failure hospitalization after acute myocardial infarction

K. Yajima[1], N. Ohte[2], S. Tanaka[1], T. Kawamiya[1], T. Fujimaki[1], K. Kato[1], T. Hibino[1], K. Yokoi[1], G. Kimura[2]. *[1]Gifu Prefectural Tajimi Hospital, Tajimi, Japan; [2]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

It has been acknowledged that matrix metalloproteinases (MMPs) are associated with the development of left ventricular remodeling after acute myocardial infarction (AMI). The prognostic values of MMPs levels in patients with an AMI have not been fully elucidated. Thus, we investigated the involvement between serum levels of a series of MMP-related proteins and mortality after AMI.
Methods: We studied 190 consecutive patients with an AMI (81 anterior wall MI, 75 inferior, 20 posterior, 11 lateral and 3 left main trunk occlusion). We measured serum levels of MMP-1,-2,-9, and tissue inhibitor of matrix metalloproteinase (TIMP)-1,2 on the first admission day with the ELISA method along with BNP and high sensitivity C-reactive protein (hs-CRP) levels. The patients were followed prospectively for the occurrence of either cardiac mortality or hospitalizations due to heart failure (HF). Cox regression analysis was performed with adjusting for age and other significantly correlated biomarkers.
Results: Patients were followed for a median of 19 months. Eleven patients died of cardiac disease and 12 were hospitalized for HF. MMP-2 level above 661ng/dl, BNP level above 91.3 pg/ml and hs-CRP level above 1570 ng/ml at a cutoff of mean serum level were predictive of combined cardiac mortality and HF hospitalization after AMI (p=0.0016, p=0.0012, p=0.0379, respectively). In Cox regression analysis, patients with MMP-2 level above 661 ng/ml were 3.3 times more likely to either die of cardiac disease or be hospitalized due to HF after AMI as compared with patients with MMP-2 levels below this cutoff point (p=0.018). MMP-1,9 and TIMP-1,2 levels were not predictive of end points.
Conclusion: This study demonstrates that MMP-2 level is an independent and powerful predictor of cardiac mortality and HF hospitalization in AMI patients.

P446 Brain natriuretic peptide and left ventricular volume and function recovery after myocardial infarction: determinants and clinical utility of early and follow-up measurements

J. Zalewski[1], N. El Massri[1], E. Stepien[2], K. Zmudka[1]. *[1]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [2]John Paul II Hospital, Cracow, Poland*

Purpose: N-terminal pro-brain natriuretic peptide (NT-proBNP) is useful in the diagnosis, risk stratification and prognosis of patients with heart failure. We sought to investigate determinants and clinical utility of early and follow-up NT-proBNP measurements in predicting of left ventricular (LV) volume and function recovery after ST-elevation myocardial infarction (STEMI).
Methods: 186 STEMI patients underwent facilitated angioplasty (PCI) were analyzed. NT-proBNP concentration (pg/ml) was measured 2 days (2D) and 6 months (6M) after PCI. At the same time echocardiography was performed in order to measure LV end-diastolic volume index (LVEDVI, ml/m^2), end-systolic volume index (LVESVI, ml/m^2) and ejection fraction (LVEF, %). The differences between measurements at 6M and at 2D were expressed as Δ=6M-2D and Δ%=6M-2D/2D$\times$100%. Simultaneous Δ%-LVEF decrease and Δ%-LVEDVI increase of >10% determined LV remodelling (LVR).
Results: 2D-NT-proBNP was moderately correlated with 2D-LVEF, 2D-LVESVI and 2D-LVEDVI (r=-0.52, r=0.48, r=0.4, respectively, p<0.001 for all). At 6M, corresponding NT-proBNP correlations considerably improved (r=-0.74, r=0.78, r=0.74, respectively, p<0.001 for all). The independent determinants of early 2D-NT-proBNP value were CK-MB release during 48 hours of reperfusion (OR=3.02, 95%CI=1.56-4.48, p<0.001), age (3.87, 1.51-6.23, p=0.001), 2D-LVEF (-4.23, -7.35–1.10, p=0.008) and 2D-LVEDVI (1.61, 0.17-3.05, p=0.029). The only LV-related parameters independently influenced Δ-NT-proBNP value (Δ-LVEDVI: OR=6.21, 95%CI=4.28-8.13, p<0.001; Δ-LVEF: -9.02, -12.37–5.7, p<0.001) and 6M-NT-proBNP value (6M-LVEDVI: 5.17, 3.53-6.82, p<0.001; 6M-LVEF: -6.63, -9.53–3.72, p<0.001). In 17 (9%) patients with LVR NT-proBNP level increased from 702$\pm$243 at 2D to 902$\pm$284 at 6M (p=0.002) whereas in non-LVR patients NT-proBNP concentration decreased from 498$\pm$169 at 2D to 396$\pm$162 at 6M (p<0.001). The area under the receiver operating characteristic (ROC) curve for predicting LVR increased from 0.77 for 2D-NT-proBNP and from 0.91 for Δ%-NT-proBNP to 0.95 for 6M-NT-proBNP. The cutoff 6M-NT-proBNP value of 550 pg/ml predicted LVR with 80% of sensitivity and 86% of specificity.
Conclusions: The early NT-proBNP concentration was mainly predicted by the size of myocardial necrosis and the age of patient whereas follow-up value was influenced only by LV-related parameters. A single, follow-up measurement of NT-proBNP has turned out the most accurate in determination of LV volume and function recovery.

P447 Determinants of survival in the current era of cardiac ventricular rupture after acute myocardial infarction

A. Koh, Y.J. Loh, Y.P. Lim, J.L Tan. *NATIONAL HEART CENTRE, Singapore, Singapore*

Background and aim: In acute myocardial infarction (AMI), ventricular free wall rupture and ventricular septal rupture (VSR) are complications associated with morbidity and mortality.In this current era of thrombolysis, percutaneous coronary intervention (PCI) and progress in surgical care, we aim to review the influence of patient characteristics and management strategies on outcome.
Methods: Between 1997 and 2008, we reviewed all patients who were admitted with free wall rupture and VSR immediately post-AMI.
Results: Thirty-one patients were included with a mean age 70$\pm$11 years and more females (58%). Overall incidence of ventricular rupture post-AMI was 0.6%. 84% had vascular risk factors; hypertension was commonest (67%). Anterior wall AMI (84%) and apical VSR (68%) formed the majority. Non-anterior wall AMI accounted for 75% of non-apical VSR. 45% received thrombolysis or percutaneous coronary intervention. Median time to rupture was 1 day from diagnosis of AMI. 58% were in Killip class 3 or 4. Mean left ventricular ejection fraction (LVEF) was 33$\pm$10%. 81% required intra-aortic balloon counterpulsation for hemodynamic support. 71% of patients underwent open surgical repair and 74% within the first day of rupture diagnosis. 29% had concomitant CABG. Those managed medically were older (p=0.002) with lower LVEF (p=0.03).Overall mortality rate was 55%. Prior thrombolysis (p=0.46) or percutaneous coronary intervention (PCI) (p=0.07) did not influence outcome. Surgical and medical survival rates were 64% and 33% respectively (p=0.23). Non-anterior wall AMI (p=0.006) and advanced age (p=0.008) were associated with poor in-hospital survival.
Conclusions: Compared to older reports, incidence of ventricular wall rupture post-AMI in the current era appears to have declined. Predictors of adverse in-hospital survival were non-anterior wall AMI and advanced age. Prior thrombolysis or PCI did not influence outcome.

P448 Depression of initial values of overall heart rate variability and risk of reinfarction

Y.G. Kevorkova, R.D. Kurbanov. *Republican Specialized Center of Cardiology, Tashkent, Uzbekistan*

Purpose: to study of interrelation of initial level of overall heart rate variability (HRV) with the risk of reinfarction within 1 year after Q-wave myocardial infarction (QMI).
Materials and methods: the object of the study were 134 men in the age 29-73 (middle age 52.2$\pm$9.2) having QMI. All patients were included to study on 10-14 days after by QMI against the standard therapy including antiplatelet agents, β-blockers, ACE inhibitors, statins and, at necessity, nitrates in individually titrated doses. To all patients 24h monitoring of an electrocardiogram with a measurement of HRV has been performed. The obtained HRV parameters were interpreted according with "Standards of measurement, physiological interpretation, and clinical use of HRV" (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). For depression of overall HRV the SDNN <100 ms was accepted. The endpoints were considered fatal or non-fatal reinfarction.
Results: Depending on SDNN initial level all patients have been parted on two groups: 1st group included 74 patients with SDNN$\leq$100 ms, 2nd group – 60 patients with SDNN> 100 ms. 1st group has considerable differences from 2nd group on age (54.8$\pm$8.6 years vs. 48.7$\pm$8.84, p=0,0002) and frequency of occurrence of a diabetes mellitus (10.8% vs. 1.6%, χ2=4,42, p=0.03). The amount of patients with anterior localization of QMI in 1st group was bigger, than in 2nd one,

however these differences were not considerable (70.3% vs. 56.6%, $\chi 2=2.67$, p=0.1). There were not essential differences between two groups under other clinical characteristics. Within the first year after QMI 14 patients (18.9%) in 1st group have reinfarction, including 5 patients (6.7%) with fatal reinfarction, while in 2nd group the reinfarction was registered only in 4 patients (6.6%) ($\chi 2=4.28$, p=0.004).
Conclusions: Frequency of reinfarction within 1 year after QMI, in our study was in inverse proportion dependence with the level of overall HRV, and particularly with SDNN, measured in acute period of QMI.

P449 Worsening renal function but not baseline creatinine levels adversely affects one year mortality in patients with myocardial infarction. The HEROES registry

G. Lazaros, D. Tsiachris, A. Patialiakas, A. Karavidas, S. Vogiatzoglou, S. Archontakis, C. Masoura, C. Vlachopoulos, D. Tousoulis, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Objective: The association between a history of renal insufficiency and poor outcome in patients with acute coronary syndrome is well known. However, little information is available about in-hospital worsening of renal function. Our goal was to determine the prognostic impact of in-hospital worsening of renal function in patients with myocardial infarction (MI).
Methods: We studied 324 patients admitted at our Coronary Care Unit from September 2006 to January 2008 with the diagnosis of acute MI within 12 hours of symptoms' onset and included in our internal MI registry. From blood sample obtained on admission white blood count, high sensitivity C-reactive protein (CRP), troponin I (TnI), plasma glucose and creatinine (Cr) were determined. Peak TnI and peak Cr levels were also measured throughout hospitalization. Natural logarithmic transformation was used for CRP and TnI analyses. Worsening renal failure was defined as Cr elevation $\geq$0.3mg/dl. All patients enrolled underwent coronary arteriography during in-hospital stay and the presence of underlying coronary artery disease was recorded. Ejection fraction was estimated on admission with 2D echocardiography by applying the Simpson's rule. The primary endpoint was 1-year mortality from any cause.
Results: Mortality rate after 1-year follow up was 16% (52 deaths). Worsening renal function at baseline was present in 72 patients (22.2%). Patients with in hospital Cr elevation compared with those without worsening of renal function exhibited significantly higher 1-year mortality (42.3% vs. 8.8%, $p<0.0001$). Univariate Cox regression analysis revealed that age (HR 1.063, $p<0.001$), female gender (HR 3.124, p=0.001), ejection fraction (HR 0.914, $p<0.001$), peak TnI (HR 1.989, p=0.005), plasma glucose levels (HR 1.003, $p<0.001$), white blood count (HR 1.091, p=0.012), logCRP (HR 2.748, $p<0.001$) as well as the presence of worsening renal function (HR 6.085, $p<0.001$) but not admission Cr levels (HR 1.16, p=0.07) were associated with the incidence of mortality. By applying multivariate Cox regression analysis, the presence of worsening renal function (adjHR 3.4, $p<0.001$), ejection fraction (adjHR 0.922, $p<0.001$) and female gender (adjHR 2.14, p=0.037) turned out to be the only prognosticators of death.
Discussion: In-hospital worsening of renal function in contrast to baseline Cr levels appears to be a strong independent predictor of late mortality in patients with MI. Physicians monitoring MI patients should be aware that mild changes in renal function even in the normal range are associated with adverse outcomes.

MECHANISMS OF DISEASE IN ACUTE AND CHRONIC CORONARY SYNDROMES

P450 ACS in patients with and without spontaneous dissections of coronary arteries. The DISCOVERY study

A. Fontanelli[1], L. La Vecchia[1], A. Benettin[2], C. Bonanno[1], E. Cabianca[1], A. Desideri[3], A. Santarelli[4], A. Manari[5], A. Benassi[6], L. Pagliani[7] on behalf of on behalf of the DISCOVERY Committee. *[1]Ospedale Civile San Bortolo, Vicenza, Italy; [2]Ca' Foncello Hospital, Treviso, Italy; [3]Hospital of Castelfranco (Treviso), Castelfranco Veneto, Italy; [4]Ospedale Infermi di Rimini, Rimini, Italy; [5]Hospital of Reggio Emilia, Reggio Emilia, Italy; [6]Hesperia Hospital, Modena, Italy; [7]Ospedale Civile San Bortolo, Vicenza, Italy - Università degli studi di Padova, Padova, Italy*

Background: Spontaneous coronary artery dissection (SCAD) is an unusual, life threatening cause of acute myocardial ischemia. Over 200 cases of SCAD have been reported in the literature but, most of the available clinical information about SCAD derives from case reports and prospective data are lacking. The purpose of this multicenter study, named DISCOVERY (DISsection of COronary Arteries: Veneto and Emilia RegistrY) was to prospectively assess clinical characteristics, treatment and outcome of SCAD pts. w/o spontaneous dissections with comparable age and gender and to attempt to assess the role of SCAD in the pathogenesis of Acute Coronary Syndromes (ACS) and to determine whether peculiar clinical characteristics may help in defining a diagnostic pattern for SCAD-ACS.
Methods: From October 2005 to December 2007, 42 consecutive pts (33F 9M, mean age 51 yrs) were enrolled in the Cardiology Units of the Veneto and Emilia Romagna regions. Only cases of angiographically-proven spontaneus dissection of major coronary branches or collaterals were included. Concomitantly, the first incoming ACS patient following a SCAD patient of comparable age and sex was enrolled. Insodoing, a control group of non-SCAD ACS was obtained. In the present analysis we report data on the group of SCAD and non-SCAD ACS pts in order to analyze the differences in presentation, treatment strategies and outcome.
Results: In the SCAD-ACS group, no case was associated with peripartum period, nor any showed associated carotid disease or lens subluxation. Baseline clinical characteristics were similar in SCAD and non-SCAD ACS. However, SCAD pts had fewer risk factors (r.f.) for coronary disease (1.6 vs 3.3 p=0.0016), The LAD coronary artery was more commonly involved in SCAD. Also, the presenting ecg pattern was more frequently ST elevation in SCAD compared to non-SCAD (58% vs 33%). Treatment strategies were significantly different in the 2 groups: 54% of SCAD population had conservative treatment vs 31% in the control group (p=0.002). In revascularized pts, PCI was by far the preferred treatment option. All pts were discharged alive in both groups. During a 18 month f.u., the incidence of MACE was 2.3% in SCAD vs 27% in non-SCAD ($p<0.001$).
Conclusions: Our data show that SCAD-ACS pts have fewer coronary r.f. compared to non-SCAD-ACS of comparable age, are less prone to undergo revascularization (especially PCI) and exibit a much better long-term prognosis. Some features of SCAD-ACS which are traditionally considered suggestive of SCAD (such as peripartum period or contraceptive use) do not appear to be such in our series.

P451 Myocardial infarction in patients without significant lesions in coronary arteries

A.M. Frycz-Kurek[1], M. Gasior[1], T. Kurek[1], M. Gierlotka[1], D. Kawecki[2], E. Nowalany-Kozielska[2], Z. Kalarus[1], L. Polonski[1]. *[1]Silesian Center for Heart Diseases, Zabrze, Poland; [2]II Department of Cardiology, Medical University of Silesia, Zabrze, Poland*

Background: Myocardial infarction in persons without significant lesions in coronary arteries is a complex problem, which etiology is not fully explained and which often causes many diagnostic issues. There is few data in literature on myocardial infarction with normal coronary angiography and long-term prognosis of such patients. The aim of the study was to assess the percentage of patients with myocardial infarction without angiographically significant lesions in coronary arteries referred for angiography, rate of adverse cardiovascular events in long-term follow-up and to compare left ventricular ejection fraction in in-hospital period and follow-up.
Material and methods: Between January 2002 and September 2006, 5673 patients have been admitted with ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), and all of them underwent coronary angiography. 122 of them had no angiographically significant changes in coronary arteries. This group was further analyzed, with regard to clinical and echocardiographical parameters, in-hospital course and follow-up.
Results: The selected group of 122 was 2.15% of all patients treated for myocardial infarction in this period. Mean patient age was 47, most of patients were males. Hypertension (in half of the patients) and excessive weight and obesity (67% of patients) were the most common risk factors of coronary artery disease. In almost 40% of the studied population thoracic pain and elevation of serum myocardial necrosis enzymes were preceded by upper airway infection, and in 90% of patients the pain occurred for the first time. There was statistically significant improvement of left ventricular ejection fraction from 50,9% in in-hospital course to 55,8% ($p<0,0001$) in follow-up. In over half of the patients (61%) ejection fraction improved with time, and in 10% deteriorated. Decreased ejection fraction in echocardiography during hospitalization was an independent predictor of LV ejection fraction improvement in follow-up. Mortality in follow-up (mean follow-up time 31 months) was 7.37%, 19 patients (15.57%) were hospitalized again due to cardiac reasons, and 3 (2,46%) had myocardial infarction diagnosed.
Conclusions: 1) in most patients left ventricular ejection fraction improves or remains stable, while 10% experience progressive impairment of ejection fraction; 2) long-term prognosis in major clinical endpoints, such as all-cause death, stroke, myocardial infarction, rehospitalization due to cardiac reasons is good.

P452 Thin fibrous cap and plaque rupture predict worse outcome of thrombolytic therapy. An optical coherence tomography study

M. Riga[1], K. Toutouzas[2], A. Karanasos[1], A. Synetos[1], M. Drakopoulou[1], E. Tsiamis[1], A. Androulakis[1], D. Tousoulis[1], E. Stefanadi[1], C. Stefanadis[1]. *[1]Hippokration General Hospital of Athens, Athens, Greece; [2]University of Athens, Athens, Greece*

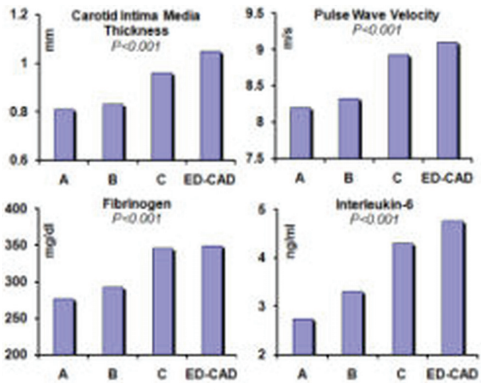
Purpose: Primary PCI has become the standard of care in ST-elevation myocardial infarction (STEMI). Nevertheless, PCI is not always available, and thrombolysis remains a popular treatment option. Thrombolytic therapy, however, fails in a significant percentage of patients (pts). Moreover, there are no morphological characteristics of the culprit lesion (CL) prediciting the success of thrombolysis. High risk characteristics for acute coronary syndromes include the presence of plaque rupture and fibroatheromas with cap thickness measuring below 65 μm. Optical Coherence Tomography (OCT) is a method with high accuracy for the identification of plaque rupture that provides exact measurements of cap thick-

ness. We hypothesized that the thickness of the fibrous cap and the incidence of plaque rupture at the CL are related to the outcome of thrombolysis.
Methods: We included 20 pts (16 men – 4 women, mean age 61±5.6 years) with STEMI who underwent thrombolysis with tenecteplace within 4 hours since the initiation of chest pain. Coronary Angiography was performed within 24 hours following thrombolysis and TIMI flow was recorded. TIMI flow III was assigned as successful thrombolytic therapy. The CL was investigated by OCT. In target vessels with TIMI flow 0 thrombus aspiration was performed. Fibrous cap thickness (FCT) was measured at its thinnest part and the presence of plaque rupture was recorded. Plaque rupture was defined as a disruption of the fibrous cap, over a lipid pool.
Results: We examined 20 culprit plaques of 20 pts. Seven of 20 pts (35%) had successful thrombolysis. Mean FCT was measured to be 56±15 μm in the entire cohort of pts and at least one plaque rupture was identified in 13 lesions. In the group with successful thrombolysis mean FCT was 85±29 μm, while in the group with unsuccessful thrombolysis mean FCT was 43±9 μm ($p<0.01$). At least one rupture was identified in 12 of 13 CL (92.31%) in the group with failed thrombolysis, while in the group with successful thrombolysis only one plaque rupture was found (14.29%, $p<0.01$). We categorized plaques according to plaque thickness (thin ≤ 65 μm; thick > 65 μm). Six of 7 pts (85.71%) with successful thrombolysis had thick cap, while in the group of pts with failed thrombolysis all pts (100%) had thin fibrous cap ($p<0.01$).
Conclusions: Our results indicate that successful thrombolytic therapy is associated with greater fibrous cap thickness and reduced incidence of plaque rupture in the CL of pts with STEMI. This study suggests that specific morphological features of the CL could predict the outcome of thrombolytic therapy in pts with STEMI.

P453 Arterial stiffness, carotid intima media thickness and systemic inflammation are gradually associated with increasing duration of erectile dysfunction

N. Ioakeimidis, C. Vlachopoulos, K. Aznaouridis, D. Terentes-Printzios, A. Bratsas, D. Tsekoura, A. Tsokanis, K. Rokkas, T. Askitis, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: Erectile dysfunction (ED) precedes coronary artery disease (CAD) by about 3 years, on average. Carotid intima media thickness (cIMT), aortic stiffness and low-grade systemic inflammation could be important elements of the association between ED and CAD. We evaluated cIMT, aortic stiffness and inflammatory state in relation to duration of ED.
Methods: 199 consecutive asymptomatic men with ultrasonography documented ED, were prospectively evaluated for CAD. According to angiographic evidence of CAD, patients were divided as follows: 55 men (61±8 yrs, mean time interval of ED= 3 yrs) with CAD (ED-CAD Group) and 144 men (58±10 yrs) without CAD. Men without CAD were divided into three groups, on the basis of ED duration: Group A (<2 yrs, n=56), group B (2-3 yrs, n=45) and group C (>3 yrs, n=43). Ultrasound-determined cIMT, carotid-femoral pulse wave velocity (PWV) as an index of aortic stiffness and levels of fibrinogen and interleukin-6 (IL-6) were used to evaluate progression of atherosclerosis.
Results: PWV, cIMT and levels of fibrinogen and IL-6 were comparable among ED-CAD patients and patients of group C and higher of those in men of groups A and B ($P<0.001$, figure). In men without CAD, there was a stepwise augmentation in PWV, cIMT and inflammatory markers throughout increasing duration of ED. This last relationship remained significant in multivariate analysis ($P<0.05$ by ANCOVA) after adjusting for age, mean pressure, metabolic profile and smoking.



ED duration, cIMT, PWV and inflammation

Conclusions: In ED patients, the longer duration of ED, the greater the progression of cIMT and impairment of aortic elastic properties and the higher level of fibrinogen and IL-6. This finding may partially elucidate the complex mechanisms linking ED with generalized vascular disease.

P454 Cardiac microvascular dysfunction in diabetes and insulin treatment: role of glucose-induced PKC-βII activity

Z. Yin, H.C. Wang, L.P. Wel. *THE FOURTH MILITARY MEDICAL UNIVERSITY, XIAN, China, People's Republic of*

Purpose: Diabetes mellitus is an independent risk factor for cardiovascular disease and little attention is addressed on PKC-βIIin cardiac microvascular dysfunction.
Methods: In animal experiment, normal Sprague-Dawley rat, streptozotocin-induced diabetic rat, insulin-treated and physiological saline-treated diabetic rat were administrated with a serial of evaluations including pressure measurements, angiogenesis and permeability observations under electron microscope, histopathologic analysis for cardiac microvascular endothelium cell (CMECs), TUNEL, and Western blotting for PKC-βII. In cell research part, CMECs in four different mediums (normal medium, high-glucose concentration medium, insulin-stimulated and physiological saline-stimulated high-glucose medium) were investigated with MTT, apoptosis, quantitative permeability assessment and Western blotting.
Results: 1. Accompanied with more active expression of PKC-βII and higher apoptosis rate in diabetic model, either increased microvascular permeability or pathological angiogenesis is observed, and which is attenuated in certain extent while receiving insulin treatment. 2. Accordant results from cell research were obtained. Compared with normal group, CMECs in high-glucose medium are demonstrated with poor proliferation, more notable apoptosis, increased permeability of cell monolayer, and augmented PKC-βII expression. Insulin-stimulated group poses a midst performance between normal and high-glucose group.

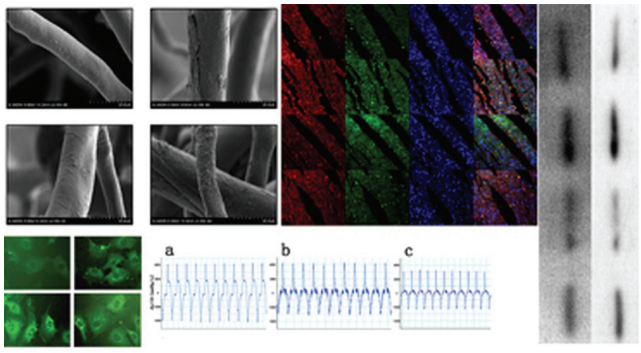


Figure 1

Conclusions: Increased PKC-βII activity has been implicated responsible for the pathogenesis of cardiac microvascular dysfunction in diabetes and elevated glucose is sufficient to induce these effects. PKC-βII is indicated to occupy an important position in the whole process of insulin treatment.

P455 Insulin induces the release of endothelial barrier stabilizing factor from platelets via PI3K/Akt-Nitric Oxide pathway

D. Guenduez[1], J. Thom[1], M. Aslam[2], I. Hussain[1], F.V. Haertel[2], M. Grebe[1], A. Erdogan[1], D. Sedding[1], T. Noll[2], H. Tillmanns[2].
[1]*Universitaetsklinikum Giessen und Marburg GmbH, Giessen, Germany;*
[2]*Universitaet Giessen Physiologisches Institut, Giessen, Germany*

Introduction: Recent findings suggest that besides its metabolic effects, insulin also modulates the cardiovascular functions. The failure of endothelial barrier function is one of the earliest manifestations of inflammation and atherosclerosis. The importance of insulin for the endothelial barrier functions in these (patho-)physiological conditions have not been well understood. The strong vascular protective effects of insulin are not explainable alone by its effect on endothelial cells.
Objective: The central hypothesis of the present study was to analyze the mechanism of insulin on platelets-mediated endothelial barrier function.
Methods: The study was performed on well established in vitro model of isolated human platelets and cultured human umbilical vein endothelial cells (HUVEC). Macromolecule permeability was measured by rate of labelled albumin flux through HUVEC monolayers cultured on membrane filters and ATP release from platelets was measured by luciferin-luciferase assay.
Results: Supernatant from freshly isolated platelets (10000-1000000/μl) reduced macromolecule permeability of HUVEC monolayer by 25±7%. Pre-incubation of platelets with insulin (1 IU/ml) resulted in a further 50±8% decrease in permeability. This permeability effect was further strengthened by addition of ARL 67156 (a specific ectonucleotidase, 100μM) and was completely abolished by apyrase (a soluble ectonucleotidase, 1 IU/ml). The ATP concentration of the supernatant from freshly isolated platelets was 1.7±0.1 μM which was raised to 2.6±0.2 μM by incubation with insulin. The insulin-mediated ATP release from platelets and hence HUVEC monolayer permeability was blocked by pharmacological insulin receptor inhibitor HNMP(AM)3 (1 μM), PI3K inhibitor, wortmannin (1 μM) and NO-synthase inhbitors L-NAME (100 μM) and L-NNA (100 μM).

Conclusion: Insulin mediates ATP release from platelets via activation of PI3K/Akt-NO pathway. This insulin-mediated released ATP has a strong endothelial barrier stabilizing effect.

P456 Mean platelet volume on admission correlates with impaired reperfusion in patients with acute myocardial infarction treated with thrombolysis

D. Pereg, M. Mosseri. *Meir Medical Center, Kfar Saba, Israel*

Background: It has been previously shown that platelet size, measured as mean platelet volume (MPV) correlates with their activity. Elevated MPV on admission predicts impaired reperfusion and increased mortality in patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI. We aimed to study whether a similar association exists among STEMI patients treated with thrombolysis.
Methods: Included were STEMI patients primarily treated with thrombolysis. Blood samples for MPV were drawn on admission. Failure of thrombolysis was defined as a need for rescue PCI, in-hospital mortality, an urgent PCI due to re-infarction or angina during hospitalization or a complete occlusion of the culprit coronary artery (TIMI flow=0) in a follow-up coronary angiography.
Results: A total of 122 patients were included in the study. In 30 patients thrombolysis failed while the other 92 patients fulfilled the criteria for successful treatment. There were no significant differences in demographic or clinical baseline characteristics of the two groups. Mean MPV was significantly higher when thrombolysis failed compared to the patients with successful treatment (9.2±1.1 and 8.7±1.0 respectively, p=0.016) and remained so after multivariate analysis (p=0.019). We further divided our population into 2 groups according to MPV level. The prevalence of thrombolysis failure was significantly higher in the high MPV compared to the low MPV group. (70% and 30% respectively, p=0.04). It remained significant following multivariate analysis (p=0.048).
Conclusions: STEMI patients that fail to respond to thrombolysis present with higher MPV. MPV may be used as a readily available early predictor for thrombolysis outcome.

P457 Factors influencing mobilisation of endothelial progenitor cells and cytokines after an extensive acute myocardial infarction

N. Rodriguez Losada[1], A. Dominguez Franco[1], F.J. Gonzalez[1], J.A. Marchal[2], F.J. Cabrera Bueno[1], E. Carrillo[2], A. Arenega[2], E. De Teresa Galvan[1]. *[1]Hospital Universitario de Malaga, Malaga, Spain; [2]IBIMER, Granada, Spain*

Purpose: Following an acute myocardial infarction (AMI), bone-marrow derived endothelial progenitor cells (EPC) are mobilised into the peripheral blood. The aim of this study was to examine the factors influencing this spontaneous cell mobilisation.
Methods: In 47 patients with extensive AMI (defined by a left ventricular ejection fraction -LVEF- <50% by echocardiography during the first week post-AMI) we studied the peripheral blood EPC populations (% of peripheral blood mononuclear cells) expressing CD133+, CD34+, KDR+, CXCR4+, as well as the cytokines VEGF (vascular endothelial growth factor), SDF-1 (stromal cell-derived factor 1) and TSP-1 (Thrombospondin 1), measured on day 5±2.5 after the AMI.
Results: The extension of the AMI correlated with the number of mobilised cells: (r=0.40; P=0.011 between CPK peak and CD133+). The patients who did not receive perfusion during the acute phase (fibrinolysis/angioplasty) (34%) had more CD34+CXCR4+ cells, with a median (interquartile ranges) of 2401 (498-7004) vs. 999 (100-1600); P=0.048), and strong correlations between VEGF and CD133+CD34+KDR+ (r=0.84; P<0.01) and SDF-1 and CD34+CXCR4+ (r= 0.67; P<0.01), and between these two cytokines (r= 0.57; p=0.01). In the reperfused patients, the correlation between VEGF and CD133+CD34+KDR+ was lower (r=0.38; P=0.03) and the correlation between SDF1 and CD34+CXCR4+ and VEGF disappeared. Multivariate analysis showed that a VEGF >7pg/mL (P<0.01) predicted the mobilisation of CD133+CD34+KDR+, whereas hypertension showed a trend (P=0.055). Diabetes (P=0.045) predicted the number of CD34+CXCR4+, with reperfusion treatment showing a trend in this subpopulation (P=0.054).
Conclusions: Mobilisation of progenitor cells after an AMI is influenced by such factors as diabetes and the cytokine VEGF. Hypertension and reperfusion therapy during the acute phase also tend to influence the cell response.

P458 TCF7L2 polymorphism rs7903146 is associated with coronary artery disease severity and mortality in non-diabetic individuals

A.C. Pereira[1], A.G.P. Sousa[2], G.F. Marquezine[1], N. Lopes[1], W.A. Hueb[1], J.E. Krieger[1]. *[1]Instituto do Coração (Incor), Sao Paulo, Brazil; [2]Federal University of Rio Grande do Norte, Natal, Brazil*

Background: TCF7L2 polymorphisms have been consistently associated with type 2 diabetes mellitus in different populations and type 2 diabetes mellitus is major risk factor of cardiovascular disease, especially coronary artery disease. This study aimed to evaluate the association between TCF7L2 polymorphism rs7903146 and coronary artery disease in diabetic and non-diabetic subjects.
Methods and Results: two populations were studied in order to assess severity of coronary artery disease and cardiovascular events. Eight-hundred and eighty nine subjects who were referred for cardiac catheterization for coronary artery disease diagnosis were cross-sectionally evaluated for coronary lesions (atherosclerotic burden) and 559 subjects from the MASS-II study population were prospectively followed-up for 5 years and assessed for major cardiovascular events incidence. As expected, rs7903146 T allele was associated with diabetes. Although diabetic patients had a higher prevalence of coronary lesions, non-diabetic individuals carrying the T allele were associated with a significantly higher frequency of coronary lesions than non-diabetic non-carriers of the risk allele (CC = 60.6%, CT = 69.7% and TT = 71.7%; p=0.46). Moreover, presence of multivessel coronary artery disease was also associated with the CT or TT genotypes in non-diabetics individuals. Similarly, from the prospective sample analysis, non-diabetics individuals carrying the CT/TT genotypes had significantly more composite end-points events (p=0.049), mainly due to death (p=0.004) (Figure).

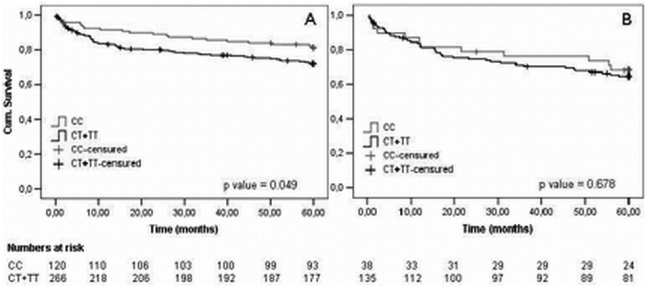


Figure 1. Composite end points

Conclusions: rs7903146 T allele is associated with diabetes and, in non-diabetic individuals, with a higher prevalence and severity of coronary artery disease and cardiovascular events.

P459 Abnormal, Tako-Tsubo-like, apical deformation in symptomatic patients during the development of a left ventricular cavity pressure gradient - the role of dobutamine stress echo

A.T. Baltabaeva[1], V. Leon[1], C. Parsai[1], B. Bijnens[2], G.R. Sutherland[1]. *[1]St George's Healthcare NHS Trust, London, United Kingdom; [2]ICREA Universitat Pompeu Fabra (CISTIB), Barcelona, Spain*

The development of a left ventricular (LV) cavity pressure gradient (LVG) during dobutamine stress echo (DSE) is often associated with symptoms and has been shown to have prognostic significance. However, the mechanism explaining the induced symptoms is not entirely understood. We aimed to study the changes in regional myocardial deformation induced by a transient LVG during DSE, in patients with clinical signs of stable angina.
Materials and Methods: 149 consecutive patients (including 2 patients with a history of apical ballooning (Tako-Tsubo)) who developed a LVG during DSE, but had a negative study with regard to inducible ischemia, were studied. Conventional echo parameters for LV geometry and systolic function were measured. Additionally, myocardial velocity data were obtained from 4 LV walls at baseline and peak dose for longitudinal strain (S) and strain-rate (SR) analysis in the segments proximal and distal to the site of the LV obstruction causing the LVG. In 38 of the patients, subsequent coronary angiography failed to reveal obstructive coronary artery disease.
Results: All patients had supernormal systolic function (EF: 71±1%, FS: 41±.7%) but a relatively small cavity size (end-diastolic diameter: 4.2±0.1 cm; end-systolic diameter: 2.5±0.1 cm and long-axis dimension 7.7±0.1 cm). There was localized hypertrophy in the basal septum (1.2±0.1 cm) while the mid-septum was normal (0.8±0.1 cm). The mean duration of the DSE was 14 min and 82% of mean predicted heart rate was reached. Regional end systolic S in the basal segments increased from baseline to peak dose (19.6 to 21.7%, P<0.01) with a more pronounced increase in peak systolic SR (1.4 to 2.6 s^{-1}, P<0.0001). At the same time, in segments distal to the cavity obstruction, there was a significant reduction in S (15.5 to 11.8%, P<0.0001) with the development of post-systolic shortening and a blunted increase in SR (1.0 to 1.2, P<0.04). At peak dose, 68 (46%) patients developed symptoms (chest discomfort and/or shortness of breath).
Conclusion: The development of a LVG, in the absence of an epicardial vessel obstruction, induces a reduction in regional deformation in the segments distal to the cavity obstruction. These changes are similar to deformation changes induced by regional ischaemia, suggesting that locally increased endocardial wall stress in the upper LV chamber due to the LVG, ia potentially causing sub-endocardial ischaemia and therefore symptoms. Regional deformation imaging could detect sub-clinical changes in this patient population who show changes in function that might precede the development of Tako-Tsubo cardiomyopathy.

P460 Antiendothelial cell antibodies in acute and chronic coronary artery disease: an emerging immune system spark in the coronaries

D.P. Papadopoulos[1], M. Daskalaki[1], S. Massias[2], A. Bratsas[2], E. Michalopoulou[2], A. Chatzizacharias[1], C. Thomopoulos[2], V. Votteas[1], T.H. Makris[2]. *[1]Departement of Cardiology, Laiko General Hospital, Athens, Greece; [2]Department of Cardiology, "Elena Venizelou" General & Maternity Hospital, Athens, Greece*

Purpose: Increased levels of circulating antiendothelial cell antibodies (AECA) have been observed in diverse vascular inflammatory diseases including hypertension and widespread atherosclerotic vascular damage. The aim of the study was to assess the possible incremental title of AECA in acute coronary syndromes (ACS) with respect to chronic coronary artery disease (CCAD).
Methods: We studied 60 consecutive subjects with ACS (40 men, 58±10 years, body mass index [BMI]=28±3 kg/m^2, smokers 43%) and 70 consecutive subjects with CCAD (45 men, 59±9 years, BMI=28.5±3 kg/m^2, smokers 41%) were studied. Traditional cardiovascular risk factors (i.e. smoking status, hypertension, hypercholesterolaemia and diabetes mellitus) and the possible ongoing therapy (i.e. aspirin, statins, renin-angiotensin axis inhibiting drugs) was registered for both groups. AECA titles (i.e. IgG and IgM) was measured by ELISA from venous blood samples in ACS subjects at the admission, while in those with CCAD in the setting of an outpatient clinic visit. A history of connective tissue disease was an exclusion criterion
Results: ACS compared to CCAD group did not significantly differ regarding age, sex, BMI and smoking status. History of hypertension and hypercholesterolaemia was higher in the ACS with respect to CCAD group (42% vs. 37%, p=0.014 and 52% vs. 38%, p<0.01), while diabetes mellitus was more prevalent in the latter group (9% vs. 19%, p<0.01). Ongoing statin and aspirin therapy resulted higher in CCAD with respect to ACS subjects (70% vs. 30% and 75% vs. 15% respectively, p<0.001 for both) while ACE inhibitors or ARBs were implemented more frequently in the former group (65% vs. 32%, p<0.001). Estimated glomerular filtration rate (eGFR), IgG-AECA and IgM-AECA were higher in ACS with regard to CCAD subjects (93±24 vs. 87±21 ml/min, p<0.001, 0.098±0.06 vs. 0.063±0.02 ng/ml, p<0.001 and 0.1125±0.03 vs. 0.101±0.02, p<0.01, respectively). In stepwise multivariable regression models significant correlates of AECA-IgG remained: history of ACS, hypercholesterolaemia and hypertension in tandem with younger age and absence of ongoing statin therapy, while significant correlates of AECA-IgM remained: history of ACS and younger age.
Conclusion: AECA title was increased in subjects with ACS with respect to those with CCAD. The incremental enhancement of AECA suggest that these molecules may be at least partly implicated in the pathophysiology of ACS and possibly represent an emerging index of adverse cardiovascular outcome in the setting of coronary atherosclerosis.

P461 Perturbation of T-cell network in acute coronary syndromes: aggressive immune responses arising from a lack of regulation

R.A. Montone, G. Liuzzo, M. Gabriele, A. Severino, G. Ferrante, G. Niccoli, L.M. Biasucci, F. Crea. *Catholic University of the Sacred Heart, Rome, Italy*

Purpose: Patients with acute coronary syndromes (ACS) show increasing levels of aggressive CD4+CD28null T-cells, as compared to patients with stable angina (SA). CD4+CD28null T-cell expansion independently predicts the recurrence of acute coronary events. Recently, a defective peripheral regulatory T-cell (Treg) compartment has been described in ACS, with impairment of Treg number and function. Therefore, the pathological immune responses observed in ACS might derive from a tolerance break in lymphocyte network. To test this hypothesis, we assessed the relationship between circulating levels of CD4+CD28null T-cell and Treg, taking into account the effect of systemic inflammation, in ACS compared to SA patients.
Methods: Consecutive patients with Non-ST elevation ACS and SA were enrolled. Circulating CD4+CD28null T-cells and Treg (CD4+Foxp3+ T-cells) were assessed by flow cytometry and expressed as percentage of CD4+ T-cells. Serum C-reactive protein (CRP) was detected by high sensitivity nephelometry. All data are presented as median and range.
Results: Sixty patients, 30 with ACS and 30 with SA were enrolled. ACS patients, compared to SA patients, had significantly higher levels of CD4+CD28null T-cells [9.5% (0.09-32.72) vs 2.95% (0.15-35.03), p=0.008], lower levels of Treg [3.48% (0.52-10.2) vs 7.93% (0.88-11.4) p<0.0005] and a higher CD4+CD28null/Treg ratio [2.56 (0.02-19.16) vs 0.43 (0.02-4.83), p=0.0002] (Mann-Whitney U-test). Baseline CRP levels were higher in ACS patients compared to SA [5.3 mg/L (0.5-52.4) vs 2.8 mg/L (0.5-11.9), p=0.006]. In ACS patients, but not in SA patients, there was a significant direct relationship between the reduction of Treg frequency and the increase of CD4+CD28null T-cell frequency [b = 1.78, 95% CI (0.49, 3.07), p=0.009, R2 = 0.26] at multiple linear regression analysis after adjustment for CRP levels and statin use. CRP levels and statins use did not affect CD4+CD28null T-cell frequency in ACS patients.
Conclusions: Our data suggest that the aggressive immune response observed in ACS depends on an altered interaction between pro-inflammatory and regulatory T cells. In fact, patients with ACS, compared to SA patients, show a higher CD4+CD28null/Treg ratio and evidence for a direct regulation of CD4+CD28null T-cell frequency by Treg cells, independent of systemic inflammation. This perturbation of lymphocyte network might play a crucial role in the pathogenesis of ACS and opens the avenue to novel preventive and therapeutic strategies.

P462 Progression of coronary artery disease is mirrored by an increased MMP-9/TIMP-1-ratio in peripheral circulating CD14$^+$ monocytes

S. Brunner, J.-O. Kim, H. Methe. *Klinikum der Universitaet Muenchen-Grosshadern, Munich, Germany*

Objectives: Atherosclerosis is an inflammatory disease in which systemic inflammation correlates with disease activity. Imbalance of matrix metalloproteinases (MMPs) and their endogeneous tissue inhibitors of metalloproteinases (TIMPs) within atherosclerotic plaques has been linked with progression and rupture of atherosclerotic plaques. In this study, we aimed to investigate if the ratio of MMP-9 and its endogenous inhibitor TIMP-1 in circulating CD14+-monocytes correlates with clinical stages of coronary artery disease (CAD).
Methods: MMP-9 and TIMP-1 expression in circulating monocytes were analyzed in 18 patients with stable CAD (SA), 14 patients with unstable angina pectoris (UA), 14 patients with acute myocardial infarction (AMI), and compared with 14 healthy age- and sex-matched controls. Monocytes were isolated from venous blood using anti-CD14-labeled magnetic beads. Expression of MMP-9 and TIMP-1 were analyzed by real-time PCR. Serum MMP-9 and TIMP-1 concentrations and activity of serum MMP-9 were assessed by ELISA and zymography.
Results: Compared with controls (0.07±0.01 relative units (RU)) and patients with SA (0.25±0.1 RU, p=0.61 vs. control), MMP-9 levels in circulating monocytes were significantly increased in UA (0.9±0.3 RU, p<0.05) and AMI (1.6±0.4 RU, p<0.05). In contrast, protein and mRNA expression of monocytic TIMP-1 levels were 2.5-fold lower in AMI when compared to controls, SA, and UA (p<0.05). Changes in monocytic expression of MMP-9 and TIMP-1 tracked with serum levels of MMP-9 and TIMP-1. Clinical instability of CAD associated with increasing ration of MMP-9/TIMP-1 levels in circulating CD14+-monocytes (control: 0.1 RU, SA: 0.3 RU, UA: 1.1RU, AMI: 5.8 RU, p<0.002). Activity of serum MMP-9 correlated with the individual MMP-9/TIMP-1 ratio in peripheral circulating monocytes (r=0.82,p<0.02).
Conclusion: Progression of CAD is mirrored by an increasing MMP-9/TIMP-1 ratio in peripheral circulating CD14+-monocytes of patients with UA and AMI. Interestingly circulating monocytes display the same pattern of dysbalance in expression of MMP-9 and TIMP-1 as previously reported for monocyte-derived macrophages within atherosclerotic plaques. Our results give further rise to the notion of atherosclerosis as a systemic inflammatory disease.

P463 Factor Seven Activating Protease (FSAP): a link between inflammation and coagulation in coronary artery disease

M. Parahuleva[1], R. Maj[1], B. Parviz[1], H. Hoelschermann[2], H. Tillmanns[1], A. Erdogan[1], S. Kanse[3]. *[1]Universitaetsklinikum Giessen und Marburg GmbH, Giessen, Germany; [2]2Department of Internal Medicine, Division of Cardiology and Angiology, Hochtaunus Kliniken gGmbH, Bad Homburg, Germany; [3]University of Giessen, Institute of Biochemistry, Giessen, Germany*

Purpose: FSAP may be involved in the progression of atherosclerosis and the development of associated clinical events. It is present in unstable lesions and its plasma level and activity are increased in patients with coronary artery disease (CAD). The molecular mechanism, however, by which circulating FSAP influences the progression of CAD is not yet entirely understood. The present study was performed to examine the relation between FSAP and the pro-inflammatory activation of macrophages.
Methods: The influence of FSAP on the activation of transcription factors of the NFkappaB family and cAMP response element-binding protein (CREB) was assessed by electrophoretic mobility shift assays. Degradation and phosphorylation of IkappaBα as well as expression of ICAM-1, IL-6, and TF was analyzed.
Results: FSAP treatment (20μg/ml) induces IkappaB-dependent NF-kappaB activation in freshly isolated human monocytes in a time-dependent fashion. It induces the phosphorylation and proteolytic degradation of the inhibitor protein IkappaBα. The phosphorylation of p65 was induced by FSAP, which is known to contribute to the enhancement of DNA-binding activity of NF-kappaB.
In parallel, FSAP induced the expression of ICAM, IL-6, and TF, genes known to be under the control of NF-kappaB. Consistent with this, aprotinin, a pharmacological inhibitor of FSAP, blocks FSAP-induced gene expression. In contrast, CREB phosphorylation and activation was not detected in FSAP-treated monocytes.
Conclusions: Biological functions of FSAP in macrophages extend beyond its role in promoting thrombosis/fibrinolysis. Thus, FSAP may play an important role in atherosclerosis by enhancing the inflammatory response of human macrophages as a novel activator of NF-kappaB.

P464 The omega-3 fatty acid docosahexaenoate attenuates insulin-induced CD36 expression in human microvascular endothelial cells

R. Madonna, D. Schiavone, R. De Caterina. *Universita G. D'Annunzio, Chieti, Italy*

Background: Microvascular dysfunction characterizes insulin resistance and/or hyperinsulinaemia and may also contribute to diabetic macrovasculopathy by compromising the blood supply to large vessels. Enhanced uptake of free fatty acids (FFA) and oxidized low density lipoproteins in the microcirculation may lead to oxidative stress and microvascular dysfunction via interaction with the scavenger receptor and long-chain FFA transporter CD36. We hypothesized that in microvascular endothelial cells CD36 is regulated by high insulin, which occurs in early stages of insulin resistance, and that the type of FFA presenting to CD36 may have differential effects on its expression. Therefore, we investigated differences in CD36 expression before and after pathophysiologically high insulin treatment of human dermal microvascular endothelial cells (MVECs), in the presence or absence of n-6 (linoleate, LA) versus n-3 (docosahexaenoate, DHA) unsaturated fatty acids.
Methods and Results: MVECs were incubated with 10-9 to 10-7 mol/L insulin for 24 and 72 h. Parallel groups of cells were pretreated with DHA or LA (10-7 to 5x10-6 mol/L) overnight before incubation with insulin. Insulin (10-8 mol/L) by itself time-dependently increased CD36 surface expression (+ Δ %: 30$\pm$13, $p<0.05$ vs untreated control after 72 h incubation, n=3), as assessed by ELISA. No change was seen in total CD36 protein (at Western analysis). In the absence of cytotoxicity, a $\geq$24 h exposure to DHA blunted both the constitutive (-Δ%: 23$\pm$3% $p<0.05$ vs untreated control, n=3) and insulin-induced CD36 surface expression (-Δ%: 45$\pm$27%, $p<0.05$ vs insulin–treated control, n=3). In contrast, LA did not alter constitutive nor insulin-induced CD36 surface expression.
Conclusions: High insulin increases surface CD36 expression in human microvascular endothelial cells, and DHA blunts such expression. Treatment with omega-3 fatty acids may, by such mechanisms, exert favourable effects in diabetic microvasculopathy.

P465 Tissue factor-protein disulphide isomerase interactions in migrating human vascular smooth muscle cells

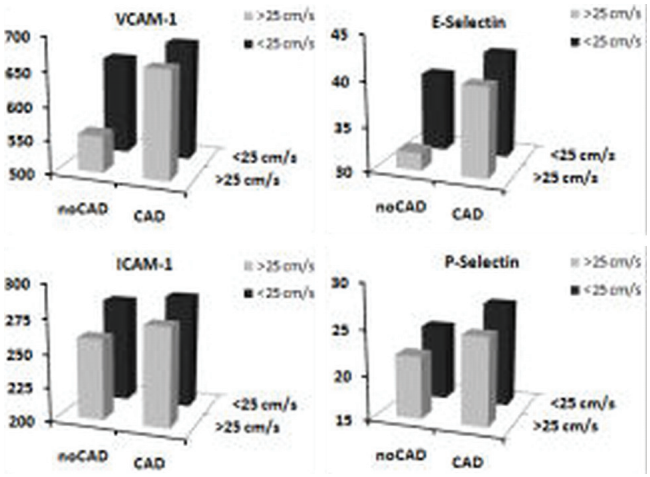
E. Pena, G. Arderiu, L. Badimon. *Barcelona Cardiovascular Research Center, CSIC-ICCC, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Purpose: Tissue factor (TF) is the most relevant physiological trigger of blood coagulation and thrombosis in response to vascular injury. Recently new information on the mechanisms of TF activation on cell membranes has been generated. Indeed, encrypted TF contains unpaired cysteine thiols that need to form disulfide bonds Cys186-Cys 209 for activation. By targeting this disulfide bond Protein Disulfide Isomerase (PDI) seems to regulate TF coagulant and signaling activities. The aim of this study has been to identify TF-PDI expression and interaction in migrating human vascular smooth muscle cells (HVSMC).
Methods: Primary cultures of HVSMC were obtained from coronary arteries of explanted hearts (Transplant Unit). The monolayer scratch model to create a double-side wound (350 μm width) was used. Analysis of TF distribution in migrating HVSMC was performed by confocal microscopy (CM) (Leica TCS SP2-AOBS). A nucleofector device was used for TF silencing (siRNA). mRNA levels of TF and PDI from transfected or control HVSMC were analyzed by real time PCR. Chemotactic migration of cells was measured in a modified Boyden chamber.
Results: In migrating cells TF locates in the leading edge of the cell membrane with an intense patch-like staining in the lamellopodias, while in resting cells TF is evenly distributed. TF highly co-localized (93%) with ganglioside GM1 rich areas (two-fold increase over static HVSMC ($p<0.05$)). PDI-TF staining showed a significant ($p<0.05$) increased association in lamellopodias with a patch pattern in the leading edge of migrating cells (co-localization rate of 80% versus % static HVSMC). TF-siRNA inhibited TF expression by over 90%, and reduced HVSMC migration by 50% ($p<0.001$). PDI expression on cell surface was diminished in TF-silenced HVSMC.
Conclusions: TF associates with lipid rafts in the HVSMC migratory front. Moreover, TF silencing modulates cell surface PDI expression and mRNA production. PDI seems to regulate TF effects in remodelling and repair.
Funded by Instituto Carlos III CIBERobn 03/06, PNS-SAF2006/10091, Fundacion Jesus Serra and Fundación Lilly.

P466 Unfavourable endothelial expression of adhesion molecules in erectile dysfunction patients with or without coronary artery disease

K. Aznaouridis, C. Vlachopoulos, N. Ioakeimidis, K. Rokkas, I. Dima, D. Terentes-Printzios, C. Antoniades, D. Tousoulis, A. Askitis, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: Erectile dysfunction (ED) is related to generalized vascular disease by an impairment of endothelial function and increased low grade inflammation. Cellular adhesion molecules may exert a relevant role in the pathogenesis of atherosclerosis. The association of soluble adhesion molecules with ED and coronary artery disease (CAD) has not been investigated.
Methods: Plasma levels of Intercellular adhesion molecule-1 (ICAM-1), Vascular cell adhesion molecule-1 (VCAM-1), E and P-Selectin were measured in three groups with similar risk factor profile: 39 patients with ED and chronic coronary syndrome, 39 ED patients without CAD and 31 volunteers with normal erectile function (controls). ED patients were evaluated with penile Doppler ultrasound. Lower Doppler velocities indicate impaired arterial function and vice versa. A mean PSV below 25 cm/sec was considered to indicate severe arterial insufficiency (SAI).
Results: In patients without CAD, subjects with ED had significantly increased concentrations of ICAM-1 ($P<0.001$), VCAM-1 ($P<0.001$), E-Selectin ($P<0.05$) and P-Selectin ($P<0.05$) compared to men without ED. VCAM-1 and E-Selectin concentrations in SAI patients without CAD were comparable to that of CAD patients with or without SAI and significantly higher than that of men without CAD and SAI ($P<0.001$, figure, upper panel). On the contrary, ICAM-1 and P-Selectin levels did not differ between ED w/o CAD and ED-CAD group (figure, lower panel).



Cellular adhesion molecules, ED and CAD

Conclusions: ED is associated with increased circulating levels of soluble adhesion molecules. Moreover, the endothelial cell activation observed in men with SAI is not significantly different compared to that of CAD patients. These findings provide a potential explanation for the increase of cardiovascular risk in such patients.

P467 Emergence of myeloid dendritic cells in the myocardium after acute myocardial infarction

A. Yilmaz[1], B. Dietel[2], I. Cicha[2], R. Hausmann[3], W.G. Daniel[2], C.D. Garlichs[2], C. Stumpf[2]. *[1]Universitaetsklinikum Jena, Jena, Germany; [2]University of Erlangen-Nuremberg, Erlangen, Germany; [3]University Hospital Basel, Basel, Switzerland*

Background: Dendritic cells (DC) are crucial for T cell mediated immune responses. Their important role has been shown in atherosclerosis. Recently, we reported a significant decrease in circulating myeloid DC precursors in patients with acute myocardial infarction (AMI), suggesting their recruitment into the infarcted myocardium. Therefore, we investigated in the present study whether myeloid DC might be detected in human myocardium after AMI.
Methods: Myocardial specimens of 10 patients with AMI and 7 accident victims as controls were collected after autopsy. The presence of myeloid DC (CD209+, fascin+), T cells (CD3+), macrophages (CD68+), and the expression of HLA-DR was analyzed in immunohistochemical stainings.
Results: Significantly higher numbers of myeloid CD209+ DC (97 vs. 44 cells/0.25 mm^2, p=0.03), fascin+ DC (54 vs. 8 cells/0.25 mm^2, p=0.02), T cells (27 vs. 6 cells/0.25 mm^2, p=0.02), and macrophages (44 vs. 6 cells/0.25 mm^2, p=0.01) were detected in infarcted myocardium compared to control tissue. Additionally, a high expression of HLA-DR was observed in the infarcted area associated with the presence of invaded immune cells. A significant correlation was detected between myeloid DC and T cells, macrophages, and HLA-DR. Frequent colocalization of myeloid DC and T cells was observed in the area of myocardial infarction. Furthermore, in the vessel wall of occluded coronary arteries, numerous myeloid DC, T cells, macrophages, and a high expression of HLA-DR were detected.
Conclusions: In the present study, we show that myeloid DC are recruited into the myocardium of patients with AMI. High expression of HLA-DR and colocalization of DC with T cells suggest that DC are triggering an immune response leading to myocardial and coronary inflammation following AMI. Myocardial inflammation in return was shown to be a major contributing factor of acute complications and progressive heart failure upon AMI.

P468 Brain natriuretic peptide mediates the effect of creatinine clearance on developing left ventricular systolic dysfunction in patients with acute coronary syndrome

C. Chrysohoou[1], P. Aggelopoulos[1], C. Pitsavos[1], J. Skoumas[1], G. Metallinos[1], A. Aggelis[1], C. Kastorini[2], C. Liontou[1], C. Stefanadis[1].
[1]*University of Athens, Athens, Greece;* [2]*Harokopio University, Athens, Greece*

Background: Data about the role of renal function on the development of left ventricular systolic dysfunction in patients with an acute coronary syndrome (ACS) are limited. Therefore, we sought to investigate whether renal insufficiency is a predictor for systolic dysfunction among patients who had an ACS.
Methods and Results: During 2006-2007, 814 consecutive patients with an ACS event were enrolled; of them. 284 male (65±14 years) and 71 female (71±12 years) developed left ventricular systolic dysfunction (ejection fraction < 40%) after the event, while 306 males (64±12 years) and 78 females (67±10 years) had preserved left ventricular systolic function (ejection fraction > 50%). Detailed information regarding their bio-clinical and anthropometric characteristics, physical activity, dietary and smoking habits was recorded. Creatinine clearance rates were estimated by the Cockcroft-Gault formula. Eight percent of patients presented with severe renal dysfunction, 30% with moderate and the rest 62% with normal. Multiple logistic regression analysis revealed that a 10 unit increase of creatinine clearance levels decreases the odds of developing heart failure by 8% (95% CI per 1 mg/dl: 0.986-0.998, $p<0.01$), after controlling for potential confounders. However, brain natriuretic peptide levels were inversely correlated with creatinine clearance ($p<0.001$), thus, when brain natriuretic peptide levels were entered in the model, creatinine clearance lost its predictive ability (odds ratio for creatinine clearance=0.997, 95%CI 0.989-1.005, p=0.473).
Conclusions: The role of renal insufficiency on the development of heart failure seems to be, partially, explained by plasma brain natriuteric peptide levels, suggesting a potential pathophysiological mechanism. Thus, patients with impaired creatinine levels and elevated brain natriuretic levels should receive more aggressive medical care as they are prone to develop left ventricular systolic dysfunction.

P469 Upregualtion of fractalkine and its receptor, CX3CR1, is associated with coronary plaque rupture in patients with unstable angina pectoris

H. Ikejima, T. Imanishi, H. Tsujioka, A. Kuroi, T. Tanimoto, H. Kitabata, N. Nakamura, K. Hirata, A. Tanaka, T. Akasaka. *Wakayama Medical University, Wakayama, Japan*

Background: Given the vital role of leukocyte recruitment at all stages of cardiovascular disease progression from early plaque development to plaque rupture, the chemokine family is thought to contribute significantly to the pathogenesis of cardiovascular disease. Recent data suggest that fractalkine (FKN, or CX3CL1) and its cognate receptor, CX3CR1, play a role in atherogenesis. In this study, we investigated the relationship between coronary plaque rupture, as observed by preintervention optical coherence tomography (OCT), and plasma levels of FKN and CX3CR1.
Methods and Results: The study population consisted of 46 patients with unstable angina pectoris (UAP), 30 patients with stable AP (SAP), and 25 healthy controls. In UAP patients, a preintervention OCT study was performed, demonstrating that the number of plaque rupture and no plaque rupture at culprit site with UAP was 27 (rupture group) and 19 (non-rupture group), respectively. Plasma levels of soluble FKN (sFKN) and CX3CR1 were measured by enzyme-linked immunoadsorbent assay and flow cytometry, respectively. We found that plasma levels of sFKN were significantly increased in patients with rupture group compared with patients with other groups. Importantly, the numbers of CD16+CX3CR1+ monocytes, CD3+CX3CR1+ T-lymphocytes and CD16+CX3CR1+ NK cells were also all significantly higher in patients with rupture group than that in patients with other groups.
Conclusions: This study identified for the first time that the increases in sFKN and CX3CR1-expressing monocytes, T-lymphocytes, and NK cells were significantly related to plaque rupture, which may provide new conceptual and therapeutic approaches for treating ACS. These findings also highlight the importance to characterize specific functions of the chemokine network to enable therapeutic intervention.

P470 Ce-magnetic resonance imaging in patients with takotsubo cardiomyophaty

R. Scardala[1], G. Benedetti[1], M. Mancone[1], F. Sconci[1], I. Carbone[2], M. Francone[2], F. Igual Perez[1], A. Di Roma[1], G. Sardella[1], F. Fedele[1].
[1]*"Sapienza" University. Dep. Cardiovasc. Resp. and Morph. Sciences, Rome, Italy;* [2]*"Sapienza" University. Dep Radiolgy, Rome, Italy*

Takotsubo syndrome (TS) is a type of cardiomyophaty induced by stress, characterized by a transient aneurismatic dilatation of the left ventricle and a compensatorial hyperkinesia of basal regions in patients with a normal coronary angiography. Contrast enhanced Magnetic Resonance Imaging (ceRMI) represent the gold standard tecnique for the evalutation of myocardial injury, represented by delayed enhancement (DE), in patients with ischemic heart disease. In the TS this tecnique could be useful to identify myocardial damage. As today in literature there are different studies about the useful of ceRMI in this setting of patients but they didn't provide definitive result until yet. The aim of our study is to evaluate if this syndrome can be associated to the presence of myocardial damage as delayed enhancement on ceRMI.
Methods: We evaluated 26 patients admitted in our Department with a possible diagnosis of TS. All patients population underwent coronary ventricular angiography that showed normal coronary arteries, associated to an apical ballooning of the left ventricle. All the patients in acute have been submitted to coronary angiography, ventriculography, echocardiography (Aplio CV,Toshiba) and to the Cardiac Nuclear Magnetic Resonance (Avanto,Siemens 1,5 T) with gadolinium (Gd-DTPA). Echocardiography was performed, also, at 1 month to confirm the recovery of left ventrcular fiunction. Perfusional study has been effected by acquisition in short axis of inversion recovery turbo flash sequencies. These sequencies are acquired at 20th minutes after administration of bolo of Gd-DPTA (0,2 mmol/kg) to evaluate delayed enhancement.
Results: All patients were female with medium age of 57.5 years old. The myocardial enzymes resulted grown in all of patients. Coronary angiography, ventriculography and echocardiography results were in according to diagnosis of takotsubo. CeRMI did not show perfusional injuries and pointed out the absence of delayed-enhancement on late sequencies. Echocardiographic follow-up confirmed the diagnosis.
Conclusion: Our data confirm that TS is not associated to myocardial necrosis, suggesting that this technique could be used to confirm the diagnosis of TS in the acute phase.

P471 Microvascular damage in patients with severe renal dysfunction after successful primary angioplasty for acute myocardial infarction

R. Ogura, Y. Hiasa, S. Miyazaki, T. Takahashi, S. Hosokawa, K. Kishi, R. Ohtani. *Tokushima Red Cross Hospital, Komatsushima, Japan*

Background: Renal dysfunction is associated with poor outcomes after reperfused acute myocardial infarction (AMI). However, little information is available about relation of renal dysfunction with microvascular damage after reperfusion.
Purpose: The purpose of this study was to determine the relationship of renal dysfunction and myocardial microvascular damage after successful primary angioplasty by intravenous myocardial contrast echocardiography (MCE) – currently the best accurate measure of reperfusion at a microvascular level.
Methods: We studied 283 consecutive patient (mean age 64.3±11.9 years, 217males) with successful primary angioplasty for anterior AMI. Glomerular filtration rate (GFR) was estimated by Modification of diet in renal desease (MDRD) study formula using serum creatinine level on admission. Severe renal dysfunction was defined as estimated GFR<30ml/min/1.73m^2. We performed intravenous MCE two weeks later from primary angioplasty and calculated contrast defect area.
Results: 191 (67.5%) patients had GFR >60 ml/min/1.73 m^2, 83 (29.3%) patients had GFR 30-59 ml/min/1.73m^2, 8 (2.8%) patients had GFR <30 ml/min/1.73m^2 (severe renal dysfunction); 4 (1.4%) patients had GFR 15-30 ml/min/1.73m^2, 4 (1.4%) patients had GFR <15 ml/min/1.73m^2. Patients with severe renal dysfunction were older and with no significant gender difference. Two weeks later MCE showed greater contrast defect area in patients with severe renal dysfunction (% defect area; 19.8±11.8% vs. 13.6±8.7%, $p<0.05$). Severe renal dysfunction was associated with higher serum C-reactive protein (CRP) levels (5.6±5.1 mg/dl vs.0.7±1.7 mg/dl, $p<0.001$) and lower Left ventricular (LV) ejection fraction (46.4±15.1% vs.55.2±12.0%, $p<0.001$).
Conclusion: Severe renal dysfunction was associated with greater myocardial microvascular damage after successful primary angioplasty for anterior AMI.

P472 Association between chromosome 9p21.3 variation and coronary heart disease

W. Koch, W. Latz, S. Tuerk, A. Erl, P. Hoppmann, A. Schoemig, A. Kastrati. *Deutsches Herzzentrum Muenchen, Munich, Germany*

Purpose: A region of approximately 100 kilobases at chromosome 9p21.3 was found to be associated with atherosclerotic diseases and type 2 diabetes. We examined the relationship between single nucleotide polymorphisms (SNPs) that represent a major portion of the genetic variation of this region and coronary heart disease (CHD).
Methods: Our study population consisted of 2000 patients with symptomatic CHD and 1211 control individuals with angiographically normal coronary arteries and without signs or symptoms of myocardial ischaemia. The SNPs rs7865618, rs1537378, rs1333040, and rs1333049 were analysed with TaqMan allelic discrimination assays.
Results: Genotype distributions and allele frequencies were substantially different between the CHD and control groups ($P\leq1.7e{-}6$). The carriers of the major alleles (rs7865618-A, rs1537378-C, rs1333040-T, and rs1333049-C) had significantly higher risks of CHD than the homozygous carriers of the minor alleles (rs7865618-G, rs1537378-T, rs1333040-C, and rs1333049-G) (Table). After adjustments were made for conventional cardiovascular risk factors (age, gender, history of arterial hypertension, history of hypercholesterolaemia, current cigarette smoking, and diabetes mellitus), the "lead" SNP, rs1537378 (Table),

showed strong association in a multiple logistic regression model of CHD (adjusted OR 1.96; 95% CI 1.55–2.49).

Risk effects in major allele carriers

SNP	Major allele	OR (95% CI)	P-value
rs7865618	A	1.76 (1.46 - 2.12)	2.6e-9
rs1537378	C	1.85 (1.52 - 2.26)	9.0e-10
rs1333040	T	1.29 (1.08 - 1.55)	5.3e-3
rs1333049	C	1.53 (1.30 - 1.79)	1.5e-7

OR, odds ratio; CI, confidence interval.

Conclusions: Genetic variation at chromosome 9p21.3 was significantly associated with CHD. The present findings are in agreement with results of prior studies addressing associations between SNPs at this locus and diseases of coronary arteries.

P473 Pathophysiologic considerations for the complex interaction between erectile dysfunction and coronary artery disease in men complaining of sexual dysfunction after an acute myocardial infarction

C. Vlachopoulos, N. Ioakeimidis, D. Terentes-Printzios, K. Rokkas, K. Aznaouridis, A. Aggelis, G. Antoniou, A. Askitis, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: ED and CAD are overlapping in terms of risk factors, the pathological basis of disease and the clinical context. The aim of this study is to investigate whether appearance of ED prior to detection of CAD is associated with a more diffuse coronary and peripheral atherosclerotic burden.
Methods: 103 consecutive men with angiographically documented CAD after an acute myocardial infarction complaining of ED were studied. Ultrasound intima media thickness IMT of carotid arteries, carotid-femoral pulse wave velocity (PWV) as an index of aortic stiffness and pharmacologically stimulated peak systolic velocity (PSV) of cavernous arteries were used to assess peripheral vascular damage.
Results: ED symptoms appeared prior to CAD detection in 78/103 (76%) of cases (Group A), whereas the remaining 25 men (24%) had CAD before the onset of ED symptoms (Group B). In Group A patients the mean time interval between the onset of ED and detection of CAD was 36.4 months (range 4–174). The incidence of multivessel disease (2 and 3 vessel disease) and Gensini score in Group A patients was higher than that of Group B patients (68 vs 42%, $P<0.05$ and modified score:18 vs 13, $P<0.05$, respectively). Compared to Group A, men in Group B were younger (60 vs 52 yrs, $P<0.01$) with a higher prevalence of family history of CAD (34 vs 12%, $P<0.01$) and a lower Framingham risk score. Furthermore, Group A patients had significantly increased IMT (0.96 vs 0.89 mm, $P<0.01$) and carotid-femoral PWV (9.3 vs 8.7 m/s, $P<0.05$) compared with Group B patients. Among CAD patients, men with ED prior to CAD presentation had significantly decreased penile Doppler velocities (24.5 vs 31.2 cm/s, $P<0.05$) compared with men without ED at time of CAD presentation. However, these patients had comparable levels of high sensitivity CRP (2.7 vs 2.3 mg/l), fibrinogen (378 vs 356 mg/dl), interleukin-6 (4.88 vs 4.36 ng/ml) and total testosterone concentration (2.96 vs 3.12 ng/ml) to those of men with proven CAD and normal erectile function ($P<0.05$).
Conclusions: Among men with established CAD, subjects with ED symptoms prior to detection of CAD exhibit an unfavorable peripheral atherosclerotic background and more diffuse coronary artery involvement as compared to men with normal erectile function at time of CAD presentation. Age –related changes in penile and coronary arteries could clarify why almost 24% of men with established CAD, did not complain for ED.

P474 Atherosclerosis progression in the coronary arteries among patients with acute myocardial infarction treated with primary angioplasty

M. Hawranek, M. Gasior, M. Gierlotka, A. Spatuszko, G. Slonka, M. Tajstra, D. Pres, J. Sikora, A. Lekston, L. Polonski. *Slaskie Centrum Chorob Serca, Zabrze, Poland*

Background: Atherosclerosis progression (AP) might be responsible for substantial proportion of poor long-term outcome after acute myocardial infarction (AMI). Data on atherosclerosis progression and factors influencing this process after myocardial infarction are limited.
Aim: The aim of this study was to access predictors of AP among patients (pts) with AMI treated with angioplasty (PCI) and to estimate the correlation between progression and long-term outcome.
Methods: 186 pts with AMI treated with PCI and control angiography performed after 12 months were analyzed. 154 pts were included into the final quantitative coronary angiography (QCA) analysis. All lesions with diameter stenosis (DS) $\geq$ 20% or minimal lumen diameter (MLD) smaller then 0,4 mm than calculated reference of the coronary segment were estimated. Progression of preexisting coronary stenosis was defined as a decrease in the MLD of at least 0,4mm or increase in DS of at least 20%. Similarly, a normal segment had to reveal a new localized narrowing of at least 20%, or with MLD smaller of at least 0,4mm then reference diameter, to be accepted as a newly formatted stenosis. Segments with culprit lesion treated with PCI were excluded from further analysis.
Results: Of the 1017 preexisting stenoses, 99 (9,7%) were classified as progressing. Additionally, 62 new lesions were recognized in previously "normal" coronary segments. Progression found in QCA concerned 93 (60,4%) pts. 44 patients (47,3%) progressed only with preexisting coronary lesions, 29 (31,2%) in newly formed ones and 20 (21,5%) both with preexisting and new lesions. Remaining 61 (39,6%) pts were classified as a pts without progression. In the multivariate logistic regression analysis, the risk of AP increased with the lack of adequate microvascular perfusion as assessed by TIMI Myocardial Perfusion Grade (TMPG) scale (OR 4,13; 95% CI = 1,17 – 14,53), non-smoking status and lower baseline cholesterol value (OR = 2,74; 95% CI 1,19 – 6,31 and OR = 1,44; 95% CI = 1,04 – 1,98 respectively).
Conclusions: Atherosclerosis progression concerns over 60% of patients 12 months after acute myocardial infarction. Poor myocardial perfusion as assessed by TMPG scale may be a simple tool for identifications of patients at greater risk of atherosclerosis progression. In the 3 years follow up AP does not correlate with the frequency of major adverse cardiac events in the analyzed population.

P475 Gender difference in prognosis after acute MI among 45,852 Chinese patients in COMMIT/CCS2

Y. Chen[1], L.X. Jiang[2], M. Smith[1], J. Xie[2], H. Pan[1], L. Liu[2], R. Collins[1], Z.M. Chen[1] on behalf of COMMIT/CCS2. *[1]Clinical Trial Service Unit, Oxford, United Kingdom; [2]Fuwai Hospital and Cardiovascular Institute, Beijing, China, People's Republic of*

Background: Previous studies have reported a higher early mortality rate among women after acute MI. Uncertainty remains, however, as to whether the poorer prognosis among women could be attributed mainly to their advanced age of onset of disease and their presenting clinical characteristics. There is still limited evidence from populations such as China, which has a relatively low disease rate compared with western populations.
Methods: We examined the data of 45,852 acute MI patients enrolled within the first 24 h of symptom onset into the large randomised COMMIT/CCS2 trial from 1250 hospitals in China. In-hospital mortality rate was compared between men (33,093) and women (12,759) after adjustment for age and other baseline variables, and standardised relative risks were calculated using a logistic regression model.
Results: Mean age was 59 years for men and 67 years for women, and in-hospital mortality was more than twice as high in women as in men (RR 2.15; 95% CI 2.00-2.31). After adjustment for age, disease presenting characteristics (e.g., blood pressure, heart rate, presenting ECG, time delay since symptom onset) and other baseline variables, there was still a highly significant 53% excess risk of in-hospital mortality among women (RR 1.53; 95% CI 1.42-1.65). The excess risk tended to be greater during the first week of symptom onset (e.g., RR 1.81 [95% CI 1.62-2.02] on days 0-1 vs RR 1.19 [95% CI 0.98-1.44] on days 8-28) and among younger patients (e.g., RR 2.02 [95% CI 1.60-2.56] for age<55 vs RR1.15 [95% CI 1.00-1.32] for age>75) ($p<0.0001$ for the interactions in both cases). Further adjustment for hospital treatment did not alter the observed difference in prognosis between men and women.
Conclusion: Compared with men, women tended to have poorer prognosis immediately following the onset of acute MI, and the difference was particularly large at younger age.

MECHANICS AND FUNCTION ASSESSED BY ECHOCARDIOGRAPHY

P476 Factors affecting the ratio of transmitral flow velocity to mitral annulus velocity

H. Sonoda[1], H. Takase[1], T. Toriyama[1], T. Okado[1], A. Hagikura[1], Y. Dohi[2], G. Kimura[2]. *[1]Enshu Hospital, Hamamatsu, Japan; [2]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

Purpose: The ratio of early transmitral flow velocity to early mitral annulus velocity (E/e') reflects left ventricular (LV) filling pressure and is considered to be a marker for LV diastolic dysfunction. We investigated relationship between E/e' and several factors.
Methods: Consecutive 683 subjects (male=449, 62±11 years) who visited our echolaboratory were enrolled. Subjects with atrial fibrillation, severe valvular diseases, and severe arrhythmia were excluded. Pulsed-wave Doppler signals from the mitral inflow and tissue Doppler imaging of the mitral annulus were obtained. According to previous studies, subjects were divided into three groups: 1) E/e'<8, 2) 8≤E/e'≤15, and 3) E/e'>15 (mean E/e'=6.5±1.2, 10.4±1.7 and 17.6±3.1, respectively). Relationship between E/e' and echocardiographic and other parameters were investigated.
Results: Baseline characteristics of subjects and the results of univariable and multivariable regression analyses are shown in the table (see p. 49).
Conclusions: E/e' does not reflect only factors that are closely related to diastolic function. LV diastolic function assessed by E/e' should be carefully interpreted.

Abstract P476 – Table 1. Characteristics and regression analyses

	E/e' < 8 (male/female = 187/95)	8 ≤ E/e' ≤ 15 (male/female = 236/127)	E/e' > 15 (male/female = 26/12)	Coefficient (Univariate)	p value (Univariate)	Coefficient (Multivariate)	p value (Multivariate)
Age (year-old)	58.8±11.4	63.9±9.1*	70.1±10.0*#	0.281	<0.0001	0.058	0.1424
Systolic blood pressure (mmHg)	130±18	135±17*	141±16*	0.180	<0.0001	0.001	0.9953
Brain natriuretic peptide (pg/ml)	17.5±12.4	22.7±16.7*	61.8±33.0*#	0.223	<0.0001	0.040	0.3122
Serum creatinine (mg/dl)	0.75±0.17	0.78±0.26	0.94±0.34*#	0.150	0.0007	0.058	0.1302
Hemoglobin (g/dl)	14.2±1.5	13.8±1.7*	13.4±1.6*	-0.153	<0.0001	-0.064	0.1273
E wave velocity (cm/sec)	58.5±15.4	64.5±15.5*	71.3±17.4*#	0.301	<0.0001	–	–
A wave velocity (cm/sec)	63.0±12.5	74.6±15.4*	87.7±21.0*#	0.485	<0.0001	0.577	<0.0001
Deceleration time (msec)	208±56	214±52	228±55	0.132	0.0006	-0.017	0.6307
Left atrial diameter (mm)	33.4±6.0	35.0±5.6*	38.0±7.8*#	0.133	0.0005	0.077	0.0329
LV ejection fraction (%)	68.1±7.7	67.8±9.7	64.9±11.8	-0.101	0.0086	-0.063	0.0600
LV mass index (g/m^2)	105±28	111±39*	127±37	0.149	0.0004	0.060	0.1006
e' velocity (cm/sec)	9.2±2.6	6.3±1.6*	4.1±1.1*#	-0.649	<0.0001	–	–
a' velocity (cm/sec)	10.2±2.4	9.7±2.2*	8.4±2.0*#	-0.204	<0.0001	-0.320	<0.0001
Systolic dysfunction (LVEF<50%), n (%)	4 (1.4%)	9 (2.5%)	2 (5.3%)	0.094	0.0138	–	–

Data are mean ± SD values except for brain natriuretic peptide [median ± median absolute deviation]. *p<0.05 vs"E/e' < 8", #p<0.05 vs "8 ≤ E/e' ≤ 15" by Scheffe's test (ANOVA).

P477 Tissue Doppler imaging-derived echocardiographic techniques in predicting left ventricle reverse remodeling after Cardiac Resynchronization Therapy (CRT) implementation

D. Czarnecka, W. Wojciechowska, J. Wilinski, M. Kloch-Badelek, A. Kwiecien-Sobstel, M. Jastrzebski, B. Bacior, K. Kawecka-Jaszcz. *I Department of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow, Poland*

Purpose: Reduction of left ventricular end-systolic volume (LVESV) observed after CRT introduction is a powerful positive long-term prognostic factor. The aim of the study was to assess the relation of initial mechanical dyssynchrony with the LVESV decrease observed 3 months after CRT implantation.
Methods: Sixty consecutive patients (aged 66,3±8,7; 57 men) with CHF of NYHA III-IV (71,7% with ischaemic and 28,3% with non-ischaemic origin) despite opitimized pharmacotherapy, with left ventricular end-diastolic diameter (LVEDd) > 55 mm, left ventricular ejection fraction (LVEF) <35% and QRS > 130ms were assessed before and 3 months after BiV stimulation implementation. Twelve segments of left ventricle (LV) (6 basal and 6 midlevel) and two segments of right ventricle (RV) were analyzed longitudinally using Tissue Doppler Imaging (TDI) techniques with times from onset of Q wave in ECG to peak systolic velocity (T) in color-coded TDI, time to peak strain (Ts) and time to peak strain rate (Tsr). Standard deviations (SD) of times of LV segments were calculated, minimal and maximal times differences between interventricular septum and other LV walls and between LV and RV in these different techniques were analyzed.
Results: In the study group LVEF increased (21,7% vs 26,6%, p<0,0001), 6-minute walk test distance rose (298,0 m vs 373,1 m, p<0,0001), left ventricular end-diastolic volume (LVEDV) and LVESV decreased (244,3 ml vs 226,4 ml, p=0,0002; 192,8 ml vs 168,7 ml, p<0,0001 respectively). Mean NYHA class dropped from 3,1 to 2,2 (p<0,0001). Significant correlation between LVESV reduction was found in maximal time differences between Ts of 12 LV segments (r=0,34; p=0,017) and time differences between T basal LV-RV segments (r=-0,29; p=0,04).
Conclusions: Only few TDI-derived parameters like maximal time differences between Ts of 12 LV segments and T difference of LV-RV basal segments can be useful in prognosing left ventricle reverse remodeling after CRT introduction.

P478 Left ventricular systolic dyssynchrony is associated with pulmonary arterial hypertension in patients with coronary artery disease

G.H. Yan, M. Wang, W.S. Yue, K.H. Yiu, C.W. Siu, H.T. Chan, Y.L. Dai, T.H. Luk, C.P. Lau, H.F. Tse. *Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Left ventricular (LV) systolic dyssynchrony is an important pathologic mechanism in patients (pts) with coronary artery disease (CAD), however, its impact on the occurrence of pulmonary arterial hypertension (PAH) remains unclear.
Methods: We studied the impact of inter- or intra-ventricular mechanical dyssynchrony on the development of PAH in 148 consecutive pts (mean age 68±10 years, 82% M) with CAD. Detailed echocardiographic studies, including pulse Doppler and Tissue Doppler imaging (TDI) were performed to measure interventricular dyssynchrony (Ts-RL=time difference between basal lateral and right free wall; and IVD=time interval between left and right outflow pre-ejection time), intra-LV dyssynchrony (Ts-SD=standard deviation of time to peak systolic velocity of 12 LV segments; and Ts-SL= time difference between basal septal and lateral wall), and pulmonary artery systolic pressure (PASP).
Results: 38 pts had PAH defined by PASP>35mmHg. There were no significant differences in age (71±9 vs. 68±10 yrs), prevalence of myocardial infarction (23 vs. 16%), hypertension (76 vs. 64%), and diabetes (45 vs. 30%), left ventricular ejection fraction (55±14 vs. 56±13%) between pts with or without PAH (all P>0.05). However, pts with PAH had significantly high prevalence of diastolic dysfunction (abnormal relaxation: 68 vs. 82%; pseudonormal: 24 vs. 17%; restrictive: 8 vs. 1%, P=0.042), greater Ts-SD (48.2±20.3 vs. 38.3±20.4ms, P=0.011) and Ts-SL (72.2±51.8 vs 49.6±42.5ms, P=0.008) compared with pts without PAH, without any difference in Ts-RL (75.5±47.8 vs. 65.8±49.3 ms, P=0.294) or IVD (16.1±9.9 vs. 16.7±13.8ms, P=0.796). Furthermore, PASP was significantly correlated with LV dyssynchrony index (Ts-SD: r=0.19, P=0.012; Ts-SL:r=0.22, P=0.004) and diastolic dysfunction (E/e', r=0.28, P< 0.001).
Conclusions: Our results demonstrate that intra- but not inter-ventricular dyssynchrony is associated with PAH in CAD pts, independent of LV systolic function, providing further insight on the potential impact of LV dysschrony on exercise capacity in CAD pts.

P479 Non-invasive quantitative Imaging of arterial wall elasticity using supersonic shear imaging

M. Couade[1], M. Pernot[2], M. Tanter[2], C. Prada[2], C. Perri[1], J. Emmerich[3], M. Fink[2], E. Messas[3]. *[1]SuperSonic Imagine, Aix En Provence, France; [2]Laboratoire Ondes et Acoustique, ESPCI, CNRS UMR 7587, INSERM, Université Paris 7, Paris, France; [3]European Hospital George Pompidou (AP-HP), Paris, France*

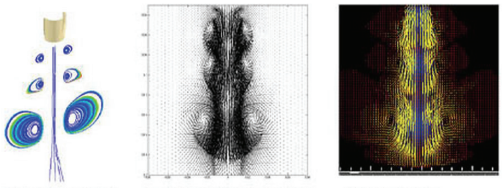
Purpose: Arterial stiffness is an important predictor of cardiovascular mortality that increases with age and in diseases associated with cardiovascular risk, including hypertension and diabetes. The goal of this study is to show the feasibility of measuring quantitatively arterial stiffness using ultrafast echo imaging. Ultrahigh frame rate imaging (up to 20000 frames/s) can provide tissue Doppler (TDI) cine-loop allowing to detect and follow pulse wave propagation in artery. This high frame rate imaging was combined with a novel ultrasound technique Supersonic Shear Imaging (SSI) based on remote palpation of biological tissues, providing quantitative, local and real time estimation of tissues elasticity during a conventional ultrasound exam. The goal of this study is to demonstrate the potential of those techniques to quantify precisely the elastic modulus of arterial walls.
Methods: Ultrahigh frame rate imaging was used to image arterial wall displacement in order to follow pulse wave propagation in the carotid artery. The pulse wave velocity (PWV) was calculated from TDI cine-loop (PRF= 800 to 1600 Hz), giving an estimate of the circumferential elastic modulus. To assess longitudinal elastic modulus, a shear wave was generated on the carotid arterial wall using the acoustic radiation force induced by a conventional linear ultrasonic probe (8MHz). Shear wave propagation was imaged in real-time using an ultrafast scanner (20 000 frames/s) and the shear wave velocity was derived and finally the longitudinal elasticity was estimated. Those two imaging modalities were tested on 20 healthy volunteers.
Results: Typical estimated PWV in the carotid segment were found between 5 and 6 m/s. Typical Young modulus estimated with SSI were found between 200 and 300 kPa. According to these first results obtained on healthy volunteers, a good correlation was found with values previously reported in literature using other techniques.
Conclusions: The feasibility of imaging simultaneously pulse wave and shear wave propagation have been demonstrated in-vivo, allowing two different estimations of the arterial wall elastic modulus. Moreover, the shear wave elastography can be performed in real time up to 10 times per cardiac cycle. In conclusion, real time shear wave elastography appears as an efficient safe and reliable technique for imaging quantitatively the elasticity of the arterial wall. Future clinical investigations will correlate this new measure of elasticity with vascular pathologies.

P480 Estimation of Flow Velocity Fields from Color Doppler Ultrasound Data: Numerical Validation of Vector Flow Mapping

T. Uejima[1], H. Sawada[1], T. Aizawa[1], T. Okada[2], A. Harada[2]. *[1]The Cardiovascular Institute, Tokyo, Japan; [2]Aloka co. ltd., Tokyo, Japan*

Purpose: Vector Flow Mapping (VFM) is new method to generate flow velocity fields by post-processing color Doppler ultrasound datasets. The basic concept that underlies this method is that non-turbulent flows in the left ventricle can be described as a combination of a laminar flow and vortex flows. In the present study, we validated this method through numerical simulation.

Methods: Three types of three-dimensional unsteady flow models (jet flow model, spiral flow model, left ventricular flow model) were created, using a commercially available computational fluid dynamics package (PHOENICS 2006, CHAM limited). Two-dimensional flow velocity field on the representative plane was obtained in each flow model as the original flow velocity dataset. It was then converted to polar coordinate format. Its radial components, as the virtual color Doppler ultrasound datasets, were processed by VFM and the velocity fields were reconstructed. The overall flow structures and velocity magnitudes were compared between the original flow velocity fields and VFM results.
Results: Figure shows the comparison between the original flow velocity field and the velocity field reconstructed by VFM in the jet flow model. VFM captured the general flow structures, including vortex, in each field. The velocity magnitude of VFM results showed a good quantitative agreement with the corresponding original velocity magnitude (jet flow model: r=0.995, p=0.0001; spiral flow model: r=0.980, p=0.0001; left ventricular flow model: r=0.985, p=0.0001).



A. Three-dimensional jet flow model B. Original flow velocity field C. Velocity field reconstructed by VFM

Conclusions: VFM can estimate the two-dimensional flow velocity fields from their radial components in the three-dimensional flow models.

P481 Estimation of myocardial viscoelastic moduli by shear-wave method in live swine

C. Pislaru, M.W. Urban, I.Z. Nenadic, J.F. Greenleaf. *Mayo Clinic College of Medicine, Rochester, United States of America*

Quantification of myocardial mechanical properties (elastic and viscous moduli, $\mu 1$ and $\mu 2$) would help with evaluation of cardiac function and structure by ultrasound. $\mu 1$ and $\mu 2$ can be estimated from the velocity of shear-waves (V) induced by an applied force over a certain frequency range. Our aim was to quantify these moduli to better understand the mechanical properties of the beating myocardium.
Methods: Four pigs were used (open-chest). Left ventricular pressure (LVP) was measured by Millar catheter. Sinusoidal mechanical excitations (at 100-350Hz, in 50Hz steps) were applied directly to the anterior LV wall using a mechanical shaker and motion amplitude (<50μm) and shear-wave V were measured using a 7.5MHz transducer. Values for full wall thickness were averaged. Estimates of $\mu 1$ and $\mu 2$ were obtained from V dispersion by fitting data with known wave equations. Data were analyzed in 40ms intervals. Each measurement was repeated 5 times.
Results: V trace closely followed LVP trace (Fig.1) and was higher during systole than during diastole (3.2±0.3 vs 1.7±0.1 m/s, p<0.01). Consequently, $\mu 1$ and $\mu 2$ showed similar systolic-diastolic variation ($\mu 1$: 31 vs 1.7 kPa; $\mu 2$: 5 vs 3.2 Pa·s; Fig.2). Repeatability of V measurement was good during systole and very good during diastole (Fig.1). Systolic and diastolic LVP: 75±2 and 10±3mmHg.

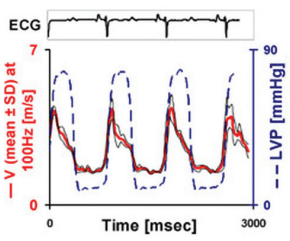


Figure 1. V vs LVP.

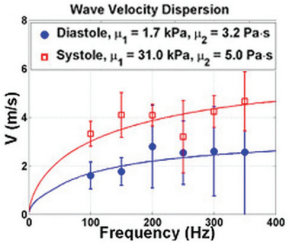


Figure 2. $\mu 1$ and $\mu 2$

Conclusions: Quantification of myocardial viscoelastic moduli measured by this new method showed results consistent with literature and cardiac mechanics. V, $\mu 1$, and $\mu 2$ showed cyclic variations consistent with contribution of active (contractile) and passive (pressure) forces to passive tissue properties. In the future, the use of ultrasound radiation as impulse force will hopefully allow quantification of active and passive tissue properties in a totally noninvasive approach.

P482 Head to head comparison of the reproducibility of different measures of systolic left ventricular function

A. Thorstensen, H. Dalen, B.H. Amundsen, A. Stoylen. *The Norwegian University of Science and Technology Department of Circulation and Medical Imaging, Trondheim, Norway*

Objectives: 1) To compare the interobserver reproducibility of new and traditional measures of the left ventricular (LV) global and regional systolic function. 2) To compare interobserver reproducibility of the same measures in separate recordings (interobserver) vs. repeated analyses of single datasets (intra- and interanalyzer).
Methods: Two experienced sonographers separately performed a complete echo/Doppler study on ten healthy subjects. All recordings were analyzed and reanalyzed by both sonographers (20 recordings and 50 analyzes). The following variables were measured: Ejection fraction (EF) by biplane Simpson, left ventricular outflow tract peak velocity (LVOT peak), global and segmental LV end systolic strain (Ses) and peak strain rate (SRs) by 2D speckle tracking, systolic annulus velocity by pulsed wave tissue Doppler (S') and systolic M-mode annulus excursion (MAE).
Results: Mean, coefficient of repeatability (COR) and mean error (absolute difference divided by the mean) are shown in table 1. Interobserver mean error was significantly lower for MAE (p=0.018). Mean error of segmental Ses and SRs was significantly higher than all the global measures (p<0.001 for all). The overall interanalyzer and intraanalyzer mean error based on single datasets was 23% (p=0.002) and 37% (p<0.001) lower than the mean error calculated by separate recordings and analyzes done by a different sonographer.

Table 1

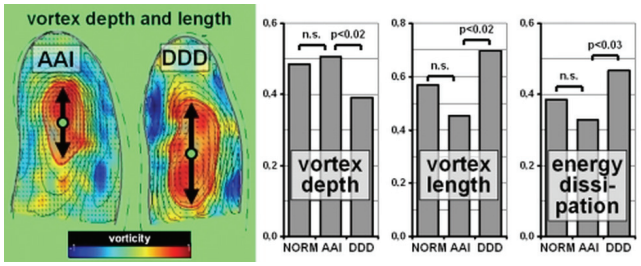
Method	Mean interobserver	COR interobserver	Mean error interobserver	Mean error interanalyzer	Mean error intraanalyzer
LVOT peak	1,0 m/s	±0,2 m/s	9,8%	2,9%	3,2%
Global S_{es}	-0,21	±0,02	5,7%	6,3%	3,4%
Global SR_s	-1,14 s^{-1}	±0,21 s^{-1}	9,4%	4,5%	5,0%
S'	9,1 cm/s	±1,7 cm/s	8,5%	3,3%	2,1%
MAE	16,9 mm	±1,6 mm	3,6%	2,8%	2,9%
EF	0,59	±0,07	5,6%	6,0%	4,9%
Segmental S_{es}	-0,21	±0,07	14,2%	12,3%	11,0%
Segmental SR_s	-1,12 s^{-1}	±0,51 s^{-1}	17,4%	11,9%	8,6%

Conclusion: 1) MAE showed better interobserver reproducibility than other traditional and newer measures of LV systolic function. 2) Repeated analyses of the same recordings underestimates the true -clinically relevant- interobserver variability by approximately 30% for most measures of LV function.

P483 The impact of function-flow interaction on left ventricular efficiency - a particle image velocimetry study

E. Gurel, K. Hristova, M. Szulik, R. Faludi, L. Van Casteren, R. Willems, J. D'Hooge, F. Rademakers, J.U. Voigt. *Catholic University of Leuven (KULeuven), Leuven, Belgium*

Blood flow vortices inside the left ventricle (LV) determine the energy efficient function of the heart. We hypothesize, that vortex formation depends on regional myocardial contraction patterns. Particle image velocimetry (PIV) is a new echocardiographic method which allowing to measure blood flow patterns in patients. We used PIV to analyze the impact of left bundle branch blocks (LBBB) on vortex formation in the LV.
Methods: We investigated 22 healthy volunteers (NORM) as well as 12 patients (PT) with pace maker (PM) in both AAI mode (normal LV conduction), and DDD mode (similar to LBBB). Regional myocardial function was assessed with strain rate imaging. PIV was performed after a contrast bolus injection. Dedicated research software, capable of tracking contrast bubbles in the images, could quantify velocity and direction of LV blood flow and characterize its patterns from regional vorticity. Main vortex depth (VD) and length (VL) were measured relative to the LV cavity. Energy dissipation (EDP) was estimated.
Results: In NORM and AAI pacing, regional shortening was simultaneous. In DDD pacing, myocardial shortening was posterolaterally delayed (p<0.0001 vs. anteroseptal). Flow patterns in NORM and AAI were similar (n.s.). In DDD, however, the main LV vortex occurred more basally (0.39±0.09 vs. 0.51±0.12, p<0.02) and was longer (0.70±0.15 vs. 0.45±0.14, p<0.02) than in AAI and energy dissipation was significantly (0.47±0.10 vs. 0.33±0.06, p<0.03) higher.



Conclusion: Echo PIV is a novel tool to investigate intramyocardial blood flow patterns. Disturbance of regional myocardial function results in changes in these patterns. Our data suggest, that due to this function-flow-interaction, efficiency of cardiac function is significantly reduced in patients with LV conduction abnormalities.

P484 Feasibility of two-dimensional speckle tracking in murine model of myocardial infarction

E. Szymczyk[1], P. Lipiec[1], M. Krzeminska-Pakula[1], M. Plewka[1], K. Kaminski[2], M. Kurpisz[3], J.D. Kasprzak[1]. *[1]Medical University of Lodz, Department of Rapid Cardiac Diagnostics, 2nd Chair and Department of Car, Lodz, Poland; [2]Medical University of Bialystok, Bialystok, Poland; [3]Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland*

Background: Coronary artery ligation in mice has already become a widely used model of myocardial infarction used in transgenic technology. We aimed to examine feasibility, reproduciblity and usefulness of two-dimensional speckle tracking (STE) and tissue Doppler (TDE) strain and strain rate for analysis of structural and functional changes occurring during myocardial infarction in the murine model.
Methods: The study group consisted of 10 mice with complete endocardial border delineation of left ventricle obtained among which 5 had myocardial infarction induced by coronary ligation. Parasternal short axis views (greyscale and tissue doppler imaging) were acquired in all anesthetized subjects with the use of M12L transducer. The data were analyzed off-line by two independent investigators using following parameters: tissue doppler radial strain and strain rate, 2D speckle-tracking radial strain and strain rate, in each view.
Results: Acquired images allowed reliable analysis of anterior/posterior radial strain and strain rate measured by TDE and STE. The mean analysis time for peak systolic radial strain and strain rate measured from TDE vs. STE was 7,36±0,5 min vs. 5,11±0,3 min. Mean values of 2D vs. TDE strain for anterior and posterior wall were 5% vs. 10%, p=NS; 7% vs. 15%, p=0,02 and STE vs. TDE strain rate for anterior and posterior wall were 15/s vs. 2/s, p=0,03; 18/s vs. 2,5/s p=0,02.
There was a good correlation between results of strain and strain rate measured from TDE and STE ranging from r=0,73 to r=0,98 in subgroup of normal mice and from r=0,89 to r=0,98 mice with myocardial infarction obtained by two investigators. Interobserver coefficient of variability for 2D strain measurements (3,4% - 8,4%) and 2D strain rate (9,5% - 46,5%) was less than half of that obtained using TDE method.
Conclusions: 2D speckle tracking is a rapid, reproducible non-Doppler method for assesing peak radial strain and strain rate not only in normal mice but also in murine model of myocardial infarction. Analyses of radial strain and strain rate measured from STE are less time-consuming than from tissue Doppler. TDE strain sligthly overestimate measurements as compared to 2D strain.

P485 Echocardiographic particle image velocimetry for the detailed analysis of left ventricular flow patterns

E. Gurel, K. Hristova, M. Szulik, R. Faludi, J. D'Hooge, F. Rademakers, J.U. Voigt. *Catholic University of Leuven (KULeuven), Leuven, Belgium*

Objectives: Complex flow patterns (FP) inside the left ventricle (LV) are prerequisite for an efficient cardiac function. Currently, there are no routine imaging modalities to image them in vivo. In this study we used echocardiographic particle image velocimetry (PIV) as new tracking based method to investigate left ventricular flow pattern in detail.
Methods: We studied 22 healthy volunteers (VOL) (41±17 years, 11m) with apical echocardiography. A contrast bolus was given to provide trackable features in the blood pool. Images were post-processed with dedicated PIV software. Flow velocity and direction was estimated in the entire LV cavity. FP were characterized based on regional flow vorticity. Their size and position (as percentage of LV cavity size) were determined throughout the cardiac cycle. Results were compared to standard grey scale echocardiography and and color Doppler (CD).
Results: In all VOL, LV cavitary flow had a typical pattern. During early diastole, a large main vortex (50±7% of LV chamber size), positioned at 63±4% of LV length could be identified with counter-clockwise rotation in the apical 4 chamber view. It was re-inforced with atrial contraction at a lower position (44±6% of LV chamber size, 43±7% of LV length). The vortex center was always located between red and blue fields from CD, emphasizing its inability to mirror true FP.

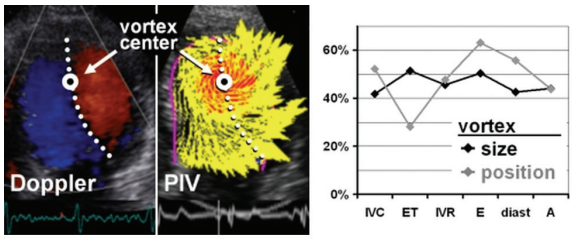


Figure 1

Conclusion: PIV allows the detailed characterization of LV FPs. In VOL vortical patterns enable an energy efficient function of the LV. These data may be of importance for identifying abnormal flow in different cardiac pathologies such as valve diseases, diastolic and systolic dysfunction as well as conduction abnormalities.

P486 Evaluation of stiffness parameters with a new non-invasive ultrasound method

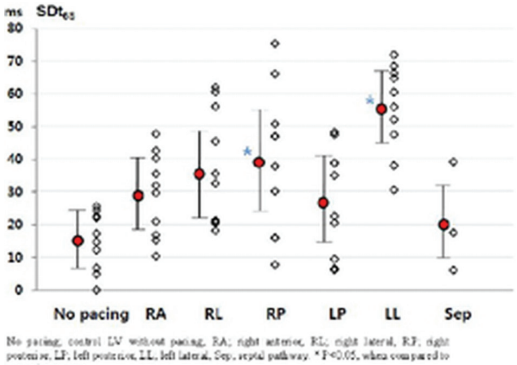
S. Mannarino, M. Pasotti, A. Serio, F.I. Gambarin, V. Favalli, C. Codazzi, E. Arbustini. *IRCCS Fondazione Policlinico San Matteo, Pavia, Italy*

Background: Much interest has been addressed to the study of arterial stiffness, an indicator of cardiovascular diseases. Different conditions are associated with increased arterial stiffness parameters (ASP). Recently a new method, "eTRACKING", allows to obtain ASP in a routine echo-examination of neck vessels. Normal ASP have already been defined in adults over 20 year-old. Purpose To evaluate normal ASP in a sample of healthy Italian children and young adults using eTRACKING method.
Methods: 173 healthy subjects (mean age 11.5 years, 3-25 years) were divided in 3 groups (gr): grA (3-9 years) (n=62), grB (10-14 years) (n=63), grC (15-25 years) (n=48). Measurements of ASP were performed in both common carotid arteries 1 cm next to the bifurcation, after 10 minutes of rest. The stiffness indicator parameter (β), pressure-strain elasticity modulus (EP), arterial compliance (AC) and pulse wave velocity (PWVβ) were calculated.
Results: β right carotid (rc) and left carotid (lc) artery were respectively 3,0±0,8 versus 3,3±1,0 in grA, 3,9±1 versus 3,9±1 in grB, 4,0±1 versus 4,1±1,1 in grC (p=NS). EP rc/lc were respectively 32,6±9,8 kPA versus 35,4±11,9 kPA in grA, 44,4±10,5 kPA versus 45,6±11,1 kPA in grB, 49,6±13,1 kPA versus 49,8±13,2 kPA in grC (p=NS). AC rc/lc were respectively 1,7±0,4 mm^2/kPa versus 1,6±0,5 mm^2/kPa in grA, 1,5±0,4 mm^2/kPa versus 1,4±0,4 mm^2/kPa in grB, 1,4±0,4 mm^2/kPa versus 1,4±0,4 mm^2/kPa in grC (p=NS). Finally, PWVβ rc/lc were respectively 3,4±0,5 m/sec versus 3,6±0,6 m/sec in grA, 4,0±0,4 m/sec versus 4,0±0,5 m/sec in grB, 4,2±0,5 versus 4,2±0,5 m/sec in grC (p=NS). Significant age relationship confirmed by calculating regression equations was found in all ASP. Age-increment was respectively of 0,092 and 0,071 per year for β rc and β lc; 1,4911 and 1,2335 kPa/year for Ep rc and Ep lc; 0,0677 and 0,05603 m/sec/year for PWVβ rc and PWVβ lc. Vice-versa AC rc and AC lc showed a negative-age-related trend with reduction of respectively –0,02413 and –0,01676 mm^2/kPa/year. No statistical significant differences were found between right and left carotid for all ASP. Parameters were gender indipendent. Significant differences were only found between grA versus grB and grA versus grC for every ASP (p=0.002).
Conclusions: eTRACKING is an easy technique for evaluation of ASP in pediatric age. Similarly to adult population, healthy children and young adults show increasingly age-related β, EP and PWVβ parameters. On the contrary, AC decreases in older ages.

P487 Effects of accessory pathway location on left ventricular dyssynchrony in canine model of Wolff-Parkinson-White syndrome

S.-A. Chang, H.-E. Park, E.-K. Choi, S.-I. Oh, Y.-S. Choi. *Seoul National University, Seoul, Korea, Republic of*

Purpose: Ventricular myocardium near the accessory pathway location is preexcited in patients with WPW syndrome. Preexcitation may result in ventricular dyssynchrony due to its abnormal ventricular activation pattern. However, the relationship between left ventricular (LV) dyssynchrony and accessory pathway location has not been elucidated. We investigated the LV dyssynchrony depending on the accessory pathway location in canine WPW model using 2D speckle tracking echocardiography.
Methods: Ten dogs were studied with following protocol. Through median thoracotomy VDD-type epicardial ventricular pacing with 50-ms AV interval was applied near the AV groove at five different sites in each animal; right anterior, right lateral, left lateral, right posterior, and left posterior. Septal pacing was performed via transjugular lead insertion. Electrocardiogram was acquired to confirm the preexcitation. Echocardiography was performed to assess standard deviation of time to peak radial strains (SRt6s) from six mid segments using 2D speckle tracking technique before and during pacing.



LV dyssynchrony in WPW model

Results: LV with left lateral and right posterior preexcitation showed significant LV dyssynchrony comparing to normal condition ($p<0.05$). LV dyssynchrony was most prominent in left lateral preexcitation ($p<0.001$).
Conclusion: Left lateral preexcitation could induce significant LV dyssynchrony. When considering the more prevalent LV dyssynchrony in heart failure patients, clinical significance of LV dyssynchrony and development of heart failure in WPW patients with left lateral preexcitation should be carefully monitored especially in patients with left lateral preexcitation presents.

P488 Exercise-induced myocardial ischemia causes diastolic dysfunction in patients with stable effort angina: a tissue Doppler echocardiographic study

Y. Ohara, M. Kusunose, Y. Take, S. Sahara, K. Banba, M. Nishimoto, K. Yamamoto. *Kochi Health Sciences Center, Kochi, Japan*

Objectives: Abnormalities in left ventricular filling and relaxation are sensitive signs of myocardial ischemia in short-term experiments in animals. It is conceivable that impaired or stunned regional diastolic function follows transient severe myocardial ischemia associated with effort angina. However, whether stunned regional diastolic function affect global diastolic function beyond normal systolic function is unknown. The aim of this study to assess whether exercise-induced myocardial ischemia impairs global diastolic function in patients with stable angina by using tissue Doppler echocardiography.
Methods: We studied 56 patients with normal sinus rhythm and suspected coronary artery disease who underwent exercise 201Tl myocardial single-photon emission computed tomography (SPECT). All patients underwent echocardiography including tissue Doppler imaging before and 5 minutes after exercise. Transmitral flow velocity signals were recorded from apical 4-chamber view and the early (E) and late (A) transmitral flow velocities were measured. Similarly, the ratio of E wave velocity to early diastolic velocity of the mitral annulus (E/Ea) in the 4-chamber view was measured. Ea were obtained at the septal and lateral sites of the annulus, and average values of these measurements were calculated for each patient. The E/Ea index was determined by dividing the E/Ea after exercise by the E/Ea at rest.
Results: According to the results of SPECT, patients were divided into 2 groups: the ischemia group (redistribution phenomenon; n=13) and the non-ischemia group (normal; n=43). At rest, E/A, E/Ea were not significantly different in the 2 groups (0.87 ± 0.44 vs. 0.91 ± 0.28, p=NS; 8.8 ± 3.2 vs. 9.3 ± 2.4, p=NS). E/Ea after exercise was significantly increased in the ischemia group compared with the non-ischemia group (11.7 ± 4.6 vs. 9.3 ± 2.9, $p<0.05$). Moreover, E/Ea index was significantly greater in the ischemia group than in the non-ischemia group (1.32 ± 0.08 vs. 1.00 ± 0.18, $p<0.0001$). For prediction of exercise-induced myocardial ischemia, E/Ea index>1.12 had a sensitivity of 79% and a specificity of 82%.
Conclusions: Exercise-induced myocardial ischemia impairs global diastolic function in patients with stable effort angina. In addition, the change in E/Ea by exercise is useful diagnostic marker for detecting exercise-induced myocardial ischemia.

P489 Usefulness of echocardiographic 2D-strain imaging for early detection of patients with allograft coronary artery disease after heart transplantation

M. Dandel, H. Lehmkuhl, C. Knosalla, M. Bettmann, O. Grauhan, D. Kemper, R. Hetzer. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Background: Frequent post-transplant angiographic screening is distressing and risky for patients (especially for those with renal dysfunction), costly and often also unable to detect early transplant coronary artery disease (TxCAD). Non-invasive early detection of TxCAD for timing of angiographies is a major goal. However, diffuse distal vessel narrowing is determinant for ventricular dysfunction in TxCAD and therefore regional wall motion alterations induced by focal stenoses are less evident. Because 2D-strain imaging reveals alterations of contractile function not detectable by conventional echocardiography, we assessed its value for detection of patients with focal coronary stenoses.
Methods: Between 1/2005 and 1/2008, all our heart-transplanted patients with post-transplant times of $>$ 6 months, normal left ventricular (LV) ejection fraction and without visible alterations of LV kinetics underwent 2D-strain analyses at rest, before routine heart catheterization. LV radial, circumferential and longitudinal strain and strain-rate were calculated from parasternal and apical views, respectively. Also dyssynchrony and end-systolic dyssynergy indexes were calculated from LV strain curves. 2D-strain parameters and indexes were tested for relationships to angiographic findings.
Results: A total of 73 patients could be included into evaluation. The peak systolic global radial, circumferential and longitudinal strain and strain-rate, as well as the time to the peak global systolic strain rates were lower in TxCAD patients, with or without focal stenoses of major coronary arteries ($p < 0.05$). Except for systolic global peak strain all systolic deformation parameters showed high (more than 85%) negative predictive values for focal stenoses of major coronary arteries, but insufficient (less than 78%) positive predictive values for these focal lesions. High positive predictive values for focal stenoses of $>$50% narrowing were however found for systolic dyssynchrony and endsystolic dyssynergy indexes. At certain cut-off values, these indexes showed high positive and negative predictive values for focal stenoses of between 90-95% and 91-98%, respectively.
Conclusions: 2D-strain imaging is reliable for non-invasive prediction of TxCAD and also for differentiation between TxCAD with and without focal coronary stenoses. The high predictive values of systolic strain dyssynchrony and dyssynergy indexes recommend 2D-strain as a non-invasive tool with the potential to facilitate early detection of coronary stenoses and to enable angiographies to be timed, sparing patients frequent routine heart catheterizations.

P490 Pattern of left ventricular systolic activation by tissue velocity imaging in patients with left ventricular systolic dysfunction with and without left bundle branch block

H. Sadeghian, M. Lotfi-Tokaldany, B. Esalmi, A. Zoroufian, A. Kasemisaeid, A. Yaminisharif, S. Sadeghian, G.H. Davoodi. *Tehran Heart Center, Tehran, Iran (Islamic Republic of)*

Aim: To study pattern of left ventricular activation in two groups of patients with impaired left ventricular systolic function; with and without bundle branch block (LBBB).
Method: A total of 66 patients with either dilated or ischemic cardiomyopathy (mean ejection fraction, $24.30\pm25.42\%$) underwent tissue velocity imaging. Patients were divided into two groups: 1, with LBBB, 2, non-LBBB. Time to peak velocity at peak systolic phase (Ts) was determined in 12 segments of LV. Data is presented as mean$\pm$standard deviation (SD).
Results: 31 patients had LBBB (including 15 ischemic, 15 dilated and one valvular cardiomyopathy) and 35 did not have LBBB (including: 21 ischemic and 14 dilated cardiomyopathies). Mean QRS duration was significantly different between the groups 1 and 2 (158.40 ± 30.45 vs 117.34 ± 27.61 ms, respectively, $P<0.001$). Ts of all LV segments had significant delay in LBBB patients compared to non-LBBB. First activated regions in LV were anterior and lateral walls in group 2. In LBBB patients, anteroseptal was the first activated wall. Septal-lateral delay was significantly different between the two groups (66.77 ± 33.51 vs 39.46 ± 29.19 ms, respectively). Dyssynchrony of all LV segments was 119.33 ± 35.62 ms in group 1 and 97.40 ± 44.55 ms in group 2 (p=0.034) while dyssynchrony of basal LV segments had no significant difference between the two groups. SD of Ts in all and 6 basal LV segments was significantly higher in group 1 compared to group 2. Pre-ejection period of aortic valve and interventricular mechanical delay were also significantly higher in LBBB group while pre-ejection period of pulmonary valve and time between septum and posterior wall contraction showed no significant difference. All of the mentioned indices showed no significant difference between ischemic and dilated cardiomyopathy patients in either LBBB or non-LBBB groups.
Conclusion: There was a delay of activation in all LV segments in LBBB compared to non-LBBB patients with impaired systolic function regardless of presence of ischemic or dilated etiology. Future studies are needed to determine exact pattern of LV activation in either ischemic or dilated cardiomyopathies in the presence and abscence of LBBB.

P491 Tissue-Doppler derived strain and strain rate underestimates myocardial deformation compared with Speckle-tracking measurements in patients with chronic severe mitral regurgitation

J.A. De Agustin Loeches, J. Zamorano, L. Perez De Isla, C. Almeria, J.L. Rodrigo, P. Marcos-Alberca, C. Fernandez-Golfin, A. Aubele, D. Herrera, C. Macaya. *Hospital Clinico San Carlos, Madrid, Spain*

Background and aim: The development of left ventricular (LV) dysfunction is a major concern in the management of patients with chronic severe mitral regurgitation (MR). Progressive LV remodelling occurs and LV dysfunction may develop insidiously. Our aim was to compare the myocardial deformation obtained by Tissue-Doppler imaging (TDI) and Speckle-tracking technology in patients with chronic severe MR.
Methods: Fifty consecutive patients with chronic severe MR scheduled for surgical correction were prospectively enrolled. Longitudinal strain (S) and strain rate (SR) at the leve of basal and mid interventricular septum (IVS) were obtained by TDI and Speckle-tracking.
Results: Mean age of patients was 62.02 ± 11 years. 22 patients (44%) were men. The etiology of MR was degenerative in 27 patients (54%), rheumatic in 21 Patients (42%), and secondary to healed endocarditis in 2 patient (4%). 31 (62%) were in atrial fibrillation and the remaining patients were in sinus rhythm. Myocardial deformation was highly underestimated by TDI compared with Speckle-tracking measurements (see table).

Table 1. Comparison between the myocardial deformation of IVS obtained by Tissue-Doppler imaging (TDI) and Speckle-tracking technology

	Speckle-tracking	TDI	p
Long. S basal IVS	-0.16	-0.10	<0.001
Long. SR basal IVS	-1.08	-0.82	<0.001
Long. S mid IVS	-0.18	-0.14	0.001
Long. SR mid IVS	-1.03	-0.94	0.018

Conclusions: TDI underestimates myocardial deformation compared with

Speckle-tracking technology. Speckle-tracking allows us to accurately measure the LV contractile function. This new tool may assist the clinician in the optimal timing of surgery in patients with chronic severe MR.

P492 3D-wall motion tracking: a new and faster tool for myocardial strain assessment

L. Perez De Isla, J. Zamorano, D. Vivas Balcones, C. Almeria, J.L. Rodrigo, C. Fernandez-Golfin, P. Marcos-Alberca, A. Aubele, D. Herrera, C. Macaya. *Hospital Clinico San Carlos, Madrid, Spain*

Background: 2D-Wall motion tracking echocardiography (WMT) is a useful method to measure myocardial strain, but it is very limited because the acquisition and analysis are time-consuming. 3D-WMT arises as a new method that might improve diagnostic usefulness and reduce those times. The aim of this study was to compare 2D and 3D-WMT results and compare the time of acquisition and analysis of regional myocardial strain by using 3D-WMT versus 2D-WMT.
Methods: measurements of radial and longitudinal strain of every left ventricular (LV) segment, and the time of acquisition and analysis of them were obtained by 3D and 2D-WMT.
Results: 30 patients were enrolled (57.2±19.6 years; 60% men). 3D-WMT provided complete radial and longitudinal LV strain information, similar to 2D-WMT (p = NS) but it was less time-consuming: time for acquisition and analysis for 2D-WMT was 14.0±1.9 minutes and for 3D-WMT was 5.1±1.1 minutes (p < 0.001). Furthermore, in the same analysis, a broader number of segments could be analyzed with 3D-WMT (72.4%) compared with 2D-WMT (52.0%). See table for results.

Main results

	Analyzed segments	Acquisition time	Analysis time	Total time	Radial strain	Longitudinal strain
2D- WMT	52.0	4.1±1.5	9.9±1.1	14.0±1.9	20.4±8.2	2.47±0.95
3D-WMT	72.4	1.7±0.9	3.3±0.8	5.1±1.1	19.5±7.9	2.14±0.15
p	<0.01	<0.01	<0.01	<0.01	0.66	0.10

WMT: wall motion tracking.

Conclusions: 3D-Wall motion tracking technology provides a faster, more complete and similar analysis to assess LV longitudinal and radial strain when compared with 2D-Wall motion tracking. Thus, 3D-Wall motion tracking is a potential clinical bedside tool for quantifying myocardial strain.

P493 Assessment of mitral annular velocities by speckle tracking echocardiography versus tissue Doppler imaging: validation, feasibility and reproducibility

B.M. Van Dalen, J.G. Bosch, O.I.I. Soliman, W.B. Vletter, F. Kauer, F.J. Ten Cate, M.L. Geleijnse. *Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Objectives: Mitral annular velocity may be measured angle independently by speckle tracking echocardiography (STE), in contrast to tissue Doppler imaging (TDI). The purpose of the current study was to compare STE and TDI, with respect to 1) the accuracy of velocity measurements in a moving phantom, 2) the feasibility and reproducibility of measurement of mitral annular velocities in a clinical setting, and 3) the estimation of left ventricular filling pressures using mitral annular velocities.
Methods: The velocity of a moving phantom, using different angles of insonation, and mitral annular velocities of 80 non-selected patients and 50 healthy volunteers were determined using TDI and STE. A subgroup of 20 patients was studied during right heart catheterization.
Results: When the motion direction of the phantom was parallel to the ultrasound beam, both TDI and STE determined velocities accurately. With increasing angle of insonation, TDI-derived velocity decreased, whereas STE-derived velocity remained unchanged. The feasibility of mitral annular velocities measured by TDI and STE was comparable (98% vs. 95%, P = NS). Although for both techniques correlations between measured mitral annular velocities at both exams were excellent, the test-retest variability of mitral annular velocities by TDI was higher. E/Em ratio by STE correlated better to pulmonary capillary wedge pressure (R2 = 0.51, P <0.001) as compared to E/Em ratio derived from TDI (R2 = 0.35, P <0.01).
Conclusions: Mitral annular velocities can be determined more accurate and reproducible by STE.

P494 The utility of tissue Doppler imaging for the noninvasive determination of left ventricular filling pressures in patients with septic shock

N. Mousavi, A. Czarnecki, R. Ahmadie, T. Fang, K. Kumar, M. Lytwyn, A. Kumar, D. Jassal. *University of Manitoba, Winnipeg, Canada*

Background: Pulmonary artery wedge pressure (PAWP) is an important indicator of volume status in septic patients. However, it requires invasive pulmonary artery catheterization (PAC), with its inherent minor complication rates. A non-invasive method to assess PAWP would be clinically useful in this population. Recent studies have suggested that diastolic indices using transthoracic echocardiography (TTE) may provide an accurate estimate of PAWP.
Objective: To determine whether echocardiographic Doppler assessment is accurate in estimating PAWP in patients with septic shock.
Methods: A retrospective chart review was performed of 253 patients admitted with a diagnosis of septic shock from 2007 to 2008 inclusive. Of the total patient population, 36 patients fulfilled the inclusion criteria, having undergone both TTE and PAC within 24 hours. Spectral Doppler indices including peak early (E) and late (A) transmitral velocities, E/A ratio, and E-wave deceleration time were measured. Tissue Doppler indices including S', E' and A' velocities were determined. Pulmonary artery wedge pressure values measured invasively were compared to the dimensionless index of E/E' in each patient.
Results: The mean age was 65±15 years with 24 males (66%). The mean left ventricular ejection fraction was 55±10%. Pulmonary artery wedge pressures ranged from 8 to 30 mm Hg with a mean of 17±6 mmHg. The mean E/E' was 12±8. Linear regression analysis between PAWP and E/E' demonstrated a strong correlation (r=0.8, p<0.05, Figure 1).

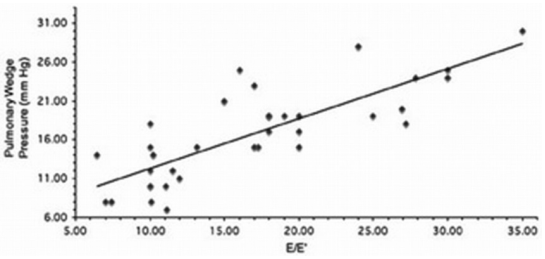


Figure 1

Conclusion: Tissue Doppler indices using TTE is a feasible and strong predictor of PAWP in patients with septic shock. Whether Tissue Doppler imaging can be used to guide hemodynamic management while avoiding the complications associated with PAC requires further study.

P495 Marked differences in presence of intraventricular mechanical dyssynchrony between tissue Doppler imaging and real-time three-dimensional echocardiography

S. Kleijn, J. Van Dijk, C.C. De Cock, C.P. Allaart, A.C. Van Rossum, O. Kamp. *VU University Medical Center, Amsterdam, Netherlands*

Purpose: Measurement of mechanical dyssynchrony by Tissue Doppler imaging (TDI) has been shown to predict clinical en echocardiographic reponse to cardiac resynchronisation therapy, and is considered the predominant technique for assessment of dyssynchrony. The aim of the study was to compare left ventricular (LV) mechanical dyssynchrony by real-time 3D echocardiography (RT3DE) with TDI in patients with (1) a wide range of left ventricular ejection fractions (LVEF) and different aetiologies of cardiomyopathy; and (2) to assess the necessity to correct dyssynchrony indices for heart rate variability to improve this correlation.
Methods: TDI and RT3DE images were acquired and systolic dyssynchrony indexes (SDI) were calculated. With TDI, standard deviation of time to peak systolic tissue velocity of 12 LV myocardial segments was assessed. With RT3DE, standard deviations of time from QRS onset to minimal volume of 16 LV subvolumes were assessed.
Results: Adequate analysis and comparison of TDI and RT3DE was possible in 90 of 100 patients (mean LVEF 36±16%). Mechanical dyssynchrony by TDI was 45 (26) ms (corrected for heart rate 4.9 (3.1)%), and with RT3DE 8.8 (4.0)%. A moderate correlation (r=0.485, p<0.001) was observed between TDI and RT3DE. The correlation did not significantly improve when TDI was corrected for heart rate (r=0.532). The presence of mechanical dyssynchrony by TDI was significantly greater than by RT3DE (60 (67%) vs 47 (52%) participants; p<0.01). Agreement between the two techniques differed markedly depending on the severity of LV dysfunction, with more than 50% disagreement in patients with an EF between 40-60%. However, no difference in agreement between techniques was observed between heart failure patients with ischemic and nonischemic cardiomyopathy.
Conclusions: In patients with normal to impaired LV function and different aetiologies of cardiomyopathy, TDI and RT3DE derived dyssynchrony indices show moderate correlations. Correction of dyssynchrony indices for heart rate variability does not significantly improve the comparison between the techniques. Marked differences between techniques are found for the presence of mechanical dyssynchrony when current cut-off values are applied, making interchangeability of these techniques questionable. Future research is warranted to further define the clinical application of RT3DE for assessment of mechanical dyssynchrony and its predictive value for acute and long-term response to CRT.

P496 Ethnic differences in left ventricular function and structure: A population study of UK Indian Asians and European whites

N.S. Chahal[1], T.K. Lim[1], P. Jain[2], J.C. Chambers[2], J.S. Kooner[2], R. Senior[1]. *[1]Northwick Park Hospital, Harrow, United Kingdom; [2]National Heart and Lung Institute, Imperial College, London, United Kingdom*

Objectives: We studied healthy UK Indian Asian and European white subjects to assess whether functional and structural properties of the left heart are independently related to ethnicity.
Background: People of Indian Asian ethnicity are known to have higher mortality from cardiovascular disease (CVD) compared to European whites and the mechanisms underlying this excess risk are not fully understood. Tissue Doppler imaging parameters, left atrial volume index (LAVI) and left ventricular mass index (LVMI) are all strong prognosticators of cardiovascular morbidity and mortality.
Methods: 453 healthy individuals were recruited from the London Life Sciences Prospective Population (LOLIPOP) study. All subjects underwent echocardiography for derivation of LAVI and LVMI. The tissue Doppler (TD) parameters of peak systolic velocity (Sa), diastolic velocity (Ea) and the ratio of Ea to transmitral E-wave (E/Ea) were measured and averaged from four mitral annular sites.
Results: Indian Asians had lower mean Sa (8.9 cm/s vs 9.5 cm/s, $p<0.001$), lower mean Ea (10.3 cm/s vs 11.0 cm/s, $p<0.001$) and higher E/Ea ratio (7.9 cm/s vs 7.0 cm/s, $p<0.001$) compared to European whites. Indian Asians had significantly smaller LAVI (14.2 ml/m^2 vs 16.3 ml/m^2, $p<0.001$) and lower LVMI (80.2 g/m vs 92.1 g/m, $p<0.001$). After adjustment for age, sex, systolic blood pressure, diastolic blood pressure and LVMI (for TD parameters), these ethnicity-related differences in left heart function and structure remained highly significant ($p<0.001$).
Conclusion: Systolic and diastolic LV function is significantly attenuated in healthy UK Indian Asians and may identify their elevated CVD risk compared to European whites.

P498 Fast and accurate assessment of left ventricular volumes and ejection fraction by 3D echocardiography

J. Hansegaard[1], S. Urheim[2], K. Lunde[2], S. Malm[3], S.I. Rabben[4]. *[1]University of Oslo, Oslo, Norway; [2]Dept. of Cardiology, Rikshospitalet University Hospital, Oslo, Norway; [3]Harstad University Hospital, Harstad, Norway; [4]GE Vingmed Ultrasound, Horten, Norway*

Introduction: Recent studies have shown that real-time 3D echocardiography gives accurate and reproducible measurements of left ventricular (LV) volume and ejection fraction (EF). We have developed a new software package for semi-automated assessment of LV volume using 3D echocardiography.
Aim: To evaluate the accuracy and repeatability of the new method compared to an offline 3D echo standard.
Methods: LV end-diastolic volumes (EDV), end-systolic volumes (ESV), and EF were measured using the new method in 35 unselected patients referred to echocardiographic examination. These results were compared to a reference, established using a commercially available offline semi-automated analysis tool. Repeated measurements were performed to investigate inter- and intra- observer variability.
Results: Average analysis time of the new method was 141s, significantly shorter than 261s with the offline tool ($p<0.001$). Bland Altman comparison of the two methods revealed high agreement of measured EDV, ESV, and EF (p=NS) (table), and similar intra-observer variability (p=NS) (table). Inter-observer variability with the new method was significantly lower for EDV and ESV (table).

New method vs. offline reference

	EDV [ml]	ESV [ml]	EF [%]
Difference	2.1±21	-0.88±17	1.6±11
Intra-observer variability:			
New method	7.5±6.2	5.5±5.6	3.0±2.7
Offline reference	7.7±7.3	5.0±5.9	2.1±2.0
Inter-observer variability:			
New method	9.0±5.9	5.0±3.6	2.7±2.8
Offline reference	17±6.3*	12±7.7*	3.0±2.1

*Significant difference ($p<0.05$). All numbers are mean ± 95% limits of agreement.

Conclusions: The new analysis software gives rapid and reproducible measurements of LV volumes and EF, with good agreement compared to an offline 3D volume quantification tool. This new software package is now fully integrated on a commercially available ultrasound scanner, for fast online LV analysis.

P499 Dynamic left ventricular mechanical dyssynchrony in hypertensive diastolic heart failure

C.M. Yu[1], P.W. Lee[1], J.K. Song[2], Q. Zhang[1], G.W.K. Yip[1], T.G. Zhu[3], C.M. Li[1], Y.Y. Lam[1]. *[1]The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China, People's Republic of; [2]Asan Medical Center, Seoul, Korea, Republic of; [3]Department of Medicine, The First Affiliated Hospital, Peking University, Beijing, China, People's Republic of*

Objectives: Left ventricular (LV) mechanical dyssynchrony may be dynamic and its role in diastolic heart failure (DHF) is unknown. We sought to examine the change of LV mechanical dyssynchrony during hemodynamic stress in hypertensive (HT) patients with DHF, compared to asymptomatic HT patients and healthy controls matched for age and gender.
Methods: A total of 139 subjects including 52 patients with HT and DHF (HT-DHF), 37 asymptomatic HT patients and 50 controls were studied by dobutamine stress echocardiography with tissue Doppler imaging. Systolic and diastolic dyssynchrony were evaluated using the standard deviation of time to peak systolic and early diastolic myocardial velocity, respectively, in a 6-basal-6-mid segment model, using the upper 2-SD of the healthy population as reference cutoffs.
Results: In normal controls, diastolic and systolic dyssynchrony did not develop during stress test. The prevalence of diastolic dyssynchrony with respect to the changes from rest to stress was significantly different between HT-DHF and HT groups (Table). However, the prevalence of systolic dyssynchrony was similar between the 2 groups (Table). Multivariate analysis revealed that stress-induced diastolic dyssynchrony [odds ratio (OR)=10.5, 95% confidence interval (CI)=2.08 to 52.96; P=0.004], long-axis myocardial systolic velocity (OR=0.65, 95% CI=0.46 to 0.93; P=0.019), long-axis early myocardial diastolic velocity (OR=0.69, 95% CI=0.48 to 0.95; P=0.025) and LV mass index (OR=1.13, 95% CI=1.10 to 1.16; P=0.048) were independent determining factors of DHF in HT.

	–/–	+/+	+/–	–/+	χ^2, P value
Prevalence of diastolic dyssynchrony (rest/stress), %					
HT-DHF	10	29	3	58	χ^2=38.2
HT	74	10	3	13	P<0.001
Prevalence of systolic dyssynchrony (rest/stress), %					
HT-DHF	69	23	4	4	χ^2=0.60
HT	65	29	3	3	P=NS

Conclusions: In HT subject with DHF, both diastolic dyssynchrony at rest, and in particular during stress, is highly prevalent when compared with those without developing DHF.

P500 Assessment of systolic function by speckle tracking echocardiography in hypertrophic cardiomyopathy. Correlation with B-type natriuretic peptide

A. Manovel Sanchez, B.C.F. Smith, S. Sulemane, D. Dawson, P. Nihoyannopoulos. *Hammersmith Hospital, London, United Kingdom*

Purpose: The presence of myocardial disarray in hypertrophic cardiomyopathy (HCM) suggests that systolic function might be impaired in these patients despite normal left ventricular ejection fraction (LVEF). B-type natriuretic peptide (BNP) is a quantitative biomarker of cardiac dysfunction which is elevated in HCM patients, although its role in this context is not well-defined. The aim of this study was to calculate myocardial strain by two-dimensional speckle echocardiography (2DSE) for quantitative assessment of myocardial function and its correlation with plasma BNP levels in HCM.
Methods: Echocardiographic examinations were performed on 16 patients with HCM and 15 healthy subjects. Standard apical views and short-axis planes of the left ventricle were acquired from each subject with a frame rate range of 60±20 frames/s. Longitudinal (LS), radial (RS) and circumferential (CS) strain was assessed by dedicated speckle tracking software. BNP analysis was performed on the same day of echocardiography study.
Results: LVEF was similar in both groups (67.2%±7% vs. 65.6%±6, p=ns). HCM patients showed elevated plasma BNP levels (480±334pg/mL). Global LS was significantly reduced in HCM patients when compared to healthy volunteers (-14.2±5 vs. -21.3±4, $p<0.001$). RS and CS were lower in HCM, although they did not reach a significant difference (-18.6±7 vs.-19.4±5 and 37.4±7 vs. 40.3±6 respectively, both p=ns). Global LS peak value of -16% had the best discriminatory power between both groups. Global LS was well correlated with plasma BNP levels (r=0.77, $p<0.05$) and LV wall thickness (r=0.81, $p<0.05$). Intraobserver and interobserver variabilities were 12.4% and 14% respectively ($p<0.001$).
Conclusions: Longitudinal strain by 2DSE objectively quantifies myocardial function in HCM. Decreased myocardial deformation and elevated BNP levels in these patients demonstrates the presence of myocardial impairment in HCM despite preserved LVEF.

P501 A comparison between right heart catheterization and a comprehensive hemodynamic assessment by Doppler echocardiography

O. Bech-Hanssen, F. Lindgren, N. Selimovic, B. Rundqvist. *Institute of Medicine at Sahlgrenska Academy, Gothenburg, Sweden*

Background and aim: The assessment of pulmonary artery (PA) pressures, cardiac output (CO) and pulmonary vascular resistance (PVR) is important for diagnosis and management of patients with heart failure. The aim of the present study was to compare a comprehensive hemodynamic assessment by echocardiography (Echo) with right heart catheterization (RHC).
Methods: Echo was performed within 24 hours of RHC at 78 occasions in 69 patients with suspected left ventricular failure (n=28), PA hypertension (n=29) or chronic pulmonary thromboembolism (n=12). The PA systolic pressure (PASP) was estimated from the tricuspid regurgitation. At the time of pulmonary valve opening, right ventricular pressure equals PA diastolic pressure (PADP). The

regurgitant velocity at the time of pulmonary valve opening was measured by superimposing the time from the QRS to the onset of pulmonary flow. The PA mean pressure (PAMP) was calculated as PADP + 0.33(PASP – PADP). The right atrial pressure (RAP) and CO was assessed using standard Echo methods. The pulmonary capillary wedge pressure (PCWP) was estimated semi-quantitatively using mitral and pulmonary vein data. To evaluate inter-observer variability, two investigators examined fourteen patients at the same occasion. The RHC was performed using Swan-Ganz catheters.

Results: The Table 1 shows the agreement between RHC and Echo variables. There were no significant differences between RHC and Echo data except for RAP. The SD of differences between the two investigators divided by the mean value for PASP, PAMP and the velocity time integral in the left ventricular outflow tract was 7%, 8% and 9% respectively.

Table 1. Catheter versus Echo

	RAP (mmHg)	PASP (mmHg)	PAMP (mmHg)	PCWP (mmHg)	CO (L/min)	PVR (Woods units)
Catheter	8±6	69±29	43±18	13±8	4.7±1.4	7±6
Echocardiography	9±5	69±27	44±17	12±5	4.7±1.6	8±5
Mean difference±SD	-1.4±4	0.7±13	1.6±9	-0.3±6	0.1±1.4	0.2±4
R-value	0.70	0.89	0.88	0.64	0.57	0.80
P-value	0.02	0.85	0.16	0.37	0.85	0.68

Conclusion: The present study shows that in groups of patients Echo can provide a comprehensive hemodynamic assessment comparable with RHC. Echo cannot replace diagnostic catheterization but the inter-observer variability is low and the method should be useful as a follow-up of hemodynamic status.

P503 Myocardial determinants of right ventricular ejection in pulmonary hypertension: 2D strain rate and spectral Doppler study

A. Calcutteea[1], P. Linqvist[1], W. Li[2], M. Hodson[2], M.Y. Henein[1]. *[1]Heart Centre, Norrlands University Hospital, Umea, Sweden; [2]Royal Brompton Hospital, London, United Kingdom*

Background: Symptoms of pulmonary hypertension (PHT) are partially explained by a decrease in right ventricular (RV) failure.

Objective: The aim of this study was to assess RV regional systolic contribution, based on longitudinal strain rate, to the ejection of blood in pulmonary hypertension.

Methods: We acquired apical 4-chamber view, short axis RV outflow tract (RVOT) in 20 normals (age 59+15 years, 7 male) and 37 patients with primary PHT (age 66+12 years, 14 male). Offline analysis was performed using 2D strain software with tracing of the entire RV endocardial border and RVOT. The time from the onset of Q-wave (ECG) to peak ejection and to peak systolic strain rate at basal, mid and RVOT levels were measured.

Results: In normals, time from onset of Q-wave to peak RV ejection was 228±22 ms (T1) and to peak systolic strain rate of basal RV free wall, mid segment and RVOT was 231±36 (T2), 237±46 (T3) and 234±38 (T4) ms, respectively (T2 vs T3, p=NS; T2 vs T4, p=NS; T3 vs T4, p= NS). T1 correlated with T4 (r = 0.7, p=0.04) but not with T2 (p= NS) or T3 (p= NS). In PHT, time from onset of Q-wave to peak ejection was 197±41 ms (T5) and to peak systolic strain rate of basal RV free wall, mid segment and RVOT was 200±40 (T6), 197±48 (T7) and 216±58 (T8) ms, respectively (T6 vs T7, p=NS; T6 vs T8, p=NS; T7 vs T8, p=NS). T5 correlated better with T7 (r = 0.6, p=0.05) but not with T6 (p=NS) or T8 (p=NS).

Conclusion: Normally outflow tract function, and not inflow tract, determines RV ejection time relations. With chronic afterload, e.g. pulmonary hypertension and outflow tract dilatation, this close relationship is retrogradely transferred to the mid segment of the right ventricular cavity. Thus, pacing outflow tract in such patients may optimise right ventricular ejection performance.

P504 Is there any echocardiographic parameter that can predict right ventricular pump function in pulmonary hypertension?

G. Teixido[1], R. Aguilar[1], E. Domingo[2], M. Lopez-Meseguer[1], A. Roman[1]. *[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [2]Physiology Dpt. Universitat Autònoma., Barcelona, Spain*

For prognostic purposes and for the evaluation of response to therapies assessment of Cardiac Output (CO) in Pulmonary Hypertension patients (PAH) is fundamental. The aim of the study was to evaluate the correlation between echocardiographic estimators of right ventricle (RV) function and CO measured invasively (Fick method).

Methods: We studied 16 patients (11 women, mean age 52,5y) with PAH Type I (mean time from diagnosis of 3,5y), with simultaneous right and left cardiac catheterization and transthoracic echocardiogram under basal and acute vasodilator test with epoprostenol (that was positive in 3 cases).

The following variables were analysed: Invasive CO, Pulmonary pressure (mPAP) and Vascular Resistances (PVR) and echocardiographic RV function parameters: TAPSE, Peak Systolic velocity in tricuspid annulus (S), isovolumic peak velocity and acceleration (IVV and IVA).

Paired Student t test was employed to analyse changes between phases. Multiple linear regression analysis modeling was used to identify the best predictor variables of CO.

Results: Non significant differences for echocardiographic RV function parameters were found between baseline and vasodilator phases despite an increase in CO (table).

For the overall prediction of CO (basal plus vasodilator) employing just one echocardiographic parameter without the addition of invasive variables, only IVV (R2=0.28; p=0,005) and S (R2=0,23; p=0,007) were significant. No single parameter was useful in the basal state. However under vasodilator test (with higher CO), only S (R2=0,40; p=0,014) remained significant.

If invasive information (PVR, mPAP, HR) is incorporated, the best explicative model is IVA and IVV in the basal state (R2=0.559, p=0.022; R2=0.531; p=0.026 respectively) and IVA and S in the vasodilator state (R2=0.611, p=0.014; R2=0.625; p=0.01 respectively).

	HR (bpm)	CO (l/min)	PVR (Uwood)	mPAP (mmHg)	TAPSE (mm)	IVA (m/s^2)	IVV (m/s)	S (m/s)
Baseline	78,7±3,1	4,1±0,3	10,79±2,0	48,3±4,8	17,2±0,9	3,3±0,4	8,6±0,8	11,2±0,5
Epoprostenol	86,9±6,7	5,4±0,6	8,52±1,6	47,8±5,2	18,0±0,9	3,8±0,5	10.8±1,1	12±0,5
p	0,144	0,018	0,032	0,839	0,267	0,434	0,142	0,304

Conclusions: Tissue Doppler parameters either isovolumic (IVV, IVA) or non isovolumic (S) offer a much better estimation of RV pump function than parameters based on absolute displacement (TAPSE) in pulmonary hypertension.

P505 Multivariate analysis of factors affecting right ventricular systolic pressure in the absence of aortic or mitral valve disease

M. Matangi[1], D.W. Armstrong[1], G. Tsimiklis[2], J.R. Vyselaar[2], G. Barber[2]. *[1]Kingston Heart Clinic, Kingston, Canada; [2]Queen's University, Kingston, Canada*

Purpose: To identify, using multivariate analysis (MVA), the major factors affecting right ventricular systolic pressure (RVSP) measured during echocardiography (ECHO) in patients (P) without aortic or mitral valve disease.

Methods: Our cardiology database was searched for all P who had RVSP measured during ECHO. Only P with all measurable fields entered were included. This means P with aortic and mitral valve disease were excluded since the fields in those P without such disease were empty. The measurements included, age, gender, height, weight, body mass index (BMI), EF (ejection fraction, biplane), E/A ratio, E/E', LV mass index (LVMI) and m-mode measurements of left atrium (LA), aortic root (AO), left ventricular end-diastolic dimension (LVDD) and left ventricular end-systolic dimension (LVSD). MVA was performed using multiple linear regression and stepwise linear regression (SLR) including cross variables. All statistics were performed with JMP software.

Results: Of the 10,259 P who had RVSP measured 4,869 had all the required fields with complete data entry. Statistically significant independent variables using MVA in both males and females included, Age, E/A ratio, E/E', LA size, and EF, Table 1. Using SLR the impact of age was expressed through its interaction between E/A ratio, E/E' and LA size.

Conclusions: In both males and females, age has the most significant influence on RVSP using MVA in P without aortic or mitral valve disease. However, using SLR the effect of age was attributed to its interaction with parameters of diastolic function and LA size.

P506 Assessment of right ventricular volumes and function by 3D real-time transthoracic echocardiography in children

S. Hascouet, G. Brierre, G. Caudron, S. Abadir, Y. Dulac, S. Paranon, G. Ohanessian, P. Acar. *CHU de Toulouse - Hopital des Enfants, Toulouse, France*

Background: 3D echocardiography is a validated method to evaluate left ventricular (LV) volumes and function. Because of its peculiar morphology, the right

Abstract P505 – Table 1

	Age	E/A ratio	E/E' ratio	LA	PW	EF	BMI	IVS	LVDD	LVSD	LVMI
Males F ratio (M, n=2,146)	149	69	48	29	8.7	6.4	5.6	3.4	1.9	1.4	0.4
P value MVA (M)	<0.0001	<0.0001	<0.0001	<0.0001	<0.005	<0.05	<0.05	NS	NS	NS	NS
F ratio (F, n=2,723)	252	48	35	59	0.5	9.5	0.5	1.1	0.8	0.1	0.04
P value MVA (F)	<0.0001	<0.0001	<0.0001	<0.0001	NS	<0.005	NS	NS	NS	NS	NS

LA = left atrial size. PW = posterior wall thickness. LVDD = left ventricular end-diastolic dimension. LVSD = left ventricular end-systolic dimension. IVS = interventricular septal thickness. LVMI = left ventricular mass index. BMI = body mass index. MVA = multivariate analysis.

ventricle (RV) volumes can not be calculated with 3D softwares used for LV quantification. Recently, new 3D software adapted for RV morphology was introduced.
Aim: The aims of this study were to evaluate the feasibility of 3D RV analysis in a pediatric population and to compare RV 3D data with LV 3D measurements.
Methods: Fifty-one pediatric patients (median age 10 years) with normal cardiac anatomy and function were included. 3D transthoracic echocardiography was performed with the X4-2 or X7-2 matrix probe (ie33, Philips Medical Systems, Andover, MA). Three LV and RV full volume sweeps were acquired from apical views. The volumes were analysed with the LV and the dedicated RV analysis softwares (TomTec Imaging Systems, Munich, Germany).
Results: Measurements feasibility was 100% for LV and 95% for RV. The RV had higher volumes but smaller ejection fraction compared to LV (RV end-diastolic volume 59 ml, LV end-diastolic volume 46 ml; RV end-systolic volume 29 ml, LV end-systolic volume 17 ml; RV ejection fraction 53%, LV ejection fraction 66%).The stroke volumes of the two ventricles were highly related with a mean difference of 1±2 ml (r= 0,95). The intra- and interobserver variabilities ranged from RV 3D volumes (0.4%-2%, and 0.2%-4%).
Conclusion: 3D echocardiography using dedicated software is a feasible and adequate method for RV volume quantification in a normal pediatric population. Further studies are needed to validate the accuracy of the method to calculate enlarged RV volumes in patients with congenital heart diseases.

P507 Long-term follow up of apical versus septal right ventricular permanent pacing shows similar effects on cardiac synchrony and function

R.C. Sisu[1], A.D. Margulescu[1], C. Siliste[1], M. Florescu[2], M. Cinteza[1], D. Vinereanu[1]. *[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [2]University Emergency Hospital, Bucharest, Romania*

Pacing at the apex of right ventricle (RV) is the most used technique for pacemaker implantation. This site might cause significant asynchrony, inducing left ventricular (LV) dysfunction, therefore, septal RV pacing, by using more physiological electrical activation pathways, might be a better alternative. We compared effects on cardiac synchrony and function, using conventional and tissue Doppler echo (TDE), between the 2 pacing sites, in pacing-dependent patients.
Methods: 40 patients (74±9 yrs, 21 men), 20 paced at the apex (age-matched), were studied 11±4 months after implantation. 32 of them (15 paced at the apex) had an 1 year follow up visit. TDE measurements were made from 6 LV basal myocardial segments, and the basal RV segment; for each segment, peak systolic and diastolic velocities, and time-to-peak systolic and diastolic velocities were measured. Systolic function was assessed from ejection fraction (EF), and mean longitudinal systolic velocity (MSV); diastolic function from mean longitudinal diastolic velocity (MDV), E/Ea ratio, and E/Vp ratio. Intra-ventricular synchrony was assessed from septal-to-posterior wall motion delay (SPD), standard deviation (systolic – SDS, and diastolic – SDD), and maximal difference (systolic – MDS, and diastolic – MDD) of the LV myocardial timings. Inter-ventricular synchrony was assessed from difference between basal lateral LV segment and the RV segment (BLBR).
Results: Although synchrony improved significantly between the 2 visits (baseline-1, and 1 year follow up-2) for both pacing sites, changes of synchrony and function were not different (table).
Conclusion: There are no major differences during long-term follow up for cardiac synchrony and function, between the two pacing modalities, in pacing dependent patients. However, although similar, there are significant changes in inter- and intra- ventricular synchrony for each pacing site.

P508 Quantification of right ventricular function by 2D speckle imaging: comparison with MRI

M.-A. Arnould[1], S. Gougnot[2], S. Lemoine[3], L. Freysz[3], O. Huttin[3], B. Popovic[3], Y. Juilliere[3], C. Selton-Suty[3]. *[1]European Hospital George Pompidou (AP-HP), Paris, France; [2]CHR Bon Secours, Metz, France; [3]CHU de Nancy - Hopital de Brabois, Vandoeuvre les Nancy, France*

Purpose: Echocardiographic assessment of right ventricular (RV) function requires many different parameters. We applied 2D speckle imaging (2DSI) to right ventricular free wall (RV) and compared our results with magnetic resonance imaging (MRI) measurement of RV ejection fraction (EF).
Methods: 32 patients (19 with FEVD ≤ 45%) underwent both complete echocardiography (including standard parameters of RV function (fractional area change (FAC), Tei index, systolic velocity (S) of tricuspid annulus by DTI) and MRI for the evaluation of RVEF. 2DSI was applied to high frame rate cine loops centred on the RV free wall with measurement of peak systolic strain (%) in the basal, median and apical segments.
Results: Strain, especially in RV median and apical segments, is significantly reduced in patients with RVEF ≤ 45% (median strain: -16,39±5,27 vs. -24,74±8,00 (p=0,002); apical strain -13,01±6,84 vs. 22,53±11,32 (p=0,03)). Both apical (r= -0,717, p=0,0001) and median (r= -0,630, p=0,0001) strain show a very good correlation with RVEF. Furthermore strain, especially apical one, is also correlated with the usual echographic parameters of RV function, (FAC: r=0,019; Tei: r=0,01; peak S: r=0,002). By multivariate analysis, apical strain (p=0,004) and FAC (p=0,029) were predictive of a decreased RVEF.
An apical strain value of >-20% allows the detection of RVEF≤45% with a sensitivity of 89%, a specificity of 67%, a positive predictive value of 81% and a negative predictive value of 80% (area under the curve 0,77).
Conclusion: Apical strain as measured from 2DSI seems a promising parameter in the estimation of RV function.

P509 Improved left- and right ventricular function after exercise training in COPD patients

C. Bjork Ingul, E. Bronstad, A.E. Tjonna, O. Rognmo, H. Dalen, U. Wisloff, S. Steinshamn. *Department of Circulation and Medical Imaging, Medical Faculty, NTNU, Trondheim, Norway*

Objective: In general, patients with cardiovascular disease obtain more beneficial cardiac and fitness adaptation from aerobic interval training (AIT) than moderate continuous exercise training (MCT). However, this has not been studied in chronic obstructive pulmonary disease (COPD) patients were lung ventilation is a clear limitation to exercise capacity. The aim of this study was to determine the effects of AIT Vs. MCT on cardiac function and fitness level in COPD patients.
Methods: 17 patients with COPD (65±7 years, 13 men) with FEV1 52.8±11 (% pred), FEV1% FVC 44±11 (% pred) and a smoking history of 34±9 packyears were randomly assigned to MCT (n = 7; 70% of peak heart rate (HR) for 47 minutes) or AIT (n= 10; 95% of peak HR for 4x4 minutes) 3/week/12 weeks.
17 age- and sex-matched healthy individuals served as reference group. Spirometry, maximal oxygen uptake (VO2max) and echocardiography were examined before and after the intervention period.
Results: Both AIT and MCT increased VO2max and work economy by 7% and 10% (p<0.02). Right and left ventricle systolic function was significantly lower in the COPD patients and improved by both modes of exercise training compared to controls (Table). Exercise training did not change, resting and peak HR, blood pressure, FEV1 and did not improve diastolic function.

Table 1. Echocardiographic variables

	Control	AIT pre	AIT post	P-value	MCT pre	MCT post	P-value
SV ml	86	69.9	81.3	0.038	63.3	76.3	0.043
LVOT Vmax m/s	1.0	0.93	1.01	0.033	0.85	0.95	0.018
CO l/min	5.3	4.3	5.2	0.035	4.3	4.9	0.049
LV S' cm/s	8.0	6.8	8.0	0.005	6.9	8.1	0.018
LV E' cm/s	8.8	7.6	8.3	0.11	8.9	9.8	0.11
TAPSE mm		22.3	25.9	0.005	21.0	24.4	0.028
RV S' cm/s	14.1	12.5	14.4	0.017	12.1	13.9	0.027
RV Global SR s^{-1}		-1.34	-1.69	0.008	-1.48	-1.70	0.028

SV - stroke volume, LV - left ventricular, LVOT - LV outflow tract, RV - right ventricular, S' - tissue Doppler systolic velocity, E' - tissue Doppler early diastolic velocity, TAPSE - tricuspid annular plane systolic excursion, SR - strain rate.

Conclusion: Both exercise regimens improved systolic cardiac function, despite moderate effect on physical fitness. In contrast to other patient groups studied, exercise intensity seems not to be important to achieve beneficial cardiac effects in COPD patients.

P510 Evaluation of longitudinal strain and strain rate of the right and left interventricular septum with a new echocardiographic 2D based method in normal subjects

C. Bussadori, M. Di Donato, C. Arcidiacono, D. Negura, L. Piazza, A. Micheletti, M. Chessa, G. Butera, J.S. Dua, M. Carminati. *Policlinico San Donato - Centro E. Malan, San Donato Milanese, Italy*

Purpose: Interventricular septal (IVS) contractility is expressed in different directions as a consequence of the varied orientation of the myo-fibers in the septum. We used 'border tracking' method to assess the right and left components of the septal motion at different levels, in terms of strain (S) and strain rate (SR).
Methods: 11 healthy volunteers, aged 36±8 years were included. Echocardiographic, 2D cine-loop of apical 4-chamber views, were acquired and stored for off-line computer analysis. The analyses included a) construction of vectors superimposed on the 2D images expressing velocity, direction and versus of each single point tracked at the endocardial border on both sides and b) graphic representation plotted against time, for S and SR, at three different levels: base, mid and apical portion.
Results: Significant differences in S and SR were found between the right and

Abstract P507 – Table 1. Comparative results between pacing sites

Pacing sites	SPD (ms)	SDS (ms)	MDS (ms)	SDD (ms)	MDD (ms)	BLBR (ms)	EF (%)	MSV (cm/s)	MDV (cm/s)	E/Ea	E/Vp
Apical1	110±66	52±16	104±40	31±20	76±50	61±61	54±8	3.8±0.8	5.2±1.8	17±9	2.3±1.0
Apical2	107±62	36±13	68±40	29±19	71±50	-26±50	54±8	4.2±0.8	4.7±1.4	18±6	2.1±0.7
Septal1	160±88	51±22	109±65	36±25	90±66	66±72	53±11	4.2±1.2	4.6±1.6	14±7	2.5±2.0
Septal2	105±60	40±19	73±50	40±28	98±67	-4±57	49±14	4.3±1.2	4.4±1.7	13±6	1.7±0.5

Right and left septal Strain and SR

	Left Septum	Right Septum	"p" value
Strain (%)			
Base	-15.8±3.5	-23.2±4.8	0.0001
Mid	-17.7±4.1	-23.3±6.1	0.0019
Apex	-24.0±5.8	-25.9±4.7	ns
ANOVA	0.0001	ns	
Strain Rate (sn^{-1})			
Base	-0.84±0.25	-1.40±0.58	0.0002
Mid	-0.94±0.20	-1.43±0.38	0.0001
Apex	-1.44±0.36	-1.43±0.38	ns
ANOVA	0.0001	ns	

Analysis of variance between the three septal regions on each side; ns: not significant; "p" value: significance of differences between left and right.

left endocardial longitudinal motion (Table). S and SR were uniform along the right side from base to apex, while a gradient existed on the left side, being higher at the apical level.

Conclusions: The observed differences in S and SR between the two sides of the IVS may reflect the difference in longitudinal distribution of myocardial fibers. The higher strain and strain rate at the apex of the left but not at the apex of the right septum, reflects the pivotal role of the left apex in left ventricular twisting during systole.

P511 Right ventricular impact of on-pump cardiac surgery

N. Hammoudi, O. Merceron, C. El Khebir, C. Chalah, R. Dorent, P.L. Michel. *AP-HP - Hopital Tenon, Paris, France*

Background: The impact of on-pump cardiac surgery on right ventricular (RV) function remain unclear.

Objective: The aim of our study was to investigate RV function in patients underwent uncomplicated on-pump cardiac surgery, using state-of-the-art Doppler echocardiography including 2D speckle tracking (2DS) technology and pulsed tissue Doppler imaging.

Methods: 18 consecutive patients (mean age 60.5±18.0 years, 14 men) were prospectively studied in the 15 days before and 15 days after cardiac surgery (7 bypasses and 11 valves surgeries).

From apical four chambers view, longitudinal RV free wall mid segment strain (ε) and systolic strain rate (SSR) were measured using 2DS.

From pulsed Doppler tissue imaging at tricuspid annular plane, peak systolic (Sat), early (Eat) and late (Aat) diastolic velocities were measured.

In addition, we determined left ventricular ejection fraction (LVEF) by Simpson method and tricuspid regurgitation velocity (TRV).

All the parameters were the average of three measures.

Results: While LVEF and TRV were similar in the two groups; the observed values of RV systolic (ε, SSR, Sat) and diastolic (Eat, Aat) function parameters were significantly lower after than before cardiac surgery (table, mean ± SD).

	Before surgery (n=18)	After surgery (n=18)	p
Heart rate (beat/minute)	67.4±13.1	73.9±13.1	0.08
LVEF (%)	54.7±9.7	49.9±9.0	0.13
TRV (m/s)	2.9±0.5	2.5±0.2	0.19
RV mid segment ε (%)	-26.6±4.9	-15.8±4.0	<0.01
RV mid segment SSR (s^{-1})	-1.5±0.3	-1.2±0.3	<0.01
Sat (cm/s)	12.0±3.3	6.4±1.5	<0.01
Eat (cm/s)	11.1±4.7	4.8±1.6	<0.01
Aat (cm/s)	12.4±4.9	6.2±3.0	<0.01

Conclusion: Our study shows that RV (systolic and diastolic) function is impaired following cardiac surgery. Pathophysiological significance and potential prognosis implications of these findings remain to be clarified.

P512 Cardiovascular complications in sickle cell disease:echocardiographic features

I.Z. Cabrita[1], C. Ruisanchez[2], M. Layton[1], F.J. Pinto[3], P. Nihoyannopoulos[1], S.J.R. Gibbs[1]. *[1]Imperial College London, London, United Kingdom; [2]Hospital Universitario Marques de Valdecilla, Santander, Spain; [3]Lisbon Cardiovascular Institute, Lisbon, Portugal*

Background: The cardiovascular complications in sickle cell disease (SCD) are being recognized and a specific SCD cardiomyopathy has been previously described, which may be in part related to the abnormal properties of sickle cell haemoglobin by either affecting left ventricle function due to its differing oxygen carrying properties, through intravascular sickling, chronic haemolytic anemia or intravascular thrombosis. Pulmonary complications remain the prime cause of morbidity and mortality in SCD.

Methods: Adults with SCD and age and gender matched controls were prospectively studied during steady state visits. Each subject underwent a history and examination, an echocardiographic assessment (including 2-dimensional, Tissue Doppler and 3-dimensional imaging), hematologic testing, and a 6 minute walk test (6MW). Echo data was compared between SCD patients and controls, and linear regression analysis was performed to assess for correlation between echo parameters and anemia and exercise parameters in SCD patients.

Results: Of the 32 SCD patients and 15 controls enrolled, 32 SCD patients and 13 controls had measurable tricuspid valve regurgitation jet velocity (TRJV) to estimate systolic pulmonary pressure. Pulmonary hypertension was found in 40% of the patients (mean TR = 2.75±0.17). Left ventricle (LV) enlargement was found in 21% of patients (by 2D echo) and in 34% of patients (by 3D echo). Only 9% of patients had evidence of systolic dysfunction (ejection fraction<55%) and 22% of the patients had evidence of diastolic dysfunction. No association was found between increase pulmonary pressures and heart chambers enlargement. After adjusting for hemoglobin concentration, a good negative correlation was found between TRJV and 6MW (r= -0.46, p=0.009). Among patients with SCD and associated pulmonary hypertension, a good negative correlation was found between TRJV and hemoglobin (Spearman's Rho= -0.69, p=0.009). There was no correlation between echo parameters and age, blood pressure and phenotype.

Conclusions: Adults with SCD have higher estimated pulmonary pressures, LV size and mass, left atrium volume and a trend toward worse diastolic function when compared to controls. Elevation of echocardiographic-determined TRJV has significant correlation with anemia and exercise capacity. We concluded that echocardiography is an important screening tool for pulmonary hypertension in SCD patients and should be used to identify a high-risk group that may benefit from intervention.

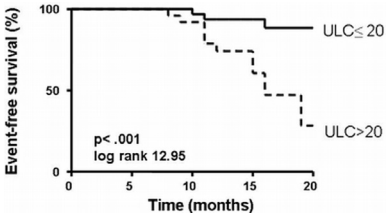
P513 Ultrasound lung comets as a long-term prognostic determinant in systemic sclerosis

L. Gargani[1], M. Doveri[2], M. Bazzichi[2], G. Agoston[3], M.F. Costantino[4], A. Nigro[4], S. Bombardieri[2], R. Sicari[1], A. Varga[3], E. Picano[1]. *[1]Fondazione G Monasterio, Pisa, Italy; [2]Rheumatology Division, Pisa University, Pisa, Italy; [3]2nd Dept. of Medicine, Albert Szent-Gyorgyi, Szeged, Hungary; [4]Azienda Ospedale San Carlo, Potenza, Italy*

Background: Pulmonary arterial hypertension and pulmonary fibrosis are established prognostic determinants in patients with systemic sclerosis (SSc). Although often assessed with invasive and/or ionizing techniques, pulmonary hypertension (by Pulmonary Artery Systolic Pressure, PASP) and fibrosis (by Ultrasound Lung Comets, ULCs) can be measured in a simpler way with cardiac and chest ultrasound. Aim: To assess the prognostic value of ULC and PASP in SSc.

Methods: 59 SSc patients (age 54±14 years, 56 females) admitted to the Rheumatology Division of the University were evaluated with a comprehensive 2D and Doppler echocardiography, and chest sonography with ULC assessment. A patient ULC score was obtained by summing the number of ULC found on anterior and posterior chest. PASP was calculated from the maximal velocity of tricuspid regurgitation flow following recommendations of European Association of Echocardiography.

Results: During follow-up (median: 15 months), 15 events occurred: 3 deaths, 8 new admission for worsening dyspnea, 4 new admission for worsening skin involvement. Age, skin score and PASP did not predict outcome on univariate analysis, which only selected number of ULCs (HR 1.012, 95% C.I.1.004-1.020, p<0.01) as a significant predictor. A ROC analysis identified 20 ULCs as the best diagnostic cut-off to predict events (see figure) with an AUC of 0.78, 80% sensitivity and 73% specificity.



Conclusion: ULC are a simple, user-friendly, radiation-free bedside sign of pulmonary fibrosis, representing a long term prognostic determinant of SSC patients, stronger than PASP.

P514 Depressed longitudinal and circumferential deformation and preserved radial deformation in patients with metabolic syndrome

B. Pirat, H. Bozbas, V. Simsek, L.E. Sade, E. Turk, A. Yildirir, H. Muderrisoglu. *Baskent University Faculty of Medicine, Ankara, Turkey*

Purpose: Metabolic syndrome is associated with atherosclerosis, and is a predictor of cardiovascular events. Myocardial strain imaging by speckle tracking allows assessment of myocardial deformation quantitatively. In this study we aimed to analyze myocardial deformation in patients with metabolic syndrome and test the hypothesis that sublinical myocardial dysfunction is present in metabolic syndrome patients.

Methods: Twenty-three patients with metabolic syndrome (mean age 63±9 years, 8 men) and 22 age- and sex-matched control subjects were studied. Patients did not have clinical coronary artery disease or diabetes. Echocardiographic

images in apical planes and parasternal short axis views were acquired and 2-dimensional speckle tracking was applied to measure mean longitudinal, circumferential and radial strain.
Results: Left ventricular ejection fractions were similar among the groups (59±2% in controls and 58±2% in metabolic syndrome patients, p>0.05). Mean longitudinal and circumferential strain was reduced in patients with metabolic syndrome when compared with controls (-14.3±2.7 vs -16.8±2.8%, p=0.008, and -19.6±4.2 vs -24.4±6.2%, p=0.01, respectively). Radial strain was not different between the groups (30.9±10.0% in metabolic syndrome and 36.9±10.4% in controls, p=0.09).
Conclusion: Left ventricular longitudinal and circumferential strains are reduced and radial deformation is preserved in patients with metabolic syndrome. Depressed longitudinal and circumferential deformation could be an early marker for myocardial dysfunction in this patient population.

P515 Two-dimensional speckle tracking strain imaging in the acute phase can predict final transmural extent of myocardial infarction

C. Raineri, M. Calcagnino, F. Fava, S. Leonardi, M. Bonardi, C. Dellabianca, M. Cottini, E. Ferrara, A. Raisaro, M. Previtali.
Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Purpose: Two-dimensional Strain Imaging (2D-SI) can predict transmural extent (TME) of myocardial infarction (MI) in the chronic phase, but its value in the acute phase is not as yet been demonstrated. Aim of the present study was to evaluate the ability of basal and dobutamine (DOB) stress 2D-SI performed in the acute phase to predict 4-months TME of MI evaluated by cardiac magnetic resonance (CMR) in patients treated with primary percutaneous coronary intervention (pPCI).
Methods: Twenty-three patients with a first ST elevation MI (STEMI) (aged 58±7 years, 87% men, 65% anterior MI) reperfused with pPCI underwent basal and low-dose (5-10 γ/kg/min) DOB speckle tracking 2D-SI at a median of 5 days after hospitalization. Longitudinal (L), radial (R) and circumferential (C) Strain (S) were evaluated on a 16-segment model of the left ventricle. CMR was performed after four months of the index event to assess segmental extent of MI. TME was defined as a delayed enhancement (DE) of the infarcted segment >50%. 2D-SI parameters and wall motion score (WMS) at baseline and after DOB were evaluated as potential univariate predictor of TME. The multivariable model was created with all univariate predictors with p<0.05.
Results: Of the 368 segments analyzed, 170 (46%) showed DE at 4-months CMR; of these, 88 (52%) showed TME (i.e. DE >50%). Basal LS (p<0.0001) and CS (p=0.008), DOB LS (p<0.0001) and CS (p=0.019), basal WMS (p<0.0001) and DOB WMS (p<0.0001) were significant predictors of TME at univariate analysis. In the multivariable model only basal LS (OR 1.137, 95% CI 1.017-1.272; p=0.024) and basal CS (OR 1.105, 95% CI 1.011-1.208; p=0.028) maintained the ability to predict TME. ROC analysis showed an area under the curve of basal LS of 0.78 (95% CI 0.70-0.86, p<0.0001) for detection of TME. A basal LS cut-off value of -8.05 had a 70% sensitivity and a 73% specificity for predicting 4-months TME of MI.
Conclusions: In STEMI patients treated with pPCI, 2D-SI performed during the acute phase can predict TME of MI at four months. Both baseline LS and CS proved to be multivariable predictors of transmurality. Thus, 2D-SI may be of clinical value for early stratification of STEMI patients.

P516 Tissue Doppler parameters of right ventricle function, prognostic impact on mortality after heart transplantation

L. Alizadeh, S.H. Varnous, R. Makri, M. Laali, F. Fernandez, J.L. Golmard, P. Leprince, I. Gandjbakhch, A. Pavie. *Pitie-Salpetriere Hospital (AP-HP), Paris, France*

Background: There are many conventional criteria of Left ventricular (LV) function in prognosis after heart transplantation but the role of right ventricle (RV) has been less studied.
In our study we have utilized echocardiographic criteria of RV function before heart transplantation and studied their relation to in-hospital mortality, early after the operation.
Method: 59 cases of heart transplantation candidates in years 2006 -2007 were chosen for this study. Echocardiography evaluation of RV function was analyzed in a period 60±12 days before the operation. The following parameters were studied in each case: RV dilation with eyeball method comparing to LV, TAPSE (tricuspid annular plan systolic excursion), tricuspid regurgitation (TR), and pulmonary flow acceleration time, we also studied tissue Doppler parameters of lateral annulus of tricuspid valve as: early (Et) and accelerated (At)waves of diastolic movement, isovolemic systolic contraction (S't), time to peak of S't, systolic ejection wave (St) and Tei index (RV performing index). Each criteria was analyzed to find its relation to all cause, in-hospital mortality.
Results: In mono-variant analysis, S't and St waves were in relation to early in hospital mortality; with hazard ratio of 0.84 (0.71-0.99) and p: 0.044 for St, hazard ratio of 0.82 (0.69-0.98)and p: 0.033 for S't. This relation was not found for Tei index. In multi variant analysis none of tissue doppeler parameters were found to be related to mortality after heart transplantation.
Conclusion: RV function has direct impact on survival after hear transplantation. Tissue Doppler parameters of lateral tricuspid annulus could be more sensitive comparing to conventional methods for estimating mortality. Larger studies with higher number of patients are needed to find independent RV parameters of mortality.

P517 Measurement of post systolic shortening during exercise to detect myocardial viability after a first acute myocardial infarction

G.P.J. Pierre-Justin, L.A. Pierard. *University of Liege, Liege, Belgium*

Purpose: Experimental studies in animals have shown that post systolic shortening (PSS) is an active process reflecting myocardial viability. We sought to determine whether left ventricular PSS during exercise may detect myocardial viability (MV)after primary PCI
Methods: 30 consecutive pts (59±14 years) with a first acute MI treated by primary PCI underwent exercise echocardiography (EE) and were compared with 18 healthy volunteers. Functional Recovery (FR) was identified at 30±4 days after PCI by means echocardiography. At rest and at each stage of exercise test and during recovery, 3 heart cycles of the apical 4-3-and 2 chamber views were captured in conventional 2D and color tissue Doppler modes. The strain rate (SR)data were processed from the Color Doppler myocardial imaging velocity data. Strain (ε) data processing SR b-mode data was postprocessed from myocardial velocities. SR profiles were obtained from a user-defined region of interest and averaged over 3 consecutive cardiac cycles to derive mean SR profiles. Mean ε profiles were obtained by time-integrating of the mean SR profiles with end-diastole (ECG) r-top) as a reference time-point. the timing of aortic valve closure (AVC) was used as a marker of end-systole parameters derived from profiles. Systolic (εsys) and peak strains (εpeak) were measured at end-systole and peak deformation, respectively. Tε is the time from AVC to εpeak. Postsystolic strain was calculated as the difference between εpeak and εsys.
Results: A total of 240 of 414 segments showing dyssnergy at rest did not show in wall motion improvement at (EE) were considered without contractile reserve (CR)and constituted the group A. And among the 174 segments showing (CR)constituted the group B. At rest the peak systolic strain rate (SRs) and early filling (SRe) phase and the Strain (εsys) were significantly reduced in infarction group compared with control group. And during the (EE) the SRs and the SRe increased significantly (p<0.05) At rest, the PSI is low in the control group, then increased significantly in the infarction group compared with control group. The SRs and PSI were able to predict the MV and area under the ROC curve the higher were obtained with the SRs (AUC=0.84) and the PSI (AUC=0.83) with a sensibility and a specificity for SRs and PSI 100%, 68% and 100%, 73% respectively. In contrast, AUC the ROC curve were lower than SRe and ε max (AUC=0.79 and AUC=0.72 respectively).
Conclusions: The combination SRs parameters and PSI had higher sensitivities and specificities than systolic parameters alone such as SRs, SRe and εsys to detect MV and predict FR

P519 Spatial characterization of myocardial shortening and rate of relaxation in left ventricular hypertrophy and relation with clinical status: a 2-dimensional speckle tracking study

K. Savino[1], A. Lilli[2], R. Lauciello[1], S. D'Addario[1], E. Bordoni[1], V. Giglio[1], E. Grikstaite[1], C. Cavallini[3], G. Ambrosio[1]. *[1]Cardiology and Cardiovascular Pathophysiology - University of Perugia, Perugia, Italy; [2]Cardiology Versilia Hospital, Lido Di Camaiore, Italy; [3]Perugia Hospital, Perugia, Italy*

Background: Left ventricular hypertrophy (LVH) is a substrate of heart failure with normal ejection fraction (EF). Some observations highlighted the presence of subtle systolic dysfunction. However its spatial features, relation to diastolic abnormalities and clinical correlates remain largely unknown.
Purpose: To characterize, with 2-dimensional speckle tracking (2DS) echocardiography, global myocardial systolic and diastolic function in different cardiac LVH.
Methods: Consecutive patients (n=49) with normal EF (≥55%) and LVH secondary to hypertension (n=14), non-obstructive hypertrophic cardiomyopathy (n=19), aortic stenosis (n=14) and amyloidoses (n=2) were evaluated by standard echo and by 2DS. Systolic strain (Sε) and early diastolic strain rate (DSR) were analyzed to assess mean longitudinal (Long), circumferential (Circ) and radial (Rad) shortening and rate of relaxation respectively. Patients were compared to a healthy control group (n=19). Sε and DSR normal values were derived from the control group (>10th percentile).
Results: Mean Long Sε was significantly reduced (-16.1±3.7% vs -20.1±2.7%, p<0.001) also within each etiology (p<0.001). Circ Sε was only midly reduced (27.9±13.7% vs 34.8±8.5%, p = 0.04) whereas Rad Sε was globally preserved (-15.6±4.8% vs -17.5±3.3%, p 0.11). DSR was reduced in Long (1.23±0.3 1/s vs 1.90±0.3 1/s, p<0.0001), Circ (1.3±0.3 1/s vs 1.78±0.4 1/s, p<0.0001) and Rad (1.3±0.34 1/s vs 1.83±0.5 1/s, p<0.0001) (p<0.001 for each etiology). Long Sε reduction was significantly related to LV mass increase (r=0.59, p<0.0001) and to Long DSR reduction (r=-0.73, p<0.00001). Per patient analysis allowed tha classification of 3 groups: Group A (normal diastolic and systolic function), Group B (isolated diastolic dysfunction) and Group C (combined dysfunction). Rate of

symptomatic patients progressively increase according to the presence and combination of diastolic or systolic abnormalities (Group A=22%, Group B=38% and Group C=67%, p = 0.01 for trend)
Conclusion: in LVH subtle systolic dysfunction is mainly longitudinal and related to both LV mass increase and myocardial relaxation abnormalities. Rate of relaxation alterations are more pronounced and diffused to all fibres. A characterization of patients with LVH according to diastolic and systolic alterations is well related to their clinical status.

P520 Assessment of left ventricular twist in patients with secundum atrial septal defect using speckle tracking imaging

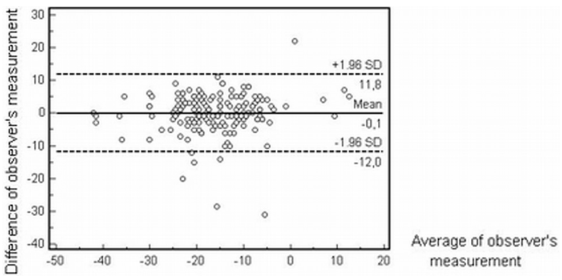
L.L. Dong, X.H. Shu, L.H. Guan, H.Y. Chen, C.Z. Pan, H.Z. Chen. *Zhongshan Hospital of Fudan University, Shanghai, China, People's Republic of*

Background: Left ventricular (LV) torsional deformation plays an important role with respect to LV ejection and filling. A novel ultrasound speckle tracking imaging (STI) allows the noninvasive assessment of LV torsion. However, there is no data available on the impact of right ventricular (RV) volume overload on LV twist and untwisting in patients with secundum atrial septal defect (ASD). This study sought to evaluate LV torsional deformation using STI method in patients with ASD.
Methods: Forty-five asymptomatic adults with isolated secundum ASD were enrolled in this study. Using commercially available 2-dimensional strain software, we analyzed basal and apical LV short-axis images in these patients and 45 age- and sex-matched normal subjects. LV twist and twist rate were defined as apical LV rotation and rotational velocity relative to the base.
Results: Patients with ASD had significantly smaller LV end-diastolic volume (62.0±11.1 ml vs. 69.9±10.1 ml, P=0.001) and lower LV ejection fraction (EF) values (65.4±5.1% vs. 69.4±5.6%, P=0.001) in comparison with the controls. The apical rotation parameters including peak counterclockwise rotation and time to the peak were similar between two groups. However, the peak basal clockwise rotation was significantly depressed (-5.4±2.8° vs. -6.9±2.6°, P<0.001) and time to the peak was significantly delayed (118.3±18.8% vs. 96.1±12.6% of systolic period, P<0.001) in patients with ASD. The peak basal initial counterclockwise rotation in ASD group was significantly higher (5.1±3.3° vs. 1.8±1.4°, P<0.001) and its duration was longer (75.4±26.7% vs. 42.5±24.4% of systolic period, P<0.001) than that in control group. LV peak twist was also reduced significantly in patients with ASD (11.9±5.9° vs. 14.6±3.5°, P<0.05) in comparison with the controls while the LV untwisting parameters including peak untwisting rate and time to the peak were not significantly different between the two groups.
Conclusions: LV systolic twist was reduced but diastolic untwisting remained unchanged in patients with asymptomatic ASD. The depressed LV twist was mainly due to the heterogenous basal rotation which was characterized by a reduced and delayed clockwise rotation following an abnormally enhanced and extended initial counterclockwise rotation during early systole.

P521 Assessment of right ventricular function with longitudinal two dimensional strain: comparison between low and intermediate risk pulmonary embolism

V. Descotes, R. Chopard, J. Dutheil, M. Morel, N. Meneveau, F. Schiele, Y. Bernard, M.F. Seronde, J.P. Bassand. *CHU de Besancon - Hopital Jean Minjoz, Besancon, France*

Purpose: Right ventricular dysfunction is a key point for the stratification of pulmonary embolism risk. Longitudinal two dimensional (L2D) strain measure is a new technique for assessment of ventricular function. The aim of our study was to determine: 1) the inter-observer variability of right ventricular L2D strain measure, and 2) whether longitudinal 2D strain may appropriately differentiate low risk pulmonary embolism patients with intermediate risk pulmonary embolism patients.
Methods: Patients with low or intermediate risk pulmonary embolism were included in the study and underwent an echocardiogram at admission. Intermediate risk was defined by troponin elevation and/or echocardiographic right ventricular dysfunction. An apical four-chamber view was recorded and analyzed off-line by two independent observers. Right ventricle was divided in six segments, lateral and septal wall being divided in basal, mid and apical region. L2D strain was calculated for each segment, and global L2D strain calculated for lateral wall, septal wall and the whole right ventricle.
Results: 28 patients were included, mean age 65 years, 13 with low risk and 15 with intermediate risk pulmonary embolism. Bland and Altman test showed a good inter-observer reproducibility. There was a significant difference between the intermediate and low risk patients for L2D strain of right ventricle (-13.3% vs -19.5%, p=0.0012), lateral wall (-12.1% vs -20.6%, p=0.0006) and septal wall (-14.5% vs -18.4%, p=0.05). A significant relation between L2D strain and right ventricular dilatation was observed (R^2=0.187, p<0.0001).
Conclusions: Right ventricle L2D strain is a reproducible technique and is potentially useful for the assessment of right ventricular function and stratification of risk of pulmonary embolism.



Inter-observers L2D strain variability

P522 Echocardiographic assessment of left ventricular structure and function in patients with symptomatic peripheral arterial disease

J.-C. Lubanda, M. Chochola, P. Varejka, P. Prochazka, O. Dostal, S. Beran, V. Mrazek, A. Linhart. *IInd Med. Dept - Clin. Dept. of Cardiology and Angiology, Charles university, 1st faculty of medicin, Prague, Czech Republic*

Background: peripheral arterial disease (PAD) is disease with high morbidity and mortality. Identifying the main determinants of disease progression, especially the interaction between left ventricle (LV) and peripheral circulation may have a great impact in the management of these patients in clinical practice. We sought to assess the main structural and functional characteristics of the left ventricle by echocardiography in patients with symptomatic PAD.
Method: the prospective database of peripheral angiography in our institution was analyzed. A total of 2.559 patients with symptomatic PAD were identified and matched to our echocardiography database.
Results: the final population includes 1089 subjects (721 men, mean age 65±10 years). Significant difference in age or in the prevalence of PAD (all stages included) was not found. The mean thickness of the interventricular septum was 11.77±2.3 mm. The mean end-diastiolic LV diameter was 51.58±7.2 mm. The mean thickness of the posterior wall was 9.98±1.65 mm. The mean LV mass indexed to height2.7 was 51.91±15.2 g/m^2. 7. LV Hypertrophy was present in 51% of subjects. The mean LV ejection fraction (LVEF) was 58±10%. There was 79% of men with LVEF > 50% and 89.7% of women with LVEF > 50%. The group of patients with critical limb ischemia showed significantly lower LVEF in comparison to the group presenting with intermittent claudication (56±13% vs 58±11%, p <0.01). The incidence of severe valvular heart disease was minimal.
Conclusion: patients with symptomatic PAD have significant cardiac involvement mainly manifesting as left ventricular hypertrophy. LV systolic function is well preserved when assessed by traditional methods. However, decrease of LV systolic function is associated with a higher incidence of critical limb ischemia. This relationship between ventricular contractility and peripheral ischemia is not fully understood and need further investigations.

P523 Can strain rate imaging predict the recovery of regional myocardial function after primary percutaneous coronary intervention?: comparison with coronary flow velocity pattern

S.-J. Kim, E.-S. Shin, S.-G. Lee. *Ulsan University Hospital, Ulsan, Korea, Republic of*

Background: It is well known that coronary flow velocity (CFV) analysis can predict the recovery of regional left ventricular function after reperfusion in patients with acute myocardial infarction (AMI). However, The value of strain rate imaging (SRI) in predicting recovery of regional left ventricular function during follow up after reperfusion has not been established in the clinical setting.
Methods: 21 consecutive patients with anterior AMI underwent transthoracic echocardiography to record CFV in the left anterior descending coronary artery (LAD) on the next day (day 1) after successful primary coronary angioplasty and on day 6. Simultaneously, SRI was performed to obtain strain rate parameters at the segment of apical septum. Regional wall motion was estimated as anterior wall-motion score index (AWMSI) on day 1, day 6 and at 6 month after the onset of AMI.
Results: Patients were divided into two groups: good wall-motion recovery group (group 1, AWMSI ≤ 2.0 at 6 month) and poor wall-motion recovery group (group

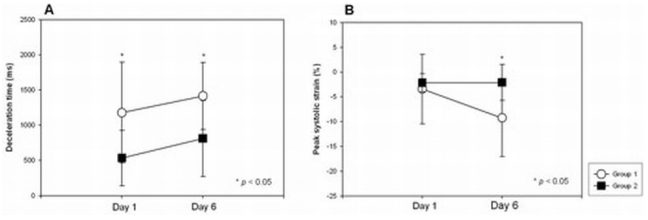


Figure 1

2, AWMSI > 2.0 at 6 month). Deceleration time of diastolic CFV in group 1 was significantly longer than in group 2: 1178 vs. 534 ms on day 1, p = 0.031; 1416 vs. 812 ms on day 6, p = 0.015 (Fig. A). On SRI, the difference of strain rate parameters was not significant on day 1, but only peak systolic strain in group 1 showed significant negative increase than in group 2 on day 6 (-9.2% vs. -2.1%, p = 0.011) (Fig. B). For the prediction of functional recovery, negative peak systolic strain > 5% had a sensitivity of 88% and a specificity of 69% on day 6.
Conclusion: SRI may predict the recovery of regional left ventricular function in anterior AMI. However, the point of time for the prediction of functional recovery was later than that by CFV analysis.

MECHANISMS OF CARDIOVASCULAR DISEASE: GENES AND ENVIRONMENT

P524 Genetic polymorphism on interleukin-6 gene is associated with onset age of coronary atherosclerosis: the role of endothelial function and inflammation

G. Hatzis, D. Tousoulis, C. Antoniades, A. Miliou, V. Psari, A. Antonopoulos, N. Papageorgiou, E. Stefanadi, K. Marinou, C. Stefanadis. *University of Athens, Athens, Greece*

Purpose: Evidence suggests that IL-6 plays a critical role in atherogenesis, but it is still unclear whether the genetic variability of IL-6 gene is involving into mechanisms of atherosclerosis. Therefore, we examined the impact of genetic polymorphism G174C on IL-6 gene, on endothelial function, acute phase response and coronary atherosclerosis burden.
Methods: The study population consisted of 123 patients with newly diagnosed, angiographically documented coronary atherosclerosis. G174C polymorphism was estimated by PCR, while serum levels of C-reactive protein (CRP) were measured by immunonephelometry. Endothelial function was measured by estimating flow-mediated dilation of the brachial artery (FMD), by ultrasound.
Results: The genotype distribution was GG: 57 (46.3%), GC: 45 (36.6%) and CC: 21 (17.1%). Importantly, homozygosity for the C allele was associated with significantly lower atherosclerosis onset age (59.1±2.3 years) compared to GC (64.7±1.24 years) and GG (65.1±1.23) (p(for trend)<0.05). No significant association was found between G174C polymorphism and the angiographic extend of coronary artery disease (1 vessel disease (VD):GG51.4%, GC:32.4% and CC:16.2%, 2VD: GG:53.1%, GC:28.1% and CC:18.8% or 3VD: GG:41.9%, GC:38.7% and CC: 19.4%, (p=NS between genotypes). Moreover, this polymorphism was not associated with differences in CRP (CC: 2.51±1.66mg/dl, GC:4.16±2.22mg/dl and GG: 2.16±0.56mg/dl, p=NS) and changes in FMD, CC (3.67±1.34%) and GC (3.97±1.04%) compared to GG (4.61±0.73%)(p=NS).
Conclusions: Genetic polymosphism G174C on IL-6 gene is associated with earlier appearance of coronary atherosclerosis. This effect is independent of endothelial function and acute phase response. These findings suggest that G174C polymorphism may be implicated in atherogenesis, by accelerating the progression of coronary artery disease.

P525 Cytokine genes polymorphisms and expression profiles in peripheral blood leukocytes of healthy individuals and patients with essential hypertension

Y. Timasheva[1], T.R. Nasibullin[1], I.A. Tuktarova[1], A.N. Zakirova[2], O.E. Mustafina[1]. *[1]Institute of Biochemistry and Genetics Ufa Science Centre of Russian Academy of Science, Ufa, Russian Federation; [2]Bashkir State Medical Academy, Ufa, Russian Federation*

Essential hypertension (EH) is a widespread disease with well-established genetic background. The aim of the present study was to investigate the role of cytokine genes polymorphisms and their expression pattern in the development of EH, and to study possible interactions between genes encoding for renin-angiotensin system and endothelial relaxation factor synthesis components. ¶Study group consisted of 355 EH patients (298 men, 57 women) and was divided into three sudgroups: first included 219 patients with non-complicated EH (162 men, 57 women), second – 95 hypertensive men with myocardial infarction (MI), third – 41 hypertensive male patients with ischemic stroke (IS). Control group included 273 unrelated healthy subjects (182 men, 91 women). Genomic DNA was extracted from peripheral blood by phenol-chloroform extraction. Genotyping was performed using of PCR followed by restriction analysis. Total RNA was isolated from peripheral blood leukocytes of 20 hypertensive patients and 20 age-matched healthy subjects. Quantitative real-time PCR was performed using RT^2 SYBR Green/Fluorescein qPCR Master Mix and microarrays, containing primers for 84 cytokines and cytokine receptors genes (RT2ProfilerTM PCR Array).¶ IL1B and IL10 genes polymorphic variants were found to be associated with EH, with IL1B -511*T/*C and IL-10−627*C/*A genotypes being predisposing to EH development, IL1B -511*T/*T and IL-10−627*C/*C genotypes being protective against EH. IL1B, IL-6, IL-10, IL-12B and TNFA genes polymorphisms were shown to be associated with cardiovascular complications of EH. Increased risk of stroke was associated with IL1B -511*C/*C, IL-6 -572*G/*G, IL-12B 1159*C/*A and TNFA-308*G/*A. VNTR-polymorphism in the intron 4 of endothelial nitric oxide syntase gene (NOS3) is associated with left ventricular hypertrophy in hypertensive patients. Patients with EH were demonstrated to have altered transcriptional activity of CCL16, CCL17, CCL18, CCL19, CCL23, CCL8, CCR6, CCR8, CX3CR1, CXCL1, CXCL13, ICEBERG, IL13, IL17C, IL1F10, IL1F6, ILF9, SPP1, CD40LG, XCR1 and CCL2 genes.Some cytokine genes polymorphisms were associated with essential hypertension and its cardiovascular complications. Hypertensive patients had altered cytokine genes expression profile. These data suggest a role for cytokines in the pathogenesis of essential hypertension.

P526 A gain-of-function TBX20 mutation causes human congenital cardiac atrial septal and valve defects

M.G. Posch[1], M. Gramlich[2], M. Sunde[3], K.R. Schmitt[4], A. Perrot[1], R. Dietz[1], F. Berger[4], R.P. Harvey[2], C. Ozcelik[1]. *[1]Charite - Campus Virchow-Klinikum, Berlin, Germany; [2]Victor Chang Cardiac Research Institute, Sydney, Australia; [3]The University of Sydney, Sydney, Australia; [4]Deutsches Herzzentrum Berlin, Berlin, Germany*

Congenital heart defects (CHD) are the most common inborn malformation. Ostium secundum atrial septal defects (ASDII) account for approximately 10% of all CHD and genetic mutations in cardiac transcription factors were identified as an underlying cause for ASDII. However, very little is known about the role of inherited mutations in the cardiac transcription factor TBX20 in ASDII patients. In an attempt to identify naturally occurring variants in TBX20, we sequenced coding regions in 170 patients with ASDII and identified a novel mutation in a highly conserved residue in the T-box DNA-binding domain (I121M) in a kindred with cribriform ASDII, large patent foramen ovale, and cardiac valve defects. Interestingly, Tbx20-I121M resulted in a significantly enhanced transcription of target genes, whereas thermal stability of the mutant T-box was only mildly affected and there were no changes in DNA binding affinity. However, the mutation destabilized tertiary hydrophobic interactions within the T-box causing it to adopt a more dynamic structure. In addition, mutated TBX20 showed enhanced synergistic interactions with its cardiac co-transcription factors Gata4/5 and Nkx2-5. We suggest a model in which TBX20-I121M adopts a more fluid tertiary structure leading to enhanced or dysregulated interactions with cofactors and other cellular components, and concomitant disruption of the cardiac gene regulatory network. Our data, combined with that of others, suggest that mutations in TBX20 account for ~1% of ASDII, similar to other transcription factors and that human ASDII may be related to loss as well as gain of TBX20 activity.

P528 Plasma aldosterone levels predict increased cardiovascular mortality

A. Tomaschitz[1], S. Pilz[1], B.R. Winkelmann[2], B.O. Boehm[3], W. Maerz[4] on behalf of Ludwigshafen Risk and Cardiovascular Health Study. *[1]Medical University of Graz, Graz, Austria; [2]Cardiology Group, Frankfurt-Sachsenhausen, Germany; [3]Division of Endocrinology, Department of Medicine, University Hospital of Ulm, Ulm, Germany; [4]Synlab Center of Laboratory Diagnostics, Heidelberg, Germany*

Purpose: Evidence has accumulated that elevated aldosterone levels are associated with increased risk for fatal cardiovascular (CV) events. With the present analysis we aimed to evaluate prospectively whether plasma aldosterone is predictive for CV mortality in a large cohort of patients with and without CV disease (CVD) and myocardial dysfunction.
Methods and results: Mean plasma aldosterone concentration (PAC, pg/mL) was 99.6±90.2 in 3153 patients referred to coronary angiography. After a median follow-up of 7.75 years a total of 454 participants (14.4%) died due to CV events. Deceased probands were older, had slightly higher PAC and lower Aldosterone-to-renin ratio (ARR)-values, whereas only 70 deceased individuals (15.4%) had plasma PAC levels above the upper limit of normal (160.0 pg/mL) and only 8 (1.76%) deceased participants demonstrated an ARR above 50 pg/ml/pg/mL, a suggestive cut-off for primary aldosteronism (PA). In addition, deceased participants suffered more frequently of previous myocardial infarction, severe coronary artery disease in terms of 20% visual stenosis and demonstrated a considerably higher proportion of severe heart failure (NYHA III and IV). We performed Cox proportional hazard regression (HR) analysis to assess the magnitude of risk for CV mortality associated with PAC quartiles. In multivariable models, adjusted for age, gender and established CVD risk factors, individuals within the highest (4th) PAC quartile were 1.50 (95% CI 1.13-1.99; P = 0.005) times more likely to experience fatal CVD events than those within the first (reference) quartile. HRs for probands within the second and third PAC quartile were 1.42 (95% CI 1.07-1.87); P = 0.014) and 1.31 (95% CI 0.98-1.75.; P = 0.065), respectively.
Conclusions: Our results underline that PAC levels predominantly within the physiological range are associated with greater CV mortality independent of major established CVD risk factors.

P529 Chemerin, vaspin, visfatin and adiponectin expression in human pericoronary and apical epicardial fat: correlation with coronary atherosclerosis

S. Spiroglou, C. Kostopoulos, J. Varakis, H. Papadaki. *University of Patras, Patras, Greece*

Objectives: Adipose tissue is a source of peptides with paracrine and endocrine actions, called adipokines. Adipokines produced by epicardial fat have been im-

plicated in vascular pathology, including atherosclerosis. We investigated the expression of novel adipokines chemerin and vaspin, as well as visfatin and adiponectin in human pericoronary and apical epicardial fat in correlation with coronary atherosclerosis.
Methods: Paraffin embedded samples of human left coronary arteries, including periadventitial fat (n=41), as well as apical epicardial fat samples from the same cases (n=41) were evaluated for chemerin, vaspin, visfatin and adiponectin expression using immunohistochemistry. AHA classification was used for atherosclerosis assessment. SPSS for Windows was used for statistical analysis.
Results: Chemerin, vaspin, visfatin and adiponectin expression of varied degree was detected in 41/41 pericoronary fat samples and in 41/41, 41/41, 39/41 and 35/41 apical fat samples, respectively. Differences in expression of adipokines were observed between pericoronary and apical epicardial adipose tissue; chemerin showed higher expression in apical fat (p=0.01), whereas visfatin expression was higher in pericoronary fat (p=0.001). Atherosclerosis was detected in 37/41 coronary arteries. Coronary atherosclerosis was negatively correlated with pericoronary fat adiponectin expression (r=-0.385, p=0.013) and positively correlated with pericoronary fat visfatin (r=0.321, p=0.04) and chemerin (r=0.377, p=0.015) expression. Pericoronary fat vaspin expression was not associated with the severity of coronary atherosclerotic lesions. None of the adipokines expressed in apical epicardial fat was associated with coronary atherosclerosis.
Conclusions: Different expression patterns of adipokines may exist even between distinct compartments of a specific adipose tissue depot, such as epicardial fat. The correlation of adipokines expressed by pericoronary fat with the severity of coronary atherosclerosis suggests a putative role of periadventitial fat in the atherosclerotic process. Pericoronary fat, due to its vicinity to the vascular wall, may differently affect the atherosclerotic process, compared with apical epicardial fat.

P530 Reactive Oxygen Species (ROS) control mitochondrial motility

M. Saotome[1], G. Hajnoczky[2], H. Hayashi[1]. *[1]Hamamatsu University School of Medicine, Hamamatsu, Japan; [2]Thomas Jefferson University, Philadelphia, United States of America*

Purpose: Mitochondrial motility (mito-motility) is regulated by the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$), providing the homeostatic circuit in Ca^{2+} signaling, which enables mitochondria to contribute to Ca^{2+} buffering and ATP supply at the region of a $[Ca^{2+}]_c$ rise. Mitochondria are also the major site for production and metabolism of ROS that serve as both a mediator and a regulator of Ca^{2+} signaling and are particularly relevant for the control of mitochondrial function in both cell survival and death. Here we tested the hypothesis that ROS target mito-motility to control mitochondrial function.
Method: H9c2 cardiac myoblasts were transfected with a mitochondrial targeted YFP, and then loaded with fura2 to monitor the mito-motility simultaneously with $[Ca^{2+}]_c$. The change in mito-motility was evaluated by the subtraction of sequential images.
Result: H2O2 (100 μM) caused a decrease in mito-motility (64$\pm$8%) and an elevation in $[Ca^{2+}]_c$ (55$\pm$8 to 91$\pm$8 nM) at the same time. When the cells were pretreated with thapsigargin (5 μM), a SERCA inhibitor, in a Ca^{2+}-free medium to prevent Ca^{2+} entry and mobilization, H2O2 inhibited the mito-motility without any changes in $[Ca^{2+}]_c$. Neither the depolarization of mitochondrial membrane potential by an uncoupler FCCP (5 μM) nor the inhibition of mitochondrial permeability transition pore by cyclosporin A (2 μM) altered the H2O2-induced mito-motility inhibition. Furthermore, the H2O2-induced mito-motility inhibition was independent from the spatial relationship between mitochondria and microtubules.
Conclusion: Thus, ROS-induced mitochondrial motility inhibition may enable to recruit additional mitochondria at the site of a local ROS elevation, and may have relevance both in physiological homeostatic process and pathophysiological cellular injury process.

P531 Proteomic analyses reveal evolving protein expression changes during atrial profibrillatory remodelling in congestive heart failure

A.I. De Souza[1], S. Cardin[2], R. Wait[3], N. Patel[1], A.J. Camm[1], S. Nattel[2]. *[1]St. George's University of London, London, United Kingdom; [2]Montreal Heart Institute and University of Montreal, Montreal, Canada; [3]Imperial College London, London, United Kingdom*

Introduction: Congestive heart failure (CHF) leads to atrial structural remodelling and susceptibility to sustained atrial fibrillation (AF). The time-dependent molecular mechanisms underlying this remodelling are poorly understood.
Methods: To elucidate protein expression changes during AF substrate development in CHF, we applied high-throughput proteomic analysis to left atrial myocytes harvested from sham (n=4) and ventricular tachypaced (VTP, 240 bpm $\times$24 hrs, n=5; $\times$2 wks, n=4) CHF dogs. Protein extracts were subjected to two-dimensional differential in-gel electrophoresis technology (DIGE). Differentially expressed proteins ($p<0.05$) were excised for identification via tandem mass spectrometry.
Results: Of a total of 1103 proteins, 123 were significantly altered between sham and 24 hr, and 225 between sham and 2 wk VTP. Heat shock proteins (HSPs) were upregulated with a changing pattern over time: HSP27 and HSP60 were increased (1.3-fold) only at 24 hrs and α-B crystallin, HSP70, and GRP78 were increased (1.7, 1.3 and 1.8-fold) only at 2 wks. HSP, alpha-crystallin related B6 was increased at both 24 hrs and 2 wks (1.4 fold at 24 hr to 1.8 fold at 2 wks). Metabolic enzymes malate dehydrogenase (DH) and pyruvate DH E1 α subunit were increased 1.2 and 1.9-fold at 24 hrs, but malate DH and pyruvate DH were decreased (1.5 and 2.7-fold) after 2 wks along with isocitrate DH and H^+ transporting ATP synthase mitochondrial F0 complex. Early changes in protein expression that persisted as CHF and fibrosis developed included downregulation of the contractile protein myosin light chain 2 (1.2 fold at 24 hr to 1.6 fold at 2 wks), which may contribute to contractile remodelling, and the metabolic enzyme ubiquinol cytochrome C reductase. Increased protein expression of the cytoskeletal protein vinculin was observed at 24 hours and remained elevated at 2 weeks (1.2 fold at 24 hr to 1.3 fold at 2 wks). Finally, decreased antioxidant expression (peroxiredoxin 3 and superoxide dismutase, 1.3 and 1.4-fold) was only observed at 2 wks along with an increase in structural proteins desmin and filamin C fragments (3 and 3.6-fold) reflecting structural damage.
Conclusions: VTP-induced CHF causes time-dependent changes in the atrial proteome that provide insights into molecular mechanisms underlying arrhythmogenic atrial structural remodelling, with potential therapeutic implications.

P532 Neural cell adhesion molecule is a cardioprotective factor upregulated by metabolic stress

K. Nagao[1], K. Ono[1], T. Horie[1], H. Nishi[1], M. Kinoshita[1], Y. Kuwabara[1], Y. Tamaki[1], Y. Kojima[1], Y. Iwanaga[2], T. Kita[3]. *[1]Graduate School of Medicine Kyoto University, Kyoto, Japan; [2]Kinki University, Osaka, Japan; [3]Kobe City Medical Center General Hospital, Hyogo, Japan*

Purpose: Failing heart is characterized by alteration in energy metabolism and diminished capacity to generate ATP. While, secretory and membrane proteins have been a considerable interest because these proteins are involved in most fundamental biological processes and preferred targets for drug development. To screen for cell-surface proteins whose expression were enhanced under metabolic stress, we performed a signal sequence trap in combination with a functional cloning method.
Methods and results: we screened for cell-surface proteins whose expression were enhanced by oligomycin, a reversible mitochondorial respiratory chain inhibitor in H9C2 rat cardiac myoblasts. One of the identified genes was neural cell adhesion molecule (NCAM, CD56), a major regulator of development, cell migration, survival and neurite outgrowth in the nervous system. In H9C2, flow cytometry analysis revealed that oligomycin treatment significantly upregulated cell-surface expression of NCAM, and the same result was observed in primary rat cardiac myocytes especially by metabolic stress such as oligomycin and doxorubicin. To analyze the expression pattern of NCAM in vivo diseased heart, we examined the NCAM expression in mouse MI model. mRNA of NCAM was upregulated in infracted area by 15.2$\pm$0.20 fold ($P<0.01$). Immunohistochemical analysis revealed that NCAM was strongly expressed in residual cardiac myocytes inside and adjacent infracted scars both at acute and chronic phase, whereas it was detectable only at the intercalated discs in non-infarcted area or sham-operation model. We also examined the NCAM expression pattern in Dahl salt-sensitive (DS) rats at LVH and CHF periods. NCAM expression was enhanced in LVH stage by 3.0$\pm$0.48 fold ($P<0.01$) and further increased by 24.1$\pm$2.34 fold ($P<0.001$) in heart failure stage. Immunohistochemical analysis revealed that strong NCAM staining was observed in subendomyocardium surrounding fibrotic area. To investigate the role of NCAM in cardiac myocytes, we introduced siRNA against NCAM by lentivirus. Akt activity in NCAM knocked down cardiac myocytes was significantly reduced (42$\pm$0.01% decrease, $P<0.001$). Survival rate of cardiac myocytes treated with oligomycin was significantly reduced when NCAM was knocked down (86$\pm$0.02% vs. 54.6$\pm$0.11%, $P<0.05$) suggesting the protective role of endogenous NCAM.
Conclusion: NCAM may play a protective role in metabolically stressed heart and can be utilized as a new therapeutic target.

P533 Family history and coronary disease risk. Interaction with genetic and behaviour factors

R. Palma Dos Reis, A. Pereira, A.C. Sousa, A.I. Freitas, S. Freitas, I. Ornelas, A. Brehm, M.I. Mendonca. *Hospital Central do Funchal, Funchal, Portugal*

The existence of family history (FH) antecedents and the causes of family coronary disease (FCD) aggregation remain still to be explained. However some studies have been suggesting, in those families, the existence of certain genetic and environmental common factors. The identification of such factors can be of extreme interest in the study of the etiopathogenesis study of this complex multifactorial disease
Aims: To investigate the coronary disease risk conferred by the existence of a positive FH, its association with some genetic risk factors and the interaction with environmental factors.
Methods: 818 individuals participated in the study, 298 coronary patients and 520 healthy controls. In all of them the following variables were studied: traditional risk factors, biochemical variables and the SRA polymorphisms (ECA I/D; AGT T174M; AGT M235T; AT1R A1166C). To compare averages between groups, the T Student test was used and for comparisons among genotypic frequencies the

Chi square was used. To evaluate the coronary risk associated to the studied variables, the Odds Ratio and their respective 95% confidence intervals were calculated. Statistical significance was accepted at $p < 0.05$. To evaluate possible synergistic/antagonistic interactions between family history and the classic risk factors, a table 4x2 and the synergism measures in the additive (SI) and multiplicative (SIM) model, was calculated. Finally the relative risk excess (RERI) and the proportion attributed to the interaction (AP) were calculated.
Results: 190 (23.2%) presented FH antecedents and 628 (76.7%), didn't refer those antecedents Of the individuals with FH, 60% were coronary patients, and 40% didn't have coronary disease (CD). The CD relative risk, in individuals with FH antecedents, was 3.62 [3.62 (2.55-5.15) $p < 0.0001$]. Only the RAS polymorphism AT1R A/C (p=0.012) demonstrated statistical significance between groups with and without FH. There was a synergistic interaction between the existence of FH and smoking habits (SI=2.86 and SIM=1.68) and between FH and dyslipidemia (SI=2.29 and SIM=1.54).
Conclusion: In this study, 60% of the individuals with FH presented DC. The AT1R CC genotype, was more frequent in these FH individuals. The interaction with smoking inhabits and dislipidemia largely increased the risk of CD.
These data suggest the existence of complex interactions between genetic and environmental factors in these patients and early measures of primary prevention, namely smoking abstention and a hypolipemic diet are justified.

P534 Paraoxonase polymorphism is a predictor of 5-year mortality in patients with stable multivessel coronary artery disease

L.A.F. Ferri, A.C. Pereira, E.G. Lima, R.D. Vieira, R. Rahmi, L.A.M. Cesar, J.A.F. Ramires, J.E. Krieger, W. Hueb, N.H. Lopes.
Heart Institute of University of Sao Paulo, Sao Paulo, Brazil

Introduction: Background: Paraoxonase1 (PON1) has been considered candidate gene for CAD (Coronary Artery Disease). However, studies of the relationship between the PON1 polymorphism and risk of myocardial infarction have produced conflicting results. In addition, there is no data on the role of PON1 polymorphism in predicting cardiovascular events in a population known to have CAD. This study fills the gap in literature about the influence on prognosis of PON1 polymorphism in patients with CAD. Objective: In this ancillary study, we investigated the association of PON1 polymorphism and 5-year all cause mortality in a prospective cohort of patients with multi-vessel CAD.
Methods: 518 patients with multivessel stable CAD from the prospective, randomized, and controlled Medicine, Angioplasty, or Surgery Study II (MASS II), which was designed to compare medical treatment (n=166), angioplasty (n=178), and surgery (n=174). We studied the association of 5 polymorphisms located on PON1 gene (rs662, rs133006698, rs854560, rs705381, and rs3917464) and 5-year-mortality. The selected polymorphisms are the most studied and are distributed in all PON1 gene extension. Other risk factors within the mortality composite end-point of need of revascularization for refractory angina, myocardial infarction, death and stroke in patients with stable coronary artery disease at 5-year follow-up were also analyzed. DNA was obtained from each participant at MASS study randomization.
Results: At baseline the lipid profile had no difference regarding Cholesterol, LDL and Triglycerides among all studied SNPs; however the HDL levels were significantly lower in allele T'carriers at rs705381: TT (33.41 mg/dL), TC (36.72 mg/dL) and CC (37.94 mg/dL), p=0.0369. There is a significant statistical association between allele G_rs13306698 and mortality (p=0.0113). Even though the allele G has a low frequency in our population, it was an independent predictor of mortality in our population in multivariable analysis.
Conclusion: In our coronary artery disease population the allele G at rs13306698 is an independent predictor of 5-year overall mortality.

P535 Analysis of different polymorphisms and the risk of restenosis after coronary stent placement

F. Rolandi[1], D. Grinfeld[2], J. Scaglia[3], I. Rifourcat[2], P. Pollono[2], D. Berrocal[1], L. Grinfeld[1]. *[1]Italian Hospital of Buenos Aires, Buenos Aires, Argentina; [2]Spanish Hospital, La Plata, Argentina; [3]Genelab, La Plata, Argentina*

Background: It has been demonstrated that platelets and nitric oxide system play a central role in restenosis. Genetic factors can contribute to this process.
Objective: To evaluate if a polymorphism of platelet glycoprotein IIb-IIIa (PIA2) and polymorphisms of the endothelial nitric oxide synthase (eNOS) gene (Glu298Asp, -786T>C, 922A/G and intronic 420/393) are associated with increased risk for restenosis.
Methods: The study included patients with a PCI performed between 1 and 12 months before, and who were referred to cath lab with clinical suspect of ischemia. Pts with confirmed angiographic restenosis (≥50%) were considered cases and those without, controls. Polymerase chain reaction (PCR) was performed for each allelic polymorphism using specifics restriction enzymes. A multiple logistic regression analysis including clinical, angiographic, and genetic features was performed to determine independent predictors of restenosis.
Results: 92 patients included: 51 with restenosis and 41 without. Age, sex and prevalence of hypertension, diabetes, lipid disorders and smoking habit were similar in cases and controls. Proportion of DES used was near 60% in both groups. Genotype distribution was: PIA (A1/A1:89.1%, A1/A2:10.9%), Glu298asp (Glu/Glu:88.0%, Glu/Asp:12.0%), _922A/G (A/A:70.7%, A/G:23.9%, G/G:5.4%), intronic (420/420:82.6%, 420/393:17.4%) and 786T>C (TT:63.0%, TC:25.2%, CC:9.8%). Pts with PIA2 polymorphyc allele had significantly higher restenosis rate than those without this allele (21.9% vs. 1.9%, OR:14.1, 95%CI:1.7-116.3). Similarly was observed in patients with 922A/G (41.5% vs. 19.6%, OR:2.9, 95%CI:1.2-7.4). Carriers of the 298Asp allele of the eNOS Glu298Asp polymorphism, those with intronic polymorphism 420/393 and those with -786C allele of the eNOS -786T>C polymorphism showed a similar frequency of restenosis than pts without polymorphisms. In the multivariate analysis only the PIA1/A2 remained as an independent predictor of restenosis.
Conclusion: This study shows that the presence of PIA2 allele polymorphism is an independent risk factor for coronary in-stent restenosis. Its detection could have important implications in decision making.

P536 The impact of the genetic polymorphism G455A on fibrinogen b-chain gene on fibrinogen levels, low-grade inflammatory process and endothelial function in patients with advanced atherosclerosis

N. Papageorgiou, D. Tousoulis, A. Miliou, G. Hatzis, C. Antoniades, A. Giolis, C. Toutouzas, M. Kozanitou, E. Bosinakou, C. Stefanadis. *1st Cardiology Unit Hippokration Hospital Athens, Athens, Greece*

Purpose: Genetic polymorphism G455A on fibrinogen b-chain gene has been associated with fibrinogen levels in healthy individuals, but its effect on fibrinogen levels, inflammation and endothelial function in patients with advanced atherosclerosis remains unknown. Therefore, in the present study we examined the impact of this polymorphism on fibrinogen levels and other prothrombotic molecules, low-grade inflammation and endothelial function in patients with coronary artery disease (CAD).
Methods: The study population consisted of 293 patients undergoing cardiac catheterization with stable or no CAD. The G455A polymorphism was estimated by polymerase chain reaction (PCR) and suitable restriction enzymes. Serum levels of C-reactive protein (CRP) and fibrinogen were measured by nephelometric methods. In addition, levels of sCD40-Ligand (sCD40L) were determined by enzyme-linked immunosorbent assay (Elisa). Endothelial function was measured by estimating flow-mediated dilation of the brachial artery (FMD), with ultrasound.
Results: The genotype distribution was GG: 51.8%, GA: 37% and AA: 11.2%. There were significant differences among fibrinogen levels across the genotypes of the studied population (AA: 517.4±145.0, GA: 431.5±130.0, GG: 434.2±127.3 mg/dl, $p<0.01$ for AA vs GA and AA vs GG respectively, p=NS for GA vs GG). Among patients with CAD AA patients had significantly higher levels of fibrinogen only than GA patients (AA: 517.5±144.0, GA: 434.0±132.2, GG: 443.0±121.0 mg/dl $p<0.05$ for AA vs GA). C-reactive protein and sCD40L levels did not differ among the study genotypes GG (2.8±4.3 mg/L and 2.4±1.1μg/ml), GA (3.1±4.5mg/L and 2.9±2.1μg/ml) and GG (3.5±3.5mg/L and 2.9±1.3μg/ml) p=NS for all. Similarly, in patients with established CAD there was no significant difference in CRP or sCD40L levels between GG (2.9±5.2mg/L and 2.5±1.2μg/ml), GA (2.5±2.5mg/L and 3.0±2.1μg/ml) and AA (3.1±2.6 and 2.7±1.2mg/L) p=NS for all. Despite the fact that AA patients with CAD had lower FMD than GG and GA this difference did not reach any statistical significance AA (3.3±3.7%) compared to AG (4.7±3.0%) and GG (4.3±4.0%) p=NS for all.
Conclusions: There is a significant correlation between specific genotypes of G455A polymorphism and fibrinogen levels in patients with CAD, but this genetic polymorphism fails to affect inflammation and endothelial function in these patients. These findings indicate that the genetic polymorphism G455A affects fibrinogen levels independently of inflammatory process and endothelial function in patients with CAD.

P537 Role of atherosclerosis-related genetic polymorphisms on morbidity of ischaemic heart disease

C. Carpeggiani[1], M. Coceani[2], N. Botto[2], S. Fantinato[3], D. Adlerstein[3], E. Shehi[3], T. Sampietro[4], D. Neglia[4], A. L'Abbate[5], M.G. Andreassi[1]. *[1]CNR Institute of Clinical Physiology, Pisa, Italy; [2]Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [3]DiaSorin SpA, Nervino, Italy; [4]Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; [5]Scuola Superiore Sant'Anna, Pisa, Italy*

Purpose: Several genetic single nucleotide polymorphisms (SNPs), that confer susceptibility to ischaemic heart disease (IHD), have been recently identified by large genetic epidemiological and genome-wide association studies. However, the role of these SNPs on recurrent cardiovascular events remains uncertain. The aim of the study was to examine the association between a group of prespecified atherosclerotic risk genotypes with cardiovascular morbidity in a secondary prevention setting.
Methods: Four hundred twenty-three patients (373 male, mean age 57.1±8.4 years) who had been admitted to our Institute for IHD (myocardial infarction =325 or stable angina without MI =98) were studied. Forty atherosclerosis high-risk SNPs, that had been previously reported to be significantly associated with cardiovascular risks, were assessed. The genotypes for SNP genes were determined with a method that combines polymerase chain reaction and sequence-

specific oligonucleotide probes with array technology. Major adverse cardiac events (MACE) - coronary-related death, nonfatal myocardial infarction, revascularization - was the endpoint taken into consideration.
Results: During a mean follow-up of 6.9±3.4 years, 92 patients (21.7%) had a MACE. Multivariate Cox proportional hazard analysis revealed that the homozygous C242T NADPH oxidase p22phox gene [HR 2.1, 95% CI 1.2- 3.3], homozygous C677T MTHFR [HR 1.8, 95% CI 1.2- 2.9], and homozygous APOC3 G482A [HR 2.0, 95% CI 1.2- 3.3] were independently associated with an increased risk of MACE.
Conclusion: Genetic polymorphisms of the NADPH oxidase p22phox gene, MTHFR, and APOC3 are associated with an increased risk of MACE and may be useful genetic predictors of recurrent IHD.

P538 Apolipoprotein E polymorphism predicts cardiovascular events in patients with stable multivessel coronary artery disease

N.H. Lopes, L.A.F. Ferri, E.G. Lima, R.D. Vieira, P.R. Soares, L.A. Cesar, W. Hueb, J.E. Kriger, A.C. Pereira, J.A.F. Ramires. *Heart Institute of University of Sao Paulo, Sao Paulo, Brazil*

Introduction: Apoliprotein E (ApoE) is a strong predictor on the variation of plasma lipid levels. It also influences the expression of hyperlipidemia and appears to modulate the susceptibility to atherosclerosis in a complex multifactorial interaction. Studies attempting to relate differences in allele in cardiovascular disease (CAD) are conflicting.
The study of the biological significance of the ApoE polymorphism in humans has emphasized the importance of gene-gene and gene-environment interactions in the pathogenesis of hyperlipidemia and atherosclerosis. Objective: In this ancillary study, we investigated the association of ApoE polymorphisms (rs429358 and rs7412) and 5-year combined events (overall mortality, myocardial infarction and revascularization for refractory angina) in a prospective cohort of patients with multi-vessel CAD.
Methods: 518 patients with multivessel stable CAD from the prospective, randomized, and controlled Medicine, Angioplastly, or Surgery Study II (MASSII), which was designed to compare medical treatment (n=166), angioplasty (n=178), and surgery (n=174). We studied the association of two polymorphisms at ApoE and 5 years combined events. These polymorphisms are the ones that define the epsilon2/epsiolon3/epsilon4 system in ApoE exon 4. One is a C/T SNP (rs429358) that encodes either arginine (C) or cysteine (T) in the ApoE at amino acid 112. The second is a C/T SNP (rs7412), which again encodes arginine (C) or cysteine (T) at ApoE amino acid 158.
Results: Baseline lipid profile had no difference regarding the polymorphism rs 7412; however LDL levels were significantly lower in allele T'carriers at rs429358: TT (105 mg/dL), TC (133.65 mg/dL) and CC (150.94 mg/dL), p=0.0031; controversially, the allele T carrier's had higher levels of Triglycerides: TT (376.5 mg/dL), TC (247.51 mg/dL) and CC (187.87 mg/dL),p= 0.0265. In the 5 year follow-up there was no difference in the lipids profile by the studied SNPs. The ApoE rs429358 genotypes had a significant statistical association with combined events (p=0.0373), ApoE rs7412 wasn't associated with combined events; however it had a significant association with overall mortality (p=0.0154). In the multivariable analysis, ApoE rs429358 was an independent predictor of combined events in our population. Genotype TT/CC had a hazard ratio of 6.03 of combined events in combined events (IC 95%: 1.468-24.78), p=0.013.
Conclusion: In our coronary artery disease population the ApoE rs429358 polymorphism is an independent predictor of 5-year combined events.

P539 Tagging SNP analysis of a locus on chromosome 9 associated with myocardial infarction

W. Koch[1], C. Ganser[1], A. Erl[1], S. Tuerk[1], A. Pfeufer[2], P. Hoppmann[1], A. Schoemig[1], A. Kastrati[1]. *[1]Deutsches Herzzentrum Muenchen, Munich, Germany; [2]Helmholtz Zentrum Muenchen, Neuherberg, Germany*

Purpose: Genetic variation in a 100 kilobase region close to position 22,000,000 of chromosome 9 has been associated with the risk of myocardial infarction (MI). The MI-related region overlaps to a great extent with the gene of a noncoding RNA, termed ANRIL (Antisense Noncoding RNA in the INK4 Locus), and is adjacent to the genes CDKN2A and CDKN2B encoding important regulators of cell proliferation, cell aging, and apoptosis. To better correlate the association of the genomic region encompassing ANRIL, CDKN2A, and CDKN2B with MI, we conducted a fine mapping analysis using tagging single nucleotide polymorphisms (SNPs).
Methods: Tagging SNPs (n=31) representing the majority of genetic variation of the 175 kilobase ANRIL-CDKN2A-CDKN2B region were inferred from data established by the International HapMap Consortium. TaqMan allelic discrimination assays were designed and used for SNP genotyping. The study population consisted of 3600 patients with myocardial infarction and 1200 control individuals with angiographically normal coronary arteries and without signs or symptoms of myocardial infarction.
Results: Complete SNP genotypes were obtained from the study participants. Twelve SNPs exhibiting a relatively high degree of pairwise allelic association among each other ($r^2 \geq 0.3$) were significantly associated with MI ($P \leq 0.005$). Among these SNPs, the highest risks were related to the rs7857345-C (OR 1.70; 95% CI 1.36–2.12) and rs1333045-C (OR 1.68; 95% CI 1.44–1.95) alleles. No association with MI was observed with the other 19 SNPs ($P \geq 0.05$), which were in relatively strong allelic association among each other ($r^2 \geq 0.3$) but not with the 12 SNPs found to be associated with MI ($r^2 \leq 0.1$). The MI-related SNPs reside in the ANRIL gene, whereas the SNPs within and near the CDKN2A and CDKN2B genes were not associated with MI ($P \geq 0.16$).
Conclusions: Tagging SNP analysis showed strong association of a specific region of chromosome 9 with MI, a result supporting and extending prior findings. Significant allelic associations among the MI-associated SNPs is suggestive of a common pathological pathway to exist, rather than independent effects contributed by individual variants. A function of the ANRIL gene in the disease mechanism remains to be established.

P540 Influence of 9p21.3 genetic variants on clinical outcome in early-onset myocardial infarction

P.A. Merlini[1], A. Pisani[1], D. Lina[2], F. Notarangelo[2], F. Mauri[1], D. Ardissino[2]. *[1]Ospedale Niguarda Ca' Granda, Milan, Italy; [2]Ospedale Maggiore, Parma, Italy*

Purpose: Genetic variants at chromosomal region 9p21.3 have been convincingly associated with ischemic heart disease however, it is not known whether these variants may have an influence on prognosis after an acute coronary event. Within the Italian genetic project of early-onset myocardial infarction, we tested the hypothesis that the 9p21.3 single nucleotide polymorphism rs1333040 influences the occurrence of cardiovascular events after early-onset myocardial infarction.
Methods: We genotyped rs1333040 in 1,508 patients hospitalised for a first myocardial infarction before the age of 45 years who underwent coronary angiography without index event coronary revascularisation, and were followed up for the occurrence of major cardiovascular events.
Results: During 16,599 person-years of follow-up, there were 683 (45.3%) cardiovascular events and 492 primary end-points: 77 (5,1%) cardiovascular deaths, 223 (14.8%) reoccurrences of myocardial infarction, and 383 (25.4%) coronary artery revascularizations. The rs1333040 genotype had a significant influence (p=0.01) on the occurrence of cardiovascular events during follow-up corresponding to an adjusted relative risk of 1.19 (95% CI 1.08,1.37) for heterozygous and 1.41 (95% CI 1.06, 1.87) for homozygous carriers of the risk allele. The analysis of the individual components of the primary end-point revealed that the genetic effect upon the primary end-point was mainly explained by a significant influence of the rs1333040 genotype on the hazard of coronary revascularization, with an adjusted hazard ratio of 1.38 (95% CI 1.17,1.63) for heterozygous and 1.90 (95% CI 1.36, 2.65) for homozygous (p = 0.00015) carriers of the risk allele.
Conclusion: In early-onset myocardial infarction, the 9p21.3 single nucleotide polymorphism rs1333040 affects the probability of undergoing coronary artery revascularisation during long-term follow-up.

P541 A common variant at chromosome 9p21.3 is associated with age of onset of coronary disease but not subsequent mortality in coronary disease cohorts

K.L. Ellis[1], A.P. Pilbrow[1], B.R. Palmer[1], C.M. Frampton[1], R.N. Doughty[2], C.J. Ellis[2], T.G. Yandle[1], R.W. Troughton[1], A.M. Richards[1], V.A. Cameron[1]. *[1]University of Otago, Christchurch, Christchurch, New Zealand; [2]The University of Auckland, Auckland, New Zealand*

Chromosome 9p21.3 has recently been identified as the genomic region most strongly associated with risk of coronary artery disease by several genome-wide association studies. Within the chr9p21.3 locus the single nucleotide polymorphism rs1333049 has been strongly associated with disease risk, however its impact on clinical outcomes in patients with established coronary artery disease has yet to be determined. Coronary disease patients (n=1054) and post-myocardial infarction patients (n=816)were genotyped for rs1333049. Clinical history, circulating lipids, neurohormones, and discharge medications were documented. Mortality and hospital readmissions were recorded over a median 2.7 years for the coronary disease cohort and for a median 5.0 years forthe post-myocardial infarction cohort. The genotype frequencies for rs1333049 were 21.9% GG, 53.6% GC and 24.5% CC in the coronary disease cohort and 21.9% GG, 52.8% GC and 25.2% CC in the post-myocardial infarction cohort. In the coronary disease cohort, patients homozygous for the high-risk C allele had earlier ages of onset for coronary disease (65yrs vs 68yrs, p=0.005), angina (58yrs vs 61yrs, p=0.034) myocardial infarction (57yrs vs 62yrs, p=0.010) and percutaneous transluminal coronary angioplasty (58yrs vs 62yrs, p=0.014) than participants heterozygous or homozygous for the G allele. Additionally, these CC patients had higher levels of cholesterol (p=0.026) and triglycerides (p=0.002) than the other genotype groups. There were no significant associations between rs1333049 genotype and age-adjusted plasma amino-terminal brain natriuretic peptide levels (p=0.170), mortality (p=0.446) or hospital readmission for myocardial infarction (p=0.617), heart failure (p=0.327) or all cardiovascular events combined (p=0.317) in the coronary disease cohort. Within the post-myocardial infarction cohort, participants homozygous for the C allele were also admitted into the study at a younger age (61yrs vs 63yrs, p=0.020). There was no significant difference in 5-year mor-

tality (p=0.340) or hospital readmission for myocardial infarction (p=0.280), heart failure (p=0.356) or all cardiovascular events combined (p=0.862) with rs1333049 genotype in post-myocardial infarction patients. No association with gender or ethnicity was observed in either cohort. This research suggests that those carrying the high-risk form of the 9p21.3 locus are at risk of developing coronary heart disease at an earlier age. In spite of this, once coronary disease is established these parients do not have poorer clinical outcome.

P542 Association between left ventricular mass and telomere length in a population study

T. Kuznetsova[1], V. Codd[2], S. Brouilette[2], L. Thijs[1], Y. Jin[1], T. Richart[1], J.A. Staessen[1], N.J. Samani[2]. [1]*University of Leuven, Leuven, Belgium;* [2]*University of Leicester, Leicester, United Kingdom*

Purpose: Telomere shortening is a possible mechanism for cellular aging, via down-regulation of telomerase reverse transcriptase (TERT). Several animal studies suggested implication of telomeres and telomerase in cardiac failure and myocytes apoptosis. Telomerase knockout mice showed progressively shortening of telomeres with aging, attenuated proliferation and increased apoptosis of cardiomyocytes. On the other hand, enhanced expression of TERT in rat cadiomyocytes preserved telomerase activity and telomere length, inducing cardiomyocyte enlargement without fibrosis or lost of function. We predicted the association between left ventricular (LV) mass (2005-2007) from telomere length in circulating leukocytes (1996-2000) in a general population.
Methods: In 334 randomly selected participants (mean age, 46.5 years; 52.5% women; 198 normotensives) from the FLEMENGHO study, we performed ECG and echocardiography, and collected blood for DNA extraction. Telomere content was compared by quantitative PCR and expressed as telomere:genomic DNA ratio (T/S). The median interval between cardiac phenotyping and T/S measurement was 7.4 years (IQR: 6.2 to 8.5 years).
Results: Age was a significant determinant of T/S ($P<0.0001$), accounting for 14.2% of the variance. In multivariable-adjusted analyses accounting for sex, age, body weight and height, systolic blood pressure, and use of antihypertensive drugs, LV mass and LV mass index significantly increased with the telomere DNA content in all subjects and in normotensive subgroup. For a 1-SD increment in T/S ratio, LV mass (mean 170 g) and mass index (mean 92 g/m^2) increased by 2.02 g (P=0.003) and 0.97 g/m^2 (P=0.009) in all subjects, and by 3.18 g (P=0.0001) and 1.46 g/m^2 (P=0.001) in normotensive subjects, respectively. In normotensive subjects, higher T/S was associated with increased LV wall thickness ($P<0.007$), but with no change in LV internal diameter (P=0.30). In contrast, higher T/S ratio was associated with shorter QRS duration on ECG in normotensive subjects (-1.70 ms; P=0.046).
Conclusion: Higher leukocyte telomere DNA content predicts increased LV mass particularly in normotensive subjects.

P543 Enhanced angiogenesis mediated by vascular endothelial growth factor plasmid-loaded thermo-responsive amphiphilic hydrogel in rat myocardial infarction model

J.S. Kwon[1], I.K. Park[1], J.J. Min[1], M.H. Jeong[1], W.J. Kim[2], S.H. Pun[3], J.G. Cho[1], J.C. Park[1], J.C. Kang[1], Y. Ahn[1]. [1]*Chonnam National University Hospital, Gwangju, Korea, Republic of;* [2]*Pohang University of Science and Technology, Pohang, Korea, Republic of;* [3]*University of Washington, Seattle, United States of America*

Purpose: Thermo-responsive hydrogel mediated local gene transfer can be preferentially applied to muscle, since release of DNA into the surrounding tissue can be controlled by 3-dimensional network structure of hydrogel. Indeed, a system for controlled release of therapeutic gene may extend the duration of gene expression, especially in the clinical environment where longer gene expression is desirable after single injection. Here, thermo-responsive and biodegradable polymeric hydrogel has been synthesized and investigated for local gene transfer in heart.
Methods and Results: Initially, luciferase gene was delivered into mouse heart to test the duration and intensity of gene expression. Gene expression intensity assessed by optical imaging is closely correlated to actual expressed protein concentration measured by luciferase assay with homogenized heart. Polymeric hydrogel-based gene transfer was shown to mediate enhanced gene expression up to 4 fold, compared to naked plasmid ($p<0.05$), and displayed two expression profiles with peaks at 2 days and around 25 days after local injection. Histological analyses have revealed that high gene expression is initially dominated by myocardium, whereas lower and longer expression is mainly governed by fibrotic and/or inflammatory cells infiltrated into injury site during injection. In an attempt to investigate polymeric hydrogel-assisted therapeutic effect at infarct area, rat myocardial infarction model was made for 1 week and vascular endothelial growth factor (VEGF) plasmid were injected at infarct area with polymeric hydrogel. Enhanced VEGF expression in infarct region mediated by polymeric hydrogel promoted increased capillary density and larger vessel formation, thus enabling efficient angiogenesis, compared to VEGF only ($p<0.05$).
Conclusion: This study observed enhanced angiogenesis mediated by VEGF plasmid-loaded thermo-responsive amphiphilic hydrogel in a rat myocardial infarction model.

THE MULTI-FACETED RESPONSE TO CARDIOVASCULAR INJURY

P544 Factor VII activating protease (FSAP) alters the pericellular proteolysis balance in the vessel wall during neointima formation

J.M. Daniel[1], O. Uslu[2], K. Hersemeyer[2], O. Rannou[2], L. Muhl[2], H.H. Tillmanns[1], K.T. Preissner[2], D.G. Sedding[1], S.M. Kanse[2]. [1]*Med. Clinic I, Molecular Cardiology, Justus Liebig University, Giessen, Germany;* [2]*Institute for Biochemistry, Justus Liebig University, Giessen, Germany*

Background: The Marburg I single nucleotide polymorphism (MI-SNP) in the FSAP gene is a novel marker for carotid stenosis. However, it is not known how this gene is involved in the disease process. We found that wild type (WT)-FSAP inhibits neointima formation in a wire induced mouse model but MI-FSAP does not (Sedding et al, 2006). Compared to WT-FSAP, MI -FSAP has lower enzymatic activity and is a poor activator of pro-urokinase (pro-uPA). Since uPA plays a major role in vascular remodelling processes, we have investigated the influence of FSAP on the pericellular proteolysis systems, plasminogen activation and matrix metalloproteases (MMP) in the vasculature in vitro and in vivo.
Methods and results: The influence of FSAP on the expression of uPA, tPA, MMP-2 and -9 (gelatinases) in endothelial cells (EC) and vascular smooth muscle cells (VSMC) was investigated in vitro using zymography, Western blotting and RT-PCR. FSAP activates pro-uPA to uPA, but subsequently it decreases the activity of uPA in a dose- and time-dependent manner. Protein levels of uPA were reduced after FSAP treatment, but there was no influence on the levels of tissue plasminogen activator (tPA) or plasminogen activator inhibitor-1 (PAI-1). In contrast, an increase in the activity of gelatinases (MMP-2 and -9) was observed by zymography, whereas pro-MMP-2 activation was much more prominent than pro-MMP-9 activation. No changes were noted in the levels of individual MMP proteins, and there was no regulation of the levels of mRNA for uPA, tPA, MMP-2 and -9 as well as tissue inhibitors of matrix metalloproteinases (TIMPs). Wire induced dilatation of the mouse femoral artery was performed, and the vessels were investigated at 2 days and at 14 days after injury with in situ zymography. Immediately after dilatation, WT-FSAP or MI-FSAP was applied to the artery in pluronic F-127 gel. WT-FSAP application reduced the uPA activity at both 2 days and 14 days after injury, whereas the MMP-2/9 activity in the vessel wall was increased. MI-FSAP-treated vessels did not alter uPA activity but MMP-2/9 activity was increased.
Conclusions: WT-FSAP reduces neointima formation and concomitantly inactivates uPA whereas MMP-2 and -9 activity is increased in injured arteries. In the same context MI-FSAP does not inhibit neointima formation, does not alter uPA but does increase MMP activity. These differences in the pattern of pericellular proteolysis in MI-SNP carriers could alter the development of the plaque or its subsequent stability and account for its association with carotid stenosis.

P545 Combined superoxide dismutase mimetic and peroxynitrite scavenger protects against neointima formation after endarterectomy in association with decreased proliferation and nitro-oxidative stress

K. Hirschberg[1], T. Radovits[1], S. Korkmaz[1], S. Loganathan[1], S. Zoellner[1], B. Seidel[1], S.Z. Pali[1], B. Merkely[2], M. Karck[1], G. Szabo[1]. [1]*Department of Cardiac Surgery, University of Heidelberg, Heidelberg, Germany;* [2]*Heart Center, Semmelweis University, Budapest, Hungary*

Purpose: Restenosis due to neointimal hyperplasia is the main limitation of longterm results after endovascular interventions. Reactive oxygene species (ROS) and peroxynitrite may trigger neointima formation. Drugs reducing ROS levels seem to effectively attenuate this process. In a rat model of endarterectomy, we investigated the effects of the Mn(III) tetrakis (4-benzoic acid) porphyrin (MnTBAP), a superoxide dismutase mimetic and peroxynitrite scavenger on neointimal hyperplasia.
Methods: Carotid endarterectomy was performed in male Sprague-Dawley rats by incision of the right carotid artery with removal of intima. Rats either received vehicle (control group; n=9) or MnTBAP ip. (treatment group; n=9) in a dose of 10 mg/kg/day for 3 weeks. Four groups of carotids were analyzed by histology and immonohistochemistry: right (endarterectomized) and left (sham) carotids of both the control and treatment groups. Antibodies against following antigenes were used: PCNA (proliferating cell nuclear antigen), NT (nitrotyrosine), TGFβ1 (transforming growth factor β1). TUNEL (terminal deoxynucleotidil dUTP nick end labeling) staining was used to evaluate nitro-oxidative DNA-damage. Quantitative real-time PCR were performed from total RNA isolated from carotid arteries to evaluate relative gene expression of c-fos protooncogene, NADPH-oxidase and TGFβ1.
Results: MnTBAP significantly reduced the stenosis rate (10.5±8.1% vs. 45.4±28.3% in the control endarterectomy group; $p<0.05$) as well as neointima/media area ratio (0.3±0.2 vs. 0.8±0.5 in the control endarterectomy group; $p<0.05$) The percentage of PCNA-positive cells in the vascular wall was significantly lower in the endarterectomized treatment group (13.4±7.1% vs. 23.3±11.0% in the control endarterectomy group; $p<0.05$). Immunohistochemical score for NT was decreased in the endarterectomized treated carotids (5.8±1.9 vs. 8.0±2.3 in the control endarterectomy group; $p<0.05$). Ratio of

TUNEL-positive nuclei were significantly lower in endarterectomized carotids from rats who received the antioxidant therapy (41.7±26.7% vs. 64.9±18.5% in the control endarterectomy group; $p<0.05$). Upregulation could be shown in c-fos gene, which decreased significantly in the treatment group. NADPH-oxidase and TGFβ1 gene expression were also significantly elevated in the operated vessels as compared to sham carotids, however no changes could be noted after treatment.

Conclusion: MnTBAP decreased neointima formation in a rat carotid endarterectomy model, which was associated with reduced vascular smooth muscle cell proliferation and attenuated nitro-oxidative stress.

P546 Chronic heart rate reduction with ivabradine prevents the increase in cerebrovascular compliance induced by severe dyslipidemia in mice

V. Bolduc[1], A. Drouin[1], M.-A. Gillis[1], P. Gluais[2], M. Bouly[3], J.-C. Tardif[1], E. Thorin[1]. *[1]Montreal Heart Institute, Montreal, Canada; [2]Institut de Recherches Servier, Suresnes, France; [3]Institut de Recherches Internationales Servier, Courbevoie, France*

Purpose: Dyslipidemia and elevated resting heart rate (HR) are important and independent risk factors for cardiovascular diseases, which may be due, in part, to their deleterious impact on arterial wall compliance. Ivabradine (IVA), is the first and only treatment reducing HR exclusively by selectively inhibiting the pacemaker If current in the sino-atrial node available for patients. We therefore tested the hypothesis that a chronic reduction of HR with IVA could normalize the increase in cerebrovascular compliance associated with severe dyslipidemia in mice.

Methods: 3-month old (m/o) sDL male mice (LDL receptor knockout and expressing the human ApoB) were treated or not for 3 months with IVA (10 mg/kg/day) or the β-adrenergic receptor antagonist metoprolol (MP, 80 mg/kg/day), both added to the drinking water. Wild type (WT) C57Bl/6 mice were used as controls. HR (beat per min, bpm) was measured under isoflurane anaesthesia at baseline and 6 m/o. Compliance was measured in isolated and pressurized cerebral arteries bathed in Ca^{2+}-free physiological solution by stepwise increase the luminal pressure (Px, mm Hg) and measuring the strain [(diameter at Px)-(initial diameter at 10 mmHg)/(diameter at Px)]. Aortas were cut longitudinally, fixed on a Petri dish, and photographed. Plaque area was quantified by pixel count (Gimp2 software) and reported as percentage of the total aortic area. Results are mean±SEM of n=3-8 mice.

Results: Age did not change resting HR. At 6-m/o, HR was lower in sDL than in WT mice (374±7 bpm vs. 450±15 bpm; $P<0.05$). Plasma levels of cholesterol and triglycerides were higher in 6-m/o sDL compared to WT (16.7±2.0 and 7.6±1.0 mmol/l for sDL vs. 2.6±0.5 and 0.9±0.2 mmol/l for WT mice; $P<0.05$), and were not modified by the treatments. IVA and MP reduced HR by 10.9% and 8.6%, respectively (ns). At 6-m/o, lesions covered 1.4±0.5% of the aorta of sDL mice, but were absent from WT mice. IVA limited atherogenesis (0.4±0.1%; $P<0.05$), while MP tended to increase it (3.0±1.0%; ns). Cerebrovascular compliance was increased in vessels isolated from sDL compared to WT mice. At a physiological pressure of 60 mm Hg, compliance was 0.80±0.01 in vessels from 6-m/o sDL compared to 0.55±0.08 in 6-m/o WT ($P<0.05$). Chronic treatment with IVA totally restored cerebrovascular compliance, contrary to MP (0.47±0.03 and 0.94±0.14 respectively, $P<0.05$).

Conclusion: Pure HR reduction with IVA, but not β-adrenergic receptor antagonism with MP, prevents cerebral artery wall remodelling associated with severe dyslipidemia in mice.

P547 Effect of autologous mononuclear bone marrow stem cells on mobilization of BM-CPCs in patients with PAD

R.G. Turan, I. Bozdag-T, C.H. Turan, J. Ortak, I. Akin, H. Scneider, S. Kische, H. Ince, C. Nienaber. *Department Internal Medicine, Division of Cardiovascular Medicine of Rostock University, Rostock, Germany*

Introduction: Preclinical trials have shown that the transplantation of autologous bone marrow cells induces and increases the collateral vessel formation. We analyzed the influence of combined intraarterial and intramuscular transplantation of adult autologous mononuclear bone marrow stem cells on the mobilization of bone marrow circulating progenitor cell (BM-CPCs) in patients with peripheral occlusive arterial disease (PAD).

Methods: 20 patients with cell therapy as well as 12 patients without cell therapy with chronically ischemic limbs due to peripheral arterial disease (Fontaine stage IIb) were recruited and underwent follow-up examinations after 2 months. CD34+ and CD133+ BM-CPCs were mesaured pre-and after 2 Monate cell therapy by FACS analyze in PB. Mononuclear cells from bone marrow were injected intramuscular and intraarterial into the ischemic limb.

Results: The concentrations of CD34+ and CD133+ BM-CPCs significantly increased 2 months after cell therapy (CD34+: p=0.002, CD133+: $p<0.001$). There was no significant increase of CD34+ and CD133+ BM-CPCs concentrations in 2 months in control groups without cell therapy.In contrast to the control group, after 2 months the pain-free walking distance of the transplanted patients significantly increased (p= 0.001). Furthermore the ankle-brachial index was significantly improved (at rest p= 0.004, after stress p= 0.001). Similar improvement was documented in capillary-venous oxygen-saturation (p= 0.001). No significant change were in control groups without cell therapy in 2 mounths.

Conclusions: Combined intraarterial and intramuscular transplantation of autologous mononuclear bone marrow stem cells is a clinically feasible. Moreover the regeneration of human ischemic muscle by combined intraarterial and intramuscular transplantation of autologous BMCs in patients with PAD may lead to enhance the mobilization of CD34+ and CD133+ BM-CPCs in PB and this might be increase the regenerative potency in ischemic tissue

P548 Transplantation of ex vivo engineered mononuclear

J. Herold[1], A. Franke[2], S. Weinert[1], A. Schmeisser[1], R.H. Strasser[2], R.C. Braun-Dullaeus[1]. *[1]Universitaetklinikum Magdeburg, Magdeburg, Germany; [2]Dresden University of Technology, Dresden, Germany*

Augmentation of collateral vessel growth (arteriogenesis) is of tremendous clinical importance for the improvement of blood flow in ischemic vascular diseases. Monocytes/macrophages (Mo) represent key players of arteriogenesis as they home to sites of collateral growth and locally create a highly arteriogenic environment through.

Purpose: We hypothesized that transplantation of Mo is able to augment collateral growth.

Method: Murine bone marrow cells were isolated and cultured in RPMI medium supplemented with M-CSF. Non adherent mature Mo were harvested after 5 days by gentle pipetting and depletion of CD117+ (c-kit) stem- and progenitor cells by MACS-technology. Cell phenotype was determined by FACS.

The left femoral artery of Balb/c mice was ligated. A perfusion index (PI= perfusion unligated leg/ligated leg) was done by laser Doppler perfusion imaging (LDPI) before ligation, directly after ligation, and subsequently on day 7, 14 and 21. Different amounts of M-CSF-activated Mo were i.v. injected 24 h after ligation.

Results: Transplantation of 0.5 Mio. syngeneic Mo (syn = same species, Balb/c) only resulted in a mild increase of vascularization (PI= 0.51±0.08, n.s.) vs. control (PI= 0.48±0.09). Increasing the number of synMo up to 2.5 Mio. did not result in better vascularization (PI= 0.56±0.06, n.s.). While transplantation of 0.5 Mio allogeneic Mo (al= other species, C57Bl/6) resulted in a mild increase in PI (PI= 0.5±0.1; n.s), transplantation of 2.5 Mio alMo resulted in a 70% increase of collateralization (PI= 0.85±0.14 vs. control 0.48±0.09, $P<0.001$). Specific immune reaction seemed to play a pivotal role in this effect as transplantation of 2.5 Mio alMo resulted in an about 137% increase of the local perivascular inflammation (Mo accumulation 5.7±0.2 vs. 2.4±0.6 in control-ligated animals, $P<0.05$). Computer-aided morphometry demonstrated a 2-2.5 fold increase of the mean vascular density within the ischemic calf from 22 to 50 vessels/mm^2 ($P<0.001$) in all groups except the recipients of 2.5 Mio alMo (29.5±5 $p<0.05$) implying that arteriogenesis had resulted in sufficient blood supply to the distal limb thereby preventing ischemia driven capillary sprouting (angiogenesis).

Conclusion: Our data imply that alMo transplantation offers a new method for cell therapeutic augmentation of arteriogenesis.

P549 Structural alterations of subcutaneous small resistance arteries in obese patients

C. De Ciuceis, E. Porteri, D. Rizzoni, C. Corbellini, E. La Boria, G.E.M. Boari, S. Paiardi, A. Pilu, M. Castellano, E. Agabiti Rosei. *Clinica Medica, Department of Medical and Surgical Sciences, University of Brescia, Italy., Brescia, Italy*

Structural alterations of subcutaneous small resistance arteries of hypertensive patients, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and or/diabetic patients, and may represent the earliest alterations that may be observed. In addition, M/L of small arteries have a strong prognostic significance. However, no data are available about the structure and endothelial function of small resistance arteries of obese patients. Therefore, we have investigated 16 patients with severe obesity. Six of them were normotensive (ONT), and 10 hypertensive (OHT), according to ESH/ESC Guidelines 2007, and only 3 of them had diabetes mellitus. We compared results obtained with those observed in 12 normotensive lean controls (LNT) and in 12 hypertensive lean patients (LHT). Systolic and diastolic blood pressure (SBP/DBP) were evaluated by a standard sphygmomanometric approach. All patients underwent a biopsy of subcutaneous fat before or during surgical intervention of gastric banding or intestinal derivation. Subcutaneous small resistance arteries were dissected and mounted on a wire myograph, according to Mulvany-Halpern technique, and M/L, and media cross-sectional area (MCSA) were measured. A concentration-response curve to acetylcholine (from 10-9 to 10-5 Mol/L) was performed, in order to evaluate endothelial function. The results are summarized in Table 1.

Obese patients, independently from the presence of hypertension, diabetes and

Table 1

	LNT	LHT	ONT	OHT
SBP/DBP (mmHg)	127/79±2/2	160/99±2/2$^{***\#\#\#}$/$^{***\#\#\#}$	120/78±5/3	140/88±4/4$^{**\#\#}$/*
BMI (kg/m^2)	25±1	26±1	47±3***	50±4***
MCSA (μm^2)	14893±1700	15469±1124$^{\#\#\#}$	28572±3029***	23225±3486*
M/L	0.066±0.004	0.099±0.003***	0.087±0.004**	0.089±0.004***

Data are mean ± SEM, *$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. LNT; $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ vs. ONT. BMI: body mass index.

dyslipidemia, show the presence of an increased M/L and of an increased media cross-sectional area. Preliminary data suggest the presence of endothelial dysfunction, as indicated by a reduced endothelium-dependent vasodilatation, especially in hypertensive obese patients. In conclusion, our data suggest that the presence of obesity is associated to structural alterations of subcutaneous small resistance arteries, mainly characterized by hypertrophic remodeling.

P550 Role of the phosphatase PTEN during vascular remodeling

R. Widmer-Teske[1], A. Mueller[1], P. Stieger[1], H. Tillmanns[1], R.C. Braun-Dullaeus[2], D. Sedding[1]. *[1]Dept. of Cardiology, Giessen University, Giessen, Germany; [2]Universitaetklinikum Magdeburg, Magdeburg, Germany*

Background: The phosphatase PTEN represents an important physiological inhibitor of phosphatidylinositol-3 kinase (PI3-K)/protein kinase B (Akt) signalling, however, the functional role of PTEN during vascular remodeling remains elusive. In the present study we sought to determine PTEN's effect on vascular smooth muscle cell (VSMC) function in vitro and following vascular injury in vivo.
Methods and Results: Immunohistochemistry indicated a faint expression and equal distribution of PTEN in uninjured rat carotid arteries. 12h following balloon-injury, PTEN expression was strongly increased in apoptotic (TUNEL+) VSMC. In vitro, stimulation with serum or different growth factors had no effect on PTEN expression, whereas stimulation with H2O2 robustly increased PTEN expression in a time- and dose-dependent manner. To evaluate the functional role of PTEN expression, human VSMC were transduced with WT-PTEN. Overexpression of PTEN increased the number of apoptotic VSMC (14.8±2.3 vs. 3.6±0.8%, $P< 0.05$) as determined by TUNEL assay. In contrast, siRNA-mediated knockdown of PTEN attenuated the basal as well as H2O2-induced apoptosis of VSMC. Mechanistically, overexpression of PTEN prevented serum-induced Akt-phosphorylation, whereas siRNA-mediated knock down of PTEN augmented Akt-activation. Moreover, co-transfection of PTEN and a constitutive active Akt mutant prevented VSMC from PTEN-induced apoptosis, indicating, that PTEN regulates VSMC apoptosis by inhibition of Akt phosphorylation/activation.
Conclusion: By interfering with the PI3-K/Akt-dependent survival signalling, the oxidative stress-induced upregulation of PTEN in VSMC of injured arteries augments the sensitivity of VSMC to apoptotic stimuli in the early phase following vascular injury. Thus, these data add substantially to our understanding of PTEN's role during vascular remodelling.

P551 The emerging role of osteoprotegerin in essential hypertension: associations with low-grade inflammation, arterial stiffening and asymmetric dimethylarginine levels

C. Tsioufis, K. Dimitriadis, A. Aggelis, N. Trikalinos, I. Darladimas, D. Syrseloudis, S. Sideris, C. Thomopoulos, D. Tousoulis, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: Evidence supports that osteoprotegerin (OPG), a regulator of bone homeostasis and vessel calcification, constitutes an emerging marker of cardiovascular risk, while arterial stiffening, low-grade inflammation and increased asymmetric dimethylarginine (ADMA) levels are related to diffuse vascular dysfunction. In the present study we examined the relationships of OPG with high-sensitivity C-reactive protein (hs-CRP), ADMA and arterial stiffness in essential hypertensives.
Methods: Our population consisted of 80 untreated patients with stage I-II essential hypertension (57 men, mean age=50 years, office blood pressure (BP) =149/96 mmHg). In all subjects aortic stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP) and venous blood sampling was performed for estimation of hs-CRP, ADMA and OPG concentrations. The distribution of OPG was split by the median (4.96 pmol/l) and accordingly subjects were stratified into those with high and low values.
Results: Patients with high OPG (n=37) compared to those with low OPG (n=43) values had greater body mass index (29.7±4.1 vs 27.6±2.4 kg/m^2, $p<0.05$) and 24-h systolic BP (145±10 vs 131±8 mmHg, $p<0.0001$), while did not differ regarding metabolic profile (p=NS for all). Moreover, patients with high OPG compared to those with low OPG levels exhibited higher hs-CRP (5.4±1.5 vs 2.8±0.7 mg/l, $p<0.05$), ADMA (0.62±0.04 vs 0.53±0.03 μmol/l, $p<0.0001$) and PWV (8.7±1.8 vs 7.7±1.1 m/sec, p=0.007). In the total population, OPG was associated with age (r=0.225, $p<0.05$), waist to hip ratio (r=0.351, $p<0.05$), 24-h systolic BP (r=0.281, $p<0.0001$), hs-CRP (r=0.33, p=0.004), ADMA (r=0.285, $p<0.05$) and PWV (r=0.439, $p<0.0001$). Regarding ADMA, it was correlated with 24-h systolic BP (r=0.278, $p<0.0001$), hs-CRP (r=0.413, $p<0.0001$) and PWV (r=0.381, $p<0.0001$). Multiple regression analysis revealed that age, 24-h SBP, hs-CRP and PWV were independent predictors of OPG levels (R2=0.55, $p<0.0001$). Additionally, analysis of covariance showed that hs-CRP, ADMA and PWV levels remained significantly different between groups after adjustment for confounders ($p<0.05$).
Conclusions: Essential hypertensives with augmented OPG levels are characterized by pronounced inflammatory activation, endothelial dysregulation and accelerated arterial stiffening. Furthermore, the interrelationships of OPG with hs-CRP, ADMA and PWV suggest an integrative role of OPG in atherosclerosis progression in the setting of essential hypertension.

P552 Contribution of calmodulin and Ca^{2+}/calmodulin-dependent kinases to the stretch-induced force response in human atrial myocardium

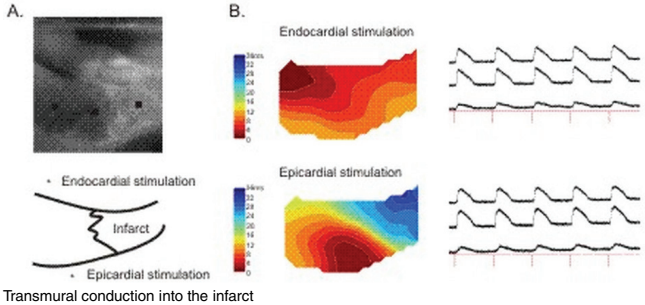
M. Khafaga[1], B. Doleschal[1], D. Von Lewinski[1], H. Machler[2], J. Kockskamper[1], B. Pieske[1]. *[1]Division of Cardiology, Medical University of Graz, Graz, Austria; [2]Medical University of Graz, Department of Cardiac Surgery, Graz, Austria*

Purpose: Stretch is an important regulator of cardiac function. In atrium, stretch alters contractility and contributes to the development of atrial fibrillation. Effects on contractility can be Ca^{2+}-dependent and Ca^{2+}-independent. Here we tested the hypothesis that Ca^{2+}-dependent effects are mediated via calmodulin and Ca^{2+}/calmodulin-dependent kinases.
Methods: Trabeculae (muscle strips) were isolated from right atria obtained from nonfailing human hearts during cardiac surgery. Trabeculae (n=35; diameter <0.8 mm) were bathed in bicarbonate-buffered Tyrode's solution (37°C) and electrically stimulated at 1 Hz. Isometric twitch force was measured by means of a force transducer. Trabeculae were pre-stretched to 88% of optimal length and equilibrated for 30 min. An increase in load was mimicked by stretching the muscle strips from 88% (L88) to 98% (L98) of optimal length.
Results: Stretch induced a biphasic increase in force, an immediate increase (Frank-Starling-mechanism, FSM) to ~180% of force at L88 followed by an additional slower increase (5-10 min; slow force response, SFR) to ~125% of the FSM. Paired stretch protocols revealed that both the FSM and the SFR were highly reproducible (n=8). Inhibition of calmodulin (using 10 μM W-7) affected both the FSM (increase from 174.3±10.2 to 187.0±10.7%; n=10; $P<0.05$) and the SFR (decrease from 123.1±1.9 to 118.1±1.7%; n=10; $P<0.01$), suggesting that Ca^{2+}/calmodulin-dependent processes impair the FSM but contribute to the force increase during the SFR. Inhibition of Ca^{2+}/calmodulin-dependent protein kinase (CaMK, using 10 μM KN-93) resulted in a similar increase of the FSM (from 175.1±10.2 to 193.2±7.4%; n=10; $P<0.05$), but had no effect on the SFR (129.7±4.8 versus 131.1±5.6%; n=10; P=N.S.). On the other hand, inhibition of Ca^{2+}/calmodulin-dependent myosin light chain kinase (MLCK, using 10 μM ML-7), which increases myofilament Ca^{2+} sensitivity via phosphorylation of MLC2a, left the FSM unaffected (189.1±13.9 versus 182.3±16.8%; n=7; P=N.S.), while the SFR was decreased from 129.4±5.7 to 118.5±4.3% (n=7, $P<0.05$).
Conclusions: Stretch elicits a FSM and a SFR in human atrium. Unlike calmodulin, which affects both stretch responses, CaMK is only involved in the FSM while MLCK is only involved in the SFR. In contrast to CaMK, which suppresses the FSM, MLCK rather mediates large part of the SFR.

P553 Conduction delay in the infarct border zone during epicardial stimulation in a rabbit model of myocardial infarction

R.C. Myles, F.L. Burton, S.M. Cobbe, G.L. Smith. *University of Glasgow, Glasgow, United Kingdom*

Introduction: Prior myocardial infarction (MI) is associated with an increased risk of sudden arrhythmic death. Slowed conduction in the infarct border zone (BZ) is thought to be implicated in the induction of re-entrant ventricular arrhythmias.
Methods: Adult male rabbits (n=5) underwent surgical coronary arterial ligation to produce apical MI. Eight weeks later hearts were excised and perfused left ventricular (LV) wedge preparations were loaded with RH237. An optical mapping system was used to record transmural optical action potentials (APs) during endocardial and epicardial pacing at a cycle length of 350ms.
Results: APs were recorded from the infarct zone (IZ) in all hearts. AP signal to noise ratio and amplitude were lower in the BZ and IZ than in the remote zone (RZ, $p<0.01$). AP rise time was slower in the IZ than in the RZ (27.9±2.2 vs. 14.4±1.4ms, $p<0.01$). There was no significant difference in mean APD90 between the RZ (144.9±2.9ms), the BZ (139.9±2.6ms) and the IZ (125.9±11.2ms). Isochronal maps of activation during endocardial and epicardial stimulation and APs from the RZ, BZ and RZ are shown in the Figure. During endocardial pacing



Transmural conduction into the infarct

(A), the spread of activation progressed smoothly across the transmural surface and the BZ was not apparent from the voltage signals. During epicardial pacing, conduction velocity into the IZ was significantly slower than during endocardial pacing (37.3±6.7 vs. 76.6±17.2cm/sec, $p<0.05$), and the delay was located at the BZ.
Conclusions: In rabbit hearts following MI, conduction delay in the infarct BZ was observed during epicardial, but not endocardial stimulation. Such a delay may be pro-arrhythmic and may therefore have implications for LV epicardial pacing in humans.

P554 Process of the progression of ventricular remodeling and arrhythmia in the systemic hyper-oxidative state. A study in glutathione depleted rat model

S. Kurokawa, S. Niwano, H. Niwano, M. Kiryu, H. Fukaya, T. Izumi. *Kitasato University School of Medicine, Sagamihara, Japan*

Background: Although the arrhythmogenic role of oxidative stress is unclear, we have recently documented that the primary increase in oxidative stress might promote ventricular arrythmogenicity in glutathione depleted rats treated with L-buthionine-sulfoximine (BSO). In this study, the time course of these changes was evaluated in BSO-treated rats to clarify the process of the promotion of the arrhythmogenic substrate in the systemic hyper- oxidative state.
Methods: Sprague-Dawley rats were treated with BSO (0 or 30mmol/L in drinking water, control n=21, BSO n=18) for 14 days. On days 7 and 14, serum levels of hepatic transaminase, glucose, triglyceride, cholesterol, creatinine, angiotensin II, and derivatives of reactive oxygen metabolites (d-ROM) were measured. On days 7 and 14, the level of total glutathione in cardiac tissue was measured and immunostaining for 8-hydroxy-2'-deoxyguanosine (8OHdG) was performed to evaluate the expression of oxidative stress. The electrophysiological study (EPS) was performed on days 7 and 14 by exposing the heart under anesthesia, to evaluate effective refractory period (ERP), duration of monophasic action potential (MAPD) and the inducibility of ventricular arrhythmia. The levels of mRNA of the cytokines (TNF-alpha and IL-10), BNP, cardiac ion channels and transporters (Kv4.2, ERG, Kv1.4, Kv1.5, Kv4.3, L-Ca^{2+}, NCX, RyR, and SERCA2a) were measured by real-time RT-PCR methods in cardiac tissue on days 7 and 14.
Results: Body weight in BSO rats became progressively lower than the control. Blood pressure showed no difference between the two groups. Serum angitensin II was higher in BSO rats, although the other serum factors did not differ from the control. BSO rats exhibited higher serum d-ROM and markedly lower total glutathione in cardiac tissue. 8OHdG was not stained in the control, but clearly stained in the cardiac tissue in BSO rats, and the degree of the staining was higher on day 14 than day 7. In the EPS, ERP was shortened (32±1 vs. 36±1ms, $p<0.01$), MAPD90 was prolonged (74±4 vs. 57±4ms, $p<0.01$), and the inducibility of ventricular arrhythmia was notably increased (32% vs. 19%, $p<0.005$) in BSO rats in comparison with the control, and these degrees were higher on day 14 than on day 7. The levels of mRNA of the cytokines and BNP exhibited no difference between the two groups. In contrast, the levels of Kv4.2 and ERG were down-regulated in BSO rats ($p<0.05$).
Conclusions: Systemic oxidative stress might be one of the primary factors to promote cardiac electrophysiological remodeling independent from major organ functional disorders.

P555 Influence of dexamethasone on early tachycardia-induced electrical remodeling in rabbit atrium

R. Laszlo, C. Eick, B. Schreiner, K. Goehring-Frischholz, S. Weretka, H.J. Weig, J. Schreieck. *Department of cardiology, University of Tuebingen, Tuebingen, Germany*

Purpose: Rapid atrial pacing (RAP) in rabbits as a model of tachycardia-induced electrical remodeling results in changes of atrial current densities already after a short pacing interval. Effects of dexamethasone on tachycardia-induced alterations of L-type calcium channel (ICa,L) and transient outward current (Ito) were examined in this study.
Methods: Rabbits (New Zealand white, 2.5-3 kg) were randomly divided in 6 groups of 4 animals each. Atrial pacing leads were implanted in animals of the control-group (C) but – in contrast to P24-group (RAP [600/min] for 24h) and P120-group (RAP for 120 h) – no RAP was applied. Animals of the dexamethasone-group (D) were instrumented as rabbits of the C-group but were additionally pre-treated with dexamethasone (0.5. mg/kg bodyweight, i.m.) for seven days. Finally, RAP was applied to animals of the DP24 and DP120 group for 24 respectively 120 h after dexamethasone pre-treatment.
Result: RAP was associated with a reduction of ICa,L (-27.3±1.6 pA/pF [C, test potential 0 mV, n=19 cells] vs. -18.8±2.1 pA/pF [P24, n=26] vs. -12.6±1.5 pA/pF [P120, n=20]. Ito was reduced after 24h of RAP (60.3±5.4 pA/pF [C, test potential +50 mV, n=20] vs. 28.0±2.5 pA/pF [P24, n=21]) but almost returned to control values after 120 h RAP (51.7±4.5 [P120, n=26]). Dexamethasone did not affect ICa,L (-26.0±2.6 pA/pF [D, n=20]) and did not prevent its reduction after 24 h of RAP (-19.1±2.4 pA/pF [DP24, n=17]) and was even pronounced after 120 h (-8.8±0.7 pA/pF [DP120, n=20]). Ito was also not affected by dexamethasone (63.7±3.4 pA/pF [D, n=25]). At first, expected reduction after RAP was not observed anymore (59.9±5.4 pA/pF, [DP24, n=18]) but did then occur delayed after 120 h (37.5±3.4 pA/pF [DP120, n=22]).
Conclusion: Influence of dexamethasone on early tachycardia-induced electrical remodeling in rabbit atrium is complex. Beside the positive impact of corticosteroids on "oxidative stress", direct impact on tachycardia-induced electrical remodeling might play a role in treatment of atrial fibrillation with these substances.

P556 Angiotensin II and TNFalpha as mediators of ATP-dependent potassium channels remodeling in post-infarction heart failure

C.H. Montessuit[1], N. Isidoro Tavares[1], P. Philip-Couderc[2], R. Lerch[1], A.J. Baertschi[2]. [1]*Division of Cardiology, Geneva, Switzerland;* [2]*Geneva University School of Medecine, Geneva, Switzerland*

Heterogeneous prolongation of the action potential in the post-infarction myocardium is one of the predominant causes of increased incidence of fatal arrhythmias. Sarcolemmal ATP-dependent potassium (KATP) channels are important metabolic sensors regulating electrical activity of cardiomyocytes by shortening the action potential. These channels are made of 4 pore-forming subunits, either Kir6.1 or Kir6.2, and 4 regulatory subunits, either SUR1 or SUR2. We previously observed in post-infarction heart failure marked alterations of KATP subunits expression and electrophysiology. In short, the Kir6.1 conductance subunit was overexpressed in the infarct border zone, conferring to failing cardiomyocytes responsiveness to the KATP opening drug diazoxide, which has no effect on normal cardiomyocytes.
Angiotensin II (Ang II) and TumorNecrosis Factor α (TNFα) have been involved in the progression from compensated hypertrophy to heart failure. We observed increased expression of both angiotensinogen and TNFα in the failing myocardium, with a regional gradient matching that of Kir6.1 expression. Indeed, both angiotensinogen and TNFα expression correlated positively with Kir6.1 and negatively with Kir6.2 expression across the post-infarction myocardium. To further identify a causal relationship, cardiomyocytes isolated from normal rat hearts were exposed in vitro to Ang II or TNFα. We observed similar mRNA expression pattern in cardiomyocytes cultured with Ang II or TNFα as in post-infarction failing hearts, with increased Kir6.1 and SUR subunits and reduced Kir6.2 subunits. Cardiomyocytes cultured with Ang II or TNFα exhibited responsiveness to diazoxide, in terms of both KATP current and action potential shortening. These responses to diazoxide were not observed in untreated cardiomyocytes.
We confirmed that Ang II induced expression of TNFα in cultured cardiomyocytes. Furthermore, in vivo in failing hearts, regional angiotensinogen expression correlated positively with TNFα expression. Accordingly, most effects of Ang II on KATP subunits expression were abolished when the cardiomyocytes were concomitantly incubated with a TNFα-neutralizing antibody.
In conclusion, exposure of normal cardiomyocytes in vitro to AngII or TNFα replicates the in vivo features of KATP expression and electrophysiology in heart failure. This model will be a useful tool to dissect the molecular mechanisms governing KATP subunits expression in heart failure.

P557 Losartan attenuates heart fibrosis induced by chronic endurance training in an animal mode

G. Gay-Jordi[1], B. Benito[2], E. Guasch[2], L. Mont[2], V. Sirenko[1], J. Brugada[2], A. Serrano-Mollar[1]. [1]*IIBB-CSIC (IDIBAPS), Experimental Pathology Department, Barcelona, Barcelona, Spain;* [2]*Hospital Clinic, University of Barcelona - Thorax Institute; Cardiology Dep. - Arrythmia Section, Barcelona, Spain*

Introduction: Chronic exercise induces changes and alters the loading conditions of the heart. These changes are known as the athlete's heart. Furthermore, endurance exercise has demonstrated to be a risk factor for atrial fibrillation and right ventricle arrhythmias. This relationship is mediated by atrial and right ventricular fibrosis Experimental evidence suggests that angiotensin II regulates the fibrotic response to tissue injury, including cardiac fibrogenesis.
Angiotensin II induces proliferation of fibroblasts and production of procollagen via activation of angiotensin type 1 receptor. The aim of this study was to evaluate the antifibrotic effect of losartan, an angiotensin II type 1 receptor antagonist, in an animal model of chronic endurance exercise induced heart-fibrosis.
Methods: The exercise rats underwent a daily running session in a Treadmill (60 min at 60 cm/s) five days a week for 16 weeks. Losartan (50 mg/kg/day) was administrated orally daily before the training session. The animals were sacrificed at 16 weeks. Heart samples were divided by the 4 different cavities. mRNA expression of TGF-b, procollagen-I and procollagen-III was analyzed by a Real-Time PCR in all four cardiac cavities. Heart hypertrophy and fibrosis was confirmed by histological studies.
Results: Daily endurance exercise caused hypertrophy in the left ventricular heart wall and an increase in mRNA expression of the major fibrotic markers in all the heart cavities (TGF-b, procollagen-I and procollagen-III). Losartan treatment was able to reduce mRNA expression of TGF-b, procollagen-I and procollagen-III, in all the heart chambers ($p<0.05$). Heart sections from trained animals stained with Masson's trichrome shown an increase in collagen deposition, losartant treatment reduced intensity of collagen deposition. However, heart hypertrophy was not significantly reduced by this dose of Losartan.
Conclusions: Losartant treatment in training animals prevents the heart fibrosis

induced by endurance exercise. The antifibrotic effect of losartan appears to be mediated by TGF-b mRNA expression dowregulation.

P558 miRNAs regulate smooth muscle cell function during neointima formation

W. Bielenberg[1], A. Prock[1], P. Stieger[1], H. Tillmanns[1], D. Sedding[2]. *[1]Dept. of Cardiology, Giessen University, Giessen, Germany; [2]Universitaetsklinikum Giessen und Marburg GmbH, Giessen, Germany*

Introduction: Micro RNAs (miRNAs) are implicated to regulate mRNA levels of up to 30% of mammalian genes, comprising key regulators for cellular function. Maturation and expression of miRNAs is tightly controlled by the two processing enzymes Dicer and Drosha. Up to now, the role of miRNAs for vascular smooth muscle cell (VSMC) function remains elusive. Thus, the aim of this study was to evaluate the regulation and impact of Dicer and Drosha for smooth muscle cell function during the development of neointimal lesions in vitro and in vivo.
Methods and Results: Following wire-induced injury of the femoral artery of C57BL/6N mice, Dicer or Drosha mRNA expression was analyzed by real-time PCR in the developing neointimal lesions. Expression of Dicer and Drosha was significantly down regulated at day 10 and 21 following injury. Microarray analysis of miRNA expression at these time points revealed a significant downregulation of miRNAs implicated to regulate key molecules of cell cycle progression. Indeed, siRNA-mediated knock down of Dicer or Drosha in human coronary SMC significantly augmented the growth factor-induced expression of CDK4, CDK6, SKP2, accelerated cell cycle progression as determined by FACS analysis and increased VSMC proliferation as determined by total cell count as well as BrdU incorporation (Drosha: 0.0983±0.0194 vs. 0.0527±0.0115; Dicer: 0.0945±0.0172 vs. 0.0527±0.0115; $P<0.005$). In contrast, overexpression of Drosha and Dicer significantly reduced VSMC proliferation. Interestingly, knock down of Dicer and Drosha had no effect on migration or apoptosis. Since oxidative stress, TNFα, IL-1β and IFNγ had no effect, mitogenic stimulation with serum resulted in a reduced expression of dicer and drosha in vitro. For in vivo experiments, dicer and drosha were successfully knocked down by specific siRNA applied in a pluronic gel around wire-injured mouse femoral arteries. Interestingly, the combined knockdown of dicer and drosha resulted in a significantly increased neointima formation.
Conclusions: These data indicate that the key miRNA-processing enzymes Dicer and Drosha are down regulated in neointimal lesions, most likely by mitogenic stimuli. Moreover, altered expression of these enzymes resulting in impaired miRNA processing seems to substantially regulate VSMC proliferation/function. Thus, these data add substantially to our understanding of the role of miRNA during vascular proliferative disease.

P559 Structural alterations in the microcirculation are potent predictors of changes of the renal function in hypertensive patients

G.E.M. Boari[1], D. Rizzoni[1], E. Porteri[1], C. De Ciuceis[1], M. Mazza[1], A. Brignani[2], C. Agabiti Rosei[1], L. Caimi[2], E. Agabiti Rosei[1]. *[1]Clinica Medica, Department of Medical and Surgical Sciences, University of Brescia, Italy., Brescia, Italy; [2]Chair of Clinical Biochemistry, Department of Biomedical Sciences and Biotechnology, University of, Brescia, Italy*

We have previously demonstrated that structural alteration of subcutaneous small resistance arteries of hypertensive patients, as indicated by an increased media to lumen (M/L) ratio, has a strong prognostic significance. Among the predictors of M/L indicators of renal function are those more closely correlated. Aim of the present study was to assess whether M/L ratio can predict subsequent changes in renal function in hypertensive patients. Sixty patients (33 males; 27 females; 15 normotensives and 45 hypertensives) underwent a biopsy of subcutaneous fat at a mean age of 56 years. Resistance-sized arteries were dissected and mounted on a wire myograph according to Mulvany-Halpern technique, and M/L was measured. Patients were re-evaluated after a mean time period of 8.5 years; serum creatinine, blood urinary nitrogen (BUN) and uric acid were measured, and glomerular filtration rate (GFR) was calculated according to MDRD formula. At baseline, we observed significant correlations between M/L and serum creatinine (r=0.32; p=0.013), GFR (r= -0.26; p=0.047), BUN (r=0.37; p=0.009), systolic (r=0.45, $p<0.001$), diastolic (r=0.29, p=0.02), mean blood pressure (r=0.38, p=0.002) and pulse pressure (r=0.40, p=0.002). In addition, we observed significant correlations between M/L and creatinine at follow up (r=0.57; $p<0.001$), % changes in serum creatinine (r=0.46; $p<0.001$), GFR at follow up (r= -0.43; $p<0.001$); % changes in GFR (as ml/min r=-0.33; p=0.008), as well as yearly changes (r=-0.34, p=0.007), BUN at follow up, (r=0.55; $p<0.001$), as well as uric acid at follow up (r=0.35; p=0.026). A multivariate analysis in which all common cardiovascular risk factors were included, showed that M/L is the most potent predictor of changes in renal function. In conclusion, our data suggest that structural alterations of subcutaneous small resistance arteries (which may be present also in other vascular beds), may predict the time-course of changes of renal function during a follow-up period of about 9 years.

P560 Role of SIRT1 in VSMC function and vascular remodeling

D. Sedding, S. Vogel, H. Koenig, J.M. Daniel, H. Tillmanns. *Dept. of Cardiology, Giessen University, Giessen, Germany*

Background: The class III histone deacetylase SIRT1 has been identified as a key regulator of ageing and longevity in model organisms such as S. cerevisiae and C. elegans, which regulates cellular functions such as differentiation, senescence and metabolism. However, the role of SIRT1 for Smooth muscle cell function and vascular homeostasis remains unknown. In this study, we investigated the role of SIRT1 for VSMC function and vascular remodeling.
Methods and Results: Here, we show that SIRT1 is highly expressed in intact blood vessels in vivo as well as in cultured human VSMC. Stimulation of SIRT1 activity by either treatment with the SIRT1 activator resveratrol or adenoviral overexpression of wild type SIRT1 but not with an inactive SIRT1 mutant attenuated serum-induced VSMC proliferation in a dose dependent manner in vitro (Ad-WT-SIRT1: 96±29% vs. Ad-Empty: 187±34% increase in cell number after 48 h; $P<0.001$). In contrast, treatment of VSMC with the small molecule weight inhibitors of SIRT1, nicotinamide and sirtinol, augmented the proliferative and migratory activity of VSMC. Consistent with these data, MEF cells isolated from SIRT-/- mice showed an augmented proliferative response to serum stimulation and were more resistant to starving-induced apoptosis compared to WT-MEF cells (SIRT-/-: 4.9±1.2% vs. WT: 12.3±3.2; $P< 0.005$). Silencing of endogenous SIRT1 using siRNA resulted in an increased proliferation and migration of VSMC under basal as well as serum-induced conditions. In vivo, following arterial injury of the mouse femoral artery, SIRT1 was downregulated in the developing neointima. Adenoviral-mediated reconstitution of wild type SIRT1 but not of the inactive SIRT1 mutant prevented neointima formation in vivo (Ad-WT-SIRT1: 0.9±0.4 vs. Ad-Empty: 1.9±0.6; $P<0.005$).
Conclusion: Taken together, these findings contribute substantially to our understanding of SIRT's role during the development of vascular proliferative disease and indicate that SIRT1 plays an essential role in proliferative, apoptotic and migratory processes which regulate vascular homeostasis and remodeling.

MYOCARDIAL ELECTRICS: SPIKES, WAVES AND STORUS

P561 Expression of FKBP 12.6 is reduced and sarcoplasmic calcium leak is increased in myocardium of diabetic mice

S. Groenke, D. Hoyer, K. Frank, C. Zobel, J. Mueller-Ehmsen, H. Reuter. *Universitaetsklinikum Koeln, Cologne, Germany*

Diminished ventricular compliance with abnormal diastolic function is one of the early cardiac manifestations of both insulin-dependent and non-insulin-dependent diabetes mellitus. Besides structural changes and interstitial fibrosis this diastolic dysfunction could arise from alterations in intracellular sarcoplasmic Ca^{2+}-handling. To test this hypothesis we analyzed sarcoplasmic Ca^{2+} release in mice with steptozotocin-induced type 1 diabetes (n=8) compared to wild type controls (n=8). Among the various proteins that regulate sarcoplasmic Ca^{2+} release, the ryanodine-receptor-2 (RyR2), FK506-bindin protein (FKBP12.6), and sorcin have been implicated in the pathogenesis of diabetes-induced hypertrophy and heart failure. Therefore, expression of these proteins was determined by immunoblot and real-time RT PCR and PKA-dependent phosphorylation of RyR2 at Ser 2809 was measured. Sarcoplasmic Ca^{2+} leak was quantitated by use of an $45Ca^{2+}$-based assay in isolated membrane vesicles.
After eight weeks of stable hyperglycemia (> 300 mg/dl), diabetic mice developed a significant left ventricular hypertrophy (diastolic septum [mm], non-diabetic: 72±4 (n=8); diabetic: 102±4 (n=8); $p<0.001$). Compared to non-diabetic controls, sarcoplasmic Ca^{2+} leak was significantly increased in isolated vesicles from diabetic animals (Ca^{2+} leak [rel. units], non-diabetic: 15.5±3.9; diabetic: 59.9±25.6; $p<0.05$). Expression and phosphorylation of RyR2 was not different between myocardium of diabetic and non-diabetic animals. However, densities of FKBP12.6, a modulator of RyR2 activity, were significantly reduced in diabetic myocardium (FKBP12.6 [rel. units], non-diabetic: 3.8±0.4; diabetic: 1.4±0.3; p=0.002).
We conclude that sarcoplasmic Ca^{2+} leak is increased in streptozotocin-induced diabetes at least in part likely due to a reduced expression of FKBP12.6. The increased Ca^{2+} leak could contribute to diastolic dysfunction and may underlie the tendency of diabetic individuals to develop heart failure.

P562 JTV 519 attenuates diastolic sarcoplasmic reticulum calcium leak induced by Na accumulation in cardiomyocytes

F.R. Heinzel[1], M. Sacherer[1], S. Sedej[1], M.A. Vos[2], B. Pieske[1] on behalf of on behalf of the CONTICA study group. *[1]Medical University of Graz, Graz, Austria; [2]Department of Cardiology, University Hospital Maastricht, Maastricht, Netherlands*

Diastolic calcium (Ca) leak from the sarcoplasmic reticulum (SR) Ca release channel (ryanodine receptor, RyR) promotes heart failure and arrhythmias. JTV519 has been shown to stabilize RyR and decrease Ca leak from the SR

in conditions of protein kinase A (PKA)-mediated hyperphosphorylation of the RyR ("leaky" RyR). However, arrhythmogenic Ca leak in cardiomyocytes is also observed in conditions of SR Ca overload following cytosolic Na ([Na]i) accumulation (mediated by the Na/Ca exchanger), as in heart failure, ischemia or digitalis toxicity. We investigated whether JTV519 attenuates RyR Ca leak independent of PKA-mediated effects on RyR gating.

Methods: In electrically stimulated (1 Hz) murine cardiomyocytes, Ca transients, diastolic SR Ca leak (frequency of Ca sparks) and SR Ca content (Ca release during rapid caffein application, 30 mM) were measured using confocal microscopy (Ca-indicator Fluo4-AM). Na/K-pump inhibitor ouabain (OUAB, 100 μM) was used to increase intracellular Na as confirmed in parallel experiments using the Na indicator CoroNa (following calibration). Cells were studied in the absence (CTRL) and presence (JTV) of JTV519 (1 mM, >1h preincubation).

Results: OUAB increased [Na]i from 13.5±3.0 to 18.9±2.8 mM (mean±SE, $P<0.001$). OUAB increased the systolic amplitude of the Ca transient (CaTsys, 5.1±0.4 vs. 3.4±0.3 F/F0), diastolic spark frequency (132±38 pL^{-1} s^{-1} in CTRL+OUAB vs. 12±7 pL^{-1} s^{-1} in CTRL) (both $P<0.05$), and SR Ca content (8.0±0.7 vs. 6.4±0.6 F/F0,P=0.07) in CTRL. In JTV (without OUAB), spark frequency was lower than in CTRL (3.8±2.9 pL^{-1} s^{-1}, $P<0.05$). With ouabain (JTV+OUAB) spark frequency increased (20.4±5.2 pL^{-1} s^{-1}, P=0.07), but remained significantly lower than in CTRL+OUAB. CaTsys (2.3±0.3 F/F0) was significantly lower in JTV vs. CTRL. In the presence of JTV, ouabain did not significantly change CaTsys (2.8±0.2 F/F0 in JTV+OUAB, P=NS vs. JTV) or SR Ca content (4.5±0.4 in JTV+OUAB vs. 4.8±0.9 in JTV, F/F0); diastolic [Ca]i tended to be increased by OUAB.

Conclusion: In summary, an increase in [Na]i leads to increased cytosolic [Ca] and diastolic Ca leak from the SR. In the presence of JTV519, diastolic Ca leak from the SR is decreased. Our results suggest that the effect of JTV519 on SR Ca leak is independent of PKA-mediated effects on the RyR.

P563 Conditional cardiac survivin deficiency results in global atrial, AV-nodal and ventricular conduction disturbances in the mouse heart

J.W. Schrickel[1], T. Lewalter[2], R. Andrie[3], M. Linhart[3], F. Stoeckigt[3], G. Nickenig[3], L.M. Lickfett[3], B. Levkau[4]. *[1]Dept. of Medicine-Cardiology, University of Bonn, Bonn, Germany; [2]St. Vinzenc Hospital, Paderborn, Germany; [3]University of Bonn, Bonn, Germany; [4]Institute of Pathophysiology, University Duisburg-Essen, Essen, Germany*

Background: Survivin is a caspase-inhibiting protein and inhibits apoptotic processes in mammalian cells. It has been shown to relevantly influence cardiomyocyte cell number, resulting in heart failure phenotype in survivin-deficient mice. The effects of survivin-depletion on cardiac electrophysiology is until now unknown.

Methods: In vivo transvenous electrophysiological studies were performes in 12 adult mice in which survivin was conditionally, cardiac-specific deleted (surv-/-) and 12 wild-type (surv+/+) littermates. Epicardial activation mapping was performed in Langendorff-perfused hearts of 16 surv-/- and 6 surv+/+ mice.

Results: Hearts of surv-/- were significantly heavier than control hearts as indicator for hypertrophy and dilatation (heart-weight to body weight ratio 8.3±2.2mg/g vs. 5.3±0.8mg/g; P=0.0005). The surface-ECG showed, at equal anaesthesia-protocols, lower heart rates due to sinus bradycardia in surv-/- (326±66bpm vs. 440.6±39ms; P=0.003), accompanied by significantly prolonged P-waves (20.3±5.8ms vs. 14.6±2.0ms; P=0.009), PQ- (47.4±8.6ms vs. 41.1±3.7ms; P=0.043), QRS- (19.5±4.8ms vs. 14.0±1.0ms; P=0.002) and QT-intervals (41.6±4.4ms vs. 36.2±3.4ms; P=0.003). The HV-interval was prolonged in surv-/- (12.1±2.4ms vs. 9.3±1.4ms, P=0.005). Functionally, we found significantly impaired sinus-nodal function (sinus node recovery times at 100ms stimulus-cycle length: 310.2±76.6ms vs. 207.8±68.6ms, P=0.003) and AV-nodal conduction (Wenckebach-periodicity: 105.9±15.9ms vs. 79.6±8.1ms, P=0.0002) in surv-/-. Atrial, AV-nodal and ventricular refractory periods were significantly prolonged. Epicardial activation mapping showed significant slowing and heterogeneity of conduction in the ventricles of surv-/- mice. Interestingly, susceptibility towards induction of atrial and ventricular tachycardia was not different among the groups, though all surv-/- animals showed supraventricular and ventricular ectopic beats ($P<0.0001$ vs. surv+/+).

Conclusions: Surv-/- mice develop severe global conduction disturbances on atrial and ventricular level as well as the specific conduction system. Proper impulse conduction and formation is thus relevantly dependent from survivin controlled cardiomyocyte number and the prevention of apoptotic processes determined by survivin in the mouse heart.

P564 Effect of adenosine A1 receptor activation on cyclic AMP-dependent modulation of intracellular calcium handling in human atrial myocytes

J. Fernandes[1], C.E. Molina[1], A. Llach[1], J. Padro[1], J. Cinca[1], L. Hove-Madsen[2]. *[1]Hospital de Sant Pau, Barcelona, Spain; [2]Centro de Investigación Cardiovascular CSIC-ICCC, Barcelona, Spain*

Purpose: Myocardial ischemia is associated with acute changes in the cellular adenosine metabolism that may alter intracellular calcium handling. On the other hand, activation of adenosine A2A receptors (A2AR) promotes a cyclic AMP (cAMP)-dependent stimulation of spontaneous calcium release from the sarcoplasmic reticulum (SR). However, the effect of concomitant activation of A2ARs and adenosine A1 receptors (A1R) is unknown, and the aim was to study how A1R activation affects cAMP-dependent modulation of intracellular calcium handling in human atrial myocytes.

Methods: Patch-clamp technique was used to measure spontaneous Na-Ca exchange currents (Incx) activated by calcium release from the SR and L-type calcium currents (ICa) elicited by repetitive 200 ms depolarizations in atrial myocytes from 14 patients. The ICa amplitude was measured at cycle lengths of 5, 2, 1.5, 1, 0.75 and 0.5 s.

Results: In four patients, cAMP-mediated stimulation was achieved with the beta-adrenergic agonist isoproterenol (ISO, 30 nM). This increased ICa density from –2.25±0.85 pA/pF to –9.50±1.94pA/pF ($p<0.05$) and it increased spontaneous Incx frequency from 0.83±0.29/min to 3.13±0.55/min ($p<0.05$). These effects were accompanied by a significant reduction in the stimulation frequency where beat-to-beat variations in ICa amplitude were observed (from 1.38±0.38 in control to 0.5 Hz with ISO, $p<0.05$). Exposure to the A1R agonist R-phenylisopropyl-adenosine (R-PIA -50nM) in the continuous presence of ISO reduced ICa to -3.19±0.88 pA/pF ($p<0.05$) and slowed the spontaneous Incx frequency to 1.17±0.5/min ($p<0.05$). Moreover, R-PIA increased the threshold frequecy for induction of a non-uniform beat-to-beat pattern to 0.78±0.08 Hz ($p<0.05$). This suggests that adenosine-mediated activation of A1Rs has the potential to cancel stimulatory cAMP-dependent effects produced by concomitant A2AR activation. However, infusion of adenosine into the myocyte during a 15 minute period gradually increased the spontaneous Incx frequency from 1.5±0.8/min to 5.7±1.0/min ($p<0.05$, n=12) and promoted chaotic beat-to-beat changes in the ICa amplitude.

Conclusions: Selective A1R activation can reverse beta-adrenergic stimulation of ICa and abnormal SR calcium release, but it can not counteract abnormal calcium release induced by elevation of cytosolic adenosine levels. These results suggest that acute changes in myocardial adenosine metabolism could contribute to arrhythmogenesis through an A2AR-mediated promotion of aberrant calcium handling.

P565 Acute inhibition of the Na^+/Ca^{2+} exchanger by SEA0400 reduces proarrhythmia in an experimental model of chronic heart failure

P. Milberg[1], C. Pott[1], M. Paul[1], G. Frommeyer[1], T. Matsuda[2], A. Baba[2], N. Osada[3], G. Breithardt[1], L. Eckardt[1]. *[1]Department of Cardiology and Angiology, Muenster, Germany; [2]Graduate School of Pharmaceutical Sciences, Osaka, Japan; [3]Department of Medical Informatics and Biomathematics, Muenster, Germany*

Introduction: We recently demonstrated that selective inhibition of NCX via SEA0400 (SEA) inhibits torsade de pointes (TdP) in an experimental model of LQT2 and LQT3. The aim of the present study was to test if these mechanisms play a role in congestive heart failure (CHF).

Methods: CHF was induced by rapid ventricular pacing. The paced rabbits developed a significant decrease of ejection fraction as compared with controls. Eight ventricular action potentials showed a prolongation of repolarization in CHF after induction of AV-block and stimulation at cycle lengths between 900 and 300ms as compared with sham hearts (+29±12ms, $p<0.05$).

Results: To further challenge repolarization reserve sotalol ((S) n=13, 100μM, IKr block; LQT2) and veratridine ((V) n=15, 0.5μM, inhibition of sodium channel inactivation; LQT3) were infused, resulting in a further increase of action potential duration (S-CHF: +62±21ms; $p<0.01$, V-CHF: +54±17ms; $p<0.01$ as compared with S and V-treated sham hearts). In addition, CHF led to a significant increase of dispersion of repolarization, as compared with S-(+22±7ms; $p<0.05$) and V-treated (+20±6ms; $p<0.05$) sham hearts. After lowering of potassium concentration, S and V reproducibly induced early afterdepolarizations and TdP in 13 (10) of 13 hearts of the S-CHF- and in 10 (6) of 15 hearts of the V-CHF- group. Under these conditions, perfusion with SEA (1μM) suppressed EAD in 6 of 13 S-CHF hearts and in nine of 10 CHF hearts that showed EAD during treatment with V. Furthermore, SEA significantly shortened MAP duration (S-CHF: -50±14ms, V-CHF: -30±9ms; $p<0.01$) and reduced dispersion of repolarization (S-CHF: -19ms, V-CHF: -36ms; $p<0.05$). This led to a reduction in the occurrence of TdP of 60% in the S-CHF-group and of 83% in the V-CHF-group.

Conclusion: In an experimental model of chronic heart failure the beneficial effects of acute NCX inhibition on proarrhythmia, recently shown in a model of LQT2 and LQT3 are preserved. Our observations indicate for the first time that selective pharmacological NCX inhibition in heart failure increases repolarization reserve.

P566 Sustained intraventricular stretch promotes ventricular arrhythmias decreasing conduction velocity and shortening refractoriness, in the isolated swine whole heart

J. Moreno Planas, J.G. Quintanilla, T. Archondo, E. Usandizaga, N. Perez Castellano, I. Nunez, R. Fernandez Cavazos, C. Macaya, J. Perez-Villacastin. *Hospital Clinico San Carlos, Madrid, Spain*

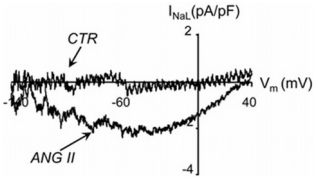
Introduction: High intraventricular pressures (IVP) promote clinical arrhythmias, but the pathophysiology remains unclear as frequently associated cate-

cholamines may act as a confusing factor. We aimed to evaluate the effects of sustained acute stretch (SAS) on wavefront propagation and arrhythmia inducibility in the normal isolated heart and under a perfusion resembling a CHF milieu.
Methods: hearts from 7 pigs (~40 kg) were isolated and optical mapping of paced beats was performed to evaluate wavefront propagation over a 3.5x3.5cm^2 area, adjacent to the pacing site, on the anterior LV. SAS was achieved by a plastic balloon in the LV to raise diastolic IVP to ~20 mmHg. Recordings were taken at low IVP and >2' on high IVP, alternating normal and a CHF-like Tyrode's perfusion (CHF-Ty). CHF-Ty contained lower K^+ (3 mM), lower Mg2+ (0.4mM) and noradrenaline to achieve a sinus rate of 100bpm. IVP was always lower than perfusion pressure to prevent subendocardial ischemia. The stimulation protocol included pacing at 500 and 300ms + 1 extrastimulus (S2) 10ms > ERP. To quantify proarrhythmia, induced arrhythmias were scored (as VF: 6, PVT: 5, MVT: 4, three ectopi: 3, two ectopi: 2, single ectopy: 1 and no arrhythmia: 0 points) and an arrhythmia ratio (AR), considering the total number of paced sequences, was calculated in each setting.
Results: conduction velocity (CV) decreased: pacing at 300ms (p 0.014), after S2 (p 0.004) and after applying SAS (p 0.008) independently of the perfusion. APD90 decreased with CHF-Ty ($p<0.001$) and after applying SAS (p 0.007). APD90 also shortened after S2 ($p<0.001$) and pacing at 300ms (p 0.001). Wavelength (WL=ERPxCV) decreased with SAS (p 0.03). An averaged AR increased with SAS from 0.4 to 1.2 under N-Ty, and from 0.8 to 1.5 with CHF-Ty (p 0.03).
Conclusions: Sustained acute stretch facilitates the induction of ventricular arrhythmias, slowing wavefront propagation and shortening repolarization. A CHF serological mileau promotes the induction of ventricular arrhythmias, adding to SAS effect, despite not modifying conduction velocities.

P567 Ranolazine normalizes action potential duration in angiotensin II exposed HL-1 cells: role of late sodium current

S. Casini[1], A. Bianchini[1], L. Sartiani[1], S. Suffredini[1], L. Belardinelli[2], A. Mugelli[1], E. Cerbai[1]. *[1]University of Florence, Florence, Italy; [2]CV Therapeutics, Palo Alto, California, United States of America*

Purpose: Late sodium current (INaL) has been shown to play a key role in action potential (AP) prolongation and arrhythmogenesis in acquired and congenital cardiac diseases. However, the molecular signals leading to enhanced INaL are unknown. Locally increased angiotensin II (ANGII) contributes to the pathogenesis of heart rhythm dysfunctions. The aim of this study was to investigate whether exposure of immortalized atrial cells (HL-1) to ANGII increases INaL and thereby causes AP prolongation. Concomitantly, we determined whether acute treatment with ranolazine, a selective blocker of INaL, could reverse the AP prolongation in cells exposed to ANGII.
Methods: HL-1 cells were incubated for 48 hours at 37°C in the presence and absence (CTR) of 100nM ANGII. INaL and AP duration (APD) were measured in patch-clamped cells at 37°C. INaL was analysed in CTR and ANG II cells as a tedrodotoxin (TTX)-sensitive current obtained by subtraction of the current recorded before and after application of 30μM TTX. APD was measured in CTR and ANGII cells in the presence and absence of 10μM ranolazine.
Results: INaL was increased in ANGII cells (Figure). Peak INaL at -50 mV was -2.1pA/pF (n=5) in ANG II and -0.4pA/pF (n=4) in CTR, respectively (p=0.04). Similarly, there was a significant AP prolongation in ANGII cells compared to CTR (APD90: ANGII (n=14) 145.7±20.5ms; CTR (n=9) 92.8±4.6ms). Acute application of ranolazine significantly reduced APD in ANGII cells (APD90: 134.2±38.4ms vs 190.6±39.5ms, n=4), without affecting APD in CTR cells (APD90: 100.7±21.4ms vs 98.4±8.2ms, n=3).



Average INaL current-voltage relation

Conclusions: Increased levels of ANGII, as observed in several cardiac diseases, prolonged APD in HL-1 cells. This prolongation was INaL-dependent. Acute exposure to ranolazine reduced AP prolongation following chronic exposure to ANGII.

P568 Cardiac Rac 1 GTPase upregulation increases atrial load and induces local atrial conduction defects in the mouse

J.-C. Reil[1], O. Adam[1], C.H. Mewis[1], M. Boehm[1], U. Laufs[1], M. Allessie[2], H.R. Neuberger[1]. *[1]Klinik für innere Medizin III, Homburg/Saar, Germany; [2]University Hospital Maastricht, Maastricht, Netherlands*

Background: It has been hypothesized that upregulation of Rac1 GTPase plays a role in the pathogenesis of atrial fibrillation (AF). Upregulation of Rac1 activates the nicotinamid adenine dinucleotide phosphate (NADPH) oxidase which leads to superoxide production. The aim of the present study was to investigate the effects of murine cardiac Rac1 upregulation on determinants of atrial load and electrophysiology
Methods: In 11 transgenic mice with cardiac overexpression of constitutively active Rac 1 (RacET) and10 wildtype controls (aged 6 months) a surface ECG was recorded (lead II). Thereafter the heart was excised and left ventricular function was measured by pressure volume analysis in these isolated "working hearts" of both groups. Conduction in the left atrium was mapped epicardially at sinus rhythm (SR) using a 16-polar custom made electrode to record unipolar electrograms (interelectrode spacing 0.5 mm). Total activation time (TAT) under the mapping electrode was measured. Local activation time differences were calculated between adjacent electrodes (conduction times). The atrial effective refractory period (AERP) was determined at a cycle length of 150 ms. To test inducibility of supraventricular tachycardias, atrial burst stimulation was performed.
Results: Systolic function was significantly reduced in RacET (load independent systolic elastance Ees, mean± SEM: 4.6±0.9 mmHg/ul vs 2.4±0.4 mmHg/ul, $p<0.001$, ejection fraction: 60.1±9.1% vs. 37.8±5.1%, $p<0.001$). Left ventricular compliance was also reduced in Rac ET (Stiffness constant b 0.08±0.02 vs. 0.12±0.02, $p<0.05$). In RacET the duration of the P-wave was significantly longer compared to controls (24.2±2.4 ms vs. 13.9±1.0 ms, $p<0.001$). Similarly, TAT during sinus rhythm was longer in RacET (6.3±1.3 ms vs. 2.2±1.1ms, $p<0.01$). In RacET the frequency of local conduction times >2ms was higher (22.7±8.4% vs. 1.2±0.7%; $p<0.01$). The AERP did not differ significantly between both groups (37.3±5.2 ms vs. 45.0±3.9 ms; p= 0.31). Interestingly, 5 out of 11 Rac1 hearts showed spontaneous or inducible atrial tachyarrhythmias (>30 s) compared to 0 of 9 controls ($p<0.05$).
Conclusion: Cardiac Rac1 overexpression is accompanied by systolic and diastolic ventricular dysfunction, thereby increasing atrial load. Furthermore it is associated with local atrial conduction disturbances. This may represent a substrate for AF in cardiac Rac1 overexpression.

P569 Knock out of Caspase 3 prevents from persistent atrial fibrillation in pigs

K. Trappe, K. Kelemen, O. Bikou, R. Soucek, M. Koch, S. Huntscha, B. Menrath, H.A. Katus, A. Bauer. *Universitaetsklinikum Heidelberg, Heidelberg, Germany*

Background: A frequent factor for the development and maintenance af atrial fibrillation (AF) is structural remodeling (SR) of the atria (At). SR can lead to atrial conduction slowing which decisively contributes to the development and maintenance of AF. Apoptotic processes are part of SR, the role of apoptosis (AP) in the development of AF, however, is not definitely clarified yet. Caspase 3 plays a key role in the signal pathway of AP. The purpose of the present study was to find out if knocking out Caspase 3 by Silencing RNA (siRNA) reduces SR in the At and hereby leads to a delay of appearence of AF in a pig model.
Methods: In 10 pigs a pacemaker (St. Jude Medical, Frontier II CRT DDDRV 5569) was implanted which induced AF by repetitive burst stimulation of the right atrium. After following thoractomy we injected an adenovirus, which codes for siRNA-Caspase 3 (knock out of Caspase 3) in both At of 5 pigs. The other 5 pigs (control group) received green fluorescent proteine (GFP) by the same way. Subsequently an epicardial elctroporation (5 cycles: 20 V, 100 ms cycle length) of the At was performed in all 10 pigs to improve the transduction of the virus. After a follow up period of 14 days an electrophysiological mapping (15 bipolar poles on a 2x2 cm patch) of both At was performed in all animals to measure atrial conduction lengths.
Results: There was a significant difference between the times until appearance of AF in the pigs treated with siRNA-Caspase 3 and the control group (9,6+1,4 days, 6,7+2,1 days, p=0,029). In the right atrium there was no significant difference of activation times between the two groups (Caspase 3 group 0,63+1,3 m/s, control group 0,39+0,09 m/s, p=0,04). It turned out a significant difference between the Caspase 3 group and control group with regard to the incidence of intraatrial conduction slowing (>30 ms) (1/10, 10%, 10/10, 100%) and conduction blocks (>50 ms) (0/10, 0%, 7/10, 70%) between two neighbouring leads in both At. Distinct conduction slowing mainly appeared in transversal fiber direction (10/10, 100% transversal, 5/10, 50% longitudinal).
Conclusions: Knock out of Caspase 3 can cause a delay of the appearence of persitent AF in pigs. This effect mainly can be explained by a reduction of apoptotic processes and the hereby resulting suppression of intraatrial conduction slowing. The fact that a longlasting suppression of persistent AF could not be achieved in this study can be explained by the early loss of effectivness of adenoviral constructions. The inhibtion of apoptosis by knocking out Caspase 3 is an effective approach to the prevention of persistent AF.

P570 Arrhythmic risk during childhood in a paediatric LQTS population of probands

V. Probst[1], F. Floch[1], A. Maltret[2], E. Villain[2], J.E.A.N.M. Lupoglazoff[3], A. Leenhardt[3], H. Le Marec[1], I. Denjoy[3]. *[1]CHU de Nantes - Hopital Guillaume et Rene Laennec, Nantes, France; [2]AP-HP - Hopital Necker, Paris, France; [3]Lariboisiere Hospital (AP-HP), Paris, France*

Introduction: Congenital long-QT syndrome (LQTS) is an arrhythmic disease

characterized by a prolonged ventricular repolarization duration and an increased risk for ventricular arrhythmias and sudden cardiac death. To date, there is few data on the clinical evolution of index children patients, a sub-group potentially at high risk.
The aim of our study was to evaluate the clinical course of LQTS in a paediatric population of index patients.
Methods: Patients were included in the study if they were index patients under age 16 at the time of diagnosis and fulfilled the diagnosis criteria for LQTS.
Results: 140 children were included in the study (75 males 56%). A follow-up was available for all the patients. The mean follow-up was 7.8±6.1 years.
The mean age at diagnosis was 7±5 years. LQTS diagnosis was performed during the neonatal period in 30 cases (21%). The mean QTc interval was 507±58 ms. One hundred and twenty-nine patients (92%) including 75 males and 54 females were symptomatic at diagnosis. Genetic analysis was available in 102 patients and was positive in 90 (KCNQ1 60%, KCNH2 34% and SCN5A 5%). During follow-up, 9 patients died (6%) and 23 patients experienced a non-fatal cardiac event (16%). Multivariate analysis showed that risk of arrhythmic events was increased by a lack of beta-blocker treatment (p = 0.02), a increased QTc interval length (p = 0.01), LQT3 genotype (p = 0.001), the need for a pacemaker implantation (p = 0.006) and a early onset of symptoms, especially during the neonatal period (p = 0.03).
Conclusion: Our study, focused on paediatric index cases of LQTS demonstrates that the risk of sudden cardiac death in this severely affected population is 6% over a period of time of 7 years. Lack of beta-blocker therapy, increased QTc interval, LQT3 genotype, pacemaker implantation and neo-natal diagnosis are link with an increase risk of arrhythmic events.

P571 Relationship of common candidate gene variants to electrocardiographic T-wave peak to T-wave end interval

K. Porthan[1], A. Marjamaa[1], M. Viitasalo[1], H. Vaananen[2], L. Toivonen[1], M.S. Nieminen[1], A. Jula[3], V. Salomaa[4], K. Kontula[1], L. Oikarinen[1]. *[1]Helsinki University Central Hospital, Helsinki, Finland; [2]Helsinki University of Technology, Espoo, Finland; [3]National Institute for Health and Welfare, Turku, Finland; [4]National Institute for Health and Welfare, Helsinki, Finland*

Purpose: Common ion-channel single nucleotide polymorphisms (SNPs) associate with QT-interval duration and may thus predispose to arrhythmic sudden death. We examined the relationship of SNPs to T-wave peak to T-wave end (TPE) interval, which is an electrocardiographic (ECG) marker of arrhythmogenic transmural dispersion of repolarization.
Methods: We measured precordial maximum TPE intervals from digital 12-lead ECGs and genotyped six common long QT syndrome (LQTS) genetic variants from 5 890 adults attending an epidemiological national survey in Finland. Results were adjusted for gender, age, systolic blood pressure, Cornell voltage-duration product, and for history of previous coronary heart disease and/or myocardial infarction.
Results: In an additive genetic model, TPE interval associated with minor alleles of KCNH2 intronic SNP rs3807375 (+0.8 ms per each minor allele) and rs1805123 (−1.2 ms per each minor allele) (Table).

Effect of SNPs on TPE interval

Gene	SNP (amino acid change)	Max TPE V1–6 change per minor allele (ms)	P P
KCNH2	rs3807375	+0.8	0.001
rs1805123 (K897T)	−1.2	0.00005	
rs36210421 (R1047L)	−0.8	0.082	
KCNE1	rs1805128 (D85N)	−1.3	0.202
rs1805127 (G38S)	−0.01	0.983	
KCNE2	rs2234916 (T8A)	−0.2	0.886

Conclusions: Minor allele of KCNH2 rs3807375 increases whereas minor allele of KCNH2 rs1805123 decreases ECG transmural dispersion of repolarization, suggesting that these SNPs may modify arrhythmic vulnerability.

P572 Electrical conduction across human adult epicardium-derived cells is influenced by epithelial-to-mesenchymal transition: Novel mechanistic insights into cardiogenesis-related arrhythmias?

D.A. Pijnappels[1], N.A.M. Bax[2], D.L. Ypey[1], A. Van Der Laarse[1], A.A.F. De Vries[3], M.J. Schalij[1], D.E. Atsma[1], A.C. Gittenberger-De Groot[2]. *[1]Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands; [2]Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, Netherlands; [3]Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, Netherlands*

Background: Epicardium-derived cells (EPDCs) are able to undergo epithelial-to-mesenchymal transition (EMT), thereby contributing to cardiac development. Disturbances in this process of transition are associated with seriously hampered cardiac function. However, there is lacking knowledge regarding the electrophysiological properties of EPDCs and whether EMT influences electrical conductivity of EPDCs. Therefore, these aspects were studied in a controlled in vitro model of electrical conduction.
Methods: EPDCs were cultured from right atrial appendages excised during cardiac surgery of adult patients. Changes in morphology, from cobblestone-like (c) to spindle-shaped (s), and β-catenin staining pattern indicated that these cells spontaneously undergo EMT in vitro. Neonatal rat cardiomyocytes (CMCs) were cultured onto micro-electrode arrays (60 electrodes), resulting in synchronously beating monolayers. After 2 days, a central conduction block was created by laser-dissection of a 360±20 μm wide channel, dividing the monolayer in two asynchronously beating fields. Then, 75×10^3 eGFP-labelled cEPDCs or sEPDCs were applied in the channel. CMCs or cardiac fibroblasts (cFBs) were applied as control. Conduction across this strip of cells was assessed for 2 days. In addition, patch-clamp experiments, and immunocytochemical analysis for gap junction and ion channel protein expression were performed in both cEPDCs and sEPDCs.
Results: Application of cEPDCs (n=8) resulted in electrical coupling of the two CMC fields within 24h. However, sEPDCs (n=8) were not able to electrically connect the CMC fields, associated with asynchronized beating of the CMC fields. At day 2, conduction velocity (CV) across cEPDCs was 3.9±0.4 cm/s. In contrast, sEPDCs were still functioning as a cellular conduction block (CV=0) ($p<0.05$). Application of CMCs (n=12) resulted in electrical coupling of the CMC fields (CV=19±1 cm/s), however, application of cFBs (n=10) resulted in a conduction block ($p<0.05$). Of note, both connexin (Cx) 40, Cx43, and Cx45 were downregulated in sEPDCs as compared to cEPDCs ($n>100$, $p<0.05$). Also, expression of SCN5A, CACNA1C, and Kir2.1 was downregulated upon EMT in EPDCs ($n>100$, $p<0.05$).
Conclusions: Electrical conduction across epicardium-derived cells is influenced by epithelial-to-mesenchymal (EMT) transition, resulting in significantly reduced conductivity of these cells, associated with conduction block. After EMT, both gap junction and ion channel protein expression was downregulated. This study may provide new insights in EMT-related cardiac dysfunction, such as the occurrence of ventricular arrhythmias.

P573 Isl-1 expression in the sinus venosus delineates a RhoA expressing cell population in the development of the sinoatrial and atrioventricular node in the chick embryo

R. Vicente Steijn, D.P. Kolditz, E.A.F. Mahtab, L.M. Van Der Graaf, L.J. Wisse, M.R.M. Jongbloed, M.J. Schalij, A.C. Gittenberger-De Groot, R.E. Poelmann. *Leiden University Medical Center, Leiden, Netherlands*

Purpose: During heart development addition of myocardial cells is necessary for proper development of chambers and cardiac conduction system. The additional myocardium derives from the second heart field by epithelial-to-mesenchymal transformation. Interestingly, RhoA (a small GTPase) is involved in epithelial-to-mesenchymal transformation relevant for the second heart field and regulates ion channels and gap junctions, important in electrical conduction system activity. We investigated RhoA expression in the developing cardiac conduction system, derived from the second heart field, and correlated the expression pattern to pacemaker potential based on atrial activation patterns.
Methods: Avian embryos (HH15-35, n=35) were stained for the myocardial proteins cTnI and Nkx2.5, second heart field transcription factor Isl-1, RhoA and the epicardial and epithelial-to-mesenchymal transformation marker WT-1. Electrophysiological recordings were conducted to evaluate the atrial activation pattern (Group A: HH20-23 (n= 25), B: HH24-27 (n = 28), C: HH28-HH31 (n = 14)).
Results: At HH17 the sinus venosus myocardium including the sinoatrial node (SAN) (right-sided, medio-lateral to the right cardinal vein) expressed Isl-1, RhoA and cTnI but not Nkx2.5. Additionally, Isl-1 expression was observed in the atrioventricular canal (atrioventricular node region) and in a cluster of cells medial of the left cardinal vein (transient left-sided SAN). At HH22 the expression patterns were maintained but the connection with the atrioventricular canal was lost. Isl-1 and RhoA expression diminished over time and in older stages (>HH28) RhoA expression was restricted to the definitive right-sided SAN and the atrioventricular node region. At this stage, the left-sided cluster of cells was no longer visible. In addition, right atrial activation preceded left atrial activation in the majority of the cases, however, a left dominant pacemaker signal was observed up to HH28.
Conclusions: Second heart field-derived myocardial cells express RhoA and are found in components of the cardiac conduction system including the definitive right-sided SAN, a transient left-sided SAN and the atrioventricular node. Electrical activity patterns revealed a left-sided transient pacemaker activity which disappears during development, suggesting that the potential pacemaker area initially covers both sides of the sinus venosus myocardium and later on becomes restricted to the right side. Furthermore, RhoA could have a clinically important function in the conduction system as expression is maintained in older stages.

P574 Effects of an atorvastatine treatment on atrial ion currents in rabbit

C. Eick, R. Laszlo, A. Menzel, B. Schreiner, J. Schreieck. *University, Tuebingen, Germany*

Purpose: Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are important in secondary prevention of cardiovascular events.

Also in treatment of atrial fibrillation, beneficial effects of statins have been reported due to "pleiotropic effects". However, little is known about potential "electrical" effects of statins in terms of modulation of atrial ion channels. In this study, effects of an atorvastatine treatment on atrial ion currents (L-type calcium current [ICa,L], sodium current [INa], transient outward potassium current [Ito], sustained outward potassium current [Isus] and inward rectifier potassium current [IK1]) of rabbits were observed.

Methods: Rabbits (New Zealand white, 2.5-3 kg) were randomly divided in 2 groups of 4 animals each. Rabbits were chosen as channel expression and atrial remodeling due to other causes (e.g. rapid atrial pacing) is similar to that in human atrium. Rabbits of the atorvastatine group (AG, n=4) received atorvastatine (10 mg/kg bodyweight, p.o.) for 7 days whereas placebo was given in the control group (CG, n=4).

Using patch clamp technique in whole-cell mode, current densities (L-type calcium current [ICa,L], sodium current [INa], transient outward [Ito], sustained outward [Isus] and inward rectifier [IK1] potassium current) were measured and compared between both groups.

Results: After 7 days of treatment with atorvastatine, there was a significant reduction of ICa,L current density (mean±SEM): 28.4±1.8 pA/pF [CG, n=20] vs. 15.3±1.5 pA/pF [AG, n=14], $p<0.001$, test-pulse±0 mV and INa current density 75.5±3.6 pA/pF [CG, n=17] vs. 32.7±3.3 pA/pF [AG, n=18], $p<0.001$, test-pulse -40 mV. Atrial potassium currents were not significant altered by atorvastatine treatment (Ito: 58.7±5.0 pA/pF [CG, n=20] vs. 47.6±5.1 pA/pF [AG, n=19], test-pulse +50 mV and Isus: 11.3±1.3 pA/pF [CG, n=20] vs. 13.1±1.4 pA/pF [AG, n=19], test-pulse +50 mV and IK1: 1.6±0.3 pA/pF [CG, n=17] vs. 1.4±0.3 pA/pF [AG, n=19], test-pulse - 90 mV).

Conclusions: Our results indicate that statins can modulate ion channel expression in rabbit atrium. However, functional consequences are not clear at the moment as the observed reduction of ICa,L and INa are rather proarrhythmic, as known from many other studies.

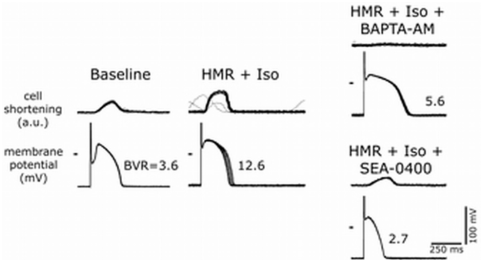
P575 Forward Na^+-Ca^{2+} exchange exaggerates beat-to-beat variability of repolarization duration in a cellular model of long-QT1 syndrome

D.M. Johnson[1], C.E. Pollard[2], J.P. Valentin[2], H.J.G.M. Crijns[1], N. Abi-Gerges[2], P.G.A. Volders[1]. *[1]Cardiovascular Research Institute Maastricht, Maastricht, Netherlands; [2]Astrazeneca R&D, Safety Assessment UK, Macclesfield, United Kingdom*

Introduction and Purpose: Intense β-adrenergic stimulation (βAS) can cause repolarization delay and torsades de pointes in long-QT1 (LQT1) syndrome. We have shown previously, both in vivo and in vitro, that beat-to-beat variability of repolarization duration (BVR) is increased by βAS in LQT1-mimicking conditions (pharmacological IKs block). Here we present a role of forward-mode Na^+-Ca^{2+} exchange (NCX) in exaggerating BVR in LQT1.

Methods: Transmembrane action potentials (APs) and cell shortening were recorded in single canine left-ventricular midmyocardial cells during intracellular pacing. LQT1 was mimicked by selective IKs block with 500 nM HMR1556. Isoproterenol (βAS) was added at 100 nM. Intracellular calcium was buffered with 5 μM BAPTA-AM. NCX was inhibited selectively by 300 nM SEA0400. BVR was quantified as short term variability: $\Sigma|APD90; i+1 \text{ minus } APD90; il/[nbeats \times \sqrt{2}]$.

Results: In LQT1 plus βAS, BVR exaggeration was almost completely rescued by intracellular-calcium buffering with BAPTA-AM (loss of contraction), despite causing increased APD. This also inhibited EAD and DAD formation. Block of NCX with SEA0400 also decreased BVR and abolished EADs. Figure shows representative AP examples, contractions and BVR for pacing cycle length 1000 ms.



Conclusion: Loss of βA-sensitive repolarizing IKs plus overriding of Ca^{2+}-dependent forward-mode NCX contribute to proarrhythmic BVR in LQT1 plus βAS.

P576 Effects of rapid augmentation of L-type calcium current on the voltage dependence of calcium release from the sarcoplasmic reticulum in rat ventricular myocytes

M. El Kadri[1], G. Hart[1], M. Hussain[2]. *[1]University of Liverpool, Liverpool, United Kingdom; [2]University of Bradford, Bradford, United Kingdom*

Purpose: L-type Ca^{2+} current (ICa) is the main trigger for calcium induced calcium release (CICR) from the sarcoplasmic reticulum (SR). The amount of Ca^{2+} released is usually strongly correlated to ICa amplitude. In this study, we investigated the effects of rapidly increasing ICa amplitude on CICR in the absence of changes in SR Ca^{2+} load.

Methods: Fura-2 loaded rat ventricular myocytes (n=5-10) were voltage clamped to -40mV (perforated patch clamp). Current-voltage and Ca^{2+} transient-voltage curves were constructed using 10 mV step depolarisations. To establish a constant SR Ca^{2+} load, each test pulse was preceded by a train of 5 conditioning pulses (–40 to 0 mV, 0.5 Hz). External bathing solutions were rapidly switched using a TTL-controlled piezoelectric device. Solutions containing 5.0 mM $[Ca^{2+}]_o$ (to increase driving force), 2.5 μM FPL 64176 (a Ca^{2+} channel agonist to increase Ca^{2+} channel open probability), or both were applied for 2.5 s prior to the test pulse to increase ICa amplitude.

Results: Increasing $[Ca^{2+}]_o$ from 1.0 to 5.0 mM increased ICa amplitude at all the potentials tested, although the increases were more pronounced at positive potentials (157±19% and 216±30% at 0 and +20 mV, respectively, $P<0.05$) compared to negative potentials (124±28% at -20 mV, $P>0.05$). These changes in ICa amplitude did not, however, significantly increase SR Ca release at 0 mV (105±5%, $P>0.05$) and only modestly increased $[Ca^{2+}]_i$ transient amplitude at -20 and 20 mV (134±11%, 137±18%, respectively, $P<0.05$). Similarly, application of FPL 64176 significantly increased ICa amplitude, although the effect was more marked at negative potentials (344±16%, 115±8% at -20 and 0 mV, $P<0.05$) compared to positive voltages (109±7% at +20 mV, $P>0.05$). A small increase in SR Ca^{2+} release was observed at negative potentials (e.g. 141±11 at -20 mV, $P<0.05$), but not at other potentials (110±3%, 107±10% at 0 and +20 mV, respectively, $P>0.05$)

The combined use of FPL and high $[Ca^{2+}]_o$ resulted in a dramatic increase in ICa amplitude throughout the whole voltage range (1113±43%, 225±10% and 210±11% at -20, 0 and +20mV, respectively, $P<0.05$). However, this was accompanied by a disproportionately modest increase in SR Ca^{2+} release; e.g. 155±14%, 112±2%, 117±10%, at -20, 0 and +20 mV, respectively, leading to a significant decrease in CICR gain (52±2%).

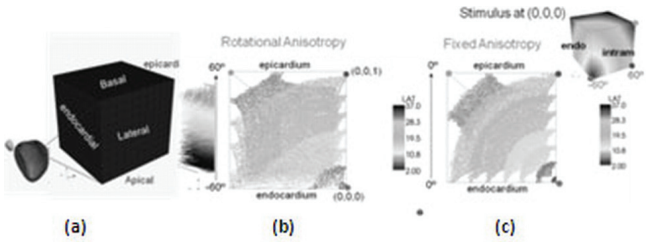
Conclusion: These data show that rapidly increasing ICa amplitude does not significantly alter CICR. Changes in SR Ca^{2+} release may therefore be mediated mainly by changes in SR Ca^{2+} load and/or ryanodine receptor activity, rather than by ICa amplitude.

P577 The role of the myocardial fiber orientation in homogenizing transmural electrical activation

R. Sebastian, B.H. Bijnens, A.F. Frangi. *Universitat Pompeu Fabra, Barcelona, Spain*

Myocardial muscle fibers are arranged helicoidally, gradually changing from epicardium (EPI) to endocardium (ENDO). This particular fiber arrangement enables the generation of a large EF, despite a relatively small myocyte shortening, thus optimizing mechanical performance. We investigated whether fiber orientation additionally plays a role in electrical excitation of the myocardium, since activation is starting from the endpoints of purkinje fibers at the ENDO and has to spread through the myocardium to reach the EPI. We used computer simulations (Cardiac Arrhythmias Research Package) in a realistic model of myocardial fiber orientation. To investigate different models in a reasonable amount of time, we used a simplified 3D geometry of a myocardial segment, representing the LV lateral wall from ENDO to EPI (Fig. 1a). Fiber orientation ranged from -60 to 60 degrees from ENDO to EPI. The activation was initiated from an ENDO point (a Purkinje fiber endpoint) and the activation isochrones were calculated and visualized.

Figure 1 shows the results of a realistic fiber orientation (1b) compared to fixed fibers (1c). Total activation took around 35 ms. It can be seen that the realistic fiber orientation, although showing slower overall activation, results in a bending of the spherical activation wave, thus making the propagation plane more parallel to the EPI surface and homogenizing arrival time at the EPI.



Conclusion: The helical arrangement of myocardial fibers contributes to more homogeneous transmural activation, thus additionally optimizing the onset and synchronicity of mechanical activation of different myocardial layers. Studying its behavior can be important to understand myocardial activation in pathologies where fibre orientation is disrupted (HVM, fibrosis).

P578 Adenosine A2A receptor inhibition stabilizes the rate dependent beat-to-beat response of L-type calcium current in human atrial myocytes

C.E. Molina[1], A. Llach[1], J. Fernandes[1], C. Munoz-Guijosa[1], J. Cinca[1], L. Hove-Madsen[2]. *[1]Hospital de Sant Pau, Barcelona, Spain; [2]Centro de Investigación Cardiovascular CSIC-ICCC, Barcelona, Spain*

Purpose: Electro-mechanical alternans heralds the onset of several cardiac arrhythmias, and adenosine A2A receptor (A2AR) stimulation favour the occurrence of beat-to-beat alternations in the L-type calcium current (ICa) at high stimulation frequencies. The purpose of this study was to test whether A2AR inhibiton is able to increase the threshold frequency for activation of ICa alternation in human atrial myocytes.
Methods: Isolated human atrial myocytes were subjected to patch-clamp technique in order to measure the L-type calcium current (ICa) activated by depolarization to 0 mV and the tail current (Itail) elicited upon repolarization. The stimulation frequency was increased stepwise from 0.2 to 2 Hz.
Results: In control conditions, uniform beat-to-beat patterns of both ICa and Itail were observed in all of 45 myocytes at low stimulation frequencies and throughout all stimulation frequencies in 8 of the 45 cells. In 26 of the 45 cells an alternating beat-to-beat pattern was observed at stimulation frequencies between 0.67 and 2 Hz. The alternating pattern was gradually replaced by an irregular pattern as the stimulation frequency was increased to 2 Hz, where an irregular pattern was observed in 35 of the 45 myocytes. When exposed to the selective A2AR antagonist ZM241385 (50 nM), a uniform pattern was maintained in a larger fraction of cells at higher stimulation frequencies. This was reflected in a shift in the frequency of appearance of non-uniform (alternating or irregular) beat-to-beat alternation from 1.5±0.2 Hz in control to 1.9±2 Hz with ZM241385 ($p=0.02$, n=17). A similar effect was seen when baseline activation of the A2AR was prevented by inclusion of adenosine deaminase (ADA, 2 units/ml) in the extracellular solution. Indeed, ADA shifted the frequency of appearance of non-uniform patterns from 1.3±0.1 Hz in control to 1.7±0.1 Hz ($p<0.001$, n=28). Infusion of 30μM adenosine, the natural A2AR ligand, through the patch pipette lowered the threshold for non-uniform patterns from 1.3±0.2 Hz in control to 0.6±0.2 Hz with adenosine. Subsequent inclusion of ZM241385 in the external solution reversed the effects of adenosine, increasing the threshold for non-uniform patterns from 0.6±0.2 to 1.4±0.2 Hz ($p<0.05$, n=4).
Conclusions: In human atrial myocytes, adenosine A2A receptor antagonism stabilizes the rate-dependent beat-to-beat response of ICa both at baseline and at elevated cytosolic adenosine levels. This points to the importance of adenosine A2A receptors in the dynamic regulation of intracellular calcium.

P579 Propafenone and Flecainide increase the current through human cardiac Kir2.1 channels

R. Caballero[1], R. Gomez[1], A. Barana[1], I. Amoros[1], D. Ponce-Balbuena[2], J.A. Sanchez-Chapula[2], J. Tamargo[1], E. Delpon[1]. *[1]Complutense University of Madrid, Madrid, Spain; [2]Centro Universitario de Investigaciones Biomédicas, Colima, Mexico*

Purpose: Propafenone (P) and flecainide (F) are two class Ic antiarrhythmic drugs widely used in the treatment of cardiac arrhythmias. Unfortunately, both exhibited also ventricular proarrhythmic effects that limit their use. The inward rectifying K^+ current (IK1), mainly carried by Kir2.1 channels, is critical in determining the resting membrane potential (RMP) and shaping the initial depolarization and the final repolarization phases of the cardiac action potential (AP). Furthermore, it has been demonstrated the importance of the IK1 increase in the establishment of a fast and stable reentry of spiral electrical waves (rotors) and fibrillation dynamics. Thus, the effects of P and F on human cardiac Kir2.1 channels have been studied.
Methods: Kir2.1 currents (IKir2.1) were recorded in transiently transfected in Chinese hamster ovary cells using the whole-cell configuration of the patch-clamp technique.
Results: F (0.5-20 μM) produced a concentration-dependent increase in IKir2.1, the effect being more marked at potentials positive than negative to the K^+ reversal potential (EK). Indeed, F (1 μM) increased ($P<0.05$) the IKir2.1 by 46.6±11% and 16.4±2.6% at -50 and -120 mV, respectively (n=6). The effects were apparent at extracellular K^+ concentrations of both 4 and 140 mM, but only blockade was observed when F was applied to the intracellular surface of the membrane in inside-out patches. When using an AP voltage clamp protocol, F increased the total charge flowing through Kir2.1 channels during the AP by 135±22% (n=6, $P<0.01$). P (0.5-50 μM) produced a concentration-dependent inhibition of IKir2.1 (IC50=4.7±0.6 μM) at potentials negative to the EK but increased the current at potentials positive to the EK (50.8±9.4% increase produced by 1 μM P at -50 mV, n=5). P (1 μM) increased the total charge flowing through Kir2.1 channels during the AP by 131±39% (n=7, $P<0.01$).
Conclusions: the results demonstrated that both P and F at therapeutically relevant concentrations increased the current through Kir2.1 channels an effect that could affect their Na^+ blocking properties by hyperpolarizing the RMP and contribute to their proarrhythmic effects.

CARDIAC REHABILITATION

P580 The Italian SurveY on carDiac rEhabilitation (ISYDE-2008). Patients characteristics and current provision of cardiac rehabilitation

R. Tramarin[1], S. De Feo[2], M. Ambrosetti[3], C. Riccio[4], M. Piepoli[5], F. Fattirolli[6], P.L. Temporelli[7], R. Griffo[8]. *[1]Fondazione Europea per la Ricerca Biomedica, Cernusco S/N, Italy; [2]Casa di Cura Dott. Pederzoli, Peschiera del garda, Italy; [3]Le Terrazze Clinic, Cunardo - Va, Italy; [4]A.O. S. Anna e S. Sebastiano, Caserta, Italy; [5]S Da Saliceto Hospital, Piacenza, Italy; [6]Ospedale Careggi, Firenze, Italy; [7]Istituto Scientifico - Fondazione Salvatore Maugeri IRCCS, Veruno, Italy; [8]La Colletta Hospital, Arenzano, Italy*

Background: comprehensive cardiac rehabilitation (CR) and secondary prevention are recognized as effective approach for cardiovascular risk reduction and long-term care of cardiac pts.
Aim: to provide specific information on characteristics of pts admitted to CR, diagnostic procedures, exercise and educational programs, treatment, and to compare current provision with National GL.
Methods: the ISYDE-2008 is a multicenter, longitudinal, prospective national registry, designed by the Italian Association for Cardiovascular Prevention Rehabilitation and Epidemiology to collect data on organization and core components of CR in Italy. The study population consisted of 2281 consecutive pts, discharged from 165 Italian CR centres from Jan 28th to Feb 10th 2008.
Results: age was 67±10.5 yrs (26.5% women). Indications for CR were: CABG in 30.1%, valvular surgery 15.8%, combined 7.5%, thoracic surgery 2.4%, ACS 8.8%, PTCA 14.2%, heart failure 12.5%, CPD 1%, angina 1.8%, other 5.8%. 67.0% of pts had ≥1 comorbidity: prior AMI 22.1%, PTCA 9.9%, cardiac surgery 11.0%, carotid atherosclerosis 7.0%, CPD 6.6%, abdominal aortic aneurism 1.8%, respiratory insufficiency 4.9%,renal failure 8.8%, hepatic disease 2.8%, neurological disease 6.4%, diabetes 20.8%, orthopedic disease 9.1%. 1159 pts (50.8%) had 3-5 CVD risk factors and 9.3% >5.
38.5% of pts had ≥1 complication during CR: 8.9% atrial fibrillation, 1.9% arrhythmias, 0.6% PM, 0.4% AMI, 0.7% stroke/TIA, 1.9% minor and 6.6% peripheral neurological damage, 7.1% anemia, 3.1 acute renal failure or 0.3% liver failure, 0.4% surgical wound revision, 1.4% thoracentesis, 0.1% pericardial drainage, 0.1% PNX, 0.1% redo surgery, 1.0% inotropic infusion, 1.0% mechanical ventilation, 0.04% pulmonary embolism, 2.9% infection, 1.4 transfusion, 15.7% other.
During CR 43.1% pts had a 6-min walk test at admission and 41.5% at discharge, 19.6% and 30.9% an exercise test, 5.3% and 6.9% a cardiopulmonary test; 0.5% electrical and 1.4% pharmacological cardioversion, 88% cardiacecho (LVEF >50% in 59%) and 16% vascular ultrasound.
At discharge, 72% pts received ACEi/ARBs, 68% b-blockers, 51% diuretics, 66% statins, 16% n-3PUFA, 26% oral anticoagulant, 66% ASA, 24% other antiplatelet agents, 2.4% LW Heparin, 19% nitrates, 5.4% digitalis, 19% CCBs, 9% insulin, 15.5%antidiabetics, 5.8% amiodarone, 6.2% anti-depressive. A long term prevention program was scheduled for 54% pts.
Conclusion: surveys and registries are effective means of assessing the implementation of GL. The ISYDE-2008 broad participation offers a detailed snapshot of current CR provision, organization and activities

P581 Comparison of hospital-based versus home-based exercise training in patients with heart failure: effects on functional capacity, quality of life, psychological symptoms, and hemodynamic parameters

H.K. Karapolat, E.D. Demir, Y.T.B. Turan Bozkaya, S.E. Eyigor, S.N. Nalbantgil, B.D. Durmaz, M. Zoghi. *Ege University Medical Faculty, Izmir, Turkey*

Objective: Heart failure (HF) is a common and disabling syndrome that is the final common pathway for a number of cardiac conditions. Despite major advances in the pharmacological treatment of HF, the number of patients afflicted with HF is rising yearly, and a large number of patients suffer from dyspnea, fatigue, diminished exercise capacity, and poor quality of life It has been suggested that exercise training is a crucial and effective method in the treatment of HF patients. In the majority of the studies that have been conducted in this area, either hospital or home-based exercise groups have been chosen as control groups, but no studies have compared the effects of these two types of exercise groups. Therefore, our study aims to compare the effects of home-based and hospital-based exercise programs on exercise capacity, quality of life, psychological symptoms, and hemodynamic parameters in HF patients.
Methods: Seventy-four patients were divided into either a hospital-based exercise (group 1) or a home-based exercise (group 2) group. Before and after the 8 week rehabilitation program, the patients in the two groups were compared with respect to functional capacity [maximal oxygen uptake (pVO2), a six minute walk test (6MWT)], quality of life (Medical Outcomes Study, the 36-item Short Form Survey, SF-36), psychological symptoms [Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI)] and hemodynamic parameters [(left ventricular diastolic dysfunction (LVDD), left ventricular diameter in systole (LVDS), Mitral Early diastolic peak flow velocity (E)/late diastolic peak flow velocity (A), Mitral E/Mitral early peak velocity (Em), Tei index, right ventricule systolic peak velocity (Sm), Tricuspid annular plane systolic excursion (TAPSE), systolic pul-

monary artery pressure (SPAP), left and right venricular ejection fraction (LVEF, RVEF)].
Results: After the exercise program, significant improvement were observed in pVO2, 6MWT and subscales of physical function, general health, and vitality of SF 36, as well as BDI, left ventricular ejection fraction (LVEF) in both groups ($p<0.05$). When the two exercise groups were compared, no significant differences were found between the two exercise groups regarding the variables that were analyzed ($p>0.05$).
Conclusion: In both the hospital-based and home-based exercise groups, significant improvement was observed in functional capacity, quality of life, depression symptoms and left ventricular ejection fraction. The administration of a regular exercise program is beneficial to HF patients.

P582 Changes in lifestyle and anthropometric measures in a novel family-centred community-based programme for cardiovascular disease prevention and rehabilitation

J. Jones[1], A. Mead[1], C. Jennings[1], E.L. Turner[2], S.B. Connolly[1], K. Kotseva[1], A. Holden[1], G. Fiumicelli[1], J. Stevenson[1], M. Hunjan[1] on behalf of The MyAction Group. *[1]Imperial College London, London, [2]London School of Hygiene and Tropical Medicine, London, United Kingdom*

We piloted a novel cardiovascular health programme integrating care of patients with coronary disease (COR) with asymptomatic high risk individuals (HRI) and their families all together in a community leisure facility.
Methods: COR, HRI >40 years (CVD risk >20% over 10 years) and their partners were invited to attend a group-based and individualised 16-week multidisciplinary (nurse-prescriber, dietitian, physical activity specialist & cardiologist) lifestyle & medical management programme. Smoking (self-report, breath carbon monoxide), diet (Mediterranean Score, anthropometric measures) and physical activity (7-day recall, aerobic fitness [Chester Step Test]) were assessed in all initially (IA) and at the end of programme (EOP).
Results: 306 patients (164 COR, 142 HRI) were invited to attend. Of these, 87 (61.3%) COR and 119 HRI (72.6%) attended the IA. 93 partners (59.6%) also attended. 59 COR (67.8%), 85 HRI (71.4%) and 58 (63%) partners attended the EOP assessment. Changes in diet and physical activity were observed (Table 1). 40 smokers (6COR, 21HRI, 10 partners) were identified at IA. 20 returned EOP of whom 5 were non smokers (0 cor, 4 HRI, 1 partner).

Table 1

	Cors (n=59)		HRI (n=85)		Partners (n=58)	
	IA	EOP	IA	EOP	IA	EOP
Mean Mediterranean Score	6.7	8.3	7.8	9.1	7.6	9.0
Δ (95% CI)	1.56 (1.0 to 2.1)*		1.3 (0.9 to 1.7)*		1.4 (1.0 to 1.9)*	
Proportion achieving physical activity recommendations (%)	17.0	64.2	17.2	71.9	20.4	35.3
Δ (95% CI)	47.2 (31.8 to 62.5)*		54.7 (40.9 to 68.4)*		44.9 (28.9 to 60.9)*	
Aerobic fitness (mean seconds achieved in CST)	253	330	318	391	304	374
Δ (95% CI)	77 (56 to 97)*		73 (50 to 97)*		70 (49 to 91)*	
Mean heart rate (beats/min) on CST at max level attained on initial CST	103.4	97.8	118.3	111.6	116.0	109.1
Δ (95% CI)	-5.6 (-8.9 to -2.2)*		-6.7 (-9.0 to -4.4)*		-6.9 (-9.5 to -4.2)*	
Mean body mass index (kg/m^2)	30.1	29.8	29.2	28.8	28.3	27.9
Δ (95% CI)	-0.3 (-0.6 to -0.6)*		0.7 (-0.8 to -0.2)*		-0.4 (-0.8 to -0.1)*	
Mean waist circumference (cm)	100.7	97.1	100.2	97.7	95.5	91.7
Δ (95% CI)	-1.0 (-2.0 to -0)*		-2.4 (-3.4 to -1.5)*		-1.9 (-2.8 to -1.1)*	

*$p<0.05$.

Conclusion: This novel programme successfully integrated the care of coronary patients, HRI and their partners with significant improvements in lifestyle, weight management and aerobic fitness.

P583 Adiponectin is reduced by exercise training in chronic heart failure patients. A prospective randomized controlled study

A.S. Ferraz[1], E.A. Bocchi[2], R.S. Meneghelo[1], C.H.V.B.G. Carvalhais[1], A.M. Doi[1], G.V. Guimaraes[2], A.R.C.N. Fuchs[1], L.E. Mastrocolla[1], A.G.M.R. Sousa[1]. *[1]Institute Dante Pazzanese of Cardiology, São Paulo, Brazil; [2]Heart Institute (InCor) University of São Paulo Medical School, São Paulo, Brazil*

Background: Adiponectin (Ad), is a newly discovered adipose tissue derived hormone. Recent studies have shown that increased Ad circulating level was associated with higher mortality in chronic heart failure (CHF) patients (pts). Exercise training (Ex) improves functional capacity, quality of life (QoL) and overload hormones evaluated by brain natriuretic peptide (BNP). The aim of our study was to investigate the role of long term Ex on Ad level.
Methods: 30 men, 54±9 yrs (mean ± sd), with non-ischemic CHF, functional class II-III, LVEF 27.7±6.5%, LVEDD 70.8±5.4 mm, peak oxygen consumption (VO2p) 17.4±3.0 mL/kg/min were randomized into 2 groups: Ex – 20 pts, and control (CO) – 10 pts, under unchanged optimal medical treatment. At baseline and at 6 months, all pts underwent maximal cardiopulmonary exercise testing, rest echo, Minnesota QoL score and Ad, BNP and HS-CRP plasma measurements. Ex was prescribed at the heart rate of the anaerobic threshold (AT). Statistics: The two way non parametric anova was used for Ad analysis.
Results: Ad level decreased only in the Ex group from 28.8 μg/dL (95% CI 18.2-39.5) (Md 23,9±5.1) to 11.2 μg/dL (95% CI 7.9-14.4) (Md 8.7±1.6) $p<0.0001$, but not in the CO group that changed from 26.2±4.5 μg/dL (95% CI 15.9-36.5) (Md 22.5±4.5) to 33.2 μg/dL (95% CI 10.0-56.4) (Md 16.3±10.2) (interaction group*time p=0,0006). Additionally, HS-CRP, BNP and QoL score, also decreased only in the Ex group (table). Cardiac function and dimensions by echo did not change in any group.

Variables	Ex-Before	Ex-After	CO-Before	CO-After
Peak VO2 (mL/kg/min)	17.2±3.0	21.2±4.2*	18.0±3.1	18.6±4.4
AT VO2 (mL/kg/min)	11.7±1.9	13.7±3.1*	11.8±2.0	11.7±2.0
Adiponectin (μg/dL)	28.8±5.5	11.2±1.6*	26.2±4.5	33.2±10.2
HS-CRP (mg/L)	7.1±1.5	3.5±1.2*	7.0±2.5	6.7±1.7
BNP (pg/mL)	473±93	253±70*	494±91	338±105
QoL (Minnesota)	42.3±5.9	25.5±5.7*	38.3±5.9	36.5±4.8

*$p<0.05$, median = Md, mean ± SEM.

Conclusions: Ex enhanced maximal and submaximal exercise capacity, and QoL. The reduction on Ad and BNP levels may have prognostic implications. HS-CRP improvement suggests that exercise could have effect on inflammatory profile of these end-stage CHF pts. Ex program is efficacious and should be stimulated.

P584 Anemia does not preclude increments in cardiac performance during a short period of intensive, exercised based cardiac rehabilitation

F. Bellotto[1], P. Palmisano[2], L. Compostella[3], P. Guida[2], M. Zaccaria[2], T. Setzu[3], A. Cati[1], A. Maddalozzo[3], S. Favale[2], S. Iliceto[1]. *[1]Department of Cardiac, Thoracic and Vascular Sciences. University of Padua. Via Giustiniani, 2 3512, Padova, Italy; [2]UO Cardiologia, Policlinico, Bari, Italy; [3]Istituto Codivilla Putti, Cortina D'ampezzo (Bl), Italy*

Purposes: Anemia, defined by the World Health Organization as a hemoglobin concentration <13.0 g/dl in men and <12.0 g/dl in women, occurs frequently after cardiac surgery, in chronic heart failure patients, and in the setting of acute coronary syndromes. For these reasons, anemia is theoretically far more common in cardiac rehabilitation units but it is not yet known whether this could negatively influence cardiovascular performance indexes immediately after an acute cardiac event. The purposes of this study were to define the prevalence of anemia in subjects admitted for intensive cardiac rehabilitation and to investigate the safety and efficacy of an intensive exercise-based cardiac rehabilitation on cardiac patients with and without anemia.
Methods: 307 subjects (75.9% males) with a mean age of 64±13 years, completed a two-week training period of three sessions per day, six days a week, of respiratory, aerobic and callisthenic exercise, without any major adverse effects. All were subjected to a six minute walking test (6MWT) at enrolment, as well as to a second 6MWT and to a cardiopulmonary test before discharge. The primary endpoint was the increment in the distance walked in relation to hemoglobin levels during the observation period.
Results: Anemia was detected in 234 patients (76.2% of the entire population) and the distance walked increased from 384±117 m. at baseline to 458±109 m. ($p<0.001$) after a mean period of 11.72±3 days. A direct correlation was found between hemoglobin concentrations and the absolute distance walked ($r=0.49$; $p<0.001$) as well as peak VO2 ($r=0.35$; $p<0.001$). Anemic patients walked a significantly shorter distance at baseline and at discharge than nonanemic patients ($p<0.001$); however, both groups showed the same increment in the distance walked: 73.65±61 m in anemic vs 73.79±61 m in nonanemic patients ($p=0.99$).
Conclusions: Our data indicate: 1) a high prevalence of anemia in the study population and 2) in spite of a clear reduction in exercise capacity, anemia does not preclude increments in cardiac performance during a short period of intensive, exercise-based cardiac rehabilitation.

P585 Functional evaluation in octogenarians patients undergoing a cardiac rehabilitation program: correlation between six minute walking test and Rivermead Mobility Index

F. Scimia, I. Casadei, E. Cerquetani, M. Piccoli, A. Villa, S. La Carrubba, A. Salustri. *U.O. Cardiologia Policlinico Luigi di Liegro, Rome, Italy*

Introduction: The aim of this study was to evaluate, in octogenarians patients admitted to a cardiac rehabilitation program, if the Rivermead Mobility Index (RMI) (scale of mobility) is correlated with the functional capacity assessed with the Six Minute Walking Test (6MWT).
Methods: We selected 108 consecutive patients ≥ 80 years (M/F = 53/55, mean age 82.5±2.7 years, after cardiac surgery n = 72, heart failure n = 36) admitted to our Center for a cardiac rehabilitation program. All patients were evaluated with the RMI and underwent 6MWT both at admission (RMI1 and 6MWT1) and after (RMI2 and 6MWT2) a period of daily physical training. The ratios RMI2/RMI1 and 6MWT2/6MWT1 were calculated as indexes of improvement (IM).

Results: The average in hospital stay was 20±11 days with an average of 11.9 sessions of training for patient. The average distance walked at 6MWT1 and 6MWT2 was 193±116 and 278±122 mt, respectively ($p < 0.001$). The average score of RMI1 and RMI2 was 8.5±3.4 and 13.1±2.9, respectively ($p < 0.001$). The values of 6MWT1 and RMI1 results were significantly correlated (rho = 0.56, $p < 0.001$). The RMI IM was correlated significantly to 6MWT IM (rho = 0.309, $p = 0.002$). At multivariate analysis, RMI IM was found predictive of 6MWT IM even after correction for age, gender, lenght of hospitalization and number of sessions of training.
Conclusions: In octogenarians patients, a cardiac rehabilitation program exerts an improvement of both RMI and 6MWT. RMI IM is independently related to 6MWT IM. Thus, RMI could be potentially used to evaluate the improvement of functional capacity even in patients who can not undergo to 6MWT.

P586 Sustained control of cardiac risk factors in a community multi-vascular prevention program at one year: comparisons of coronary artery disease, non-disabling stroke and peripheral artery disease

N.B. Giacomantonio, W. Firth. *QEII HSC Community Cardiovascular Hearts in Motion Program, Halifax, Canada*

Purpose: Cardiac rehabilitation (CR) programs have successful impact on cardiovascular risk factor management for patients with Coronary Artery Disease (CAD) but there are few comparable comprehensive programs for patients with non-disabling stroke or Peripheral Artery Disease (PAD). Another limitation of the traditional CR programs is a lack of follow-up beyond the 3 months, and variable long term impact evaluation. The Community Cardiovascular Hearts in Motion (CCHIM) program delivers managed care to patients at high risk for vascular disease as well as those with established vascular disease. The purpose our research was to compare risk factor outcomes between patients with CAD, Stroke, PAD and high risk, and evaluate the sustainability at one year.
Methods: CCHIM is a multidisciplinary, 3 month multi-vascular program with risk factor management, nutrition intervention, weekly exercise, and education with application of behavior change strategies. To date, 224 patients completed the program with one year follow-up data. Clinical outcome data, anthropometric measures, and medication adherence was evaluated at study entry, 3 months, 6 months and 1 year.
Results: CCHIM program effect at 3, 6 and 12 months for LDL change was -4% (medications were unchanged), -1.8% and – 6.4% ($p=0.02$) respectively for CAD patients (n=129). Stroke patients (n=23) had changes of -13.4% ($p=0.05$) at 3M, -7.3% at 6M, and -14.2%($p=0.04$) at 12M. PAD patients (n=7) had changes of -6.9% at 3M, -11.2% at 6M, and -20.8%($p=0.07$) at 12M. Primary prevention patients (n=65) showed the most profound LDL changes with -5.1% at 3M, -16.3% at 6M ($p=0.0002$) and -13.5% at 12M ($p=0.0002$). Similar trends were noted in weight changes. CAD patients had significant weight loss with changes of -2.1% ($p=0.0001$) at 3M, -2.2% ($p=0.0001$) at 6M, and -1.5% at 12M ($p=0.001$). Stroke patients had weight loss changes of -2.1% ($p=0.01$) at 3M, -2.7% ($p=0.002$) at 6M, and -1.7% at 12M and PAD patients had weight loses of -2.4% at 3M, -3.5% at 6M, and -5.5% at 12M. Equally significant changes were noted in blood pressure management, glycemic control and exercise capacity for all groups, with a maintained risk factor reduction at one year.
Conclusions: Patients with CAD, non-disabling stroke and PAD equally benefit from participating in a comprehensive vascular management program as noted in LDL cholesterol and weight outcomes. On average all patient groups; CAD, Stroke, PAD and high risk Primary Prevention patients achieved LDL-cholesterol targets. Multiple vascular risk factor improvements were sustained for one year beyond the 3 month program effect.

P587 Inter-practice variation in assessed needs for cardiac rehabilitation

N. Peek, R. Goud, M.M. Van Engen-Verheul, I.M. Hellemans, A. Hasman, N.F. De Keizer. *Academic Medical Center, Amsterdam, Netherlands*

Purpose: To determine inter-practice variation in assessed patient needs for cardiac rehabilitation, and identify the influence of different measurement instruments on assessed needs.
Methods: A prospective cohort study was conducted in 16 Dutch cardiac rehabilitation outpatient clinics from November 1, 2005 to October 31, 2006. Participating clinics all followed the Dutch Guidelines on Cardiac Rehabilitation, and assessed each patient's rehabilitation needs by determining exercise capacity, psychosocial status, marital status, employment status, and lifestyle parameters. Intra-cluster correlation coefficients (ICCs) were calculated for all rehabilitation needs and lifestyle parameters, before and after adjusting for patient case mix (demographic factors and reason for referral to cardiac rehabilitation), and stratified by assessment method.
Results: Data from 4157 patients were analyzed. High ICCs were found for insufficient exercise capacity (0.301±0.085), unrealistic subjective exercise capacity (0.165±0.046), and social problems (0.188±0.037); moderate ICCs were found for psychological problems (0.096±0.027), absence of partner (0.052±0.017), unhealthy eating habits (0.080±0.026), and inactive lifestyle (0.059±0.015); ICCs were low for expected work problems (0.010±0.006) and smoking status (0.000±0.001). Adjustments for case mix hardly influenced ICCs. The assessment of patients' exercise capacities by clinical interview led to a lower percentage of patients being judged as having an insufficiency than when bicycle ergometry or incremental Shuttle walk test was used (73.4% vs. 84.1%, $p<0.01$). Similarly, clinical interviews led to 32.8% of the patient being judged as having an unrealistic subjective exercise capacity, whereas use of the MacNew questionnaire resulted in 62.3% of the patients being judged as such ($p<0.01$). Also for psychological and social problems, use of the MacNew leads to significantly higher percentages of positive assessments.
Conclusions: The assessments of cardiac rehabilitation needs are subject to moderate to high inter-practice variation, especially when they are solely based on clinical judgment. In addition, the numbers of patients judged to have rehabilitation needs are smaller in that case. We recommend that guidelines for cardiac rehabilitation provide well-defined and unambiguous procedures for assessing the rehabilitation needs of patients. Assessing the needs solely by clinical judgment should be avoided. Reliable and practical instruments should be developed for the assessment of cardiac patients' lifestyle parameters.

P588 A low glycemic and insulinemic diet (LOGI) is superior to the traditional low fat diet in improving cardiac function and metabolic syndrome in spite of a 55% reduction of antidiabetic therapy

H. Von Bibra[1], G. Wulf[2], P. Heilmeyer[2]. [1]*Staedtisches Klinikum Muenchen, Bogenhausen, Munich, Germany;* [2]*Rehabilitation Clinic Ueberruh, Isny, Germany*

Purpose: Diastolic myocardial dysfunction in people with type 2 diabetes and metabolic syndrome (D) may be improved by optimizing metabolic control by medical therapy. The beneficial effects of optimized postmeal glucose levels by medical therapy and also by life style changes are known for cardiovascular risk/disease. We tested the hypothesis that, by lowering postmeal glucose levels, a low glycemic and insulinemic diet (LOGI) exerts superior effects on cardiac function and metabolism in D patients compared to the traditional low fat diet (LoFa).
Methods: 25 overweight D patients on oral antidiabetic therapy (OAD) or diet (n=5) without overt heart disease were studied before and after a 3-week rehabilitation programme with LOGI and compared to 16 D patients with the same inclusion criteria (diet alone in 6 patients) on isocaloric LoFa. Systolic (S') and diastolic (E') myocardial velocity was measured by tissue Doppler. Metabolic control was assessed before and 2 h after a standardized breakfast (400 kcal) with LoFa at baseline (carbohydrate 55%, fat 25% and protein 20%) and with LOGI composition (25%, 45% and 30%, respectively) at the final test for the LOGI group. Both groups had supervised aerobic training 2 hours a day.
Results: After LOGI diet, HbA1c ($p<0.0001$), fasting glucose ($p<0.001$) and postmeal glucose (144±52 to 123±34 mg/dl, $p<0.01$) decreased although OAD was reduced by 55% (diet alone in 16/25 vs. 5 initial patients). Cholesterol ($p<0.04$) and triglycerides decreased (192±131 to 145±81 mg/dl, $p<0.001$). Weight parameters decreased ($p<0.001$). Physical work capacity increased by 20% ($p<0.004$) whilst blood pressure decreased ($p<0.003$). S' increased ($p<0.05$) and so did E' from 9.6±1.1 to 10.5±1.4 cm/s ($p<0.001$) into the normal range. After LoFa, there were similar reductions in weight, HbA1c, fasting glucose and cholesterol. But postmeal glucose and triglycerides were unchanged whilst OAD was reduced by 30% (diet alone in 9/16 vs. 6 initial patients). Also blood pressure, S' and E' (10.8±1.7 to 10.7±1.5 cm/s) remained unchanged.
Conclusion: In overweight people with D during a 3 weeks rehabilitation programme, LOGI but not the traditional low fat diet improved postmeal glucose levels, triglycerides, blood pressure and cardiac function. The associated 55% reduction of OAD may be beneficial for a reduction of public health costs.

P589 Long-term beneficial effects of an expanded cardiac rehabilitation after an acute myocardial infarction or coronary artery by-pass grafting: a five year follow-up of a randomized controlled study

C. Edstrom-Pluss[1], E. Billing[2], C. Held[3], P. Henriksson[1], A. Kiessling[1], M. Rydell Karlsson[1], N.H. Wallen[1]. [1]*Karolinska Institutet, Dept of Clinical Sciences, Danderyd Hospital, Stockholm, Sweden;* [2]*Dept of Medical Sciences, Uppsala University, Uppsala, Sweden;* [3]*Uppsala Clinical Research Centre and Department of Cardiology, University Hospital, Uppsala, Sweden*

Background: Current guidelines broadly recommend comprehensive cardiac rehabilitation after an acute myocardial infarction (MI) or post coronary artery bypass grafting (CABG). However, the evidence of the effects of cardiac rehabilitation on cardiovascular morbidity is limited. There are few long term randomized trials comparing expanded cardiac rehabilitation and usual care.
Material and methods: A single centre prospective randomized controlled clinical trial was performed which included 224 patients with a recent MI or who were planned for CABG. Patients were randomized to either expanded cardiac rehabilitation (intervention group n=111) including a 5 days stay at a "Patient Hotel" after discharge, increased physical training, cooking sessions and, importantly, a one year stress management program, or to routine rehabilitation (control group n= 113). Five-year follow-up data were obtained on all included patients from the registry of the Swedish National Board of Health and Welfare. The primary

endpoint was first cardiac event, including cardiovascular (CV) death, myocardial infarction or readmission for CV disease.
Results: The primary endpoint occurred in altogether 121 patients (54%). There was a significant reduction in CV events in the expanded rehabilitation group compared to the control group when data were collected from the start point of rehabilitation (47.7% vs. 60.2%; hazard ratio 0.69; 95% CI 0.48 -0.99; p=0.049). This was mainly due to a reduction in MI in the intervention group compared to the control group (4.5% vs. 13.3%; hazard ratio 0.47; 95% CI 0.21-0.97; p=0.047). The days at hospital during the 5-year follow-up were significantly less in patients who received expanded rehabilitation as compared to patients in the control group (p=0.02).
Conclusion: An expanded multifactorial cardiac rehabilitation program after an acute myocardial infarction or coronary artery by-pass grafting reduced cardiovascular morbidity and days at hospital for cardiovascular reasons.

P590 Survival after coronary artery bypass grafting in adult and elderly patients

F. Cacciatore[1], F. Mazzella[1], G. Longobardi[1], A. Nicolino[1], G. Furgi[1], C. Napoli[2], F. Rengo[1]. *[1]Division of Cardiac Rehabilitation, IRCCS, Salvatore Maugeri Foundation, Telese Terme - Bn, Italy; [2]Dept of General Pathology and Excellence Center on Cardiovascular Disease, II University, Naples, Italy*

To date there is no exact information on the outcome of elderly patients after coronary artery bypass grafting (CABG). Whether the increase in distance walked after a therapeutic intervention translates into improved survival in patients after CABG is still debated. The aim of the study was to investigate the prognostic value of distance walked in 6 min (6MWT), ejection fraction (EF) and change in distance walked between admission and discharge in 6 min (Δ 6MWT) on survival in patients undergoing CABG. Patients were admitted to cardiovascular rehabilitation unit. We studied 940 CABG patients enrolled consecutively from October 2000 to July 2004. A standardized echocardiography and 6MWT was performed at baseline and at discharge. All patients were followed up until April 2006. Mean age of the 940 patients was 63.8±8.9 years (range 34-84). Mean EF was 52.1±8.9%, mean 6MWT was 303.7±103.4 meters and mean Δ 6MWT was 90.7±68.5. After a mean follow-up of 44.7 months, 93 patients (9.9%) died. Cox regression analysis demonstrated that EF and 6MWT were predictive of mortality independently by both the effect of age and Δ 6MWT. When patients were divided into two subgroups according to age (< 65 and ≥ 65 years), EF was predictive in the group of patients with age < 65 years, while distance walked at baseline was predictive of mortality in patients with age ≥ 65 years (Table 1).

Table 1. Cox regression analysis to eval

Variables	All			<65 years			≥65 years		
	HR	95,0% CI		HR	95,0% CI		HR	95,0% CI	
Age	1.009	0.971	1.048	1.061	0.968	1.162	1.084	0.985	1.194
6MWT	0.997	0.993	0.999	1.001	0.995	1.006	0.994	0.988	0.999
EF	0.952	0.920	0.985	0.911	0.864	0.960	0.982	0.936	1.031
Δ6MWT	0.998	0.993	1.002	0.997	0.990	1.003	1.002	0.994	1.010

6MWT = distance walked in 6 min; EF = ejection fraction; Δ6MWT = change in distance walked in 6 min between admission and discharge.

Our results show that EF and 6MWT provide independent prognostic information in CABG patients. Different results are observed between adult and elderly patients in which functional capacity (addressed by means of 6MWT) predicted survival.

P591 Prior exercise training improves survival, infarct healing and left ventricular function after myocardial infarction

D.J.G.M. Duncker, M.C. De Waard. *Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Purpose: There is evidence that exercise initiated after a cardiac event, such as myocardial infarction (MI), ameliorates left ventricular (LV) remodeling and dysfunction and improves clinical outcome. In contrast, there is substantially less information available as to whether prior exercise affords any protection in situations where, despite regular exercise, a major cardiovascular event like MI does occur. Consequently, we investigated the effects of exercise prior to an acute MI on survival, LV remodeling and dysfunction, and determined whether exercise prior to and after MI provides superior protection compared to either exercise intervention alone.
Methods: After 2-weeks of voluntary exercise (~6 km/night) on a running wheel (EX), or sedentary (SED) housing, MI was induced in C57Bl/6 mice (>18 mice per group) after which exercise stopped (EX-MI-SED, SED-MI-SED) or continued (EX-MI-EX, SED-MI-EX) for a period of 8-weeks.
Results: MI was associated with reduced survival (~60% versus 100% survival in sham-operated mice) and with marked LV dilation as well as a decrease in LV fractional shortening from 37±1% in sham mice to 8±1% in SED-MI-SED mice (P<0.05). Furthermore, collagen content and apoptosis more than doubled in the remote surviving myocardium. Exercise after MI (SED-MI-EX) had no effect on survival (~60%), infarct-size and LV remodeling, but prevented fibrosis and apoptosis in the remote surviving myocardium and improved LV fractional shortening (from 8±1% in SED-MI-SED to 13±1% in SED-MI-EX; P<0.05). Exercise prior to MI (EX-MI-SED), improved post-MI survival to ~80% (P<0.05). In addition, fibrosis and apoptosis in the remote area were almost prevented, while LV fractional shortening improved (11±1%) compared to SED-MI-SED (P<0.05 versus). Interestingly, the infarct-area was ~60% thicker than in either SED-MI-SED or SED-MI-EX, which was accompanied by thickening of the subendocardial rim of surviving cardiomyocytes. Surprisingly, the beneficial effects of either pre-MI or post-MI EX alone were partly lost in EX-MI-EX mice. It could be speculated that is somehow related to the increased self-imposed exercise load in the first week post-MI in EX-MI-EX versus SED-MI-EX mice.
Conclusion: Exercise prior to or after MI blunted left ventricular dysfunction. In addition, exercise prior to MI improved survival, possibly due to improved scar healing. These findings indicate that when regular physical activity fails to prevent an acute MI it can still exert a beneficial effect by improving left ventricular function and survival after MI.

P592 Cardiovascular risk benefits of the CHOICE (Choice of Health Options In prevention of Cardiovascular Events) program are maintained for four years: randomised controlled trial

L. Neubeck[1], J. Redfern[2], T. Briffa[3], R. Ascanio[2], S.B. Freedman[1]. *[1]The University of Sydney, Sydney, Australia; [2]ANZAC Research Institute, Concord Hospital, Sydney, Australia; [3]University of Western Australia, Perth, Australia*

Purpose: Approximately 80% of acute coronary syndrome (ACS) survivors do not access cardiac rehabilitation (CR). We have shown patients participating in CHOICE compared with usual care have significantly lowered multiple risk factors at one year than those in usual care. We examined whether these benefits were maintained for four years.
Methods: ACS survivors not accessing CR were randomised to either conventional care (n=72) or CHOICE (n=72) comprising tailored risk factor reduction packaged as a clinic visit plus three months telephone support. Blinded risk assessment occurred at baseline, 12 months and 48 months.
Results: Follow up was comparable for CHOICE and controls (68% complete). Groups were equivalent at baseline, with the majority male (74% vs 75%) and of similar mean age (62±14 vs 67±11years) respectively. At 12 months, the CHOICE group achieved a significantly lower risk profile than controls. At 48 months, the controls only had significantly lower total cholesterol (TC) than baseline, whereas the CHOICE group maintained the favourable risk profile with significantly lower TC, systolic blood pressure (SBP), proportion inactive or smokers and proportion with three or more risk factors (table).

Results of the CHOICE program at 4 years

	Control			CHOICE		
	baseline (n=72)	12 months (n=69)	48 months (n=50)	baseline (n=72)	12 months (n=67)	48 months (n=56)
TC mmol/l (SD)	4.6 (0.8)	4.7 (0.9)	4.2 (0.8)**	4.7 (0.9)	4.0 (0.9)*	4.0 (0.8)**
SBP mmHg (SD)	137 (18)	144 (19)	136 (14)	136 (17)	132 (15)*	133 (14)**
BMI kg/m^2	30.5 (5.9)	31.3 (5.9)	30.2 (6.6)	29.5 (5.9)	28.9 (5.7)*	28.3 (6.9)
Smoker, n (%)	16 (23)	16 (23)	9 (19)	10 (14)	4 (6)*	2 (5)**
Inactive, n (%)	54 (75)	47 (68)	32 (69)	45 (62)	19 (28)*	17 (42)**
≥3 risk factors	44 (61)	49 (68)	34 (47)	35 (49)	11 (15)*	12 (17)**

*P<0.05 within a group at one year compared to baseline, **P<0.05 within a group at 4 years compared to baseline.

Conclusions: The brief, patient-centred CHOICE program significantly improved coronary risk profile in ACS survivors over 12 months and these benefits were maintained for four years.

P593 New model of home-based tele-ecg-monitored cardiac rehabilitation in patients with heart failure: safety, effectiveness, quality of life and compliance

E. Piotrowicz, M. Stepnowska, R. Baranowski, M. Bilinska, M. Piotrowska, T. Zielinski, R. Piotrowicz. *Institute of Cardiology, Warsaw, Poland*

Home-based early cardiac rehabilitation (CR) following hospitalization seems to be the most acceptable for chronic heart failure (HF) patients (pts).
Purpose: To compare safety, effectiveness, quality of life (QoL) and compliance in two models of CR in HF pts. Model 1 - interval training on ergometer in outpatient facilities, Model 2 – a new model of home tele-ecg-monitored specially prepared walking training.
Methods: The study group comprised 152 pts (58.3±9.9 years) with HF (NYHA II and III; EF<40%). After three weeks of clinical stability, the pts were randomized into two groups and underwent an 8-week CR. Group 1 (75 pts) underwent Model 1. Group 2 (77 pts) underwent Model 2. The programmed workload level for two groups was 40% - 70% of peak VO2.
In order to perform Model 2, a special device was created which made it possible to: (1) do the training according to a preprogrammed plan, (2) send ecg via mobile phone to the Monitoring Center. Impact of CR on exercise tolerance (ET) and QoL was assessed by delta peak oxygen consumption (ΔpVO2) and delta points

(∆SF-36) in Medical Outcome Study Short-Form respectively, as a result of comparing pVO2 and SF-36 points from the beginning and the end of the program.
Results: The groups were comparable in terms of demographic data, baseline clinical parameters and pharmacotherapy.
Safety of CR: In neither group were there deaths, necessity for hospitalization because of HF decompensation. In Group 1, there was one atrial fibrillation (AF) event. In Group 2, there were 3 AF events including one asymptomatic discovered by ecg monitoring, and 2 non sustained ventricular tachycardia events. Arrhythmias occurred during daily activity and were irrelevant of CR.
Impact of CR on ET and QoL: CR significantly improved all parameters studied in both groups. In Group 1 ∆pVO2 was +1.06±2.42 (ml/min) p=0.0021, ∆SF-36 was -12.77±31.53 points p=0.0253. In Group 2 ∆pVO2 was +1.83±2.65 (ml/min) p=0.0001, ∆SF-36 was -9.57± 25.60 points p=0.0435. The differences between Group 1 and Group 2 were statistically insignificant.
Compliance in CR: 15pts (20%) in Group 1 discontinued CR. All pts in Group 2 completed CR.
Conclusions: (1) In HF pts in the early phase after discharge, a home tele-ecg-monitored walking training is as safe, effective and improves the quality of life as a traditional ergometer training performed in out-patient facilities. (2) Home tele-ecg-monitored physical training improves compliance in CR. (3) Due to the limitations associated with the disease a home tele-ecg-monitored training seems an optimal form of comprehensive CR for HF pts.

P594 Less weight gain and a healthier lifestyle after quitting smoking in EUROACTION: a family based preventive cardiology programme for coronary patients

A. Mead[1], C. Jennings[1], J. Jones[1], E.L. Turner[2], S.B. Connolly[1], K. Kotseva[1], G. De Backer[3], D. De Bacquer[3], G. Frost[1], D. Wood[1] on behalf of EUROACTION Study Group. *[1]Imperial College London, London, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]University of Ghent, Ghent, Belgium*

Purpose: Patients and partners attending the EUROACTION hospital programme had support of a nurse, dietitian and physiotherapist to stop smoking, eat more healthily, become physically active (PA) and lose weight. We assessed the impact of this programme on weight change at 1 year in those that quit smoking in this cluster randomised controlled trial in 6 European countries.
Methods: Patients included in this analysis had quit smoking at the time of their cardiac event, or whilst attending the programme. Intervention patients received a comprehensive lifestyle management programme. All quitters (validated by breath CO ≤6ppm) were assessed for changes in weight, waist, diet and PA. Measurements included a food habit questionnaire, 7-day PA recall.
Results: Using random effects meta-analysis, anthropometric, dietary and PA changes were compared in the 142 (43.8%) patients who quit smoking in intervention with the 45 (34.9%) patients in a random sub-sample from usual care (Table 1).

Table 1

Change from inital to 1 year assessment	Intervention (n=142)	Usual Care (n=45)
Change in mean weight (kg) (95% CI)	+1.7 (0.16:3.2)†	+3.9 (2.9:5.0)†
Difference in change (95% CI)*	-2.32 (-4.23,-0.41)†	
Change in mean waist (cm) (95% CI)	+1.5 (-1.0:4.0)	+4.5 (1.1:8.0)†
Difference in change (95% CI)*	-2.1 (-7.4:3.1)	
Change in mean BMI (kg/m^2) (95% CI)	+0.56 (0.01:1.11)†	+1.11 (0.77:1.61)†
Difference in change (95% CI)*	-0.61 (-1.36:0.15)	
Change in proportion meeting physical activity target (≥30min, ≥4/wk) (95% CI)	+34.7 (14.6:54.7)†	+8.2 (-19.4:35.8)
Difference in change (95% CI)	+26 (-6.6:58.7)	
Change in proportion meeting fruit & veg target (>400g/d) (95% CI)	+35.8% (23.2:48.4)†	+1.4 (-21.7:24.5)
Difference in change (95% CI)	+33.0 (9.5:56.5)†	
Change in proportion meeting oily fish target (≥3/wk) (95% CI)	+21.7 (0.1:43.3)†	-3.7 (-14.4:7.1)‡
Difference in change (95% CI)	+20.7 (-2.3:54.9)	

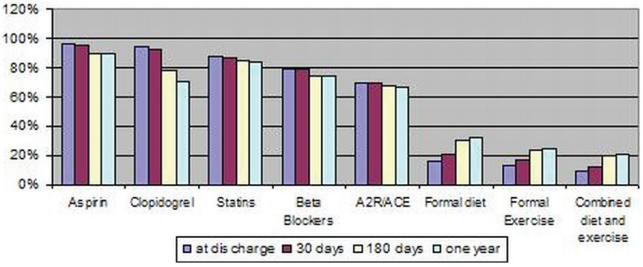
*Adjusted for age, sex, diabetes & years smoked (INT n=139; UC n=44); †p≤0.05; ‡t test used.

Conclusions: The EUROACTION programme significantly mitigated the weight gain normally associated with smoking cessation compared with usual care and this was achieved through a healthier diet and increased PA levels. In coronary patients, smoking cessation should therefore be integrated with a comprehensive diet and PA programme.

P595 12-month patterns of supportive therapies in acute coronary syndrome patients undergoing PCI in 2007-08: results from the AntiPlatelet Treatment Observational Registry (APTOR)

A. Bakhai[1], A. Iniguez[2], J. Ferrieres[3], C. Schmitt[4], M. Sartral[5], M. Belger[4], U. Zeymer[6] on behalf of APTOR investigators. *[1]Barnet and Chase Farm NHS Trust, Barnet, United Kingdom; [2]Hospital de Meixoeiro, Vigo, Spain; [3]CHU de Toulouse - Hopital de Rangueil, Toulouse, France; [4]Eli Lilly and Company Ltd, Windlesham, United Kingdom; [5]Eli Lilly and Company Ltd, Paris, France; [6]Institute for MI Research, Ludwigshafen, Germany*

Purpose: To describe the use of lifestyle supportive therapies in patients admitted to hospital with an acute coronary syndromes (ACS) and undergoing percutaneous coronary intervention (PCI).
Methods: the Antiplatelet Treatment Observational Registry (APTOR) is a prospective, international observational study that recruited ACS patients undergoing PCI in 2007-08, capturing practice patterns, resource use and QoL over a 12-month duration.
Results: A total of 1525 ACS-PCI patients were recruited: France – 483; Spain – 538; UK – 504. 38% patients presented with STEMI, 37% with NSTEMI, and 25% with UA. Post-discharge data are available for a total of 1335 (88%) patients: France – 394 (82%); Spain - 497 (92%); UK – 444 (88%). The figure demonstrates that while the use of pharmacological therapies is reasonable at 12 months, other key supportive therapies have very poor uptake. Across the three countries 21% of patients were reported as being on both diet and exercise programmes. At 12 months post-PCI, these percentages were: France – 44%; Spain – 16%; UK – 5%. Of the 1150 patients where QoL VAS data was available at both discharge and 12 months, overall mean change was 16.8 (sd=31.2). This varied from 10.6 (sd=26.4) for exercise only, to 18.0 (sd=31.9) for those not on supportive therapy. Mean change in VAS by country was: France – 17.0 (sd=30.7); Spain 21.0 (sd=33.2); UK 11.0 (sd=27.8).



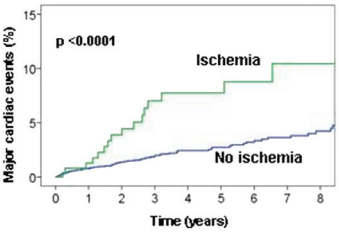
Conclusions: Our carefully conducted prospective registry in patients with life threatening events, who have interventional and pharmacological resources committed to them, have poor uptake of lifestyle therapies, and there is a marked variation across countries. There is an important need to determine and increase factors related to uptake of dietary and rehabilitation therapies after an acute coronary syndrome.

SPORT AND EXERCISE PHYSIOLOGY

P596 Prognostic value of exercise echocardiography in patients with suspected but not previously known coronary artery disease and normal exercise ECG

A. Bouzas Mosquera, J. Peteiro, F.J. Broullon, N. Alvarez Garcia, V.X. Mosquera, A. Garcia Campos, O. Prada, J.P. Abugattas, L. Garcia Bueno, A. Castro Beiras. *Hospital Universitario A Coruña, A Coruña, Spain*

Purpose: To assess the value of exercise echocardiography (EE) for predicting outcome in patients with suspected but not known coronary artery disease (CAD) and normal exercise electrocardiogram (ECG).
Methods: We evaluated 2851 consecutive patients (1446 men, mean age [± SD] 59.3±12.9 years) with interpretable resting ECG and suspected but not known CAD who underwent treadmill EE and did not develop chest pain or ischemic ECG changes during the tests. Wall motion score index (WMSI) was evaluated at rest and with exercise, and the difference (∆WMSI) was calculated. Ischemia was defined as the development of new or worsening wall motion abnormalities with exercise. End points were major cardiac events (MACE, i.e., cardiac death or myocardial infarction). Patients who were revascularized during follow-up were censored at the time of the procedure.
Results: A total of 293 patients (10.3%) developed ischemia on EE. During a mean follow-up of 4.2±3.2 years, 83 patients experienced a MACE. The 5-year MACE rate was 2.7% in patients without ischemia vs. 7.8% in those with ischemia (p<0.001). The association of ischemia and outcome remained significant after stratification by pretest probability of CAD. In the multivariate analysis, ∆WMSI remained an independent predictor of MACE (HR 3.59, 95% CI 1.42-9.07, p=0.007). The addition of the EE results to the clinical, resting echocardiographic and exercise treadmill data significantly increased the global chi-square of the model for the prediction of MACE (p=0.009).



Conclusions: EE provides significant prognostic information in patients with no prior CAD despite a normal exercise ECG. Patients with abnormal results on EE, who might be misdiagnosed or stratified incorrectly on the basis of exercise ECG results alone, might benefit from appropriate management.

P597 Exercise stress test results in patients with bare metal stents or drug eluting stents: pathophysiological and clinical implications

A. Di Monaco, R. Nerla, G.A. Sgueglia, C. Aurigemma, R. Mollo, L. Barone, G. Pinnacchio, C. Pisanello, G.A. Lanza, F. Crea. *Catholic University of the Sacred Heart, Rome, Italy*

Background: Drug eluting stents (DES) have dramatically reduced restenosis in patients undergoing PCI, but they seem to be associated with increased coronary endothelial dysfunction compared to bare metal stents (BMS). Exercise stress test (EST) was shown to be of limited value to predict coronary events in PCI patients, but there are scarce data in patients with stent implantation.
Methods: We studied 160 patients with coronary artery disease (CAD) (60±9 years, 135 men) who underwent complete revascularization by PCI with coronary stent implantation. 86 patients (53.7%) received ≥1 BMS and 74 (46.3%) ≥1 DES. The two groups were comparable as to age, gender, cardiovascular risk factors and severity of CAD (1.3±0.5 vessels treated in the BMS group vs 1.3±0.4 vessels treated in the DES group). EST was performed 1 month after PCI. Clinical outcome was assessed at a median follow-up of 18 months (range, 3 to 36 months).
Results: Patients with DES had a significant higher rate of positive EST (≥1 mm ST segment depression) compared to those with BMS (49% vs 30%; p=0.02). During follow-up, patients with BMS had a higher incidence of target vessel revascularization compared to DES (16% vs 5%; p=0.04), but patients with DES had a higher rate of hospitalization for acute myocardial infarction compared to patients with BMS (10% vs 4%; p=0.06). At multivariate Cox-regression analysis the only predictor of target vessel revascularization was time to 1 mm ST depression (p=0.003), whereas only the duration of exercise (p=0.03) and DES use (p=0.05) predicted the occurrence of hospitalization for acute myocardial infarction. Finally, time to 1 mm ST depression was the only predictor of the composite endpoint of target vessel revascularization or hospitalization for acute myocardial infarction (p=0.02).
Conclusions: DES implantation seems to be associated with a higher rate of positive EST, compared to BMS, 1 month after the procedure, likely due to a higher prevalence of endothelial dysfunction. EST seems to be helpful in predicting clinical outcome in patients who underwent coronary stent implantation.

P598 Endothelial dysfunction in normotensive adolescents with exaggerated blood pressure response during treadmill test

A. Gonzalez, E. Silva, G. Bermudez, J. Villasmil, S. Briceno, M. Bracho, C. Esis. *Instituto de Investigacion y Estudios de Enfermedades Cardiovasculares, Maracaibo, Venezuela*

Purpose: To evaluate endothelial function in normotensive adolescents with exaggerated blood pressure response during exercise.
Methods: This was a cross-sectional study conducted with 157 high school students (80 boys and 77 girls), aged between 13 to 18 years old (15.0±1.6), normotensive, without smoking habits, non-obese, normolipidemic and normal glucose. An exaggerated blood pressure response was defined as a systolic pressure rise of more than 70 mm Hg, during the treadmill test with Bruce protocol. The endothelial function was assessed through endothelium-dependent vasodilation with the reactive hyperemia test by high-resolution vascular ultrasound. The cohort was split into quartiles, according to flow-mediated dilation (FMD). The study comparison was made between the lowest quartile versus the rest of them.
Results: An exaggerated blood pressure response was observed in 13 adolescents (8.3%), 10 (13.0%) females and 3 (3.8%) males (P=0.036). For adolescents in the lowest FMD quartile, a higher prevalence of exaggerated blood pressure response was observed, in comparison with the others quartiles (17.5 vs. 5.1%, respectively; P=0.014). Even after adjustment for factors known to affect endothelial function, the logistic regression analysis revealed that an exercise-induced hypertension was a predictor of impaired FMD (OR=3.924; I.C. 95%:1.233-12.488).
Conclusions: Normotensive adolescents with exercise-induced hypertension have impaired endothelium-dependent vasodilation. Exercise blood pressure may thus be a useful marker of nitric oxide bioactivity, and hence an important cardiac prognostic factor.

P599 Screening for anomalous proximal coronary artery trees in 360 competitive athletes and non-athletes with 3-Dimensional MR coronary angiography: feasibility for clinical implication and findings

N.H.J. Prakken, M.J. Cramer, M.A. Olimulder, B.K. Velthuis. *University Medical Center Utrecht, Utrecht, Netherlands*

Purpose: Under 35 years of age, 15% of sudden cardiac death is caused by a coronary artery anomaly (CAA). Although rare and mostly asymptomatic, only a "malignant" coronary artery course between aorta and pulmonary artery can lead to fatal ischemia during exercise.
Can free-breathing 3-dimensional magnetic resonance coronary angiography (3D MRCA) be used to identify the proximal anatomy of CAA in competitive athletes and non-athletes?
Methods: 360 healthy asymptomatic men and women aged 18-60 years (37% women) were selected and underwent free-breathing 3D MRCA angiography with the Steady State Free Precession protocol: 55 elite endurance athletes (exercising >18 hrs/wk), 152 regular endurance athletes (9-18 hrs/wk), and 153 healthy matched non-athletes (exercising ≤3 hrs/wk). The 3D dataset was screened for CAA.
Results: Technically satisfactory 3D MRCA's were obtained in 335 subjects (93%). 14 (4%) showed an abnormality 4 (1%) had a malign variant CAA with a right coronary artery origin from the left sinus of Valsalva coursing between the aorta and pulmonary artery. 6 showed bridging of a left coronary artery segment; 3 had asymptomatic stenosis of the right coronary, 1 of the left.
CAA diagnosis was confirmed by multidetector CT coronary angiography. Overall 3D MRCA quality was better in athletes than controls due to lower heart rates with longer diastolic resting periods.

CAA judgeability on 3D MRCA

	Non-athletes		Regular athletes		Elite athletes	
	n	%	n	%	n	%
Unsatisfactory	12	8	8	5	5	9
Moderate	26	17	16	11	5	9
Good	107	70	106	70	35	64
Excellent	8	5	22	14	10	18

Conclusion: 3D MRCA can be used as part of the standard Cardiac MRI protocol to screen young competitive athletes and non-athletes for anomalous proximal coronary arteries.

P600 The impact of race on electrocardiographic repolarisation changes in highly trained female athletes: relevance to pre-participation ECG screening for cardiomyopathy

J.C. Rawlins[1], F. Carre[2], M. Papdakis[1], N. Chandra[1], C. Edwards[1], S. Sharma[1]. [1]*King's College Hospital, London, United Kingdom;* [2]*University Hospital, Rennes, France*

Sinus bradycardia, high voltage QRS complexes and repolarisation changes are recognised electrocardiographic features in athletes. Certain repolarisation changes, specifically T wave inversions and marked (>0.2mV) ST segment elevation overlap with those observed in HCM and ARVC. Male black athletes (BA) with morphologically normal hearts show a significantly higher prevalence of T wave inversions compared with male white athletes (WA) (28% vs 4%) raising concerns about the impact of pre-participation screening in countries with a high number of BA. The prevalence and significance of T wave inversions is unknown in female athletes. We examined the prevalence and significance of T wave inversions in highly trained black and white female athletes.
Methods: Between 2004 & 2009, 320 female athletes (38% black; mean age 20.4yrs±4.4 range 14-35yrs) participating in a range of ball, racket & endurance sports at National level were evaluated with 12 lead ECG and 2D echocardiography. Measurements of the amplitude & duration of the P, Q, R, S, & T waves and ST segment were taken from the resting 12-lead ECG. Standard echocardiographic measures of cardiac chamber size were made in all athletes. Left ventricular hypertrophy was defined as a maximum left ventricular wall thickness (LVWT) ≥12mm.
Results: Female BA exhibited a significantly higher prevalence of T wave inversions (14% vs 2% p<0.001), deep (>-0.2mV) T wave inversions (2% vs 0% P<0.001) and significant ST segment elevation (11% vs 1% P<0.001) compared with female WA. T wave inversions in BA were confined to the anterior precordial leads (V1-4). In contrast, T wave inversions in WA were observed only in leads III and aVF. Pathological Q waves, ST depression, left bundle branch block, and epsilon waves were absent in the entire study population. There was no relationship between T wave inversions or ST elevation and magnitude of LVWT in either group (BA p=0.12, WA p=0.07). None of the athletes demonstrated any echocardiographic features of cardiomyopathy.
Conclusion: As with male BA, a substantial proportion of female BA show T wave inversions which is greater than the documented prevalence in male WA. As with male BA, T wave inversions are confined to leads V1-4 and, are not associated with echocardiographic features of cardiomyopathy. Such changes may be regarded as innocent ethnic variants. T wave inversions in the lateral leads or deep T wave inversions in any leads other than V1-4 were not observed and their presence should instigate further investigation in female BA. The recommendations in female WA remain as per the current ESC consensus protocol.

P601 The athlete's heart: influence of gender on cardiac morphological and electric patterns

G. Kervio[1], J. Gueneron[2], L. Uzan[2], H. Douard[3], F. Carre[4], N. Ville[1]. [1]INSERM, CIC-IT 804, Rennes, France; [2]National Institute of Physical Education and Sport, Paris, France; [3]Cardiology Department, Haut Levêque Hospital, Bordeaux, France; [4]INSERM, U642, Rennes, France

The limits of athlete's heart patterns have been largely described. However, to our knowledge, few studies have compared the heart patterns between top-level trained men and women.

Aim: This prospective multicentric study aimed to describe echocardiographic (echo) patterns and electrocardiographic (ECG) parameters recorded in a large population of French top-level athletes according to their gender.

Methods: Anthropometric, echo and ECG data have been analyzed in 347 athletes (246 men), aged 16 to 32 yrs old. All athletes performed an intermediate sport discipline ($\geq$ 8 hours.week-1), in regards to the dominant bioenergetic component. Soccer and rugby players were excluded.

Results: Men were younger than women (19.5±4.5 vs 20.7±5.1 yrs old, $p<0.05$). They had higher values of body surface area (BSA) and body mass index (BMI) ($p<0.01$).

ECG parameters: Mean resting heart rate was not different between men and women (58.2±9.9 vs 58.6±9.4 beats min^{-1}). Concerning classical ECG parameters duration, only the QT duration corrected with Bazett's formula was higher in women (391.9±20.2 vs 403.7±22.4, $p<0.001$). Men have more incomplete right bundle branch blocks than women (53.2 vs 34.6%, $p<0.01$). According to Pellicia's modified classification (2000), distinctly abnormal ECG were more frequent in men (11.4 vs 4.0%, $p<0.05$) with electrical left ventricular hypertrophy (10.2 vs 3.0%, $p<0.05$), inverted T wave > 2 mm except for DIII, AVR, V1 (0.4 vs 1.0%) and Q wave depth $\geq$ 4 mm (1.6 vs 0.0%).

Echo parameters: Men have higher absolute values than women ($p<0.001$), for left ventricular (LV) end diastolic (5.41±0.4 vs 4.95±0.3 cm), interventricular septum wall thickness (IVSWT, 1.00±0.1 vs 0.85±0.1 cm), posterior wall thickness (0.91±0.1 vs 0.83±0.1 cm), LV mass (198.0±43.9 vs 143.8±27.7 g), aortic diameter (3.04±0.3 vs 2.78±0.3 cm) and left atrial diameter (3.58±0.4 vs 3.33±0.4 cm). After indexation with BSA, gender's differences disappear except for IVSWT and LV mass, which remain higher in men (0.52±0.07 vs 0.48±0.08 cm/m^2 for IVSWT/BSA and 101.5±18.5 vs 81.7±15.3 g/m^2 for LV mass/BSA, $p<0.001$).

Conclusion: Gender must be taken into account concerning some athlete's heart patterns. Distinct abnormal ECG, mainly electrical LVH, is more frequent in men. Concerning echocardiography, classical absolute parameters are more increased in men. However, after BSA indexation, most of the difference disappears.

P602 Impact of physical exercise on parameters of arterial stiffness and wave intensity measured at carotid artery level

O. Vriz[1], F. Antonini-Canterin[2], S. Carerj[3], M. Bettio[1], D. Pavan[4], E. Leiballi[2], R. Enache[5], E. Bossone[6], G.L. Nicolosi[2]. [1]Cardiology, San Daniele Del Friuli, Italy; [2]Azienda Ospedaliera S. Maria Degli Angeli, Pordenone, Italy; [3]Policlinico Universitario, Messina, Italy; [4]Cardiology, San Vito Al Tagliamento, Italy; [5]Institute of Cardiovasc.Diseases C.C.Iliescu/Inst. De Boli CV, Bucharest, Romania; [6]CNR-Istituto di Fisiologica Clinica, Lecce, Italy

Background: The positive role of physical exercise on cardiovascular system is well-known. There is little information about the impact of different degrees of physical activity on parameters of arterial stiffness and wave intensity (WI), measured at the carotid artery level in normal subjects.

Methods: We examined 78 normal subjects (asymptomatic subjects, without known cardiovascular pathology, 54 men, mean age: 41±15 years). Our study population was divided in 3 groups considering the degree of physical exercise (sedentary n=29; leasure activity n=38; competitive sports n=11). All subjects underwent a comprehensive carotid ultrasound study (using a Prosound Alfa 10 Aloka echocardiographic machine) and parameters of arterial stiffness were assessed at the level of right common carotid artery. The following indices were measured: beta index, arterial compliance (AC), pulse wave velocity (PWV) and WI expressed as (dp/dt)(dU/dt). The first peak of WI, which represents the forward compression wave, was assessed. The group differences were adjusted for age and assessed using ANOVA test.

Results: The indices of carotid stiffness were significantly different in the 3 groups (table). The AC was significantly higher with increasing physical exercise. Beta index and PWV were significantly lower in subjects performing competitive sports. When adjusted for age, this difference was not statistically significant. The WI was significantly higher, independently of age, in subjects performing competitive sports.

Conclusions: In normal subjects, physical exercise has a positive impact, in terms of decreased carotid arterial stiffness and increased WI.

Stiffness indices and WI in study groups

	Group 1	Group 2	Group 3	p value	p adjusted for age
Beta Index	6.3±2	5.5±2.2	3.3±0.9	0.000	Ns
AC, mm^2/kPa	0.78±0.3	0.92±0.3	1.4±0.4	0.000	0.01
PWV, m/sec	5.6±0.9	5.2±0.8	3.9±0.6	0.000	0.06
WI, mmHg m/s^3	17.4±10.5	19.7±10.5	50.5±26.5	0.000	0.001

P603 Early changes in VEGF, angiopoietin-2 and erythropoietin in response to acute exposure to hypoxia: differentiation between resting and submaximal exercise challenge

M. White[1], M.G. Sirois[1], J. Laramee[1], L. Bussieres[2], C. Poirier[3], P. Nguyen[1], A. Mathieu[3], H. Ross[4], P. Mayer[3]. [1]Montreal Heart Institute and University of Montreal, Montreal, Canada; [2]Centre Hospitalier du Centre du Valais, Sion, Switzerland; [3]Sleep Clinic of Hotel Dieu Hospital and University of Montreal, Montreal, Canada; [4]Toronto General Hospital, Toronto, Canada

Purpose: Chronic exposure to hypoxia increases plasma levels of some markers of angiogenesis, such as vascular endothelial growth factor (VEGF). The impact of acute exposure to hypoxia on the changes in selected markers of angiogenesis (stress) during poikilocapnic hypoxic challenges (11.5% O2) at rest compared with submaximal exercise has not been investigated in humans. The objective of this study was to investigate the effects of poikilocapnic hypoxic challenges, in a resting state for 20 minutes and followed by 5 minutes of exercise on the changes in selected markers of angiogenesis in 10 healthy volunteers and two organ transplant subjects.

Methods: Twelve subjects, 8 male and 4 female including two transplant subjects (one heart, one kidney), aged of 42.8±13.4 years were recruited for the study. Peak VO2 achieved on a bicycle ergometer was 37.1±6.7 (27.6-50.6) ml/kg/min. Subjects completed the investigation (Richalet protocol) prior departure for Mera Peak (6476 meters) in Nepal. Samples for the determination of VEGF, angiopoietin-1 and 2 (Angio-1 and Angio-2), erythropoietin (EPO) were harvested in normoxia, after 20 minutes of hypoxia at 11.5% and following 5 minutes of hypoxic submaximal exercise set at a workload corresponding to 30% of peak VO2max. Hemodynamics, echocardiographic parameters and oxygen saturation were measured during the hypoxic challenges.

Results: See Table.

O2 saturation and selected biomarkers

	O_2 saturation (%)	VEGF (pg/ml)	Angio-1 (pg/ml)	Angio-2 (pg/ml)	EPO (pg/ml)
Baseline	97.4±1.1	58.1±36.4	5876±2359	1892±588	11.1±13.6
Rest (11.5%)	72.3±12.3*	59.6±28.6	5494±2284	1852±611	11.1±15.0
Exercise (11.5%)	69.8±7.8*	82.8±48.4*	10001±9222	2056±532*	13.5±17.6*

Mean ± SD. *$p<0.05$ vs baseline. Two transplant patients presented similar changes compared with the 10 healthy subjects.

Conclusions: Exposure to normobaric hypoxia combined with low intensity exercise caused an early and significant increase in selected mediators of angiogenesis. No effect is measured after 20 minutes of exposure at 11.5% O2 concentration in resting state. These data challenge the use of exposure to low O2 content during rest compared to exercise as a stimulus to enhance cardiovascular performance.

P604 Initial experience with real time exercise magnetic resonance imaging

G.V. Szantho[1], M.S. Turner[1], R. Duerden[1], R. Greenwood[1], A.G. Stuart[1], J. Fulford[2], M.P. Frenneaux[3], M.C.K. Hamilton[1]. [1]University Hospitals Bristol, Bristol, United Kingdom; [2]University of Exeter, Exeter, United Kingdom; [3]University of Birmingham, Birmingham, United Kingdom

Purpose: Several methods have been used to study the heart during stress. Pharmacological stress is flawed, as it does not mimic real physical exercise. We set out to find a non-invasive method of providing accurate left ventricle (LV) volume measurements during continuous exercise, as volume changes reverse immediately on ceasing exercise.

Methods: We developed a device that allows prone exercise within the bore of a MRI scanner, using resisted knee flexion, and then studied the feasibility of MRI assessment of ventricular volumes during continuous exercise. We used real time non-gated MRI to produce images suitable for volume analysis during free-breathing exercise.

We examined 6 healthy volunteers [all male, mean age 36 years, range 22-49] and assessed LV volumes under the following four conditions:

1. Supine rest - standard MRI (expiratory breath held steady state free precession – 7 mm thick slice every 10 mm).
2. Prone rest standard MRI.
3. Prone rest real time MRI (free breathing 10 mm thick contiguous slices).
4. Prone real time MRI during submaximal exercise.

Real time MRI volumes were assessed by visually determining end-diastole (ED), end-systole (ES), and manually contouring the cavity to determine blood volume (V) per slice. Volumes per slice position were summed to determine LVEDV and LVESV. Stroke volume (LVSV) was determined by subtracting LVESV from LVEDV. Mean and standard deviations of LVEDV, LVESV and LVSV were recorded.

Results: 1. All subjects achieved a reasonable level of sub maximal exercise to a mean heart rate of 101 beats per minute [range 88 to 114] and all studies were of diagnostic quality.

2. Standard prone and supine volume measurements are highly correlated [>0.85]

3. Real time and standard volume measurements are highly correlated [>0.86]. Real time MRI consistently showed higher LVEDV and LVESV. This is likely due to lower temporal resolution leading to an overestimation of LVESV; reduced spatial resolution leading to an overestimation of blood pool; and finally standard imaging was acquired during a breath hold, which effects preload and cardiac output.
4. LVEDV increased by a mean of 13.1ml [95% CI -5.5 to 31.7], LVESV fell by a mean of 11.8ml [95% CI 3.6 to 19.9], and stroke volume rose in all subjects during exercise.
Conclusions: This pilot study has demonstrated that real time exercise MRI is feasible and that ventricular volumes can be measured using real time MRI with reasonable accuracy. The consistency seen in stroke volume under the different conditions and its ability to demonstrate sensitivity to change makes it the ideal variable to use for research.

P605 Intense physical exercise adversely affects monocyte function

F.S. Czepluch[1], R. Barres[2], K. Caidahl[2], A. Krook[2], J. Zierath[2], J. Waltenberger[1]. *[1]Maastricht University Medical Center, Maastricht, Netherlands; [2]Karolinska Institute, Stockholm, Sweden*

Intact monocyte function is crucial for cardiovascular repair. Regular physical exercise is an important CAD prevention tool. In contrast, acute training interventions can induce temporary impairment of immunological functions. We investigated whether short-term, intense endurance exercise affects monocyte function. 13 young, healthy, inactive individuals (< 2h sport/week) participated in a 3-weeks intense endurance training consisting of 2 exercise sessions/day (60 min running, 90 min cycling). Training intensity corresponded mainly to the lactate threshold level. The training led to a significant increase in VO2max from 42.9 to 49.3 ml/kg/min ($p<0.01$). Venous blood samples were taken before, immediately after the 3-weeks training and after a 4-weeks recovery period (without sport). Monocytes were isolated from peripheral blood. Monocyte chemotaxis towards the (patho)physiologically important ligands Monocyte Chemoattractant Protein-1 (MCP-1), Vascular Endothelial Growth Factor-A (VEGF-A) and Transforming Growth Factor-β1 (TGF-β1) as well as various serological markers were investigated.
At study start, MCP-1-induced monocyte migration measured 231%. It declined to 185% after the training period ($p<0.01$) and improved only partially within the following recovery period (200%; $p<0.05$ compared to baseline). For VEGF-A- and TGF-β1-induced chemotaxis (186% and 185% at baseline), the training effect was even more dramatic, as monocyte chemotaxis towards these ligands was completely inhibited directly after the training period, and remained so after 4 weeks of recovery. Monocyte chemokinesis (i.e. random migration) as well as VEGF-A and TGF-β1 blood levels were unchanged during the study course. The serum level of the inflammatory chemokine MCP-1 decreased during the study and was significantly lower after the 4-weeks recovery compared to study start ($p<0.01$). Total blood antioxidant capacity was improved at this time point ($p<0.01$).
An intense 3-weeks sport training in young, healthy, inactive individuals impairs monocyte chemotaxis. A subsequent 4-weeks recovery period does not lead to complete cell function recovery. These data show for the first time that the known positive cellular sport effects are not applicable to monocyte chemotaxis after a short-term, tiring exercise training. Presumably, this acute intervention did not leave enough time for adaptation processes to occur within the monocytes. The observed transient monocyte dysfunction indicates that the used training intensity was probably too high for allowing proper cardiovascular repair and it should therefore not be recommended to CAD patients.

P606 Chronic physical exercise produces an electrophysiological stabilizer effect on ventricular myocardium that is independent of the myocardial cholinergic neurons activity

M. Zarzoso, J. Guerrero, L. Such-Miquel, I. Trapero, G. Parra, B. Diaz, A. Cebria, L. Such Belenguer, F.J. Chorro, A. Alberola. *University of Valencia, Valencia, Spain*

Authors have reported that physical training could prevent against ventricular fibrillation (VF), although the underlying exact mechanisms are not completely understood. It is well-known that the dispersion of refractoriness and other modifications produced by electrophysiological instability of myocardium are a key in the initiation and maintenance of VF. We hypothesized that training could increase myocardial electrical stability. To test this hypothesis we have analyzed the similarity among the local activation waves of the induced VF in a model of isolated heart from trained rabbits. We have also considered interesting to investigate the role of the myocardial cholinergic neurons on the obtained results. Five NZW rabbits were submitted to a training program and four were not trained. After training rabbits were anaesthetized (ketamine, 10 mg/kg i.v.), killed, their hearts excised, isolated and perfused in a Langendorff system. A pacing electrode and a plaque with 256 recording electrodes were positioned on the left ventricle. VF was induced by pacing. We used an analysis that allows to obtain an index of regularity (IR). IR quantifies, as a percentage, the signal regularity and indicates the similarity among local activation waves recorded by each electrode. IR was analyzed in control and trained groups at the onset of VF and 30, 60, 90, 120, 150, 180, 240 and 300 s after. VF was reverted in order to determine other parameters in sinus rhythm. After atropine administration (1 μM), VF was again induced and IR determinations were performed 30, 60, 90, 120, 150, 180, 240 and 300 s after. An ANOVA test with repeated measures was applied. Results are shown in the table. VF spontaneously reverted to sinus rhythm in the third and fourth minute in two trained animals. Although data are not shown, no differences before and after atropine were observed within control and trained group.

Index of regularity

	0s	30s	60s	90s	120s	150s	180s	240s	300s
Control	82±6 (n=4)	83±4 (n=4)	83±4 (n=4)	82±5 (n=4)	83±3 (n=4)	85±4 (n=4)	85±3 (n=4)	85±3 (n=4)	87±4) (n=4)
Trained	88±4 (n=5)	90±3* (n=5)	90±2* (n=5)	90±2* (n=5)	90±3* (n=5)	88±3 (n=5)	88±3 (n=4)	89±4 (n=4)	87±4 (n=3)

Mean and SD of IR values (as a percentage) at different times of VF. *p<0,05 respect to control, at the same moment of the experiment.

In conclusion, the electrophysiological stability of ventricular myocardium could increase by regular exercise and it does not appear to be due either to extrinsic nor intrinsic parasympathetic control.

P607 Hypertensives with an exaggerated exercise blood pressure response are characterized by arterial stiffening, augmented asymmetric dimethylarginine and osteopontin levels

K. Dimitriadis, C. Tsioufis, D. Syrseloudis, C. Thomopoulos, D. Chatzis, E. Tsiamis, E. Andrikou, D. Tousoulis, A. Michaelides, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: A hypertensive response to exercise (HRE) is associated with high cardiovascular risk, while elevated levels of asymmetric dimethylarginine (ADMA) and osteopontin (OPN) are related to atherosclerosis progression. In this study we sought to determine the relationships of HRE with ADMA, OPN and arterial stiffness in essential hypertensives.
Methods: 156 newly diagnosed never treated non-diabetics with stage I to II essential hypertension [96 men, mean age=51 years, office blood pressure (BP)=151/97 mmHg] with a negative treadmill exercise test (Bruce protocol) were divided into those with HRE (n=47) (peak exercise systolic BP $\geq$210mmHg in men and $\geq$190 mmHg in women) and those without HRE (n=109). In all subjects arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV) values, by means of a computerized method (Complior SP) and venous blood samples were drawn for estimation of metabolic profile, ADMA and OPN concentrations.
Results: Patients with HRE compared to those without HRE were older (56±8 vs 51±6 years, $p<0.05$), had greater 24-h systolic BP (143±10 vs 132±8 mmHg, $p<0.05$), while did not differ regarding metabolic profile and left ventricular mass index (p=NS for all). Patients with HRE as compared to those without HRE exhibited greater levels of ADMA (0.64±0.05 vs 0.51±0.06 μmol/l, $p<0.0001$), OPN (81.6±14.5 vs 38.5±11.1 ng/ml, $p<0.0001$) and PWV (8.9±1.5 vs 7.4±0.9 m/sec, $p<0.0001$). In the total population, peak exercise systolic BP was related to 24-h systolic BP ($r=0.257$, $p<0.05$), PWV ($r=0.229$, $p=0.002$), ADMA ($r=0.248$, $p=0.005$) and OPN ($r=0.219$, $p<0.05$). Regarding OPN, it was associated with age ($r=0.229$, $p<0.05$), body mass index ($r=0.373$, $p<0.05$), 24-h systolic BP ($r=0.269$, $p<0.0001$), ADMA ($r=0.259$, $p<0.05$) and PWV ($r=0.412$, $p<0.0001$). Multiple regression analysis showed that apart from 24-h systolic BP ($b=0.225$, $p<0.0001$) and male sex ($b=0.295$, $p<0.05$), ADMA ($b=0.234$, $p=0.006$) and OPN ($b=0.178$, $p<0.05$) were independent predictors of peak exercise systolic BP. Furthermore, analysis of covariance revealed that PWV, ADMA and OPN values remained significantly different between groups after adjustment for confounders ($p<0.05$).
Conclusions: In essential hypertension, a HRE is accompanied by a state of increased arterial stiffening, endothelial dysregulation and progressive atherosclerosis, as reflected by PWV, ADMA and OPN values. The interrelationships of ADMA and OPN with exercise BP response and stiffness, further support that diffuse vascular dysfunction contributes to HRE-related risk in hypertension.

P608 Haemostatic balance disorders and the exaggerated blood pressure response to exercise treadmill testing in pre-hypertensive non-smoking men

O. Papazachou[1], A. Bratsas[1], S. Massias[1], C. Thomopoulos[1], D.P. Papadopoulos[2], M. Daskalaki[2], E. Michalopoulou[1], M. Fragkaki[1], T.H. Makris[1]. *[1]Department of Cardiology, "Elena Venizelou" General & Maternity Hospital, Athens, Greece; [2]Departement of Cardiology, Laiko General Hospital, Athens, Greece*

Purpose: Exaggerated blood pressure response to exercise (exBPR) has been associated with autonomic and endothelial dysfunction. Given that endothelium has a foremost place to the modulation of the haemostatic properties, we investigated the level of haemostatic balance disorders in pre-hypertensive non-smoking men with ExBPR to exercise treadmill testing.
Methods: From an initial male population of 127 consecutive untreated subjects who were referred to our hypertensive unit for BP evaluation, we studied 49 pre-hypertensive non-smokers. The range of the mean systolic/diastolic office BP

of 120-139/80-89mmHg was considered diagnostic of pre-hypertension, while masked hypertensives were preliminarily excluded by ambulatory BP measurement. Additionally we excluded those with a history of cardiovascular disease, impaired glucose tolerance or diabetes mellitus as well as those with a significant concurrent illness, or being under treatment with any potentially vasoactive drug. All eligible to participate underwent echocardiography while metabolic profile and haemostatic markers (plasminogen activator inhibitor 1 [PAI-1], tissue plasminogen activator [tPA], thrombomodulin [TM] and fibrinogen [Fib]) were also estimated. An ExBPR at sub-maximal workload level during testing (i.e. end-stage 2, Bruce protocol, Framingham criteria) was considered to divide population into two groups.

Results: Subjects with exBPR (n=32, 65%) compared to those without exBPR (n=27, 55%) did not differ regarding age, body mass index (BMI) and levels of office systolic/diastolic BP (47±8 vs. 46±9 years, 25±3 vs. 24±3 kg/m^2, 135±3/86±3 vs. 134±4/85±2 mmHg, respectively, p=NS for all). The exBPR with respect to non-exBPR group did not differ regarding metabolic profile and left ventricle mass index (97±13 vs. 94±18 gr/m^2) (p=NS for both), while had higher levels of PAI-1, tPA, TM and Fib (11±6 vs. 6.8±5 IU/ml, 9±4 vs. 6.4±6 ng/ml, 30±12 vs. 25±8 ng/ml, 340±37 vs. 300±30mg/l respectively, $p<0.01$ for all). In logistic multivariable regression model determinants of exBPR (adjusted OR, 95% CI) were PAI-1 (1.27, 1.07-1.4), tPA (1.34, 1.1-1.7), TM (1.45, 1.2-1.9), 24h systolic BP (1.42, 1.23-2.1) and plasma glucose (1.4, 1.23-1.82) ($p<0.05$ for all).

Conclusions: ExBPR is associated with haemostatic abnormalities in pre-hypertensive non-smoking men. That phenomenon may justify at least partially the increased cardiovascular risk related to the pre-hypertensive clinical phenotype and that exercise treadmill testing may contribute to the amelioration of cardiovascular risk stratification in this setting.

P609 Minimizing right ventricular pacing in patients with DDDR pacemaker improves cardiopulmonary exercise test results and reduces BNP level

T. Chwyczko, R. Dabrowski, A. Maciag, A. Borowiec, A. Labecka, M. Sterlinski, M. Pytkowski, I. Kowalik, J. Janas, H. Szwed. *Institute of Cardiology, Warsaw, Poland*

Purpose: Right ventricular (RV) apical pacing causes ventricular desynchronization and increases risk of atrial tachyarrhythmias. In long-term follow-up it may lead to development of heart failure. Optimalisation of atrio-ventricular delay (AVD) in DDDR pacemakers reduces unnecessary RV stimulation. The aim of the study was to compare exercise tolerance and BNP level in patients with sinus node dysfunction (SND) and various pacing modes during DDDR stimulation.

Methods: This prospective, double-blind, cross-over, randomized trial included 31 patients (17M/14W, 71.6±8 yrs) with DDDR pacemaker implanted due to SND. All patients underwent cardiopulmonary exercise test (CPX) with expired gases analysis and had BNP measured before pacemaker implantation. Patients were randomized either to 150ms AVD program (predominant RV stimulation) or to minimizing ventricular pacing program (MVP): prolonged AVD (250ms) with intrinsic AV search. After 4 months all tests were repeated and pacemaker program was crossed-over to the alternate mode (150ms or MVP, depending on previous program). After another 4 months patients underwent all tests again.

Results: Percentage of right ventricular pacing (%VP) was significantly higher in 150ms AVD than in MVP (81.7±22.6 vs 14.2±20.5%, $p<0.0001$). Peak oxygen uptake (peak VO2) in MVP was significantly higher than in 150ms AVD (19.9±6.3 vs 14.2±4.3 ml/kg/min, respectively, p=0.006). Peak VO2 in 150ms AVD was lower than baseline peak VO2 (14.2±4.3 vs 17±4.6 ml/kg/min, p=0.03). Maximal minute ventilation-carbon dioxide production (VE/VCO2max) and VE/VCO2slope were lower in MVP vs 150ms AVD (40.3±5.7 vs 47.3±12.8, p=0.006 and 32.6±4.9 vs 35±6.1, p=0.03, respectively). Patients in MVP reached anaerobic threshold later than patients with 150ms AVD (16.8±12.9 vs 11±9.6 ml/kg/min, p=0.0002). Mean BNP level in 150ms AVD was significantly higher than in MVP (72.3±48.3 vs 49.4±43.9 pg/ml, p=0.001) and vs baseline (72.3±48.3 vs 37.2±26.3 pg/ml, $p<0.0001$). Above all, VE/VCO2max level in MVP correlated positively with %VP (r=0.46, p=0.0133).

Conclusions: Patients with DDDR implanted due to SND and predominant right ventricle pacing perform worse in CPX and have significantly higher BNP levels than patients with minimized ventricular pacing program. Exercise tolerance, circulatory and respiratory system adaptation to exercise in CPX are better when MVP program is implemented. Optimal DDD pacemaker programming promotes physiological AV conduction and prevents pacemaker induced decrease of exercise capacity.

P610 Safety of cardiopulmonary exercise test in hypertrophic cardiomyopathy

C. Blank, B. Pfeiffer, A. Neugebauer, H. Seggewiss. *Leopoldina Krankenhaus, Schweinfurt, Germany*

Purpose: According to international guidelines hypertrophic cardiomyopathy (HCM) is regarded as a relative contraindication of exhaustive cardiopulmonary exercise testing (CPET) based on the association of sudden cardiac death (SCD) and vigourous exercise in HCM. On the other hand CPET provides helpful information for differential diagnosis, graduation of exercise limitation and evaluation of effects of therapeutic interventions. Data on complication rates of exhaustive exercise testing in HCM are rare. We conducted a retrospective study on patients with HCM with focus on adverse events like SCD, syncope and life-threatening arrhythmias.

Methods: 396 patients with HCM (55±17 [8-89] y, 183 women) performed exhaustive CPETs (cycling ergometry, ramp protocoll, 10 W/min) as a part of the first presentation in our clinic during the years 2001 – 2003. Clinical characterics, history and diagnostic test results: CCS I-IV, NYHA I-III. History of exercise induced syncope 5.8% and unexplained syncope 12.6%. Non sustained ventricular tachycardia (nsVT) 11.8%, paroxysmal supraventricular tachycardia (SVT) 14.1%. Maximal septal diameter 20±5 mm. Echocardiographic proof of left ventricular outflow tract gradient (LVOTG) 72.7% (= HOCM), in case of HOCM LVOTG at rest 53±33 mmHg, provoced LVOTG (Valsalva maneuver) 77±45 mmHg. In the analysis of CPET maximal oxygen uptake (VO2max), maximal power output (Wmax), indication for terminating CPET and adverse events during recovery were evaluated.

Results: Patients achieved a VO2max of 20,7±7.2 ml/kg/min and a Wmax of 107.4±46.2 Watts. 41.9% (n=166) stopped CPET subjectively exhausted or due to extracardial limitations. 44.4% (n=176) stopped due to angina pectoris, dizziness or dyspnea. In 1.3% (n=5) ST segment displacement, in 0.3% (n=1) nsVT, in 6.6% (n=26) hypertensive reaction (systolic blood pressure >230 and diastolic >115 mmHg respectively) and in 5.6% (n=22) hypotensive reaction (systolic drop > 10 mmHg of baseline value) led to termination of CPET. No SCD, syncopes or life-threatening arrhythmias were reported.

Conclusion: In unselected patient populations mortality of exercise testing is reported as < 0.01% and morbiditiy < 0.05%. The lack of occurance of life-threatening arrhythmias, syncopes or SCD in the above-mentioned population during and after exhaustive CPET supports the notion of a low risk of CPET in patients with HCM.

P611 Peak circulatory power is a powerful predictor of arrhythmic events in patients with implantable cardioverter-defibrillator

R. Cale, M. Mendes, J. Brito, P. Sousa, P. Carmo, R. Gomes, A. Ferreira, P. Adragao, J. Calqueiro, J. Aniceto Silva. *Hospital de Santa Cruz, Lisbon, Portugal*

Cardiopulmonary Exercise Test (CPET) is useful to risk-stratify chronic heart failure (CHF) pts and to select them for heart transplant. However, there are no data about its capability to identify the CHF pts more susceptible to sudden cardiac death.

Objectives: Evaluate the value of CPET parameters to predict an arrhythmic event in CHF pts with an ICD.

Methods: Prospective single centre registry of 61 consecutive pts (mean age 55±15 years, 18% female) with dilated cardiomyopathy and an ICD who underwent maximal symptom CPET. A composite end point was defined, considering mortality due to arrhythmic cause, appropriate shock and/or sustained ventricular tachycardia. Univariate and multivariate analysis were performed. Peak VO2, VE/VCO2 slope, peak circulatory power (PCP, i.e., the product of peak VO2 and peak systolic arterial blood pressure), resting heart rate and heart rate decrease during the first minute of recovery were the analysed variables.

Results: During a mean follow-up period of 813±505 days, 8 pts died (13%), 2 of them due to an arrhythmic cause (3.3%); 16 (26%) pts received at least one appropriate ICD shock, 8 (13%) due to ventricular fibrillation. Sustained ventricular tachycardia was recorded in 23 pts (38%). Univariate analysis identified peak VO2, VE/VCO2 slope, PCP and rest heart rate as predictive for an arrhythmic event. On multivariate analysis, PCP was the only independent predictor of arrhythmic events (HR 0.93, 95%CI 0.88-0.97, p=0.003), with a good discriminative value (area under the ROC curve 0.72, 95%:0.59-0.83, p=0,0007). A PCP cut-off value of 2730 mmHg·ml/kg/min identified pts with an arrhythmic event with a sensibility, specificity and negative predictive value of 96%, 44% and 94%, respectively.

Predictors of Combined Arrhythmic Event

CPET variables into the univariate model	Hazard Ratio (CI 95%)	P
Peak VO2, ml/kg/min	0,87 (0,80-0,95)	0,002
VE/VCO2 slope	1,05 (1,01-1,09)	0,009
Peak circulatory power, mmHg ml/kg/min*	0,92 (0,88-0,97)	0,002
Rest heart rate	1,04 (1,01-1,07)	0,020
Heart rate recovery during 1st min	0,98 (0,96-1,01)	0,242

*For each 100 units.

Conclusion: Peak circulatory power is a powerful predictor of arrhythmic events in CHF pts with ICD. Cardiopulmonary exercise testing seems to be a good method to identify CHF pts who will benefit from an ICD.

P612 The influence of dynamic mitral regurgitation on exercise capacity in patients with chronic heart failure

M. Izumo, Y. Akashi, K. Yoneyama, K. Suzuki, N. Osada, F. Miyake. *St. Marianna University School of Medicine, Kawasaki, Japan*

Background: Functional mitral regurgitation (MR) is frequently observed in patients with chronic heart failure (CHF). Increased MR becomes a

trigger of worsened dyspnea, and it causes poor prognosis in patients with CHF. Many echocardiographic studies evaluated MR during rest condition. The aim of this study was to clarify the influence of exercise-induced MR changes in patients with CHF.

Method: Fifty CHF patients with functional mitral regurgitation (MR) underwent symptom limited semi supine bicycle exercise stress echocardiography. Of the twenty five patients underwent cardiopulmonary exercise testing. Effective regurgitant orrifice (ERO) area was measured at rest and during exercise by the proximal isovelocity surface area (PISA) method to quantify MR. The sphericity index was calculated from ESV divided by the volume of a sphere with a diameter corresponding to the major end-systolic LV long axis by real-time three-dimensional echocardiography (RT3-DE). The LV long axis was obtained from 3D echocardiographic data as the longest distance between the center of the mitral annular and the endocardial apex. In addition, real-time three-dimensional echocardiography (RT3-DE) which is another novel method for evaluation the timing of regional volume changes and systoric dyssynchrony index (SDI) as a parameter of global intraventricular mechanical synchronicity was performed at rest and during exercise.

Results: We divided all CHF patients into the exercised-induced MR (EMR) group (15 patients with increasing ERO $>13mm^2$) or the non exercise-induced MR (NEMR) group (35 patients with increasing ERO $<13mm^2$). No difference were observed systoric blood pressure, BNP, left ventricular end-systoric volume, end-diastoric volume, ejection fraction (EF), ERO, and SDI at rest between two groups. The EMR group revealed significantly higher SDI ($p<0.01$) during exercise, and VE/VCO2 slope (p=0.02). In addition, the EMR group revealed lower exercise duration (p=0.01), peak load (p=0.01) and peak VO2 ($p<0.05$). Rest-exercise difference in ERO was correlated with ΔSDI (r=0.50, $p<0.01$), peak VO2 (r=-0.45, p=0.01) and VE/VCO2 slope (r=0.38, p=0.04). The number of patients who stopped exercise due to dyspnea was greater in the EMR (12 patients, 80%) than NEMR group (6 patients, 23%; p=0.0004)

Conclusion: This study suggested that exercise could alter the level of intraventricular dyssynchrony which induced functional mitral regurgitation in heart failure patients. Exercise-induced changes in mitral regurgitation severity limit the exercise capacity.

P613 Cardiopulmonary exercise testing in adult survivor's of operated fallot's tetralogy: CPEX results may be better than symptoms

D. Mcaroe[1], L.J. Freeman[2]. [1]*University of East Anglia, Norwich, United Kingdom;* [2]*Norfolk and Norwich University Hospital, Norwich, United Kingdom*

Treated Fallot's Tetralogy (ToF) patients have excellent long term survival but may later develop impaired RV function, often associated with PV regurgitation. Timing of intervention is imprecise due to a long intermediate phase of well being. Currently, symptoms of dyspnoea, and RV size and function on echo are used as indicators for PV replacement. However, symptoms may not develop until an advanced stage. This study compared experience of dyspnoea (BORG scale) RV function on echo with exercise capacity (CPEX).

Patients attending a GUCH clinic at a DGH in the UK were approached after ethical approval had been obtained. Following informed written consent, patients completed the modified BORG scale and performed a maximal exercise test. (RER for all patients $\geq$1, all tests terminated following onset of symptoms). As part of routine follow up, an echocardiogram recorded global RV function and TAPSE in mm. Correlations were assessed using Spearman's Rho or Pearson's r, as appropriate. Mean values were compared using a paired t-test.

Of 38 patients approached, 30 participated in the study. Mean age= 41 years (17-68), M:F= 1:1. All participants had undergone total surgical correction (RVOT resection= 19, annular patch= 9, annular dilation= 4). 8 required subsequent PV replacement. 5 had severe PVR on echo. Mean V02max was 1797.87 ml/min vs. an expected of 2098.33 ml/min (p= 0.004). The mean VE/VCO2 slope was 29.1. There was good correlation between VO2max and RV function on echo (Correlation coefficient= -0.387, p = 0.034) and between VO2max and TAPSE (0.441, p= 0.031). Correlation was also found between the VE/VCO2 slope and RV function (0.361, p= 0.050). Mean BORG score was 1.7 (0-5). There was no correlation between BORG score and any outcomes on echo or CPEX.

This study finds good correlation between falling V02max and rising VE/VCO2 slope and deteriorating RV function (echo). No correlation existed between symptoms and either CPEX or echo assessment of RV function. The mean VO2max in this study was significantly lower than expected and these patients may have habituated to reduced activity, thus not recognising deviation from the norm. We suggest that reliance on symptoms in adult ToF patients during follow up is inadequate and does not identify deterioration requiring intervention. This could result in the optimum window for intervention being missed. CPEX testing is a functional assessment of exercise capacity which is reproducible and well validated. We suggest that it be integrated into follow up for ToF patients and may identify patients requiring intervention earlier than previously considered.

P614 Cardiopulmonary exercise testing for predicting outcomes in patients with heart failure - advantage of a multivariable score?

A. Toste[1], R.M. Soares[1], J. Feliciano[1], V. Andreozzi[2], A. Mamede[1], A. Lousinha[1], A. Abreu[1], L. Ferreira[1], R.C. Ferreira[1]. [1]*Hospital Santa Marta, Lisbon, Portugal;* [2]*CEA, Universidade de Lisboa, Lisbon, Portugal*

Purpose: To evaluate whether the predictive accuracy of a cardiopulmonary exercise test (CPX) can be increased by a multivariable score, that integrates the additive prognostic information of several not related parameters, in patients (pts) with chronic heart failure (CHF).

Methods: 206 pts with CHF (153 male, 53±13 years, 35% of ischemic aetiology, left ventricular ejection fraction 28±8%, 81% in sinus rhythm, 97% receiving ACE-I and/or ARB, 78% beta-blocker, 60% spironolactone, and 33% with an ICD or a CRT-D device implanted in the follow-up) – underwent a first maximal symptom limited, treadmill CPX, and were followed for major cardiac events (death, mechanical ventricular assistance or urgent transplantation) during a mean of 33±15 months.

We analysed peak oxygen uptake (pVO2), circulatory power (CP=pVO2 x peak systolic blood pressure), minute ventilation to CO2 production (VE/VCO2) slope, VE/VCO2 slope normalized for pVO2 (VE/VCO2/pVO2) and for CP (dVE/VCO2/PC*100), heart rate recovery at first minute (HRR1), end-tidal carbon dioxide pressure (PetCO2) at rest and during peak exercise, and the oxygen uptake efficiency slope (OUES).

ROC curves were plotted to assess optimal cut-offs. The prognostic power of each variable was assessed through Cox proportional hazards models, and R2 percent (R2%) and Vindex were used as measures of predictive accuracy for events. Variables were weighted, and a multivariate score was built whose predictive power was assessed through Cox multivariate model.

Results: All variables proved to be independent predictors of the composite outcome, which occurred in 58 pts (28%). CPX parameters, who were not related with each other, that showed the greatest prognostic power, and that thereby were used to build the score were: VE/VCO2/pVO2 ($\geq$ 2.12, hazard ratio [HR]=15.54, R2%=36.89), HRR1 ($<$16 beats at 1 minute, HR=8.76, R2%=20.86), OUES ($>$1.6, HR=7.01, R2%=22.37) and peak PetCO2 ($<$4.00 kPa, HR=4.72, R2%=15.71). The derived score showed a HR=8.04 (lower than HR for VE/VCO2/pVO2 and for HRR1), and R2%=33.38 (lower than R2% for VE/VCO2/pVO2).

Conclusions: A multivariable score that integrates the prognostic information of not related, and readily available, CPX parameters, does not increase the association with events or the predictive accuracy of CPX in pts with CHF. The VE/VCO2/pVO2 was the parameter with the highest prognostic power in this population.

P615 Maximal exercise capacity in adults with congenital heart disease

R. Buys, W. Budts, C. Delecluse, A. Stevens, S. Amandels, S. Onkelinx, T. Thomaes, L. Vanhees. *Catholic University of Leuven (KULeuven), Leuven, Belgium*

Introduction: Investigations on exercise capacity in grown-up patients with congenital heart disease (GUCH) mostly report on small groups without comparison to matched control subjects. Our aim is to evaluate whether GUCH can perform an exercise test as maximal as healthy subjects, and to investigate submaximal substitutes of exercise capacity.

Methods: Adult patients with Tetralogy of Fallot (TF, age 25,7±7,6 years), Transposition of the Great Arteries (TGA, age 22,4±6,0 years) and Coarctation of the Aorta (COA, age 27,4±8,9 years), and 138 healthy adults (Controls, age 32,4±11,4 years) performed a cardiopulmonary exercise test until exhaustion. VO2 and VCO2 were determined during the exercise test. The Oxygen Uptake Efficiency Slope (OUES) and VE/VCO2-slope were calculated and the ventilatory anaerobic threshold (VAT) was defined. Comparisons of means were performed by ANOVA. Correlations between peak VO2 and the OUES, VE/VCO2 slope and VAT were calculated.

Results: GUCH showed a significantly lower exercise tolerance than controls, ranging from 80% in COA to 64% in TGA. Peak RER reached values indicating a near maximal exercise, but was significantly lower than controls. Therefore the lower values of maximal exercise capacity may be partly explained by a lower degree of exercise intensity. The same information on exercise capacity can be withdrawn by using submaximal exercise parameters. Of all submaximal parameters, OUES (r=0.818, $p<0.0001$) and VAT (r=0.825, $p<0.0001$) correlated best with peak VO2, followed by VE/VCO2 slope (r=-0.453, $p<0.0001$).

Exercise parameters

	Controls (n=138)	COA (n=145)	TF (n=91)	TGA (M/S) (n=59)
Peak VO2 (ml/min/kg)	37,4±8,6	31,6±8,2°‡	29,5±8,04° *	27,1±7,9°‡*
% predicted peak VO2	101±17,5	79,6±14,8°†‡	72,4±16,9°†*	64,2±13,8°‡*
Peak RER	1,22±0,12	1,16±0,09°†‡	1,12±0,12°†	1,12±0,1°‡
VAT (W)	129±48,6	115±36,4°‡	109±33,3°	97,7±26,5°‡
OUES	3020±796	2646±778°‡	2481±735°	2311±756°‡

Data are presented as means ± SD, ° Significant difference with control group $p<0,0001$, †Significant difference between COA and TF $p<0,05$,* Significant difference between TF and TGA $p<0,05$, ‡Significant difference between COA and TGA $p<0,05$.

Conclusion: Although near maximal exercise testing can be performed in GUCH, OUES and determination of VAT may be useful to accurately interpret the exercise tolerance.

P616 Treadmill exercise electrocardiography and mortality risk in patients with an intermediate pretest probability of coronary artery disease

S. Balakrishnan Nair[1], R. Rezai[2], W. Turkie[1], R.S. Khattar[1]. *[1]Manchester Royal Infirmary, Manchester, United Kingdom; [2]The University of Manchester, Manchester, United Kingdom*

Purpose: Guidelines recommend non-invasive stress imaging for patients with suspected cardiac chest pain and an intermediate pretest probability of coronary artery disease (Int-CAD). However, the Rapid Access Chest Pain (RACP) service model aims to fast-track patients with suspected cardiac chest pain using exercise electrocardiography (ExECG).The aim of this study was to compare the demographic characteristics and death rates of Int-CAD patients with and without a diagnostic ExECG.
Methods: We performed a retrospective analysis of 1,174 Int-CAD patients who attended the RACP service from January 2004 to December 2006. The parameters analysed included age, sex, ethnicity, diabetes, hypertension, hypercholesterolaemia, smoking and all-cause death during a mean follow-up period of 3.3±0.8 years.
Results: Group 1 consisted of 828 patients with a diagnostic ExECG (91% negative, 9% positive), and group 2 consisted of 346 patients without a diagnostic ExECG (equivocal result or unable to exercise). Univariate analysis is shown in the table. Multivariate analysis for the full study population showed that age ($p<0.01$) and diabetes ($p<0.01$) were positive independent predictors and a diagnostic exercise ECG ($p<0.01$) was a negative independent predictor of death.

	Group 1 (n=828)	Group 2 (n=346)	P- value
Age	53.2±13.7	62.9±12.1	<0.001
Gender (% male)	60.9	40.8	<0.001
Ethnicity (% white)	56.5	64.2	NS
Diabetes (%)	12.1	17.3	0.01
Hypertension (%)	33.7	56.9	<0.001
Hypercholesterolaemia (%)	25.6	36.4	0.001
Smoking (%)	53.0	51.4	NS
Pre test probability (%)	40.9±20.5	52.8±16.0	<0.001
Deaths (%)	1.5	7.6	<0.001

Conclusion: In conclusion, the majority of Int-CAD patients (71%) had a diagnostic exercise ECG associated with a 1.5% 3-year risk of death. Those with a non-diagnostic exercise ECG had a 5-fold increased risk of death and require early access to pharmacological stress imaging.

AGEING AND SEX

P617 Variation in myocardial mass is associated with aortic stiffness and endothelial function in low risk individuals by early adult life

I. Kylintireas, M. Lazdam, I. Bechar, J. Diesch, C. Trevitt, J.M. Francis, S. Neubauer, P. Leeson on behalf of Department of Cardiovascular Medicine, University of Oxford, Oxford, UK. *University of Oxford, Oxford, United Kingdom*

Purpose: Increased arterial stiffness assessed by tonometry as pulse wave velocity (PWV) is associated with myocardial hypertrophy. Endothelial dysfunction has been linked both to arterial stiffness and myocardial hypertrophy. We determined whether variation in myocardial mass evident by the end of childhood, in a group at low risk for cardiovascular disease, is related to PWV and endothelial function.
Methods: Seventy six young volunteers [mean age = 25, (40 female)], without history of cardiovascular disease, obesity or hypertension underwent CMR (1.5T Siemens). Aortic pulse wave velocity was measured from ECG-gated, spoiled gradient echo sequences with velocity-encoding gradient for phase contrast applied during free breathing to the ascending and descending aorta. Transit time method was used to calculate PWV calculated as the distance between assessed sites divided by the time delay between arrival of the pulse wave at each site. Myocardial mass and left ventricular systolic function was determined using Argus software with tracing of the endiastolic and endsystolic phase of multiple short-axis steady-state free precession cine images covering the entire left ventricle. Myocardial mass was expressed as absolute myocardial mass (MM), myocardial mass indexed to height (MIH), myocardial mass indexed to body surface area (MIX). Conduit vessel endothelial function was assessed by standard ultrasound protocols from flow mediated dilatation (FMD) of the brachial artery.
Results: PWV positively correlated with MM ($r=0.41$, $P<0.001$), MIH ($r=0.38$, $P<0.005$) and MIX ($r=0.43$, $P<0.001$). Endothelial function inversely correlated with MM ($r=-0.3$, $P<0.05$), MIH ($r=-0.34$, $P<0.05$) and MIX ($r=-0.3$, $P<0.05$). However, after adjustment for aortic stiffness the association between endothelial dysfunction and myocardial mass was no longer significant. Multivariate analysis confirmed that PWV was associated with MM [$\beta=92.3$ (±34.4), $P<0.05$, $R^2=0.8$], MIH [$\beta=53.2$ (±22.1), $P<0.05$, $R^2=0.66$], and MIX [$\beta=46.6$ (±20.5), $P<0.05$, $R^2=0.59$], independently from demographics, anthropometric data, blood pressure, left ventricular systolic function and other cardiovascular risk factors.
Conclusions: Myocardial mass is associated with aortic stiffness by the end of childhood in the absence of significant cardiac risk factors, left ventricular dysfunction, hypertension or obesity. The association between endothelial function and myocardial mass was not independent of aortic stiffness and the contribution of endothelial function to myocardial thickening in early life may relate to its impact on aortic stiffness.

P618 Determinants of circulating leukocyte telomere length in patients with acute myocardial infarction

S. Saliques[1], M. Zeller[1], C. Vergely[1], S. Amoureux[1], P. Sicard[1], J.E. Wolf[2], A. Donzel-Javouhey[2], Y. Cottin[2], J.R. Teyssier[2], L. Rochette[1]. *[1]LPPCE,IFR 100, UNIVERSITY OF BURGUNDY, Dijon, France; [2]Centre Hospitalier Universitaire de Dijon, Dijon, France*

Objectives: Recent data showed reduced telomere length (TL) in patients with coronary artery disease (CAD), linked with accelerated cardiovascular ageing. Circulating transcript of the c-Fos gene, involved in cellular inflammation and oxidative stress, has been evoked to play a role in CAD. In patients with acute myocardial infarction (MI), we aimed to analyze the relationship between factors potentially associated with TL of circulating leucocytes, in particular cFos transcripts.
Materials and Methods: The telomere length was determined prospectively by real time quantitative Polymerase Chain Reaction method from circulating leukocytes of consecutive patients admitted <24 h in intensive care unit for an acute MI, as well as leukocyte expression of c-Fos. Left ventricular ejection fraction (LVEF) was assessed by echocardiography <3 days after admission.
Results: Among the 69 patients included in the study, mean age was 66±2 y and 78% were male, and TL was 1.34±0.01. A negative correlation was found between leukocyte TL and age ($r=-0.37$, $p=0.002$), cFos transcript ($r=-0.46$, $p<0.001$), logNT-proBNP ($r=-0.30$, $p=0.019$) and CRP ($r=-0.29$, $p=0.018$). In contrast, creatinine clearance ($r=+0.30$, $p=0.02$), and LVEF ($r=+0.26$, $p=0.04$) were positively correlated with TL. Leukocyte count was not related with TL ($p=0.54$). Age-adjusted TL was significantly reduced in male vs. female ($p=0.001$), and in patients with hypertension ($p=0.023$), family history of CAD ($p=0.006$), smokers ($p<0.001$), or clinical heart failure on admission ($p=0.009$). Backward multivariable linear regression analysis identified cFos ($\beta=0.51$, $p<0.001$), smoking ($\beta=0.25$, $p=0.031$) and prior CAD ($\beta=-0.266$, $p=-0.011$) as factors independently associated with LT ($R^2=0.43$).
Conclusion: Our data suggest that in patients with acute MI, circulating leukocyte TL reflects the burden of cFos, while the independent influence of age is limited. Whether in such patients, reduced TL could be considered as surrogate marker for the accumulation of increased oxidative stress and inflammation remains to be determined.

P619 Regular aerobic exercise corrects age-related declines in endothelial function

M. Deljanin Ilic[1], S. Ilic[1], G. Kocic[2], R. Pavlovic[2], V. Stoickov[1]. *[1]Institute of Cardiology, University of Nis, Niska Banja, Serbia; [2]Institute of Biochemistry, University of Nis, Nis, Serbia*

Purpose: To examine the influence of regular aerobic exercise on the age-related decline in endothelial function, assess through changes of circulating blood markers of endothelial function: the stable end products of nitric oxide (NOx) and S – nitrosothiols (RSNO – reservoir for bioavailable nitric oxide), in older sedentary patients (pts) with left ventricular dysfunction (LVD).
Methods: 60 pts: 42 middle-aged (40 to 55 years: 19 physical active - MA group, and 23 sedentary; MS group), and 18 older sedentary (65 to 75 years; O group) with ejection fraction <40% were studied. At baseline in all pts, values of NOx and RSNO were evaluated and bicycle exercise test was performed. After initial study, pts in O group underwent a supervised 3 weeks aerobic exercise training (40 minutes of exercise training daily over a period of three weeks at residential center), and after that period NOx, RSNO and exercise capacity were determined again. The NOx and RSNO concentration were determined according to the modified Saville-Griess method.
Results: Baseline value of NOx was significantly lower in O than in MS and MA group ($P< 0.02$ and $P< 0.0001$) and lower in MS than in MA group ($P< 0.005$). After 3 weeks of exercise training NOx increased significantly in O group (from 27.2±13.9 to 49.5±11.9 μmol/l, $P< 0.001$). This value of NOx in O group was significantly higher than in MS group ($P<0.01$), but was similar to the value in MA group (49.5±11.9 vs 54.2±16.9 μmol/l, ns). At baseline, value of RSNO was significantly higher in MA than in MS and O group ($P<0.001$ and $P<0.0001$), and higher in MS than in O group (ns). Significant increase of RSNO in O group during exercise training (from 2.6±1.1 to 6.0.±2.6 μmol/l $P<0.001$), abolished difference in RSNO values between O and MA group which was present at baseline, and resulted in significantly higher RSNO value in O than in MS group ($P<0.001$). Level and duration of exercise test at baseline were significantly lower in O than in MA ($P<0.0001$ both) and MS group ($P<0.001$ both). At the end of exercise

period level and duration of exercise test were similar in O and MA group, but higher in O than in MS group ($P<0.001$ both).
Conclusion: Regular aerobic exercise in older pts with LVD corrects age-related declines in endothelial function documented through significant increase of NOx and RSNO, and restores level of NOx and RSNO to the level similar in physical active middle-aged pts with LVD. Those positive changes in endothelial function were associated with significant improvement in exercise capacity.

P620 Normotensive salt sensitivity in the elderly: possible role of endothelin-1 and sodium-potassium pump

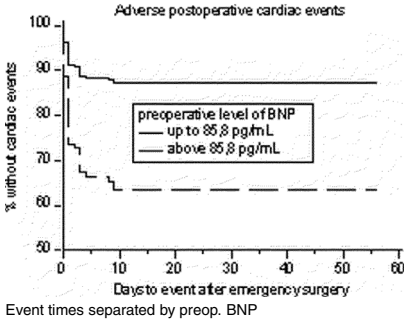
G.V. Simonia, I.T. Andronikashvili, P.A. Nozadze, N.M. Kantaria, T.V. Kristesiashvili. *Tbilisi State Medical Unversity, Tbilisi, Georgia, Republic of*

Age related hypertension is generally linked to salt sensitivity. Numerous studies showed association of Endothelin-1 and membrane Na,K-ATPase activity in salt-sensitive hypertension. However, little is know about normotensive salt sensitivity in the elderly. The study was aimed to assess Endothelin-1 plasma levels and erythrocyte Na,K-ATPase activity in normotensive salt-sensitive elderly.
Methods: Salt sensitivity was assessed in 62 normotensive elderly males ages 65-72 yrs and 48 middle aged normotensives (32 – 46 yrs). Salt sensitivity was assessed by the difference of mean arterial pressure ($\geq$3 mm Hg) on high (200 mmol/day) vs. low (40 mmol/day) salt diet. Na^+K^+-ATPase activity was determined spectrophotometrically from ghost erythrocyte membrane prepared by osmotic lysis. Endothelin 1 was detected using radioimmunoassay
Results and Discussion: Fourteen (29,2%) of 48 middle aged subjects and 29 (46,8%) of 62 elderly considered to be salt sensitive while the rest of participants were salt resistant. Our results revealed depressed Na,K-ATPase activity in salt-sensitive normotensives (0,31$\pm$0,03 and 0,34$\pm$0,05 mcMPi/mg.protein/h, $p>0,05$) compared to salt-resistant subjects (0,42$\pm$0,04 mcMPi/mg.protein/h, $p<0,05$). Slight elevation of Endothelin-1 plasma levels was observed in salt-sensitive subjects with the highest concentrations in the elderly compared to salt-resistant normotensives. Significant negative correlation was found only between ET-1 plasma levels and erythrocyte membrane Na,K-ATPase activity in salt-sensitive normotensive elderly.
Conclusion: Our findings suggest that (1) salt sensitivity increase in normotensive elderly; (2) membrane Na,K-ATPase activity is suppressed in salt-sensitive subjects irrespective of age; (3) Endothelin-1 might contribute to inhibition of sodium-potassium pump activity development of salt-sensitivity in normotensive subjects.

P621 Prognostic value of brain natriuretic peptide before emergency surgery

C. Sankin, T. Marko, T. Stojakovics, S. Archan, N. Vicenzi. *Medical University of Graz, Graz, Austria*

Purpose: Brain natriuretic peptide levels (BNP) reflect myocardial ischemia, stretch and congestion, which may be reversible with appropriate therapy, thus yielding a tool for postoperative risk stratification. We hypothesized that BNP at admission for emergency surgery provides prognostic information for postoperative adverse cardiac outcome.
Methods: 170 patients admitted for emergency surgery (surgery within 24 hours) were prospectively monitored for adverse events (cTnT >0,03ng/mL, myocardial infarction, unstable angina, heart failure, cardiac death) occurring during their hospital stay. BNP was measured before surgery and a ROC curve determined the best discriminatory value. Kaplan Meier function and the Cox Proportional Hazards model evaluated event times and confounders. Significance was generally set to $p<0,05$.
Results: 32,9% (95% CI: 4,3) of the patients (mean/SD: 75/11 years; n for trauma: 100, abdominal: 42, vascular surgery: 28) suffered adverse events after surgery. In-hospital mortality was 8,5% (95% CI: 3,3). The AUC of the ROC for BNP was 0,773. Optimum discriminatory threshold for preoperative BNP was 85,8pg/mL (76,6% sensitivity, 69,9% specificity). Adjusted for patient characteristics and periprocedural specifics, BNP remained an independent predictor of adverse in-hospital cardiac outcome. With BNP above 85,8pg/mL, 36 of 170 patients had events, whereas with BNP up to 85,8pg/mL, only 11 suffered events.



Event times separated by preop. BNP

Thus, BNP above 85,8pg/mL was associated with a threefold increased risk of adverse cardiac outcome.
Conclusions: BNP at admission for emergency surgery provides substantial prognostic information for postoperative adverse cardiac outcome and may improve postoperative cardiac risk stratification when preoperative stratification and timely treatment attempts are impossible.

P622 Red cell distribution width is an independent indicator of outcome in elderly patients with coronary artery disease

0 Pfister, S. Muzzarelli, L. Grize, M.E. Pfisterer. *University Hospital Basel, Basel, Switzerland*

Background: Red cell distribution width (RDW) is a numerical measure of anisocytosis in erythrocytes that is routinely reported on blood counts. Higher levels of RDW may be associated with adverse outcomes in patients with coronary artery disease (CAD). Because RDW increases with age, the prognostic value of RDW in elderly patients with CAD is unknown. We determined the association between RDW and the risk of all-cause mortality and adverse cardiovascular outcomes in elderly CAD patients (aged $\geq$75 years).
Methods: We performed a post hoc analysis of the TIME study. Baseline RDW was measured in 148 patients $\geq$75 years with chronic angina who were randomized to either an invasive or medical treatment strategy and followed for a median of 4 years. RDW threshold was set at 13.4% according to the previously published mean for CAD patients <75 years of age. Cox proportional hazard models were used to examine the association of RDW values >13.4%, respectively $\leq$13.4% with adverse clinical outcomes.
Results: At baseline, 80 patients (54%) had RDW values >13.4% (RDW-high), compared to 68 patients (46%) with RDW $\leq$13.4% (RDW-low). There were no significant differences in baseline characteristics regarding age, hypertension, diabetes, smoking status, hypercholesterinemia or history of previous myocardial infarction (MI) between groups. After 4 years of follow up 83.8% of RDW-low patients and 67.7% of RDW-high patients were alive ($p<0.01$). RDW-low patients exhibited significantly less cardiac death and major adverse clinical events (MACE) compared to RDW-high patients (11.8% versus 28.8% for cardiac death, $p<0.02$; 61.8% versus 80% for MACE, $p<0.02$) with negative predictive values of 0.88 for cardiac death and 0.92 for myocardial infarction. After adjusting for age, sex, anemia and renal function RDW >13.4% remained an independent indicator of death (adjusted hazard ratio: 1.94) and MACE (adjusted hazard ratio: 1.48).
Conclusion: We found an independent increase in cardiovascular risk and all cause death in elderly CAD patients with RDW >13.4%. Given the wide availability of RDW as part of the regular blood count, inclusion of RDW in the general risk assessment of elderly CAD patients might be an alternative to novel, expensive markers of cardiovascular risk.

P623 Progression from paroxysmal atrial fibrillation to more sustained forms: clinical correlates and therapeutical consequences

C.B. De Vos, R. Pisters, R. Nieuwlaat, M.H. Prins, R.G. Tieleman, M.A. Allessie, H.J.G.M. Crijns. *University Hospital Maastricht, Maastricht, Netherlands*

Purpose: Despite adequate therapy, patients with paroxysmal atrial fibrillation (PAF) progress to more sustained forms of AF. The treatment strategies applied for each AF type are quite different. In the present study, we evaluated the clinical correlates and therapeutical consequences of AF type progression in a large population.
Methods: We included 1219 patients with PAF or first detected AF who participated in the Euro Heart Survey on AF. Patients who experienced AF progression were identified (paroxysmal AF at baseline becoming persistent or permanent AF at one year follow-up or first detected AF at baseline with spontaneous conversion to sinus rhythm during admission becoming persistent or permanent AF at one year follow-up).
Results: Progression from PAF to more sustained forms of AF occurred in 178 patients (15%). Independent factors associated with AF-progression are presented in the Table. Using the regression coefficient as benchmark, we determined the relative contribution of each factor to the prediction of AF progression. This resulted in the HATCH score. Nearly 50% of the patients with PAF and a HATCH score >5 had AF progression after one year versus only 6% of the patients with a HATCH score of 0. The predictive value of the HATCH score was higher than all other independent predictors of AF progression individually.

	OR	OR 95%CI	Regression Coefficient	P-value	Score
Heart Failure in history	2.22	1.54-3.22	0.80	<0.001	2
Hypertension	1.52	1.05-2.20	0.42	0.024	1
Chronic obstructive pulmonary disease	1.51	0.95-2.39	0.41	0.088	1
Stroke or TIA in history	2.02	1.24-3.31	0.71	0.007	2
Age > 75 years	1.57	1.07-2.30	0.45	0.024	1

Conclusions: A substantial number of patients with PAF progress to sustained AF within one year. Factors known to provide atrial structural remodeling (age and

underlying heart disease) were also independent predictors of AF type progression. The HATCH score enables detection of patients that are likely to develop more sustained forms of AF in the near future.

P624 Contribution of resting heart rate to mortality and coronary heart disease events in free-living older adults. The three city study

C. Legeai[1], X. Jouven[1], J.F. Dartigues[2], C. Helmer[2], K. Ritchie[3], P. Amouyel[4], C. Tzourio[5], P. Ducimetiere[6], J.P. Empana[1] on behalf of The Three City Study. *[1]INSERM U970, Paris V University, Paris Cardiovascular Research Center (PAARC), Paris, France; [2]INSERM U897, Bordeaux, France; [3]INSERM U888, Montpellier 1 University, Montpellier, France; [4]INSERM U744, Lille, France; [5]INSERM U708, Paris, France; [6]IFR69-Paris Sud University, Villejuif, France*

Elevated Resting Heart Rate (RHR) has been consistently associated with mortality in the middle-aged. We investigated its association with mortality and with incident coronary heart disease (CHD) in free-living elderly participants of the Three City Study.

The study population included 5855 men and women (62.5%) aged ≥65 years who had no personal history of CHD, no cardiac arrhythmias or pacemaker and who were not using beta blockers at baseline between 1999 and 2001. RHR was measured twice at baseline in a seated position using an electronic tensiometer, and the mean value of these two measures was considered for analysis. Mortality and CHD events (revascularization procedures, angina pectoris, myocardial infarction and coronary death) were followed up over 6 years and adjudicated by an expert committee. The hazard ratios of each upper quartile against the first quartile of RHR were estimated using a Cox proportional hazard model.

The mean (SD) age was 73.7 (5.4) years and mean RHR was 71.7 (10.4). After a mean follow up of 4.9 years, 457 died including 15.8% from cardiovascular causes (n=72) and 40.0% from cancer (n=183). Compared to those from the first quartile of RHR (<65 bpm), subjects from the top quartile (≥78 bpm) had a 72% (95% confidence interval, 1.29-2.30) increased risk of mortality, after adjustment for age, gender, study centre, body mass index, systolic blood pressure, antihypertensive treatment, smoking, alcohol consumption, diabetes, total cholesterol and incapacity for activities of daily living. Corresponding hazard ratios for cancer and cardiovascular mortality were 1.61 (1.05-2.48) and 2.39 (1.11-5.14) respectively. Association between RHR and mortality was consistent according to gender, diabetes and hypertension statuses (all p values for interaction>0.15). During the same period, RHR was not associated with CHD events (n=195 events; top vs. lowest quartile: hazard ratio: 1.07; 95%CI: 0.70-1.65) after adjustment for the above risk factors.

This study cohort suggests that in free-living elderly, elevated RHR is an independent marker of cardiovascular and non cardiovascular mortality but not a marker of CHD risk.

P625 The inflammatory component of cardiovascular aging on albuminuria and arterial stiffness in essential hypertensive subjects

K. Dimitriadis, C. Tsioufis, D. Tsiachris, A. Kasiakogias, H. Tatsis, C. Papastasinos, A. Aggelis, N. Trikalinos, I. Kallikazaros, C. Stefanadis. *First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece*

Purpose: Evidence suggests that subclinical inflammation may be a link between aging and diffuse vascular dysfunction, while urinary albumin excretion and arterial stiffening are associated with subclinical atherosclerosis.

In the present study, we examined the interrelationships between aging, high-sensitivity C-reactive protein (hs-CRP), urinary albumin excretion expressed as the albumin to creatinine ratio (ACR), and arterial stiffness in essential hypertensive patients.

Methods: 295 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [192 men, mean age=50±8 years, office blood pressure (BP)=148/95 mmHg] were divided into two groups according to age: Older group (mean age >or=60 years, n=43) and younger group (mean age<60 years, n=252). In all subjects arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP), while ACR values were determined as the mean of two non-consecutive morning spot urine samples.

Results: Older compared to younger group had lower office and 24-h diastolic BP (90±8 vs 96±9 mmHg and 74±9 vs 83±9 mmHg, respectively; p<0.0001 for both), and greater left ventricular mass index (114.3±15 vs 105.2±11 g/m^2, p<0.05) while did not differ regarding sex, body mass index and metabolic profile (p=NS). Moreover, older compared to younger patients exhibited increased levels of hs-CRP (3.2±0.7 vs 2.1±0.7 mg/l, p<0.05), ACR (36.5±12 vs 22.8±7 mg/g, p<0.05) and PWV (8.8±1.5 vs 7.9±1.2 m/sec, p=0.001). In the entire population, age was associated with hs-CRP (r=0.120, p<0.05), ACR (r=0.221, p<0.05), and PWV (r=0.399, p<0.0001), while it was negatively related to 24-h diastolic BP (r=-0.319, p<0.0001). Furthermore, hs-CRP was correlated with body mass index (r=0.281, p<0.0001) ACR (r=0.631, p<0.0001) and PWV (r=0.233, p<0.05). In multiple regression analysis, age and hs-CRP were independent predictors of both PWV and ACR (p<0.05). Analysis of covariance revealed that hs-CRP, ACR and PWV concentrations were significantly different between groups after adjusting for confounders (p<0.05 for all).

Conclusions: Hypertensive patients of more than 60 years of age are characterized by increased levels of hs-CRP, ACR and PWV, whereas the main determinants of early renal dysfunction and arterial stiffness are age and low-grade inflammation. These findings provide an insight into the accelerated atherosclerotic mechanisms of cardiovascular aging.

P626 The effect of estrogen on bone morphogenetic protein receptor signal pathway in pulmonary arterial endothelial cells

H. Ichimori, S. Kogaki, H. Ishida, J. Narita, T. Uchikawa, S. Maekawa, S. Matsumoto, Y. Okada, K. Ozono. *Osaka University Graduate School of Medicine, Suita, Japan*

Background: Epidemiologic investigations have shown that the female predominance in the morbidity of Idiopathic PAH (pulmonary arterial hypertension) in the world, which suggests a role of female sex hormones in the pathogenesis of PAH. Our previous study demonstrated the contradictory effect of estrogen on pulmonary arterial endothelial cells (PAEC) via BMPR (Bone Morphogenetic Protein Receptor) signal pathway depending on celllar oxygen environment.

Purpose: The aim of this study is to investigate the mechanism of the contradictory effect of β-estradiol (E2) upon BMPR signal pathway in PAEC in vitro.

Materials and Methods: Human and rat PAEC were cultured and the expression of BMPR2, Smad1/5/8, Id1, and eNOS were examined under normoxic and hypoxic condition in the presence of E2. We investigated the effect of estrogen receptor antagonist (ICI 182.780.) and searched for an evidence of binding interaction between estrogen receptor (ER) and Smad using immunoprecipitation (IP) and immunoblotting (WB) method. On the other hand, we examined whether the signal switch between normoxia and hypoxia was associated with HIF (hypoxia-inducible factor)-1α expression, using HIF-1α inhibitor (YC-1) or cobalt chloride to control (CoCl2) degradation of HIF-1α. In addition, estrogen renponse element (ERE) activities were measured under normoxia and hypoxia using dual-lucifearase assay.

Results: In the presence of E2 (10-7M), the expression of BMPR2, phosphorylated Smad (p-Smad)1/5/8, Id1 was augmented under normoxic condition and suppressed under hypoxic condition. These alterations of BMPR signal expression were partly inhibited by ICI182.780. An IP-WB experiment demonstrated that possible binding interaction between ER and smad1 proteins. Moreover, eNOS mRNA was also augmented by E2 under normoxia, but it couln't express under hypoxia. In addition, under normoxic condition with CoCl2, the presence of E2 decreased the expression of p-Smad1/5/8. Conversely, under hypoxic condition with YC-1, the presence of E2 augmented the expression of p-Smad1/5/8. The presence of E2 induced ERE activity under normoxia, but couldn't induce under hypoxia.

Discussion: We demonstrated that the alteration of BMPR signal pathway in PAEC under hypoxia or normoxia was associated with HIF-1α expression in the presence of E2. This alteration may also relate to an interaction between BMPR signal pathway and receptor-mediated estrogen pathway. Our observations provide the new mechanism how sex hormone affects on BMPR signal pathway, a key signal pathway for PAH, which can offer novel strategies for the treatment of PAH.

P627 Females undergoing percutaneous coronary intervention have increased risk of contrast induced nephrophathy compared to males

E. Chong[1], L. Shen[2], K.K. Poh[3], H.Y. Ong[1], C.Y. Soon[1], H.C. Tan[3]. *[1]Alexandra Hospital, Singapore, Singapore; [2]Biostatistic Unit National University of Singapore, Singapore, Singapore; [3]The University Heart Center, Singapore, Singapore*

Purpose: Females have higher incidence of contrast nephropathy (CIN) than males. This was mainly due to higher prevalence of baseline renal impairment in female subgroup in published studies. We test the hypothesis that female gender may be an independent predictor of CIN after adjustment of baseline renal function.

Methods: A cohort of 8853 consecutive patients who underwent percutaneous coronary intervention (PCI) from May 1996 to April 2008 was studied. 1886 (21.3%) were females. Patients with estimated glomerular filtration rate (GFR) ≤60 (ml/min/1.73m^2) received saline pre-hydration and oral N-acetylcysteine prophylaxis. Patients with GFR>60 received no prophylaxis. We examined CIN risk predictors and gender influence on CIN after adjusting for co-existing risk factors.

Results: CIN occurred in 12.4% of females and 6.9% of males (p<0.0005). Multivariate analysis adjusting for potential confounding risk factors confirmed that female gender was an independent risk predictor of CIN (OR = 1.69, 95%CI: 1.24 - 2.31; p=0.001). Other significant CIN predictors include baseline renal impairment (GFR≤60), age>70 years, presence of anemia, hypotension, depressed left ventricular ejection fraction, myocardial infarction and high creatinine kinase level. Analysis based on GFR subgroups showed that females with GFR>60 who did not receive prophylaxis had significantly higher risk of developing CIN than males (6.2% in males vs. 12% in females, OR=2.07, 95%CI: 1.46-2.92; p<0.0005). Age>70 in this subgroup was the most important CIN risk predictor

(OR=1.64, 95%CI: 1.01-2.67; p=0.04). In patients with abnormal baseline GFR who received prophylaxis, there were less differences of CIN rate between the genders. GFR 40-60 group (5.2% vs. 9.7% p=0.063); GFR <40 group (28.3% vs. 20.5% p=0.243).
Conclusion: In patients with normal baseline renal function defined by GFR >60 undergoing PCI, females had significantly higher risk of developing CIN compare to males. Old age is a important CIN predictor. CIN prophylaxis should be considered for elderly female patients undergoing PCI.

P628 Females have a higher rate of mortality after primary PCI

K.S. Rathod, D. Jones, E. Wicks, C. Knight, M.T. Rothman, A. Wragg.
Barts and The London NHS Trust, London, United Kingdom

Background: Women are less likely to receive acute reperfusion treatment for STEMI in clinical practice. Little data exist on gender differences in adjunctive treatment and outcome in the setting of primary PCI in Europe. We examined the impact of female gender on hospital outcome of primary PCI in patients with STEMI in clinical practice in the UK.
Methods: From January 2004 to December 2007, 1,163 consecutive patients undergoing primary PCI at a London tertiary referral centre were included. Clinical information was prospectively collected onto a database at the time of the procedure and outcome assessed by all-cause mortality provided by the Office of National Statistics.
Results: Female patients (24%) were (8 years) older than males. There were similar incidences of hypertension (41% vs 35%), hypercholesterolemia (28% vs 30%), diabetes (19% vs 15%), previous MI (11% vs 13%), and previous CABG (1.1% vs 1.5%). Despite the older age no differences in the degree of coronary artery disease were observed. Adjunctive medical treatment including GPIIb/IIIa blocker was similar in women and men. There was similar in hospital mortality between the groups at discharge (1% vs 0.8%), however from 60 days there is a significantly higher mortality in the female group. This difference persists up to the 5 year post MI (13.5% vs 7.5%, P=0.002) (figure 1). The sex difference in mortality persisted after age correction using multivariate analysis (p=0.01)

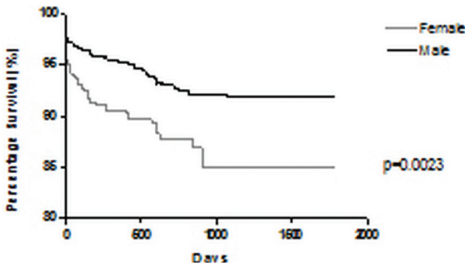


Figure 1. Survival of male and female patients after primary PCI for STEMI

Conclusion: Women undergoing primary PCI were significantly older than there male counterparts. There was a significantly higher mortality in the female group despite similar risk factor profiles and degree of coronary artery disease. This difference is still significant when correcting for age.

P629 Gender differences in management and outcomes of European patients with symptomatic atherothrombotic disease in the REACH Registry

J. Morrell[1], U. Zeymer[2], I. Baumgartner[3], T. Limbourg[2], P.G. Steg[4], D.L. Bhatt[5] on behalf of the REACH Registry investigators.
[1]Conquest Hospital, St Leonards On Sea, United Kingdom; [2]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [3]University Hospital, Bern, Switzerland; [4]Bichat-Claude Bernard Hospital (AP-HP), Paris, France; [5]Brigham and Women's Hospital, Boston, United States of America

Purpose: The REACH Registry is an international prospective registry of outpatients with symptomatic atherothrombotic disease or multiple risk factors (RFs) for atherothrombotic events (67,888 patients enrolled in 44 countries). Previous studies reported fewer interventions, and less aggressive medical therapy in women compared with men, with variable differences in outcomes.
Methods: We compared baseline medication and 2-year interventions and outcomes between women and men enrolled in the REACH Registry in Europe. Interventions and outcomes were analysed in a multivariate model, adjusting for variables including age.
Results: Of 19926 symptomatic patients enrolled in the REACH Registry in Europe 18406 (women, 29.6% [age, 69.1±9.8]; men, 70.4% [age, 65.8±9.6 years]) completed 2-year follow-up. At baseline, a higher proportion of women had diabetes (29.2% women vs. 26.6% men, P<0.001, OR: 1.14 [95%-CI: 1.06–1.22]), hypertension despite treatment (58.7% vs. 45.6%, P<0.0001, OR: 1.70 [1.59–1.81]) and elevated cholesterol levels (70.8% vs. 56.9%, P<0.0001, OR: 1.84 [1.71–1.99]), while a lower proportion of women were smokers (7.7% vs. 14.1%, P<0.0001, OR: 0.51 [0.46–0.57]). Despite higher levels of treatable RFs, the intensity of antithrombotic and lipid-lowering medical therapy was lower in women (Table). At 2-year follow-up, fewer women had undergone interventions (coronary angioplasty/stenting [3.3% vs. 5.0%, p<0.0001, OR: 0.66 (0.55–0.78)]; carotid angioplasty/stenting [0.4% vs. 0.6%, ns, OR: 0.66 (0.40–1.08)] or peripheral bypass graft [1.2% vs. 2.0%, p<0.001, OR: 0.61 (0.46–0.81)]. The combined rate of MACCE was not different between women and men (7.0% vs. 6.8%, ns, OR: 1.03 [0.91–1.17]). Multivariate adjustment did not alter the significance of between-sex differences in interventions (and MACCE, ns [all patients]).

Baseline medication use (symptomatic)

	Women (%) n=6717	Men (%) n=14521	Odds ratio (95% CI)
≥1 antithrombotic agent	91.9	95.0‡	0.60 (0.53–0.68)
≥1 lipid-lowering agent	68.6	73.4‡	0.79 (0.74 0.85)
Hypertensive patients with ≥1 antihypertensive agent (%)	99.6	99.2*	2.05 (1.21–3.48)
Diabetic patients with ≥1 antidiabetic agent (%)	89.5	85.7†	1.41 (1.18–1.69)

*P<0.01, †P<0.001, ‡P<0.0001; Women vs Men.

Conclusions: Considerable differences were found between women and men in risk profile and medical treatment, and revascularisation procedures. No difference was found in MACCE at 2-years follow up.

P630 Female gender and vascular disease are true risk factors for stroke in patients with atrial fibrillation: data from the Euro Heart Survey

R. Pisters[1], R. Nieuwlaat[2], G.Y.H. Lip[3], D.A. Lane[3], C.B. De Vos[1], H.J.G.M. Crijns[1]. *[1]University Hospital Maastricht, Maastricht, Netherlands; [2]McMaster University, Hamilton, Canada; [3]City Hospital, Birmingham, Birmingham, United Kingdom*

Purpose: Heterogeneity exists in the risk factors used among available stroke risk classification schemes for atrial fibrillation (AF) patients. Consequently, individual patient classification and predictive accuracy of the schemes differ.
Methods: Using data from Euro Heart Survey AF patients who were not treated with oral anticoagulation (OAC), we assessed the predictive power of established and 'less well validated' stroke risk factors for the occurrence of TE (stroke, pulmonary or peripheral thromboembolism) during one year follow-up.
Results: 1084 (20%) patients did not receive OAC, of whom 802 (74%) were taking an antiplatelet drug. Twenty-five (2.3%) patients experienced a TE during follow-up. Univariate analysis identified female gender, stroke/TIA, diabetes and vascular disease as TE risk factors (all p<0.05) Multivariate logistic regression (Table 1) revealed that only female gender was significantly associated with TE [OR 2.53 (1.08-5.92); p= 0.029]. There was a positive trend for vascular disease [OR 2.27 (0.94-5.46); p=0.063]. Heart failure and LVEF ≤40% were not associated with an increased risk for TE.

Uni- and multivariate TE predictors

	Event rate with risk factor	Event rate without risk factor	Univariate p-value	Odds Ratio#	Multivariate p-value#
Age >75	11 (3.6)	14 (1.8)	0.083	1.46 (0.63-3.35)	0.383
Female	16 (3.6)	9 (1.4)	0.017	2.53 (1.08-5.92)	0.029
Stroke/TIA	5 (5.9)	20 (2.0)	0.023	2.22 (0.78-6.35)	0.163
Hypertension	19 (2.6)	6 (1.7)	0.349	1.01 (0.38-2.66)	0.992
Diabetes	8 (4.3)	17 (1.9)	0.048	1.79 (0.73-4.40)	0.220
Heart failure	6 (2.4)	19 (2.3)	0.967	0.72 (0.27-1.88)	0.493
LVEF <40	1 (0.8)	12 (2.1)	0.335	0.34 (0.04-2.73)	0.243
Vascular disease*	16 (3.6)	9 (1.5)	0.022	2.27 (0.94-5.46)	0.063

#All other results than LVEF (not available for 37%) from model without LVEF. *Coronary artery disease, peripheral vascular disease or a previous thromboembolism other than stroke/TIA.

Conclusions: Female gender and vascular disease, both infrequently used in current stroke risk classification schemes, were important risk factors of TE after one year among this cohort of AF patients. These results suggest that the incorporation of female gender and history of vascular disease into stroke risk schemes might improve risk classification.

P631 Spectacular decrease in mortality in women with STEMI: an effect of public awareness campaigns?

T. Simon[1], J.M. Lablanche[2], J.J. Dujardin[3], P. Gueret[4], D. Blanchard[5], G. Mulak[6], E. Drouet[6], J.P. Cambou[7], J. Ferrieres[7], N. Danchin[8] on behalf of FAST-MI investigators. *[1]AP-HP - Hopital St Antoine, Paris, France; [2]Hopital Cardiologique CHRU de Lille, Lille, France; [3]CHG, Douai, France; [4]AP-HP - Hopital Henri Mondor, Creteil, France; [5]Clinique St Gatien, Tours, France; [6]Societe Francaise de Cardiologie, Paris, France; [7]CHU de Toulouse - Hopital de Rangueil, Toulouse, France; [8]European Hospital George Pompidou (AP-HP), Paris, France*

Background: Public campaigns have stressed the specific CV risk of women. We assessed the potential impact of these campaigns on management and outcomes in younger and older women with STEMI.
Methods & results: 3 nationwide 1-month registers in France in 1995, 2000 and 2005. Evolution of baseline parameters, management and outcomes was anal-

ysed according to age group (<65 v. ≥65 years). There were 4985 STEMI patients, with 1384 women (28%), a proportion which did not change over time.
The 10-year age gap between women and men persisted throughout the observation period. In women, however, the % ≤50 years increased from 3.7% to 8.3% to 11.0% from 1995 to 2005, and there was a concomitant increase in current moking in this age group, from 30% to 47% and 52%. In men, the % ≤50 years (20% to 23%), as well as the prevalence of current smoking (60% to 61%) remained stable.
Reperfusion therapy use increased more markedly in women than men (20% vs 12%), as did the use of in-hospital PCI (12% to 66%). Early (<48 hours) treatment with statins (6% to 74%), antiplatelet agents (88% to 95%), beta-blockers (51% to 68%) or ACE-I (44% to 48%) increased in women, whereas in men only statin therapy significantly increased (11% to 80%), while there was no substantial change for the other classes (94% to 96%, 71% to 74%, 49% to 50%, respectively).
From 1995 to 2005, 30-day mortality in women decreased from 23.7% to 12.9% to 9.7% (p<0.001). In the ≥ 65 age group, mortality decreased by 51% in women, compared to 31% in men so that the gender difference in early mortality in 1995 (26.4% v 16.5%, p<0.001) was no longer significant in 2005 (12.8% v 11.4%). In the younger age group (<65 years), there was a huge decrease in mortality in women (12.0% v 7.1% v 1.6%, p=0.009), while it did not substantially change in men (2.9% v 2.7% v 2.3%).
Conclusion: over the past 10 years, early mortality of women, including younger women, with STEMI has become comparable with that of men. This goes along with marked increases in reperfusion therapy, PCI and recommended medications. Of note, however, among STEMI patients, the proportion of younger women has increased, with a concomitant increase in the prevalence of current smoking in this population. In spite of these remarkable achievements, efforts to combat risk factors in women should therefore continue.

P632 Evolution of myocardial infarction prognosis by sex in the last 30 years

M. Grau[1], A. Sureda[2], C. Sala[3], J. Vila[1], R. Elosua[1], J. Sala[2], R. Masia[2], R. Ramos[4], J. Marrugat[1] on behalf of REGICOR. *[1]Institut Municipal D'investigacio Medica - Imim, Barcelona, Spain; [2]Hospital Universitari Dr Josep Trueta, Girona, Spain; [3]CAP Sagrada Familia, Manresa, Spain; [4]Unitat de Recerca d'Atenció Primària, Girona, Spain*

Purpose: The aim of the study was to assess sex differences in 28-day and 2-year major coronary heart disease (CHD) event rate over the last 30 years.
Methods: We analyze 28-day mortality, and 2-year unstable angina, or fatal or non-fatal myocardial infarction in 28-day survivors in a cohort of first Q-wave MI patients aged 25-74 years, consecutively recruited in a population-based hospital registry. The 30-year study span was divided in 4 periods: 1978-84, 1985-91, 1992-98, and 1999-2005.
Results: We included 3,845 patients. Women were significantly older, had more frequently history of diabetes and hypertension (44.7% vs., 20.3% and 63.4% vs., 42.7%, p-value<0.001), and also developed more severe events (acute pulmonary oedema or cardiogenic shock (25.9% vs., 11.2%, p-value<0.001) than men. Thrombolysis tended to be used less often in women (23.5% vs 33.0%, p-value<0.001). Although 28-day, and 2-year overall prognosis improved over time, both were worse in women than men in all periods (See table) [Average OR 2.2 (1.7-2.8) and 2.0 (1.4-2.8), respectively]. These differences were related to severity at short-term and with comorbidity at long-term.
Conclusions: Overall first Q-wave MI patients short- and long-term prognosis improved over the last 30 years but women continue to fare than men. These differences are mainly related to the comorbidity and the severity of the events.

P633 Correlation of estimated glomerular filtration rate with left ventricular hypertrophy and remodeling in women

A. Yoshikawa, S. Hamasaki, S. Ishida, T. Kataoka, K. Saihara, H. Okui, T. Shinsato, S. Yoshino, K. Nakashiki, C. Tei. *Kagoshima University, Kagoshima, Japan*

Purpose: Chronic kidney disease (CKD) is a risk factor for cardiovascular disease. And it's well known that left ventricular (LV) hypertrophy is a strong predictor of women's cardiovascular mortality. The purpose of this study was to investigate gender differences in effect of CKD on LV hypertrophy and remodeling.
Methods: Using the resource of University Hospital cardiac catheterization labo database, 3,094 consecutive patients (2,081 men, mean age 64±14 years) were investigated. We defined CKD if the estimated glomerular filtration rate (eGFR) was less than 60mL/min/1.73m^2. Left ventricular (LV) interventricular and posterior wall thickness (IVSth, PWth) and LV mass index (LVMI) by 2D and M-mode echocardiography, and LV end diastolic volume index (LVEDVI) and LV end systolic volume index (LVESVI) by LV graphy were assessed.
Results: SBP and DBP were comparable between CKD patients (n=1142) and non-CKD patients (n=1952) in both gender. IVSth, PWth and LVMI were greater in CKD patients than those in non-CKD patients in women (12.1±3.0 vs 11.0±3.2 mm, p<0.01; 11.2±2.1 vs 10.2±1.9 mm, p<0.01; 146.0±57.3 vs 120.8±48.9 g/m^2, p<0.01, respectively), but not in men. Moreover, inverse correlations of eGFR existed with IVSth, PWth, and LVMI in women (r=-0.20, p<0.01; r=-0.26, p<0.01; r=-0.28, p<0.01, respectively), but not in men. LVEDVI and LVESVI were greater in CKD patients than those in non-CKD patients in women (81.6±40.7 vs 71.4±32.5mL/m^2, p<0.01; 37.0±28.5 vs 28.9±20.3 mL/m^2, p<0.01, respectively), but not in men. eGFR had inverse correlation with LVEDVI and LVESVI in women (r=-0.13, p<0.05; r=-0.20, p<0.01), but not in men.
Conclusion: In women, renal dysfunction is associated with LVH and has a contribution to LV remodeling, which may explain the mechanism that LVH is a strong predictor of women's cardiovascular mortality.

P634 Role of abdominal fat compartimentation on wave reflections: differences between men and women

V. Katsi, G. Moustakas, E. Chatzistamatiou, D. Tousoulis, E. Androulakis, C. Vlachopoulos, C. Stefanadis, I. Kallikazaros. *Hippokration General Hospital of Athens, Athens, Greece*

Objective: Central obesity is an established cardiometabolic risk factor. Howerver, gender specific abdominal fat compartimentation is less well studied. The aim of our study was to evaluate the effect of subcutaneous and preperitoneal fat compartments, expressed by abdominal fat index (AFI) on metabolic profile and arterial properties seperately in essential hypertensive men and women.
Methods: We studied 369 consecutive never treated essential hypertensive men (n=183, aged 52±10 years) and women (n=186, 57±12 years), non diabetic, with normal waist circumference (92±9 and 73±13, respectively). In all participants were recorded anthropo,etrics variables and venous blood sample wa taken to determine their metabolic profile. Aortic stiffness was evaluated, on the basis of c-f PWV by means of a computerized method (Complior SP). Heart rate-corrected augmentation index (AIx75) was estimated as a measure of wave reflections. Ultrasonography was used for the assessment of abdominal fat distribution. Subcutaneous (S) and preperitoneal (P) fat layers were measured at their maximum and minimum thickness sites on the upper median abdomen. AFI was calculated as Pmax to Smin ratio.
Results: Women had better metabolic profile than men, according to fasting plasma glucose, total cholesterol, low-density lipoprotein, Triglyceride and high-density lipoprotein levels (97±9 vs. 97±5 mg/dl p=0,869, 201±43 vs. 213±38 mg/dl p=0.036, 133±40 vs. 139±43 mg/dl p=0.043, 116±52 vs. 140±79 mg/dl p=0.010, 59±14 vs. 42±10 p<0.001, respectively) and lower AFI (0.87±0.52 vs. 1.24±0.72 p<0.001), though more subcutaneous (18±7 vs. 15±6 p<0.0001) than preperitoneal fat accumulation (14±6 vs. 16±6 p=0.078). On the contrary, women had increased AIx75 than men (30.3±6 vs. 23±10 p<0.001), while they did not differ regarding PWV (8.52±1.6 vs. 8.6±1.9 p=0.611).
Conclusion: This findings indicate that in essential hypertensive women with normal waist circumference, lower abdominal fat index and higher subcutaneous fat accumulation is associated with lower levels of total cholesterol, low-density lipoprotein, triglyceride, high-density lipoprotein and augmented peripheral wave reflections. Thus, central obesity mainly affects the metabolic profile and peripheral wave reflections in women.

P635 Inflammatory indices and glycaemic control in Post-menopausal diabetic women

T.H. Gialernios[1], K. Gialernios[1], A. Triantafyllou[1], S. Kougialis[1], E. Skopelitis[1], A. Antonopoulos[1], M. Lambropoulos[1], A. Polydorou[2]. *[1]3rd Hospital of IKA Cardiology Department, Athens, Greece, Athens, Greece; [2]Evangelismos General Hospital of Athens, Athens, Greece*

Objective: Inflammation and glycohemoglobin (HbA1c) are established risk factors for the development of cardiovascular disease. Recent evidence implicates hs-CRP, IL1 and IL4 and thus inflammation, in the metabolic syndrome and diabetes mellitus, particularly in women. We investigated the synergy of pro-inflammatory state and glycaemic control of post-menopausal NIDDM women (in order to avoid IDDM like mechanism diabetes where inflammatory indices are elevated in any case).
Methods: Several inflammatory markers among them high sensitivity C-reacting protein (hsCRP), Inteleukin 1 (IL1) and Interleukin 4 (IL4) were measured in 1002 NIDDM post-menopausal women. Homocysteine (HOMO), white blood count (WBC) and traditional risk factors such as age, body mass index, triglycerides,

Abstract P632 – Table 1

	28-day mortality				2-year mortality or reinfarction (28-day survivors)		
	OR [95%CI]	OR* [95%CI]	OR** [95%CI]	OR† [95%CI]	OR [95%CI]	OR* [95%CI]	OR**[95%CI]
1978-1984	2.3 [1.4, 3.7]	1.7 [0.9, 3.2]	1.4 [0.6, 3.4]	1.4 [0.6, 3.4]	1.2 [0.6, 2.3]	1.0 [0.5, 2.1]	0.7 [0.3, 1.5]
1985-1991	2.7 [1.8, 4.2]	1.8 [1.1, 3.1]	1.5 [0.8, 2.9]	1.4 [0.7, 2.7]	2.2 [1.4, 3.7]	2.0 [1.2, 3.3]	1.8 [0.9, 3.4]
1992-1998	1.8 [1.1, 3.0]	1.1 [0.6, 2.0]	0.8 [0.4, 1.6]	0.8 [0.4, 1.6]	2.0 [1.2, 3.3]	1.7 [1.0, 2.8]	1.4 [0.8, 2.4]
1999-2005	2.3 [1.3, 3.9]	1.3 [0.7, 2.4]	1.1 [0.5, 2.5]	0.8 [0.3, 2.2]	2.2 [1.3, 3.6]	2.0 [1.2, 3.3]	1.6 [0.9, 3.0]

*Model adjusted for severity. **Model adjusted for severity and comorbidity. †Model adjusted for severity and comorbidity and acute phase treatments.

LDL cholesterol, HDL cholesterol, haemoglobin A1c (Hba1c) were also measured at drug free baseline.
Results: Univariate analysis revealed a significant correlation between Hba1c and hsCRP (Pearson r=0.45, p<0.001), SAA (Pearson r=0.40 p<0.001), IL1 (Pearson r=0.47 p<0.001) and IL4 (Pearson r=0.37 p=0.02) in post-menopausal women and to HOMO (Spearman ρ =0.33, p<0.001) only in patients after hysterectomy. Multiple linear regression analysis was applied in order to verify the relation of Hba1c to inflammation markers, adjusted to age, plasma creatinine, systolic blood pressure, hyperlipidemia and duration of menopause. In women with hysterectomy SAA (β=0.034 p=0.012) and WBC (β=0.0004 p=0.02) were significant independent predictors of glycaemic control whereas for hysterectomy patients IL1 (β=0.032 p=0.01) and IL4 (β=0.046 p<0.001) but also hsCRP (β=0.35 p=0.03) were positively related to Hba1c increase.
Conclusion: These results suggest that inflammatory response is strongly related to glycaemic control in post-menopausal diabetic women and this effect could be a great tool for diabetic screening and follow up of those patients.

P636 Gender-specific differences in initial clinical presentation and outcome of idiopathic dilated cardiomyopathy

J. Franke, L. Frankenstein, P. Ehlermann, A. Remppis, C. Zugck, H.A. Katus. *Universitaetsklinikum Heidelberg, Heidelberg, Germany*

Background: It is known that the clinical course of patients with dilated cardiomyopathy depends largly on the stage of the disease at initial presentation. Gender-specific differences concerning the time of initial clinical presentation have not yet been thoroughly examimed.
Patients and Methods: Between 1994 and 2007, 789 patients (257 women and 658 men) with idiopathic dilated cardiomyopathy were prospectively included and examined on an outpatient setting at the specialist cardiomyopathy clinic at the University Hospital. Concomitent diseases, medication and clinical status were documented, echocardiography, six-minute-walk-test, ECG, blood tests including neurohumoral parameters were performed at baseline and each follow up visit.
Results: see Table 1.

Table 1. Baseline clinical presentation and outcome

	Men (n=658)	Women (n=257)	p-value
Age (median in years)	52	55	n.s.
NYHA I [n (%)]	181 (27.5%)	54 (21.0%)	n.s.
NYHA II [n (%)]	261 (39.7%)	93 (36.2%)	n.s.
NYHA III [n (%)]	208 (31.6%)	106 (41.2%)	<0.01
NYHA IV [n (%)]	8 (1.2%)	4 (1.6%)	n.s.
Left ventricular systolic function			
40-49% [n (%)]	61 (9.3%)	34 (13.2%)	n.s.
30-39% [n (%)]	136 (20.7%)	70 (27.2%)	p<0.05
<30% [n (%)]	436 (66.3%)	131 (51.0%)	p < 0.0001
pVO_2 in ml/min/kg (mean ± SD)	16.6±5.9	15.0±5.4	n.s.
6'WT in meters (mean ± SD)	500.4±116,5	462.7±98,2	p < 0.001
NTproBNP in pg/ml (median)			
Interquartile range	1179392–2837	984220–2439	n.s.
HF in bpm (mean ± SD)	74±15	74±16	n.s.
RR in mmHg (mean ± SD)	97±15	98±25	n.s.
Freedom of death			
1 year	91,9% [0,85–0,93]	91,5% [0,81–0,10]	n.s
3 year	82,2% [0,76–0,89]	82,7% [0,72–0,94]	n.s
5 year	73,7% [0,66–0,81]	79,4% [0,68–0,91]	n.s

Conclusion: Although women initially present with more severe functional impairment, severly impaired left ventricle ejection function is more common in men. Outcome up to five years does not differ between genders.

P637 Impaired fasting glucose, diabetes and early phase of menopause are the strongest determinants of premature coronary artery disease in women

E. Skora[1], B. Lubiszewska[1], M. Kruk[1], G. Broda[2], E. Ksiezycka[1], P. Kurjata[2], W. Piotrowski[2], W. Ruzyllo[1]. *[1]Institute of Cardiology, Department of Coronary Heart Disease, Warsaw, Poland; [2]Department of CVD Epidemiology, and Prevention, and Health Promotion, Institute of Cardiology, Warsaw, Poland*

Purpose: To assess the significance of metabolic syndrome (MS) as a whole versus its components (according to AHA/NHLBI definition with lowering the threshold for impaired fasting glucose (IFG) to 5.6mmol/l) including diabetes, and to define the contribution of menopause to premature coronary artery disease (CAD) in women.
Methods: A single-center, case-controlled study comprised 323 women with established premature CAD (before 55 years), enrolled between April 2005 and December 2007, and 347 age-matched healthy women selected from the National Health Study.
Results: In women with premature CAD the prevalence of MS was 42.9% versus 17.4% (prevalence ratio 2.5). By multivariate analyses (adjusted for smoking, BMI and menopause), presence of MS with diabetes was strong independent determinant of early onset CAD in women with odds ratio (OR) 3.9;95%CI 2.5-5.9. However, in multivariate models comprising MS components adjusted for the same variables, OR for IFG or diabetes was higher than MS as a whole (5.6;95%CI 3.6-8.7). Menopausal status, particularly its early phase up to 5 years of its duration occurred strong and independent marker of premature CAD (OR 3.4;95%CI 2.2-5.2) as opposed to OR 2,1; 95%CI 1,2-3,5 for menopause lasting above 5 years.
Separate analyses performed for 150 women admitted with the onset CAD showed enhanced role of IFG and diabetes as a marker of premature CAD up to eightfold (OR 7.9; 95%CI 4.7-13.3), decreasing the role of MS as a whole (OR 3.7;95%CI 2.2-6.1). OR for smoking, and early phase of menopause was 3.65;95%CI 2.2-6.1, 3.0;95%CI 1.8-5.1, respectively. Other components of MS were insignificant. Additional adjustment for hormone replacement therapy did not change the influence of IFG, however decreased the role of menopause (OR<2.0).
Conclusions: Impaired fasting glucose or diabetes was the strongest determinant of premature CAD in women, stronger than the metabolic syndrome as a whole. Early period of menopause, below 5 years of its duration was also significant and independent marker of premature CAD in women.

P638 Association between endogenous serum testosterone concentrations and arterial stiffness in erectile dysfunction patients

A. Aggelis, C. Vlachopoulos, D. Terentes-Printzios, N. Ioakeimidis, K. Rokkas, K. Aznaouridis, N. Alexopoulos, G. Sakellariou, C. Fassoulakis, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: ED is a silent marker of vascular disease, particularly coronary artery disease (CAD), in otherwise asymptomatic men. Low testosterone levels and increased arterial stiffness are predictive markers for those at high risk of cardiovascular disease. The relationship between testosterone and arterial stiffness in patients with ED is unknown.
Methods: Total testosterone levels were measured in 202 asymptomatic men with ED who were prospectively evaluated for CAD. Carotid-femoral pulse wave velocity (PWV) as an index of aortic stiffness, augmentation index (AIx) as an index of wave reflections and pharmacologically stimulated penile peak systolic velocity (PSV) were used to assess vascular dysfunction. Lower penile Doppler velocities indicate impaired arterial function and vice versa.
Results: Testosterone levels were correlated with PSV (r=0.28, p<0.01), PWV and AIx (figure, upper panel). In multivariate regression models adjusting for potential confounders, testosterone was an independent predictor of penile (PSV) (p<0.01) and systemic (PWV, AIx) arterial function parameters (p<0.05). The combination of lower testosterone level (<4.1ng/ml) with higher carotid-femoral PWV (>8.4 m/s) and AIx (>21%) values showed greater effect on 10-year risk of a cardiovascular event (figure, lower panel).

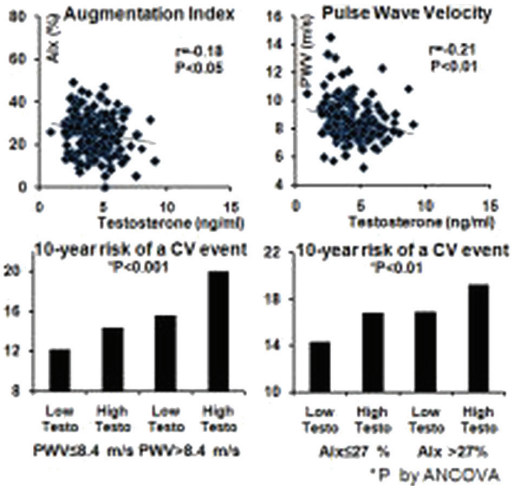


Figure 1. Testosterone and arterial stiffness

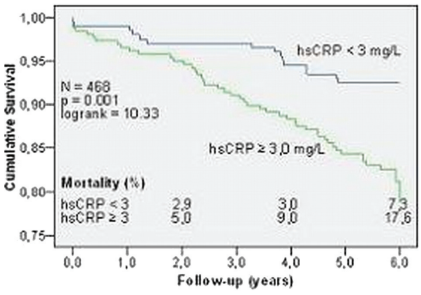
Conclusions: In ED patients, low testosterone levels are independently associated with aortic stiffening and wave reflections. This finding underlines the important role of testosterone as a marker of arterial damage, and implies a contribution of this compound to the pathophysiology of cardiovascular disease.

PERCUTANEOUS CORONARY INTERVENTION: LONG-TERM OUTCOME AND PREDICTOR FACTORS OF FAILURE

P639 High-sensitivity C-reactive protein predicts long-term survival in a sirolimus-eluting stent population. Insights from 6 years of follow-up in the RESEARCH registry

R.M. Oemrawsingh[1], Y. Onuma[1], M. Degertekin[2], H.P. Stoll[3], E. Boersma[1], P.W. Serruys[1], R.T. Van Domburg[1]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]Yeditepe University Hospital, Istanbul, Turkey; [3]Cordis Corporation, Waterloo, Belgium*

Purpose: Elevated levels of high-sensitivity C-reactive protein (hsCRP) at the time of admission for acute coronary syndromes (ACS) are associated with significantly worse in-hospital to one year outcome. Scarce data exist on the longer-term prognostic value of hsCRP in the "real world" drug eluting stent population, comprising both stable angina and ACS-patients.
Methods: Periprocedural plasma levels of hsCRP were determined in 468 PCI patients with sirolimus-eluting stent implantation from April to October 2002. The median hsCRP value of 3,0 mg/L was used as a cut-off point between a low (control) and high hsCRP group. Kaplan-Meier and Cox' regression analyses were applied to evaluate the relation between hsCRP and the occurrence of all-cause death.
Results: Follow-up duration comprised 6 years, with survival being similar in both groups until 2 years. Thereafter divergence of the curves was observed until the end of follow-up (p= 0,001). After adjustment for all baseline characteristics hsCRP $\geq$ 3,0 mg/L remained a significant outcome determinant for the occurrence of death (HR 2,47 [95% CI: 1,36; 4,51]).



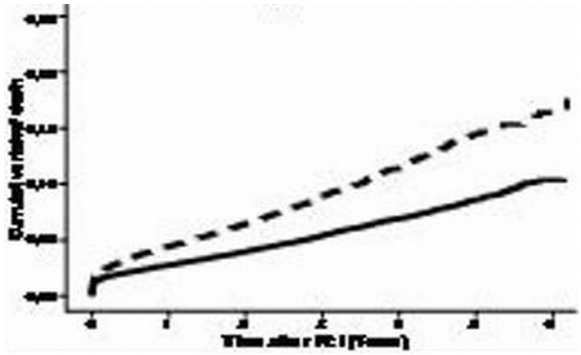
Six year follow-up by after SES

Conclusion: Periprocedural hsCRP levels $\geq$ 3,0 mg/L are associated with higher long-term mortality in an "all comers" DES population. The survival curves displayed ongoing divergence from 2 until 6 years of follow-up.

P640 Long-term mortality after PCI in patients with diabetes mellitus. Results from Swedish coronary angiography and angioplasty registry

A. Norhammar[1], B. Lagerqvist[2], N. Saleh[1]. *[1]Karolinska, Stockholm, Sweden; [2]Uppsala University Hospital, Uppsala, Sweden*

Purpose: Patients with diabetes mellitus have a worse outcome following acute coronary syndromes and coronary revascularisation. However knowledge on long-term outcome after revascularisation in a real life situation is spares. We analysed long-term mortality after a first PCI in patient with no previous revascularisation.
Methods: Patients included in the Swedish Coronary Angiography Angioplasty Registry (SCAAR) between the years 2002-2007 and with no previous revascularisation, were followed for mortality after a first PCI until the end of 2007 (mean follow up time 1059 days). Differences in background and procedural characteristics were adjusted for in a multivariable Cox regression model.



Results: Among 57 708 patients 18.8% had diabetes. Patients with diabetes had more risk factors, more often multiple vessel disease and had less often a complete revascularisation. Adjusted mortality after PCI was higher in patients with diabetes than those without OR (95%CI); 1.66 (1.33-1.72). Even after consideration of different indications for PCI outcome was worse in patients with diabetes with higher adjusted mortality after stable angina OR (95%CI); 2.01 (1.69-2.40), unstable angina 1.73 (1.58-1.90) and STEMI 1.44 (1.30-1.59).
Conclusion: Adjusted long-term mortality is higher in patients with diabetes compared to those without after a first PCI. This increased risk is especially obvious among diabetic patients with stable angina and among patients at lower age. Improved secondary preventive measures are needed to improve this situation.
Figure: Adjusted mortality after first PCI for patients with (broken line) and without (solid line) diabetes.

P641 5-year incidence and risk factors of late definite thrombosis of paclitaxel-eluting stents

X. Flores Rios, J.P. Abugattas De Torres, G. Aldama Lopez, P. Pinon Esteban, R. Calvino Santos, J.M. Vazquez Rodriguez, N. Vazquez Gonzalez, A. Castro Beiras. *Hospital Juan Canalejo, A Coruna, Spain*

Background: Natural history and long-term incidence of drug-eluting stent (DES) thrombosis is not well known to date. It has been suggested that there is a linear relationship between time and occurrence of late thrombosis of DES, so incidence could rise as duration of follow-up increases. We sought to investigate the frequency, chronological evolution and risk factors of late and very late thrombosis after DES implantation after 5-year follow-up.
Methods: Consecutive patients (N = 604) who received $\geq$1 paclitaxel-eluting stent(s) (PES) between June 2003 and December 2004 at our institution were enrolled. Late and very late definite thrombosis (LST) of PES, according to current definitions of the Academic Research Council, were the main endpoint of our study. Cumulative incidence of LST was estimated using the Kaplan-Meier method. A multivariate Cox regression analysis was performed to detect possible risk factors for LST, accounting for clinical and angiographic variables that have been previously associated with stent thrombosis.
Results: During long-term follow-up (median 58.1 months, IQR 8.4), we found 20 cases of LST (cumulative incidence 3.3%, 95% CI 2.0% - 5.1%). The median time to LST was 22.1 months (IQR 16.8). Late and very late definite PES thrombosis occurred at a constant rate throughout the 5-year follow-up period (incidence rate 0.7% patient-years, 95% CI 0.4% to 1.1% patient-years). Withdrawal of antiplatelet therapy (HR 5.3, 95% CI 1.9 to 14.6), left ventricular ejection fraction (HR 0.96, 95% CI 0.93 to 0.99), average stent diameter (HR 0.1, 95% CI 0.02 to 0.39), and use of a PES for the treatment of in-stent restenosis (HR 3.9, 95% CI 1.2 to 12.4) were identified as risk factors for LST in multivariate analysis.
Conclusions: After one of the longest follow-up periods available to date, LST of PES continues to happen at a constant rate during time. Average stent diameter, left ventricular function, stent restenosis and withdrawal of antiplatelet therapy were independent predictors of LST in our series.

P642 Sirolimus-eluting versus bare-metal stents for the reduction of coronary restenosis: 3-year clinical outcome and economic analysis of the GERSHWIN study

S. Willich[1], B. Brueggenjuergen[1], D. Mcbride[1], C. Bode[2], C. Hamm[3], K.H. Kuck[4]. *[1]Charite University Medical Center, Berlin, Germany; [2]University of Freiburg, Freiburg Im Breisgau, Germany; [3]Kerckhoff Klinik GmbH, Bad Nauheim, Germany; [4]Asklepios Klinik. St. Georg, Hamburg, Germany*

Background: The GERSHWIN Study (German Stent Health Outcome and Economics Within Normal Practice) was designed to evaluate long-term outcome and economic implications of drug-eluting sirolimus stents (SES) vs. bare-metal stents (BMS) in the treatment of coronary artery disease (CAD).
Methods: In this prospective intervention study in 35 hospitals in Germany, CAD patients undergoing elective PCI were treated with BMS or SES (sequential control design with case:control ratio of 2:1). Standardised questionnaires were completed by patients and their physicians at 3, 6, 12, 18, 24 and 36 months following PCI to document major adverse cardiac events (MACE) including death, myocardial infarction (MI), coronary bypass surgery (CABG) and intervention for restenosis, as well as disease-related direct and indirect costs. Patient health-related and disease-specific quality of life was assessed with the SF-36 and MacNew heart disease questionnaires. Results are adjusted for significant baseline differences.
Results: From April 2003 until June 2005, 658 patients were treated with SES (mean age 63$\pm$9, 87% male) and 294 patients with BMS (mean age 64$\pm$10, 79% male). After 36 months, 16% of the SES vs. 25% of the BMS group had undergone PCI for restenosis (p=0.014) and there was no difference in the respective rates of MI (4% vs. 5%, p=0.809), CABG (3% vs. 3% p=0.781) nor death (5% vs. 4%, p=0.483). Overall MACE tended to be lower in SES compared to BMS (25% vs. 31%, p=0.099). The initial hospital costs associated with SES were higher than with BMS (6,001$\pm$57 vs. 3,913$\pm$69 Euro, p$<$0.01), and the respective 36-month follow-up direct and indirect costs were similar (11,666$\pm$585 vs. 11,566$\pm$702 Euro, p=0.886), leading to higher overall disease-related costs over 36 months in the SES compared to BMS group: 17,666$\pm$590 vs. 15,480$\pm$709 Euro, p$<$0.01. The cost-effectiveness ratio of SES equaled 21,285 Euro per avoided PCI for

restenosis. Quality of life (MacNew) was significantly higher in SES compared to BMS patients 6 and 12 months after PCI, but not significantly different thereafter.
Conclusions: In comparison to patients with BMS, patients with implantation of SES experienced less intervention for restenosis but similar overall MACE during a 36-month follow-up. The higher initial cost associated with SES compared to BMS were followed by similar economic consequences in both groups during 36-month follow-up.

P643 Clinical and angiographic predictors of stent thrombosis after drug-eluting stent implantation: results from the prospective multicentre German drug-eluting stent registry (DES.DE)

R. Toelg[1], M. Sherif[1], S. Schneider[2], A. Khattab[1], G. Richardt[1], S. Janko[3], C. Bode[4], M. Haude[5] on behalf of the German drug-eluting stent registry investigators. *[1]Segeberger Kliniken GmbH, Bad Segeberg, Germany; [2]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [3]Städtisches Klinikum München GmbH, Krankenhaus Bogenhausen, München, Germany; [4]Medizinische Universitaetsklinik, Freiburg, Germany; [5]Lukaskrankenhaus GmbH, Neuss, Germany*

Background: Although the efficacy of drug-eluting stents (DES) in reducing restenosis is well established, there remains a safety concern about the risk of stent thrombosis (ST). We evaluated the incidence and predictors of ST after DES implantation in an unselected patient population of the German DES registry.
Methods and Results: A total of 4,857 patients underwent percutaneous coronary intervention with a sirolimus-eluting stent (SES) (n=2,131), paclitaxel-eluting stent (PES) (n=2,680) or both (n= 46) and were followed up for one year. Dual anti-platelet therapy was given for 6 to 12 months. ST at one year as defined by the Academic Research Consortium (ARC) occurred in 185 patients (3.8%), and definite ST was observed in 0.7% of the studied population. Univariate predictors of ST (all ARC definitions) are shown in the table. Multivariate analysis for independant predictors of ST will be presented at the meeting. The cumulative hierarchical incidence of major adverse cardiac and cerebrovascular events (MACCE) -defined as death, myocardial infarction (MI) and stroke- in the study population at one year was 8.3%. Death occured in 4.1% of patients and MI in 3.3%. Target vessel revascularization was necessary in 10.8% of patients. Of all ST patients, 167 patients (90.3%) had MACCE and 135 patients (73%) died.

Table 1. Univariate predictors of stent thrombosis (all ARC definitions) at one year follow-up

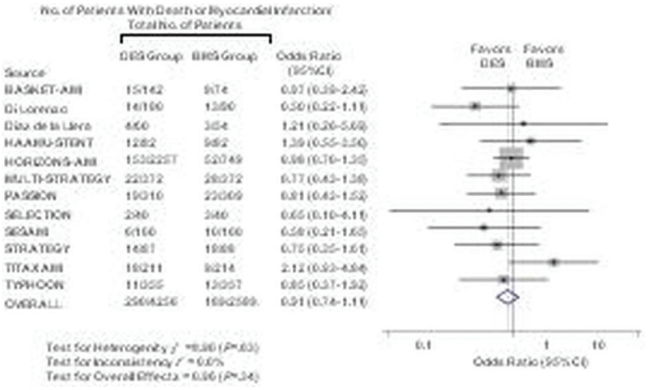
	ST	No ST	OR (95%-CI)	p-value
Atrial fibrillation	17.4%	7.6%	2.55 (1.71-3.79)	<0.0001
Diabetes mellitus	40.1	30.7%	1.51 (1.12-2.05)	<0.01
Heart failure	37.1%	14.3%	3.53 (2.56-4.88)	<0.0001
Renal impairment	27.3%	11.6%	2.86 (2.04-4.01)	<0.0001
Previous myocardial infarction	41.7%	29.8%	1.68 (1.24-2.29)	<0.001
STEMI	13.0%	8.40%	1.63 (1.05-2.53)	<0.05
Cardiogenic shock	3.2%	1.1%	2.97 (1.26-7.02)	<0.01
Ejection fraction < 30%	15.2%	3.0%	5.81 (3.55-9.50)	<0.0001
3-vessel disease	54.6%	38.0%	1.96 (1.46-2.64)	<0.0001

Conclusion: We identified a number of risk factors for stent thrombosis at one year among patients treated with DES in a large "real world" registry. The clinical consequences of stent thrombosis are generally severe including non-fatal myocardial infarction and death.

P644 Drug-eluting stents in acute myocardial infarction: updated meta-analysis of randomized trials

K. Tiroch, A. Dibra, S. Schulz, J. Mehilli, A. Schoemig, A. Kastrati. *Deutsches Herzzentrum Muenchen, Munich, Germany*

Context: Use of drug-eluting stents (DES) in patients with acute myocardial infarction (AMI) remains an "off label" indication due to safety and efficacy concerns.
Objective: To evaluate the safety and efficacy of DES in patients with AMI by incorporating important new evidence into an updated meta-analysis of randomized trials.
Data Sources and Study Selection: We searched relevant Internet-based sources of information on clinical trials in cardiology for randomized trials comparing DES with bare metal stents (BMS) in patients with AMI.
Data extraction: Hazard ratios for the composite of death or recurrent myocardial infarction, (primary safety endpoint), reintervention (primary efficacy endpoint), death, recurrent myocardial infarction, and stent thrombosis were calculated performing a meta-analysis of 14 randomized trials with 7781 patients.
Data synthesis: There was no difference in the hazard of death or recurrent myocardial infarction (hazard ratio [HR], 0.90, 95% confidence interval [CI]: 0.75 to 1.08, P=0.25) between patients treated with DES versus patients treated with BMS. Treatment with DES resulted in a significant reduction in the hazard of reintervention (HR, 0.41; 95% CI: 0.32 to 0.52, P<0.001). The hazards of death (HR, 0.90, 95% CI: 0.71 to 1.15, P=0.41), myocardial infarction (HR, 0.81; 95% CI: 0.63 to 1.04, P=0.10), and stent thrombosis (HR, 0.86; 95% CI: 0.62 to 1.19, P=0.35) were not significantly different between patients treated with DES versus patients treated with BMS. Conclusions Use of drug-eluting stents in patients with acute myocardial infarction is safe and markedly reduces the need of reintervention as compared to bare metal stents.

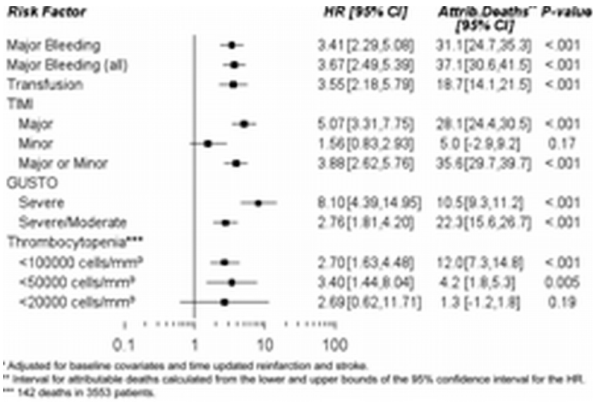


Odds Ratio of death or myocardial infarction associated with drug-eluting stent vs bare-metal stent.

P645 Relative impact of ischemic complications and varying definitions of major bleeding on one year mortality in patients with AMI: results from the HORIZONS-AMI trial

R. Mehran[1], H. Parise[1], B. Witzenbichler[2], G. Guagliumi[3], J.Z. Peruga[4], B.R. Brodie[5], S.J. Pocock[6], G.D. Dangas[1], A.J. Lansky[1], G.W. Stone[1]. *[1]Columbia University Medical Center, New York, United States of America; [2]Charite - Campus Benjamin Franklin, Berlin, Germany; [3]Ospedali Riuniti di Bergamo, Bergamo, Italy; [4]University of Lodz, Lodz, Poland; [5]LeBauer Cardiovascular Research Foundation, Greensboro, United States of America; [6]London School of Hygiene and Tropical Medicine, London, United Kingdom*

Purpose: Ischemic (MACE) and bleeding complications are strongly associated with subsequent early mortality in AMI pts treated with anticoagulant and antiplatelet therapies. The relative impact of MACE and bleeding on overall late mortality in AMI is not well understood. We sought to assess the relative impact of MACE and major bleeding events on mortality in 3,602 pts with STEMI undergoing primary PCI in the HORIZONS-AMI trial.
Methods: A multivariable Cox model identified significant baseline predictors of mortality within the first year. The components of the primary composite endpoint from the trial (reinfarction, ischemic TVR, stroke and major bleeding) were added to the model as time updated covariates. Bleeding was assessed using various bleeding scales.
Results: Within the first year after randomization, there were 147 deaths (4.1%); 44 following a major bleed (non CABG-related) in 268 pts, 16 following a reinfarction in 138 pts, 13 following ischemic TVR in 223 pts, and 9 following stroke in 40 pts. In the fully adjusted model, time updated reinfarction, stroke, and non-CABG major bleeding were significantly associated with one year mortality, while ischemic TVR was not. Major bleeding was strongly associated with mortality regardless of the definition (Figure).



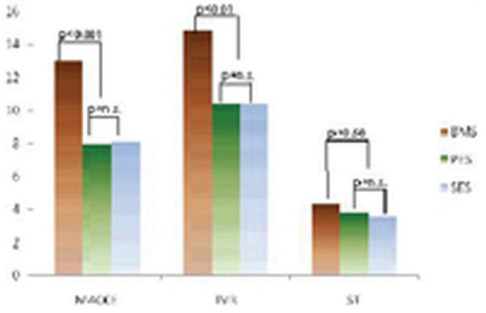
† Adjusted for baseline covariates and time updated reinfarction and stroke.
** Interval for attributable deaths calculated from the lower and upper bounds of the 95% confidence interval for the HR.
*** 142 deaths in 3553 patients.

Conclusions: After accounting for baseline predictors, both reinfarction and major bleeding have a significant impact on mortality at one year in this population. While the hazard ratio for reinfarction is nominally higher, there are more deaths attributable to major bleeding as compared to a reinfarction. These findings illustrate the importance of reducing both major bleeding and reinfarction in preventing deaths after primary PCI for STEMI.

P646 Sirolimus- and paclitaxel-eluting stents compared to bare-metal stents in a real world setting - results from the prospective multicenter German DES.DE registry

I. Akin[1], C.A. Nienaber[1], S. Schneider[2], J. Senges[2], T. Fetsch[3], G. Richardt[4], K.H. Kuck[5] on behalf of DES.DE Study group. *[1]Klinikum der Universitaet Rostock, Rostock, Germany; [2]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [3]IKKF, Munich, Germany; [4]Segeberger Kliniken GmbH, Bad Segeberg, Germany; [5]Asklepios Klinik. St. Georg, Hamburg, Germany*

Purpose: The prospective multicenter German DES.DE registry is an observational study to analyze and evaluate the therapeutic principle of both, the differential drug-eluting stents [Sirolimus (SES) - and Paclitaxel-eluting (PES)] and BMS under real world conditions in the context of the German Health System.
Methods: Baseline clinical and angiographic characteristics, predefined procedural as well as clinical in-hospital and follow-up events were recorded for all enrolled patients 3,6,9 and 12 months after stent placement. The composite of death, myocardial infarction, and stroke defined as MACCE and target vessel revascularization (TVR) were utilized as primary endpoints.
Results: Between October 2005 and October 2006, 6384 patients were enrolled (SES: n= 2137; PES: n=2740; BMS: n=485) at 99 DES.DE sites. At similar baseline clinical and descriptive morphology of coronary artery disease (CAD) between both DES groups, there were no differences in one-year follow-up with respect to rates of overall mortality (3.8% vs. 4.1%), TVR (10.4% vs. 10.4%), overall stent thrombosis (3.6% vs. 3.8%) and MACCE (8.1% vs. 8.0%) between both DES. Compared with BMS, patients treated with DES had significantly lower rates of myocardial infarction (3.2% vs. 6.0%; $p<0.01$), stroke (1.2% vs. 2.7%; $p<0.05$) and TVR (10.4% vs. 14.9%; $p<0.01$) without any difference in stent thrombosis rate (3.7% vs. 4.3%; p=0.57) and mortality (4.0% vs. 5.2%; p=0.21)



Conclusion: Data generated in the DES.DE registry revealed as well as no differences between patients receiving PES and SES and a significant superiority of both DES in a "real-world" setting with regards to clinical outcomes without any compromise in safety parameters such as mortality and ARC definition stent thrombosis at 1year.

P647 First in man application of bevacizumab eluting stent:a novel approach for the inhibition of plaque neovascularization. Long term results

K. Toutouzas[1], E. Stefanadi[1], J. Karampelas[1], A. Synetos[1], E. Tsiamis[1], D. Tousoulis[1], N. Kipshidze[2], C. Stefanadis[1]. *[1]Hippokration General Hospital of Athens, Athens, Greece; [2]Cardiovascular Research Foundation, New York, United States of America*

Background: Neovascularization is mainly mediated by vascular endothelial growth factor. Bevacizumab is a monoclonal antibody specific for vascular endothelial growth factor. In this study we present the long-term results of the safety and efficacy study of the first-in-man application of bevacizumab–eluting stent.
Methods: Patients with acute coronary syndromes and $\geq$ 2 angiographically significant coronary artery stenoses were included in the study. The culprit lesions were successfully treated. The non-culprit lesions to be included were $\leq$ 20 mm in length, producing a significant stenosis ($\geq$ 50%, in vessels with reference diameter $\geq$ 2.25mm). Local delivery of bevacizumab was accomplished via BiodivYsio stents, which bear a phosphorylcholine coating that adsorbs the drug with a "sponge-like" mechanism. Patients were discharged under aspirin (indefinitely) and clopidogrel for 24 months. All patients were scheduled for angiographic follow-up at 24 months and clinical follow-up at 36 months. Intravascular ultrasound of the target vessel was performed immediately after the procedure and at 24 months.
Results: Twenty consecutive patents were included. All stents were successfully delivered (mean stent length 13.55±4.1 mm) and all patients were discharged without any complication. During a follow-up period of 34.15±3.21 months there were no adverse cardiac events such as death, myocardial infarction and target vessel revascularization. Angiographic and intravascular ultrasound follow-up were performed at 22.25±2.84 months. Acute, subacute or late thrombosis was not observed. Angiographic and intravascular ultrasound follow-up did not reveal any restenosis (50% vessel narrowing) in any target vessel. Stent malapposition was not observed in any patient. In-stent late loss was 0.15±0.9 mm, and in-lesion late loss was 0.16±0.03 mm. Mean neointimal hyperplasia in stented segments as measured with intravascular ultrasound was 0.82±0.29 mm. There was no adverse event between the 2nd and 3rd year of clinical follow-up
Conclusions: The implantation of bevacizumab-eluting stents in human coronary arteries is feasible and safe and elicits minimal neointimal proliferation. Moreover, there were no late adverse cardiac events. Futher randomized trials need to be performed.

P648 Impact of body mass index on mortality in patients with acute myocardial infarction

E. Omerovic[1], O. Angeros[2], B. Lagerqvist[3], K. Karason[1], G. Matejka[1], T. Ramunddal[1], P. Albertsson[1] on behalf of SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *[1]Sahlgrenska University Hospital, Gothenburg, Sweden; [2]Norra Alvsborgs Hospital, Trollhattan, Sweden; [3]Uppsala University Hospital, Uppsala, Sweden*

Introduction: The aim of this study was to investigate the impact of the body mass index (BMI) on short-term (30-days) and long-term (2.5 year) mortality in patients (pts) with acute myocardial infarction (MI) undergoing revascularization with percutaneous coronary intervention (PCI).
Methods: We have analyzed the data of 15 383 consecutive patients with MI (both STEMI and non-STEMI) undergoing PCI between 2002 and 2007 in Sweden from SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry). SCAAR holds data on consecutive patients from all hospitals in Sweden that perform coronary interventions. The registry is sponsored by the Swedish Health Authorities and is independent from the industry. The cohort was divided into nine BMI categories: <18.5 (n= 91); 18.5 to <21.0 (n=474); 21.0 to <23.5 (n=1498); 23.5 to <25.0 (n=1742); 25.0 to <26.5 (n=1883); 26.5 to <28.0 (n=1568); 28.0 to <30.0 (n=1592); 30.0 to <35.0 (n=1800) and 35.0 (n=504). Adjusted mortality rate was analyzed using Cox regression model with the following covariates: age, gender, STEMI/non-STEMI, previous MI, previous PCI, previous coronary surgery, stroke, renal failure, dementia, chronic obstructive lung disease, heart failure, cancer, coronary disease burden, smoking, diabetes, anticoagulation treatment, hypertension, number and type of stents, completeness of revascularization and peripheral vascular disease.
Results: Mean follow-up was 917±1.9 days and the total number of deaths was 889. First MI occurred at a younger age in the very obese pts who were on average 10 years younger than the normal weight pts ($p < 0.001$). After MI, the overweight (25.0 to <26.5; 26.5 to <28.0; 28.0 to <30.0), and obese (30.0 to <35.0) pts had the lowest while under-weight (<18.5) and morbidly obese (>35) pts had the highest adjusted mortality rates both at 30-days ($p< 0.05$) and at 2.5 years ($p<0.05$).
Conclusion: Our data show that obesity is a risk factor for developing MI at a younger age compared to normal weight patients. After MI, overweight and obesity are associated with lower mortality while under-weight and morbid obesity have the most detrimental prognosis. Future studies should address the mechanisms behind protective and detrimental effects of different BMI phenotypes after MI.

P649 Circulating endothelial progenitor cells in patients who underwent late coronary stent thrombosis

E. Lev, D. Leshem, A. Mager, N. Harel, A. Solodky, A. Assali, A. Battler, R. Kornowski. *Rabin Medical Center, Petah Tikva, Israel*

Background and purpose: An important factor that may contribute to the development of late stent thrombosis (ST) after drug eluting stent (DES) implantation is delayed arterial healing and poor endothelialization. Endothelial progenitor cells (EPCs) have been shown to play an important role in repair and re-endothelialization following vascular injury, such as balloon angioplasty. We, therefore, hypothesized that patients who develop late ST may have reduced levels and/or function of EPCs as a factor contributing to their risk of ST. Accordingly, we aimed to compare EPC level and function in patients who underwent ST vs matched controls.
Methods: Patients who developed late (>4 weeks following stenting) ST, within the past 3 years, were compared to a matched group of patients who underwent stenting and did not develop complications [matching according to gender, age, diabetes status, type of stent (DES vs. BMS), and current treatment with aspirin, clopidogrel and statins]. All patients had blood samples taken at least 3 months from the ST or index procedure. The percentage of peripheral mononuclear cells expressing VEGFR-2, CD133 and CD34 was evaluated by flow cytometry. EPC colony forming units (CFUs) were grown from peripheral blood mononuclear cells, characterized and counted following 7 days of culture (of non-adherent cells) on fibronectin-coated wells.
Results: The two groups (n=18 each) were well matched (89% men, mean age 61-63 years, 33% diabetes, 83% DES). The proportion of cells co-expressing

EPC level and CFU in ST group vs control

	ST group (n=18)	Control group (n=18)
CD133+, VEGFR-2+ cells (%)	0.68±0.6	0.85±0.6
CD34+, VEGFR-2+ cells (%)	1.18±1.3	1.46±1.1
EPC CFUs (per 10^6 cells)	5.3±2*	11.1±5*

*P=0.002.

VEGFR-2 and CD133 or VEGFR-2 and CD34 was similar in both groups. However, the mean number of CFUs was lower among the patients who underwent late ST (Table).
Conclusions: Our study suggests that patients who have undergone late coronary ST have reduced levels of EPC CFUs, which reflect impaired EPC functional properties. These findings require validation by larger studies, but may contribute to the understanding of the pathogenesis of late ST.

P650 Mortality rate after coronary stent thrombosis in patients treated with drug-eluting or bare metal stents. From Western Denmark heart registry

L.O. Jensen[1], A. Kaltoft[2], P. Thayssen[1], H.H. Tilsted[3], M. Maeng[2], J.F. Lassen[2], K.N. Hansen[1], J. Ravkilde[3], M. Madsen[4], L. Thuesen[2]. *[1]Odense University Hospital, Odense, Denmark; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Aarhus University Hospital, Aalborg Hospital, Aalborg, Denmark; [4]Department of Clinical Epidemiology, Aarhus, Denmark*

Background: Stent thrombosis is a serious complication after percutaneous coronary intervention (PCI). Therefore, we assessed the risk of mortality after early and late definite stent thrombosis and examined predictors for definite stent thrombosis in patients treated with PCI and paclitaxel- (PES) or sirolimus-eluting (SES) or bare metal (BMS) stent implantations in Western Denmark.
Methods: From January 2002 to June 2005 all consecutive patients, who had SES, PES or BMS implantation where identified in the population based Western Denmark Heart Registry. All patients received dual antiplatelet therapy for 12 months. The last treated patient was followed for 36 months. We used Cox regression analysis to estimate relative risk controlled for potential confounding. Stent thrombosis was characterized as early (<30 days) or late (≥30 days).
Results: A total of 12,374 patients were treated with PES (1,304), SES (2,212) and BMS (8,858). Mortality after definite stent thrombosis amounted to 14.5% at 3 years; in patients suffering from early 17.3% vs. 10.9% in patients suffering from late definite stent thrombosis. During the entire observation period of 3 years, 21 patients suffering from definite stent thrombosis subsequently died. Death after the diagnosis of definite stent thrombosis occurred in 0.2% of the entire population and accounted for 1.7% of all 1,243 deaths.
ST-segment elevation myocardial infarction (STEMI) at the time of stent implantation (RR: 2.86 95% CI 1.83 to 4.48), stent length (RR: 1.03 95% CI 1.00 to 1.05), use of PES (RR: 1.81 95% CI 1.16 to 2.84), younger age (RR: 0.97 95% CI 0.96 to 0.99), reference vessel diameter (RR: 0.66 95% CI 0.47 to 0.93) were independent predictors of overall definite stent thrombosis. STEMI (RR: 3.54 95% CI 1.92 to 6.50), and stent length (RR: 1.03 95% CI 1.00 to 1.06), were the only predictor of early stent thrombosis, whereas STEMI (RR: 2.10 95% CI 1.07 to 4.10), younger age (RR: 0.96 95% CI 0.94 to 0.98) and use of PES (RR: 3.87 95% CI 2.08 to 7.18), were independently associated with and increased risk of late stent thrombosis.
Conclusion: The long-term mortality rate after definite stent thrombosis is high. STEMI at the time of stent implantation, stent length, use of PES, younger age and reference vessel diameter were associated with definite stent thrombosis.

P651 Obesity and cardiovascular thrombotic events in patients undergoing percutaneous coronary intervention with drug-eluting stent

Z.J. Wang, Y.J. Zhou, Y.L. Liu, M. Yu, D.M. Shi, Y.X. Zhao. *Anzhen Hospital, Capital Med. University, Beijing, China, People's Republic of*

Objectives: To evaluate the effect of obesity, determined by body mass index (BMI), on cardiovascular thrombotic events in patients undergoing percutaneous coronary interventions (PCI) with drug-eluting stent (DES).
Methods: We studied 4,996 patients between January 2004 and December 2006. Patients were divided into three groups according to body mass index: normal (BMI < 24.9 kg/m^2, n = 1,284); overweight (BMI 25- 29.9 kg/m^2, n = 2,475) and obese (BMI > 30 kg/m^2, n = 1,213). Median follow-up was 26 (interquartile range 20–33) months.
Results: Composite cardiovascular thrombotic events, including cardiac death and non-fatal myocardial infarction, were significantly higher in obese patients (5.9%) than in normal (3.2%) and overweight (3.8%) patients (p = 0.001). The incidence of definite or probable stent thrombosis steadily increased with increasing body mass index (0.9% vs 1.0% vs 1.9% in normal, overweight, and obese patients, respectively; p = 0.029). Multivariate analyses showed that obesity was an independent predictor of 3-year composite thrombotic events (hazard ratio = 1.86; 95% confidence interval = 1.25-2.75; p = 0.003) and definite or probable stent thrombosis (hazard ratio = 2.17; 95% confidence interval = 1.04-4.55; p = 0.040).
Conclusions: Obese patients have a higher risk for long-term cardiovascular thrombotic events following PCI with drug-eluting stent than patients with normal weight.

Long-term thrombotic events

	Over all (n=4,972)	Normal weight (n=1,284)	Overweight (n=2,475)	Obesity (n=1,213)	p value
Composite thrombotic events, n (%)	207 (4.2)	41 (3.2)	94 (3.8)	72 (5.9)	0.001
Cardiac death	78 (1.6)	16 (1.2)	33 (1.3)	29 (2.4)	0.029
Non-fatal MI	129 (2.6)	25 (1.9)	61 (2.5)	43 (3.5)	0.036
All cause death, n (%)	103 (2.1)	26 (2.0)	43 (1.8)	34 (2.8)	0.143
Stent thrombosis (definite/probable), n (%)	59 (1.2)	11 (0.9)	25 (1.0)	23 (1.9)	0.029
definite	29 (0.6)	5 (0.4)	12 (0.5)	12 (1.0)	0.096
probable	30 (0.6)	6 (0.5)	13 (0.5)	11 (0.9)	0.285
Early (0 to 30 days)	18 (0.4)	4 (0.3)	8 (0.3)	6 (0.5)	0.675
Late (30 to 360 days)	19 (0.4)	3 (0.2)	7 (0.3)	9 (0.7)	0.064
Very late (>360 days)	22 (0.4)	4 (0.3)	10 (0.4)	8 (0.7)	0.391

P652 Antiplatelet therapy discontinuation and stent thrombosis of sirolimus-eluting stent: observation from the RESTART (REgistry of Stent Thrombosis for review And Re-evaluaTion)

T. Kimura[1], T. Aizawa[2], T. Isshiki[3], K. Mitsudo[4], S. Miyazaki[5], T. Yamaguchi[6], E. Hiyoshi[7], E. Nishimura[7] on behalf of the RESTART (REgistry of Stent Thrombosis for review And Re-evaluaTion). *[1]Graduate School of Medicine Kyoto University, Kyoto, Japan; [2]The Cardiovascular Institute Hospital, Tokyo, Japan; [3]Teikyo University, Tokyo, Japan; [4]Kurashiki Central Hospital, Okayama, Japan; [5]Kinki University, Osaka, Japan; [6]Toranomon Hospital, Tokyo, Japan; [7]Johnson & Johnson kk., Tokyo, Japan*

Background: Although discontinuation (D/C) of antiplatelet therapy (APT) was reported to be the strongest predictor of stent thrombosis (ST) of drug-eluting stent, time intervals between D/C of APT and ST were not adequately addressed yet.
Method: RESTART is a Japanese nation-wide registry of patients (pts) with ST of Sirolimus-eluting stent (SES). Among 1334 centers invited, 543 centers agreed to participate in the registry. As of January 30th. 2009, 458 pts with ARC definite ST (early ST (EST) 239 pts, late ST (LST) 78 pts and very late ST (VLST) 141 pts) were enrolled.
Results: Status of APT at the time of ST was significantly different among the 3 groups (Table). ST in 24 pts (5.3%) occurred within 30 days of surgical procedures.

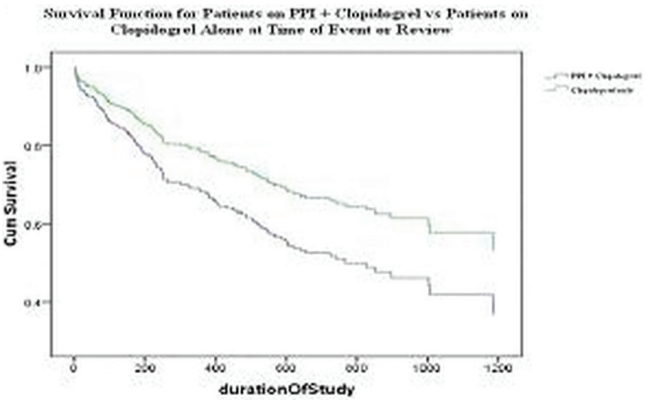
	EST	LST	VLST	
APT at time of ST				p=0.0001
Dual	74%	51%	21%	
Apirin alone	11%	24%	47%	
Thienopyridine alone	6.7%	2.6%	2.1%	
None	7.1%	19%	22%	
Unknown	1.3%	2.6%	8.5%	
Interval between D/C and ST				
D/C of thienopyridine and aspirin (days (IQR))	4 (2-7)	12.5 (7-20.5)	35 (7-277)	
D/C of thienopyridine only (days (IQR))	12 (7.5-65)	80 (39-137)	578 (248-808.5)	
	p=0.03	p=0.0002	p<0.0001	

D/C of APT was reported in 157 pts (34%) with median interval between D/C and ST of 124 (IQR 13-562) days (D/C of both thienopyridine and aspirin 54 pts, D/C of thienopyridine only 94 pts, D/C of aspirin only 9 pts). The interval was significantly (p<0.0001) shorter in pts with D/C of both thienopyridine and aspirin (11 (IQR 6-49) days) as compared with pts with D/C of thienopyridine only (282 (IQR 79-728) days).
Conclusions: Although the proportion of pts with aspirin monotherapy increased with time after SES implantation, long intervals between D/C and ST cast doubt on the causal link between D/C of thienopyridine only and ST, particularly in cases of VLST. Relatively short intervals between D/C and ST suggest causal relationship between D/C of both thienopyridine and aspirin and ST.

P653 Proton pump inhibitors increase the risk of major adverse cardiovascular events in post-PCI patients who are on clopidogrel

S. Banerjee[1], C. Varghese[1], R. Weideman[1], M. Weideman[1], B.B. Little[2]. *[1]Dallas VA hospital, Dallas, United States of America; [2]Tarleton State University, Stephenville, United States of America*

Purpose: It is suspected that PPI's inhibit enzymes like CYP-450 2C-19 which convert clopidogrel to its active form, consequently decreasing its anti-platelet effect. This study evaluates whether exposure to PPI(s) in post-PCI patients on clopidogrel increases the risk of adverse cardiovascular events (MACE).
Methods: The effects of concomitant use of PPI(s) with clopidogrel in a cohort of 533 patients from the Dallas VA patient database who had PCIs between January 2004 and July 2006 was investigated. Patients were followed for incidents of MACE, which included all cause mortality, MI, repeat revascularization and stroke. Only patients with DES stents who took clopidogrel+PPI (n=111, 98% male, 54% MACE) or clopidogrel monotherapy (n=86, 95% male, 34.9% MACE) were included in the study. Mean follow-up period for the cohort was 557 and 615 days in combination and monotherapy respectively.
Results: Multivariate logistic regression analysis of PPI(s) use with clopidogrel is associated with a 1.54 fold higher risk for MACE compared to clopidogrel monotherapy. In the group that took clopidogrel only, the major risk factor for MACE was prior MI (OR=13.9%, P<0.002). In the group that took clopidogrel+PPI the major risk factors for MACE were hypertension (OR=4.5, P=NS),

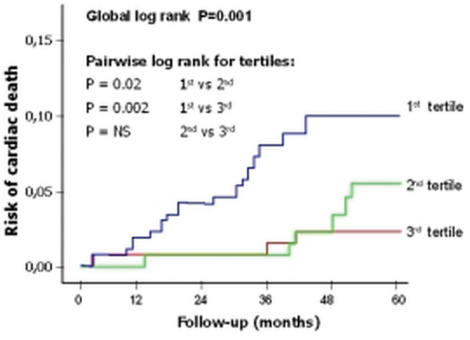


ACS (OR=2.0,P=0.09), and prior CABG (OR=2.8, P<0.03). Cox regression proportional hazard analysis revealed a significant difference in survival between the two groups (P<0.006). This implies a possible link of MACE with attenuated clopidogrel activity when used with PPI, independent of traditional cardiovascular risk factors (hypercholesterolemia, smoking) and clinical presentation.
Conclusion: Concomitant use of PPI(s) with clopidogrel is associated with an increased risk of MACE post-PCI.

P654 QT dispersion modifications predict late survival after percutaneous coronary intervention

M. Zimarino, A. Corazzini, A. Tatasciore, V. Cicchitti, E. Genovesi, R. Tommasi, C. Rossi, R. De Caterina. *Universita G. D'Annunzio, Chieti, Italy*

Aim of the study: QT dispersion (QTD), a measure of inter-lead differences of the QT interval, has been suggested to provide a measure of repolarization inhomogeneity. We already documented that PCI reduces corrected QTD (cQTD) and that cQTD modifications are related to 1-year outcome. We tested whether a defective recovery of cQTD after percutaneous coronary interventions (PCI) is associated with reduced long-term survival.
Methods: We consecutively recruited 612 patients (mean age 63±10 years, 84% males), undergoing elective PCI. They were grouped into tertiles of ΔcQTD (=cQTD baseline – 6 h post-PCI) and followed-up for 49±10 months,
Results: 46 deaths (7.5%) occurred, 25 for cardiac causes (all classified as arrhythmic) and 21 for non-cardiac causes. At Cox regression analysis, a reduced ΔcQTD was an independent predictor of cardiac mortality, with a 1.50 Hazard Ratio (HR) (95% confidence interval 1.08- 2.08 (P=0.015) for each 20 ms decrease, together with age (HR 1.67 per 10 years increase; P=0.034), diabetes (HR 2.62; P=0.028), peak CK-MB (HR 1.80 per each U/L increase over normal level; P=0.029), 3-vessel coronary artery disease (HR 3.63; P=0.037) and the number of treated lesions (HR 2.07; P=0.008). The 82 patients (13%) in the first tertile of ΔcQTD also having a post-procedural increase of CK-MB had a 6-fold higher cardiac mortality than the remaining population (14.6 vs 2.4%, P<0.001).



Conclusions: A defective recovery of cQTD is related to long-term cardiac mortality, probably due to a relationship with sudden death.

P655 Efficacy of statins in patients after percutaneous coronary interventions: relation with baseline CRP values and with post-procedural TnI

C. Auguadro, F. Scalise, M. Bonadies, E. D'Elia, V. Pacher, V. Casali, M. Manfredi, G. Specchia. *Policlinico of Monza, Monza, Italy*

Backgroud: The negative prognostic value of Troponin I (TnI) and of CRP in patients with Acute Coronary Syndrome (ACS) is well established. Objective of the present study was to define in a large population of patients who underwent planned percutaneous coronary intervention (PCI) the prognostic value of chronic statin therapy in relation with baseline values of CRP and post-procedural TnI values.
Method: 898 stable patients planned for PCI were enrolled in the study. In all patients TnI and CK were evaluated in basal condition and every 6 hours for the first 48 hour after PCI. CRP was evaluated on baseline in all patients. TnI values ≥ 1.0 ng/ml were considered indicative of post-procedural myocardial injury; CRP ≥4.0 was considered abnormal. The cardiovascular events taken into consideration during FU were: 1. cardiac death; 2. non cardiac death; 3. hospitalization for myocardial infarction or unstable angina. Major adverse events (MACE) were defined death for cardiac cause, non fatal myocardial infarction (MI) and unstable angina (UA).
Results: The patients were divided into 4 groups according to postPCI TnI <1.0/≥1.0 and to baseline CRP <4.0/≥4.0. The incidences of CV events in each group are reported in table1. Secondary, we evaluated the influence of chronic statin therapy on cardiac death and MACE in pts of G2 and G3 (G2 noST vs G2 ST: cardiac death 15.3% vs 0%, p=0.01; MACE 31% vs 5.2%, p=0.01; G3 noST vs G3 ST: cardiac death 9% vs 2.7%, p=0.05; MACE 18% vs 7.4%, p=0.04).

Table 1

	G1: n=539 TnI<1.0 CRP<4.0	G2: n=54 TnI≥1.0 CRP≥4.0	G3: n=194 TnI<1.0 CRP≥4.0	G4: n=111 TnI≥1.0 CRP<4.0	p value
Cardiac death	0.93%	5.6%	4%	1.8%	0.01
Non cardiac death	1.1%	1.8%	1.5%	0%	0.60
MI, UA	3%	7.4%	5.6%	1.8%	0.13
MACE	4%	13%	9.7%	3.6%	0.002

Conclusion: these data documented a higher incidence of CV events in patients with baseline CRP ≥4.0 associated or not to TnI increase after PCI. Statin therapy reduced the risk of CV events in all patients with abnormal baseline CRP but particularly in those with both CRP≥4.0 and TnI≥1.0. According to these results all patients after a myocardial revascularization should be treated with statins in order to reduce the risk of cardiac events in follow-up.

P656 Time dependent differences in the demographics and clinical outcome of stent thrombosis of sirolimus-eluting stent: observations from the RESTART

T. Kimura[1], T. Aizawa[2], T. Isshiki[3], K. Mitsudo[4], S. Miyazaki[5], T. Yamaguchi[6], E. Hiyoshi[7], E. Nishimura[7] on behalf of the RESTART (REgistry of Stent Thrombosis for review And Re-evaluaTion) investigators. *[1]Graduate School of Medicine Kyoto University, Kyoto, Japan; [2]The Cardiovascular Institute Hospital, Tokyo, Japan; [3]Teikyo University, Tokyo, Japan; [4]Kurashiki Central Hospital, Okayama, Japan; [5]Kinki University, Osaka, Japan; [6]Toranomon Hospital, Tokyo, Japan; [7]Johnson & Johnson kk., Tokyo, Japan*

Background: Although stent thrombosis is a dreaded complication of Sirolimus-eluting Stent (SES), it has not been adequately characterized yet due to its low prevalence.
Method: RESTART is a Japanese nation-wide registry of patients (pts) with stent thrombosis (ST) of SES. Among 1334 centers invited, 543 centers agreed to participate in the registry. As of January 30th. 2009, 458 pts with ARC definite ST (early ST (EST) 239 pts, late ST (LST) 78 pts and very late ST (VLST) 141 pts) were enrolled.
Results: Baseline demographic features were significantly different according to the timing of ST. Pts with LST/VLST as compared with those with EST more often had renal failure and current smoking habit and were less often treated in the setting of acute myocardial infarction. Pts with VLST as compared with those with LST were younger, more often current smokers and were less often associated with heart failure, diabetes, hypertension, renal failure and multivessel disease. Clinical sequelae of ST were MI in 87% of pts (Q wave 66%, Non-Q wave 21%) without significant differences among the 3 groups. Mortality at one year after ST was significantly lower in pts with VLST as compared with those with EST or LST.

	EST	LST/VLST	p Value	LST	VLST	p Value
Age	67.3±11.1	65.3±11.6	0.06	69.0±9.7	63.3±12.0	0.0004
Heart failure	20%	22%	0.75	38%	13%	0.0001
Diabetes	43%	40%	0.51	56%	30%	0.0003
Hypertension	73%	75%	0.54	84%	70%	0.02
Current smoking	31%	37%	0.03	24%	44%	0.0001
e-GFR <30	7.8%	19%	0.0003	36%	10%	0.0001
Dialysis	4.6%	14%	0.0005	28%	5.7%	0.0001
Acute MI	32%	21%	0.009	21%	22%	0.8
Multivessel disease	60%	58%	0.88	69%	52%	0.04
Mortality at 1 year	24%	16%	0.19	24%	13%	0.01

Conclusions: Time dependent differences in the demographic features and clinical outcome of pts with ST suggest the possible differences in the pathophysiologic mechanisms of ST according to the timing after SES implantation.

P657 Risks and benefits of drug-eluting stent in patients with atrial fibrillation

F. Marin Ortuno[1], J.M. Ruiz-Nodar[2], J. Sanchez-Paya[2], J.A. Hurtado[1], J. Valencia[2], S. Manzano-Fernandez[1], V. Roldan[3], F. Sogorb[2], M. Valdes[1], G.Y. Lip[4]. *[1]Hospital Universitario Virgen de la Arrixaca, Murcia, Murcia, Spain; [2]Hospital General Universitario de Alicante, Alicante, Spain; [3]Hospital Morales Meseguer, Murcia, Spain; [4]City Hospital, Birmingham, Birmingham, United Kingdom*

Drug-eluting stents (DES) have never been sufficiently studied in the patients with atrial fibrillation (AF). The latter are considered as a high risk population due to the existing doubts about the optimal thrombotic therapy as well as the high risk of haemorrhagic complications. The aim of this study was to evaluate the safety and efficacy of the use of DES vs. bare-metal stents (BMS) in a cohort of patients with AF.

Methods: We reviewed 604 patients with AF that had undergone PCI with stent over a period of 7 years (January 2001-January 2008). After a propensity score selection, we identified 2 matched cohorts who received DES (n=207) or BMS (n=207). Clinical follow-up was performed, and all bleeding episodes, thromboembolism and major adverse cardiac events (MACE; i.e. death, acute myocardial infarction, target vessel failure) were recorded.

Results: Complete follow-up was achieved in 95.9% of the cohort (mean 693±427 days, median 564). The incidence density of MACE in both groups was similar as well as the incidence of all-cause mortality. There was a higher incidence of major bleeding in DES group (2.26 vs 1.19 per 10000 days of exposure, p=0.03). In a multivariate analysis, age, chronic AF, chronic renal failure and non use of dicoumarin were predictors of MACE and of all-cause of mortality. The use of DES was not a predictor of reduced events.

Conclusions: The benefit of DES in patients with AF may well be lower compared to non-AF populations, and DES use was not a predictor of reduced adverse events post-PCI. A higher risk of major bleeding with DES in comparison to BMS raises the possibility that DES should be limited to lesions or patients with a high risk of restenosis.

P658 Antiplatelet treatment and noncardiac surgery in patients with prior coronary stent implantation

T.H. Bampali, A. Konstantinidis, B. Salma, T.H. Pappas, K. Kalantzi, A. Papathanasiou, C.H. Katsouras, J. Goudevenos. *University of Ioannina Medical School, Ioannina, Greece*

Purpose: The current recommendations state that the patients with previously implanted coronary stent should be treated with dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg for one month after Bare-Metal-Stent (BMS) and one year after Drug-Eluting-Stent (DES), followed by aspirin for lifetime. Our purpose was to register the daily practice of physicians in those patients, who undergo a noncardiac surgery, relatively to their antiplatelet treatment.

Methods: In this cross-sectional study we enrolled every patient with history of coronary stenting (BMS/DES) who had undergone noncardiac surgery. From November 2007 until January 2009 we registered every patient who proceeded for hospitalization in our department and was fulfilling the criteria above. The main outcome was the combined (cardiac, bleeding) complication rate.

Results: We identified 115 patients (102 men) with prior coronary stenting (BMS:77, DES:26, both:9) who underwent in totally 128 noncardiac surgeries. The type of the procedures was high-risk (3 cases), intermediate-risk (56 cases) and low-risk (69 cases), according to the ACC/AHA Cardiac-Risk-Stratification. In a median time of 3.8 years (IQR 1 month-11 years) after the stenting, 41 patients (35%) were receiving monotherapy with aspirin preoperatively, 15 patients (13%) clopidogrel and 54 (47%) dual antiplatelet therapy. Perioperatively, discontinuation of the aspirin was done in 24 patients (median time 6.7 days), of the clopidogrel in 23 patients (median time 17.7 days) and both of them in 23 patients (median time 6.2 days). During a time frame of 28 days after the procedure, the serious perioperative outcomes were 1 case of acute coronary syndrome (ACS) and 2 bleedings (Gusto Stratification: high-risk) when aspirin was stopped for a median time of 2 days. Respectively, when clopidogrel was stopped (median time 8.5 days) we reported 2 cases of ACS and 1 bleeding (low-risk). In total, 2 patients suffered postoperative myocardial infarction but the catheterization showed neither had stent occlusion, whereas there were 3 new lesions. No patient died. All surgeries were of low and intermediate risk. In the category of the patients who didn't stop the antiplatelet agents perioperatively, neither bleedings were reported, nor ACSs.

Conclusions: The risk of suffering an event was 8.5% when the antiplatelet therapy was discontinued whereas 0% when not ($p < 0.05$). Despite of the recommendations to maintain the antiplatelet treatment in low and intermediate risk surgeries, physicians still do not abide them.

P659 The impact of unsuccessful percutaneous coronary intervention on short and long-term mortality in STEMI and NSTEMI

M. Mazurek[1], J. Kowalczyk[1], R. Lenarczyk[1], A. Swiatkowski[1], O. Kowalski[1], A. Sedkowska[1], T. Was[1], M. Swierad[1], L. Polonski[2], Z. Kalarus[1]. *[1]Cardiology Department, Silesian Centre For Heart Disease, Medical University of Silesia, Zabrze, Poland; [2]Third Department of Cardiology, Silesian Centre For Heart Disease, Medical University of Silesia, Zabrze, Poland*

Purpose: The aim of the study was to assess and compare the impact of the efficacy of percutaneous coronary intervention (PCI) on early and late mortality in STEMI and NSTEMI with respect to the type of infarct related artery (IRA).

Methods: Study population consisted of 2733 consecutive patients (2179 patients in STEMI group and 554 patients in NSTEMI group) treated with PCI in acute phase of myocardial infarction. Efficacy of PCI (TIMI 3 after PCI vs TIMI<3 after PCI) was assessed with respect to the type of IRA (LAD, Cx or RCA) in STEMI and NSTEMI group respectively. The mean follow-up period was 37.5 months. Mortality rates were compared using log-rank test. Independent predictors of death were identified with multivariate Cox-regression model.

Results: The rate of unsuccessful PCI was similar in STEMI and NSTEMI group irrespectively of IRA (14,1% vs 17,7%; p=0,062). Differences in mortality rates with respect to efficacy of PCI of IRA are presented in Table 1. The comparison analysis between STEMI and NSTEMI group revealed that among all IRA only unsuccessful PCI of LAD in STEMI group was associated with significantly higher mortality rates compared to NSTEMI group (early mortality: 23,1% vs 0%, p<0,05; late mortality: 29,9% vs 0%, p<0,05). Similar relations in case of Cx and RCA were not identified. The multivariate analysis revealed that unsuccessful PCI of IRA is an independent risk factor for death in STEMI (HR 1,64,±95% CI 1.49-1.79; p<0,05), but not in NSTEMI.

Table 1

	Early mortality		p	Late mortality		p
	TIMI 3 after PCI (%)	TIMI<3 after PCI (%)		TIMI 3 after PCI (%)	TIMI<3 after PCI (%)	
STEMI						
LAD	5,6	23,1	<0,001	12,8	29,9	<0,001
Cx	2,7	27,3	<0,001	9,2	36,4	<0,001
RCA	3,7	18,0	<0,001	8,5	24,3	<0,001
NSTEMI						
LAD	7,5	0	0,16	10,4	0	0,09
Cx	0,9	19,0	<0,001	6,3	27,3	0,002
RCA	1,3	4,8	0,31	11,4	14,3	0,72

Conclusions: Significance of unsuccessful PCI of IRA seems to be different in STEMI and NSTEMI. Unsuccessful PCI of IRA is an independent risk factor for death in STEMI, but not in NSTEMI.

P660 Evaluation of 5 years follow up of myocardial function after primary percutaneous intervention by Cardiac MRI

T. Springeling, S.W. Kirschbaum, T. Baks, Y. Karamermer, A. Moelker, G.P. Krestin, P.J. De Feijter, R.J.M. Van Geuns. *Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Background: We investigated the early and late effect of primary percutaneous coronary interventions (PCI) for acute myocardial infarction on recovery of left ventricular ejection function (LVEF), end diastolic volume (EDV), end systolic volume (ESV) and segmental wall thickening (SWT) using Cardiac MRI.

Methods: All patients were admitted to the Erasmus MC, thoraxcenter Rotterdam for primary PCI (n=24) for acute ST-elevation myocardial infarction. Cardiac MRI was preformed in 24 patients within 10 days, at 4 months and at 5 years. LVEF, EDV, ESV and SWT quantified on cine-images, the transmural extent of the infarction (TEI) was quantified on delayed-enhancement images.

Results: EDV increased significantly between baseline and 5 months (98±33ml, 113±24ml, p=0.03), with no additional late remodelling at 5 years (116±29ml, p=0.37). The ESV shows no improvement at 4 months or 5 years follow up (resp. 61±19ml; 62±20ml p=0.60; 67±26 ml p=0.35). LVEF showed recovery between baseline and 4 months (41±9% to 46±1%, p=0.03), with no further change after 5 years (44±12%, p=0.45).

SWT improved significantly in the 126 dysfunctional segments between baseline and 4 months follow up (13±17% to 30±23%, p≤0.01), no additional improvement was seen at 5 years (to 27%, p=0.22). The 88 remote functional segments decreased in the first 4 months (90±36% to 70±35%, p≤0.01) with a further decrease in 5 years although not significant (27±22%, p=0.18).

In the 3 TEI groups (<25%, 25-75%, >75%) there is an increases in SWT in the first 4 months in all groups (resp. 19±22% to 49±29%, p≤0.01; 15±17% to 29±23%, p≤0.01, 10±16% to 26±22%, p≤0.01). There was no further improvement in 5 years in the segments with a TEI of 25-75% or >75% (resp. to 27±23%, p=0.51; to 25±20%, p=0.86). In the segments with a TEI of <25% the SWT decreased in 5 years although not significant (to 37±27%, p=0.39).

TEI at baseline showed a good correlation with SWT at 4 months and 5 years follow up (resp. p=0.01 and p=0.04).

Conclusion: Ejection fraction and SWT improve in the first 4 months after primary

PCI in patients with an acute ST-elevation myocardial infarction with no further remodelling in 5 years.

P661 Scoring of percutaneous coronary intervention events (ScoPE): results of the Delphi-RAND analysis of predictive risk factors for long term outcomes following PCI

R. Denton-Beaumont[1], A.S. Banning[1], M.P. Holt[2], N.I. Siddiqi[2], K.R. Abrams[2], A.H. Gershlick[1]. *[1]Glenfield Hospital, Leicester, United Kingdom; [2]University of Leicester, Leicester, United Kingdom*

Purpose: The Scoring of Percutanoeus Coronary Intervention Events (ScoPE) study aims to develop a robust and accurate tool for estimating risk to patients undergoing PCI. ScoPE will combine published data with expert opinion on perceived impact of PCI risk factors using a modified Delphi-RAND method. We present the findings of the Dephi-RAND analysis for mortality at 36 months post-PCI and compare this with a retrospective analysis of 900 patients.
Method: Seven UK Interventional experts were independently asked to score risk factors according to perceived risk of mortality at 36 months post-PCI (0=low risk, 9=high risk). Scores for individual risk factors were collated and weighted according to the lowest scoring risk factor. A retrospective analysis of 900 patients was performed assessing these risk factors against mortality outcome at 36 months post PCI. For each risk factor, the proportion of patients dying at 36 months was expressed as a percentage.
Results: see table 1.

Table 1

Risk Factor	Delphi Score	% death 36 mths	Risk Factor	Delphi Score	% death at 36 mths
Cardiogenic shock	33	50	Rescue PCI	13	5.3
Renal impairment	30	42.1	MI within 24hr	13	7.9
NYHA $\geq$ class 3	29	20.9	Diabetes Mellitus	13	7.4
LVEF $<$ 30%	28	9.7	Stent Thrombosis	12	0
Age $>$ 75yrs	27	16.5	Emergent PCI	12	8.2
VT	21	0	Chronic lung disease	11	11.1
Previous CABG	17	10.9	Multivessel Disease	8	6.1
LMS disease	16	21.4	CCS Class IV angina	6	10.7
ST elevation/LBBB	15	4.4	PVD	6	13.0
Cardiac arrest	14	9.1	Recent CVA	5	0

There was a total of 43 deaths at 36-months post-PCI. There is a significant correlation between Delphi Scores and relative risk of mortality (Pearson Coefficient=0.69, p=0.001). Three variables were excluded from the analysis as they had incomplete Delphi Scores; Preoperative IABP, planned incomplete revascularisation and Trifurcation lesions. The mortalities were 55.6%, 7.4% and 0% respectively.
Conclusions: These initial findings show that the results of the Delphi-RAND method correspond with findings from actual data in predicting impact of risk factors on long-term outcomes from PCI.

P662 Outcome of non-cardiac surgery after stent implantation in the DES era: results of the surgery after stent (SAS) registry

M.F. Brancati, M. Giammarinaro, F. Burzotta, C. Trani, I. Porto, A. Tommasino, A.M. Leone, G. Niccoli, G. Schiavoni, F. Crea. *Catholic University of the Sacred Heart, Rome, Italy*

Purpose: The optimal management of patients with coronary artery disease treated by stent implantation and needing non-cardiac surgery has not been established. We assessed in a single-centre registry the peri-operative outcome of patients undergoing non cardiac surgery after coronary bare metal stent (BMS) or drug-eluting stent (DES) implantation.
Methods: Consecutive patients treated by percutaneous coronary interventions (PCI) with stenting between 2005 and 2007 were screened. Those who underwent non-cardiac surgery after PCI entered the study. Clinical, angiographic and procedural (including type of stent) data of PCI were prospectively recorded. Surgical procedure details, peri-operative antiplatelet therapy and in-hospital clinical outcome after surgery were retrospectively collected. As a general approach, patients with planned surgery at time of PCI received BMS and those operated within 1 month since BMS or 12 months since DES implantation were kept on double antiplatelet therapy during operative period. Primary end-point was the incidence of major adverse events (MAE), defined as the occurrence of major adverse cardiovascular events (MACE) (death, non-fatal myocardial infarction, stent thrombosis [ST] and target vessel revascularization) and/or haemorrhagic complications (peri-operative bleeding requiring blood transfusions or surgical haemostasis) during hospitalization for non-cardiac surgery.
Results: The study population comprised 101 patients: 70 treated by BMS (BMS group) and 31 treated by DES (DES group). The mean interval between PCI and surgery was 288 days (range 6-911) with no significant difference for BMS and DES group (p=0.41). The average number of antiplatelet drugs during surgery was higher in the DES group vs BMS group (1.55 vs 1.19; p=0.02). Fifteen patients (15%) experienced MAE, with no significant difference between BMS group and DES group (15.7% in BMS group vs 13% in DES group, p=0.72). Peri-operative MACE (which comprised no death, no ST, no re-PCI) occurred in 6 patients (5.9%), who developed non-ST-elevation myocardial infarction. Haemorrhagic complications (no surgical haemostasis) occurred in 12 patients (12%), who required blood transfusions. At multivariate analysis, the only predictor of MAE was the time interval between PCI and non cardiac surgery (p= 0.022).
Conclusions: Patients with previous BMS or DES implantation appear to have similar outcomes after non-cardiac surgery in a study population characterized by an approach of BMS selection for planned surgery and higher peri-operative antiplatelet maintenance in DES patients.

P663 The GRACE risk score- usefulness for predicting 5-year survival of patients with ST-elevation myocardial infarction treated invasively

A. Kozieradzka, K.A. Kaminski, D. Maciorkowska, M. Olszewska, S. Dobrzycki, K. Nowak, P. Kralisz, P. Prokopczuk, W.J. Musial. *Medical University of Bialystok, Bialystok, Poland*

Objectives: The GRACE risk score is the most widespread tool for predicting in-hospital mortality in all forms of acute coronary syndromes (ACS). It is recommended by European Society of Cardiology for risk stratification in non-ST elevation ACS. The aim of our study was to test its utility for prognosing 5-year survival in a "real-life" population of patients with ST-elevation acute myocardial infarction (STEMI) treated with primary percutaneous coronary interventions (pPCI).
Methods: Our registry consisted of consecutive unselected patients with STEMI treated with pPCI. Five-year follow-up was performed with all-cause mortality as an end-point. In statistical analysis we used chi-square, t-Student, Mann-Whitney tests, logistic regression and receiver operator curves.
Results: Out of 505 patients 32 died during first 30 days (6.3%) and additional 74 within 5 years (15.6%). Mean age was 58.6$\pm$11.3, women constituted 24.5% (n=124), pPCI was successful in 95.2% (n=481). Prognostic values (c-statistics) of the GRACE score equaled: 0.869 (95% CI 0.79-0.95) for 30-day outcome, 0.809 (CI 0.74-0.88) for 1 year and 0.742 (CI 0.69-0.79) for 5-year observation. In an univariate analysis several variables were associated with 5-year outcome, including data from history (age, type 2 diabetes, previous angina or myocardial infarction), physical examination (baseline systolic blood pressure, heart rate, Killip class, weight), diagnostic tests (anterior STEMI in ECG, creatinine clearance, ejection fraction), TIMI flow after pPCI and 2 risk scores (GRACE and the TIMI risk score for STEMI). In a multivariate analysis an independent correlation with survival showed the GRACE risk score (OR 1.018, CI 1.009-1.03, $p<0.001$), the TIMI score (OR 1.235, CI 1.07-1.42, $p<0.05$) and TIMI flow after pPCI (OR 0.66, CI 0.46-0.94, $p<0.05$).
Conclusions: The GRACE risk score predicts well not only short-term, but also 5-year all-cause mortality in patients with STEMI treated with pPCI. Our data show that usefulness of initial bedside risk assessment can be further extended for long-term follow-up.

P664 Quality of life after percutaneous coronary intervention in the elderly

R.J. Li, B. Yan, M. Zhang, Q. Zhang, Q.H. Zhang, M. Dong, G.W.K. Yip, C.P. Chan, D. Ding, C.M. Yu. *Prince of Wales Hospital, Hong Kong, China, People's Republic of*

Background: Impact of Percutaneous Coronary Intervention (PCI) on health related quality of life (HRQoL) is as important as survival in patients with Acute Coronary Syndrome (ACS), particularly with elderly pts. This study aimed to evaluate health status outcomes of elderly pts with ACS.
Methods: We prospectively enrolled 526 pts admitted to our institution with ACS from Feb '08 to May '08. MOS SF-36 health survey was used to assess HRQoL at baseline & 6 months. Baseline characteristics & HRQOL were compared for pts treated with PCI vs. medical therapy across 3 age groups ($<$60, 60-80 and $>$80 yrs). We performed multivariate analysis to identify the impact of revascularization on HRQoL in elderly pts. Propensity score of probability in undergoing PCI was used to adjust for potential bias in treatment selection. Missing data were imputed in multiple imputation.
Results: 128 pts (24.3%) were $<$60 yrs, 286 pts (54.4%) between 60-80 yrs & 112 pts (21.3%) $>$80 yrs. Elderly pts were more likely to be female (16.4 vs. 39.2 vs. 55.4%, $p<0.01$), had associated comorbidities as heart failure (2.3 vs. 7.3 vs. 18.8%, $p<0.01$) and hypertension (63.7 vs. 69.2 vs. 71.4%, $p<0.01$). Older pts were less likely to present with ST-elevation myocardial infarction (42.2 vs. 29.7 vs. 21.4%, $p<0.01$) and to undergo PCI in 30 days after acute onset (68.7 vs. 54.1 vs. 16.1%, $p<0.01$). Elderly pts underwent PCI experienced most improvement in PCS than do in other groups (Table). PCI in 30 days was an independent predictor

Comparison of PCS across 3 age groups

Age Group	Baseline			6M			Improvement PCS		
	PCI	Conservative	p	PCI	Conservative	p	PCI	Conservative	p
$<$60	38.3$\pm$13.5*	39.2$\pm$13.7*	0.6	43.5$\pm$12.9*	42.8$\pm$15.6*	0.12	5.3$\pm$14.5*	3.5$\pm$16.1	0.07
60-80	29.9$\pm$16.9*	27.5$\pm$15.0*	0.3	39.0$\pm$13.8*	33.9$\pm$16.3*	0.07	9.1$\pm$16.8*	6.4$\pm$15.5	0.6
$>$80	22.6$\pm$8.9*	20.3$\pm$12.6*	0.5	39.9$\pm$12.0*	27.9$\pm$13.8*	0.001	17.4$\pm$14.6*	7.6$\pm$14.4	0.008

*$p<0.001$ across 3 age groups; PCS: Physical Component Summary; PCI: Percutaneous coronary intervention.

(β = 4.24; 95%CI 1.24-7.24) of improvement in PCS at 6 months. There were no differences in mental scores between groups.
Conclusion: Elderly pts undergoing PCI experienced most improvement in physical status and had better health status at 6 months than did those in the same age group who were treated conservatively. These findings suggest that age should not deter against revascularization to given the combined survival and quality of life benefits.

P665 Prognostic impact of drug eluting stent supported percutaneous coronary intervention for chronic total occlusion of left anterior descending artery

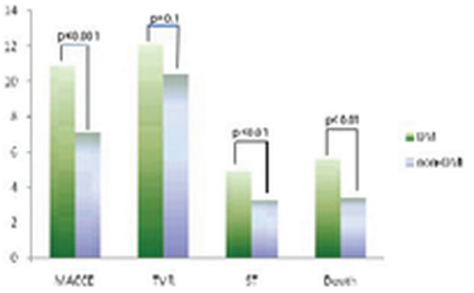
R. Valenti, G. Giuliani, A. Migliorini, G. Cerisano, N. Carrabba, G. Parodi, A. Santini, E. Dovellini, D. Antoniucci. *Division of Cardiology - Careggi Hospital, Florence, Italy*

Purpose: Registries have shown improved long-term survival in patients with successful percutaneous coronary intervention (s-PCI) for chronic total occlusion (CTO). Few data exist about the prognostic impact of drug eluting stent (DES) supported PCI for left anterior descending (LAD) artery CTO.
Methods: From Janaury 2003 to September 2008, 208 patients underwent PCI for LAD-CTO (> 3 months). The prognostic impact of s-PCI for LAD-CTO and of complete coronary revascularization on cardiac mortality was assessed by Kaplan-Meier estimation and by forward stepwise Cox regression multivariate analysis.
Results: s-PCI of LAD-CTO was achieved in 146 patients (70.2%). There were no significant differences in baseline characteristics of patients with s-PCI vs unsuccessful PCI (u-PCI): mean age 69.1±10.8 vs 70.7±11.7 yrs, male 81.5% vs 74.2%, diabetes 26.7% vs 17.7%, previous myocardial infarction 53.4% vs 54.8%, acute coronary syndrome at admission 34.2% vs 38.7%, 3-vessel coronary disease 48.6% vs 51.6%, left ventricular ejection fraction (EF) <40% 44.5% vs 50%. All patients with s-PCI of LAD-CTO received DES (mean stent length 43.6±22.1 mm). No procedural death occurred. Multivessel PCI was performed in 64% of the patients (64% in the s-PCI and 60% in the u-PCI group respectively) and 60% had complete coronary revascularization. The clinical follow-up rate was 100% (median 1.45 yrs, IQ 0.85 – 2.13). Cardiac survival rate was higher in the s-PCI group compared to u-PCI group (89.7±3% vs 81.6± 5%; p=0.036) and in patients with complete revascularization compared to patients with incomplete revascularization (90.4±3.3 vs 82.5±4.3%; p=0.027). Six-month angiographic follow-up (76%) showed a patency rate of 92.4% for LAD-CTO. At multivariate analysis the independent predictors related to cardiac mortality were the completeness of revascularization (HR 0.42; p=0.04) and EF <40% (HR 28.0; p=0.001).
Conclusions: Successful DES supported PCI for LAD-CTO confers a long-term survival benefit. The improvement in survival is driven by completeness of coronary revascularization. Our data suggests that in the setting of patients with LAD-CTO, the therapeutic target should be a complete coronary revascularization.

P666 Clinical outcomes in diabetic versus non-diabetic patients after treatment with drug-eluting stents in a real world setting - results from the prospective multicenter german DES.DE registry

I. Akin[1], A. Bufe[2], L. Eckardt[3], H. Reinecke[3], G. Richardt[4], S. Schneider[5], K.H. Kuck[6], C.A. Nienaber[1] on behalf of DES DE Study Group. *[1]Klinikum der Universitaet Rostock, Rostock, Germany; [2]Helios Klinikum Wuppertal, Wuppertal, Germany; [3]Universitaet Muenster, Munster, Germany; [4]Segeberger Kliniken GmbH, Bad Segeberg, Germany; [5]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [6]Asklepios Klinik. St. Georg, Hamburg, Germany*

Purpose: The prospective multicenter German DES.DE registry is an observational study to evaluate the therapeutic principle of Sirolimus (SES) - and Paclitaxel-eluting (PES) Stent and Bare Metal Stent (BMS) under real world conditions.
Methods: Baseline and procedural characteristics as well as clinical follow-up events (3,6,9 and 12 months after initial stent placement) were recorded for all enrolled patients. The composite of death, myocardial infarction, and stroke defined as MACCE and target vessel revascularization (TVR) were utilized as primary endpoints.
Results: Overall 1659 diabetic and 3559 non-diabetic patients, treated either with PES, SES or BMS, were enrolled at 99 DES.DE sites. The baseline clinical and descriptive morphology of coronary artery disease revealed more severe findings in diabetic patients. Compared with non-diabetics, diabetic patients treated with DES had significantly higher rates for overall death (5.6% vs. 3.4%; p<0.01), myocardial infarction (4.8% vs. 3.4%; p=0.05), stroke (1.7% vs. 0.9%; p<0.05), overall MACCE (10.9% vs. 7.1%; p<0.001) and a numerically higher TVR rate (12.0% vs. 10.4%; p=0.1). Similar differences, however on a higher level were obtained in the BMS group for TVR (18.6% vs. 13.9%; p<0.01), myocardial infarction (6.4% vs. 4.3%; p<0.01) and overall death rate (6.1% vs. 3.7; p<0.05). Rates of overall stent thrombosis were in the expected range and higher in diabetics than in non-diabetics in both, DES (4.9% versus 3.3%; p<0.01) and BMS (5.1 vs. 3.6; p<0.01) group.
Conclusion: The use of DES in patients with diabetes mellitus reduces the need for repeat revascularization compared to BMS. Despite the use of DES, the risk

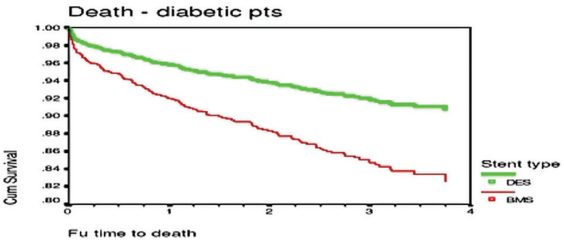


of myocardial infarction, death and thrombotic events remains higher in diabetic patients as compared to non-diabetics.

P667 A comparative analysis of major clinical outcomes using drug-eluting stents versus bare metal stents in diabetic versus non-diabetic patients

T. Bental, A. Assali, S. Fuchs, H. Vaknin-Assa, E. Lev, D. Brosh, I. Teplitsky, R. Kornowski. *Rabin Medical Center, Petah Tikva, Israel*

Purpose: Diabetic patients have been defined as a preferential target population for the use of drug eluting stents (DES) by the Israeli reimbursement policy. We aimed to check the safety and possible benefit of DES use in diabetics versus non diabetics.
Methods: We compared risk-adjusted total mortality, myocardial infarction, repeat target vessel revascularization rates and event-free survival in a consecutive cohort of 4700 patients undergoing PCI at our institution between 1/4/2004 and 30/6/2007, of whom 1830 were diabetic and 2870 were non diabetic. Follow up time was 9 months to 4 years (mean 2.44 years).
Results: Drug eluting stents were used in 44.9% of diabetics vs. 40.4% of non-diabetics (p=0.002). Diabetic patients were older, had more hypertension, congestive heart failure, prior CABG, multivessel disease and had more lesions treated, with slightly longer stents. Diabetic patients had a lower 4 year cumulative mortality rate with use of a DES (9.7%) versus use of a BMS (18.3%) with a propensity score adjusted hazard ratio of 0.51 (CI-0.37-0.72; p<0.0001). Non diabetic patients had overall lower mortality rates but only a trend for benefit using DES (DES 6.61% vs. BMS 9.59%; p=0.2). This pattern was similar for other cardiac outcome measures.



Mortality by stent types - diabetic pts

Conclusions: Our risk-adjusted survival analysis would indicate a prognostic advantage for DES utilization primarily in diabetic patients which sustains up to 4 years following PCI, whereas non diabetic patients derive less prognostic benefit from DES coronary treatment.

P668 Clinical implications of stent fracture after sirolimus-eluting stent implantation at 20-month follow-up

K. Kadota, K. Mitsudo, T. Goto, H. Yamamoto, Y. Fuku, S. Hosogi, H. Tanaka, S. Habara, D. Hasegawa, M. Imai. *Kurashiki Central Hospital, Kurashiki, Japan*

Background: As drug-eluting stent use in more complex lesions is increasing, the incidence of stent fracture could increase and its clinical implications could be important. In this study, we evaluated the prevalence of stent fracture and stent fracture related restenosis or stent thrombosis after sirolimus-eluting stent (SES) implantation in the real-world percutaneous coronary intervention (PCI) at long-term follow-up.
Methods: Between November 2002 and December 2006, a total of 2417 consecutive patients with 3888 lesions underwent SES implantation. Of these, 2291 patients with 3621 lesions were treated with SES exclusively and successfully. A total of 1984 patients with 3090 lesions who were followed by angiography constituted the study population. Follow-up coronary angiography (f/u CAG) was planned serially at 8 and 20 months after SES implantation. In addition, 3-month f/u CAG was planned after left main trunk stenting or stenting for chronic total occlusion. If a clinical evidence of myocardial ischemia developed at any time, unscheduled CAG was recommended.

Results: Prevalence of stent fracture was 5.3% (163/3090). The prevalence of restenosis, stent thrombosis, and target lesion revascularization (TLR) of lesions with or without stent farcture were shown in the table.

Stent Fracture and Clinical Event

Follow up	Early (–149 days)	Mid term (150–365 days)	Late (366 days–)	Total
Day	99±12.6	245.6±26.7	603.0±72.1	
Fracture (+), n	89	144	116	163
Restenosis, % (n)	14.6† (13)	21.5† (31)	25.0† (29)	36.2† (59)
Thrombosis, % (n)	2.2 (2)	0 (0)	2.6† (3)	3.1† (5)
TLR, % (n)	10.1* (9)	13.2† (19)	15.5* (18)	28.2* (46)
Fracture (–), n	955	2752	2212	2927
Restenosis, % (n)	4.8† (46)	8.5† (234)	8.6† (191)	13.5† (394)
Thrombosis, % (n)	0.5 (5)	0 (0)	0.09† (2)	0.2† (7)
TLR, % (n)	3.1* (30)	5.6† (154)	5.4* (119)	5.6* (303)

*p<0.01, †p<0.001 Fracture(+) vs Fracture(–).

Conclusions: Stent fracture after SES implantation was an occasional phenomenon and linked to restenosis or stent thrombosis in the real-world PCI. Although the incidences of stent fracture related restenosis and thrombosis were low, they could occur even 1 year after SES implantation. Thus, stent fracture could have clinical implications for long periods.

P669 Increased bleeding complications early and late after angioplasty and coronary stenting due to combined antiplatelet and anticoagulant therapy

A. Hoffmann, C. Haelg, C. Kaiser, R. Jeger, S. Osswald, M. Pfisterer, H. Brunner-La Rocca. *University Hospital Basel, Basel, Switzerland*

Background: Due to the use of drug eluting stents an increasing number of patients are being treated with dual antiplatelet drugs who additionally are on oral anticoagulants for other reasons. In these patients, bleeding complications are expected to be higher, but the true rate has not been assessed in a prospective study.
Methods: In a consecutive series of "real-world" patients undergoing PCI and stenting, major bleeding complications necessitating hospital admission were prospectively recorded during a follow-up period of three years. The bleeding rates were related to clinical variables and drug treatment.
Results: All 813 patients included in this study were assigned to dual antiplatelet therapy with Aspirin and Clopidogrel for at least 6 months and continued aspirin therapy thereafter. Of these, 44 patients (5.4%) had oral anticoagulants (coumadine) for either atrial fibrillation or prosthetic heart valves in addition to antiplatelet agents.
There were 25 early (during initial hospitalisation) and 26 late major bleedings. The rate of late bleeding was 6.1% per year with vs. 0.8% without coumadine use (p<0.0001). In univariate analyses, in-hospital bleeding was significantly correlated to age, female gender, and glycoprotein IIb/IIIa antagonist use. Late bleeding was correlated to age, diabetes, renal insufficiency, malignancy, and coumadine use. Bleeding did not correlate with history of bleeding or ulcer, and NSAID use. In multivariate analyses glycoprotein IIb/IIIa antagonists (OR=3.8, 95%-CI 1.6-8.8, p=0.002), female gender (OR=2.5, 95%CI 1.1-5.8, p=0.04) and age (OR=1.44 per decade, 95%CI 0.99-2.08, p=0.05) were independent predictors of early bleeding; LVEF (OR=0.65 per 10% increase, 95%CI 0.48-0.87, p=0.004), history of malignancy (OR=5.1, 95% CI 1.5-17.0, p=0.009) and coumadine use (OR=3.5, 95%CI 1.1-11.5, p=0.04) were predictors for late bleeding.
Conclusions: Bleeding complications on combined antiplatelet and anticoagulant therapy were increased 8-fold. Thus in patients on oral anticoagulants, drug eluting stents necessitating sustained dual antiplatelet therapy should be used with caution. In addition, specific risk stratification for bleeding complications should be used to guide anticoagulation in patients undergoing coronary stenting.

P670 No association of chromosome 9p21 variation with angiographic and clinical outcomes after placement of drug-eluting stents in coronary arteries

W. Koch, P. Hoppmann, M. Eichinger, U. Weiss, A. Schoemig, A. Kastrati. *Deutsches Herzzentrum Muenchen, Munich, Germany*

Purpose: Genome-wide analyses with single nucleotide polymorphisms (SNPs) have identified a locus on chromosome 9 (approximately 100 kilobases in band p21.3) as the strongest genetic factor for coronary heart disease (CHD) in populations of European origin. The SNPs rs7865618, rs1537378, rs1333040, and rs1333049 are representatives of the common genetic variation within this region and strongly related to CHD. We examined the association of the SNPs with angiographic and adverse clinical outcomes after implantation of drug-eluting stents in coronary arteries.
Methods: Consecutively recruited patients (n=2028) with symptomatic CHD were treated with percutaneous coronary intervention and implantation of sirolimus- or paclitaxel-eluting stents. Follow-up angiography was performed in 1683 patients (83%) 6-8 months after stenting. Records of three-year adverse clinical outcomes were obtained from all stented patients. SNP genotypes were determined with TaqMan assays.
Results: The CHD-associated SNPs rs7865618, rs1537378, rs1333040, and rs1333049 were not significantly related with angiographic measures, including minimal lumen diameter (P≥0.11), diameter stenosis (P≥0.25), late lumen loss (P≥0.09), and binary restenosis (≥50% diameter stenosis) (P≥0.24) at follow-up. No association of the SNPs was found with death (P≥0.19), myocardial infarction (P≥0.22), repeat revascularisation (P≥0.10), and the composite endpoint of adverse clinical events (death, myocardial infarction, repeat revascularisation) at three years (P≥0.20).
Conclusions: No support was obtained for associations of CHD-related SNPs at chromosome 9p21.3 with angiographic results and adverse clinical events after placement of drug-eluting stents. Thus, while effects of this locus on the development and progression of atherosclerosis are well documented, no influence on the outcome of stenting in coronary arteries was observed in this study.

P671 Long term clinical outcomes in the patients treated with a new generation drug eluting stent

B. Chevalier[1], S. Silber[2], E. Garcia[3], W. Wijns[4], S. Worthley[5], I. Meredith[6], H. Suryapranata[7], K. Hauptmann[8], G. Schuler[9], L. Thuesen[10] on behalf of NOBORI 1 study group. *[1]ICPS, Massy, France; [2]Kardiologische Praxis, Munich, Germany; [3]Hospital General Universitario Gregorio Maranon, Madrid, Spain; [4]Cardiovascular Center OLV Hospital, Aalst, Belgium; [5]Royal Adelaide Hospital, Adelaide, Australia; [6]Monash Medical Centre, Clayton, Australia; [7]Isala Klinieken, Zwolle, Netherlands; [8]Krankenhaus der Barmherzigen Brüder, Trier, Germany; [9]Herzzentrum der Universitaet Leipzig, Leipzig, Germany; [10]Aarhus University Hospital, Aarhus, Denmark*

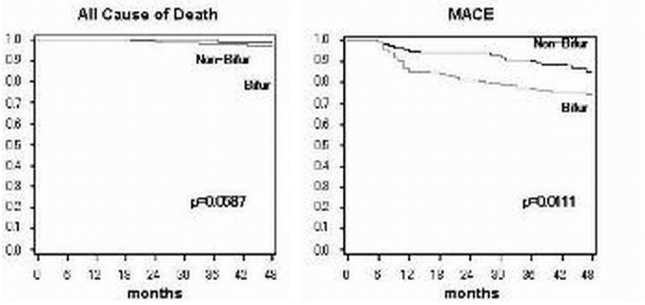
Background: Despite the excellent efficacy of drug eluting stents (DES) in reducing restenosis, safety of those devices has been under scrutiny in the past few years. Moreover, the long term clinical outcome of newly developed DESs is largely unknown. Our aim was to investigate three years safety of a new DES coated only abluminally with a matrix of biodegradable polymer and rapamycin derivative, Biolimus A9.
Methods: We conducted a randomized (2:1), controlled trial comparing the Biolimus A9 eluting stent, Nobori, and the paclitaxel eluting stent, Taxus, in 120 patients (85 and 35 respectively) at 28 centres in Europe, Asia and Australia. Patients with documented ischemia due to coronary artery disease in up to two native coronary arteries were considered for enrolment. The primary endpoint was angiographic in-stent late loss at 9 months, while secondary clinical endpoints included stent thrombosis and composite of major adverse cardiac events (MACE) comprising death, myocardial infarction and target vessel revascularization at 9 months, one year, and yearly up to 5 years.
Results: At nine months the in-stent late loss was significantly lower in the Nobori group as compared to the Taxus group (0.15±0.27 mm versus 0.32±0.33 mm) confirming the primary hypothesis of non-inferiority of Nobori stent versus Taxus stent. Major cardiac adverse events at 3 years were 11.8% in Nobori versus 17.1% in Taxus treated patients. The rate of death and MI was 9.4% and 14.3% in Nobori and Taxus arms respectively. Although this study was not powered for clinical endpoint, the particularly important finding is absence of stent thrombosis in Nobori arm, whereas there were 2 (5.7%) very late stent thromboses in Taxus arm. One of the patients with stent thrombosis was still on dual antiplatelet therapy on the time of event, and both events resulted in non-fatal myocardial infarction. At three years, 75% of the patients were no longer on dual antiplatelet therapy.
Conclusions: The long term results of this study indicate that biodegradable polymer and abluminal coating might have a beneficial impact on the safety profile of this new stent. Larger studies are underway to further evaluate the encouraging trends as seen in the present study.

P672 Comparison of 4 years efficacy and durability of drug-eluting stent implantation in non-bifurcation and bifurcation lesion of unprotected left main coronary arteries: multicenter registry in Asia

S. Nakamura[1], H. Ogawa[2], J.H. Bae[3], Y.H. Cahyadi[4], W. Udayachalerm[5], D. Tresukosol[6], S. Tansuphaswadikul[7]. *[1]New Tokyo Hospital, Chiba, Japan; [2]Kumamoto University Hospital, Kumamoto, Japan; [3]Konyang University Hospital, Daejeon, Korea, Republic of; [4]Husada Hospital, Jakarta, Indonesia; [5]King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [6]Her Majesty's Cardiac Center, Siriraj Hospital, Bangkok, Thailand; [7]Chest Disease Institute, Bangkok, Thailand*

Aim: The aim of this study is to compare the 4 years safety and durability of drug-eluting stent implantation in non-bifurcation (ostium and/or mid shaft) (Non-Bifur) and bifurcation (Bifur) lesion of unprotected left main coronary arteries (LMT).
Methods: A prospective analysis of 448 patients with LMT stenosis (324 Bifur and 124 Non-Bifur) in five high volume Asian centers after successful stenting in LMT was performed. LMT was treated with 5 strategies (single stenting 195 cases, T-stenting 47 cases, crush stenting 38 cases, Mini-crush stenting 93 cases, culotte stenting 54 cases, kissing stenting 21 cases). Complete clinical follow-up to 4 years is being analyzed for all 448 patients.
Results: The baseline clinical characteristics between 2 groups were similar. Angiographic and clinical success were achieved in all patients without any major complication. At 4 years overall cardiac events of Non-Bifur (14.5%) were significantly lower than Bifur (28.0%) (p=0.011). See figure for clinical results.

4 years cumulative freedom from all cause of death and MACE: major adverse cardiac events (death, myocardial infarction, CABG and re-PCI) in Non-Bifur and Bifur groups



Conclusion: The use of drug-eluting stent in patients with LMT was safe and feasible with low acute complication and low incidence of restenosis. Drug-eluting stent implantation in non-bifurcation lesion of LMT showed lesser incidence of cardiac events (death, myocardial infarction, CABG and PCI) compared with those of bifurcation lesion at 4 years clinical follow-up.

P673 Possible stent thrombosis: fact or fiction?

C.A. Kaiser[1], R. Jeger[1], B. Friedli[1], P. Rickenbacher[2], H.P. Brunner-La Rocca[1], M.E. Pfisterer[1] on behalf of BASKET Investigators. *[1]University Hospital Basel, Basel, Switzerland; [2]University Hospital, Bruderholz, Switzerland*

Background: According to the Academic Research Consortium Stent Thromboses (ST) are subdivided into definite, probable and possible. Whereas in the case of a probable ST a ST can be assumed at a high level of certainty, a possible stent thrombosis (PST) is considered in every unexplained death from 30 days after stenting. Despite the fact that pathologic-anatomic findings have proven the concept of PST, these cases are not counted in most randomized trials and registries due to the vague definition. The aim of the present analysis was to define the probability of a ST in all PST patients in a real-world population.
Methods: In the BAsel Stent Kosten-Effektivitaets trial (BASKET) 826 consecutive patients were prospectively randomized in a 2:1 fashion to receive a DES or a BMS. For the present analysis all deaths during 36-month follow-up classified as PST by the Critical Events Committee were re-classified by reviewing of patient files, autopsy reports and angiographic films as well as interviews with the patient relatives and family doctors. All sudden deaths with clinically suspected acute myocardial infarction or in patients with preserved left ventricular ejection fraction were considered to be most likely due to ST. All sudden deaths in patients with severe comorbidities, reduced ejection fraction or with suspected pulmonary embolism were considered most likely to be not due to ST.
Results: During the 36 month follow-up 36 definite, 17 probable and 17 PST were observed. 12 (71%) of PST occurred in patients after DES and 5 (29%) in patients after BMS. 10 (59%) of PST were most likely due to ST: 6 sudden deaths in patients with preserved left ventricular ejection fraction and 4 in patients with high grade suspicion for acute myocardial infarction. In 7 (41%) patients death was most likely not due to ST: 2 sudden deaths in patients with reduced left ventricular ejection fraction and 4 deaths in patients with severe comorbidities or suspected pulmonary embolism.
Conclusions: In the 17 events classified as PST by the independent Critical Events Committee, this diagnosis was most likely true in 59%, whereas in the remaining patients another cause for the acute death has to be assumed. The circumstances of death classified as PST have to be analyzed carefully in order to assign these events correctly at a high level of certainty.

P674 The routine early invasive strategy in women with non-st-segment elevation acute coronary syndrome: is it time for a paradigm shift?

A.L. Guler, R. Elkoustef. *University of Connecticut, Farmington, United States of America*

Background: The overall benefits associated with an early interventional strategy in patients who present with non-ST-segment (NSTE) acute coronary syndrome (ACS) are heterogeneous (TACTICS-TIMI18, ACTUS). Two of the three recent randomized trails (FRISC-II and RITA-3) have shown that virtually all the benefit associated with this strategy occurred in men with no clear benefit for women. We hypothesize that there may be a significant harm for high-risk NSTE ACS women (positive biomarkers, and ischemic ST changes) managed with the early invasive strategy.
Methods: Using data from a large tertiary care center, we identified 1534 patients with NSTE ACS (488 women; 1036 men) who underwent percutaneous coronary intervention (PCI) during their index hospitalization. We evaluated gender difference in acute medications, in-hospital procedures, and in hospital clinical outcomes.
Results: There were clear differences in baseline demographic and clinical characteristics. Women were older than men and more often had hypertension, diabetes mellitus, dyslipidemia, but less often had prior revascularization. There were also treatment disparities in pharmacologic interventions. Women less often received acute treatment with direct thrombin inhibitors, thrombolytics, and more importantly glycoprotein IIb/IIIa inhibitors. Men had higher rates of diagnostic coronary angiography on the index admission. Women had a higher incidence of in-hospital target lesion revascularization (5.7% vs 3.3%, p=0.42), and any RBC transfusion (10.9% vs. 2.80%, $<$0.01) as well as higher rate of myocardial infarction at 9 month follow up (4.10% vs. 1.70% p=0.50).
Conclusion: There is an increased hazard of myocardial infarction and target lesion revascularization associated with the early invasive strategy in women with high risk NSTE ACS. The mounting evidence of this increased risk for women from randomized clinical trials, observational data bases and 'real world' experience should lead to a re-examination of risk stratification guidelines for women presenting with NSTE ACS.

P675 Effects of proton-pump inhibitors on outcome of patients discharged on dual-antiplatelet therapy after percutaneous coronary intervention and stent implantation

R. Jarai, I. Brosovic, I. Tentzeris, S. Farhan, G. Unger, K. Huber. *Wilhelminen Hospital, Vienna, Austria*

Background: Recently, the CREDO trial showed a significant higher risk of major gastrointestinal bleedings associated with dual antiplatelet therapy after coronary intervention. Therefore, routine prescription of proton-pump-inhibitors (PPI) in addition to clopidogrel and aspirin might be essential for prevention of gastrointestinal complications. However, it has been suggested that PPI might reduce the effect of clopidogrel and increase the risk of adverse thrombembolic events.
Methods: In this retrospective analysis we investigated the effect of concomitant PPI and dual antiplatelet therapy on all-cause mortality and in-stent restenosis in 1506 consecutive patients who underwent PCI and stent implantation between the 1st of January 2003 and 31st of December 2006 in our hospital. The patients were followed-up for median 723 (390-1080) days.
Results: Dual antiplatelet therapy with concomitant PPI therapy was associated with significantly higher proportion of female patients (33.6% vs. 27.4%; p=0.015), significantly more patients with drug eluting stent (35.1% vs. 28.4%; p=0.01), significantly more patients discharged on statins (87.4% vs. 80.3%; p$<$0.001) and significantly less patients with diabetes mellitus (19.5% vs. 26.6%, p=0.002) compared to those who had no PPI at discharge. Clinical characteristics of patients with or without PPI therapy were not significantly different. All-cause mortality and in-stent restenose did not differ significantly with respect to use or non-use of PPI-therapy (7.4% vs. 7.6%; p=0.87). Even in different subgroups of patients e.g. acute vs. elective, BMS vs. DES, diabetics vs. no diabetics, had concomitant PPI-therapy no significant influence on outcome.
Conclusion: Our data suggest that the combination of dual antiplatelet therapy with proton-pump inhibitors obviously does not significantly influence thrombembolic events.

P676 Cytochrome p450 2C19 genotype is a major determinant of clopidogrel response and a predictor of post-stenting ischemic event occurrence

P.A. Gurbel[1], K. Bliden[1], K. Ryan[2], W. Herzog[1], U.S. Tantry[1], A. Shuldiner[2]. *[1]Sinai Center for Thrombosis Research, Baltimore, United States of America; [2]University of Maryland School of Medicine, Baltimore, United States of America*

Background: Clopidogrel nonresponsiveness (CN) has been linked to adverse clinical outcomes. In addition to functional variability at cytochrome (CYP) P450 level, influence of genetic variability in CYP2C19 on CN has been suggested.
Study: We studied the relation of CYP2C19*2 variant to platelet function as measured by 20uM ADP-induced platelet aggregation and 1 year cardiovascular outcomes in 227 patients on clopidogrel therapy who underwent PCI.
Results: The relation between the CYP2C19*2 polymorphism and platelet aggregation was present in PCI patients (p=0.02, additive model). Patients with the CYP2C19*2 genotype had more ischemic events in the 1 year following PCI. (Hazard Ratio =2.42;p=0.02).
Conclusions: The Cyp2C19*2 gene variant is strongly associated with a diminished antiplatelet effect of clopidogrel and reduced cardiovascular protection following PCI.

P677 Long-term outcomes of 1921 patients following percutaneous coronary intervention without on-site surgery

A.C.C. Ng, A. Yong, R. Alcock, V. Chow, C. Cheruvu, B. Aliprandi-Costa, L. Kritharides, H. Lowe, D. Brieger. *The University of Sydney, Sydney, Australia*

Background: Long-term outcome studies on percutaneous coronary intervention without onsite surgical support (PCI-WOS) are few. We present the in-hospital and long-term outcomes of our institution which has performed PCI-WOS since 2000.

Methods: From 2000-2006, 1921 patients underwent PCI. Procedural details and outcomes were obtained using hospital records and phone follow-up. Patients uncontactable were cross-matched with the local state Death Registry Database.
Results: Mean (±SD) age was 64±12yrs, 1398 (73%) males. Indications included primary PCI for acute myocardial infarction (MI):183 (10%), rescue PCI for failed fibrinolysis: 60 (3%), non-ST-elevation MI (NSTEMI): 344 (18%), unstable angina (UAP): 365 (19%) and elective PCI for stable angina: 969 (50%). 1076 (56%) patients had single-vessel disease; 535 (28%) two-vessel; and 310 (16%) three-vessel disease. Mean number of lesions treated was 1.3±0.5, with 1.2±0.5 stents placed. Angiographic success was 96%. There were 2 (0.1%) urgent transfers for bypass surgery for severe coronary disease after successful PCI to culprit lesion for acute MI (no patients required urgent transfer for PCI-related complications), 3 (0.2%) inpatient stroke and 28 (1%) inpatient deaths (75±11yo, all non-elective PCI: 15 primary, 3 rescue, 9 NSTEMI, 1 UAP). Among hospital survivors, mortality during follow-up (4±2yrs) was 9% (mean 1-yr mortality: 2.5±1.0%, with no significant change during study period). Specific causes included 58 (3.1%) cardiac-related, 14 (0.7%) strokes, 2 (0.1%) pulmonary embolus, 10 (0.5%) from respiratory failure, 29 (1.5%) sepsis, 45 (2.4%) malignancy, 1 ruptured aorta and undefined in 13 patients. Mortality for females was worse than males (annual-mortality 3.4% vs. 2.1%, P=0.001).
Conclusion: Acute adverse events are rare with PCI-WOS and long-term prognosis is comparable to reported cohorts with onsite surgery.

P678 Should all STEMI patients who have successful thrombolysis undergo routine pre-discharge angiography? A single centre experience

A. Hailan, J. Silberbauer, P. Prior, M. Asgari, R. Heppell, I. Mirza, J. Fisher, K. Kamalvand. *William Harvey Hospital, Ashford, United Kingdom*

Purpose: Primary PCI is the optimal treatment for STEMI. This is not widely available in the UK and thrombolysis remains the main therapeutic modality. Rescue PCI is undertaken in a proportion of patients in whom thrombolysis is unsuccessful. Early angiography in those who have had successful reperfusion is not standard practice in UK, reserved for patients with ongoing symptoms or a positive exercise test.
Methods: We instituted a policy of undertaking early inpatient angiography in all patients who had successful reperfusion in 2006. The records of 135 consecutive patients admitted between Feb 2006 and July 2007 were studied retrospectively and post discharge data was obtained through the cardiac rehabilitation service. We analysed mortality, re-infarction, revascularisation and subsequent admission for any cardiovascular events and compared the data to local MINAP data from 2002.
Results: 135 patients mean age 66 (SD 15) 76% male presenting with STEMI were included. 4 had LBBB and reperfusion could not be assessed by ECG criteria. 100 patients (74%) had successful reperfusion at 90min. 3 patients died prior to angiography (all within 24hrs). 83 underwent inpatient angiography (median 4 days) and 72 (87%) underwent early revascularisation. 14 did not undergo angiography due to protocol violation (8), renal impairment (5), and patient refusal (1). Of the 83 patients who had early angiography, 59 (71%) proceeded to PCI (10% multivessel) and 5 had a staged elective PCI to non-culprit lesions. 13 (16%) underwent CABG (69% inpatient) and 11 (13%) were managed conservatively. The overall mortality in 135 patients was 7% in-hospital (2002 data 15%, p=0.06) and 11% (26%, p=0.002) at 1 year. In the 100 pts with successful thrombolysis, the cumulative mortality/re-infarction rate at one month and one year was 3%/4% and 5%/8% respectively. The mortality/re-infarction rate in 83 patients with early angiography was 0%/0% in hospital and 1%/5% at 1 year. Of the 31 patients with no reperfusion, only 11 (35%) were transferred to tertiary centre for rescue PCI and the overall mortality of the 31 patients was 23% in-hospital and 32% at 1 year.
Conclusions: Routine early coronary angiography following successful reperfusion leads to high rates of successful and safe early revascularisation. This translates into a significantly lower mortality, re-infarction, and subsequent outpatient revascularisation rate. We therefore recommend that until primary PCI service is available 24/7, all patients who have successful reperfusion should have early pre-discharge angiography ideally by the following day.

P679 Is the phenotype of n-acetylation a predictor of coronary stents fate in mid-term follow-up after stenting with bare metal stents?

D. Iosseliani, I. Kuznetsova, S. Semitko, O. Sukhorukov, D. Guranda. *Moscow City Center of Interventional Cardioangiology, Moscow, Russian Federation*

Background: It is known, that the synthesis as well as the catabolism of connective tissue's extracellular component is closely dependent on the rate of acetylation processes. Meanwhile this component can play an important role in the development of coronary in-stent stenosis. Thus, our study was aimed at the analysis of eventual relation between the phenotype of N-acetylation and the development of coronary in-stent stenoses within the first six months after stenting with bare metal stents.
Material and methods: Our retrospective study comprised 100 consecutive male patients, aged on the average 56.8+6.1 years. All of them electively received 116 bare metal stents BX Sonic. Patients' selection for the study was based on the data of control coronary angiography performed at least 6 months (7.2+1.3 months) after stenting. The selected patients were divided into two groups: 50 patients with in-stent coronary stenosis (Group 1) and 50 patients with good angiographic results of stenting (Group 2). Baseline clinical, laboratory and history characteristics of both groups, including risk factors for in-stent stenosis development in the follow-up, were not significantly different.
The determination of N-acetylation phenotype was performed using a standard substance, sulfadimesine, as test drug.
Results: our study revealed a certain prevalence of subjects with fast acetylation type among the studied patients (62%). We have also found a significant prevalence of patients with fast acetylation type in Group 1 (76%), while in Group 2 there was a significant prevalence of patients with slow acetylation type (62%) The division of patients into two groups depending on the rate of acetylation has shown that in-stent stenosis was seen in 86% of cases in the group of fast acetylation and in 14% of cases in another group (P<0,01). We have also revealed a high direct correlation between the rate of in-stent stenosis and the fast acetylation (r=0,641).
Conclusions: N-phenotype of acetylation can, at least, serve as a predictor of the fate of coronary stents in the mid-term follow-up. Under otherwise equal conditions the patients with fast acetylation type are at significantly higher risk of in-stent stenosis development than the patients with slow acetylation type.

P680 The use of fractional flow reserve to defer revascularisation of moderate coronary stenoses and to re-classify multi-vessel disease: a 2.5 year follow up study

T. Lockie, D. Perera, K. Naeem, I. Webb, S. Redwood. *Guy's and St Thomas' NHS, London, United Kingdom*

Background: Fractional flow reserve (FFR) is an accepted standard to detect ischemia. The DEFER and FAME studies suggest that revascularisation of a moderate coronary stenosis can be safely deferred if the FFR is >0.75 and that FFR can potentially be used to guide therapy in multi-vessel disease.
Methods: Consecutive patients who had a pressure wire assessment 2005-07 were included. FFR was calculated as (Pd – Pv)/(Pa - Pv) where Pa, Pv and Pd are simultaneous aortic, right atrial and distal coronary pressure during an iv infusion of adenosine. We assessed a) influence of FFR on lesion revascularisation, b) outcome of patients who had intervention deferred or performed based on an FFR threshold of 0.75 and c) impact of multi-vessel FFR assessment on revascularisation strategy. Outcome data was collected through patient questionnaires and database analysis. Data are presented as mean ± standard deviation.
Results: Of 300 patients, 264 were included. Patients were 62±11 years old and 1.3±0.5 vessels examined per case. 92% of lesions with a FFR<0.75 underwent revascularisation and 94% of lesions with a FFR >0.75 had intervention deferred. FFR was 0.71±0.07 in the revascularisation group (12 CABG, 96 PCI) and 0.86±0.06 in the deferred (P<0.001). At 2.57±0.56 years, the composite endpoint of death, MI or target vessel revascularisation (TVR) occurred in 8% in the "perform" vs. 13% in the "defer" group (P=0.36) (figure 1). Overall, 77% of patients avoided revascularisation of at least one vessel on the basis of the FFR.

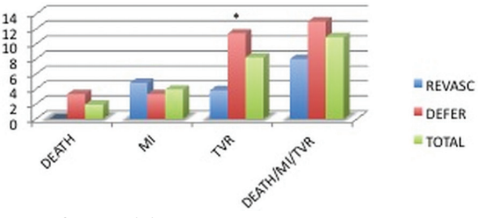


Figure 1.Outcomes (%)

Conclusions: Deferring revascularisation of moderate coronary lesions on the basis of an FFR threshold of 0.75 appears to be a safe strategy. FFR can be used to further classify multi-vessel disease and tailor therapy. These results are consistent with recent large trial data.

P681 Effect of long-term clopidogrel treatment on platelet function and inflammation in patients undergoing coronary arterial stenting

U.S. Tantry, M.J. Antonino, E. Mahla, K. Bliden, P.A. Gurbel. *Sinai Center for Thrombosis Research, Baltimore, United States of America*

Background: A clopidogrel loading dose administered during stenting attenuates inflammation marker (IM) release. However, less is known of the anti-inflammatory effect of clopidogrel maintenance therapy (CMT).
Methods: Platelet reactivity to ADP and IMs were measured in 110 consecutive patients [n=69 clopidogrel naïve (CN) and n=41 patients on >6 months CMT] prior to non-emergent stenting by aggregometry/flow cytometry and multi-analyte profiling. All patients were treated with aspirin.

Results: Pre-stenting ADP-induced platelet aggregation, p-selectin and activated GPIIb/IIIa expression were lower in CMT patients compared to CN group ($p<0.001$) and was accompanied by lower levels of selected IMs ($p<0.05$) (Table). Additionally, there was a strong correlation between platelet aggregation and flow cytometry measurements ($p</=0.04$)

Inflammation Markers

	Clopidogrel naïve (n=69)	Clopidogrel maintenance therapy (n=41)	p-value
IL-1a (pg/ml)	153±41	45±19	0.05
IL-2 (pg/ml)	32±9	4.5±2	0.03
IL-6 (pg/ml)	144±33	32±9	0.01
IL-13 (pg/ml)	27±8	3.7±1	0.03
IL-10 (pg/ml)	52±13	27±12	0.19
TNF-b (pg/ml)	30±9	3.4±0.8	0.03
TNF-a (pg/ml)	6.9±0.7	4.7±0.4	<0.01
CRP (mg/l)	22±4	16±2	0.18

Conclusions: In addition to markedly lowering platelet reactivity to ADP, CMT is associated with an anti-inflammatory effect. Large scale studies are required to investigate the clinical significance of the anti-inflammatory properties of thienopyridine treatment and to determine whether they demonstrate a class effect or specific to clopidogrel.

P682 Are drug eluting stents safe in warfarin-treated patients?

A.-P. Annala[1], P.P. Karjalainen[1], P. Porela[2], M. Niemela[3], K. Nyman[4], M. Puurunen[5], S. Vikman[6], A. Ylitalo[1], K.E.J. Airaksinen[2]. *[1]Satakunta Central Hospital, Pori, Finland; [2]Turku University Hospital, Turku, Finland; [3]Oulu University Hospital, Oulu, Finland; [4]Jyvaskyla Central Hospital, Jyvaskyla, Finland; [5]Helsinki University Hospital, Helsinki, Finland; [6]Heartcenter, Tampere University Hospital, Tampere, Finland*

Purpose: We sought to determinate whether drug eluting stents (DES) are safe in patients on long-term warfarin treatment.
Methods: We conducted long-term follow-up (mean 46 months) of all consecutive patients on warfarin treatment (n=375) who underwent PCI in 5 Finnish hospitals between 2002-2006. During the follow up, data on major bleeding and major adverse cardiovascular or cerebrovascular events (MACCE) were collected.
Results: A total 167 patients received DES, and 169 bare metal stents (BMS). In addition, 39 patients were treated with balloon angioplasty (POBA). Complete follow-up datasets were available on all patients. The,rate of MACCE was 37.7% for DES and 46.2% for BMS (P=0.12, Table 1). Major bleeding occurred in 15.6% of patients in DES group and in 15.4% in BMS group. Outpatient Bleeding Risk Index was a significant (P=0.006) predictor of major bleeding during follow-up.

Table 1

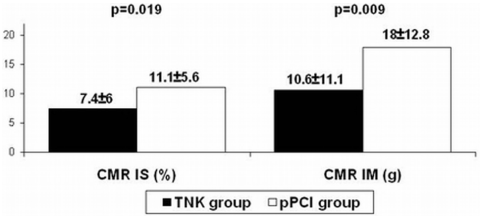
	DES (n=167)	BMS (n=169)	p
Age, (years)	69±8	70±10	0.06
Male, n (%)	121 (72)	130 (77)	0.38
Radial Access, n (%)	36 (22)	51 (30)	0.08
Outpatient Bleeding Risk Index, (mean±SD)	1.2±0.8	1.3±0.8	0.26
Duration of Follow-up, (months,mean±SD)	46±10	46±13	0.96
MACCE, n (%)	63 (37.7)	78 (46.2)	0.12
– Myocardial Infarction	31 (18.6)	28 (16.6)	0.67
– Death	32 (19.2)	45 (26.6)	0.12
– Target vessel revascularization	16 (9.6)	17 (10.1)	0.88
– Stroke	13 (7.8)	13 (7.7)	0.98
– Stent Thrombosis	6 (3.6)	6 (3.6)	0.98
Major Bleeding, n (%)	26 (15.6)	26 (15.4)	0.96

Conclusion: In this long-term follow-up, DES were as safe as BMS in patients with warfarin therapy. The prognosis of this patient group with many co-morbidities is quite poor and major bleeding events are common irrespective of stent type.

P683 Reduction of infarct size and left ventricular remodeling after prehospital thrombolysis in patients with early presentation of STEMI transferred for mechanical reperfusion

J. Legutko[1], P. Kleczynski[1], T. Rakowski[1], Z. Siudak[1], L. Rzeszutko[1], L. Bryniarski[1], A. Brzozowska-Czarnek[2], A. Urbanik[2], J. Dubiel[1], D. Dudek[1]. *[1]Institute of Cardiology, Jagiellonian University, Krakow, Poland; [2]University Hospital, Department of Radiology, Krakow, Poland*

Purpose: Reperfusion strategy using full-dose lytics followed by immediate PCI (facilitated PCI) in STEMI is harmful. However combination of prehospital lysis with delayed PCI (pharmaco-invasive treatment) can be beneficial, especially in patients (pts) presenting early with long time delay to intervention.
Methods: We randomized 45 pts with STEMI < 3h from pain onset, with anticipated delay to PCI >90 minutes to receive prehospital tenecteplase (TNK group, n=22) or placebo (pPCI group, n=23). All pts underwent PCI after cathlab admission. Primary endpoint was the infarct size (IS, %) and infarct mass (IM, g) assessed by delayed enhancement cardiac magnetic resonance (CMR) at 6-month. CMR left ventricular (LV) end-diastolic volume index (LVEDVI, ml/m^2) was also assessed as a marker of LV remodeling.
Results: Time from first medical contact to intervention was similar in both groups (TNK vs pPCI: 144±51 vs 129±24 minutes; p=0.2). Angiography revealed more frequent infarct-related artery patency in TNK group (TIMI 2+3: 81% vs 43%; p=0.01). Better ST-segment resolution before PCI was found in TNK group (resolution >70%: 53% vs 6%; p=0.003). After PCI no difference in TIMI 3 flow and ST-segment resolution >70% rate was found. The 6-month CMR IS and IM was significantly lower in TNK group (graph). The 6-month CMR LVEDVI was also lower in TNK group (128±45 vs. 161±48, p=0.047).



Conclusions: In patients with early presentation of STEMI transferred for mechanical reperfusion with time delay from first medical contact to intervention >90 minutes faster reperfusion with prehospital thrombolysis followed by PCI resulted in lower infarct size and LV remodeling at 6-month follow up in comparison to primary PCI. Large scale clinical trials are needed to compare clinical outcomes of those two strategies.

P684 Long-term outcomes with paclitaxel- and sirolimus-eluting stents for unprotected left main coronary artery disease

J. Mehilli, A. Kastrati, R.A. Byrne, S. Schulz, J. Pache, M. Seyfarth, S. Kufner, O. Bruskina, A. Schomig. *Deutsches Herzzentrum, Munich, Germany*

One year results of the ISAR-LEFT MAIN trial showed that implantation of either paclitaxel-eluting stents (Taxus) or sirolimus- eluting stents (Cypher) in unprotected left main coronary artery (uLMCA) lesions is safe and effective with a cumulative incidence of death, myocardial infarction or left main area revascularization – the primary endpoint of the study – of 13.6% in the Taxus and 15.8% in the Cypher group. In view of the high-risk profile of this patient group follow-up beyond one-year is of particular relevance. Moreover, very-long-term follow-up data with drug-eluting stents implantation in uLMCA disease are still limited.
Methods: In this randomized study, 607 patients with symptomatic coronary artery disease undergoing PCI for uLMCA were enrolled: 302 assigned to receive Taxus and 305 assigned to receive Cypher. The aim of the present analysis is to evaluate three-year outcomes, in particular stent thrombosis, mortality, myocardial infarction and repeat revascularization, both in the entire cohort and specific subgroups as defined by lesion location and stenting technique.
Results: Updated results will be presented at the meeting. Follow-up will be extended to 3 years.

P685 Comparison between percutaneous coronary intervention and coronary-artery bypass graft for the treatment of left maindisease: results from a multicenter registry

C. Ruperto[1], A. Caggegi[1], G. Barrano[1], G. Cincotta[1], M. Miano[1], M.E. Di Salvo[1], S. Tolaro[2], L. Patane'[2], A.M. Calafiore[1], C. Tamburino[1]. *[1]Azienda Ospedaleria-Universitaria V. Emanuele Ferrarotto S. Bambino, Catania, Italy; [2]Clinica Morgagni, Catania, Italy*

Background: The recent randomized SYNTAX study has recorded comparable safety outcomes, including death, myocardial infarction and cerebrovascular accident, in Coronary Artery Bypass-Graft (CABG) and Percutaneous Coronary Intervention (PCI) patients at 12 months. However, in PCI group there was a significantly higher rate of revascularization leading to higher rate of overall MACCE in PCI group, when compared with CABG group.
Objectives: To compare clinical outcome of patients underwent to PCI or CABG for treatment of left main coronary artery in a contemporaneous cohort of real world patients.
Methods: We analyzed data from 930 consecutive patients underwent PCI or CABG in two high-volume centres. Endpoint was the Major Adverse Cardiac Events (MACE): death, cardiac death, myocardial infarction (MI) and need for repeat target vessel revascularization (TVR).
Results: From June 2002 to December 2008 a total of 930 patients were included in our analysis and were divided in two groups: 431 pt (46.4%) in PCI group, 499 (53.6%) in CABG group. PCI patients were more likely to have renal failure (17.9% vs 1.2%; p=0.006), peripheral vascular disease (18.3% vs 12.1%; p=0.008), left ventricular dysfunction – defined as LVEF ≤ 30% - (12.8% vs 3.7%; $p<0.001$) and previous revascularization procedures, as compared with CABG group. Patients who underwent PCI presented with higher values of Euroscore (5.9±3.4 vs 4.6±2.7; $p<0.001$), but lower values of Syntax-Score (27.1±11.9 vs 33.1±12.6; $p<0.001$). At follow-up (28±21 months) patients treated with PCI

showed higher rates of overall MACE (25.4% vs 13.1%; p<0.001) and TVR (PCI patients 12.9% vs CABG patients 4.2%; p<0.001) as compared with patients treated with CABG.
Conclusions: In clinical practice the use of PCI for treatment of left main disease is common and may be efficacious and safe. However, our results confirm higher rates of MACE and TVR after percutaneous revascularization procedures in "real world" when compared with surgical revascularization.

P686 First clinical application of an actively reversible direct factor IXa inhibitor in elective percutaneous coronary intervention

M.G. Cohen[1], D.A. Purdy[2], J.S. Rossi[3], L.R. Grinfeld[4], L.H. Aberle[5], A.B. Greenbaum[6], E.T. Fry[7], J.A. Alexander[5], C.P. Rusconi[8], R.C. Becker[5]. *[1]University of Miami, Miami, United States of America; [2]Black Hills Cardiovascular Research Group, Black Hills, United States of America; [3]The University of North Carolina at Chapel Hill, Chapel Hill, United States of America; [4]Italian Hospital of Buenos Aires, Buenos Aires, Argentina; [5]Duke Clinical Research Institute, Durham, United States of America; [6]Henry Ford Health System, Detroit, United States of America; [7]St. Vincent Hospital, Indianapolis, United States of America; [8]Regado Biosciences, Durham, United States of America*

Purpose: The ideal anticoagulant should prevent ischemic complications without increasing bleeding risk. Controlled anticoagulation is possible with the REG1 System, an intravenous RNA aptamer comprising a direct factor IXa inhibitor (RB006) and its active reversal agent (RB007). We conducted a phase 2a, open-label, multicenter randomized study testing the feasibility of using RB006 as the anticoagulant in patients undergoing elective PCI and 2 anticoagulation reversal strategies.
Methods: A roll-in group (n=2) treated with REG1 + GP IIbIIIa inhibitors was followed by 2 groups randomized 5:1 to REG1 (1mg/kg RB006) or UFH. In group 1 (n=12), RB006 was reversed in a step-wise fashion, with a partially reversing dose of RB007 given post PCI and the remaining fully reversing dose given 4 hrs later followed by sheath removal (total RB007 dose 2mg/kg). In group 2 (n=12), RB006 was fully reversed with RB007 on procedure completion, followed by sheath removal. UFH was dosed to an ACT >250 sec. All patients received aspirin and clopidogrel 600mg. Endpoints were major bleeding within 48 hrs; the composite of death, MI or urgent TVR within 14 days; and pharmacodynamic measures.
Results: All cases were successful, with final TIMI 3 blood flow and no procedural thrombotic complications. Clinical events included 1 MI and 1 TVR with REG1; 1 MI and 1 major bleed with UFH. RB007 rapidly and consistently reversed RB006 in a dose-dependent manner (figure). Both reversal strategies allowed scheduled sheath removal.

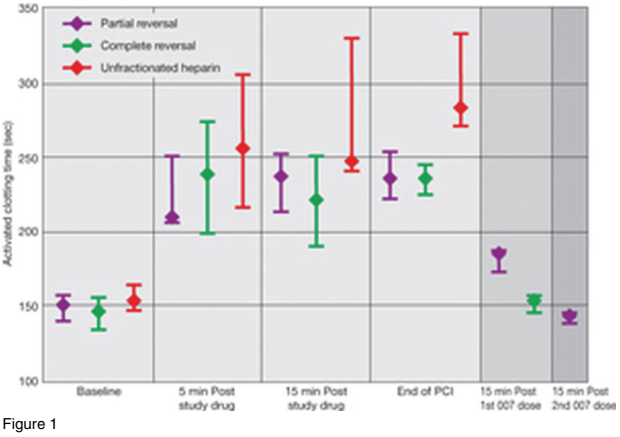


Figure 1

Conclusion: Anticoagulation with RB006, a direct FIXa inhibitor, followed by reversal with RB007 is feasible and permits an individualized approach to balancing thrombosis prevention and hemostasis in patients undergoing elective PCI. Larger clinical trials of the REG1 System are warranted.

P687 Unprotected left main coronary stenting in high-risk patients in a non-surgical centre

G. Pulikal, K.W. Lee, J. Tomson, M. Pitt. *Heart of England NHS Foundation Trust, Birmingham, United Kingdom*

Background: Data on long-term survival in unprotected left main stem (ULM) percutaneous coronary intervention (PCI) is limited. We present our experience of ULM PCI in an acute hospital, with no onsite surgical cover in the UK.
Methods: Retrospective analysis of consecutive patients (n=115, age 73±10, males 64%) who had ULM PCI between Jan 2004 and Oct 2008 was performed. Procedural complications, MACE (death, target lesion revascularisation and myocardial infarction) and survival status was ascertained in all patients.
Results: Majority were high-risk patients: 77% had high EuroScore ≥ 6, 70% were surgical-rejects, 43% had poor left ventricular (LV) function, 17% had cardiogenic shock (CS) periprocedure, and 81% presented with acute coronary syndrome. Drug eluting stents was used in 92 (80%) and bare metal stents (BMS) in 23 patients. The in-hospital mortality was 7% (n=8) and long-term mortality was 28% (n=32) after a median follow up of 19 mths (IQR 8–30). MACE at 12 mths was 24%. Procedural complications occured in 12%. A high EuroScore, poor LV function, periprocedural CS and use of BMS were significantly associated with in-hospital and long-term mortality (see Table). Logistic regression analysis identified CS as independent predictor of in-hospital mortality (OR, 0.18, p=0.035) whilst both CS (OR, 0.25, p<0.04) and a high EuroScore (OR, 1.15, p=0.007) were independent predictors for long-term mortality. Median survival duration for high EuroScore and 'surgical-reject' patients was 17 (6–28) and 15 (6–27) mths, respectively.

Follow-up survival status comparison

	All (n=115)	Alive at Follow-up (n=83)	Death at Follow-up (n=32)	P-value
EuroScore (IQR)	9 (6–15)	8 (5–11)	15 (12–18)	<0.001
High EuroScore ≥ 6 (%)	89 (77)	60 (72)	29 (91)	0.035
"Surgical-reject" (%)	81 (70)	52 (63)	29 (91)	0.003
Cardiogenic shock (%)	19 (17)	6 (7)	13 (41)	<0.001
Bare metal stent (%)	23 (20)	7 (31)	16 (69)	0.038
Poor LV function (%)	49 (43)	27 (33)	22 (69)	0.002

Data in median (interquartile range, IQR). LV, Left ventricular function.

Conclusion: We have demonstrated acceptable in-hospital and long-term mortality rate in our very high risk patients undergone ULM PCI. ULM PCI is a viable option for high risk patients in an acute hospital with no onsite surgical support.

LATE INSTENT RESTENOSIS AFTER DRUG ELUTING STENT IMPLANTATION

P688 Late catch-up in restenosis following sirolimus-eluting stent implantation

M. Kimura, O. Matsuda, T. Ito, N. Tanaka, K. Nasu, Y. Kinoshita, M. Ehara, E. Tsuchikane, Y. Asakura, T. Suzuki. *Toyohashi Heart Center, Toyohashi, Japan*

Background: Despite the suppression of intimal hyperplasia (IH) in coronary arteries with drug eluting stents (DES) compared with bare-metal stents at 6 months postprocedure, there appears to be a "late catch-up" in IH growth among patients treated with DES after 1 year. However, late restenosis after sirolimus-eluting stent (SES) implantation has not been sufficiently evaluated. The aim of our study was to determine whether in-stent restenosis (ISR) occurring >1 year ("late catch-up") after SES implantation is a real clinical entity.
Methods: We analyzed data on all SES implanted in patients treated at our institution from June 2004 to April 2007 and evaluated the incidence, clinical presentation, and angiographic ISR pattern after SES implantation. "Late catch-up" required demonstration of a patent stent at 6 to 9 months, with restenosis demonstrated on repeat angiography after 1 year.
Results: There were 3,420 lesions in 2,414 patients treated with SES over the length of the study period at our institution. Of this population, angiographic follow-up was performed in 1,763 patients (73.0%) with 2,506 lesions (73.3%). Angiography was performed after 1 year because of patient symptoms or to treat other vessels. Overall, restenosis occurred in 265 lesions (10.6%). "Late catch-up" in restenosis was observed in 20 lesions (0.80%) at second angiographic follow-up (median 23.5 months; range of 17.7 to 29.3 months). Of 20 lesions, 13 (65%) were located at the stent edge. Almost all cases of "late catch-up" (92.8%) expressed a focal angiographic ISR pattern. Clinical presentation of late target lesion revascularization (TLR) included silent ischemia (43%) and recurrent angina (57%). Late TLR was performed in 18 patients with 19 lesions. Serial quantitative coronary angiographic analysis of these lesions showed a minimal lumen diameter of 2.71±0.55 mm immediately after SES implantation, 2.44±0.59 mm at 9-month follow-up, and 1.04±0.26 mm at second follow up (p<0.001).
Conclusions: "Late catch-up" is an infrequent but real entity. The clinical presentation of late TLR was either silent ischemia or recurrent angina, but not acute coronary syndrome. Careful clinical and angiographic follow-up 1 year after SES implantation should be considered.

P689 Late restenosis in sirolimus eluting stent, is it late catch up?

S. Takahashi, S. Saito. *Shonan Kamakura Hospital, Kamakura, Japan*

Background: Drug-Eluting Stents (DES)have shown the efficacy for prevention of coronary in-stent restenosis. However, besides late thrombotic events, late restenosis in DES remains unclear and could be an unresolved issue. The purpose of this study was to investigate the incidence of late restenosis in Sirolimus-Eluting Stents (SES) beyond one year after its implantations.
Methods and Results: We analyzed 1910 lesions underwent SES implantations in our hospital from August 2004 to April 2008. We routinely performed follow

up coronary angiograms at 8 months after SES implantations and coronary angiograms were also performed when patients had symptoms after 8 months' follow up. Restenosis occurred in 122 lesions (100 patients) and the restenosis rate of SES was 6.4%. Among them, 100 lesions in 91 patients were needed the target lesion revascularization (TLR) by percutaneous coronary interventions (PCI) and the rate of TLR was 5.2%. 70 lesions/100lesions (70%) were treated with PCI within one year after SES implantations. And 30 lesions/100 lesions (30%) were needed PCI beyond one year after the SES implantations (481-1330 days, median 610 days), even though 14 lesions (14%) showed excellent results without restenosis at 8 months' follow up angiograms. The rates of TLR were 3.7% at one year follow up and 1.5% beyond one year.
Conclusions: 30% of SES restenosis was seen beyond one year after SES implantations, however it has been reported that late catch up was not seen in SES. We need a long term follow up for patients who received the DES carefully, since the number of late restenosis in DES could be increasing in the future.

P690 Late restenosis of sirolimus-eluting stent implantation for aorto-ostial lesions: comparison of right coronary artery and left main artery

S. Otsuru, K. Kadota, D. Hasegawa, S. Habara, H. Tanaka, S. Hosogi, Y. Fuku, H. Ymamoto, T. Goto, K. Mitsudo. *Kurashiki Central Hospital, Kurashiki, Japan*

Background: Recently, late restenosis after Sirolimus-eluting stent (SES) implantation has been reported. Although a complex lesion, such as ostial lesion, could have an impact on the late restenosis, any specific lesion evaluation of late restenosis has not been reported. Thus, we evaluated the prevalence of late restenosis after SES implantation in aorto-ostial lesions. Furthermore, the effect of each site of aorto-ostial lesions on its late restenosis was studied.
Methods: We analyzed the angiographic findings of 131 aorto-ostial lesions treated with SES from November 2003 to December 2006. Scheduled angiography was performed at 3-8 months and 20 months after percutaneous coronary intervention. Early restenosis was defined as one at the early follow-up and late restenosis at the late follow-up without early restenosis. Early and late restenosis rates, late loss of the right coronary artery (RCA) ostial lesions (39 lesions),and left mein trunk (LMT) ostial lesions (25 lesions) were evaluated.
Result: Data are shown in table 1.

Table 1

Follow-up	RCA ostium	LMT ostium	P value
Early (3-8 months)	N=63	N=32	–
Reference Diameter	3.18±0.44	3.58±0.63	<0.001
Minimal Lumen Diameter (MLD) pre	1.18±0.45	1.59±0.41	<0.001
MLD post	2.87±0.38	3.32±0.50	<0.001
Restenosis Rate	28.6%	6.3%	<0.001
Late Loss (from post-PCI to late follow-up)	0.56±0.85 mm	0.22±0.65 mm	<0.001
Late (20 months)	N=39	N=25	–
MLD 8 months	2.53±0.52	3.26±0.4	<0.001
MLD 20 months	2.21±0.67	63.17±0.76	<0.001
Restenosis Rate	28.2%	4.0%	0.016
Target Lesion Revascularization	17.9% (7/39)	0% (0/25)	0.037
Late Loss (from early to late follow-up)	0.32±0.69 mm	0.09±0.57 mm	<0.001

Conclusions: Late restenosis was observed at both RCA and LMT ostial lesions after SES implantation. However, only late restenosis of RCA ostial lesion linked to a clinical event.

P691 Peri-strut ulcer-like appearance, a unique finding of optical coherence tomography after sirolimus eluting stent implantation: the prevalence and the clinical characteristics

S. Hosogi, H. Shimizu, H. Tanaka, Y. Fuku, H. Katoh, H. Yamamoto, S. Fujii, T. Goto, K. Kadota, K. Mitsudo. *Kurashiki Central Hospital, Kurashiki, Japan*

Background: Late stent thrombosis (LT) is still a major problem after sirolimus eluting stent (SES) implantation. Some cavities formation between the stent strut, Peri-strut ulcer-like appearance (PSU), has been reported from the Optical Coherence Tomography (OCT) study in the case of LT after SES implantation. However, the prevalence and the clinical characteristics of PSU are unknown.
Methods: We analyzed the findings of PSU and incomplete stent apposition (ISA), in consecutive 37 PCI cases with OCT for in-stent restenosis (ISR) lesion after SES (n=31) and bare metal stent (BMS) (n=6) implantation. PSU was defined as peri-stent cavity formation which depth was over 0.5mm in OCT. Furthermore, we examined the clinical characteristics of the lesions with PSU, such as original lesion type (AMI/UAP: n=7, AP: n=8, CTO: n=10 or ISR: n=6) and periods to restenosis (beyond 1 year or not).
Results: We observed PSU in 11 cases (AMI/UAP: n=2, AP: n=4, CTO: n=5 or ISR: n=0) and ISA in 8 cases (AMI/UAP: n=2, AP: n=3, CTO: n=2 or ISR: n=1) of SES group. No PSU and ISA were observed in BMS group. Prevalence of PSU and ISA were 35.5% and 26% in SES group and both 0% in BMS group, respectively. PSU tended to occur when the period to ISR was beyond 1 year after PCI (1 year<: 47%, 1 year>: 21%).

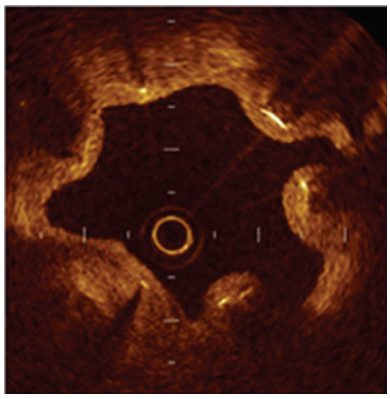


Figure 1. Peri-strut ulcer-like appearance

Conclusions: PSU is a unique finding of OCT after SES implantation. PSU might be worsening beyond 1 year after PCI in some SES cases. Further investigation is needed to reveal the clinical implication of PSU.

P692 The difference of restenosis pattern between overlapping TAXUS and overlapping Cypher stents for diffuse lesion from analysis using intravascular ultrasound

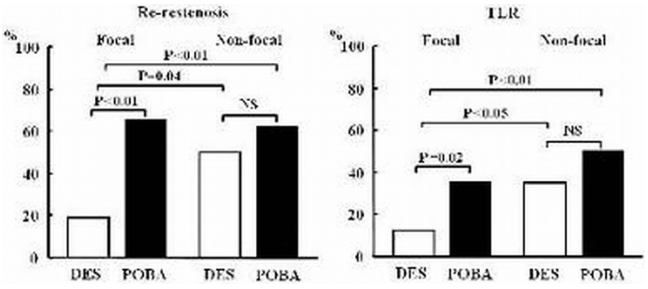
H. Mukawa, T. Sone, H. Tsuboi, I. Morishima, M. Uesugi. *ogaki municipal hospital, Ogaki, Japan*

Purpose: Overlapping drug eluting stents (DES) for diffuse lesion has been reported to be a risk factor of instent restenosis. However, the mechanisms of restenosis of overlapping DESs remains unclear. We compared the restenosis pattern of overlapping Cypher stents and overlapping TAXUS Express2 stents using intra-vascular ultrasound analysis.
Methods: Overlapping Cypher stents (OL-Cyphr) were implanted in 306 pts (318 lesions) from Aug 2004 to Nov 2007, and overlapping TAXUS Express2 stents (OL-TAXUS) were implanted in 60 pts (74 lesions) from May 2007 to Nov 2007. Restenosis rate at 6 month after PCI was 9.3% in OL-Cypher and 16.4% in OL-TAXUS (not significant). For patients with restenosis of OL-Cypher and OL-TAXUS, we performed IVUS and measured the average of intimal hyperplasia volume (IH) at the following site; (1) overlapping site (OL), (2) 5mm proximal site of overlapping edge (P-OLE), (3) 5mm distal site of overlapping edge (D-OLE), (4) proximal non-overlapping site (P-NOL), (5) distal non-overlapping site (D-NOL). We compared the restenosis pattern, IH and %IH (IH/stent volume, %) between OL-Cypher (n=26) and OL-TAXUS stents (n=9).
Results: There were no differences in lesion characteristics between OL-Cypher and OL-TAXUS. Although restenosis pattern was focal in both overlapping DESs, restenosis site was frequently seen at overlapping edges in OL-Cypher, and at non-overlapping site in OL-TAXUS. IVUS analysis showed significantly greater volume of increased %IH at the overlapping edges (P-OLE and D-OLE) than that at non-overlapping site in OL-Cypher (22.0% vs. 15.4%, p=0.005). In OL-TAXUS, on the other hand, there was no significant difference in %IH among each segment.
Conclusions: Overlapping stents resulted in the increased intimal hyperplasia volume and higher restenosis rate at overlapping edges in overlapping Cypher stents, but not in overlapping TAXUS stents. TAXUS may be more useful to overlap stents for diffuse lesion.

P693 High re-restenosis after treatment of diffuse sirolimus-eluting stent restenosis irrespective of devises for target lesion revascularization

H. Kitahara[1], Y. Kobayashi[1], H. Takebayashi[2], Y. Fujimoto[3], Y. Nakamura[4], N. Kuroda[1], T. Himi[3], A. Miyazaki[4], S. Haruta[2], I. Komuro[1]. *[1]Chiba University Graduate School of Medicine, Chiba, Japan; [2]Fukuyama Cardiovascular Hospital, Fukuyama, Japan; [3]Kimitsu Chuo Hospital, Kisarazu, Japan; [4]Chiba Cardiovascular Center, Ichihara, Japan*

Background: High re-restenosis rates have been shown in lesions with diffuse sirolimus-eluting stent (SES) restenosis compared to those with focal SES restenosis. However, there is little information about optimal management of either focal or diffuse SES restenosis.
Methods: A total of 102 lesions in 101 patients that underwent target lesion revascularization (TLR) for SES restenosis were classified according to 1) restenosis pattern and 2) use of drug-eluting stents (DES) for TLR: 1) focal restenosis treated with DES (focal-DES, n=40), 2) focal restenosis treated by balloon angioplasty (focal-balloon, n=31), 3) non-focal restenosis with DES (non-focal-DES, n=17), and 4) non-focal restenosis by balloon angioplasty (non-focal-balloon, n=14).
Results: There is no significant difference in the incidence of diabetic patients among the 4 groups. Figure shows re-restenosis and TLR rates after the treatment of SES restenosis.



Conclusion: Re-DES implantation for focal SES restenosis results in lower re-restenosis and re-TLR rates compared to re-DES implantation for non-focal SES restenosis or conventional balloon angioplasty either for focal or non-focal SES restenosis.

P694 RANTES gene promoter polymorphisms and susceptibility to coronary artery disease and restenosis after percutaneous coronary intervention

K. Vogiatzi[1], V. Voudris[2], S. Apostolakis[1], G.E. Kochiadakis[3], S. Thomopoulou[2], A. Zaravinos[1], D.A. Arfanakis[3], D.A. Spandidos[1], P.E. Vardas[3]. *[1]Laboratory of Clinical Virology, Faculty of Medicine, University of Crete, Heraklion, Greece; [2]Onassis Cardiac Surgery Center, Athens, Greece; [3]Cardiology Dept. Heraklion University Hospital, Heraklion, Greece*

Purpose: Regulated on activation, normal T cell expressed and secreted (RANTES) gene promoter is a regulatory region and a site of notable genetic diversity. The aim of the present study is to explore a possible interaction between RANTES promoter genetic diversity and susceptibility to coronary artery disease (CAD) and in stent restenosis (ISR).
Patients and Methods: We initially sequenced a locus extending from -516 to 40 covering the entire region of the RANTES promoter in 100 subjects randomly selected from our cohort. Four single nucleotide polymorphisms (SNPs) were identified: -403G/A, -256G/A, -109C/T and -28C/G. The frequencies of the -109C/T and -256G/A variations were <0.01, and were considered to be of limited significance. The frequencies of the -403G/A and -28C/G polymorphisms were evaluated in the entire sample, which consisted of 118 patients subjected to percutaneous coronary intervention (PCI) without ISR on angiographic re-evaluation (no IRS group), 74 CAD patients with ISR on angiographic re-evaluation (IRS group) and 146 controls without angiographic evidence of CAD (no CAD group).
Results: No association was established between the RANTES promoter genotype and ISR. A genotype-phenotype interaction was observed between the -403G/A polymorphism and CAD. The -403A homozygotes were significantly more common in the CAD group than in the controls (6.8% vs. 0.7 respectively; OR=11.2, 95%CI: 1.4-87.8, p=0.004). The latter observation retained statistical significance when the results were adjusted for age, gender and conventional CAD risk factors in a multiple regression analysis (adjusted OR=12.8, 95%CI: 1.14-144, p=0.039). Finally, the severity of CAD among case subjects, expressed as the mean number of diseased vessels, was significantly higher among -403A homozygotes as compared to wild-type homozygotes and heterozygotes (2.9 vs. 2.2, p=0.02).
Conclusion: The RANTES -403A allele was associated with the presence and severity of CAD independently of conventional cardiovascular risk factors. The RANTES promoter genotype did not influence susceptibility to ISR in patients subjected to PCI.

P695 Coronary instent-restenosis: local delivery of fluid paclitaxel - 3 years follow up of LOCAL TAX ISR register

C.S. Zuern, K. Goehring-Frischholz, A.E. May, M. Gawaz, C. Herdeg. *Medizinische Universitaetsklinik Tuebingen, Tubingen, Germany*

Background: The interventional treatment of coronary instent-restenoses (ISR) reveals a high incidence of repeated restenoses. Drug eluting stents (DES) are associated with the problem of a second stent implantation in the same vessel lesion. Our concept of conventional PTCA plus catheter-based application of fluid paclitaxel allows for local antiproliferative therapy with homogenous drug delivery to the vessel wall without any additional stent implantation. We evaluate angiographic results and clinical follow up of patients included in our LOCAL TAX ISR register for more than 3 years now. Primary endpoints are MACCE: cardiovascular death, myocardial infarction, target vessel revasculatization and ischemic stroke.
Patients and methods: 24 female and 63 male patients with angiographically significant instent-restenosis (37 patients with DES) were consecutively included. 35.3% of patients presented with instable angina pectoris. Mean ejection fraction was 51.8%. Target lesion was RCA in 42.4%, LAD in 40.2% and LCX in 17.4% of cases. After PTCA of the restenosed target lesion local antiproliferative treatment with fluid paclitaxel was performed via GENIE™-catheter (application pressure 2 atm, a mean of 18.4 ml of 10μM Taxol™, mean application time 130 seconds). All patients underwent clinical follow-up (at least telephone interview), and when necessary, repeat coronary angiography was performed.
Results: The intervention was technically feasible and safe in all patients. No acute local or systemic side effects of local paclitaxel delivery were documented. In 45 patients a repeat angiography was performed. None of the 10 patients who underwent target lesion revascularization presented with an acute myocardial infarction. 35 patients had a good angiographic result. One patient died 7 months after intervention because of cholangiocellular carcinoma. The rest of the patients stayed clinically event-free without repeat angiography.
Discussion: Catheter-based delivery of fluid paclitaxel for local antiproliferative treatment of ISR is a technically easy and safe procedure with encouraging long-term results. The majority of repeat coronary angiographies showed a good result. Three years after initiation of our register, 76 patients (87.4%) remained clinically and angiographically without pathologic finding. Our data show, that stent-independent local antiproliferative therapy is a promising new alternative for the treatment of instent-restenosis.

P696 Evaluation of intra-stent neointima hyperplasia in the approach trial (assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history)

H.M. Garcia-Garcia[1], P.W. Serruys[1], H.C. Gerstein[2], C.P. Cannon[3], G.A. Van Es[4], N.S. Kolatkar[5], B.G. Kravitz[5], C. Huang[5], D.M. Miller[5], R.W. Nesto[6]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]McMaster University, Hamilton, Canada; [3]Brigham and Women's Hospital, Boston, United States of America; [4]Cardialysis, Rotterdam, Netherlands; [5]GSK, Philadelphia, United States of America; [6]Lahey Clinic Medical Center, Burlington, United States of America*

Purpose: To study the effect of rosiglitazone on intra-stent neointima hyperplasia.
Methods: A total of 462 patients with T2DM were randomized to rosiglitazone or glipizide for up to 18 months in the APPROACH trial and had evaluable baseline and follow-up IVUS examinations. Of these patients, 173 had evaluable angiographic data and 113 had serial IVUS data from a vessel with percutaneous coronary intervention at baseline.
Results: Glycemic control and use of background cardiovascular medications did not differ between groups. No significant differences in restenosis parameters as assessed by either IVUS (plaque behind stent or intra-stent intima hyperplasia volume) or QCA (intra-stent late loss, intra-stent DS or binary restenosis) were observed between the rosiglitazone and glipizide groups.
Conclusion: In contrast to prior studies, there was no difference between rosiglitiazone and glipizide on in-stent restenosis. Given the relatively small proportion of patients undergoing PCI within the present trial and the positive findings from prior studies, further investigation may help elucidate the potential effects of thiazolidinediones on in-stent restenosis.

P697 C-reactive protein serum levels predict in-stent restenosis pattern after drug eluting stent implantation

G. Niccoli, M. Conte, N. Cosentino, G. Ferrante, D. Todaro, S. Brugaletta, F. Burzotta, C. Trani, F. Crea. *Catholic University of the Sacred Heart, Rome, Italy*

Background: In-stent restenosis after implantation of drug eluting stent (DES) is associated with a high rate of recurrence. A diffuse pattern of restenosis has been shown to have a worse prognosis when compared to a focal pattern. Baseline C-reactive protein (CRP) levels are associated with an increased risk of in-stent restenosis. However, whether CRP levels may predict pattern of restenosis after DES implantation it is not known.

Abstract P696 – Table 1

IVUS Measurement	Bare metal stent		Treatment difference	Drug-eluting stent		Treatment difference
Change from baseline	Glipizide (N=21)	Rosiglitazone (N=21)	(95% CI), P value	Glipizide (N=40)	Rosiglitazone (N=31)	(95% CI), P value
Plaque behind stent mean (SD), mm^3.	1.90 (19.1)	-5.6 (26.0)	-4.3 (-21.2, 12.6), p=0.61	5.5 (16.9)	12.1 (22.4)	8.6 (-1.4, 18.5), p=0.09
% intra-stent intima hyperplasia volume	19.8 (11.1)	24.1 (17.1)	4.9 (-6.2, 15.9), p=0.38	8.3 (8.7)	9.8 (11.3)	1.3 (-3.2, 5.8), p=0.57
QCA Measurement	Bare metal stent		Model-adjusted p value	Model-adjustedP valueDrug-eluting stent		Model-adjusted p value
	Glipizide (N=37)	Rosiglitazone (N=35)		Glipizide (N=57)	Rosiglitazone (N=44)	
Intra-stent late loss (mm), mean (SD)	-0.71 (0.38)	-0.76 (0.57)	0.51	-0.25 (0.30)	-0.37 (0.59)	0.41
Intra-stent DS (%), mean (SD)	30.4 (15.3)	32.3 (18.1)	0.50	17.9 (11.7)	22.1 (19.9)	0.28
Binary angiographic restenosis, n (%)	4 (10.81)	8 (22.86)	0.21*	1 (1.75)	2 (4.55)	0.58*

Methods: Our database was searched for cases of in-stent restenosis occurring after DES implantation at our catheterization laboratory from January 2005 to December 2007. Seventy-two patients (age 66±8, male sex 64%) found to have in-stent restenosis after implantation of DES were enrolled. Restenosis pattern was evaluated by angiography according to the simplified Mehran classification and patients allocated either to the diffuse pattern group or to the focal pattern group. Variables predicting pattern of restenosis, recorded at the time of the first percutaneous intervention, were assessed among clinical, angiographic, procedural and laboratory data. In particular CRP serum levels were measured by a high sensitivity nephelometric assays. Independent predictors of the restenosis pattern were assessed by logistic regression analysis.
Results: DES showing restenosis were Cypher (n=20), Taxus (n=18), Endeavor (n=18) and Janus (n=16). Thirty four patients (age 67±8, male sex 65%) presented with a focal pattern, whereas thirty eight patients (age 65±8, male sex 63%) presented with a diffuse pattern. At univariate analysis variables associated with a diffuse pattern were previous history of ischemic heart disease (p=0.05) and CRP levels (p=0.0001) whereas presentation with an acute coronary syndrome and vessel size were of borderline statistical significance (p=0.07). The type of DES did not predict pattern of restenosis (p=NS). At multivariate analysis CRP levels were the only independent predictor of a diffuse pattern of restenosis (OR 2.5, 95% CI 1.4-4.3, p = 0.001). Rising C-reactive protein tertiles were associated with an increased rate of diffuse pattern (13% vs 26% vs 61%, p=0.0001).
Conclusion: CRP serum levels predict a diffuse pattern of in-stent restenosis after implantation of DES. This finding may be clinically useful in order to identify patients developing aggressive restenosis which may benefit from additional therapeutic approach after DES implantation.

FROM ACUTE PULMONARY EMBOLISM TO CHRONIC THROMBOENBOLIC PULMONARY HYPERTENSION

P698 Symptomatic and silent pulmonary embolism (PE): risk factors and prognosis at 3 months

S. Accassat[1], D. Delsart[1], C. Chapelle[2], N. Moulin[1], K. Rivron-Guillot[2], A. Buchmuller-Cordier[2], S. Laporte[2], P. Mismetti[1]. *[1]department of internal medecine, Saint-Etienne, France; [2]Thrombosis research group, Saint-Etienne, France*

Background: Prevalence of silent PE systematically assessed in case of DVT has been reported in few studies but data about the patient characteristics and the prognosis remain unclear.
Methods: A retrospective cohort study compared the characteristic and prognostic of patients with symptomatic PE to those with silent PE associated with DVT and systematically assessed by V/Q scan or tomodensitometry.
Results: From 2005 to 2007, 432 consecutive patients with objective diagnosis of PE were recorded, 315 with a symptomatic PE, and 117 without any symptoms of PE (27.1%). Compared to symptomatic PE, patients with silent PE were significantly younger (69 vs 74 years, p = 0.003) and less frequently associated with chronic heart failure (0.9% vs 9.6%, p=0.03). No significant difference in terms of previous history of PE, cancer, thrombophilia and transient risk factors was found. According to the Aujesky score, symptomatic PE had a 2-fold higher risk of short-term mortality and adverse medical outcomes than silent PE (OR = 2.13 [1.58;2.87]). However, there was no significant difference during hospitalization between symptomatic and silent PE in terms of PE recurrences (1.0% vs 1.7%, p=0.55), clinically significant bleedings (3.8% vs 3.4%, p=0.89) and a trend in a higher risk of death between symptomatic and silent PE (3.2% vs 0.9%, p=0.21). At 3 month of follow up, there was no difference, with about 7% of deaths in all PE patients.
Conclusions: Risk factors and prognosis of silent PE associated with DVT are not strongly different from those of symptomatic PE. This deserves to be prospectively confirmed regarding the potential implications in terms of systematic screening.

P699 Rheolytic thrombectomy in patients with massive and submassive acute pulmonary embolism

G. Spaziani[1], S. Vecchio[1], T. Chechi[1], G. Giuliani[1], F. Giannotti[1], C. Arcangeli[1], A. Rubboli[2], M. Margheri[3]. *[1]Azienda Ospedaliero Universitaria Careggi, Florence, Italy; [2]Ospedale Maggiore 'Carlo Alberto Pizzardi', Bologna, Italy; [3]Ospedale Civile S.M. delle Croci, Ravenna, Italy*

Purpose: The management of patients with acute pulmonary embolism (PE) and hemodynamic compromise, based mainly on anticoagulant and thrombolytic therapies, is challenging and still suboptimal in many patients. In such a setting, mechanical removal of thrombus from pulmonary circulation holds the promise of significant clinical benefits, albeit remains under debate.
Aim of this study was to appraise the impact of AngioJet rheolytic thrombectomy (RT) on angiographic and clinical endpoints in patients with acute PE.
Methods: We retrospectively report on 51 patients referred to our catheterization laboratory and treated with AngioJet RT. Patients were classified according to the degree of hemodynamic compromise (shock, hypotension and right ventricular dysfunction) in order to explore thoroughly the degree of angiographic pulmonary involvement (angiographic massive PE was defined as the presence of a Miller index ≥17) and the impact on angiographic (obstruction, perfusion and Miller indexes) and clinical (all-cause death, recurrence of PE, bleeding, renal failure and severe thrombocytopenia) endpoints of AngioJet RT.
Results: Angiographic massive PE was present in all patients with shock, whereas patients with right ventricular dysfunction and hypotension showed a similar substantial pulmonary vascular bed involvement. Technical success was obtained in 92.2% of patients, with a significant improvement in obstruction, perfusion and Miller indexes in each subgroup (all p<0.0001). Four patients reported major bleedings and 8 (15.7%) died in-hospital. Laboratory experience was significantly associated to a lower rate of major bleedings. All survivors were alive at long-term follow-up (35.5±21.7 months) except 3 who expired due to cancer and acute myocardial infarction.
Conclusions: In experienced hands AngioJet RT can be operated safely and effectively in most patients with acute PE, either massive or submassive, and substantial involvement of pulmonary vascular bed.

P700 Right ventricular reverse remodeling and pulmonary artery flow dynamics in the clinical follow-up of patients with acute pulmonary embolism: initial experience with cardiac MRI

F.A. Klok, S. Romeih, J.J.M. Westenberg, L.J.M. Kroft, M.V. Huisman, A. De Roos. *Leiden University Medical Center, Leiden, Netherlands*

Introduction: Right ventricular dysfunction (RVD) can be identified frequently in patients with acute pulmonary embolism (PE). Persisting RVD after 6 months of treatment might be an indication of chronic thromboembolic pulmonary hypertension (CTEPH). We studied ventricular recovery after PE by cardiac MRI and evaluated its potential use in the clinical follow-up of patients with PE.
Methods: CT-scans were performed in consecutive patients with suspected PE to detect PE and assess ventricular heart function. Fifteen patients with and 10 without PE were studied (10 men/15 women, average age 53). At 6 months after presentation, an MRI was performed to reevaluate ventricular function and to assess flow characteristics and distensibility index (DI) of the pulmonary artery. CT and MRI assessed ventricular volumes have been shown to be reliably comparable. Significant reversed cardiac remodeling was defined as a change in end-diastolic or -systolic volumes (EDV, ESV) over 15% or in ejection fraction (EF) over 5%.
Results: RV and LV EDV and LDV changed <1.0% in the patients without PE, indicating good comparability of CT and MRI. PE patients with baseline normal right ventricular function (RVEF≥47%) displayed significant improvement of RVEF (+5.4±3.1%) due to a decrease in RVESV. Patients with baseline abnormal RV function (RVEF<47%) displayed significant improvement of RVEF (+14±15%) due to decrease in RVESV and RVEDV. In addition, LVEDV increased significantly. Decreased pulmonary DI (p=0.027) and altered pulmonary flow dynamics were found in PE patients with persistent RV dysfunction compared to both PE patients with normalized RV function and patients without PE. These altered flow curves share characteristics with the curves of patients with established CTEPH.
Conclusions: The degree of RV reversed remodeling after PE is dependent on the severity of baseline RV dysfunction. Compared to patients without PE and PE patients with normalized RV function during follow-up, PE patients with persistent RV dysfunction have decreased pulmonary artery DI and altered pulmonary flow dynamics. Whether these alterations predict CTEPH remains to be studied.

P701 Derivation and validation of a simple prediction rule for prognostication in patients with acute pulmonary embolism

S. Vanni, F. Socci, G. Viviani, G. Polidori, P. Nazerian, E. Bondi, G. Pepe, F. Moroni, S. Ponchietti, S. Grifoni. *Azienda Ospedaliero Universitaria Careggi, Florence, Italy*

Purpose: To derive and validate a simple prognostic rule for risk stratification of patients with acute pulmonary embolism, without the use of echocardiography.
Methods: Consecutive adult patients presenting to an Italian third level ED for acute PE were considered for the study. Diagnosis of acute PE was established in ED by spiral computed tomography. During their initial evaluation arterial blood samples and venous blood samples were drown to measure troponin I and lactate levels respectively. Right ventricular strain pattern (RVS) was defined in the presence of at least one of the following on initial ECG: right bundle branch block, S1Q3T3 sign, T wave inversion in V1-V3 and pulmonary P wave. Right ventricular dysfunction (RVD) was assessed by echocardiography, blinded to troponin I and blood lactate levels and to elettrocardiographic findings. Primary outcome was the composite of death due to pulmonary embolism or any of the following: shock, need for endotracheal intubation, catecholamine infusion for sustained hypotension, cardiopulmonary resuscitation or recurrent pulmonary embolism. The association between the test results and the endpoint was evaluated by univariate and multivariate logistic regression analysis.
Results: From January 2001 to September 2007, 250 patients were included, 142 were females (58%), with a mean age of 72±14 years. During in hospital follow-up, 13 patients died due to PE (5.2%) and 16 (6.4%) experienced other adverse events. The first 152 patients were used for derivation of multivariate logistic regression model including RVS on ECG (OR 3.6, p=0.034), troponin I >

0.15 ng/dl (OR 3.9, p=0.008), lactate > 2 mEq/L (OR 13.6, p=0.001) by backward analysis. Prediction rule was computed adding 1 for each item present, ranging from 0 to 3. Patients with 0 showed no in-hospital mortality and an incidence of primary endpoint of 2.1%; patients with 1,2 and 3 showed progressive increase in the incidence of primary endpoint until 35% in class 3, with a mortality rate of 17% (p=0.001). In the remaining 98 patients the rule was prospectively validated. In the validation cohort the risk of primary endpoint ranged from 0 (class 0) to 44% (class 3), without significant differences with the derivation cohort. Moreover, the rule showed a significant association (OR 30.8, p<0.001) with the presence of acute RVD on echocardiographic examination.
Conclusions: We successfully validated our simple prognostic rule based on humoral and electrocardiographic data in patients with acute pulmonary embolism.

P702 Angioscopic detection of pulmonary thromboemboli and their classification

K. Shimizu, Y. Uchida, T. Tomaru. *Toho University Medical Center, Sakura, Japan*

We used angioscopy (AS) for detection and classification of pulmonary thrombo embolism (PTE).
Methods: Fiberscopes incorporated in guiding catheters were us ed for pulmonary angioscopy. Forty one patients clinically diagnosed or suspected as PTE or pulmonary hypertension (PH) underwent pulmonary AS.PTE was detected in 32 patients. The time from onset was as follows: Within 1 W (n=6), 1 to 4 W (n=7), 4W to 3m (N=8), More than 3 M (n=6), Recurrence (n=3),PH (n=2). We also compared AS with angiography (AG), intravascular ultrasound (IVUS) or computerized tomography (CT).
Results: AS could demonstrated globular thrombus in 16 (11 was detected by AG), mural thrombus in 5 (only 1 by AG), cap thrombus in 2, web thrombus in 4, patch thrombus in 15 and micro thrombus in 5. AS is more sensitive for detection of thrombus than AG (P=0.05).In 7 Pts with globular, sensitivity of IVUS was 85% and that of CT was 72%. In cap, web, patch or micro group, no thrombus was detected by AG, IVUS or CT (P=0.0001). Pulmonary thrombi were also classified by color into red, white, dark red, yellow and red and yellow in mosaic fashion.
Conclusions: Pulmonary thrombi detected by AS could not be necessarily detected by AG,CT or IVUS.Pulmonary angioscopy is a sensitive and safe diagnostic tool for diagnosis of PTE.

P703 Surgical embolectomy as primary management for acute massive pulmonary embolism

S.C. Huang, H.Y. Yu, N.H. Chi, I.H. Wu, Y.S. Chen, W.J. Ko, S.S. Wang. *National Taiwan University Hospital, Taipei, Taiwan*

Introduction: Acute pulmonary embolism is a potentially fatal disease. Surgical embolectomy could provide remove the thrombus burden quickly. We report our experience with surgical embolectomy as the primary treatment for acute massive pulmonary embolism.
Materials and Methods: The pulmonary embolism was diagnosed first impressed by echocardiography and confirmed by computed tomography. Surgical indications included cardiac arrest, hypotension, right ventricular failure, saddle or massive thrombus noted in the right atrium or ventricle. Surgery was performed with cardiopulmonary bypass, through pulmonary arteriotomy, thrombus was removed under direct vision. None patient received thrombolytic therapy in our hospital at the study period.
Results: There were 20 (M/F=11/9) patients received surgical embolectomy in our institute since January 2001. The median age was 56 years old (range 13-82 year-old).
Among the 20 patients, 7 (35%) had cardiac arrest and received cardiopulmonary resuscitation (CPR), and extracorporeal membrane oxygenation (ECMO) was required in six of them because of failure to achieve return of spontaneous circulation (ROSC). All ECMO was removed soon after surgical embolectomy.
The overall survival rate was 85% (17/20). The mortality rate of patients with pre-operative cardiac arrest and those without cardiac arrest was 28% (2/7) and 8% (1/13), respectively (p=NS). The cause of mortality was multi-organ failure in two patients with pre-operative CPR and brain hemorrhage in one. Two patients had neurological deficit after CPR, and the neurological intact survival rate of the CPR group was 42% (3/7). The follow-up period was 3.8±2.7 years, there was no late mortality and no evidence of chronic thromboembolic pulmonary hypertension (CTEPH) in the survivors.
Conclusion: Surgical pulmonary embolectomy is an effective treatment for patients with acute massive pulmonary embolism. ECMO support and surgical embolectomy provided chance of survival for the patients with pre-operative cardiac arrest.

P704 Endothelin is not elevated in acute pulmonary embolism

M. Kostrubiec, J. Pedowska-Wloszek, M. Ciurzynski, P. Bienias, S. Pacho, P. Pruszczyk. *Medical University of Warsaw, Warsaw, Poland*

Introduction: In acute pulmonary embolism (APE) the increase of pulmonary vascular resistance depends on the thromboli load and potentially on the pulmonary bed contraction caused by neurohormonal reaction. Plasma levels of endothelin were reported to be elevated in pulmonary arterial hypertension. However, there are only a few studies assessing endothelin in patients with APE.
Materials & Methods: Therefore in our study we evaluated endothelin concentration in 55 patients (29M, 26F, age 57±19yrs) with confirmed APE for potential value in risk stratification. Patients were compared with 24 healthy volunteers at similar age. On admission blood samples were collected for plasma endothelin concentration. The quantitative assessment of right ventricular (RV) function was performed by echocardiography.
Results: Endothelin concentrations were similar in APE patients and in control group (1.41 (0.22-9.68) pg/mL vs. 1.62 (0.27-8.92) pg/mL; p=NS). There was no differences in endothelin levels between APE patients with and without RV dysfunction (1.46 (0.38-4.54) pg/mL vs. 1.41 (0.22-9.68) pg/mL; p=NS). Endothelin concentration did not differ between patients with serious adverse events and APE group with event-free clinical course (3.19 (0.38-4.27) pg/mL vs. 1.38 (0.22-9.68) pg/mL; p=NS). There was no significant correlation between endothelin levels and blood saturation, time from the first symptoms, heart rate, blood pressure, tricuspid valve regurgitation pressure gradient and other echocardiographic parameters.
Conclusions: We concluded that plasma endothelin concentrations assessed on admission are not elevated in patients with APE and it does not play as important role in acute phase of increase of pressure in pulmonary arteries as in chronic pulmonary hypertension.

P705 Brain natriuretic peptide and troponin I kinetics in pulmonary embolism

E. Ferrari, C. Crouzet, L. Drogoul, P. Lanfranchi. *Pasteur Hospital, Nice, France*

Background: TnI and BNP have taken a major place in the prognosis of patients with PE. However, the best time for the accurate evaluation of these 2 biomarkers is still unclear.
Objectives: Our aim was to analyze the kinetics of TnI and BNP in patients hospitalized for PE.
Method: BNP (Biosite Access) and TnI (Beckman Access method) were measured at admission, then every 8 hours for 72h in 101 patients hospitalized for PE. Patients were classified into 4 groups: TnI-/BNP-; TnI-/BNP+; TnI+/BNP-; and TnI+/BNP+.
Results: TnI peak occurred on average at H8: 0.67±0.55 ng/ml. TnI values then decreased quickly, but remained positive (>0.06 ng/ml) beyond the 72 hour surveillance period. In the subgroup of patients hospitalized early, the profile was similar, but the TnI peak level was higher (1.12 ng/ml± 0.91); while, for those hospitalized later, TnI value was maximum on admission. BNP kinetic values showed a maximum level on admission then gradually decreased. The highest BNP rate occurred in the TnI+BNP+ group: 607 pg/ml.
The biological profile of patients varied widely after admission. 23.5% of 34 patients initially TnI-/BNP- became positive for at least one biomarker. Among patients hospitalized early, within 24 hours of onset of initial symptoms, 29.4% for TnI and 47% for BNP were misclassified on admission. In all cases, accurate classification was obtained at the second assessment at H8.
Conclusions: Our study clarifies the kinetics of TnI and BNP in PE and highlight the situations in which TnI and BNP can be false negatives because of a too-early assessment. Many misclassifications could be avoided by taking into account not only the 1st values of the 2 biomarkers but also those obtained 8 hours later.

P706 Application of 64-MDCT in pulmonary embolism with emphasize to incidental findings

C. Sohns[1], S. Sossalla[1], G. Hasenfuss[1], S. Obenauer[2]. [1]*Cardiology and Pneumology, Goettingen, Germany;* [2]*Radiology, Goettingen, Germany*

Aim: There is still debate about the optimal diagnostic algorithm for acute pulmonary embolism (PE). In this retrospective study, we present a 64-MDCT-scan procedure of chest, pelvis and tight that enables to detect PE,
(deep-) venous thrombosis and incidental finding into one analysis.
Method: 200 patients have undergone 64-MDCT of chest, pelvis and thigh for an indication that suspected PE. CT scans were reviewed, the degree of contrast enhancement and presence of pulmonary embolism and/or (deep-) venous thrombosis recorded. In case of PE the level of thrombus was noted. If the scan was positive for a thrombosis the intravenous localization was noticed, too. As well incidental findings were registered.
Results: PE was detected in 60 of the 200 patients with a high clinical probability of PE (30%). 34 patients had a positive CT scanning for venous thrombosis (17%). 24 of the 60 patients had proximal deep venous thrombosis (40%), and 2 had an arm venous thrombosis (3%). 34 of 60 patients had PE without venous thrombosis (57%). 8 of 200 patients had deep venous thrombosis without the suspect of PE (4%). The distribution of the proximal thrombus showed 15 central (25%), 13 in a main pulmonary artery (22%), and 32 in a lobarsegmental artery (53%). CT scan noted in total 180 incidental findings (e.g. Renal cyst, Bronchial cancer).
Conclusion: The algorithm used in our study shows a high rate of detected PE

Distribution of CT findings for venous thrombosis

Localization of the Thrombus	Right	Left
V. illiaca communis	2	2
V. illiaca interna	0	1
V. illiaca externa	0	1
V. femoralis communis	4	4
V. femoralis superficialis	1	0
V. poplitea	5	7
V. saphena magna	4	1
V. axillaris	1	1
Sum	17	17
Total		34

from the main up to the segmental arteries and as well (deep-) venous thrombosis even if MDCT did not detect PE. Furthermore, incidental findings can be identified.

P707 Renal function improves troponin-based short term prognosis in patients with acute pulmonary embolism

M. Kostrubiec, A. Labyk, J. Pedowska-Wloszek, A. Hrynkiewicz, K. Jankowski, S. Pacho, P. Dul, A. Wojciechowski, P. Pruszczyk.
Medical University of Warsaw, Warsaw, Poland

Objective: Risk stratification of patients with acute pulmonary embolism should include assessment of biomarkers of myocardial injury. Since impaired renal function is one of the important indicators of increased mortality in various cardiovascular diseases we tried to evaluate if assessment of renal function improve risk stratification in APE.
Material and Method: We evaluated 157 consecutive pts (60M, 97F, aged 64±18 years) with APE proven by spiral CT. On admission blood samples were collected for troponin and creatinine assays, GFR was estimated using Modification of Diet in Renal Disease (MDRD) formula.
Results: Seventeen pts died during hospitalization. GFR below 60 ml/min was noted in 68 (43%) pts, while <30 ml/min in 14 (9%) pts. Elevated troponin levels were detected in 62 (39%) pts. In 10 (6%) pts GFR<30ml and elevated troponins were found, while in 83 (53%) pts GFR was >30 and tropnins assay was negative. Creatinine levels were significantly lower in survivors than in nonsurviors (median 1.0 mg/ml (range: 0.4-3.1) vs median 2.0 mg/ml (range: 0.8-5.0), p<0.0001) and GFR was higher in survivors than in nonsurviors (median 67.3 ml/min (range: 15.0-181.5) vs median 34.8 ml/min (range: 9.0-68.0), p<0.0001). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in mortality prognosis for significantly troponin were 77%, 65%, 21% and 96%, while for GFR <30 ml/min 35%, 94%, 43% and 92%, respectively. Area under ROC curve of GFR tended to be higher to troponin for in hospital mortality (0.867 (95%CI: 0.774-0.918) vs. 0.743 (95%CI: 0.647-0.824), p=0.12).Sensitivity, specificity, PPV and NPV in mortality prognosis for significantly elevated troponin in patients with GFR<30 ml/min were 29%, 96%, 50% and 92%, respectively
Conclusion: About 40% of patients with APE has at least moderatly impaired renal function. GFR <30 ml/min indicates high risk patients similarly to troponin. Moreover, GFR estimation can improve the troponin-based risk stratification in APE.

P708 Tissue Doppler myocardial imaging of right ventricular deformation in patients with acute pulmonary embolism

K. Hristova[1], G. Pencheva[2], R. Radeva[2], S. Milanov[3], D. Petrov[3].
[1]University Hospital "St. Iv. Rilski", Medical University, Sofia, Bulgaria; [2]IV City Hospital„ Sofia, Bulgaria; [3]National Hospital of Intensive Care, Sofia, Bulgaria

Aim: The aim of our study were to evaluate the clinical utility of TDI–echocardiography for diagnostic of patients presenting in the Emergency department with acute RV dysfunction and severe pulmonary arterial hypertension due to pulmonary embolism.
Methods: During the last one year we studied 58 patients-23 women and 35 men (mean age 69±12y.), who were with clinical database and diagnosed as having massive or sub massive pulmonary embolism. All patients were examined by 2D –echocardiography with Tissue Doppler Imaging (TDI), ECG, X-ray and 30 with computer tomography of chest. TDI mapping from apical 4 camber view of the RV segments was performed in all patients between initial presentation and till 24hours and after one month follow up. We included in our study 10 normal health volunteers as controls (mean age 26y ±5). Regional RV strain, strain rate curves and velocity were analyzed intra and interobserver.
Results: Were found in all patients enlargement of right ventricle (43±17,5mm), severely impaired systolic function for RV, moderate to severe tricuspid regurgitation, dilated vena cava inferior. Severe increased systolic pulmonary pressure (mean 85±45,5mmHg), was detected in 38 patients (85%). We found severe right ventricular hypokinesia and septal dyskinesia. A pattern of normal wall motion of the apex and abnormal wall motion in the middle- free wall segment of the right ventricle were detected.
Max strain values were reduced in the basal (4,5±3%,p<0.001) and mid-segment (6,7±3,5%,p<0.001) and significantly increased in the apical segment (19,5±4,5%) in free wall of the RV. We found too reduced velocity and strain rate in basal (8.3±2.3cm/s,; 7.0±2.4 s^{-1}, p<0.01) in middle segment (10.3±2.1cm/s; 8.3±3.5 s^{-1}, p<0.01) compared with controls.
After one month follow up we found improvement in decreased peak systolic velocity, peak systolic strain and strain rate, there were no significant differences compared to the results in the normals. The enlarged RV, dilated vena cava inferior, severe pulmonary hypertension and tricuspid regurgitation were significantly reduced in the patient group.
Conclusion: The present study confirms the fairly good sensitivity of strain and strain rate and tissue velocity to detect segmental deformation in patients with acute pulmonary embolism. After one month were improved signifcantly acute right ventricular dysfunction and severe pulmonary hypertension. The regional myocardial deformations of the free wall in RV were significantly recovered and TDI allowed a non-invasive assessment in patients with acute pulmonary embolism.

P709 The role of ST-segment elevation in lead aVR of ECG in patients with acute pulmonary embolism

T.H. Hoechtl[1], K.J. Janata[2], C.W. Wenzel[2], R.J. Jarai[1], B.F. Fellner[1], V.H. Havranek[1], A.G. Geppert[1], J.W. Wojta[2], K.H. Huber[1].
[1]Wilhelminen Hospital, Vienna, Austria; [2]Medical University of Vienna, Vienna, Austria

Purpose: Patients with acute pulmonary embolism (APE) present with a variability of symptoms and ECG abnormalities. As lead aVR has been recently described to predict right ventricular overload we documented characteristic ECG changes for APE with special focus on ST-elevation in aVR and related them to the severity of disease.
Methods: 396 consecutive patients (pts) in two centers with proven APE were retrospectively analyzed with respect to symptoms at presentation (dyspnoea at rest, tachypnoea, pleuritic pain, haemoptysis, syncope), 12-lead-ECG (P-pulmonale, S1Q3T3- and S1S2S3-types, clockwise rotation, incomplete or complete right bundle branch block (RBBB), ST-depression in all leads, ST-elevation in V1 and aVR as well as T-wave inversion in the precordial leads), echocardiographic signs of right ventricular dysfunction (RVD), Troponin T, need for thrombolysis and outcome. Data were compared between pts with and without ST-elevation in aVR.
Results: ST-elevation in aVR was present in 34.3% (n=136) and was associated with significantly more frequent occurence of other ECG changes which are commonly ascribed to APE. Further it was associated with more severe clinical presentation at admission (dyspnoea at rest: 44.9% vs. 29.2% p=0.002; tachypnoea: 30.9% vs. 11.5% p<0.001; systolic blood pressure< 90 mmHg: 17.0% vs. 6.5% p=0.001; syncope 16.2% vs. 6.5% p=0.002) as well as with the use of thrombolysis (29.1% vs. 7.5% p<0.001) and a higher in hospital mortality (10.3% vs. 5.4% p=0.070). Haemoptysis (2.9% vs. 7.3%; p=0.078) and pleuritic pain (38.2% vs. 48.8%; p=0.044) were less frequently documented in pts with ST-elevation in aVR. Moreover pts with that ECG pattern had higher troponin levels (median 0.035 [0.01-0.2] vs. 0.01 [0.01-0.02]; p<0.001) and were significantly more often diagnosed for RVD (74.5% vs. 46.6%; p<0.001). With respect to in hospital mortality, a significant increase could be shown when combining ST-elevation in aVR with complete RBBB (35.0%), S1Q3T3 (16.3%), ST-elevation in V1 (14.1%) and T-wave inversion (17.8%). Similarly pts with RVD had a higher mortality rate in presence of ST-elevation in aVR (16.4% vs. 8.3%; p=0.198) as did pts with positive troponin (16.4% vs. 10.3%; p=0.454) and thrombolytic therapy (20.5% vs. 5.3%; p=0.132).
Conclusions: In pts with APE ST-elevation in aVR is associated with a more severe course of the disease. Especially when combined with other ECG-pattern and clinical variables of increased risk this ECG change could predict worse outcome. Therefore ST-elevation in aVR might play a major role in risk stratification of APE in future.

P710 Role of MDCT in detection of ventricular dysfunction and pulmonary obstruction index in patients with acute pulmonary embolism

D. Nassar[1], S. Omar[2], A. Ibrahim[2], F. Zeinhom[2] on behalf of ERFAN Hospital. *[1]Al-Azhar University, Cairo, Egypt; [2]Cairo University, Cairo, Egypt*

Purpose: To retrospectively quantify right ventricular dysfunction (RVD) and the pulmonary artery obstruction index in MDCT on the basis of various criteria proposed in the literature and to assess the predictive value of these CT parameters for mortality it has been compared to the echocardiographic assessments
Methods & materials: In a retrospective study we reviewed 80 patients where there primary clinical and laboratory diagosis are suggestive of Pulmonary embolism, 20 patient were negative on CT Study while 60 patient were positive (25 men, 35 women; mean age ± standard deviation, 50 years ± 16) with proved PE, by dectection of the extent of RVD by quantifying the ratio of the right ventricle to left ventricle short-axis diameters (RV/LV) and the pulmonary artery to ascending aorta diameters, the shape of the interventricular septum, and the extent of obstruction to the pulmonary artery circulation on MDCT. Regression analysis was used to correlate these parameters with the echocardiography and patient outcome.

Results: CT signs of RVD (RV/LV ratio, >1.0) were seen in 35 patients (58.3%) in the follow-up, 5 patients died of PE. Both the obstruction index and RV/LV ratio were shown to be significant risk factors for mortality (P=0.01 and 0.03, respectively). No relationship was found for the ratio of the pulmonary artery to ascending aorta diameters (P=0.99) or for the shape of the interventricular septum (P=0.30). The positive predictive value for PE-related mortality with an RV/LV ratio greater than 1.0 was 10.1%. The negative predictive value for an uneventful outcome with an RV/LV ratio of 1.0 or less was 100%. There was a 14 -fold increased risk of dying of PE for patients with an obstruction index of 40% or higher.
Conclusions: The Measurement of RVD and pulmonary vascular obstruction index evaluated with MDCT CT at baseline, help predict the prognosis during follow-up.

P711 Anticoagulation after pulmonary embolism secondary to a reversible risk factor: till death do us apart?

R. Baptista, E. Jorge, R. Teixeira, P. Mendes, S. Monteiro, F. Goncalves, P. Monteiro, G. Castro, M. Freitas, L.A. Providencia. *Hospital and Medical School, Coimbra, Portugal*

Background: The duration of anticoagulant therapy with vitamin K-antagonists (VKA) after pulmonary embolism (PE) is still a matter of debate, most of the evidence coming from post-deep venous thrombosis (DVT) data. Although effective, indeterminate duration anticoagulation benefit is commonly offset by the risk of major bleeding.
Objectives: To determine, in patients with idiopathic anatomically extensive PE who had been subjected to fibrinolysis, the safety and efficacy of long-term anticoagulation with VKA, even not guideline-based (whose recommendation is to stop anticoagulation at 3 moths).
Population and Methods: A total of 27 patients, with anatomically extensive acute PE due to a reversible risk factor, subjected to fibrinolisys with alteplase, were followed for a mean duration of 2.2 years (0.5 – 8.0 years). We created 2 groups, based on the actual duration of anticoagulant (AC) therapy on those patients: group A: 3 months (n=21; 77.8%) and group B: more than 3 months (n=6; 22.2%)]. Two endpoints were created: recurrence of DVT/PE and bleeding events.
Results: After 3 months, 22.2% of patients with a reversible cause of PE withdrew VKA (in-line with the recommendations), whereas 77.8% maintained it off-label. The incidence of recurrent DVT or PE on those who abandoned VKA after 3-months was four-fold than in those who maintained it after the 3-month period (16.7% vs. 4.8%, p=NS). This better prognosis was slightly offset by a small increase in non-fatal bleeding (23.8 vs. 16.7%, p=NS). Considering all patients taking VKA post-thombolysis in the context of PE in our centre (idiopathic or secondary to a reversible risk factor, n=72), those who were on VKA by the guidelines had a higher recurrence of DVT or PE, as expected, compared with those taking it off-label (11.8 vs. 4.8%, p=NS).
Conclusions: Although conferring a slightly higher incidence of non-fatal bleeding, prolonged VKA therapy appears to be of value preventing recurrence of DVT/PE in the population with PE secondary to a transient risk factor. Newer agents under investigation, without the need of INR monitoring and enhanced safety profile, can be of use in this population.

P712 Thromboembolic right heart failure in the elderly: is age a contraindication to pulmonary endarterectomy?

M. Morsolini, G. Silvaggio, S. Nicolardi, D. Berwick, C. Monterosso, A.M. D'Armini, M. Vigano'. *Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

Purpose: Among the European population, between 11% and 18% of the people are older than 65 years. Since the population is rapidly aging, an increasing number of older patients affected by chronic thromboembolic pulmonary hypertension (CTEPH) are referred for pulmonary endarterectomy (PEA). As outcomes following PEA in the elderly have never been reported, we sought to assess our early results in patients older than 70 years and compare them with those from younger patients.
Methods: We compared in a prospective analysis all patients aged less than 70 years (Group I, 166 pts, mean±SD age 50±14 yrs) that underwent PEA at our Centre from April 1994 to January 2009 with patients over 70 years old (Group II, 51 pts, mean±SD age 75±4 yrs). Preoperative, operative and early postoperative data were collected and analyzed. In Group II we observed a higher number of patients with at least one major comorbility (67.0% vs. 37.8%, P<0.05), such as NIDDM, chronic renal insufficiency, COPD, arteriopathy, chronic AF. Follow up was 100% complete.
Results: A total of 217 patients underwent PEA during the study period. The proportion of patients older than 70 years increased from 10.8% (from April 1994 to December 2002) to 28.1% (January 2003-January 2009). Early postoperative results are shown in table I.
Conclusions: In our experience we never considered age as a contraindication to PEA. Early hemodynamic results after PEA are excellent and not affected by age: pulmonary vascular resistance dramatically and equally decreased in both groups. However, as expected, early after surgery older subjects are more susceptible to infections, with a consequent higher early postoperative mortality and longer postoperative hospital stay. Moderate instead of deep hypothermia and shorter periods of circulatory arrest seem reduce early morbidity and mortality in older patients: from January 2008 up to date, out of 43 PEA performed, none of the 16 patients over 70 years old died.

Table 1. Early postoperative outcomes

Outcome	Group I (<70 yo)	Group II (≥70 yo)	p-value
Hospital mortality (%)	7.8 (13/166)	14.0 (7/51)	<0.05
PVR preop (dyne cm sec^{-5})	1070±496 (149-2248)	1096±575 (265-2776)	NS
PVR postop (dyne cm sec^{-5})	277±141 (85-727)	315±160 (84-800)	NS
Infections (%)	33.7 (56/166)	46.0 (23/51)	<0.05
Postoperative hospital stay (days)	16±12 (4-73)	23±18 (7-84)	NS

PVR: Pulmonary vascular resistance.

P713 Platelet function in patients with chronic thromboembolic pulmonary hypertension

R. Sadushi, S. Panzer, D. Bonderman, N. Skoro-Sajer, W. Klepetko, I.M. Lang. *Medical University of Vienna, Vienna, Austria*

Background: Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is caused by obstruction of pulmonary arteries with organized thrombus. Platelet function in CTEPH is unexplored.
Patients and Methods: Platelet function was studied in 39 patients (pts) at the time of diagnosis and at a 12 months' follow-up visit, off anticoagulation (Table 1). Eighteen patients underwent pulmonary endarterectomy (PEA) with a decrease in pulmonary vascular resistance by 610 dynxsecxcm-5 [(95% CI: -700, -388); p < 0.001]. Eighteen age-matched 6±2.1 year-survivors of pulmonary embolism without PH served as controls (ctrls).
Results: Platelet surface coverage (SC) and average size of aggregates (AS) assessed by the Impact-R analyzer were elevated in CTEPH patients [SC (%), 12 (7.7-14); AC (μm^2),52 (31-93)] but did not decrease to normal levels [SC (%), 9 (4.8-20); AC (μm^2),34 (21-137)] after surgery.
Soluble P-selectin (sP-selectin) was markedly elevated [median (IR); CTEPH 77.99 (60.76-87.39) versus ctrls 48.10 (39.35-64.50); P<0.001], and had not returned to normal levels [mean±SD; 36.8±11)] 12 months after PEA [50 (43.89-58.72)].
Both heterotypic aggregates between monocytes and platelets (MPA) estimated by the co-expression of CD14+/CD41+%, and between leukocytes and platelets (LPA) estimated by the co-expression of CD45+/CD41+% [median (IR); MPA: 65.28 (38.18-82.65); LPA: 12.71 (8.67-21.53) decreased to near-normal levels after successful PEA [MPA: 32.97 (26.81-73.28) P<0.05; LPA: 6.99 (6.11-13.07); P<0.021].

Patient characteristics

Patient number, n	39
Age, years	62±13
Sex, n (%) female	16 (41%)
Body mass index, kg/m^2	26.17±4.23
Mean pulmonary arterial pressure, mmHg	49±12
Pulmonary vascular resistance, dyn sec cm^{-5}	724.98±326.66

Values are numbers, percentages and means ± SD.

Conclusion: In stable pts with CTEPH, independent tests indicate that platelets are activated. Soluble P-selectin, MPA and LPA significantly decreased in patients who underwent PEA and normalized their hemodynamics. The data suggest that activated platelets may contribute to thrombus non-resolution.

P714 Persistent right ventricular dysfunction at hospital discharge after acute pulmonary embolism is associated with chronic thromboembolic pulmonary hypertension

S. Vanni, G. Viviani, F. Socci, G. Pepe, S. Magazzini, A. Petrioli, G. Polidori, S. Grifoni. *Azienda Ospedaliero Universitaria Careggi, Florence, Italy*

Purpose: Persistent right ventricular dysfunction at hospital discharge after acute pulmonary embolism is associated with increased risk of fatal and non fatal recurent pulmonary embolism (PE) in the long term. Present study was planned to investigate the association between persistent right ventricular dysfunction and chronic thromboembolic pulmonary hypertension (CTEPH).
Methods: Consecutive adult patients admitted from January 2000 to September 2007 to a third level hospital in Florence for acute PE were considered for the study. Patients older than 85 years and who were unable to attend at follow-up were excluded. Acute RV dysfunction was diagnosed in the presence of 1 of the following: RV dilatation (without hypertrophy), paradox septal systolic motion, and Doppler evidence of pulmonary hypertension (transtricuspidal gradient >30 mmHg). Echocardiography was performed on admission, at hospital discharge and after at least 6 months. CTEPH was diagnosed by CT pulmonary angiography.
Results: Out of 364 patients considered, 339 survived at in-hospital phase. Of these, 84 patients were excluded because of age, 11 were inaccessible to follow-up and 9 declined to participate. Thus 235 patients were included with a mean follow-up duration of 50.3±26.2 months (min 6, max 96). Of 130 patients (55%) with RVD on admission, 39 (17%) showed persistent RVD at hospital discharge. Out of 235 patients, thirteen (5.5%) showed pulmonary hypertension at echocar-

diographic follow-up. In 7 of these patients (3%) CT pulmonary angiography showed residual pulmonary thrombosis. All except one of these 7 patients with CTEPH had persistent RVD at hospital discharge ($p<0.001$).
Conclusions: Persistent RVD at hospital discharge is frequent (17%) in patients with acute PE, and is associated with development of CTEPH in the long term.

P715 A role for PECAM-1 in venous thrombus resolution

B. Redwan, J. Kellermair, M.-K. Renner, H. Panzenboeck, J. Jakowitsch, P. Petzelbauer, D. Bonderman, I.-M. Lang. *Medical University of Vienna, Vienna, Austria*

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by intraluminal thrombus organization and fibrous obliteration of pulmonary arteries, with concomitant endothelial dysfunction. Thrombi resolve by a process of organization and recanalization. Leukocyte recruitment and angiogenesis are key components of this process. Platelet endothelial cell adhesion molecule-1 (PECAM-1 or CD31) is a molecule expressed on all cells within the vascular compartment, and plays an important role in leukocyte-endothelial cell adhesion and transmigration. Thus, PECAM-1 represents a link between these two key components of thrombus resolution. We investigated the role of PECAM-1 in a murine model of stagnant flow venous thrombosis.
Methods: Thrombosis was induced in the infrarenal vena cava of PECAM-1 -/- mice on an FVB/n background by creating a venous stenosis with a silk suture. Thrombi were harvested on days 3, 7, and 14 after surgery for analysis (n=8 per time point). Wild-type mice served as controls.
Results: Thrombus cross-sectional area analysis demonstrated a significant increase in thrombus area over time in PECAM-1 -/- animals compared with controls (ANOVA<0.05). Immunohistochemical staining using antibodies against F4/80 for detecting thrombus macrophages revealed a decreased number of macrophages in PECAM-1 -/- animals compared with controls (ANOVA<0.05). The number of Isolectin B4-positive micro vessels was significantly decreased on days 3 and 7 in PECAM-1 -/- mice (ANOVA<0.05).
Conclusion: Deletion of PECAM-1 results in misguided thrombus resolution with a decrease of monocytes and micro vessels. PECAM-1 is critically involved in venous thrombus resolution.

P716 Isobaric analysis of pulmonary arterial compliance of idiopatic and chronic thromboembolic pulmonary hypertension: correlation with right ventricular remodeling

J.C. Grignola, M.J. Ruiz-Cano, P. Escribano, M.A. Gomez-Sanchez, R. Tello De Meneses, J. Delgado, C. Jimenez Lopez-Guarch, C. Saenz De La Calzada. *Unidad de HTPulmonar y Tx Cardíaco, Servicio de Cardiología, Hospital Universitario "12 de Octubre", Madrid, Spain*

While it is likely that the functional adaptation of the pulmonary circulation to disease processes is generaly monotonous (any change in pulmonary vascular resistance (Rp) is associated with proportional changes in compliance and wave reflections), chronic thromboembolic pulmonary hypertension (CTEPH) is particular by more predominant wave reflection as a cause of a disproportionate increase of systolic (Ps) and decrease of diastolic (Pd) PA pressures.
Our aim was to compare the pulmonary arterial compliance between idiopathic pulmonary arterial hypertension (IPAH) and CTEPH in patients with isobaric steady component of right ventricular (RV) load and its consequence in RV remodeling.
Methods: Forty five patients (p) with IPAH (48±20 years, 56% men) and preoperative twenty p with CTEPH (52±18 years, 59% men) were included. RV catheterization was performed. Rp, pulsatility index (fractional pulse pressure - fPp), capacitance index (Cp), and arterial time constant (tau: Rp×Cp) were calculated. RV end-diastolic diameter (RVDd) was also measured by echocardiography. The resistance to flow across the pulmonary circulation results in the pressure drop from the large pulmonary artery to the left atrium. We partitioned Rp (RpU) into upstream and dowstream resistance by the ratio (Pm-Pd)/(Pm-Ppao) (Pm: mean PA and Ppao: PA occlusion pressure, CO: cardiac output). A higher upstream resistance determines a lower Pd and a faster pressure decay profile and viceversa.
Results: Cardiac index and heart rate were similar in both groups.

CTEPH and IPAH data

	Pm mmHg	Pp mmHg	fPp	Cp ml/mmHg	Rp dyn s cm^{-5}	Tau sec	RpU %	RVDd mm
CTEPH	48±15	59±20	1.22±0.15	1.1±0.5	731±336	0.5±0.13	60±15	49±7
IPAH	47±10	41±10‡	0.90±0.22‡	1.5±0.7	789±384	0.6±0.3	43±15‡	42±9‡

Data are expressed as mean±SD. ‡$p<0.01$; $p<0.05$ (Unpaired student t-test). Pp: pulse pressure.

Conclusions: isobaric steady component analysis allows to differentiate the pulsatile component between IPAH and CTEPH. The dynamic RV afterload in CTEPH p was higher than IPAH. The lower Cp and tau of preoperative CTEPH would be related to different vascular wall remodeling and would be explained the higher RVDd. The lower RpU in IPAH p is in agreement with a more homogeneous distribution of steady component of RV afterload.

P717 Exercise capacity and pulmonary artery pressure-flow relations in patients after successful pulmonary endarterectomy

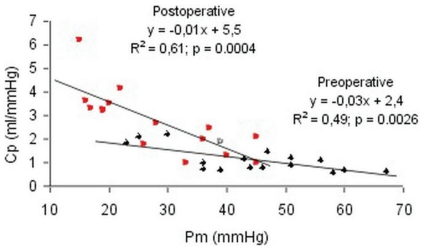
D. Bonderman[1], A. Martischnig[1], K. Vonbank[1], M. Nikfardjam[1], B. Meier[1], G. Heinz[1], R. Naejie[2], I.M. Lang[1]. [1]*Medical University of Vienna, Vienna, Austria;* [2]*Erasme University Hospital, Brussels, Belgium*

Background: Pulmonary endarterectomy (PEA) provides potential cure for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Successfully operated patients have been shown to normalize hemodynamic parameters in long-term studies. The aim of the present study was to assess exercise capacity, and to test the hemodynamic response to exercise at least one year after successful PEA.
Methods: 13 successfully operated CTEPH patients and 14 healthy volunteers underwent cardiopulmonary exercise testing (CPET). In addition, patients and 10 age-matched controls without precapillary pulmonary hypertension underwent right heart catheterization at rest and after 10 minutes of submaximal supine bicycle-exercise. Between-group differences were analyzed utilizing the unpaired t-test, ANOVA or the Fisher's exact test. P-values <0.05 were considered statistically significant.
Results: Peak work rate (110.5±50.9 Watt) and O2 uptake at maximum exercise (1.8±0.7 l/min) were reduced as compared to healthy volunteers (166.9±49.2 Watt, p=0.01 and 2.3±0.6 l/min, p=0.03).
There were no differences between patients and controls with respect to resting hemodynamic parameters. After 10 minutes of exercise, CTEPH patients displayed significantly higher levels of pulmonary vascular resistance than controls with a steeper pressure-flow gradient (p=0.005).
Conclusions: The decline in PVR that occurs as a physiological reaction to exercise in healthy individuals is reduced in successfully operated CTEPH patients. This abnormal hemodynamic response to physical stress is associated with a limited exercise capacity of CTEPH patients after PEA.

P718 Impaired pulmonary compliance in patients with long term residual pulmonary hypertension after endarterectomy for chronic thromboembolic pulmonary hypertension

J.C. Grignola[1], M.J. Ruiz-Cano[1], P. Escribano[1], J. Cortina[2], T. Velazquez[3], M.A. Gomez-Sanchez[1], J. Delgado[1], C. Saenz De La Calzada[1]. [1]*Unidad de HTPulmonar y Tx Cardíaco, Servicio de Cardiología, Hospital Universitario "12 de Octubre", Madrid, Spain;* [2]*Servicio de Cirugía Cardíaca, Hospital Universitario "12 de Octubre", Madrid, Spain;* [3]*Servicio de Hemodinamia, Hospital Universitario "12 de Octubre", Madrid, Spain*

Contributions of proximal thromboembolism and distal disease in chronic thromboembolic pulmonary hypertension (CTEPH) is a matter of debate. Postoperative residual PH (RPH) after 'successful' pulmonary endarterectomy (PEA) often indicates a significant contribution of small-vessel pathology.
The aim of the present work was to analyze the changes of steady and pulsatile right ventricular (RV) load in patients (p) with CTEPH one year after PEA.
Methods: sixteen CTEPH p (11 men, 54±14 years) who underwent PEA between 2004 and 2007 were studied. RV catheterization was performed preoperatively (Pre) and one year after PEA (Pos). We analyzed pulmonary arterial resistance (Rp) (steady component), pulsatility index (fractional pulse pressure -fPp-: Pp/Pm) and capacitance index (Cp: stroke volume/Pp) as pulsatile components. RPH was defined as Rp of 240 dyn.s.cm-5 or greater.
Results: stroke volume and heart rate did not change Pos. Pm, Pp, fPp and Rp decreased (47±13 to 29±11 mmHg; 56±16 to 31±12 mmHg; 1.22±0.15 to 1.06±0.19; 688±200 to 328±160 dyn.s.cm-5, respectively) and Cp increased (1.1±0.5 to 2.5±1.0 ml/mmHg) significatively. The increase of Cp is accompanied by a higher slope of the relation between Cp and Pm with respect to Pre (see Fig.). This allow us to consider an improvement of the arterial cushioning function. However, ten p had RPH one year after PEA. These p showed a significant lower improvement of Cp (2.0±0.8 vs. 3.9±1.1 ml/mmHg) and Pp (38±11 vs. 18±6 mmHg), despite similar values of Pre (1.02±0.6 vs. 1.07±0.4 ml/mmHg and 58±15 vs. 58±16 mmHg).



Correlation between Pm and Cp

Conclusions: PEA improves long-term RV afterload. However, the lower increase of Cp at the expense of lower decrease Pp, is associated with RPH. This would be related to a persistent impairment of the vessel wall viscoelastic properties.

P719 Prevalence and predictors of thromboembolic pulmonary hypertension in the long term follow-up of patients with acute pulmonary embolism

S. Vanni, F. Socci, G. Viviani, F. Moroni, P. Nazerian, A. Petrioli, B. Paladini, S. Grifoni. *Azienda Ospedaliero Universitaria Careggi, Florence, Italy*

Purpose: Previous studies investigated the prevalence of chronic thromboembolic pulmonary hypertension (CTEPH) with different results. Aim of present study was to investigate the prevalence and predictors of thromboembolic pulmonary hypertension during long term follow-up of patients with acute pulmonary embolism (PE).
Methods: Consecutive adult patients admitted to a third level italian hospital for acute PE from January 2000 to September 2007 were considered for the study. Patients older than 85 years and who were unable to attend follow-up were excluded. The follow-up included physical evaluation, emogasanalysis, NTpro-BNP and DDimer determination, 6 minutes walk corridor test (6WCT) and echocardiography. Patients with pulmonary hypertension by Doppler analysis (pulmonary arterial systolic pressure $\geq$ 40 mmHg) underwent CT pulmonary angiography.
Results: Out of 364 patients considered, 339 survived at in-hospital phase. Of these, 84 patients were excluded because of age, 11 were inaccessible to follow-up and 9 declined to participate. Thus 235 patients were included with a mean follow-up duration of 50.3±26.2 months (min 6, max 96). Of these, 64 (27.4%) died during follow-up, 2 due to recurrent PE (1.2%). Thirteen patients (5.5%) had pulmonary hypertension at follow-up and in 7 (3%) CT angiography showed residual pulmonary thrombosis and CTEPH was diagnosed. One of these patients died and one underwent to thromboendoarterectomy. Patients with CTEPH had significantly higher levels of NT-proBNP (598±639 vs 159±229 pg/ml), and lower walked distance at 6WCT (314±148 vs 450±145) than patients with normal pulmonary pressure. No differences in gender, Pa02, DDimer values and NYHA class were found.
Conclusions: Thromboembolic pulmonary hypertension is not frequent (3%) after acute PE. Simple humoral and clinical data beyond symptoms (NYHA class) are associated with CTEPH and may aid to select patients that need further instrumental work-up.

P720 Effects of pulmonary thromboendarterectomy on echocardiographic parameters in patients with chronic thromboembolic pulmonary hypertension: one-year follow-up

T. Palecek, D. Ambroz, P. Jansa, J. Lindner, K. Taborska, M. Vitovec, P. Polacek, P. Kuchynka, M. Aschermann, A. Linhart on behalf of Cardiovascular research project of the Charles University Prague, nr. 0021620817. *Charles University in Prague, 1st Medical Faculty, Prague, Czech Republic*

Background: Pulmonary thromboendarterctomy (PEA) is a method of choice for treatment of chronic thromboembolic pulmonary hypertension (CTEPH). Short-term studies have demonstrated significant improvement in morphological and functional parameters of right (RV) and left (LV) ventricle. However, mid and long-term studies focused on this topic are still lacking.
Aim of the study: To evaluate the mid-term (one-year) changes in echocardiographic parameters obtained from patients who underwent PEA.
Methods: Echocardiography was performed before and 1, 6 and 12 months after PEA in first 50 patients with CTEPH operated in our centre. Final study population consisted of 43 subjects (53±13 years) in whom 12 months follow-up was completed. The investigated parameters comprised pulmonary artery systolic pressure (PASP), right ventricular end-diastolic diameter (RVEDD), area (RVEDA) and fractional area change (RVFAC); left ventricular end-diastolic diameter (LVEDD), end-diastolic volume (LVEDV), eccentricity index (LVEI) and ejection fraction (LVEF).
Results: The results are summarized in Table 1.

Table 1

	Before PEA	1 month after	6 months after	12 months after
PASP (mmHg)	87±24	36±21***	33±20***	34±19***
RVEDD (mm)	45±8	31±7***	28±5***,†	28±5***,†
RVEDA (cm^2)	37±22	24±4**	21±5**	21±5**
RVFAC (%)	0,20±0,35	0,35±0,10*	0,42±0,09**,†	0,44±0,08**,†
LVEDD (mm)	39±7	49±6***	51±6***	51±4***
LVEDV (ml)	54±20	84±20***	93±18***	95±25***,‡
LVEI	1,58±0,33	1,07±0,15***	1,03±0,16***	0,99±0,13***
LVEF (%)	63±10	63±7	62±7	64±6

*,**,***p<0,05, p<0,01, p<0,001 ... others vs. before PEA; †,‡p<0,05, p<0,01 ... 6 months after or 12 months after vs. 1 month after.

Conclusions: Effective PEA leads early to significant decrease in pulmonary artery pressure which lasts in mid-term, one-year follow-up. This decline in RV afterload is combined with significant and persistent decrease in RV size and is accompanied by gradual improvement in RV systolic function. The removal of RV pressure overload and corresponding improvement in LV filling leads early after PEA to significant increase in LV size and normalization of its shape; these favorable LV changes persist in one-year follow-up after PEA.

P721 Electrocardiographic detection of pulmonary hypertension after prior pulmonary embolism

I.R. Henkens[1], U. Hoke[1], M.J. Schalij[1], E.E. Van Der Wall[1], A. Boonstra[2], C.A. Swenne[1], A. Vonk Noordegraaf[2], H.W. Vliegen[1]. *[1]Leiden University Medical Center, Leiden, Netherlands; [2]VU University Medical Center, Amsterdam, Netherlands*

Purpose: To determine whether using the electrocardiogram-derived ventricular gradient (VG, mV·ms), may help to detect patients who develop chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (estimated incidence two years after pulmonary embolism = 3.8%). The VG is a measure of ventricular action potential duration heterogeneity, which is highly sensitive to changes in myocardial pressure load. A VG <25mV·ms along the X axis of the heart (normal 99.9%-range: 35-150mV·ms) was previously found to be 100% specific for increased right ventricular pressure load in a group of 72 patients with idiopathic pulmonary arterial hypertension and 144 controls, matched for sex and heart rate.
Methods: We retrospectively evaluated 88 consecutive patients with chronic thromboembolic pulmonary hypertension, who underwent a diagnostic right heart catheterization and a standard 12-lead electrocardiogram recording on the same day. With dedicated electrocardiogram analysis software the VG along the X axis of the heart was calculated.
Results: Measured mean pulmonary artery pressure was 44±11 mmHg, and pulmonary vascular resistance was 707±367 dynes·s•cm^{-5} in these CTEPH patients. In 62 out of 88 patients the VG was <25mV·ms, rendering a sensitivity of 70% for CTEPH. Subsequently, we calculated the positive and negative predictive values based on the pre-determined specificity of 100% and a given chance of 3.8% of developing CTEPH after pulmonary embolism. Based on a fictional population of 1000 individuals, the positive predictive value was (38)×0.7)/(38×0.7)=1.0. Similarly, the negative predictive value was 962/(962+38×(1-0.7))=0.99.
Conclusions: In a selected population of individuals with past pulmonary embolism, electrocardiogram-derived VG analysis may aid in diagnosis of CTEPH. Despite the suboptimal sensitivity for CTEPH of a VG <25mV·ms, this approach prevents false-positive diagnosis of CTEPH. The use of the electrocardiogram-derived VG is therefore a promising screening tool for repeated evaluation of CTEPH in larger groups of patients with past pulmonary embolism. The clinical efficacy of the proposed method deserves further study.

P722 Sildenafil therapy for both operable and inoperable chronic thromboembolic pulmonary hypertension

E. Leci, M. Palazzini, A. Manes, L. Negro, A. Marinelli, S. Gambetti, E. Beciani, E. Conficoni, A. Branzi, N. Galie'. *Institute of Cardiology, University of Bologna, Bologna, Italy*

Purpose: Pulmonary endoarterectomy (PEA) is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH) patients. Medical therapy may have a role in reducing pulmonary vascular resistance (PVR) prior to PEA and for patients deemed inoperable. We assessed the effects of the phosphodiesterase type-5 inhibitor sildenafil in CTEPH patients.
Methods: Between July 2003 and October 2008, 34 patients with inoperable and 19 patients with operable CTEPH received sildenafil. Data from 6-minute walk distance (6MWD) and right-heart catheterization were collected at baseline, after a treatment period of 3.0±2.1 months in operable CTEPH patients (immediately before PEA) or after a treatment period of 4.1±1.9 months in inoperable patients.
Results: 6MWD distance improved in the inoperable group, from 361±163 at baseline to 425±156 m after sildenafil treatment (p<0.001). The improvement was maintained at one year (454±139 m). 6MWD increased also in the operable group from 345±97 at baseline to 440±98 m after sildenafil treatment, prior to surgery (p=0.0018). Mean hemodynamic parameters at baseline and after sildenafil treatment in all 53 patients are shown in the table.

Hemodynamic parameters

	RAP (mmHg)	mPAP (mmHg)	mSAP (mmHg)	CI (L/min/m^2)	PVR (WU)	MVO2 (%)
Baseline	10±5	55±10	93±14	2.4±0.7	12±5	55±8
Sildenafil	7±3	51±9	85±14	2.9±0.7	9±4	62±7
p	0.02	0.008	0.03	0.0012	0.0003	0.0003

Right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), mean systemic arterial pressure (mSAP), cardiac index (CI), pulmonary vascular resistance (PVR), mixed venous oxygen saturation (MVO2).

Conclusions: sildenafil treatment of patients with both operable and inoperable CTEPH is associated with improvements in exercise capacity and hemodynamics. Medical therapy prior to PEA can reduce PVR into a range associated with lower operative risk, although this strategy requires further studies and correlation with surgical outcome data.

P723 Assessment of early outcome and residual pulmonary hypertension after pulmonary endarterectomy by preoperative analysis of dynamic right ventricular afterload

J.C. Grignola[1], M.J. Ruiz-Cano[1], P. Escribano[1], J. Cortina[2], T. Velazquez[3], M.A. Gomez-Sanchez[1], J. Delgado[1], C. Saenz De La Calzada[1]. *[1]Unidad de HTPulmonar y Tx Cardíaco, Servicio de Cardiología, Hospital Universitario "12 de Octubre", Madrid, Spain; [2]Servicio de Cirugía Cardíaca, Hospital Universitario "12 de Octubre", Madrid, Spain; [3]Servicio de Hemodinamia, Hospital Universitario "12 de Octubre", Madrid, Spain*

Pulmonary artery (PA) pressure waveform and PA occlusion pressure decay analysis can be useful for differential diagnosis of proximal versus distal obstruction in pulmonary hypertension (PH). A more proximal occlusive site determines an earlier and greater wave reflection, which in turn increases systolic (Ps) and decreases diastolic (Pd) PA pressures, with non significant changes in mean (Pm) and pulmonary artery occlusion pressure (Ppao).

Aim: To determine if preoperative (Pre) dynamic right ventricular (RV) afterload predicts short-term survival and residual PH (RPH) in patients (p) with chronic thromboembolic pulmonary hypertension (CTEPH) that underwent pulmonary endarterectomy (PEA).

Methods: Pre and postoperative (56±41 hours after PEA) RV catheterization was performed in 25 p (14 men, 23-82 years). Pulmonary arterial resistance (Rp) (steady component) was partitioned (RpU) into proximal upstream and small distal blood vessels (downstream) component. RpU was calculated as the ratio (Pm-Pd)/(Pm-Ppao). Therefore, RpU is in proportion to the upstream resistance (a higher upstream resistance determines lower Pd and faster pressure decay profile and viceversa). Pulsatile afterload component was assessed by the fractional pulse pressure (fPp: Pp/Pm) and the capacitance index (Cp: stroke volume/Pp). RPH was defined as a Rp of 240 dyn.s.cm-5 or greater. Values are presented as mean±SD. Paired student t test and nonparametric receiver-operator characteristic (ROC) plots were used.

Results: Pre values were Rp 852±420 dyne.s.cm-5, Cp 1.0±0.5 ml/mmHg and RpU ranged from 88 to 36%. Five p died during short term follow-up (<30 days), and they had higher Pre Rp and lower Pre RpU and fPp than survivors ($p<0.05$), with nonsignificant difference in Cp (p=0.08). Ten p had RPH.

ROC analysis

Pre	Cut-off	Mortality				Residual PH			
		AUROC (95% CI)	p	S	E	AUROC (95% CI)	p	S	E
RpU	48	0.9 (0.769-1.031)	0.007	83	100	0.893 (0.743-1.042)	0.002	100	79
Rp	1200	0.878 (0.715-1.041)	0.011	89	60	0.810 (0.628-0.992)	0.014	100	36
fPp	1.055	0.835 (0.658-1.012)	0.123	95	40	0.769 (0.525-0.971)	0.049	100	36

AUROC: area under ROC; CI: confidence interval; S: sensitivity; E: specificity.

Conclusions: Pre partitioning of steady component of RV afterload by RpU may discriminate poor outcome and RPH after PEA. P with RpU values ≤ 48% appear to be at highest pos risk.

P724 Impact of thrombus borne active endothelin on the vasoconstrictive capacity of thrombi from patients with chronic thromboembolic pulmonary hypertension

C. Adlbrecht, C. Plass, B. Redwan, J. Jakowitsch, D. Bonderman, A. Panzenboeck, W. Klepetko, I.M. Lang. *Medical University of Vienna, Vienna, Austria*

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) can occur after acute pulmonary embolism. Surgical pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH. Recently, medical treatment with endothelin- (ET) receptor antagonists has been attempted as a treatment option for inoperable patients. However, the pathophysiologic basis of this treatment effect in a disease were mechanical obstruction is thought to play the major role in impairing hemodynamics is unclear.

We hypothesized that in CTEPH, thrombus-associated ET mediates vasoconstriction in the distal vascular bed, impairing pulmonary capillary flow and furthering adverse remodeling.

Aim: The aim of the present study was to investigate the role of thrombus borne ET in CTEPH.

Methods: 19 surgical thrombus samples from patients with CTEPH undergoing PEA were homogenized and subjected to in-vitro vasoconstriction experiments on porcine artery rings evaluating dual and selective ET-A receptor antagonism. Thrombus ET synthesis was analyzed in an animal model of CTEPH.

Results: CTEPH thrombi exerted pronounced vasoconstrictive properties in 17 of 19 (90%) samples. Pre-incubation with a dual ET antagonist inhibited thrombus-induced constriction by 30.4 (18.6-62.9)% of the crossover self control. Immunohistological evaluation revealed colocalization of ET-1 positivity with CD-68 positive macrophages within the thrombi.

Conclusion: The vasoconstrictive capacity of CTEPH thrombi is caused by thrombus borne ET to a major extent. Our data may explain the effect of ET receptor antagonists in some CTEPH patients and may represent a link between failed thrombus resolution and ET mediated microvascular remodeling.

PULMONARY CIRCULATION AND RIGHT VENTRICULAR FUNCTION

P725 Size of pulmonary right-to-left shunt predict migraine with aura

M.C. Post[1], M.W.F. Van Gent[1], H.W.M. Plokker[1], C.J.J. Westermann[1], J.J. Mager[1], W.J. Schonewille[1], V. Thijs[2], R.J. Snijder[1]. *[1]St Antonius Hospital, Nieuwegein, Netherlands; [2]University Hospital Gasthuisberg, Leuven, Belgium*

Purpose: An increased prevalence of migraine with aura (MA) has been described in the presence of pulmonary arteriovenous malformation. The size of this pulmonary right-to-left shunt (RLS) and the relation to MA has never been investigated.

Methods: A sufficient transthoracic echocardiography with contrast (TTCE) was performed in 377 consecutive persons who were referred for screening for hereditary hemorrhagic teleangiectasia (HHT). TTCE was positive for a pulmonary RLS if microbubbles appeared in left atrium after four cardiac cycles. Opacification of the left ventricle was graded as either minimal, moderate, or large. All patients received a structured headache questionnaire prior to TTCE.

Results: The questionnaire was filled in by 350 persons (age 44±15y, 60% female). The prevalence of MA was 16% in patients with a pulmonary RLS, and 6% in those without a pulmonary shunt (p=0.004). A pulmonary RLS was present in 21 patients with MA (62%) and in 100 non-migraine controls (35%) (OR 3.0: 95%CI 1.4–6.2, p=0.003). Only a moderate or large shunt was found more often in MA patients (56%) compared to non-migraine controls (22%) ($p<0.001$). The presence of a large pulmonary shunt increased the odds of having migraine with aura 7.0 times (95%CI 3.1–15.8, $p<0.001$), also after adjustment for gender and a history of a cerebral ischaemic event (OR 6.4: 95%CI 2.6–15.7, $p<0.001$).

Conclusion: A pulmonary RLS was found more often in patients with MA compared to non-migraine controls. A larger shunt size is associated with MA in patients screened for HHT.

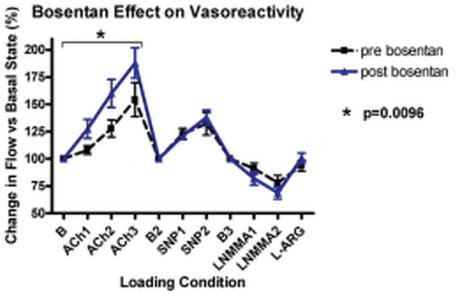
P726 Bosentan improves pulmonary microvascular endothelial function in adults with pulmonary arterial hypertension

R. Ilsar, J. Levitt, M.R. Adams, D.S. Celermajer. *Royal Prince Alfred Hospital, Sydney, Australia*

Purpose: The endothelin receptor antagonist Bosentan improves clinical endpoints in patients with idiopathic or scleroderma-related pulmonary artery hypertension (PAH). Its effect on the structure and function of the pulmonary circulation in humans, however, have not been studied.

Methods: Eight drug-naïve PAH patients were studied before and after 6 months of open-label, clinically-indicated Bosentan. Proximal pulmonary artery (PA) structure was studied using intravascular ultrasound (IVUS; n=8). Pulmonary microvascular function was assessed using intravascular Doppler to measure flow responses to infusions of acetylcholine (ACh; endothelium-dependent vasodilator), sodium nitroprusside (SNP; smooth muscle-dependent vasodilator), L-NMMA (nitric oxide synthase inhibitor) and L-arginine (nitric oxide precursor)(n=7). Analyses were blinded to subject identity and study date. The prespecified primary endpoints were change in flow response to ACh and change in PA wall thickness, after 6 months Bosentan.

Results: Compared with baseline, Bosentan significantly improved pulmonary microvascular endothelial function (p=0.0096 for dose-response curve comparison); eg. maximal ACh dose (10^{-6}M in local tissue) augmented flow 54±16% before and 89±14% after Bosentan (Figure 1). No difference was found in SNP (p=0.9) or L-arginine (p=0.3) flow responses. Bosentan therapy was associated with a trend to more marked L-NMMA constrictor response (10% greater flow reductions at 6 months, p=0.20). Significant PA wall thickening was observed at baseline (% intima-media thickness/total lumen area, 34±2%) but this was not altered by Bosentan (36±4%, p=0.6).



Conclusions: Six months treatment with Bosentan leads to improved pulmonary endothelial function in the microcirculation.

P727 Sympathetic nervous system activation is an independent prognostic factor of clinical deterioration in pulmonary arterial hypertensive patients

A. Ciarka, V. Phuong, S. Huez, J.L. Vachiery, R. Naeije, P. Van De Borne. *Universite Libre de Bruxelles, Brussels, Belgium*

Background: Pulmonary arterial hypertension (PAH) is accompanied by increased muscle sympathetic nerve activity (MSNA), related to the severity of disease. We wanted to investigate whether MSNA is a prognostic factor in PAH patients.
Methods: We have included 33 PAH patients into the study, hospitalised between 2001 and 2007 in University Hospital for evaluation of pulmonary hypertension. All patients underwent right heart catheterisation, six minutes walk test (SMWT) and their functional NYHA class was evaluated. A MSNA recording was performed in the all patients. The mean follow up time was 57±4 months. The patients were classified as survivors or clinically deteriorated (transplanted or dead).
Results: The deteriorated patients as compared to the survivors presented with increased MSNA (79±3 vs. 52±4 burst/min, $p<0.0001$), increased heart rate (88±4 vs. 74±3 bpm, $p<0.05$), lower SMWT (328±30 vs. 434±23 m, $p<0.01$) and increased NYHA class (3.5±0.1 vs. 2.9±0.2, $p<0.05$). No difference was found between the hemodynamic variables between the two groups. MSNA was directly related to NYHA class, heart rate and inversely related to SMWT. An univariate analysis revealed that MSNA, heart rate, SMWT and class NYHA were associated with clinical deterioration. A multivariate analysis showed that MSNA was an independent predictor of clinical deterioration. For every increase of 1 burst per minute, the risk of clinical deterioration increased by 6%. The Kaplan-Meier curves revealed that patients with MSNA>66 burst/min presented with decreased survival in comparison with those, who were characterised by MSNA < 66 burts/min (log rank test, $p<0.01$), (Figure 1).

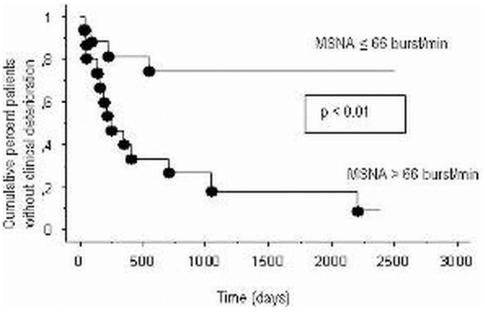


Figure 1. Survival and sympathetic activation

Conclusion: MSNA is an independent prognostic factor of death or major clinical deterioration justifying lung transplantation in PAH patients.

P728 Arterial stiffness evaluation in patients with systemic sclerosis: an interesting correlation with right ventricular function and cardiopulmonary performance

P. Marchese, G. Delle Donne, A. Nuzzo, F. Franchi, F. Rollini, D. Giuggioli, C. Ferri, R. Rossi, M.G. Modena. *Universita di Modena e Reggio Emilia, Modena, Italy*

Objective: Systemic sclerosis (SSc) is characterized by widespread vasculopathy with alterations in physical properties of pulmonary and systemic arteries (increased rigidity and impaired distensibility). Our aim is to define if carotid-femoral pulse wave velocity (cfPWV), the gold standard for the assessment of the peripheral arterial stiffness, is associated with the impairment of right ventricular function (as indirect evaluation of the concomitant increase of pulmonary arterial stiffness) and reduced exercise capacity (as index of global impairment of cardiopulmonary performance).
Methods: We evaluated 52 women (26 consecutive patients with SSc and 26 healthy women matched for Framingham risk score) with echocardiography and six minute walking test (SMWT). ECG-gated waveforms of the right carotid and right femoral artery were obtained by applanation tonometry, and cfPWV was calculated using non invasive established methods.
Results: cfPWV was interestingly correlated with right ventricular middle diameter (RVMD) (r=0.67; r2=0.33; $p<0.0001$) and SMWT (r=-0.60; r2=0.34; p=0.001). SSc patients differed significantly for the parameters shown in the table 1.

Table 1

Parameter	SSc patient	Controls	p
Age (years)	58.4±12.4	56.8±4.4	ns
Framingham Risk Score	4.6±2.2	4.4±2.8	ns
cfPWV (m/s)	10.1±3.8	6.1±2.7	0.007
SMWT (m)	414.1±95.5	509.4±49.9	0.003
RVMD (mm/m^2)	19.2±3.9	14.5±0.6	<0.0001
Right atrial volume (ml/m^2)	24.2±5.9	15.9±5.3	0.003
PAP (mmHg)	33.6±10.6	20.5±3.0	<0.0001
Tricuspid Annular Plane Systolic Excursion (mm)	2.3±0.7	5.7±0.7	0.004

Conclusions: cfPWV, is significantly increased in SSc patients. Our study suggests a relationship between cfPWV, the impairment of right ventricular function and reduced exercise capacity. Because pulmonary and peripheral arteries share the same underlying phatophysiological process that causes widespread vasculopathy with rigidity and impaired distensibility of the vasculature, increased cfPWV may indirectly reflect the concomitant increased pulmonary arterial stiffness. Thus cfPWV could be further evaluated as useful diagnostic and prognostic tool in SSc patients.

P729 Increased pulmonary vascular resistance in chronic heart failure is linked to parallel stiffening of pulmonary and systemic arteries

V. Melenovsky, H. Al Hiti, T. Gazdic, M. Kotrc, I. Malek, J. Kettner, J. Kautzner. *Institute for clinical and experimental medicine, Prague, Czech Republic*

Purpose: Development of pulmonary hypertension in patients with chronic heart failure (CHF) is incompletely understood. The study aimed to examine the link between evelation of pulmonary vascular resistance (PVR) and mechanic properties of arterial wall in CHF patients.
Methods: Patients with advanced CHF (age, NYHA, 45% CAD) undewent right heart catherisation with thermodilution cardiac output measurements (Corodyn, Braun). Mechanical arterial properties were quantified by calculation of compliance (stroke volume/pulse pressure) of pulmonary arterial tree and systemic arteries.
Results: Of 204 patients examined, 83 (41%) had high PVR (>2.5 w.u., H-PVR). H-PVR group had similar body size, disease severity (NYHA 3.0 vs 3.1, p=0.8) and CAD frequency (48% vs 42%, p=0.5), but longer CHF duration (6.7 vs 5.1y, p=0.06) and more often diabetes (33 vs 19%, p=0.03) than low-PVR group. H-PVR subjects had higher right atrial (7±6 vs 11±6), PA mean (27±9 vs 42±9), PA pulse (24±8 vs 38±11) and PA wedge pressure (20±8 vs 26±6, mmHg) but lower cardiac output (4.5±1 vs 3.8±0.8, l/min) and systemic arterial compliance (1.8±0.7 vs 1.3±0.5 ml/mmHg) (all $p<0.001$). PA compliance was by 48% lower in H-PVR group (1.4±0.6 vs 2.7±1 ml/mmHg, $p<0.001$) and was inversely (exponencially) related to PVR. In the whole CHF cohort, PA compliance correlated with systemic arterial compliance (Figure).

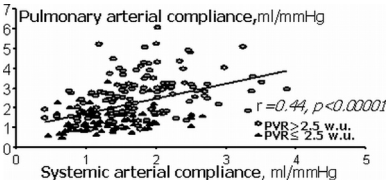


Figure 1

Conclusion: H-PVR patients had reduced both pulmonary and systemic arterial compliance compared to low PVR, indicating that stiffening of pulmonary arterial tree occurs particularly in those who have also less compliant systemic arteries. The process of combined stiffening of both arterial systems may contribute to development of pulmonary hypertension in advanced CHF.

P730 The prevalence of pulmonary hypertension in patients with untreated Graves disease

K.I. Cho[1], B.H. Kim[2], J.H. Suk[1]. *[1]Maryknoll Medical Center, Pusan, Korea, Republic of; [2]Pusan National University Hospital, Pusan, Korea, Republic of*

Background and aims: Graves' disease is a common metabolic disorder that is associated with prominent cardiovascular manifestations, like marked reduction in peripheral vascular resistance and increased total blood volume and heart rate. Hyperthyroidism can consequently exacerbate preexisting cardiac disease or cause de novo cardiovascular abnormalities, such as atrial fibrillation and heart failure. Recent reports suggested a potential link between hyperthyroidism and pulmonary hypertension (PHT). But, the potential pathogenic mechanisms of hyperthyroidism-related PHT remain unclear. This study was performed to investigate the prevalence of PHT and the hemodynamic changes using echocardiographic measurements in untreated patients with Graves' disease and to determine the relation between PHT and thyroid autoantibodies. Subjects and Methods: We performed serial echocardiographic examinations in 61 patients with newly diagnosed or relapsing GD without or with less than 4 weeks of treatment with antithyroid drugs to estimate pulmonary artery systolic pressure (PASP), cardiac output (CO), total vascular resistance (TVR), and left ventricular filling pressure. Examinations were performed at baseline and 6 months after initiation of antithyroid treatment. Thyroid antoantibodies titer was measured in sera from the patients. Results were compared with 35 age- and sex-matched healthy controls. PHT was defined as PASP of at least 35 mmHg.
Results: In our study the prevalence of PHT using echocardiographic measurements in untreated patients with Graves' disease was 39.6%. The presence of systemic hypertension was associated with PHT. The systolic and diastolic blood pressures was significantly higher in patients with PVH than those with PAH.

There was no relationship between PHT and thyroid autoantibodies in untreated patients with Graves' disease. Aortic regurgitation was more prevalent in Graves' patients with PHT.
Conclusion: These data show that PHT is prevalent in patients with Graves' disease and thyrotoxicosis itself, not underlying autoimmune process, might contributes to the pathogenesis of PHT related to Graves' disease.

P731 Compliance has greater influence than resistance on Cardiac Index in Pulmonary arterial hypertension

G. Teixido[1], E. Domingo[2], R. Aguilar[1], M. Lopez-Meseguer[1], A. Roman[1]. [1]*Hospital Universitario Vall d'Hebron, Barcelona, Spain;* [2]*Physiology Dpt. Universitat Autònoma., Barcelona, Spain*

In the clinical setting, pulmonary vascular resistances (PVR) are used as a prognostic follow-up variable in patients with Pulmonary arterial hypertension (PAH). However, PVR does not represent most of the RV afterload, since arterial flow is pulsatile, and Compliance (C) but not resistance is related to pulsatility.
The aim of the study is to analyse the changes in PVR, C, PVRxC (index of decay of pulmonary artery pressure in diastole) and L (vector's length between the basal and epoprostenol status in the PVR/C graphical relationship) from baseline to maximal epoprostenol in an acute vasodilator test, and their influence in cardiac index (CI) changes.
Methods: 18 PAH patients (13females), mean age 52.9yrs, functional class II-III, were studied with right and left cardiac catheterisation. The following variables were collected at baseline and after maximal tolerated dose of epoprostenol in the acute vasodilator test that was positive in 3 patients: Heart Rate (HR), Fick CI, Pulmonary artery pressure (PAP), Pulmonary wedge pressure, PVR (Wood Units) and C were calculated. L was calculated as: $L = \sqrt{\Delta PVR2 + \Delta C2}$.
Mean L was 2,85±0,96. PVR, C and PVRxC values from baseline to epoprostenol were compared with paired samples Student's Test (two-tailed). Different regression models were used to explain the changes in CI (ΔPVR, ΔC and L separately and the first two together).
Results: The table shows results of paired samples Student t test. The best model of linear multiple regression for predicting CI changes incorporates ΔC and ΔPVR (R2=0,48). When using only one variable, changes in CI are much better explained by ΔC (R2=0.40) than by L (R2=0,24) or ΔPVR (R2=0,20).

Parameter	Mean ± se Basal	Mean ± se Epoprostenol	p
PVR	11,15±1,79	8,36±1,32	0,01
C	1,41±0,23	1,69±0,27	0,115
PVRxC	10,27±0,67	9,6±0,73	0,323

Conclusions: the product PVRxC representing the decay of pulmonary artery pressure in diastole remains equal between both hemodynamic status since PVR and C are inversely related. Changes in CI are quantitatively more influenced by changes in compliance than by changes in Resistance suggesting that C is a greater component of RV afterload than PVR.

P732 Relaxin is a candidate drug for lung preservation

K. Alexiou[1], K. Matschke[1], G. Baumann[2], K. Stangl[2], T. Dschietzig[2]. [1]*Heart Centre, Dresden, Germany;* [2]*Charité, Campus Mitte, Department of Cardiology and Angiology, Berlin, Germany*

Early allograft dysfunction following lung transplantation is mainly caused by ischemia/reperfusion (IR) injury which originates from multiple pathogenic events, including endothelial damage, neutrophil extravasation into tissue, peroxidation of cell membrane lipids, pulmonary cell alterations, pulmonary hypertension, and oedema. The potent vasoconstrictor and pro-inflammatory mediator endothelin (ET)-1 plays a major role in this cascade. The purpose of this study was to determine whether treatment with relaxin-2, a hormone with anti-inflammatory and vasodilatory properties, could prevent the rise of ET-1 and, correspondingly, ischemia-reperfusion injury.
Isolated male Wistar rat lungs were perfused in recirculatory mode in the presence of 5 nM human relaxin-2 (RLX) or vehicle (n = 6-10 each). After 45 min ischemia and 60 min reperfusion we determined wet-to-dry (W/D) weight ratio and vascular release of ET-1, neutrophil elastase (NE), myeloperoxidase (MPO), and malondialdehyd (MDA).
IR lungs displayed significantly elevated W/D ratios (270% of control), mean arterial pressure (300%), as well as release of ET-1 (320%), NE (840%), MDA (270%), and MPO (600%) compared with control lungs. In the presence of RLX, these parameters were markedly improved, to 150% of baseline (W/D), 200% (vascular pressure), 180% (ET-1), 410% (NE), 150% (MDA), and 290% (MPO).
These results show that human RLX exerts a protective effect in IR-induced lung injury, likely due to ET-1 reduction, decreased leukocyte recruitment and hindrance of free radical-mediated tissue injury. This renders RLX a candidate drug for lung preservation.

P733 Left ventricular diastolic dysfunction as an early initiator of pulmonary hypertension relating to hypoxemia in acute mountain sickness syndrome (amss)

J. Nakata[1], M. Takayama[1], T. Matsuzaki[2], I. Takagi[3], M. Tsurumi[4], M. Kawamoto[5], Y. Kobayashi[4], H. Mihara[1], K. Mizuno[4]. [1]*Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan;* [2]*Center for Physiological Function, Nippon Medical School Hospital, Tokyo, Japan;* [3]*Department of Internal Medicine, Tsurumi University, School of Dentistry, Kanagawa, Japan;* [4]*Department of Internal Medicine, Division of Cardiology, Hepatology, Geriatrics, and Integrated Medi, Tokyo, Japan;* [5]*Department of pathology, Nippon Medical School, Tokyo, Japan*

Background: Hypobaric hypoxic circumstances in high altitude has been suggested to cause pulmonary vasoconstriction and RV pressure overload, which is related and may lead to LV diastolic dysfunction. We hypothesized that LV diastolic dysfunction would be more marked in AMSS subjects, and we investigated the predictive markers of echocardiography (Echo) to clarify diastolic dysfunction in high risk subjects of AMSS.
Method: We examined the cardiopulmonary performance by Echo at the height of 3000m and the summit of 3776m both in healthy subjects and AMSS subjects, who visited the mountain clinic there. The specialists of Echo performed the whole recording using GE Vivid-I. Hypoxemia was also assessed with the pulseoximetry in room air after 20 minutes' rest. Clinical backgrounds were obtained by personal interview. Evaluates such as left ventricular (LV) ejection fraction (EF), LV and right ventricular (RV) inflow velocity pattern (E/A), LV and RV annular relaxation velocity (e'), systolic pressure gradient across tricuspid valve (TRPG) and strain rate (SR) were calculated using off-line analysis. Longitudinal SR(L) was used for early diastolic peak value (Esr), atrial contraction peak value (Asr), and their rate (E/Asr).
Result: Echo evaluation was performed in 49 volunteers in total (31 males/18 females, aged 40.3±13) at the height of 3000m and the summit of 3776m altitude. SpO2 level, pulse rate, and TRPG of those were 81.4±5.6%, 95±13bpm, 35.0±9.5mmHg respectively. At the height of 3000m, TRPG in AMSS subjects (n=6) was significantly higher than that of healthy subjects (n=8)(43.0±3.6 vs 26.9±5.2mmHg; p=0.001). Prolonged e', shortening of LV, and RV DCT were also significantly different between AMSS and healthy subjects (14.0±28.9 vs 10.0±3.22msec; p=0.05, 187.5±57.8 vs 117.8±56.9msec; p=0.057, 160.0±54.5 vs 88.9±40.2mmHg; p=0.02). In healthy subjects, TRPG at the summit of 3776m were significantly higher than that at the height of 3000m (28.4±6.0 vs 38.1±6.0mmHg; p=0.03), no remarkable change of diastolic dysfunction was shown in echocardiography.
Conclusion: The mountaineers of acute mountain sickness syndrome showed the obvious LV diastolic dysfunction, which is considered to be closely related to the mechanism of acute mountain sickness syndrome.

P734 Pharmacogenomic tailoring of warfarin dose in pulmonary hypertension patients: beyond inr control

R. Baptista, E. Jorge, J. Pego, M. Lourenco, I. Marques, P. Monteiro, G. Castro, P. Monteiro, L.A. Providencia, F. Antunes. *Hospital and Medical School, Coimbra, Portugal*

Background: WFN (WFN) is part of the comprehensive treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients. However, it has a wide inter-individual variability in dose requirement, which can be determined by genetic factors in a value of 35 to 40%. The most important genes related to WFN metabolism are CYP2C9 (cytochrome P450 2C9 and VKORC1 (vitamin K epoxide reductase complex subunit 1).
Objectives: We investigated the influence of variants of VKORC1 and CYP2C9 loci on the mean weekly WFN dose, in order to estimate the contribution of the polymorphisms of these two genes in a population of pulmonary hypertension patients.
Methods: A total of 14 consecutive patients were enrolled. Clinical and demographic data were collected and each participant was genotyped.
Results: The mean age of patients was 59 years; eight were PAH patients, whereas 10 where CTEPH patients. Ten patients where under specific therapy (bosentan, sildenafil, treprostinil). Table 1 summarizes the prevalence of the different genotypes influencing the response to oral anticoagulants and the respective dose of WFN required to maintain patients on their desired anticoagulation target. Such doses were significantly different among carriers of the different CYP2C9 (p=0.034) and VKORC1 genotypes (p=0.002).

Table 1

Genotype		%	WRF daily average dose (mg/kg)
CYP2C9	1/1	64.3	0.100
	1/2	28.6	0.053
	1/3	17.1	n/a
VKORC1	GG	37.5	0.113
	GA	64.3	0.054
	AA	0.9	n/a

Conclusions: Our results confirm recently published data regarding the role of these two genes in modifying WFN metabolism and maintenance dosage, by

showing a significant correlation between genotype and WFN dose required for optimal anticoagulation. Future large prospective studies may demonstrate the safety, cost-effectiveness and feasibility of individualized dose regimens based on genotyping.

P735 INCIdence of pulmonary hypertension in Italian ulTrasonography's laboratories

I. Enea[1], S. Ghio[2], A. Bongarzoni[3], F. Casazza[3], A.M. D'Armini[2], G. Favretto[4], L. Roncon[5], A. Rubboli[6], P. Zonzin[5], C. D'Agostino[7] on behalf of INCIPIT study group. *[1]A.O.R.N. S. Anna and S. Sebastiano, Caserta, Italy; [2]IRCCS Policlinico S. Matteo, Pavia, Italy; [3]Ospedale S. Carlo Borromeo, Milano, Italy; [4]Ospedale Riabilitativo Alta Specializzazione, Treviso, Italy; [5]Presidio Ospedaliero, Rovigo, Italy; [6]Ospedale Maggiore, Bologna, Italy; [7]Ospedale di Venere, Bari, Italy*

Purpose: pulmonary arterial hypertension (PAH) includes a group of disease characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death.
With the advent of specific therapies for PAH to differentiate PAH from other causes of pulmonary hypertension (PH) is critical.
Echocardiography (echo) is a useful technique in the screening of patients with suspected PH by measurement of the systolic regurgitant tricuspid flow velocity. Echo estimates pulmonary artery systolic pressure that is equivalent to right ventricular systolic pressure in the absence of pulmonary outflow obstruction. The cut off of PH at echo is not well defined, but is generally accepted a tricuspid flow velocity of 2.8-3.4 m/sec.
Methods: in order to evaluate the frequency of PH in Italian patients, from 10 to 29 November 2008, we asked echo laboratories to report, every day, on a special electronic file, all the echocardiograms made and, on another file, those with a peak flow velocity $\geq$ 3m/sec.
Results: 120 Italian echo labs and one Swiss lab participated in the study. We examined 20837 echocardiograms from 106 centres (55 in the north, 17 in the Centre, 34 in the South of Italy). 1323 (6.3%) exams showed a systolic regurgitant flow velocity $\geq$ 3 m/sec (3.44$\pm$0.48); they were predominantly female (♀:♂=698:625), with the average age of 72.3$\pm$11.7, and a body mass index of 25.5$\pm$3.8; 233 of them were smokers. 277 (21%) patients had no symptom, 644 (48.6%) had dyspnoea, 149 (11%) had asthenia, 52 (4%) had chest pain, 98 (7%) had dyspnoea and asthenia, 11 (1%) had dyspnoea and chest pain, 66 (5%) had other symptoms. 1064 (80%) patients presented a well known cause of PH at the moment of echo, while 259 patients presented PH of unknown origin. Among these 259 patients, 128 presented a likely cause of PH, so only 131 (10%) presented PH of unknown cause. Among the 1323 patients with elevated PASP, 677 (51.1%) had left heart disease; 6 (0.4%) had congenital heart disease; 106 (8%) had lung disease; 19 (1.4%) had chronic thromboembolic pulmonary hypertension; 13 (0.9%) had collagen disease; 2 (0.1%) had liver disease; only one was a HIV patient, 320 (24%) had a double likely cause of PH, 43 (3.2%) had a triple likely cause of PH.
Conclusions: in Italian echo labs the occurrence of PH is unusual (6.3%) but it's not so rare if we consider the absolute number. Thus it's really important the cardiologists in the echo labs direct the patients with PH of unknown origin to the Italian reference centre so as to determine the cause and make the appropriate therapy for PAH as soon as possible.

P736 Impact of left ventricle diastolic function in the prognosis of pulmonary arterial hypertension

R. Placido, P. Loureiro, J. Marques, S. Martins, C. David, A. Diogo, S. Ribeiro, A. Ameida, M. Lopes. *Hospital Santa Maria, Lisbon, Portugal*

Pulmonary arterial hypertension (PAH) is associated with progressive increase in pulmonary resistance leading to right ventricle (RV) failure and death. In spite of therapeutic advances, mortality remains high and variables with prognostic impact are not well established.
Objectives: To assess the relationship of left ventricle (LV) diastolic function indexes with right ventricle (RV) dimensions and function, hemodynamic variables and mortality in patients (pts) with PAH.
Methods: We conducted a retrospective study of pts with PAH included consecutively in a Pulmonary Hypertension Ambulatory Clinic, in the period of 2002 to 2007. Exclusion criteria: incomplete data registry, presence of arterial hypertension or left heart pathology. Mortality was analysed at a follow-up period of 2.9$\pm$1.1 (1.5-5.8) years. In the first observation, the following variables were analysed: a) age, gender, BMI, NYHA class, cardiac rhythm; b) Echo-Doppler: LV and RV diastolic dimension and wall thickness, pulmonary artery systolic pressure (PASP), maximal velocity of tricuspid regurgitation (Vmax), mitral E and A velocity, E deceleration time (Dec), lateral mitral annulus velocity E' and A', tricuspid annular plane systolic excursion (TAPSE), RV maximal longitudinal strain. For strain measure, Velocity Vector Imaging software was used. Pts were divided in 2 groups, with and without criteria for LV diastolic dysfunction (LVDD), using any of the criteria: a) E/A$<$1 e Dec$>$220 ms and/or E'/A'$<$1; b) E/A$>$2 and Dec$<$150ms.
Results: 36 pts were included, 64$\pm$13 years-old, 24 women (66.7%), BMI 28.91$\pm$6.78kg/m^2. Twenty pts (55.55%) were in class III/IV NYHA and 32 pts (88.9%) were in sinus rhythm. All were treated with conventional medications and Bosentan. Echo variables: VE diastolic dimension was 47$\pm$6mm, septum thickness 10,8$\pm$2,3mm, posterior wall thickness was 10,0$\pm$1,6mm, RV diastolic dimension was 34$\pm$9mm, Vmax was 416$\pm$60cm/s, PASP was 86$\pm$23mmHg, TAPSE was 13$\pm$3mm and longitudinal strain was 21$\pm$5%. During follow-up, mortality was 28%. Fourteen pts (39%) showed criteria for LVDD. Comparing the two groups, with and without LVDD, no significant differences were found in clinical and echocardiographic variables. Mortality was significantly higher in patients with LVDD ($p<0.001$).
Conclusion: In this study of pts with PAH, a high prevalence of LV diastolic dysfunction was found, which was associated to higher mortality. No relationship was found with dimensional or functional indexes or with hemodynamic variables. Further study must be conducted to clarify mechanisms of LFDD in PAH.

P737 Contrast echocardiography guides treatment of pulmonary right-to-left shunt

M.W.F. Van Gent, M.C. Post, R.J. Snijder, M.J. Swaans, H.W.M. Plokker, C.J.J. Westermann, T. Overtoom, J.J. Mager. *St Antonius Hospital, Nieuwegein, Netherlands*

Purpose: Because of its association with neurological complications, screening for pulmonary arteriovenous malformations (PAVMs) is routinely performed in patients with hereditary hemorrhagic telangiectasia (HHT). Transthoracic contrast echocardiography (TTCE) can effectively detect pulmonary right-to-left shunting (RLS). We prospectively studied the predictive value of TTCE grading to detect PAVMs on chest HRCT and the indication for embolotherapy.
Methods: All consecutive persons screened for HHT, who underwent both a chest HRCT and showed a pulmonary shunt on TTCE, were included. TTCE was considered positive for a pulmonary right-to-left shunt if microbubbles appeared in the left atrium after four cardiac cycles. Pulmonary shunts were divided in grade 1 (minimal), grade 2 (moderate) and grade 3 (extensive). We excluded all patients without a pulmonary shunt on TTCE (n=239), a poor image quality (n=5), and indistinguishably between a pulmonary and cardiac RLS (n=4). Embolotherapy was performed of all PAVMs judged large enough for treatment.
Results: In total 151 persons could be included (mean age 43.1$\pm$15.4 yr; 64% female). Chest HRCT was positive in 74 (49%), negative in 74 (49%) and indeterminate in 3 (2%) patients, respectively. The positive predictive value of shunt grade for the presence of PAVMs on chest HRCT was 12% for grade 1 (n=50), 36% for grade 2 (n=33) and 86% for grade 3 (n=65), respectively. Of the patients with PAVMs on chest HRCT and a TTCE grade 1 (n=6), 2 (n=12), and 3 (n=56); none, 2 (17%), and 35 (63%) patients underwent embolotherapy. Kappa interobserver variable 0.83.
Conclusion: An increased echocardiographic shunt grade correlates with increased probability of PAVMs on chest HRCT. Only patients with a TTCE grade 2 and 3 displayed PAVMs on chest HRCT large enough for embolotherapy.

P738 Pulmonary artery pressure and right ventricular function in healthy children and adolescents after rapid ascent to 3'450m

S.F. Rimoldi[1], T. Stuber[2], S.F. De Marchi[1], H. Duplain[3], S. Garcin[3], C. Sartori[3], U. Scherrer[3], Y. Allemann[1]. *[1]Swiss Cardiovascular Center Bern, University Hospital Bern, Bern, Switzerland; [2]Imperial College Healthcare NHS Trust, St.Mary's Hospital, London, United Kingdom; [3]Department of Internal Medicine, CHUV, Lausanne, Switzerland*

Objectives: High-altitude tourist destinations are reached by increasing numbers of children and adolescents after rapid ascent by mechanical transportation. The high-altitude induced increase of pulmonary-artery pressure in these non-acclimatized young persons is expected to be substantial and may have adverse effects on the right ventricular function, but there is no information.
Methods: We performed echocardiographic assessments of pulmonary-artery pressure and systolic right ventricular (RV) function in 118 healthy, non-acclimatized children and adolescents (55 female, mean$\pm$SD age 11$\pm$2.4 y, range 6-16 y) with no previous high-altitude experience, at low altitude (540 m) and 40 hrs after rapid ascent to 3450 m.
Results: As expected, the altitude-induced decrease in arterial oxygen saturation (from 97$\pm$1.2 to 90$\pm$2.4%, $P < 0.0001$) was accompanied by a more than two-fold increase of the systolic right ventricular to right atrial pressure gradient (from 16$\pm$3 to 35$\pm$11 mm Hg, $P<0.0001$). Surprisingly, this dramatic increase in pulmonary-artery pressure did not have any adverse effects on RV function, but was associated with a significant increase in the systolic RV function parameters. Peak systolic tissue Doppler contraction velocity signal of the lateral tricuspid annulus (14.5$\pm$2.0 to 15.7$\pm$2.6 cm/s, $P<0.0001$), tricuspid annular plane systolic excursion (TAPSE) (20.1$\pm$1.8 vs. 20.8$\pm$2.5 mm, $P<0.02$), and isovolumic myocardial acceleration, a proxy of the RV contractile function (2.7$\pm$0.7 vs. 5.0$\pm$1.1 cm/s^2, $P<0.0001$) were all significantly greater at high than at low altitude. Moreover, at high altitude there was a significant correlation between pulmonary artery pressure and strain ($r=0.33$, $P=0.0006$) and strain rate ($r=0.60$, $P<0.0001$), a proxy of contractility.
Conclusions: These data provide the first evidence that in young healthy non-acclimatized children and adolescents, the dramatic increase of pulmonary-artery pressure induced by rapid exposure to high altitude is associated with increased systolic RV function. These findings contrast with observations in adults in whom systolic RV function remains unchanged under similar conditions.

P739 A Novel 3D echocardiographic geometrical model of the tricuspid valve for the assessment of different modalities of right ventricular remodeling

J. Grapsa, D. Pandis, D. Stefanou, D. Dawson, L.S.G.E. Howard, J.S.R. Gibbs, P.P. Punjabi, P. Nihoyannopoulos. *Hammersmith Hospital, London, United Kingdom*

Purpose: Using a novel Real Time Three-dimensional (3D) echocardiographic model, we examined the relationship between right ventricular (RV) remodeling, based on the tricuspid remodeling.
Methods: 260 patients were included and four different groups were created: 80 patients with pulmonary arterial hypertension (PAH) (58 women, mean age 41.8±14.2 years), 85 patients with pulmonary hypertension, secondary to left heart disease (LHD) (42 women, mean age 49.6±18.2 years), 40 patients with chronic thromboembolic pulmonary hypertension (CTEPH) (31 women, mean age 35.4±3.5 years) and 55 healthy subjects (H) (34 women, mean age 41.8±9.2 years) were examined with 3D echocardiography. A full volume acquisition for volumes and a tricuspid zoom view were obtained. The geometrical excursion of the tricuspid leaflets was assessed with the calculation of the leaflets angulation towards the tricuspid annulus in end-diastole and end-systole (θs-d: end-diastolic septal angle, θp-d; end-diastolic posterior angle, θa-d: end-diastolic anterior angle, θs-s: end-systolic septal angle, θp-s: end-systolic posterior angle, θa-s: end-systolic anterior angle). End-diastolic (EDV) and end-systolic (ESV) volumes as well as RV ejection fraction (RV-EF) were measured with the method of disk summation. RV systolic pressure was also calculated from Bernoulli equation. Spearman's test was employed. SPSS 13.0 was employed for the data analysis.
Results: The angulation of septal leaflet had preserved mobility in PAH patients, while anterior and posterior angles were decreased, demonstrating an anteroposterior dilatation of the tricuspid annulus. In PAH, the right ventricle was more dilated and hypertrophied when compared to CTEPH. LHD patients, had normalRV volumes, but the angle of the septal leaflet was decreased, when compared to the other leaflets, possible due to hypokinesis of the interventricular septum. CTEPH patients had the most decreased angulation of all leaflets possibly due to acute embolic process and pressure loading right ventricular pattern, demonstrated to CTEPH disease. Healthy volunteers had normal tricuspid pattern, independent to the RV-EF (RVEF- θs-d: r= 0.06, p=0.92) For LV disease, anterior and posterior mobility was independent to RV-EF (r=0.45, p=0.05 and r=0.32,p=0.072 respectively). The tricuspid mobility was independent to RV systolic pressure; therefore the remodeling seems to be more dependent to volume rather than pressure loading.
Conclusion: RV remodeling is different in PAH, LHD, CTEPH and normal subjects, as demonstrated with 3D and that includes the shape and mobility of the tricuspid valve.

P740 Assessment of right-ventricular size and function by real-time three-dimensional echocardiography - comparison with magnetic resonance imaging

G. Leibundgut, A. Rohner, A. Kessel, A. Bernheim, M. Zellweger, P. Buser, M. Handke. *University Hospital Basel, Basel, Switzerland*

Background and objectives: Due to the complex right-ventricular geometry, 2D-echocardiography is limited in determining volumes and ejection fraction. Using a novel software package, real-time 3D echocardiography (RT3DE) enables rapid quantitative assessment of right ventricular size and function. Aim of the study was to validate this novel technology using magnetic resonance imaging (MRI) as method of reference.
Methods: 60 Patients with normal or abnormal right ventricle (RV) due to various cardiac diseases (coronary artery disease, myocarditis, valvular heart disease, arrhythmogenic right ventricular cardiomyopathy, amyloidosis, iron overload, and connective tissue disorders) were included in the study. Patients were recruited following cardiac MRI. Acquisition of a pyramidal data volume was done by transthoracic RT3DE. Off-line reconstruction of a dynamic polyhedron model of the RV was performed based on the endsystolic and enddiastolic contours at predefined standard cutting planes. RV volumes and ejection fraction (EF) were determined and compared with MRI data. All measurements were done in a blinded fashion.
Results: Enddiastolic volumes (RVEDV), endsystolic volumes (RVESV) and stroke volumes (RVSV) measured by RT3DE were slightly lower but showed a good correlation with the values determined by MRI (Table 1). Importantly, no significant difference was found for right ventricular ejection fraction (RVEF). Bland-Altmann analysis showed moderate mean differences for RVEDV (-12±27ml), RVESV (-7±17ml) and RVSV (-6±18ml) but no significant mean difference for RVEF (0±8%).

Table 1

	RT3DE	MRI	p-Value	Correlation	p-Value
RVEDV (ml)	127±33	139±39	<0.001	0.72	<0.01
RVESV (ml)	68±26	75±26	0.004	0.79	<0.01
RVSV (ml)	58±19	64±27	0.011	0.74	<0.01
RVEF (%)	46±10	46±12	0.549	0.79	<0.01

Abbreviations for RT3DE, MRI, RVEDV, RVESV, RVSV and RVEF as indicated in abstract text.

Conclusion: RT3DE may become a time- and cost-saving alternative to MRI in the assessment of the right ventricle. Particularly, there is close agreement between the two modalities in the determination of RV systolic function.

P741 Apelin decreases myocardial injury and improves right ventricular function in monocrotaline-induced pulmonary hypertension

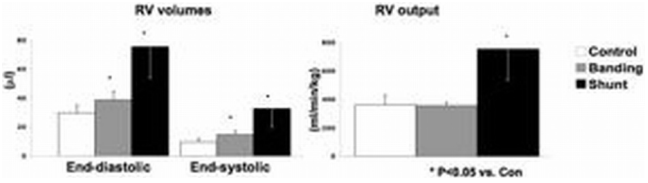
I. Falcao-Pires, N. Goncalves, T. Henriques-Coelho, D. Moreira-Goncalves, R. Roncon-Albuquerque Jr, A.F. Leite-Moreira. *Faculdade Medicina do Porto, Porto, Portugal*

We investigated the endogenous production of apelin and the cardiac and pulmonary effects of its chronic administration in monocrotaline (MCT)-induced pulmonary hypertension (PH). Male Wistar rats were injected with MCT (60mg/kg, sc) or vehicle (day 0). One week later, these animals were randomly treated during 17 days with Pyr-apelin-13 (Pyr-AP13, 200μg/kg/day, ip) or a similar volume of saline, resulting in 4 groups: SHAM (n=11); SHAM-AP (n=11); MCT (n=16) and MCT-AP (n=13). On day 25, right (RV) and left ventricular (LV) hemodynamic and morphometric parameters were assessed. Tissue and plasma samples were collected for histological and molecular analysis. Compared to SHAM, MCT group presented a significant increase of RV mass (166±1%), cardiomyocyte's diameter (40±0%), myocardial fibrosis (95±3%), peak systolic pressure (99±1%), dP/dtmax (74±1%), dP/dtmin (73±1%) and time-constant-τ (55±1%). In these animals, RV expression of apelin (-73±0%) and its receptor APJ (-61±1%) was downregulated, whereas mRNA expression of BNP (9606±198%), angiotensinogen (191±73%), ET-1 (RV: 497±7%; LV: 799±109%), plasmatic levels of apelin (104±2%) and angiotensin 1-7 (ANG-(1-7), 261±76%) were increased. Interestingly, apelin and ANG-(1-7) plasmatic levels were significantly correlated (r=0.7669, p<0.001). Chronic treatment with Pyr-AP13 significantly attenuated or normalized these changes, preventing apelin-APJ mRNA downregulation and PH-induced neurohumoral activation of several vasoconstrictors, which exacerbates apelin-APJ vasodilator effects. Therefore, apelin delayed the progression of PH, RV hypertrophy and diastolic dysfunction. Together, these observations suggest that the apelin-APJ system may play an important role in the pathophysiology of PH, representing a potential therapeutic target as it significantly attenuates RV overload and PH-induced neurohumoral activation.

P742 Right ventricular response to abnormal loading conditions in mice

B. Bartelds[1], A. Smit-Van Oosten[1], J. Takens[1], M. Nederhoff[2], L.J. De Windt[2], W.H. Van Gilst[1], R.M.F. Berger[1]. *[1]University Medical Center, Groningen, Netherlands; [2]Julius Center - University Medical Center Utrecht, Utrecht, Netherlands*

Purpose: Right ventricular (RV)dysfunction is an important determinant of long-term outcome of patients with congenital heart diseases, associated with abnormal ventricular loading conditions (pressure and/or volume load). The pathophysiological mechanisms are yet poorly understood. We aimed to characterize two mice models inducing different types of RV overload.
Methods and Results: We developed a mouse model of RV pressure load by banding of the pulmonary artery (Band) and of volume load by an aorto-caval shunt (Shunt). Exercise capacity, measured by voluntary cage-wheel exercise before and 4 wks after surgery, was reduced in Band-mice, whereas it was unchanged in Shunt-mice (Con vs. Band vs.Shunt: -100±64 vs. -374±255* vs. -150±174 min., *p<0.05 vs. Con).
Cardiac MRI (9.4T-scanner) 4 wks after surgery revealed increased enddiastolic and-systolic RV volumes with preserved RV-stroke volume, and output in Band-mice (Figure). Shunt-mice also showed increased RV-volumes, but in contrast to Band-mice, increased RV-stroke volume and -output,while RV ejection fraction was decreased (Con vs. Band vs. Shunt:67.9±4.3 vs. 61.9±5.8 vs. 58.0±8.6*). At autopsy, Band- and Shunt-mice showed similar degrees of severe RV-hypertrophy, expressed as RV/BW (Con vs. Band vs. Shunt: 0.88±0.17 vs. 1.61±0.25* vs. 1.49±0.27*). Expression of of modulatory calcineurin interacting protein, indicating Calcineurin-mediated hypertrophy, was higher in Band than in Shunt-mice.



MRI-derived RV volumes

Conclusions: Pressure vs. volume overload of the RV in these mice models induced similar degrees of RV-hypertrophy, but marked differences in functional characteristics. These mice models, with rodent-MRI and exercise-testing, allow for further unraveling the functional and molecular adaptation of the RV to different types of abnormal loading.

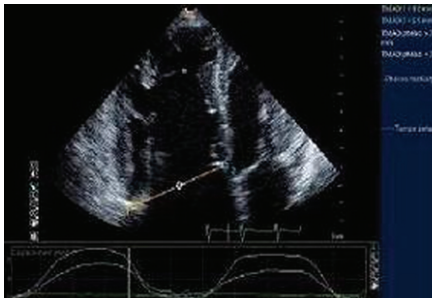
P743 Interest of tricuspid annular displacement in evaluation of right ventricular ejection fraction

T. Hugues[1], F. Lemoigne[2], D. Ducreux[2], F. Berthier[1], N. Saoudi[1], P. Gibelin[2]. *[1]The Princess Grace Hospital Centre, Monaco, Monaco; [2]CHU de Nice - Hopital Pasteur, Nice, France*

The ultrasound assessment of right ventricular (RV) function is often sub-optimal. The range of excursions of the mitral or tricuspid annulus measured in mm by 2D or TM mode echocardiography has been shown to reflect the systolic function of both ventricles.

Methods: We studied a new technique based on a tissue tracking algorithm that is ultrasound beam angle independent for automated detection of tricuspid annular displacement (TAD) (QLAB, Philips Medical Imaging). Twenty six patients (pts) with pulmonary arterial hypertension (n= 13), heart failure (n= 9), valvulopathy (n= 3) or myocarditis (n= 1) were reffered for magnetic resonance imaging (MRI) and underwent a complete transthoracic echocardiography (TTE). MRI was performed on a 1.5 T MR scanner. MRI RV ejection fraction (RVEF) was correlated by linear regression with TAD, peak systolic tricuspid annular velocity (Sa) and RV fractional area change (FAC). Sixteen pts (61.5%) exhibited right ventricular systolic dysfunction (RVEF $<$ 40%). TTE was performed in 44 healthy subjects in order to assess normal TAD value.

Results: In the pts group, MRI RVEF was positively correlated with TAD (R^2= 0,65; p$<$ 0,0001), Sa (R^2= 0,56; p$<$ 0,0001) and FAC (R^2= 0,39 p= 0,0025). The strongest relation was observed with TAD. A value of TAD$<$ 14 mm predicted right ventricular dysfunction with a sensitivity of 87.5% and a specificity of 90%. All healthy subjects exhibited TAD values exceeding this cut-off point (mean 16,9±1,64 mm, range 13,3 to 24,8 mm).



Apical 4chamber view with TAD in PAH pt

Limitations: the echocardiographic and MRI parameters were not obtained simultaneously but at an interval of 24 hours.

Our study is the first to correlate TAD with MRI RVEF. We conclude that TAD provides a simple, rapid, and non-invasive tool for assessing right ventricular systolic function.

P744 Right ventricular function angiographic assessment

S. Estrada Gomez, I. Santos, J. Martin Moreiras, I. Cruz-Gonzalez, J. Rodriguez-Collado, M.J. Ruiz, M. Diego, M. Cascon, J.M. Gonzalez-Santos, C. Martin-Luengo. *Hospital Universitario de Salamanca, Salamanca, Spain*

Purpose: To describe a new angiographic method to assess right ventricular systolic function (RVSF) using three parameters analogous to the systolic displacement of the tricuspid annular (TAPSE) obtained by echocardiography.

Methods: Retrospective observational study; 80 consecutive patients were included (60 with mitral disease and 40% with aortic disease) undergoing left and right cardiac catheterization before valvular replacement (mean age 71±8.5y/o; 67% female). The OSIRIS DICOM visualization program was used to measure the tricuspid annular systolic displacement (SDTA) in 3 levels: superior (S), medium (M) and inferior (I). Tricuspid annular displacement area (TADA) and length in diastole (TALD) and systole (TALS) were measured. Correlation with hemodynamic and angiography parameters was analyzed; cardiac index (CI), mean pulmonary pressure (MPP), tricuspid (TR) and mitral (MR) regurgitation angiography degree, size left auricle (LA), right and left ventricle ejection fraction (RVEF and LVEF).

Results: TADA was 9,2±4,9cm^2; the S, M and I SDTA were 22±14, 25±16 and 24±19mm respectively; TALD and TALS were 53,4±11 and 43±9mm respectively. There was significant relation between TADA and RVEF (R 0.6 p$<$ 0.001), CI (R 0.25 p$<$ 0,003) and MPP (R-0,3 p$<$0,003). Also TALD and TALS were related significantly to the TADA and size of LA. There was no correlation between TADA with LVEF, TR or RM.

Table 1

	MPP $>$ 25mmHg	MPP $<$25 mmHg	p value
TADA (cm^2)	7,6±3,6	11,2±5,5	0,001
SDTA sup (mm)	19±14	26±13	$<$0,03
SDTA med (mm)	21,5±13,5	29±18	$<$0,04
SDTA inf (mm)	22±19	27,5±21	0,2
RVEF (%)	39±9	48±11	0,001

Conclusions: We have described a new angiographic method to evaluate the RVSF. The TADA and the SDTA (S) and (M) showed significant relation with MPP and RVEF. These results should be validated and the clinical prognostic value must be determined.

P745 Echocardiographic predictors of long-term survival in adults with pulmonary hypertension

R.A. Krasuski[1], S.A. Hart[1], A. Wang[2], J.K. Harrison[2], T. Bashore[2]. *[1]Cleveland Clinic, Cleveland, United States of America; [2]Duke University Medical Center, Durham, United States of America*

Background: Echocardiography is an important diagnostic tool for the assessment of patients with pulmonary hypertension (PH). Complex measurements of right ventricular (RV) function have been correlated with clinical outcome. Whether simple and commonly collected measures have similar prognostic implications is unknown.

Methods: Transthoracic echocardiograms of 168 patients referred for invasive evaluation of PH at two U.S. academic medical centers were reviewed. Echo measurements were graded on a continuous scale from 1 (trivial) to 4 (severe). Follow-up echocardiograms were available for 119 patients (70%) and the SSDI was used to determine survival.

Results: Demographic differences between survivors and decedents during the follow-up period included age (53.0±14.2 vs. 61.8±14.9 years, p=0.001), function class (34/52/14 vs. 15/54/31, % class II/III/IV, p=0.02) history of atrial fibrillation (9.5 vs. 21.4%, p=0.04) and oxygen saturation (91.7±5.4 vs. 89.3±7.3%, p=0.04). There was a median interval of 1.7 years between echos. Survival was assessed at a median interval of 2.0 years during which 42 patients died (25%). Univariate analysis demonstrated that decedents exhibited greater right ventricular (RV) dilation (p=0.002), greater RV dysfunction (p=0.02), more tricuspid regurgitation (p=0.001) and higher estimated RV systolic pressure (p=0.008) at baseline; and these differences were magnified at follow-up echo (all p$<$0.001). Increases in RV size (p=0.03), RV dysfunction (p=0.04) and RV systolic pressure (p=0.03) also appeared to predict death. Proportional hazards analysis demonstrated that RV indices such as RV size and change in RV size carried hazard ratios between 2 and 3 during the follow-up period (Table).

Proportional hazards analysis

Variable	Hazard Ratio	95% CI	p-value
Age (year)	1.1	[1.0 - 1.1]	$<$0.001
NYHA (class IV)	1.8	[1.1 - 2.8]	0.03
Combination PH therapy	0.2	[$<$0.1 - 0.7]	0.01
Baseline RV size (grade)	3.3	[1.6 - 7.2]	0.001
Change in RV size (grade)	2.6	[1.3 - 5.5]	0.004

Conclusions: Standardly collected echo measurements at baseline and serially appear to independently predict long-term survival in PH patients.

P746 Three-dimensional echocardiography in pulmonary arterial hypertension: echocardiographic validation of a new method for right ventricular volumes quantification

J. Silva Marques, S. Martins, A.G. Almeida, A. Nunes Diogo, S. Ribeiro, A. Feijao, C. Bastos, M.G. Lopes. *Hospital Santa Maria, Lisbon, Portugal*

Purpose: Pulmonary arterial hypertension (PAH) is often difficult to diagnose and is characterized by the progressive increase in pulmonary vascular resistance leading to right ventricular (RV) failure and death. The prognosis of PAH patients seems to be related mainly to RV dimensions and function rather than to pulmonary artery pressure. The gold standard for the assessment of RV function is the summation-of-disks method by short axis cardiac magnetic resonance imaging. Three dimensional echocardiography is an alternative for RV volume assessment but relies on anatomic assumptions made by semi-automated border detection software. Our aim is to investigate whether a new 3D echocardiography method for right ventricular volume and function assessment relates to validated echocardiographic parameters.

Methods: Sixteen patients with the diagnosis of PAH, were studied with M mode, 2D, Doppler and 3D echocardiography. Nine short axis views of the right ventricle were obtained from 3D echo full volume acquisition. The first slice was positioned at the tricuspid valve ring level and the last on RV apex. The RV long axis dimension was used to determine the slice interval and volumes were calculated by the summation of disc areas multiplied by the slice thickness. The RV volumes obtained by this method were compared to those obtained by semi-automated RV volume calculation software and to bidimensional parameters of RV function recommended by ESC and ASE.

Results: Good quality 3D images for 9-slice post-procession were obtained in all patients with PAH. Mean diastolic volume (DV) determined by the short-axis echocardiographic method was 158±65mL and showed linear correlation to 3D semi-automated DV (R2=0,58; p$<$0,01) and correlated to M Mode RV diameter and 2D RV area (R2=0,58; p$<$0,01, and R2=0,73; p$<$0,01). Mean systolic volume obtained was 106±49mL and also correlated to 3D semi-automated volume, M Mode and 2D determinations (R2=0,53; R2=0,58; R2=0,79; p$<$0,01). RV Ejection

Fraction (EF) correlated to 3D semi-automated RVEF and tricuspid annular plane systolic excursion (P<0,01 and p=0,03).
Conclusion: Right ventricular volume quantification by the short-axis method is fiseable in patients with pulmonary arterial hypertension. Volumes determined by this technique have good correlation to those obtained by 3D semi-automated method and to MM and 2D parameters of ventricular function. These results suggest that three dimensional echocardiography may have an important role in the evaluation of RV function of PAH patients.

P747 D-dimer indicates patients with right ventricle overload in acute pulmonary embolism

M. Kostrubiec, A. Labyk, J. Pedowska-Wloszek, S. Pacho, A. Hrynkiewicz, B. Lichodziejewska, K. Kurnicka, P. Dul, A. Wojciechowski, P. Pruszczyk. *Medical University of Warsaw, Warsaw, Poland*

Objective: Elevated D-Dimer level is highly sensitive for acute pulmonary embolism (APE). It can be expected that high intrapulmonary thrombi burden can potentially result in higher d-dimer concentration and right ventricular overload. Therefore, we assessed the association of D-dimer levels with right ventricle (RV) overload in patients with acute pulmonary embolism (APE).
Material and Method: We evaluated 160 consecutive pts (58M, 102F, aged 64±18 years) with APE proven by spiral CT. On admission blood samples were collected for d-dimer assay and echocardiography was performed to assess the RV function.
Results: In 109 (68%) of patients RV overload (RV+) defined by enlarged RV and elevated TRPG>30mmHG was found on echocardiography. D-dimer concentrations were significantly higher in RV+ than in RV- group (5820 pg/ml (range: 600-30000) vs median 2920 pg/ml (range: 288-12770), p<0.02). Area under the ROC curve in prediction of RV+ for d-dimer was 0.671 (95%CI: 0.578-0.755). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of RV overload prediction for d-dimer >4300 pg/ml were 71%, 62%, 80% and 50%, respectively. Moreover, d-dimer concentration correlated with echocardiographic measurements: LV/RV ratio (r=0.49, p<0.001), acceleration time of pulmonary ejection (r=-0.22, p<0.05) and presence of RV hypokinesis (r=0.24, p<0.01).
Conclusion: D-Dimer levels >4300 pg/ml are associated with right ventricular overload and its concentration correlates with echocardiographic parameters of RV function in acute pulmonary embolism.

P748 Right ventricular speckle tracking in right and left heart disease. Correlation with conventional two dimensional echocardiographic indices

J. Grapsa, D. Dawson, S. Sulemane, L.S.G.E. Howard, J.S.R. Gibbs, P. Nihoyannopoulos. *Hammersmith Hospital, London, United Kingdom*

Purpose: The two dimensional (2D) speckle tracking (ST) is a new technique for the regional encoding of the ventricle and possibly it can be applied to the right ventricle (RV). Furthermore, ST is less volume dependent when compared to the conventional strain. The aim of this study was the application of RV ST to three different groups of patients and its correlation with conventional 2D echocardiographic indices.
Methods: Three groups of patients were studied: 51 patients with pulmonary arterial hypertension (PAH) (age: 45±16 years), 45 patients with 3 vessel disease (left heart disease-LVD – age: 62±15.3 years) and 29 normal subjects (age: 53±17.4 years). Patients with arrhythmias were excluded from the study. All the patients underwent (1) the conventional 2D echocardiographic examination and measurement of the right ventricular systolic pressure (RVSP) from the tricuspid regurgitant velocity and the right atrial pressure, and the tricuspid annular plane systolic exertion (TAPSE), (2) RV dedicated ST, applied to the apical four chamber view – right systolic strain and the peak S wave from basal, mid, apical lateral RV wall were recorded. Data were analysed with SPSS 13.0
Results: In PAH patients, there was a significant degree of correlation between RVSP and RV strain rate of the RV free wall (lateral) (Mid lateral: Strain-RVSP: r=-0.52, p<0.001) while S wave correlated significantly with RVSP, only from the basal lateral wall (Basal lateral: S-RVSP: r= -0.66, p<0.001). S wave did not correlate with RVSP in LVD patients and normals, while on the contrary RV strain rate correlated with RVSP in LVD patients (r=-0.62, p<0.001). The three groups were statistically different when compared with paired T-test: PAH-normals: (RVstrain basal septal: (-16.2)±(-7.7) vs (-22.2)±(-6.8), p=0.0026, RVstrain basal lateral: (-16)±(-6.8) vs (-19)±(-8.1), p=0.013).
TAPSE correlated with S wave of the basal lateral wall in PAH and LVD patients (PAH: r = 0.72, p<0.01, LVD: r =0.67, p=0.02)
Conclusions: – Interventricular dependency affects the septal strain in RV pressure overload
– There is velocity gradient from the base to the apex of the right heart consistent with longitudinal contraction.
– TAPSE correlates with S wave of the RV free wall
– Speckle tracking and especially RV strain rate is less volume dependent than TDI waveforms, with a better correlation with pulmonary arterial pressures.

P749 The assessment of right ventricular function by tissue Doppler imaging in patients with end-stage idiopathic pulmonary fibrosis referred for lung transplantation

J. Nowak[1], W. Streb[1], D. Jastrzebski[2], P. Rozentryt[1], M. Kalinowski[1], B. Hudzik[1], L. Polonski[1], T. Kukulski[1]. *[1]Silesian Center for Heart Diseses, Zabrze, Poland; [2]Department of Lung Diseases and Tuberculosis, Zabrze, Poland*

Introduction: The impact of severity of idiopathic pulmonary fibrosis (IPF) on the deterioration of right ventricular (RV) function is not well established.
The aim of the study was to assess RV systolic function in patients with end-stage IPF referred for lung transplantation (LT) using conventional echocardiography and tissue Doppler imaging (TDI).
Methods: Forty five consecutive patients with end-stage IPF and mild-to-moderate pulmonary hypertension referred for LT were assessed. Twenty of them (mean age 46.6±12 years) fulfilled the ATS/ERS criteria for LT: mean forced vital capacity 1.4±0.8L, mean diffusing capacity for carbon dioxide<50% of predicted (active group). The other 25 patients (mean age 48.5±12 years) who did not meet these criteria for LT were placed on the waiting list. Conventional echocardiography and TDI were used for the evaluation of RV and LV systolic function. TDI parameters of RV longitudinal function including peak myocardial velocity (VEL), time to peak velocity (TVEL), peak strain (S) and strain rate (SR) were evaluated for the inflow and outflow RV tract and medial and apical segments of interventricular septum (IVS) during ejection period.
Results: Patients in active group had significantly lower values of tricuspid annulus plane systolic excursion (4.3±3.3 vs 20.6±6.2 mm, p=0.01) and shorter acceleration time (70.3±23.3 vs 96.9±12.4 ms, p=0.01). No differences were found for the other parameters of RV function in conventional echocardiography. Among TDI parameters peak SR of the RV outflow tract was significantly less negative and TVEL in the medial septal segment was significantly longer in active group compared to waiting group (-1.1±0.3 vs -3.21±1.2s-^{1}, p=0.03 and 159.22±38.1 vs 129.94±47.9 ms, p=0.01 respectively).
Conclusions: The severity of idiopathic pulmonary fibrosis triggers the impairment of RV systolic function which could be assessed by conventional echocardiography and TDI.

P750 Measurement of right ventricular size and function by real-time three-dimensional echocardiography: validation against magnetic resonance and comparison with two-dimensional and M-mode measurements

L. Badano, E. Zakja, M.T. Grillo, R. Onut, D. Muraru, D. Ermacora, P. Gianfagna, P.M. Fioretti. *University Hospital, Department of Cardiopulmonary Sciences, Udine, Italy*

Background: Assessment of right ventricular (RV) size and function is hampered by its complex shape. Proposed estimates of RV size and function (2D diameter at basal level, EDDbas; 2D diameter at mid-cavity level, EDDmid; end-diastolic cavity area, EDA; end-systolic cavity area, ESA; fractional area change, FAC; and tricuspid annular plane systolic excursion, TAPSE) have been validated only against questionable angiographic calculations based on geometric assumptions about RV shape. Three-dimensional echocardiography (3DE) overcome limitations of 2D echo and angiography in that image planes are precisely defined and geometry assumptions unnecessary. Limited data exist about the accuracy of 3DE in the assessment of RV volumes and the relationship of M-mode and 2D measurements of RV size and function with 3DE RV volumes and ejection fraction remain to be assessed.
Method: 13 patients (validation group) underwent 3DE and magnetic resonance imaging (MRI) 73±43 min apart. In addition, 58 patients (35 M, 59±17 years), 12 control subjects and 46 with various heart diseases (study group) were studied at the same visit with 2D and 3DE (Vivid 7 Dimension, GE Healthcare, Horten, N). 2D measurement of RV size and function were performed following EAE/ASE guidelines, and RV volumes and ejection fraction were calculate using the 4D RV function analysis software (TomTec, Unterschleissheim, D).
Results: In the validation group, RV end-diastolic volume (EDV) was 78±18 ml at 3DE and 81±9 ml at MRI (r= 0.97, limits of agreement -4, + 9 ml), RV end-systolic volume (ESV) was 37±12 ml at 3DE and 39±8 at MRI (r= 0.98, limits of agreement -3, +8 ml). Study group patients showed a wide range of RV EDV (49 ml - 222 ml) and ejection fractions (21% - 70%). RV EDV (89±32 ml) showed significant (all p<0.0001) but weak relationship with EDDbas (r= 0.53), EDDmid (r= 0.48) and EDA (r= 0.59). RV ESV showed a significant but weak correlation with ESA (r= 0.65, p<0.0001). Relationship of RV ejection fraction with FAC and TAPSE were very weak (r= 0.32, p= 0.019 and r= 0.30, p= 0.029, respectively). In pts with TAPSE< 15 mm (n= 8), RV ejection fraction ranged from 24% to 60%.
Conclusions: 3DE provides an accurate measurement of RV volumes in comparison to MRI. Conversely, due to the complex structural geometry of the RV, M-mode and 2D parameters provides only a rough estimate of actual RV size and function that prevents their use for clinical decision making in the single patient.

P751 Right and left ventricular and atrial function assessed by Speckle Tracking in patients with arrhythmogenic right ventricular cardiomyopathy and in their relatives

S. Comenale Pinto, R. Ancona, P. Caso, C. Cavallaro, S. De Vivo, F. Vecchione, A. D'Onofrio, V. Di Palma, R. Calabro'. *Ospedale Vincenzo Monaldi, Naples, Italy*

Backgraund: The evolution of arrhythmogenic right ventricular cardiomyopathy (ARVC) is more diffuse RV involvement and, sometimes, left ventricular (LV) abnormalities, that may result in heart failure.
Aim of the study: is to evaluate the potential utility of two-dimensional (2D) Strain-Strain rate (S-SR) echocardiography to quantitatively assess RV and LV function in ARVC and its potential role in asymptomatic family members, with apparently normal right ventricles.
Methods: we studied 70 subjects: 25 patients (pts) with ARVD, diagnosed by task force criteria, 25 healthy controls and 20 ARVD family members with apparently normal RV at conventional echocardiography. By echocardiography System Seven GE with TVI function we measured LV and RV ejection fraction (EF%), LV diameters and volumes, RV dimension at level of apex, outflow tract and infero-basal segment, near tricuspidal valve. By DTI we measured velocity of early (E') and late (A') diastolic wave and systolic wave (S) at level of tricuspidal annulus of free wall of RV. 2D acquisitions were analyzed to measure longitudinal peak systolic ventricular 2D S and SR in apical 4 and 2-chambers views, at level of LV segments (4 basal, 4 mid, 4 apical) and RV segments (1 basal, 1 mid, 1apical).
Results: RV dimensions were bigger in all pts with ARVC. RV diameters were normal in all family members. At TVI of tricuspidal valve all pts with ARVC had significantly higher prevalence of abnormal relaxation than controls (ratio E'/A'=0,73 vs E'/A'=1,2) and in 16/20 ARVD family members, too. RV peak systolic 2D SR and S were significantly lower in pts with ARVD compared with controls, respectively (SR= -1,37±0,37 vs -2,37±0,51 s^{-1}, $p<0.001$; S=-12,45±4,4% vs -26,6±8,1%, $p<0.001$). Also LV peak systolic 2D SR (-1,01±0,21 vs -1,53±0,49 S-1, $p<0.003$), and LV peak systolic 2D S (-15,2±4,3% vs -20,59±4,47%, $p<0.003$) were significantly lower in pts with ARVC compared with controls, even if LV diameters and LVEF were normal. RV systolic 2D S (-18,5±4,8%, $p<0.002$) and SR (-1,54±0,4, $p<0.002$) were significantly lower than in controls, even in 14/20 family members with apparently normal RV by conventional echocardiography, while no significant differences were found for LV S (-19,59±5,15%) and SR (1,49±0,38 s^{-1}) in family members than in controls.
Conclusions: RV 2D S and SR were significantly lower in ARVC pts compared with controls. 2D S and SR imaging enables to show early LV dysfunction in these pts, when standard echocardiography doesn't show any impairment. It may have potential clinical value in the assessment of ARVC asymptomatic family members.

P752 Follow up of right ventricular remodeling in idiopathic pulmonary arterial hypertension with 3D echocardiography and cardiac MRI

J. Grapsa, H. Pavlopoulos, D. Dawson, P. Nihoyannopoulos. *Hammersmith Hospital, London, United Kingdom*

Purpose: The aim of the study was the follow up of RV remodeling in idiopathic pulmonary arterial hypertension (IPAH) with two dimensional (2DE), real time three dimensional (3DE) echocardiography and cardiac magnetic resonance scan (CMR).
Methods: Thirty-one IPAH patients were examined with 2DE, 3DE and CMR every 6 months, for a total follow up period of 24 months. Patients were divided into two groups: (1) 15 patients who were newly-diagnosed and therapy was initiated after the first study, and (2) 16 patients who were diagnosed more than 6 months ago. All patients had a right heart catheterization at baseline to make the diagnosis. RV end-diastolic (EDV) and end-systolic (ESV) volumes, stroke volume (SV) and ejection fraction (EF) were calculated with both 3DE and CMR. A six-minute walk test (6MWT) was performed every 6 months. Bland-Altman analysis was employed for agreement of methods and paired t-test for the assessment of significant difference between the groups. Analysis was conducted in SPSS 13.0.
Results: All patients had a baseline right heart catheterization, with a mean pulmonary capillary wedge pressure (PCWP): 9.2±2.8 mmHg and mean pulmonary vascular resistance (PVR): 12.6±3.4 Wood units and mean RV systolic pressure (RVSP): 78±12.1 mmHg. 21 patients (67.7%) were on bosentan, 9 patients (29%) on sildenafil and 1 patient (3.2%) on treprostinil infusion. Patients from group (1) demonstrated a decrease in EDV the first six months (125±32.6 ml vs 107±21.3 ml, $p<0.001$) with CMR, but there was a further increase of ESV (56.7±17.8 ml vs 68.3±10.2 ml, p=0.002) with a concomitant decrease in EF (39.2±7.8% vs 34.1 vs 5.4%, $p<0.001$). These patients demonstrated an increased distance in the 6MWT after initiation of therapy (267±43 m vs 335±48 m, p=0.01) Patients from group (2) demonstrated a gradual increase in EDV, ESV, SV and a decrease in EF within 24 months: EDV: 145±45 ml vs 189±32 ml (after 24 monhs), $p<0.001$), as measured with CMR. The distance of 6MWT was stable overall (303±52 m vs 314±47 m, p=0.67). RV volumes, SV and EF demonstrated a significant degree of agreement between 3DE and CMR, throughout the follow up (EDV3DE-CMR (6 months): p= 0.87, $p<0.001$, mean bias: -23.8 ml, SD: 26.7 ml).
Conclusions: IPAH patients may decrease their RVEDV with initiation of therapy and this is possibly connected to increase of functional capacity, although ESV increases and EF decreases. The natural history of the disease will include further dilatation of the right heart, accompanied with gradual failure as demonstrated by the decreased EF.

P753 Impaired preoperative right ventricular function is associated with increased postoperative intensive care unit length of stay in patients with mitral regurgitation

A. Chrustowicz, A. Gackowski, J. Sadowski, W. Piwowarska. *Krakowski Szpital Specjalistyczny im. Jana Pawlall, Krakow, Poland*

Introduction and aims: Right ventricular function is a predictor of poor late outcome in patients with mitral regurgitation and left ventricular dysfunction (Eur Heart J 2007;28:2510–6). The aim of this analysis was to assess the relation between preoperative right heart parameters and perioperative outcome in patients with mitral regurgitation.
Methods: Right ventricular (RV) function was echocardiographically assessed by determining the tricuspid annular plane systolic excursion (TAPSE). 40 patients were included (50% men, aged 61±9 years). Preoperative NYHA class was 2.6±0.4, mean right ventricular end-diastolic diameter (RVEDD) was 28.7±4mm, TAPSE was 20±4mm, mean right ventricular systolic pressure (RVSP) was 38±13mmHg, left ventricular end-systolic diameter (LVESD) was 43.5±11mm, left ventricular end-diastolic diameter (LVEDD) was 60±11mm, left ventricular end-diastolic volume (Simpson) was 155±47ml, LVEF was 55±11% and mean regurgitation fraction was 58%. Median intensive care unit (ICU) stay was 2 days (range 1-10), mean TISS-28 was 623±293 and mean NEMS 151±85. The cause of prolonged ICU stay was hemodynamic compromise requiring inotropic support; patients with rethoracomy, stroke, infection or significant bleeding were excluded.
Results: All patients survived the operation. Preoperative RV dysfunction, defined as TAPSE<22 mm had 66.6% of the patients. ICU length of stay was significantly higher in patients with preoperative RV dilatation (p=0.01), higher RVSP (p=0.01) and/or RV dysfunction (p=0.03); other predictors for the ICU length of stay were preoperative NYHA (p=0.01), LVEF (p=0.01), forward stroke volume (p=0.001), left ventricular dp/dt (p=0.01) and RF (p=0.01).
Conclusion: Preoperative right heart parameters are significant determinants of the perioperative hemodynamic status in patients with mitral regurgitation.

ATRIAL FIBRILLATION: FOLLOW UP

P754 A novel double balloon technique for atrial fibrillation: cryoablation of pv la junction with occlusion of ipsilateral pulmonary artery

K.H. Kuck[1], N. Coulombe[2], M. Dubuc[3], P. Guerra[3], F. Ouyang[1]. *[1]Asklepios Klinik. St. Georg, Hamburg, Germany; [2]CryoCath Technologies Inc., Montreal, Canada; [3]Montreal Heart Institute, Montreal, Canada*

Background: Balloon cryoablation has been introduced for pulmonary vein isolation (PVI) to treat AF. Reducing blood flow from the PVs may affect treatment by increasing circumferential tissue-balloon contact and decreasing heat load around the balloon. This may further improve rapid and permanent PVI. In this study, the effects of occluding the ipsilateral pulmonary artery (PA) to reduce PV blood flow during balloon cryoablation were investigated.
Methods: An occlusion balloon was inflated at the PA of canines (n=7) and hemodynamic parameters (pulmonary artery pressure (PAP), arterial pressure (AP), right atrial pressure (RAP), cardiac output (CO), pulmonary capillary wedge pressure (PCWP) were measured before, during and after balloon cryoablation of the PV-LA junction (Arctic Front 23mm, CryoCath Technologies Inc.,). In addition to the standard inner balloon temperature, 4 thermocouples (TC) recorded temperature changes during cryoablation. These were positioned within the outer layer of the balloon, one in each quadrant, to measure changes at the tissue-balloon interface. Assessment of PV conduction was also performed pre-and post-treatment.
Results: Occlusion of either PA did not affect cardiac function; during the procedures, 100% (7/7) of animals were hemodynamically stable. A significantly greater mean PAP (mmHg) was noted between baseline and post-treatment values (12.5±1.0 vs. 13.8±1.6, p=0.02); this was not seen in other measured parameters (AP (mmHg): 82±17.4 vs. 73.6±9.3, p=0.35; RAP (mmHg): 8±0.8 vs. 7.8±1.3, p=0.81; CO (L/min): 4.1±1.3 vs. 4.7±1.8, p=0.29; PCWP (mmHg): 9.1±1.0 vs. 10.4±1.4, p=0.08). ECG activity was not adversely affected during procedures. Steady-state inner balloon temperature for all ablations (n=13) averaged -64±9.6°C; temperatures from the 4 TCs (n=43) averaged -50±13.1°C. Complete acute bidirectional block was obtained in 100% (13/13 PVs) after a single ablation. No complications were noted.
Conclusion: Occlustion of the ipsilateral PA can be safely performed during balloon cryoablation. This technique may theoretically have the potential to achieve permanent PVI

P755 Cost-effectiveness model of Implantable Cardiac Monitors (ICM) for patients treated with radiofrequency catheter ablation for atrial fibrillation (PAAF)

J.L. Merino[1], J.M. Rodriguez-Barrios[2], M. Brosa[3], S. Tsintzos[4]. [1]Hospital Universitario La Paz, Madrid, Spain; [2]Medtronic Iberica, Madrid, Spain; [3]Oblikue Consulting, Barcelona, Spain; [4]Medtronic International Trading Sarl, Tolochenaz, Switzerland

Objectives: ICM is aimed at detecting arrhythmias and their long term trending. Since long-term continuous AF monitoring is not yet used in patients with PAAF in Spain, its implications in the management of these patients (including possible OAC discontinuation) are still unknown. This study aimed to model the cost-effectiveness of OAC management using ICMs in patients treated with radiofrequency catheter ablation for atrial fibrillation (PAAF) in Spain.
Methods: A Markov model was built to simulate the outcomes and costs of Standard of Care (SOC, traditional intermittent 24H monitors) and continuous AF monitoring with an ICM. Efficacy data was obtained from clinical studies showing that ICMs were able to detect asymptomatic episodes in AF patients, thus facilitating an optimized disease management that may reduce long-term complications. The risks of stroke, adverse events management and utility figures where taken from international literature; Local Spanish costs where used to model 5-years, 10-years and lifetime clinical and economic consequences of PAAF. Expert opinion allowed to define eventual treatment pathways when ICM is used. Costs and effects were discounted at 3%. Different sensitivity analysis will test the influence of main model parameters in study results.
Results: Model results show that the continuous long-term AF monitoring with ICMs of PAAF patients aged 50 may be associated to a gain of 0.145, 0.35 and 2.87 QALYs at an extra cost of 5,870 €, 5,864 € and 6,233 €, showing corresponding iCERs of 40,610 €, 16,630 € and 2,173€ per QALY gained (at 5-years, 10-years and lifetime analyses respectively).
Conclusions: The preliminary results of this study show that ICMs may improve PAAF outcomes but extra healthcare costs have to be considered. The inclusion of quality of life gains which may be associated with a reduction of patients' uncertainty regarding their disease may improve the economic value of this novel strategy using AF monitoring systems. Further research is needed to test different assumptions regarding treatment pathways and long-term consequences of a better diagnosis of AF recurrences in PAAF patients.

P756 His bundle pacing. A new option for no option patients, not suitable for or after unsuccessful AF ablation, low ejection fraction and narrow QRS

P. Dabrowski[1], E. Kozluk[2], P. Stefanczyk[1], A. Kleinrok[1], G. Opolski[2]. [1]The Pope John Paul IInd Hospital, Zamosc, Poland; [2]Medical University of Warsaw, Warsaw, Poland

Atrial fibrillation in patients with low left ventricle ejection fraction (EF) diminishes already poor cardiac output. For this reason restoration of sinus rhythm is the best choice treatment. However it fails sometimes. In patients with LBBB or wide QRS - CRT combined with A-V nodal ablation may be an option, but there was no good option for patients with narrow QRS.
Purpose: was to assess patients with low EF, after unsuccessful AF ablation, or disqualified from AF ablation, candidates to permanent ventricular pacing and a-v nodal ablation due to tachycardiomyopathy or tachy-bradycardia syndrome refractory to medical treatment.
Methods: 11 patients mean age 69 years (4 female), with EF <45% after unsuccessful AF ablation or disqualified from pulmonary vein ablation (long AF time, enlarged atria and advanced age) underwent the procedure. Mean observation time was 5 months. All patients had His bundle electrode and a backup electrode screwed in a septal region of right ventricle implanted. Patients were tested on spiroergometry before and three months after the procedure. Also an echo parameters were collected, and ecg QRS compared.
Results: majority of patients improved VO2 max: mean value 11,8 vs 15,8ml/kg*min, four of them did extremely well 8.68 vs 17.55 ml/kg*min. Three did not improve: 16,7 vs 13.6ml/kg*min, however none deteriorated clinically. Echo measurements also did not deteriorated: LV diameter 59.6/48 vs 56.4/45mm, EF 36,7 vs 43,6%, LA 51 vs 44.8mm. QRS did not differ before and after implantation+ ablation: 115ms vs 113ms and remained unchanged during observation. There were no complications related to implantation.
Conclusions: Direct His bundle pacing together with a-v nodal ablation may be used in patients not suitable for, or after unsuccessful AF ablation as an option for treatment. It seems to improve both functional and structural measurements. Further studies on a larger group of patients are necessary to validate this treatment.

P757 Right ventricular rapid pacing in cryoballoon catheter ablation of atrial fibrillation

K.J. Chun, A. Fuernkranz, A. Metzner, I. Koester, B. Schmidt, T. Zerm, R. Tilz, F. Ouyang, K.H. Kuck. *Asklepios Klinik. St. Georg, Hamburg, Germany*

Background: Cryothermal energy (CTE) ablation via a balloon catheter (Arctic Front, Cryocath™) represents a novel straight forward technology for acute PV isolation (PVI). CTE balloon lesion formation primarily depends on local tissue contact which is modulated by left atrial (LA) and PV blood flow. We tested the hypothesis of whether right ventricular rapid pacing (RVRP) induced reduced LA/PV blood flow would (1) modulate balloon temperature curves (2) be safe in patients (pts) with paroxysmal atrial fibrillation (PAF).
Methods: After double transseptal punctures one Lasso catheter (Biosense Webster) and the cryoballoon catheter using a steerable sheath were inserted into the left atrium (LA). PV angiographies and ostial Lasso recordings were obtained from all PVs. RVRP was performed using a non-steerable catheter placed in the right ventricular apex (RVA). To exclude the impact of different cryoballoon positions, only freezes with identical balloon position were included in the analysis. Systemic arterial blood pressure and balloon temperature were constantly recorded. Absolute minimal balloon temperature [°C], temperature slopes (time in [s] to reach 80% minimal temperature; dT/dt), area under the curve [AUC] and systemic blood pressure [mmHg] were compared (group I: with RVRP vs. group II: without RVRP).
Results: RVRP (mean duration: 55±7s) was performed in 11 consecutive pts (41 PVs, mean age: 58±9 years, LA size: 44±6 mm, normal ejection fraction, no structural heart disease, hypertension: n=2 pts). In 10/41 PVs the cryoballoon could be positioned in the identical location documented by fluoroscopy allowing comparative analysis. RVRP (mean pacing cycle length: 333±3 ms) induced a significant drop in arterial blood pressure (group I: 45±3 mmHg vs group II: 100±18 mmHg). Minimal temperature was statistically not different between group I and group II (-45.0±4.4°C vs. -44.3±3.4°C, p=0.46), whereas slope (38.0±4.6s vs. 51.6±14.4s p=0.003) and AUC (1090±4.6 vs. 1181±111.2, p=0.02) was significantly changed. In one pt a ventricular tachycardia was induced. No further complications occurred. Successful PVI was achieved in 41/41 PVs (100%).
Conclusion: RVRP accelerates cryoballoon cooling during the initial phase of a freeze and can be safely performed in patients with PAF. The impact of RVRP on cryothermal lesion size and clinical outcome needs to be determined.

P758 Surgical versus catheter ablation of lone AF determination of acute and long term success rate. SCALAF study design

A. Elvan, H.T. Sie, W.P. Beukema, P.P.H.M. Delnoy, J. Minten, B. Kleijnen, A.R. Ramdat Misier. *Isala Klinieken, Zwolle, Netherlands*

Purpose: Studies have shown that continuous rhythm monitoring enables detection of significantly more atrial fibrillation (AF) episodes than routine follow up of patients (pts). As a result the positive outcome of ablation therapy may easily be overestimated.
Methods: This study is a prospective randomized trial comparing the efficacy of surgical (n=40) versus catheter (n=40) ablation of paroxysmal lone AF (SCALAF). Prior to randomization, an implantable loop recorder (ILR, Reveal XT) will be implanted in 80 consecutive pts with symptomatic drug refractory AF. After ILR implantation AF burden will be measured over a period of at least 1 week up to 6 months. Only pts with an AF burden of >10% are eligible for randomization. Pulmonary vein isolation is applied in both groups. Left atrial appendage is removed during surgery. All pts are followed up at 1, 3, 6, 12 and 24 months.
Results: These are the preliminary results of this trial. 23 pts are included in the study. 5 pts showed an AF burden of <2% after an observation period of 6 months. 18 patients showed an AF burden >10% and were randomized for treatment. 1 patient refused further study participation. The ILR allowed to make the following observations, which are essential to design a solid paroxysmal AF related trial:

- A baseline assessement is essential to compare with post treatment arrhythmia burden.
- Duration of baseline observation period needs to be long enough to have a solid average of AF burden in paroxysmal AF patients.
- Symptoms and arrhythmia episodes don't always concur.
- ILR allows continuous monitoring, however short episodes (<1 min) cannot be detected.

Conclusions: Continuous rhythm monitoring over long time periods is essential to establish a solid baseline and to be able to assess accurately the outcome of ablation for AF. Ideally, rhythm outcomes needs to be compared with baseline over equal periods of observation time.

P759 Termination or persistence of atrial fibrillation during left atrial substrate modification does not correlate with long-term outcome in longstanding, Persistent atrial fibrillation

K. Otomo[1], K. Uno[2], Y. Nagata[2], H. Taniguchi[2], H. Fujiwara[2], Y. Iesaka[2]. [1]Asklepios Klinik St. Georg, Hamburg, Germany; [2]Tsuchiura Kyodo Hospital, Tsuchiura, Japan

Introduction: It was recently reported that abolition of atrial fibrillation (AF) during the LA ablation targeting AF maintenance substrates (LAAb) correlated with better clinical outcome in longstanding, persistent AF (LPAF). This study was aimed to test if AF termination or conversion to atrial tachycardia (AT)during LAAb was related to better subsequent clinical outcome in LPAF.
Methods: This study included 121 consecutive patients (pt) with LPAF (duration

>1 year, mean: 79±74 months, LA diameter: 48±4 mm) who underwent the initial LAAb after encircling PV isolation (EPVI). The LAAb targeting the continuous, fractionated electrograms was performed sequentially at the roof, inferoposterior wall, septum, mitral annulus, mitral isthmus and base of LA appendage until AF terminated. The results of the initial session and follow-up data after the initial session were reviewed.
Results: Of the 121 pts, conversion of AF to AT (n=45)and/or AF/AT termination (n=43) were observed in 67 pts (55%: Group 1). In the remaining 54 pts (45%: Group 2), neither AF termination nor conversion to AT was observedduring the LAAb. During the early phase (<1 month) of the follow-up, 52 pts (43%) had acute recurrences of AF (n=21) or AT (n=31) 8±8 days after the LAAb session, and its incidence was significantly lower in Group 1 than in Group 2 (19/67 (29%) vs 33/54 (61%); P<0.05). During the later phase (≥1 month; mean = 287±132 days), 94 (78%) of the 121 pts were free from AF/AT episodes with antiarrhythmic medications in 52 pts (43%), while the remaining 27 pts (22%) had recurrence of AF (n=12) or AT (n=15). The AF/AT-free rate during the later phase of the follow-up was not significantly different between the groups (Group 1 vs Group 2: 53/67 pts (79%) vs 41/54 pts (76%); P=NS).
Conclusion: Although termination of AF/AT or conversion of AF to AT during LAAb correlated with better clinical outcome in the early phase, it did not correlate with subsequent freedom from AF/AT in LPAF. Termination of AF/AT or conversion of AF to AT might not be an optimal procedural endpoint during the LAAb.

P760 Long-term follow-up on success rate, anti-arrhythmic therapy, anticoagulation and embolism event after catheter ablation of paroxysmal atrial fibrillation

Y. Lin, Y. Xia, Z. Chu, D. Chang, P. Cong, S. Zhang, D. Yang, X. Yin, L. Gao, Y. Yang. *1st hospital of Dalian Medical University, Dalian, China, People's Republic of*

Objective: Catheter ablation of paroxysmal atrial fibrillation (AF) has a high successful rate in one or two-year follow-up, however, long-term data on success rate, anti-arrhythmic therapy, anticoagulation therapy and embolism event after catheter ablation is still lack.
Methods: 97 drug-refractory paroxysmal AF patients were recruited consecutively from January 2000 to December 2004 (65 males, age 54.8±11.3 yrs). Segmental pulmonary vein isolation (SPVI) was routinely performed by radiofrequency energy under the guidance of Lasso catheter. The patients were followed up with 24h-holter, ECG and telephone. The long-term recurrence of AF, anti-arrhythmic therapy, the anticoagulation therapy and the incidence of embolism were observed.
Results: After follow-up of 60.0±11.3 months, 27 had recurrence of AF (Group R), and 70 remain free of AF (Group S, 72.2%) with 8.2% of patients had very late recurrence (32.33±14.17months) (Figure1). 3 cases died from cancer, 1 case died from embolism and renal failure. 55 stopped anti-arrhythmic therapy in Group S, and 14 in Group R (80.9% vs. 56%; p<0.05) (Table1). In Group S, 56 discontinued anticoagulation (82.4%), and aspirin was continued in the rest 12 patients. No embolism event was found in Group S during follow-up. In Group R, only 1 case continued with warfarin; 2 out of 11 cases suffered from cerebral embolism although aspirin was continued. In the rest 14 cases refusing anticoagulation (53.8%), cerebral embolism happened in 1 case. The embolism event in Group R is significantly higher than Group S (p=0.008). In Group R, no significant difference of embolism event was observed between those with and without aspirin taken (10% vs. 7.1%;p>0.05).
Conclusions: Catheter ablation has a good long-term success rate in patients with paroxysmal AF, and can significantly reduce anti-arrhythmic therapy and the incidence of embolism without anticoagulation. It is necessary for those recurrent cases to continue anticoagulation therapy.

P761 Incidence of atrial tachycardias after cryoballoon pulmonary vein ablation in patients with paroxysmal or persistent atrial fibrillation

L. Koch[1], H. Schuett[2], U. Zacharzowsky[2], E. Safak[1], S. Spencker[1], H.-P. Schultheiss[1], A. Schirdewan[1]. *[1]Charite - Campus Benjamin Franklin, Berlin, Germany; [2]Helios Clinic Berlin-Buch, Berlin, Germany*

Introduction: Up to 30% of patients undergoing radiofrequency (RF) pulmonary vein (PV) ablation for atrial fibrillation (AF) develop postprocedural left atrial tachycardias. We evaluated the incidence of atrial tachycardias (AT) after antral cryoballoon PV ablation without on-top-therapy.
Methods: Fourty-seven patients (24 male, age 57.8±9.3 years) with highly symptomatic paroxysmal (n=34) or persistent (n=13) AF underwent cryoballoon ablation using the 28mm (n=43) or 23mm (n=4) balloon catheter without segmental on-top-therapy. 13 of these patients had a history of prior ablation of the cavotricuspid isthmus due to typical atrial flutter (AFL). Preservation of sinus rhythm (SR) and occurrence of AT was evaluated every three months by a 5-day Holter-ECG or a 7-day event recorder, respectively, and occasional 12-lead-ECG's or 24h-ECG's.
Results: A hundred eighty-five PV's were treated by 406 cryoapplications (2.2±0.4 applications per vein). Complete PV isolation (PVI) was achieved in 82% of all PV's. Three months after PV ablation, 68.1% of the patients showed SR. Seven patients (14.9%) had ECG documentation of new-onset atrial tachycardias. An electrophysiological (EP) study revealed isthmus-dependent AFL in 6 of these patients. In all of them, successful isthmus ablation was performed and none of these patients showed AFL recurrence during further follow-up. In the other patient, EP study revealed a left atrial macro-reentrant tachycardia that could successfully be ablated after activation and entrainment mapping.
Conclusion: We saw new-onset isthmus-dependent atrial flutter in 12.8% and left atrial tachycardia in 2.1% of patients after antral cryoballoon PV ablation. Therefore, prophylactic isthmus ablation in combination with cryoballoon PV ablation may be advisable. A possible pathophysiological correlation between antral cryoballoon PV ablation and the postprocedural incidence of isthmus-dependent atrial flutter needs to be clarified.

P763 Clinical results of vagal denervation guided by evoked vagal reflex to treat atrial fibrillation

C.F. Pisani, S. Lara, D. Hachul, F. Darrieux, E. Sosa, M. Scanavacca. *Incor - Heart Institute of Sao Paulo Medical School, Sao Paulo, Brazil*

Introduction: Autonomic nervous system plays an importantrole on genesis of atrial fibrillation. Recently, techniques of vagal denervation by catheter ablation are under study to prevent AF recurrence. Although, the results achieved are not clearly beneficial. A possible mechanism for the failure is the ablation of the "integration center" that inhibits evaluation of vagal response, falsely indicating denervation.
Methods: Between 2005 and 2006, we performed vagal denervation guided by evoked vagal response after high frequency stimulation (HFS) without eletroanatomic mapping where the endpoint was complete inhibition of response following repeated stimulation (Phase I) in 9 patients and in 2008 we performed vagal denervation of all areas (tagged on eletroanatomic mapping) where evoked vagal response was achieved after HFS (Phase II) on 5 patients.
Results: The mean age of the patients was 45.9±10.1 years on Phase I and 31.6±4.5 on Phase II (P=0.01). The time of AF was 4.6±2.4 and 4.8±1.3 years (P=0.83), left atrium size, 38.6±5.5 and 35.4±1.1mm (P=0.23) and ejection fraction 67.4±5.2 and 61.18±6.7% (P=0.10) on Phase I and II respectively. On Phase I it was applied 21.6±10.6 RF pulses and on Phase II 33.4±8.6 (P=0.057). The time of follow-up was 27.6±10.2 (5-37m) on Phase I and 6.6±4.0 months (1-12m; P=0.001). Eight of the nine patients (88.9%) that underwent ablation on Phase I and four of the five (80%) of Phase II presented AF recurrence. The time for recurrence was 9.8±14.8 (1-36) months on Phase I and 3.2±2.7 (1-7m) on Phase II (P=0.35). After recurrence, 3 (33.3%) patients remained on sinus rhythm using antiarrhytmic drugs (AAD) and 5 (55.5%) after PVI on Phase I group. On Phase II group, one patient is in Pill-in-the-pocket strategy, and 3 are in continuous AAD regimen. The patient that do not presented AF recurrence on Phase II, is using propafenone for symptomatic automatic atrial tachycardia. After Kaplan-Meier analysis no difference in AF recurrence was observed between both phases (P=0.69).
Conclusion: Most patients that underwent vagal denervation guided by evoked vagal response presented AF recurrence in the follow-up, even if all areas of evoked response were ablated.

P764 First clinical application of three-dimensional rotational angiography for cryoablation of paroxysmal atrial fibrillation: A safety and feasibility study

S. Kircher, G. Hindricks, T. Gaspar, C. Eitel, A. Bollmann, D. Husser, U. Wetzel, P. Sommer, A. Arya, C. Piorkowski. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Purpose: Cryoablation (CA) is increasingly used to treat paroxysmal atrial fibrillation (PAF). The aim of this pilot study was to evaluate clinical and procedural endpoints of cryoablation procedures integrating the three-dimensional (3D) left atrial (LA) and pulmonary vein (PV) anatomy reconstructed from 3D rotational angiography (RA) for the first time.
Methods: 3D RA was performed immediately prior to the ablation procedure in the electrophysiological laboratory. Contrast agent was transseptally administered during cardiac output reduction achieved by rapid ventricular pacing at 250 beats per minutes. After segmentation, the 3D RA model was registered to the live fluoro screen with the carina of trachea serving as landmark. At the end of the routine ablation procedure complete isolation of the PVs was assessed by Lasso catheter.
Results: Twelve consecutive pts. with highly symptomatic PAF underwent CA (8 female, age 59±8 years, median AF duration 59 [18;96] months, previous AF ablation procedures in 1 pt). Mean procedure time and fluoroscopy time measured 159±20 minutes and 43±7 minutes, respectively. Radiation dose measured 11716±7381 cGycm^2. Complete PV isolation was achieved in 31 of 36 targeted PVs (86%) with the right lower PVs being completely isolated in 8 (67%) cases. In the postinterventional 7-day-Holter-monitoring 10 pts. (83%) were free from AF recurrences. No major peri- or postinterventional complications occurred.
Conclusion: Cryoablation of PAF based on 3D RA appears to be effective and safe. Visualization of the complex PV anatomy might result in procedural and efficacy improvements as compared to approaches solely based on fluoroscopy. Additionally, 3D RA might reduce overall radiation exposure and improve preinterventional work flow as compared to computed tomography generally used for image integration.

P765 First experience in long-term follow-up of patients with atrial fibrillation after pulmonary vein isolation with the high density mesh ablator

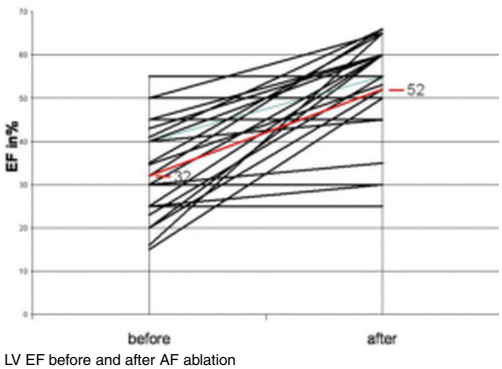
P. Maagh, M.V.B. Van Bracht, R.B. Borchard, M.C. Christ, G.P. Plehn, T.B. Butz, H.J.T. Trappe, A.M. Meissner. *Universitaetsklinik Marienhospital Herne, Herne, Germany*

Background: A novel single, expanable electrode catheter for both circumferential mapping and direct radiofrequency (RF) delivery at the left atrium/PV junctions (High Density Mesh Ablator, HDMA) has been developed to map and isolate the pulmonary veins in patients with atrial fibrillation (AF). Despite the high acute ablation success rate in patients undergoing segmental pulmonary vein isolation (PVI) using the HDMA, there is a scarcity regarding the long term data of this innovative approach.
Methods: Segmental PV isolation via the HDMA was performed using a customized pulsed RF energy delivery program (target temperature 55-60°, power 70-100 Watt, 600-900 second RF application time/PV). To identify the Quality of life (QoL) after PVI, a standardised questionnaire had been used as valuable complement to the clinical history and in the assessment of treatment efficacy.
Results: Fourty-five consecutive patients (27 male (60.0%) and 18 female (40.0%), mean age 57.5±11.8) with drug-refractory AF, were referred for ablation. Nineteen patients had paroxysmal AF (42.2%), eighteen patients had persistent AF (40.0%) and eight patients (17.8%) had persistent-permanent AF. All patients were discharged in SR, two patients with persistent AF after external cardioversion (ECV) during hospital stay. None of the patients died, none of the patients experienced serious complications or a stroke in the peri-interventional period.
After 8,6±3,3 months (range 3 to 15 months), patients filled out a standardised questionnaire. Out of nineteen patients with paroxysmal AF, 12 patients (73.3%) had definite improvement of the clinical signs, four patients had not (26.7%). One patient with AF one month after PVI was lead to ECV. Out of eighteen patients with persistent AF, twelve patients (66.6%) had definite improvement of the clinical signs, six patients had not. Two patients with AF three month after PVI were lead to ECV. Out of eight patients with persistent-permanent AF, five patients (62.5%) had definite improvement of the clinical signs, three patients had not. Two were provided with a permanent pacemaker after ablation of the AV node. In all fourty-five patients PV stenosis was ruled out by magnetic resonance imaging.
Conclusion: The mapping and ablating HDMA catheter in a single unit yields to an improvement of the QoL in a 6 months follow-up, especially in patients with paroxysmal AF but also in those with persistent AF. More extended follow-up periods are mandatory, including a larger study cohort and a detailed description of the re-occurence of AF and/or sinusrhythm.

P766 Significantly improved left ventricular ejection fraction after ablation of atrial fibrillation in patients with heart failure and impaired LV function

P. Sommer[1], C. Piorkowski[1], A. Arya[1], A. Bollmann[1], U. Wetzel[1], H. Kottkamp[2], G. Hindricks[1]. *[1]Herzzentrum der Universitaet Leipzig, Leipzig, Germany; [2]Heart Center Hirslanden, Zurich, Switzerland*

Background: Heart failure with impaired LV function is frequently associated with atrial fibrillation. In small studies it was demonstrated that ablation of atrial fibrillation (AF) can have a positive effect on left ventricular function and therefore may not only be indicated because of symptomatic improvement but also for prognostic reasons.
Methods: We analyzed retrospectively patients that were ablated in our centre and presented with impaired LV function and signs of heart failure. In long term follow up we revealed echocardiographic data as well as sequential 7 day holters were performed to control rhythm stability.
Results: We identified 26 patients (69% male) with impaired LV function that were ablated between 7/05 and 7/08 in our centre for atrial fibrillation. 4 had an ischemic (ICM) and 22 a non-ischemic cardiomyopathy (NICM). Mean age was 52 (34-72), LA was moderately dilated (46mm) and LV function was severely impaired (EF 29%; 10-55%). In 13 (50%) AF was persisting, in 13 (50%) it was paroxysmal. Mean history of AF was 80 months.
17 patients were ablated once, 9 patients (35%) underwent a second procedure.



LV EF before and after AF ablation

At 6 months follow up complete rhythm stability was shown in 19 (73%) patients, 3 of them (11%) were still under antiarrhythmic drugs (amiodarone). In echo mean LV ejection fraction was 53% (25%-65%). Complete restitution of LV function was achieved in 2 ICM patients (50%) and in 17 NICM patients (71%).
Conclusion: In our retrospective analysis we could demonstrate that effective rhythm control with ablation of atrial fibrillation in the setting of heart failure and impaired LV function was able to improve left ventricular function from EF 23% to 53%. This means that for this subgroup of patients ablation therapy may also be relevant with respect to mortality.

P767 Device safety with the use of remote magnetic navigation

S. Johar, D.G. Jones, J.C. Lyne, R.A. Kaba, T. Wong, V. Markides, J.R. Clague, J.A. Till, S. Ernst. *Royal Brompton Hospital, London, United Kingdom*

Introduction: Magnetic fields are normally avoided in patients with implantable devices due to possible adverse effects. However remote magnetic navigation with permanent magnets is used for procedures in some catheter labs. The safety of the low magnetic field strength (0.08T) used for remote magnetic navigation (Stereotaxis Niobe II) in these patients has not been studied so far.
Methods: From May to December 2008 3 groups were studied. Group A – device implants were performed with the permanent magnets in the parked position. Group B – patients who already had devices underwent a magnetically-guided ablation procedure. Group C – patients underwent coronary angiography/intervention with the permanent magnets in the parked position. The devices were programmed to back-up pacing with low output before the procedure and reprogrammed to normal settings post-procedure in Group B. The devices were left programmed at usual settings and checked after the procedure in Group C.
Results: In Group A a total of 58 devices were implanted (32M; 28F mean age 66±15); 5 implantable loop recoreders, 5 single chamber pacemakers, 25 dual chamber pacemakers, 8 dual chamber ICDs and 15 CRT devices (8 with defibrillator capability). There were no problems observed with the device, pacing parameters or communication with the programmer. 4 patients (2M; 2F mean age 37±13, 3 dual chamber pacemakers, 1 single chamber pacemaker) had electrophysiological studies performed using the remote magnetic navigation system for catheter ablation of 2 atrial tachycardias, 1 atrial flutter and 1 atrial fibrillation in Group B with a mean procedure time was 208±47 min. 7 patients (5M; 2F mean age 74±8, 4 dual chamber pacemakers, 2 single chamber ICDs and 1 CRT-D device) underwent coronary angiography with a mean procedure time of 34±28 min. in Group C with no significant differences in threshold, sensing, lead impedance and battery voltage pre- and post-procedure.
Conclusions: Remote magnetic navigation using permanent magnets is safe in patients with a wide variety of implanted devices without any adverse events. With the magnets parked in the 'off' position it is safe to perform device implantation or coronary angiography/intervention with no adverse effects in the implanted devices.

P768 Feasibility of real time magnetic resonance imaging in interventional electrophysiology using a novel carbon catheter

P. Nordbeck[1], W.R. Bauer[1], F. Fidler[2], M. Warmuth[3], K.H. Hiller[2], M. Nahrendorf[4], J. Broscheit[5], P.M. Jakob[3], O. Ritter[1]. *[1]Internal Medicine I, University of Würzburg, Würzburg, Germany; [2]Research Center Magnetic-Resonance-Bavaria, Würzburg, Germany; [3]Experimental Physics V, University of Würzburg, Würzburg, Germany; [4]Center for Molecular Imaging Research, Harvard Medical School, Boston, United States of America; [5]Department of Anesthesiology, University of Würzburg, Würzburg, Germany*

Background: Magnetic resonance imaging (MRI) offers the cardiologist a broad spectrum of superior diagnostic information, providing unsurpassed soft tissue contrast without X-ray exposure and enabling acquisition of detailed 3D cardiac morphological and functional data. For these reasons there is a trend to use preprocedural MRI in diagnostic and therapeutic electrophysiological (EP) procedures. To use this imaging modality to its full potential, we aimed at developing a setup for real time MR guided interventional EP minimizing imaging artifacts and safety concerns.
Methods and Results: The setup, including a steerable carbon ablation catheter, was tested for image distortion, safety, and feasibility of diagnostic EP studies and radiofrequency ablation at 1.5 Tesla. MR imaging was performed in three different 1.5-T whole-body scanners using various receive coils and pulse sequences. To assess unintentional heating of the catheters by radio frequency (RF) pulses of the MR scanner in vitro, a fluoroptic thermometry system was used to record heating at the catheter tip. Programmed stimulation and ablation therapy was performed in eight pigs. There was no significant heating of the carbon catheters while using short, low energy MRI pulse sequences. The catheter was visualized using a passive catheter tracking technique. Since there was no image distortion when using the carbon catheters, exact targeting of the lesion sites was possible. Both atrial and ventricular RF-ablation procedures including AV node modulation were performed successfully in the scanner. Potential complications such as pericardial effusion after intentional perforation of the RV free wall during ablation could be monitored in real time as well.

Conclusion: A newly developed EP technology based on carbon catheters was used to enable MR-guided interventional electrophysiology. The feasibility of this approach was demonstrated by in vitro safety testing and performing in vivo EP studies and ablation therapy in the MRI environment.

P769 P-wave modifications after wide area circumferential ablation of atrial fibrillation

S.S. Bun, D.G. Latcu, P. Ricard, T. Hugues, N. Zarqane, K. Yaici, J.P. Rinaldi, N. Saoudi. *The Princess Grace Hospital Centre, Monaco, Monaco*

Background: P-wave morphology-based algorithms for localizing the origin of atrial tachycardias (AT) may not be reliable after wide atrial circumferential ablation of atrial fibrillation (WACA), as the later may alter intra-atrial conduction.
Methods: we prospectively studied morphology, amplitude and duration, of paced p-waves on surface 12 lead-magnified ECG, before and after WACA in patients in sinus rhythm, and at twelve different pacing sites (pacing at 600 ms), in the right atrium (high right atrium, proximal and distal coronary sinus, septal and lateral parts of cavo-tricuspid isthmus [CTI]); and in left atrial (LA) roof, mid-posterior wall (MPW), appendage, and mitral annulus (MA) in four positions (3,6,9 and 12 hours when seen in left anterior oblique view). Patients were excluded in case of previous LA (n=8) or right atrial (n=10) radiofrequency catheter ablation.
Results: 6 patients were finally included (5 men; mean age 53,5 years). P-wave morphology was modified in all patients in at least three leads after WACA. Significant decrease of the paced P-waves amplitude was observed in the following sites: proximal (125 [59] to 100 [52]μV; $p<0,0001$) and distal coronary sinus (115 [54] to 97 [45]μV; p=0,0002), in septal part of CTI (128 [77] to 107 [60]μV; $p<0,0001$), in LA roof (165 [86] to 109 [54]μV; $p<0,0001$) and MPW (119 [60] to 94 [44]μV; p=0,013), and MA 6h (108 [54] to 83[41]μV; $p<0,0001$). Significant decrease of paced P-waves duration was observed in the following sites: LA roof (163 [18] to 156 [23]ms; $p<0,05$) and MPW (173 [19] to 153 [30]ms; p=0,043); while it was significantly prolonged in MA 9h (131 [11] to 152 [22]ms; p=0,046) and 12h (149 [10] to 164 [20]ms; p=0,0431) pacing sites.
Conclusion: WACA profoundly alters p-wave morphology, amplitude and duration, and thereby may render analysis of post-ablation AT ECG quite difficult.

P770 Ablation of perimitral flutter following catheter ablation of atrial fibrillation: impact on outcomes from a randomized study

L. Di Biase[1], J.D. Burkhardt[2], R. Horton[2], J. Sanchez[2], P. Mohanty[2], S. Bailey[2], D. Patel[2], R. Hongo[3], S. Baheiry[3], A. Natale[3]. *[1]Texas Cardiac Arrhythmia Institute at St David Medical Center, Un. of Texas and University of Foggia, Austin, United States of America; [2]Texas Cardiac Arrhythmia Institute at St David Medical Center, Austin, United States of America; [3]Sutter Pacific Hospital, San Francisco, United States of America*

Introduction: Perimitral flutter can be observed after pulmonary vein isolation (PVI). Patients with previous AF ablation, who presented for redo-procedure and peri-mitral left atrial flutter, were randomized to ablation of peri-mitral flutter versus cardioversion and repeat isolation with ablation of additional triggers.
Methods: A total of 65 patients were randomized. Thirty two underwent perimitral flutter ablation only and 33 were cardioverted and underwent repeat isolation plus ablation of others triggers disclosed by administration of isoproterenol up to 30 ug/min.
Results: The clinical characteristics were similar in both groups. Most patients had history of persistent or chronic AF. The success rate after a follow up of 14±4 months off of AADs is shown in the table.

	Mitral Isthmus (n=32)	Repeat PVI plus isoptroterenol (n=33)	P value
Age	63±11	62±12	NS
Sex/M	25	23	NS
Paroxysmal/Non paroxysmal	5/27	5/28	NS
LA size	4.6±0.6	4.7±0.5	NS
E.F.	50±5	49±7	NS
Procedural success %	16	85	P <0.001
% of additional triggers	NA	48	NA

Conclusion: This study showed that peri-mitral flutter ablation alone has limited impact on cure rate in patients with previous ablation and clinical recurrence of peri-mitral flutter. In such group, triggers outside the PVs and the posterior wall were seen in 48% of patients.

P771 Can concomitant beta-blocker treatment increase Amiodarone effectiveness in maintaining sinus rhythm in patients with persistent atrial fibrillation ?

M. Mezzetti, M. Marconi, G. Piovaccari. *Cardiology Division, Rimini, Italy*

Amiodarone (A) is effective in reducing atrial fibrillation (Afib) recurrences but few data are available about the effectiveness of the concomitant treatment with A and beta-blockers (BB) in maintaining sinus rhythm (SR). A total of 399 patients (pts) with persistent Afib (more than 7 days duration) of diverse etiologies (ischemic 16%, hypertension 65.4%, valvular 17.5%, diabetes 6.8% and lone 10.3%) were divided at the time of electrical cardioversion in three groups according to Afib prophylaxis: A 89 pts (22.3%), BB 211 pts (52.8%) and A plus BB (ABB) 99 pts (24.8%) and were followed for a mean of 15 months. No significative differences were found between groups regarding major clinical and echocardiographic parameters (pts mean age 67±9 years, index Afib duration 109±98 days, left atrial (LA) dimension 45±6 mm, EF% 53±10). Primary end point, freedom from first persistent Afib recurrence at 6 and 12 months, resulted respectively 69% and 62% for A and 70% and 58% for ABB (p = 0.93 log rank test); freedom from Afib recurrence at 6 and 12 months was respectively 51% and 38% for BB, significantly lower (p = 0.02 log rank test) compared to both A or ABB. The subgroups analysis didn't identify any subset that benefited from the combined ABB therapy; in addition ABB therapy was not tolerated in 24.8% pts, mainly due to bradycardia. The corresponding percentage in A and BB arms was respectively 15% and 8%. Interestingly the patients that benefited most from A therapy was those with LA $<$ 45 mm and/or EF $>$ 40% respectively p= 0.019 and p = 0.006 (log rank test). In conclusion the combined therapy ABB doesn't reduce significantly Afib recurrence compared to A and increases the risk of side effects. The major benefit of A over BB in maintaining SR could be observed in pts with less severe structural damage (such as those with less atrial dilatation and maintained EF%) in whom the arrhythmia probably is not yet a marker of the severity of the cardiomyopathy.

P772 Mid-term results of minimally invasive surgical treatment of lone atrial fibrillation

P. Piccoli[1], A. Repossini[2], A. Curnis[3], A. Negri[2], A. Moggi[1], A. Manzato[4], C. Muneretto[1]. *[1]University of Brescia, Brescia, Italy; [2]Division of Cardiac Surgery, Spedali Civili di Brescia, Brescia, Italy; [3]Division of Electrophysiology, Spedali Civili di Brescia, Brescia, Italy; [4]Cardiothoracic Intensive Care Unit, Spedali Civili di Brescia, Brescia, Italy*

Purpose: Atrial fibrillation is the most common cardiac rhythm disturbance causing increased morbidity an mortality. Despite the development of minimally invasive/endoscopic techniques and the availability of different energy sources for treatment of lone atrial fibrillation, the efficacy and the mid-term results of these procedures is unknown.
Methods: Since December 2003 through August 2008, 41 drug-resistant symptomatic patients with lone atrial fibrillation underwent minimally invasive/endoscopic surgical ablation. There were 35 men (85.4%) and 6 females (14.6%) with a mean age of 62.0±11.6 years (range 30-85) who suffered of a long-standing atrial fibrillation (mean AF duration 79±40 months). Among them, 31 Patients (75.6%) had paroxysmal and 10 (24.4%) had permanent atrial fibrillation. Pre-operative mean LA dimension was 46.6±8 mm. Left atrial isolation was achieved by means of pulmonary veins encircling (box lesion) and was performed in thoracoscopy in 31 pts (75.6%), while mini-sternotomy was performed in 10 cases (24.4%). The box lesion was obtained with the use of microwave device or monopolar radiofrequency device. Most of the procedures (37 pts, 90.2%) were performed with epidural anesthesia on awake patient in spontaneous breathing.
Results: There were no hospital deaths nor major post-operative complications except 1 patient who had an embolic cerebro-vascular accident on 4th post-operative day (full recovery).
Mean post-operative length of stay was 2±1.2 days. Mean follow-up (100% complete) was 37.6±19.2 months (range 2-58). There were no late deaths. At 1-year follow-up 37 pts. (90.2%) were in sinus rhythm. At the mean follow-up (37.6 months) 34 patients (82.9%) were in stable sinus rhythm confirmed by Holter-EKG. Synus rhythm restoration rate in patients affected by paroxysmal atrial fibrillation was higher (87.1%) than in those affected by the permanent form. At the end of the follow-up 65.8% of patients were no longer taking warfarin nor antiarrhythmic drugs.
Conclusions: Minimal invasive surgical treatment of atrial fibrillation proved to be feasible and safe with minimal risk for the patient. The "box lesion" proved to be an effective ablation pattern with an high rate of stable restoration of sinus rhythm even at mid-term follow-up. The use of high thoracic epidural anesthesia and the avoidance of mechanical ventilation made the minally invasive endoscopic techniques feasible even in a "day surgery" environment.

P773 First episode of auricular fibrillation during acute coronary syndrome identifies patients at risk of thromboembolism. Implications for treatment at discharge

L. Nombela Franco, A. Garcia-Touchard, C. Gutierrez-Landaluce, J.M. Escudier, J.A. Fernandez-Diaz, L. Silva-Melchor, I. Fernandez-Lozano, J. Goicolea Ruigomez, F.J. Ortigosa Aso, L. Alonso-Pulpon. *Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain*

Introduction: Atrial fibrillation (AF) during an acute coronary syndrome (ACS) is frequent (up to 10%). The management with antithrombotics (anticoagulants and/or antiplatelet drugs) therapy at discharge is not clearly defined, above all if sinus rhythm has been restored.
Methods and results: A prospective follow-up was performed on 825 consec-

utive patients admitted for ACS between July 2006 and December 2007. 47 patients (5.7%) developed AF during hospitalization (transient AF). The mean age was 71.5±11 years, 63% were male, 64% were hypertense, 30% smokers, 30% diabetic and 57% with CHADS score >2. ACS with ST-segment-elevation occurred in 51% and half of the patients had left ventricular ejection fraction more than 50%. 83% of the AF revert to sinus rhythm during the period of admission. 9 patients (19.1%) were discharged with acenocumarol plus aspirin plus clopidrogrel, 29 patients (61.7%) with double antiaggregation, 5 patients (10.6%) with acenocumarol plus single antiaggregation, and 4 (8.5%) with acenocumarol or antiaggregation. Clinical follow-up was completed (median 355±196 days) in 89% of the patients. 3 patients (7.6%) presented an ischemic event (2 ictus and 1 peripheral embolism) during the follow-up period. One patient had 1 point for CHADS score and the other two had four points. All patients with thromboembolism were being treated with double antiaggregation without acenocumarol.

Conclusions: Transient atrial fibrillation during ACS is a frequent complication which identifies a group at risk of suffering embolic complications during follow-up despite having reverted to sinus rhythm. The results of this study suggest the need to treat with anticoagulants, patients with transient atrial fibrillation during ACS.

P774 Prevalence and prognostic value of atrial fibrillation in patients with stroke

H. Ribeiro[1], R. Margato[1], S. Carvalho[1], C. Ferreira[1], J. Gabriel[2], A. Velon[2], P. Guimaraes[2], A. Ferreira[1], P. Mateus[1], I. Moreira[1]. *[1]Centro Hospitalar de Trás-os-Montes e Alto Douro, Cardiology Department, Vila Real, Portugal; [2]Centro Hospitalar de Trás-os-Montes e Alto Douro, Neurology Department, Vila Real, Portugal*

Purpose: Atrial fibrillation (AF) is the most frequent sustained disrrythmia found in clinical practice and is well recognized as a strong risk factor for ischemic stroke. The aim of this study was to assess the prevalence, clinical characteristics and prognosis associated with AF in patients admitted for stroke.

Methods: Retrospective analysis of patients consecutively admitted to a cerebrovascular disease unit with stroke or transient ischemic attack (TIA) over a period of 7 years. Isquemic stroke patients were classified according to Bamford Topographic Classification in total/partial anterior circulation infartion-TACI/PACI, posterior circulation infarction–POCI and lacunar circulation infarction–LACI. The population was divided into 2 groups: Group A-with AF and Group B-without AF. The prevalence of AF was determined and the two groups were evaluated and compared concerning demographic and clinical features, scales of functional capacity (SFC) (Rankin, NYH) and mortality. In statistical analysis, X^2 and Student's t test were used; logistic regression was performed for multivariate analysis.

Results: We studied 3508 patients (pts), 52.3% male, mean age of 73.2±11.5 years. The prevalence of AF was 18.8%. Group A pts were older (77.5±8.7 vs 72.2±11.8 years, p<0.001), more frequently women (56.9 vs 45.6%, p<0.001), had larger ischemic stroke's (TACI-39.8 vs 19.4%), lower proportion of hemorrhagic stroke (HS)(5.8 vs 18.3%, p<0.001), higher percentage of cardiac disease (33.2 vs 19.5%, p<0.001) and worst SFC (table 1). The two groups did not differ (p=NS) regarding the existence of vascular risk factors (hypertension - 52.2 vs 55.9%, diabetes - 8.8 vs 19.5%, obesity - 4.4 vs 5.3%) and comorbidities (chronic renal failure - 3.8 vs 3.3%, cerebrovascular disease - 6.4 vs 4.8%). The mortality was similar in both groups (A=16, 4 vs B=15,1%, p=ns), but when adjusted for age, risk factors, comorbidities, type of stroke and functional scales, proved to be higher in the group of patients with AF (OR=1,4, 95% CI 1,1-1,8, p=0,003).

Table 1

	Group A	Group B	p
Rankin Scale (admission/discharge)	3.6±1.5/2.7±1.7	3.2±1.6/2.3±1.6	<0.001
NIH Scale (admission/discharge)	11.2±8.9/7.6±8.3	8.6±8.5/5.1±6.5	<0.001

Conclusions: This study showed a prevalence of AF similar to other published series and identified this arrythmia as an independent determinant of higher mortality in stroke.

ARRHYTHMIAS IN CHILDREN

P775 Low incidence of sudden infant death syndrome but high incidence of Non-autopsied cases

B.G. Winkel, A.G. Holst, J. Theilade, J.H. Svendsen, S. Haunsoe, J. Tfelt-Hansen. *Dept. of Cardiology, Rigshospitalet and Danish Arrhythmia Research Center, DARC, Copenhagen, Denmark*

Purposes: The purpose of this study was to perform a retrospective investigation of the incidence of Sudden Infant Death Syndrome (SIDS) and autopsy ratio in sudden unexpected infant death cases in the Danish population (total 5.4 million). This is the first nationwide study to describe incidence of SIDS and autopsy ratio in sudden unexpected infant deaths (age under 1 year) by examining death certificates and autopsy reports.

Methods: All infant deaths in a 7-year period (2000-2006) were included and death certificates were read and categorized by two trained physicians. Discrepant cases were discussed to obtain consensus. The number of infants autopsied was ascertained and diagnoses were revised based on autopsy findings.

Results: There were a total of 455.091 births in Denmark in 2000-2006 (average 65.013 births/year). In this period a total of 2061 deaths occurred in the age group younger than 1 year (average 294 deaths per year or 0.5% of all births). Among these 2061 deaths approximately 40% died in relation to birth and another 40% died later of non-cardiac causes. 234 infants (12%) had severe congenital heart disease diagnosed either in uteri or immediately after birth and their deaths were neither sudden nor unexpected.

166 infants (8% of total 2061 deaths) died suddenly and unexpectedly, suspicious of sudden cardiac death. 11% (n=18) of these had been diagnosed with heart disease prior to death. Among the cases with no known disease, 28% (n=40) was demonstrated with congenital heart disease upon autopsy. 24% (n=34) were denoted borderline SIDS, as mild to moderate infectious disease of typically respiratory tract and/or middle ear was found at autopsy. In 40% (n=56, 3% of the total 2061 deaths) no cause of death were established and were subsequently denoted SIDS (median 1, range 0-10 months). The autopsy ratio among the sudden and unexpected deaths was 85% and independent of prior disease.

The incidence of SIDS was 22 pr 100.000 newborns or on average 14 cases pr year.

Conclusions: In a large nationwide retrospective study of 2061 consecutive infant deaths we found a low incidence of definite and borderline SIDS cases in Denmark. Surprisingly the results revealed that no autopsy was conducted in 15% of possible SIDS cases, thereby possibly underestimating the true incidence of SIDS. No data are available that describe autopsy ratios in possible SIDS cases in other populations. Mandatory autopsy in cases of sudden deaths in infants would provide valuable information, both in regards to counselling of the parents and when following SIDS over time.

P776 Multi-center study of the effectiveness of ICDs in children and young adults with heart disease

N. Von Bergen[1], D.L. Atkins[1], M. Dick[2], D.J. Bradley[2], S.P. Etheridge[2], E.V. Saarell[2], P.S. Fischbach[3], S. Balaji[4], N. Sreeram[5], I.H. Law[6]. *[1]University of Iowa Children's Hospital, Iowa City, United States of America; [2]Primary Children's Hospital, Salt Lake City, United States of America; [3]Sibley Heart Center, Atlanta, United States of America; [4]Oregon Health Sciences University, Portland, United States of America; [5]University Hospital, Cologne, Germany; [6]Las Vegas Children's Heart Center, Las Vegas, United States of America*

Introduction: ICDs are an established therapy for prevention of sudden cardiac death in patients with electrical disease (ED), cardiomyopathy (CM) or congenital heart disease (CHD). The indications for implantation and effectiveness of ICDs in young patients are not well described. This multicenter study evaluates the indications for placement and appropriateness of discharges of ICDs in young patients within these 3 categories of heart disease.

Methods: A retrospective study was performed of all patients <30 years who underwent ICD implantation at one of 7 institutions from October 1992 until January 2007. Data included patient demographics and diagnosis, ICD discharge data, and appropriateness of ICD therapy. Primary prevention was defined as implantation prior to ventricular arrhythmia or sudden death event. Secondary prevention was defined as implantation after ventricular arrhythmia or aborted sudden death event, or event associated with undefined syncope. ICD discharges were categorized as life-saving discharges (LD: ventricular tachycardia >250 bpm, VF, or syncope), appropriate discharges (AD: LD criteria or VT<250 bpm), or inappropriate discharges (ID).

Results: ICDs were implanted in 210 patients, median age 15.4 years (0.2 - 29) at implant, for ED (n=90), CM (n=62), and CHD (n=58). The most common indication was secondary prevention (n=122, 58%). The majority (82%) of patients with CHD underwent implant for secondary prevention, compared to ED (58%) and CM (32%). At follow-up (average 3.3 years, median 2.6 years), 86 patients (41%) had an ICD discharge, 34 (16%) had received a LD, 58 (28%) received an AD, 40 (19%) received an ID. ID was more common in CHD. Overall patients averaged 0.63 discharges per patient per year. Those who underwent implant for secondary prevention were more likely to have received AD. There was no difference in the number of patients who had received an AD and/or LD per category. Ten patients died.

Conclusions: The majority of ICD implants in young patients were for ED. Most ICDs were implanted for secondary prevention; those implanted for secondary prevention were likely to receive an AD and/or LD. IDs remained common, with increased risk of ID in CHD patients. There is no difference in ID when implanted for primary or secondary prevention.

P777 Dyssynchrony and left ventricular strain in pediatric patients paced at right ventricular outflow versus apical septum

R. Juneja, S. Ramakrishnan, C. Vyas, N. Naik, S.S. Kothari, A. Saxena, V.K. Bahl. *All India Institute of Medical Sciences (AIIMS), New Delhi, India*

Background: Right ventricular (RV) outflow pacing has distinct advantages as compared to RV apical septal pacing. The extent of dyssynchrony seems to corre-

late with the left ventricular (LV) dysfunction seen with chronic ventricular pacing. However, data regarding the optimal site of pacing and dyssynchrony are sparse in children.
Methods: We studied sixteen consecutive patients of RV pacing, eight each in outflow septal (mean age 5.68±3.03 years) and apical septal group (mean age 7.75±3.01 years). Echocardiographic analysis of dyssynchrony was done with standard technique using M mode, 2D imaging-doppler and tissue Doppler imaging. Strain and strain rate at different LV walls were also measured.
Results: There was no statistically significant difference in the interventricular mechanical dyssynchrony between the two study groups (21.12±10.24 ms in apical septal paced versus 22.87±13.57 ms in outflow septal paced; P = 0.83). There was no significant difference in intraventricular dyssynchrony evaluated at 12 segments of the left ventricular (LV) wall except at the basal anteroseptal-posterior wall (13.74±18.03 ms in apical septal paced versus 26.66±20.85 ms in outflow septal paced; p = 0.05). There was no significant difference in the dyssynchrony index (23.53±7.14 in apical septal paced versus 22.58±7.03 ms in outflow septal paced; P = 0.67). There was significant difference in longitudinal systolic strain at the anteroseptal basal wall (-24.01±2.16% in apical septal paced versus - 20.34±2.75% in outflow septal paced; P = 0.02). In rest of the segments, there was no significant difference among both the groups.
Conclusions: Right ventricular outflow septal pacing in children does not lead to demonstrable advantages in intraventricular or interventricular dyssynchrony, and LV strain or strain rate. A larger randomized study with a more homogenous population and a longer follow up is mandated.

P778 Cardiac synchrony and function with chronic single-site left versus right ventricular epicardial pacing in paediatric patients after patch closure of ventricular septal defects

M. Tomaske[1], O.A. Breithardt[2], U. Bauersfeld[1]. *[1]University Children's Hospital, Zurich, Switzerland; [2]Klinikum Coburg, Coburg, Germany*

Purpose: Numerous anatomical pathologies or post-surgical injuries of the conduction system may cause ventricular dyssynchrony in paediatric patients. We evaluated the impact of chronic single-site left (LVP) versus right ventricular pacing (RVP) on ventricular synchrony and function in patients with patch closure of a ventricular septal defect (VSD).
Patients and Methods: A total of 14 paediatric patients with patch closure of a large perimembraneous VSD (≥ 5mm) were enrolled. Surgical complete heart block was the indication for single-site epicardial left ventricular free wall pacing (LVP, n= 10, pacing duration: 5.0±3.9 years) or right ventricular apex pacing (RVP, n= 5, pacing duration: 6.2±2.5 years). Patients with less than 99% ventricular pacing, and less than 1 year of pacing were excluded. Conventional echocardiographic parameters, colour Doppler M-mode and myocardial circumferential 2D strain analysis were obtained. To define the severity of LV dyssynchrony, LV-mechanical delay was measured as a 12 segment LV model including the mitral valve and papillary muscle level. Data are given as mean ± SD.
Results: Paced QRS duration was far above normal levels but did not differ between groups (LVP: 167±28 ms; RVP: 173±14 ms). Interventricular mechanical delay (LVP: 17±15; RVP: 50±32 ms), septal-to-lateral wall motion delay (LVP: 39±24, RVP: 73±26 ms) and LV-mechanical delay (LVP: 45±12, RVP: 75±24 ms) was preserved for LVP but not RVP. Early systolic bulging of the VSD patch towards the right ventricle led to a prolonged septal-to-posterior wall motion delay for both, LVP (142±99 ms) and RVP (313±29 ms). Global systolic function determined by LV ejection fraction was normal for LVP but not RVP (LVP: 56±9%, RVP: 49±5%).
Conclusions: Conventional and 2D strain echocardiographic measurements indicate preserved LV synchrony and function in paediatric patients after VSD patch closure with LVP but not RVP. However, large VSD patches are acting like a functional aneurysm with paradoxical motion on echocardiography in both groups.

P779 Catheter ablations in children with ventricular tachycardia

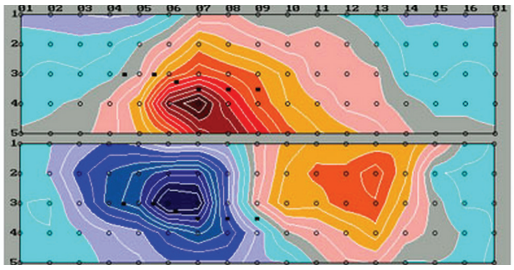
E. Pokushalov, A. Romanov, S. Artemenko, P. Shugaev, A. Turov, N. Shirokova. *State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation*

Purpose: The aim of this study was to expand data on the outcomes of catheter ablation of ventricular tachycardia (VT) in young patients and to identify obstacles to success.
Methods: In this study 143 children with monomorphic VT (mean age 13.8±2.9 years, ranging from 6 to 18 years) who underwent catheter ablation for different VT were observed.
Results: The structure of the arrhythmias was as following: right ventricular outflow tract tachycardia (RVOT; 24%), aortic sinus of valsalva (27%), arrhythmogenic right ventricular cardiomyopathy (ARVC; 14%), left VT (34%). VT originating from the OT: septum of the RVOT (41%), free wall of the RVOT (5%), near the His-bundle region in the RVOT (12%), endocardium of the LVOT (15%), left sinus of Valsalva (24%), LV epicardium remote from the LSV (3%). During 13±7 months of the follow-up period after a single ablation procedure, the results were as follows: RVOT ablation (n=50) - 64% successful, 36% - unsuccessful, 8% showed recurrence of VT; LVOT ablation (n=24) - 83% successful, 17% - unsuccessful, 4% - recurrence of VT. The second ablation procedure (RVOT+LVOT) was performed in 22 patients. In 16±9 months after the last ablation procedure the success rate was 96%. Idiopathic left fascicular VT. During 11±8 months of the follow-up period after a single ablation procedure the results were as follows: ventricular activation guided ablation (n=21) - 33% successful, 67% - unsuccessful, 19% showed recurrence of VT; P potential guided ablation (n=28) - 71% successful, 29% - unsuccessful, 10% - recurrence of VT. The second ablation procedure (ventricular activation + P potential guided ablation) was performed in 22 patients. In 9±8 months after the last ablation procedure the success rate was 88%. ARVC. During 8±7 months of the follow-up after a single ablation procedure (n=21; endocardial ablation) - 91% of the procedures were successful, 9% - unsuccessful, 9% -showed recurrence of VT. The second ablation procedure (epicardial ablation) was performed in 5 patients. In 7±6 months after the last ablation procedure the success rate was 60%.
Conclusion: Catheter ablation can be effective, safe, and life saving technique for children with medically resistant VT.

P780 Specific features of the heart electric field in children with Long QT Syndrome by body surface potential mapping

M. Shkolnikova, I. Polyakova, L. Kalinin. *Moscow Institute For Paediatry&Surgery, Moscow, Russian Federation*

Diagnostics of the LQTS is based on the ECG, clinical and genetic data (especially in genotyped families). Before DNA testing specific ECG patterns could be helpful in identifying gene-specific variants inside population of affected people. The dynamics of QT on exercise test and the character of provocative stimuli for syncope are also helpful. Research for elaborating additional noninvasive diagnostic criteria is relevant.
We aimed to evaluate the predictive power of the specific features of ventricular depolarization (VD) and repolarization (VR) in patients with LQT1 and LQT2 by analyzing of QRS and ST-T distribution on the body surface potential mapping (BSPM). The BSPM was carried out in 46 probands (21 girls and 25 boys; mean age 11.9±3.6) from unrelated families with LQTS. The diagnosis was confirmed by QT prolongation, family history, course of disease and genetic analysis. Computer ECG system Cardiag (The Czech Republic) with simultaneous ECG registration in 80 unipolar chest leads was used. Isopotential and isointegral maps of QRS and ST-T were computed. Control group consisted of 25 healthy children, aged from 5 to 17 (14.7±2.9).
The LQT1 was associated with specific pattern (additional extreme) of VR: 64% of LQT1 probands revealed additional negative extreme during VD in projection of ventricular septum and left ventricular anterior wall. The same was found only in 15% cases in the control. The sensitivity (Se) was 0.64; specificity (Sp) was 0.85. The LQT2 type was associated with an extensive negative zone during VR: it was found in 16 of 18 (89%) with LQT2 (blue zone on fig 2) and in 0 form the control (Se = 0.89; Sp = 1.0; fig 1).



BSMP. Isopotential repolarization maps.

Conclusion: Specific features on BSPM could be useful for differentiation of LQT1 and LQT2 pts before performing genetic studies.

P781 Prevalence of interatrial block in healthy school-aged children: definition by P wave duration or morphological analysis

P.E. Dilaveris, L. Raftopoulos, G. Giannopoulos, S. Katinakis, D. Maragiannis, D. Roussos, K. Gatzoulis, A. Michaelides, C.H. Stefanadis. *University of Athens, Athens, Greece*

Background: P waves ≥110 ms in adults and ≥90 ms in children are considered abnormal, signifying interatrial block, particularly in the first case.
Methods: We obtained 12-lead digital ECGs (Cardioperfect 1.1, CardioControl NV, Delft, The Netherlands) of 664 healthy children (349 males/315 females, age range 6-14 years old). P wave analysis indices [mean, maximum and minimum (in the twelve leads) P wave duration, P wave dispersion, P wave morphology in the derived orthogonal (X,Y,Z) leads, as well the amplitude of the maximum spatial P wave vector] were calculated in all study participants.
Results: P-wave descriptor values were: mean P-wave duration 84.9±9.5 ms, maximum P-wave duration 99.0±9.8 ms, P dispersion 32.2±12.5 ms, spatial P amplitude 182.7±69.0 μV. P wave morphology distribution in the orthogonal leads

were: Type I 478 (72.0%), Type II 178 (26.8%), Type III 1 (0.2%), indeterminate 7 (1%). Maximum P-wave duration was positively correlated to age ($p<0.001$) and did not differ between sexes (p=0.339). Using the 90-ms value as cut-off for P-wave duration, 502 (75.6%) children would be classified as having maximum P-wave duration above reference range. The 95th and the 99th percentiles were in the overall population 117 ms and 125 ms, respectively. P-wave morphology type was not in any way correlated to P-wave duration (p=0.715).
Conclusion: P wave analysis parameters in a healthy pediatric population are provided to assess the significance and presence of electrocardiographic evidence of interatrial block and to serve as future reference.

P782 Asymptomatic ventricular preexcitation in children

G. Fazio, L. D'Angelo, G. Novo, S. Novo. *Policlinico P. Giaccone, Palermo, Italy*

Aim: This retrospective study was planned for a good risk assessment in asymptomatic patients affected by ventricular preexcitation.
Methods: From 1985 to 2007, 120 patients with an atrioventricular pathway (electrocardiographic signs of ventricular pre-excitation) were admitted to our cardiology division. The average age was 7 years (Range 1 month – 18 years).
The mean follow-up period in the whole population of patients was 4.2 years (range 1-13 years).
4 patients were lost during the follow up. During this period, all patients remained in good health.
In all of them we performed a Holter evaluation every year. It was detected an intermittent pathway in 18 cases, and 4 of them (22%) showed a supraventricular tachycardia even though they were asymptomatic patients. An ergometric test was performed in 76 asymptomatic patients: 16 children showed a total abrupt vanishing of delta wave. A trans-oesophageal electrophysiological evaluation was performed and in 8 of the asymptomatic patients for competitive sport activity. We planned an ablation in 2 of them.
Conclusions: According to our experience, asymptomatic patients with Wolff-Parkinson-White syndrome showed good health. However 4 asymptomatic patients out of 10 were evaluated for sport activity at a competitive level by a trans-oesophageal study and this was helpful in determining the characteristics of a dangerous accessory pathway, in spite of a total absence of symptoms.

P783 The utility of the implantable loop recorder in a national paediatric cardiology centre

B. Hynes, A. Babikar, K. Walsh, N. Ward, P. Oslizok, D. Keane. *Our Lady's Hospital Crumlin, Dublin, Ireland*

Purpose: The implantable loop recorder (ILR) has proved highly efficacious in the management of syncope, pre-syncope and palpitations in selected populations. Limited information regarding patient selection and diagnostic yield exists in the paediatric setting.
Methods and results: A retrospective evaluation of patients who underwent ILR implantation over a 66 month period, in a tertiary paediatric cardiology unit was conducted. Twenty three patients (10 male, 13 female) following initial assessment and investigation, were referred for device implantation. The mean age at time of ILR insertion was 11.39±4.34 (range: 2.0-16.8) years. The indications for ILR were recurrent syncope (n=11), presyncope (n=3), or palpitations (n=9). Four (17.4%) patients had structural heart disease, 3 (13%) had a positive family history of sudden cardiac death, and 1 (4%) had perinatal arrhythmia. One patient required ILR repositioning, and pocket infection necessitated explantation in one further patient. Minimum follow-up was 7.8 months during which symptoms were reported in 15 (65.2%) patients post ILR insertion. 8 (34.7%) remained asymptomatic. Of the 15 who experienced symptom recurrence, 8 (53.3%) had an arrhythmia recorded. Tachycardias recorded were polymorphic ventricular tachycardia (n=1) and supraventricular tachycardia (n=5). Clinically significant bradycardias documented, included sinus bradycardia (n=1) and Mobitz type II second degree atrioventricular block (n=1).
Conclusion: The ILR had a high diagnostic yield, enabling an arrhythmic or non-arrhythmic diagnosis in 65.2% of patients with recurrent syncope, presyncope or palpitations in a selected paediatric population.

P784 Compound heterozygous SCN5A mutations in an asymptomatic child: a case report in the Brugada syndrome cohort of the San Raffaele hospital

E. Sommariva[1], M. Vatta[2], K. Samani[3], S. Sala[4], T. Ai[3], F.M. Sacco[4], V. Santinelli[4], C. Pappone[4], M. Ferrari[5], S. Benedetti[6]. *[1]Center for Genomics, Bioinformatics and Biostatistics, San Raffaele, Milan, Italy; [2]Department of Pediatrics, Section of Cardiology, Baylor College of Medicine, Huston, Texas, United States of America; [3]Electrophysiology Research Laboratory, Texas Heart Institute/St. Luke's Episcopal Hospital, Huston, Texas, United States of America; [4]Department of Arrhythmology, Electrophysiology and Cardiac Pacing Unit, San Raffaele, Milan, Italy; [5]Vita-Salute San Raffaele University, Milan, Italy; [6]Laboratory of Clinical Molecular Biology, Diagnostica e Ricerca San Raffaele S.p.A., Milan, Italy*

Purpose: Loss-of-function mutations in SCN5A gene have been associated with Brugada syndrome. Genetic and clinical data of 55 patients were collected and associated to determine genotype-phenotype correlations.
Methods and Results: We identified 11 mutations in SCN5A, 6 of which were novel: 4 missense and two frameshifts causing an early truncation of the putative protein. 10 out of 20 first-degree relatives of the SCN5A-positive probands carried the same mutation, however, only 1 out of 10 was symptomatic. We found that ECG type I pattern seems poorly predictive of patients' symptoms, while it correlates with ventricular inducibility at EPS. In addition, our observations suggest that type I ECG and inducibility to the EPS study may be more frequently associated with the presence of a mutation in SCN5A and that SCN5A-positive patients are more often symptomatic than those without a mutation. However, more data are needed to confirm these trends. Despite the low prevalence of the disease among Caucasian subjects we report an occasionally-diagnosed asymptomatic child carrier of 2 heterozygous SCN5A mutations on separate alleles, inherited from the asymptomatic parents: a new deletion causing frameshift and premature truncation of the putative protein and a missense variation, previously reported twice, firstly as a disease causing mutation, but also as a variant among apparently healthy individuals. The effects of the mutations on the Na channel function were evaluated by electrophysiology studies in transfected NIH-3T3 and HEK-293 cells. Whole-cell sodium current density was significantly reduced by 60% in the deletion mutant, 40% in the missense, and an additive effect of the two mutations was observed. In addition, the missense mutation was found to rightward shift the voltage-dependency of the steady-state inactivation. Despite the mutations compromised the functionality of both alleles, Brugada-like ECG was observed only in the compound heterozygous child and not in his parents.
Conclusions: These observations underline the difficulty of genotype/phenotype correlations in Brugada syndrome patients and support the idea of a complex disorder, where different mutations and variants can contribute to the clinical phenotype. The role of genetics is for the moment restricted to the identification of pre-symptomatic mutation carriers. Anyway this role is pivotal: in our families it allowed Brugada diagnosis in 10 hidden, but potentially at risk, relatives. A longer follow-up will allow to identify parameters to improve risk stratification and to evaluate the contribution of putative modifier alleles.

P785 Regional differences in bipolar voltages during post-operative atrial tachyarrhythmias in patients with congenital heart disease: clinical implications

N.M.S. De Groot, N.A. Blom, W.K. Chan, M. Bartelings, M.J. Schalij. *Leiden University Medical Center, Leiden, Netherlands*

Introduction: Bipolar voltage (Bi-V) maps can be used to localize the arrhythmogenic substrate. This study examined the spatial distribution of Bi-V during late post-operative atrial tachyarrhythmias (AT) in patients with tricuspid atresia (TA) in order to determine whether there are predeliction sites for low voltages to occur.
Methods: CHD patients with TA (N=11, 5 males, 31±10 years) referred for ablation of AT were studied. The interval between the first surgical procedure and the first documentation of the AT was 24±9 yrs. Voltage maps were constructed by measuring the peak-to-peak amplitude of bipolar electrograms. Regional differences in Bi-V were studied by dividing maps into eight quadrants using anatomical structures and the X, Y and Z-axis.
Results: All AT (n=14, 303±77 ms) were intra-atrial reentrant tachycardias. For the entire right atrium, median Bi-V was 0.49±0.38mV and the incidence of Bi-V< 0.1mV was 17±10%. Bi-V recorded from the posterior part of the reconstruction were significantly lower than from the anterior part (posterior 0.36±0.35 mV versus anterior 0.90±0.80 mV, $p<0.001$). There were no differences in Bi-V between the lateral and septal quadrants (lateral: 0.48±0.53 mV, septal: 0.66±0.79 mV, p=0.11). Consistent with regional differences in voltages, there was a larger amount of scar tissue at the posterior quadrants (7±8%) than at the anterior quadrants (17±21%, $p<0.001$). Crucial pathways of conduction targeted for ablation were bordered by areas of scar tissue in all pts. Ablation was successful in 12/14 AT.
Conclusion: The right atrial posterior wall is a predilection site for low voltages in patients with TA. Hence, scar tissue is not mainly confined to previous incision sites. Scar tissue bordering crucial pathways of conduction in all patients emphasizes the role of scar tissue in arrhythmogenesis of post-operative AT. Based on these findings, it can be hypothesized that due to persisting pressure overload, the relative thinner smooth walled parts of the atria will be more damaged than the thicker trabeculated parts.

P786 Recurrent syncope caused by asystole provoked by vasovagal reaction during venipuncture in children

M. Shkolnikova, E. Polyakova, S. Termosesov, V. Bereznitskaya, E. Bortsova, R. Garipov, I. Ilich on behalf of Russian Federal Center fo Children's Arrhythmia. *Moscow Institute For Paediatry&Surgery, Moscow, Russian Federation*

Vasovagal mechanism is a major contributor to syncope in children. Vasovagal syncope are leading to hypotension and bradycardia. The asystole associated with venipuncture (VP) is also considered as the cardioinhibitory effect of vasovagal reaction. Even dramatic asystole during vasovagal syncope in adults is not generally accepted as an indication for pacemaker implantation. At the same time, consequences of the cardioinhibitory malignant syncope in children remain un-

clear. Objective. To evaluate effects of asystole during VP and risk of cardiac arrest in children with recurrent cardioinvashibitory vasovagal syncope.
Methods: Of 630 consecutive pts with history of recurrent syncope aged 3 to 17, in 87 pts (14%) syncope episodes occurred in response to blood or injury stimulus. Incidence of syncope varied from 1/month to 1/year (mean=1.7/ year). 24-hr Holter monitoring (HM) was performed in all 87 pts twice: on the day of VP (HM1) and on the other day (HM2).
Results: Of 87 pts, 48 did not show any symptom at VP in clinical settings, remaining 39 pts developed syncope or pre-syncope episodes. In 22 (56%) of these 39 pts asystole lasting 2.9 to 40 s (11.2±9.9 s) were registered on HM1 during the symptoms. In 9 cases syncope were associated with convulsions. One patient aged 17 experienced second episode of cardiac arrest and clinical death just after the first syncope provoked by VP. Another 3-yrs-old child experienced cardiac arrest at VP. Both pts were successfully resuscitated. In 13 of 22 pts consecutive asystoles of increasing duration (cascades) were registered at VP's syncope on HM1. HM2 revealed moderate bradycardia with the min nighttime heart rate (HR) of 39-42 bpm in 14 pts (64%) and AV block with asystole about 2 s in 1 patient. Pacemaker (only switch in case of significant pauses in HR $\geq$ 2s) was implanted in 15 of 22 pts with malignant vasovagal syncope (cardiac arrest or asystole lasting longer than 6 s). None of these pts has developed syncope during follow-up from 9 months to 2.5 years (1.9±0.6 years).
Conclusion: Our study suggests that syncope during VP in children is quite often associated with severe asystole that can lead to life threatening cardiac events. In spite of absence of generally accepted indication for pacemaker implantation for such patients, cardiac pacing in selected patients at young age can successfully prevent cardioinhibitory malignant vasovagal syncope.

ANTIBRADYCARDIA DEVICES

P787 Efficacy of CPAP therapy in patients with obstructive sleep apnea syndrome and nocturnal asystoles

N. Kurlykina. *Federal state enterprise Rosmedtechnologies. Russian Cardiologic Scientific and Industrial Complex., Moscow, Russian Federation*

Aim: To study prevalence of obstructive sleep apnea syndrome (OSAS) in patients with nocturnal asystoles, and assess the therapeutic efficiency of constant positive air pressure applied to the upper respiratory tract in this category of patients.
Methods: The study incorporated 58 patients (33 men and 4 women) of average age 50±11 years with nocturnal heart beat interruptions of over 3 seconds duration. Upon primary examination, arterial hypertension of grade II - III was revealed in 67.5% of patients, coronary heart disease in 19% of patients, diabetes mellitus in 8% of patients, and the rest 5.5% of patients lacked any cardiovascular diseases. Sinus rhythm was registered in 51 (88% of patients), and 7 (12%) of them had the constant form of atrial fibrillation. The causes of deteriorated cardiac conductance were as follows: sinoatrial blocks and sinoatrial arrests in 28 cases, atrio- ventricular block of grade II - III in 20 cases, combination of indicated forms of bradiarrhythmias in 3 cases and ventricular conductance block during the constant form of atrial fibrillation in 7 patients. According to electrophysiological study, the function of sinus node and atrio – ventricular conductance appeared to be undisturbed in all patients with sinus rhythm. All patients have undergone the polysomnographic examination. For patients with OSAS, an individual selection of therapeutic pressure was carried out using the CPAP apparatuses.
Results: OSAS was registered in 37 cases (64%) (the mean AHI was 54.9 OSAS was registered in 37 cases (64%) (the mean AHI was 54.9±28.7), of which 27 patients (73%) had severe grade of this syndrome. The effect of CPAP therapy with regard to cardiac conductance abnormalities was attained in all 31 patients with sinus rhythm and only in one patient with the constant form of atrial fibrillation.
Conclusions: In patients with sinus rhythm and severe nocturnal bradiarrhythmias associated with obstructive sleep apnea syndrome, the efficient elimination of nocturnal respiration disturbances using CPAP therapy in all cases secures stable prevention of nocturnal pauses in cardiac activity. In majority of cases this makes possible to avoid the electric cardiostimulator implantation.

P788 Comparison of the efficiency and safety of the implantation of definitive pacemaker and ICD through dissection of cephalic vein vs puncture of subclavian vein

T. Ripoll Vera, X. Fosch Mur, L. Socias Crespi, A. Garcia Sanchez, M. Borges Sa, J.M. Gamez Martinez, J. Torres Marques, D. Cremer Luengos, E. Moranta Ribas, J. Serra Creus. *Hospital Son Llatzer, Palma De Mallorca, Spain*

Introduction and objectives: The most common strategies to implant endocardial leads of definitive pacemaker (PM) and implantable cardioverter defibrillators (ICD) are through puncture of subclavian vein (SV) or dissection of cephalic vein (CV). In the last years we live through a progressive minor utilization of the CV supported by a supposed major rapidity, efficiency and safety. This prospective observacional study of cohorts compares the success and the safety of both technics.
Methods: consecutive series of 571 patients submitted to implant definitive PM or ICD in one center, from November 2002. There are compared clinical variables, success of the procedure, and intra and postoperatory complications. Includes follow-up up to january 2009.
Results: 571 patients were included (538 PM and 33 ICD). 5 operators worked in the center but only 2 used habitually the CV as first option. The CV was used successfully in 155 pacients, which supposes a success in the implant of 65% in one chamber PM and of 40% in two chamber PM (both leads through CV). Paradoxically better results were obtained in VDD leads by CV (success of 71%). In the rest (SV as first option and/or unsuccessful CV) the success of the implant was 100%. The global incidence of complications intra or postoperatory was low (7,5%), being the most frequent the displacement of the auricular lead (51%). In spite of there being a major incidence of neumothorax (0 vs 4), haematomas (2 vs 5), infections (0 vs 3), lead displacement (5 vs 13) and reinterventions (3 vs 11), were not observed statistically significant differences between 2 groups. In implants of both auricular and ventricular leads through CV (12) there was not registered any complication (p>0,05).
Conclusions: The implantation of endocardial leads of PM and ICD through SV puncture is a technic of similar safety to CV dissection, and with a superior success. The utilization of the CV is a useful and very safety alternative.

P789 Antiarrhythmia device implantation is safe under dual antiplatelet therapy

H. Dreger, A. Grohmann, H. Bondke, G. Baumann, C. Melzer. *Charite - Campus Mitte, Humboldt-Universitaet, Berlin, Germany*

Objective: The aim of this study was to compile and analyse data about complications of antiarrhythmia device implantation under dual antiplatelet therapy.
Methods: We collected data on all antiarrhythmia device implantations in our department between 2002 and 2008 and the complications that occurred under dual antiplatelet therapy (80 patients). The control group consisted of patients on acetylsalicylic acid alone or no anticoagulant therapy at all (94 patients).
Results: Procedure times did not differ significantly between the two groups for both the pacemaker implantations ($p = 0.929$) and the ICD implantations ($p = 0.066$). Fluid loss via drainage systems was increased by more than two-fold in the dual antiplatelet therapy group as compared to the control group ($p < 0.001$). However, there were no significant differences in complication rates, particularly the hematoma rate, between the dual antiplatelet therapy and the control group.
Conclusion: Antiarrhythmia device implantation is safe and can be performed without significantly increased risk of clinically relevant hematoma in patients on continued dual antiplatelet therapy.

P790 Low device implant rates in the UK: 24 hours of monitoring is just not long enough

M. Kalla, V. Brooks, G.R. Ellis, R.A. Bleasdale. *Royal Glamorgan Hospital, Cardiff, United Kingdom*

Purpose: Palpitations,presyncope and syncope are amongst the commonest cardiac symptoms presenting to an acute medical service (AMS). They may be manifestations of life threatening arrhythmias, resulting in investigations with low diagnostic yield. Holter monitoring (HM) is one such investigation. We hypothesized that in a secondary care hospital with general physicians and cardiologists providing AMS, HM continue to be requested despite access to event monitors (EM), implantable loop recorders (ILR) and further specialist investigation. We also hypothesised that although a normal HM does not exclude important arrhythmias, it would frequently result in the end of a diagnostic pathway.
Methods: 147 (53% F, mean age 60.±19.7 years) patients undergoing HM between November 2007 and March 2008were included. Requests were analysed for requesting specialty, indication, and diagnostic yield. A subset (30%) of patients' notes were reviewed to determine if further investigations were requested after a non-diagnostic HM.
Results: HM request patterns varied between specialties. General Medicine (GIM)/Care of the elderly (COTE) physicians investigate patients with syncope commonly with HM (50%/42.9% of all requests) compared to 3.8% of patients from Cardiology. Cardiologists predominantly investigated palpitations with HM. 28.6% of HM from COTE were for 'other' indications such as falls. Across all specialties, requests for presyncope±palpitations were uncommon. 16.5%(8/48) of HM for palpitations (inc AF rate assessment) were diagnostic. HM for syncope was diagnostic in 2.3% (1/43). 48 vs 24 hour recording did not improve efficacy (13% vs 23%). In patients being investigated for syncope or palpitations, 21.1% had asymptomatic arrhythmias. A review of 44 patients' medical records revealed that 70% of HM were non-diagnostic, with only 2 proceeding to further investigations (1 EM, 1 Electrophysiological Study).
Conclusions: These data show that HM continues to be requested for a wide range of indications. Despite a high percentage of non-diagnostic tests, few patients being investigated by non-cardiologists proceed to further testing. Indications for HM vary between specialties; non-cardiologists requested primarily for syncope. This may go some distance towards explaining why UK device implant rates fall well below other European nations on average. With the increasing availability of EM and ILR implantation, a change in practice is required to effectively diagnose and treat this cohort of patients.

P791 Can knowledge of coronary angiography followed by coronary revascularization change the indication and the need for pacemaker implantation ?

D. Herman, P. Osmancik, P. Stros, L. Pavkova, T. Budesinsky, J. Dvorak, V. Kocka, L. Lisa, P. Widimsky. *Cardiocenter, Department of Cardiology, 3rd Medical School Charles University and University Hospita, Prague, Czech Republic*

Background: The etiology of some kinds of bradyarrythmias has not been well esthablished yet. There only limited data about the importance of coronary revascularization as a treatment option of these bradyarrhythmias. The aim of the prospective study was to describe coronaroangiography findings and treatment in pts.bradycardia indication for pacemaker.
Methods: Fifty consecutive patients (70% male, age 73.3±10.6yrs.) admitted for enrolled pacemaker implantation with bradycardia indication were prospectivelly.All patients fulfilled standard criteria for pacemaker implantation according the national guidelines. All of them underwent coronary angiography before pacemaker implantation. Based on the finding on coronary angiography, revascularization with PCI or CABG was performed. Holter recording and clinical follow-up were performed at one and six months after coronary angiography. The pacemaker was implanted if the indication for implantation persisted at these visit.
Results: The indication for implantation of pacemaker were (15pts (30%) sick sinus syndrome, 18pts.(36%) second-degree AV block, 12pts (24%) third-degree AVblock and 5pts (10%) atrial fibrillation with bradycardia. 21 (42%) patiens were asymptomatic. Coronaroangiography referend significant stenosis in 27 (54%) pts and 19 (38%) pts. undervent revascularisation (Table 1). Out of 19 pts with revascularisation, 5 (26%) of them were without pacemaker and free of symptoms at 6month follow-up, and therefore without further indication for pacemaker implantation.

Table 1. Coronary angiography findings and r

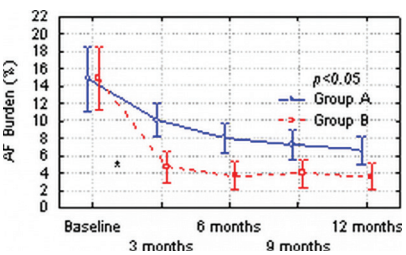
	Normal	Lession <50%	Stenosis ≥50%	Revascularization	PCI+stenst	CABG
Coronary angiography findings, pts (%)	12pts (24%)	11pts (22%)	27pts (54%)	19pts (38%)	14pts (28%)	5pts (10%)

Conclusion: The knowledge of coronary anatomy by coronary angiography before pacemaker implantation is useful and can lead to complex care of patients with bradyarrrhythmia and to change of the indication for pacemaker implantation. The prospective randomisation study is needed for other evaluation of this attitude.

P792 Atrial pacing with or without antiarrhythmic drug therapy for the prevention of atrial fibrillation in sick sinus syndrome

P. Flevari, D. Leftheriotis, D. Katsaras, S. Lagou, V. Souridis, D. Kremastinos. *Athens University Hospital Attikon, Athens, Greece*

Background: In patients (pts) with sick sinus syndrome (SSS) and paroxysmal atrial fibrillation (AF), atrial pacing may protect against AF, but data are limited. In addition, the possible additional effectiveness of sotalol is unknown. Aim of the present study was to compare atrial pacing vs atrial pacing plus sotalol for their effectiveness regarding the ability to reduced AF arrhythmic burden.
Methods: We studied 56 pts with SSS, normal AV conduction and clinical episodes of atrial fibrillation, all with an indication for permanent pacing. After implantation of an atrioventricular pacemaker, all pts were discharged from hospital in a 'back-up' pacing mode (AAI 45 bpm), for one month. Following this period, pacemakers were interrogated for the estimation of AF burden (%), and pts were randomized (1:1 fashion) to AAIR pacing (min rate 70-75 bpm, Group A) vs same pacing mode plus d,l-sotalol 120-240 mg/24h (Group B). The AF burden was assessed every 3 months for the first 12 months following randomization.
Results: As shown in the figure, a significant decrease in AF burden was observed in Group A, continuing to decrease during follow-up. In Group B, the addition of sotalol increased the therapeutic effect of AAIR pacing. The difference between groups tended to decrease over time.



Conclusions: In pts with SSS and paroxysmal AF, atrial pacing exerts a significant protection against AF. The addition of sotalol further decreases AF burden, especially during the first months following pacemaker implantation.

P793 Mode of death in patients with pacemaker and implantable cardioverter defibrillator

M. Sepsi[1], M. Sindler[2], K. Muckova[3], L. Krivan[1], M. Kozak[1], J. Vlasinova[1]. *[1]Clinic of Internal Medicine and Cardiology, Faculty Hospital, Brno, Czech Republic; [2]Department of Forensic Medicine, St. Anne's University Hospital, Brno, Czech Republic; [3]Department of Pathology Faculty Hospital Brno, Brno, Czech Republic*

Purpose of the study was to analyse mode of death in patients with pacemaker (PM) or impantable cardioverter – defibrillator (ICD) in South Moravian Region, Czech Republic together with device interrogation.
Methods: We analyzed 285 patients, who died between 2005-2007 and had autopsy. Explanted devices were examined after autopsy.
Results: In this time period 163 patients with PM VVI, 93 patients with PM DDD, 4 patients with PM CRT anad 1 patient with PM AAI died. In ICD patients, 17 patients with ICD VVI, 5 patients with ICD DDD and 2 patients with ICD CRT died. Mean age at time of implantation was 72,5±9,6 years, mean age at time of death was 77,4±9,4 years. Mean survival with device was 4,8±4,0 year (median for ICD patients 2,5 year, for PM DDD patients 4,3 years, for PM VVI 4,0 year). Immediate mode of death among ICD patients was: acute myocardial infarction (AMI) 13,6%, heart failure 59,1%, other 27,3%, in PM VVI patients: acute MI 9,8%, HF 56,4%, other 33,8%, in PM DDD patients: acute MI 14%, HF 46%, other 40%. The difference in the dead mode between Pm and ICD group was not statistically significant. Primary cause of death was atherosclerosis: 60% in ICD patients, 76,7% among PM VVI and 62,4% u PM DDD (p=0,026). All devices were functional. Depleted battery was found in 12.3% patients (elective replacement indicator). 1 device (0.4%) displaed end-of-life. We did not found any lead failure. Malignant arrhythmia was terminally found in 42% patients of the ICD group.
Conclusions: Majority of patients with implanted pacemaker or ICD die because of heart failure based on atherosclerosis. We did not found any dysfunction of implanted devices.

P794 Definitive pacemaker implantation after cardiac surgery

S. Iacopino, G. Fabiano, P. Sorrenti, A. Talerico, G. Campagna, G. Colangelo, R. Alemanni, G. Martinelli, M. Cassese. *Casa Di Cura Villa Sant'Anna, Catanzaro, Italy*

Introduction: About 2% of the patients who underwent a cardiac surgery need the implantationof a definitive pacemaker (PM) before being discharged. When it is prescribed,the early implantation of a PM lowers morbidity and hospital stay. A retrospective analysis of thepopulation who underwent cardiac surgery was carried out inorder to highlight useful predictors for the implantation of a definitive PM.
Methods: 2944 patients underwent cardiac surgery between 2005 and 2008, the average age was of 65+27, 65% were male. 1972 patients (67%)underwent a myocardial revascularization through by-pass, 472 (16%) underwent asubstitution of the aortic valve, 235 (8%) underwent a substitution of the mitralvalve, 265 (9%) underwent a correction of a double valve disease (both mitraland aortic).
Results: 72patients (2,4%) underwent the implantation of a definitive PM (the averagenumber of days from the surgical intervention to the implantation of the PM wasof 9+4 days). The prescription to the PM implantation included completeatrioventricular block in 47 patients, symptomatic bradycardia/atrialfibrillation with a low ventricular response in 19 patients, AV dissociation in6 patients. Predictors for an early PM implantation were mitral valve surgery and double valve disease (both mitral andaortic), left branch blockand recently occurred conductiondiseases (p<0,001). After an average of 24+10 months follow-up, 72%of the patients kept on being dependent on the PM.
Conclusions: Mitral valve surgery and double valve disease (both mitral andaortic), as well as pre-existentleft branch block are predictors of a high risk of definitive PM implantation after cardiac surgery.About 1/3 of the implanted patients has an AV conduction recovery in along-term follow-up. In the high risk patients it is recommendable theimplantation of a definitive PM after 5-7 days from the cardiac surgery to getearly mobilization and discharge.

P795 Direct His Bundle pacing preserves the mechanical atrial function compared to right ventricular apical pacing: a mid-term cross-over study

F. Zanon[1], S. Aggio[1], G. Pastore[1], E. Baracca[1], L. Conte[1], C. Piergentili[1], G. Rigatelli[1], G. Braggion[1], D. Cavazzini[2], L. Roncon[1]. *[1]General Hospital, Rovigo, Italy; [2]General Hospital, Adria (Ro), Italy*

Aim: to evaluate the effects of direct His bundle pacing (DHBP) versus traditional right ventricle apical pacing (RVAP) on left atrial (LA) function in patients candidate to PM implantation.
Methods: 41 patients (mean age 74±9 yo, 31 male) with narrow QRS and preserved His conduction underwent PM implantation with one lead implanted in the His Bundle and another lead in the RVAP. The study had a cross-over design: each pt was randomly paced for 3 months in one of the 2 pacing sites and at the end of each period the following echo parameters were collected: 1) LA maximal volume (V max) 2) LA minimal volume (V min) 3) LA volume at the end of passive

empting (Vp) 4) LA ejection fraction (%) 5) LA stroke volume passive emptying (Vmax-Vp/Vmax)
Results: Results are displayed in the table. (All values are indexed and corrected for heart rate and body surface)

	DHBP	RVAP	p
V max (ml/mq·sec$^{-0.5}$)	55±20	60±28	0.07
LA V min (ml/mq·sec$^{-0.5}$)	37±21	44±28	<0.001
LA Vp (ml/mq·sec$^{-0.5}$)	45±21	55±29	<0.001
LA ejection fraction (%)	35±17	30±16	<0.005
LA stroke volume passive emptying (%)	21±10	11±10	<0.001

Conclusions: in pts with standard indication for PM, narrow QRS and normal His conduction DHBP preserves the mechanical atrial function compared to RVAP after a cross over period of 3 months.

P797 Far-field-R-wave sensing avoidance through the use of a lead with very short tip-to-ring spacing

C. Kolb[1], G. Noelker[2], U. Lotze[3], H. Jetter[4], K. Puerner[5], K. Lang[6], L. Binner[7], V. Schibgilla[8] on behalf of AVOID-FFS-Study group. *[1]Deutsches Herzzentrum Muenchen, Munich, Germany; [2]Klinikum Coburg, Coburg, Germany; [3]Saale-Unstrut-Klinikum Naumburg, Naumburg, Germany; [4]Klinikum Memmingen, Memmingen, Germany; [5]Kreisklinik Ebersberg, Ebersberg, Germany; [6]Marienhausklinik Ottweiler, Ottweiler, Germany; [7]Universitätsklinikum Ulm, Ulm, Germany; [8]Klinik Fränkische Schweiz, Ebermannstadt, Germany*

Introduction: Far-field-R-wave-sensing (FFS) is the most common cause for inappropriate mode switching (AMS) in dual chamber pacemakers. Optimisation of the postventricular atrial blanking period (PVAB) significantly reduces FFS. The aim of the prospective randomised AVOID-FFS study is to investigate whether a new bipolar atrial lead with a very short tip-to-ring spacing shows equally low incidence of FFS with short PVAB as compared to optimised PVAB with standard bipolar atrial leads.
Methods: Patients (P) with indication for dual camber pacemaker implantation were included in the AVOID-FFS-Study. The patients were randomly assigned to either receive a bipolar atrial lead with a very short tip-to-ring spacing of 1.1 mm or a lead with conventional tip-to-ring spacing of 10 mm (Tendril 1388, 1688, 1788 or 1888, St. Jude Medical; control group). PVAB was not optimised in the study group but programmed to the shortest possible value of 60 ms. In the control group PVAB was optimised to a value at least 25 ms longer than the measured interval between QRS and sensed FFS at an atrial sensitivity of 0.1 mV. Atrial sensing threshold was programmed to 0.3 mV in both groups. False positive AMS caused by FFS was evaluated using stored intracardiac electrograms at 1 and 3 months post implant.
Results: A total of 204 P (121 male; age 73±10 years) were included in 10 centers. Pacemaker indications were Sinus node disease (40%), AV-Block (41%), binodal disease (16%) and other indications (2%). 104 P were randomised into the study group, 100 P into the control group. Patient characteristics did not differ between both groups. PVAB in the study group was 68±26 ms vs. 121±32 ms in the control group ($p<0.005$). False positive AMS caused by FFS was detected in 1 (1%) P of the study group and 2 (2%) of the control group (p=0.62).
Conclusions: The use of a lead with a very short tip-to-ring spacing avoids inappropriate AMS caused by FFS without need for PVAB optimisation and shows similar results as the use of a conventional lead combined with PVAB optimisation. The implantation of a lead with a very short tip-to-ring spacing has the potential to reduce the follow up burden and increases the validity of pacemaker diagnostic data.

P798 Prevalence and outcome of bacterial endocarditis

S.H. Zaky, A.W. Andraos, K.H. Hussein, S.H. Omar, G. Hamed, D. Ragab, A. Alazab. *Critical Care Department, Kasr Al Eini University Hospital, Cairo, Egypt*

Background: cardiac device infection (CDI) is a devastating complication of permanent pacemakers (PPM) or implantable cardioverter-defibrillators (ICD).The incidence and outcome of endocarditis among patients (Pts) with CDI is not well defined.
The purpose of this study is to report the experience in the prevalence, clinical presentations, and management of bacterial endocarditis (BE) among patients with CDI in a tertiary care cardiac center over 25 years.
Methods: A cohort of 2258 patients with cardiac devices implanted over 25 years (1982-2007) were studied. Out of these, 117 (5%) Pts presented with pocket infection (PI). Clinical, bacteriologic and both transthoracic (TTE) and trnsoesophageal Echocardiographic (TEE) assessments were done.
Results: Of the 117 Pts with PI, 87 (74%) had redo procedures (battery replacement in 50, repositioning of leads in 12, device extrusion in 15 or evacuation of significant haematoma in 10 pts). Of these 87 pts, 65 had re-implants on the same day of explantation. In 30 pts (26%) no apparent cause of PI was identified.
Out of the 117 Pts with PI, 30 pts (26%) had Device–related BE with vegetations appeared in all pts by TEE (15 DDD, 9 VVI, 3 CRT & 3 ICD). The clinical presentation was prolonged fever in 25 pts (83%), significant pulmonary hypertension in 3 pts (10%), severe sepsis & multi-organ failure in 2 pts (6%). Twenty-eight pts (93%) had positive blood culture (staph.aureus in 23 and enterococci in 5). There were only 2 pt with negative blood culture. Device lead vegetations (>10 mm diameter in 13) were evident in 20 pts. Ten pts presented with only right heart valves vegetations. Out of the 30 BE pts, 28 (93%) had PI while 2 pts had no apparent cause but frequent intravenous injections (one drug addict and one on regular haemodialysis). Out of the 20 pts with lead endocarditis 15 had their leads removed surgically with re-implantation of epicardial leads. Fifteen pts had only medical treatment with proper antibiotics (5 pts with lead BE and all 10 pts with valvular BE). Only one patient (7%) died in the surgical pts, vs 3 pts in the medically treated ones.
Conclusion: cardiac devices Redo procedures are major risk factors for CDI specially re-implantation on same day. Device related BE carries a serious morbidity and mortality, yet surgical removal of the whole system is the management of choice. Blood stream bactraemia is a potential risk factor in patients with cardiac devices and warrant prophylaxis against BE.

P799 The feasibility of day-case electrophysiology procedures

J.P. Boullin, A. Rajwani, C. Campbell-Cole, N. Gall, F. Murgatroyd. *King's College Hospital, London, United Kingdom*

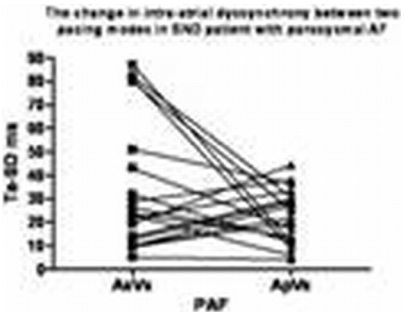
Introduction: Traditionally, invasive electrophysiology procedures - especially ablation - are performed on an inpatient (IP) basis; the principal justification is to observe for complications arising in the first 24 hours. However, this leads to longer hospital admissions which increase the burden on service provision. We hypothesised that a proportion of cases can be identified that can be planned safely on a day-case (DC) basis.
Methods: All invasive EP procedures in our unit over a three-year period were triaged according to pre-specified criteria to DC or IP treatment. Emergency cases and certain complex ablations were excluded as were patients with significant comorbidity or social issues. The DC protocol included observation for 4 hours before discharge, routine transthoracic echocardiography following transseptal procedures and specific anticoagulation requirements. Patients were followed up by telephone at 2 weeks and outpatient review at 3 months.
Results: Of 651 cases, 382 satisfied our criteria and were admitted as DC. These comprised 252 catheter ablations, 78 diagnostic studies, and 52 internal cardioversions. 345 (90.3%) were discharged as planned on the day of the procedure. 269 cases did not meet the DC criteria and underwent IP procedures (predominantly urgent cases and AF ablation). Complications occurred in 4 DC and 14 IP cases (p = 0.01). All DC complications (3 femoral haematomas, 1 AV block) were identified within the 4 hour observation period; none occurred in the following 3 months. A further 24 (6.3%) DC patients were admitted for prolonged observation (procedure completion late in day, minor pericardial effusion, etc) but did not develop complications, and 9 (2.7%) were admitted because of positive findings at EP study (7 for ICD implantation). Among IP cases, three major complications (2 tamponade, 1 AV block), and 11 minor complications (5 puncture-site) occurred during the hospital stay. Several complications were only identified >4 hours post procedure, and one patient required readmission for late pulmonary oedema following AF ablation.
Conclusions: More than 50% of invasive EP procedures in a medium-sized unit can be safely be planned for DC, though allowance should be made for a small proportion to be admitted for observation or further treatment on the basis of findings. We propose that identifying a suitable day-case population will have significant benefits for the provision of an efficient service whist maintaining patient safety.

P800 Atrial pacing improves atrial mechanical function only in patient with sinus nodes disease with paroxysmal atrial fibrillation existing atrial dyssynchrony

M. Wang, C.P. Lau, K. Lee, X.H. Zhang, C.H.W. Siu, H.F. Tse. *The University of Hong Kong, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Minimizing ventricular pacing for bradycardia reduces 40% risk of developing persistent atrial fibrillation (AF) in sinus node disease (SND). However, the impact of atrial pacing on atrial mechanical dyssynchrony and function in SND pts with paroxysmal AF (PAF) remains unclear.
Methods: 19 SND pts with PAF (mean age 71±9 years, 13 F) implanted with DDDR pacemaker for symptomatic bradycardia and normal left ventricular ejection fraction (>60%) were enrolled for study. Detailed echo with tissue Doppler imaging (TDI) during intrinsic sinus rhythm when backup AAI 40 bpm (AsVs mode) and atrial pacing at 10 bpm above sinus rhythm (ApVs mode) were performed. The peak atrial contraction velocities (Va) and the timing of mechanical events (Ta) were measured at the middle of left atrial (LA) and right atrial (RA) free wall by TDI. Intra-atrial delay was defined by the standard deviation of Ta among six segments of LA (Ta-SD >40ms).
Results: During AsVs mode, 13 pts were found Ta-SD <40ms (mean age 71±9 years, 9F) and 6 pts was found Ta-SD >40ms (mean age 71±9 years, 4F). In pts with Ta-SD >40ms, ApVs mode significantly increased in LA filling fraction (25±8 vs. 39±11, p=0.035), trended to improve in LA active emptying fraction (14±8 vs. 25±11, p=0.07), and also significantly improved Va of LA (2.0±0.8 vs.

2.6±0.7, p=0.02) compared to AsVs mode. However, there were no changes in PAF pts with Ta-SD <40ms when AsVs mode compared to ApVs mode. Intra-atrial dyssynchrony in PAF pts was present between two pacing mode in figure.



The change in intra-atrial dyssynchrony

Conclusion: Our results demonstrate that atrial pacing in SND pts with PAF significantly improved LA mechanical function in those with presence of intra-atrial dyssynchrony. However, atrial pacing had no significant impact on atrial mechanical function in those without intra-atria dyssynchrony.

P801 Which is the optimal site for atrial lead implantation in myotonic dystrophy patients? A two years follow-up study

G. Nigro[1], V. Russo[1], A. De Chiara[1], A. Rago[1], G. Arena[1], L. Politano[2], P. Golino[1], R. Calabro'[1]. *[1]Chair of Cardiology - Second University of Naples, Naples, Italy; [2]Department of Clinical and Experimental Medicine, Section of Cardiomyology and Medical Genetics, Naples, Italy*

Aim: The aim of our study was to compare the long term electrical characteristics of leads positioned in the right atrial appendage to those placed in the high atrium in the region of Backmann's Bundle in myotonic dystrophy type 1 (MD1) patients.
Methods: Twenty-five consecutive MD1 patients (18 males; 54±13 years) who underwent pacemaker implantation in our division were enrolled in the present study. The patients was divided into two groups in relation to the optimal atrial site, defined as the location with lowest pacing and highest sensing thresholds. In group I (13 patients; age 52±14; 4 F) the atrial lead was placed in the right atrial appendage (RAA) and in group II (12 patients, age 56±12, 3F) the lead was placed in the Backmann's bundle (BB) region. Measurements of intrinsic P-wave voltage, pacing threshold at a pulse duration of 0.4 ms, bipolar pacing impedance at 5 V and 0.4 ms were recorded at follow-up intervals of 6 weeks and then 12 and 24 months' post-implant.
Results: There was no statistically significant different in P wave amplitude, pacing threshold and impedance values between the two groups at 6 weeks. At 24 months follow up, the intrinsic P wave amplitude was 2,05±1,45 mV in RAA group versus 3,28±1,09 mV in BB group (P<0.05); the pacing threshold was 1,85±1,8 V in RAA group versus 0,50±0,39 V in BB group (P=0,03); the impedance was 580,08±117,15 Ohms in the RAA group versus 601,11±127,11 Ohms in the BB group (P=NS).
Conclusions: In a direct two years follow-up comparison between the right atrial appendage and Backmann's bundle atrial pacing sites, we showed a statistically significant increased pacing threshold and decreased intrinsic P wave amplitude during right atrial appendage stimulation in MD1 patients.

P802 The role of pacemaker in hypersensitive carotid sinus syndrome

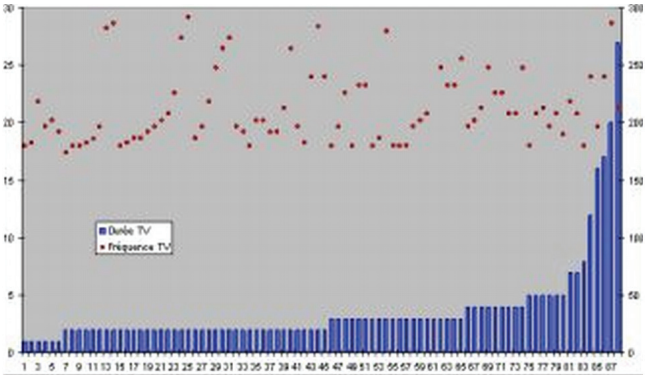
R. Lopes, A. Goncalves, J. Campos, C. Frutuoso, A. Gouveia, C. Touguinha, J. Freitas, M.J. Maciel. *Hospital de São João, Porto, Portugal*

Purpose: About 15% of patients with pure or predominant cardioinhibitory hypersensitive carotid sinus syndrome (HCS) do not experience clinical improvement after permanent pacemaker (PP) implantation, and up to 50% continue to have minor symptoms, such as dizziness. We aimed to assess the outcome of patients with HCS treated with PP and to determine predictors of symptoms recurrence.
Methods: We retrospectively analysed patients who had PP implantations for cardioinhibitory or mixed HCS from February 1990 to October 2008. Diagnosis was made based on a cardioinhibitory response (asystole>3 sec), with or without vasodepressor response (drop in blood pressure>50 mmHg), plus reproducibility of symptoms with carotid sinus massage (CSM).
Results: We included 138 patients. Mean age was 69±10.7 years and 104 (75.4%) were men. Mean follow-up period was 4.9±4.4 years. Prior to PP implantations 123 (89.1%) patients had syncope and 15 (10.9%) had near-syncope. During CSM, 117 patients (84.8%) presented a pure cardioinhibitory response and 21 (15.2%) a mixed response. Table tilt test (TTT) was performed in 93 patients (67.4%). It was negative in 66 (71.0%) patients, showed pure vasodepressor response in 18 (19.4%; 5 symptomatic) and mixed response in 9 (9.6%; 3 symptomatic). Dual-chamber PP (DDD) was implanted in 87.7% and single-chamber PP (VVI) in 12.3% of patients.
After PP implantation 115 (83.3%) patients had no further symptoms, 8 (5.8%) had minor symptoms and in 15 (10.9%) the symptoms remained unchanged. Among the patients with symptoms recurrence, 8 (38.1%) had presented a mixed response and 15 (12.8%) had a previous pure cardioinhibitory response during CSM. In Cox regression univariate analysis mixed HCS was predictor of symptoms recurrence after PP implantation [HR 2.8 (95%CI 1.2-6.7)]. The PP mode and TTT result were not related to symptoms recurrence. However, patients who had a mixed response on CSM were more likely to present a vasodepressor response (61,9% vs 19,4%; p<0,00001) and to have symptoms (28,6% vs 2,8%; p= 0,001) on TTT.
Conclusions: The rate of symptoms recurrence after PP implantation for patients with pure cardioinhibitory or mixed HCS was lower than reported in the literature. Mixed response on CSM was the only predictor of symptoms recurrence, probably due to the vasodepressor component persistence. The more frequent positive TTT results in patients with mixed HCS raises the hypothese that HCS and neurocardiogenic syncopes may have some common mechanisms.

P803 Ventricular Arrhythmias in Pacemaker Population: VAPP study

M. Guenoun[1], M. Hero[2]. *[1]Clinique Bouchard, Marseille, France; [2]Medtronic-France, Boulogne-Billancourt, France*

Aim: evaluate and describe the occurrences and characteristics of unknown ventricular arrhythmias (VA) in the population implanted for conventional indications, through the memory functions (MF) featuring EGM recordings.
Methods & Results: a continuous series of 93 pts, M 66%, F 34%, 75±10 yrs implanted for AVB 41% and SD 55% were seen in PM follow-up (f/u) between Jan and June, 2006. 497 f/u were analyzed over 2 to 81 months after implantation, and VA validated by EGMs, defined by at least 5 QRS complexes >175/mn. Number of episodes, duration and heart rate of the longest arrhythmia episodes were recorded. 24 pts (26%) 74±13 yrs of whom 78% males, showed ventricular arrhythmias in 88 f/u (18%). The avg. number of episodes was 9 per f/u (1-140), avg. duration was 4±4 seconds (1-27 sec), and avg. rate was 214±33 bpm. (174-307). The totality of the episodes were classified as non-sustained ventricular tachycardia (NSVT). The ejection fraction was 51±11%. 84% showed cardiopathy: CAD (12), HCM (4) and DCM (4). Statistical analysis showed that age, pacing indication, pacing mode and cumulated percentage of pacing are not relevant factors in NSVT.



Conclusion: VA are observed in $\frac{1}{4}$ of pts implanted for standard pacing indications. A major determining factor in the occurrence of NSVT is the presence of an associated cardiopathy. MF featuring EGM recordings are a tool for reliable diagnostic and monitoring of these events. Further studies are required to evaluate the prognostic significance of these arrhythmias.

P804 Good correlation between LV dyssynchrony and ECG (QRS duration & axis) guides the selection of the optimal RV pacing sites in patients with permanent pacemaker indication

H. Alhous[1], A. Hannah[1], G.R. Small[1], G.S. Hillis[2], P. Broadhurst[1]. *[1]Aberdeen Royal Infirmary, Aberdeen, United Kingdom; [2]The George Institute for International Health, Sydney, Australia*

Introduction: Right ventricular apical (RVA) pacing may induce LV mechanical dyssynchrony with deleterious effects on LV function. Lead placement in the RV mid inter ventricular septum (RV mIVS) or RV outflow tract (RVOT) may reduce LV dyssynchrony and improve LV performance. There are, however, few data on how to identify the optimal pacing site for each individual patient at the time of permanent pacemaker (PPM) implantation
Methods: Twenty two patients [16 (73%) male, mean age 73 years] with standard indications for PPM underwent temporary dual chamber pacing. The RV lead was placed sequentially at the RVA, RV mIVS and RVOT in random order. Detailed

echocardiographic studies and 12 lead surface ECG were undertaken at baseline (no RV pacing) and at each lead position. QRS duration and axis were calculated. Intra-ventricular dyssynchrony was assessed by the calculation of the standard deviation of the time-to-peak systolic velocity in the 12-basal and mid LV walls segments (the 'dyssynchrony index': Ts-SD). Continuous data are expressed as median values and compared using the Wilcoxon signed ranks test. Correlation coefficient calculated using Spearman's rho and its significance level

Results: RVA pacing significantly increased Ts-SD compared to baseline (39 vs. 18, p=0.001). RV septal pacing at either RVOT or RV mIVS significantly reduced Ts-SD compared to RVA pacing (15 vs. 39, p=0.001) and (18 vs. 39, p=0.011) respectively. There was a significant positive correlation (r=0.31, p=0.01), between Ts-SD and QRS duration at all RV pacing sites combined. Left axis deviation (LAD) induced by RV pacing from any site resulted in a significant increase in Ts-SD compared to baseline (41 vs. 18, p=0.005). Conversely, RV pacing with normal or right axis deviation resulted in a decrease although, not significant, in the Ts-SD compared to baseline (18 vs 15, p=0.3)

Conclusions: RV septal pacing induced less LV dyssynchrony compared with RVA pacing. The RV pacing site least likely to induce LV dyssynchrony can be selected at the time of PPM implantation by identifying the site which results in the narrowest QRS duration on ECG and does not cause LAD

P805 Efficiency of an anticoagulation algorithm in patients undergoing intracardiac device implants

B. Thibault, H. Chakor, L. Vaillancourt, M. Robitaille, M. Dubuc, P. Khairy, L. Macle, D. Roy, M. Talajic, P. Guerra. *Montreal Heart Institute, Montreal, Canada*

Balancing the risk between thromboembolic (TE) andhemorrhagic (H) complications in anticoagulated (ACO) pts undergoing pacemaker (PM) or defibrillator (ICD) implant is difficult. We designed an algorithmthat stratifies pts according to their TE risk (low vs. high TE risk) and type of procedure (low or high Hrisk). Using this algorithm ptsare divided into 3 groups: Low TE risk where ACO is stopped 3 days before theprocedure, high TE risk with low H risk where procedures are performed underACO (target INR 2.0-2.5) and high TE and H risks where ACO is stopped withheparin bridging. The purpose ofthis study was to evaluate the effects of this algorithm on hospital stay andcomplications in pts receiving ACO undergoing device implantation.

Methods: The algorithm was applied bya nurse practitioner and a pharmacist in 150 consecutive patients referred fordevice implantation. Results were compared to 366 historical controls for whomanticoagulation management was left to the physician's discretion.

Results: The 2 groups of pts weresimilar in terms of clinical characteristics and types of procedures. Ptsmanaged with the algorithm had a lower rate of heparin use compared to controls (17% vs. 42%, $p<0.001$). This was due to a very low usage in pts with low TEand H risks (1/90) and moderate usage in pts with high TE and low H risk (21/56: due to INR lower than expected). The mean duration of stay in hospitalwas significantly shorter for pts managed with the algorithm compared tocontrols (3.1±3.7days vs. 6.1±10.4,$p<0.001$). Use of heparin was associated with longer hospital stay in bothgroups (algorithm: 6.7±5.3vs. 2.4±2.8and controls: 9.4±13.7vs. 3.4±5.7 days).No TE events occurred and the number of H complications resulting inprolongation of hospitalization or re-intervention was similar in both groups (6%), most of the time occurring in pts with heparin bridging (78%).

Conclusions: In pts undergoing a PM orICD procedure, the use of an algorithm which stratifies thromboembolic (TE) andhemorrhagic (H) risks results in lower heparin use. This reduces hospital staywithout increasing the risk of TE and H complications. However, itsapplicability remains difficult with 42% of the patients presenting with lowerthan expected INR around the procedure itself, justifying heparin usage in thehigh TE risk patients. A better-refined algorithm may be needed to improve thisperformance and lower even further the need for heparin bridging.

P806 Vagal stimulation by transvenous permanent lead implantation to modulate av node function: safety and feasibility in humans

S. Bianchi[1], P. Rossi[2], A. Della Scala[3], P. Schauerte[4], P. Azzolini[1]. *[1]Fatebenefratelli Hospital, Rome, Italy; [2]OSP. BELCOLLE, Viterbo, Italy; [3]medtronic italia, Rome, Italy; [4]Universitaetsklinikum Aachen, Medizinische Fakultaet der RWTH, Aachen, Germany*

Background: Atrio-ventricular (AV) node vagal stimulation (AVNVS) has recently emerged as a novel approach to control AV dromotropic function. Animal studies demonstrated that selective epicardial AVNVS is effective in controlling VR acutely and in the long-term. Some data are available that endocardial AVNVS significantly reduces VR acutely during AF in humans.However, no data is available about long-term reproducibility of efficacy.Objectives: Our purpose was to demonstrate that postero-septal right atrium could represent a suitable site for permanentpacing and allow atrio-ventricular (AV) node vagal stimulation (AVNVS) in humans both acutely and in the follow-up.

Methods: In 12 candidates for ICD implant with history of AF, the atrial lead was implanted in the postero-septal right atrium (see fig.1), where an advanced AV block was achieved during temporary high frequency stimulation (HFS). At implant and 3-month follow-up, HFS was delivered over the permanent lead to demonstrate the possibility to gradually slow VR untilcomplete AV block.

Results: At implant, VR during AF could begradually slowed until complete AV block, elicited at 4.3V (0.2ms, 50Hz). This negativedromotropic effect remained reproducible after 3 months. No significant variationof pacing thresholds was observed after 3 months. No significant adverse eventswere reported.

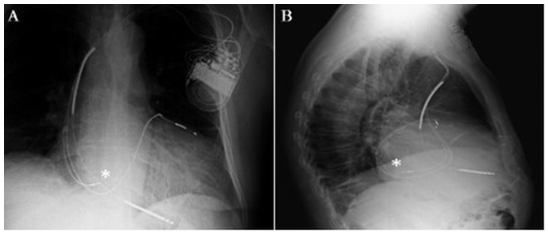


Figure 1

Conclusions: Our study demonstrates, for thefirst time in humans, that selective placement of atrial lead allows electrical characteristics suitable for permanent pacing and a significant VR decrease under HFS. These results are reproducible in the follow-up, providing data for the development of an alternative to drug treatment and/or AV node ablation.

P807 Chronic intracardiac neurostimulation in atrial fibrillation

K. Mischke, M. Zarse, C. Gemein, N. Hatam, M. Schmid, O. Rana, E. Saygili, C. Knackstedt, M. Kelm, P. Schauerte. *Universitaetsklinikum Aachen, Medizinische Fakultaet der RWTH, Aachen, Germany*

Purpose: Pharmacological ventricular rate control is a standard therapy in patients with atrial fibrillation but might be limited in some patients due to side effects of the medication used. An increase in negative dromotropy and thus decrease in ventricular heart rate can also be achieved by electrical stimulation of parasympathetic fibers that innervate the AV-node. Selective intracardiac vagal stimulation might thus be a new therapeutic approach for rate control in atrial fibrillation.

Methods: In 9 mongrel dogs, a pacemaker lead was implanted in the inter-atrial parasympathetic ganglionated plexus (IAGP) and connected to an implantable neurostimulator. An addition, a conventional DDD pacemaker was implanted for AF induction by rapid atrial pacing and for continuous ventricular rate monitoring. In a first group (n=5), intermittent neurostimulation was performed once a week during rapid atrial pacing for 6 months.

In a subsequent group (n=4), chronic AF was induced and continuous neurostimulation was used for 1-2 years. Neurostimulation output was adjusted to achieve a ventricular target rat of 100-140/min. The ventricular rate was assessed once a week without concomitant neurostimulation.

Results: In the first group weekly intermittent neurostimulation (n=5) was effective and well tolerated. Chronic continuous neurostimulation resulted in an effective ventricular rate control within the target range with a rate reduction of about 40%.

Conclusion: Chronic cardiac neurostimulation allows an effective ventricular rate control during long-term follow up.

P808 Atrial-based dual chamber pacing improve atrial mechanical function immediately in sinus nodes disease with or with paroxysmal atrial fibrillation

M. Wang, C.P. Lau, K. Lee, D. Siu, X.H. Zhang, H.F. Tse. *The University of Hong Kong, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Minimizing ventricular pacing for bradycardia reduces 40% risk of persistent atrial fibrillation (AF) in sinus node disease (SND) has been found. It is, however, not known if atrial based dual-chamber pacing will affect on atrial mechanical function in SND patients with or without AF.

Objective: The impact of atrial pacing on atrial mechanical function and dyssynchrony in SND pts with or without AF

Methods: We studied symptomatic SND patients who had DDDR pacemaker implantation and normal left ventricular ejection fraction. 28 pts (mean age 72.5±8 years old, 22female) with paroxysmal AF (PAF group, n=19) and without AF (Non AF group, n=9) were enrolled for detailed echo with tissue Doppler imaging during intrinsic sinus rhythm at least 40 bpm (AsVs model) and atrial pacing at 10 bpm above sinus rhythm (ApVs model). The peak atrial contraction velocities (Va) and the timing of mechanical events (Ta) were measured at the middle of left atrial (LA) and right atrial (RA) free wall by TDI. Intra and inter-atrial time delay was measured as the standard deviation (SD) of Ta among six segments of LA, and the time difference between LA and RA free wall, respectively. The hemodynamic changes of LA function were also assessed.

Results: As compared to AsVs, ApVs model was significant increased in LA active emptying volume and LA filling fraction either in Non AF (12±5 vs. 19±8, p=0.009; 35±7 vs. 55±14, p=0.007 respectively) and in PAF groups (9±6 vs.

12±5, p=0.009; 30±8 vs. 37±8, p=0.005 respectively). ApVs model was significant improved in mean of Va of LA in PAF group compared to AsVs (2.6±0.9 vs.3.0±1.0, p=0.028), and trended to improve in Non AF group (3.4±1.0 vs. 3.9±0.7, p=0.07). There was no difference in Va of RA both in two groups. Furthermore, neither inter- nor intra- atrial dyssynchrony did show improvement both in two groups when AsVs modulated to ApVs.
Conclusion: Atrial based dual chamber pacing in SND significant improved LA function not only in hemodynamic but also in atrial mechanical changes immediately. It may play important role to prevent the risk of AF.

P809 Magnetic resonance imaging of pacemakers and implantable cardioverter-defibrillators without specific absorption rate restriction

M. Mollerus, G. Albin, M. Lipinski, J. Lucca. *St. Mary's Duluth Clinic, Duluth, Minnesota, United States of America*

Background: Several series have been published demonstrating the relative safety of performing magnetic resonance imaging (MRI) of patients with pacemakers, but the peak Specific Absorption Rate (SAR) has been limited to 2.0 W/kg. The current study evaluates the safety profile of patients with pacemakers or implantable cardioverter-defibrillators (ICDs) undergoing an MRI scan without limitation on peak SAR.
Methods: All patients underwent scanning in a Siemens 1.5T Symphony MRI scanner. Scans were performed using usual protocols with standard peak SAR limitations for the scans. Device thresholds were obtained immediately prior to entering and immediately after leaving the MRI scanner. Pacing thresholds were measured at a fixed pulse width of 0.5 msec. Analysis was performed on all leads as an aggregate and subdivided into High-SAR (greater than 2.0 W/kg) and Low-SAR (less than or equal to 2.0 W/kg) groups. Data are expressed as median (25th, 75th percentiles).
Results: Ninety-five patients with a total of 192 leads underwent a total of 101 scans. For all scans, the median peak SAR was 2.5 (1.3, 3.2) W/kg. High-SAR scans had a median peak SAR of 3.2 (2.9, 3.2) W/kg, while Low-SAR scans had a median peak SAR of 1.3 (1.0, 1.5) W/kg. No changes in pacing thresholds were seen.

Pre- and Post-Scan Thresholds

	Pre-Scan	Post-Scan	p-Value
All Leads (192 leads)			
Pacing (V)	0.7 (0.5, 0.8)	0.6 (0.5, 0.8)	NS
Sensing (mV)	6.8 (3.0, 11.9)	6.6 (2.9, 11.2)	< 0.0001
Impedance (Ω)	492 (437, 609)	490 (430, 588)	< 0.0001
Low-SAR Leads (90 leads)			
Pacing (V)	0.6 (0.5, 0.9)	0.6 (0.5, 0.8)	NS
Sensing (mV)	6.3 (3.0, 11.2)	6.0 (2.9, 10.7)	0.02
Impedance (Ω)	495 (430, 607)	475 (429, 591)	< 0.0001
High-SAR Leads (102 leads)			
Pacing (V)	0.7 (0.5, 0.8)	0.7 (0.5, 0.8)	NS
Sensing (mV)	8.0 (3.1, 12.9)	7.2 (3.0, 12.5)	0.001
Impedance (Ω)	492 (441, 609)	490 (431, 579)	< 0.0001

Conclusion: MRI scanning may be performed safely up to a peak SAR of 3.2 W/kg. Peak SAR does not predict threshold changes.

NEUROENDOCRINE MECHANISMS IN HEART FAILURE

P810 Renal specific designer natriuretic peptide with GFR enhancing but no hypotensive properties

H. Chen, A. Cataliotti, J. Schirger, F. Martin, J. Burnett. *Mayo Clinic, Rochester Mn, United States of America*

Background: C-type natriuretic peptide (CNP) is a 22-amino-acid peptide produced mainly in the endothelium and is a ligand for a guanylyl cyclase-coupled receptor, the NPR-B receptor. Recent studies have revealed that in overt heart failure (HF), the predominant natriuretic peptide (NP) receptor in the kidney is the NPR-B receptor. CNP has a potent cardiac unloading action and reduces blood pressure but has minimal renal actions. Based on our previous knowledge, we altered the amino acid (aa) sequence in the ring structure of CNP and fused a 5 aa sequence from ANP to the N-terminus and a 6 aa sequence from BNP to the C-terminus of CNP. We hypothesized that this novel hybrid peptide ABC-NP would maintain CNP's inherent cardiac unloading characteristics plus gaining renal enhancing properties without hypotensive effects.
Methods: We determined the cardiorenal and humoral actions of intravenous infusion of ABC-NP at 2 pmol/kg/min, 10 pmol/kg/min and 100 pmol/kg/min in 7 dogs with rapid ventricular pacing induced overt HF with cardiorenal dysfunction (240 bpm for 10 days). We also assessed the cGMP response in human aortic endothelial cells (HAEC), human cardiac fibroblast (HCF) and isolated canine glomeruli * $p<0.05$
Results: IV infusion of ABC-NP enhanced glomerular filtration rate (GFR), from 31±5 to 45±7, 51±6 and 60±7 ml/min*, induce natriuresis (from 3±2 to 12±8, 17±13 and 29±19 μEq/min*) and diuresis (from 0.13±0.03 to 0.4±0.1, 0.6±0.2 and 0.8±0.3 ml/min*) with a modest reduction in pulmonary capillary wedge pressure (PCWP) (from 21±1 to 19±1, 20±1 and 21±1 mmHg*). Importantly, mean arterial blood pressure was maintained. These actions were associated with suppression of plasma renin and increases in urinary cGMP* and cAMP* excretion. cGMP generation in HAEC and HCF was minimal with ABC-NP but was significant in isolated glomeruli.
Conclusion: We report for the first time that this novel peptide ABC-NP has potent natriuretic and GFR enhancing actions without hypotensive properties in an experimental model of overt CHF. The increase of urinary cAMP excretion in addition to cGMP excretion suggests that this novel peptide may have biological effects beyond the known natriuretic peptide receptors. This renal specific peptide may have potential therapeutic benefit in states of renal dysfunction with volume overload to enhance GFR and sodium excretion without the detrimental side effect of hypotension.

P811 Prognostic values of big endothelin and NT-proBNP in predicting of mortality in patients with heart failure

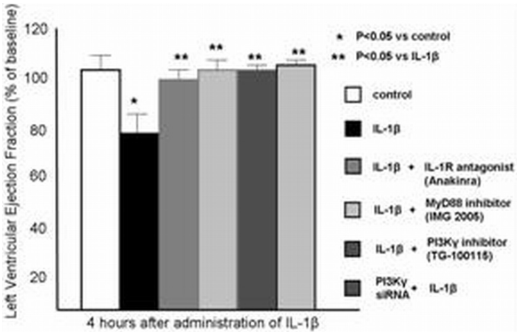
J. Zhang[1], K.M. Goode[1], J.G.F. Cleland[1], F. Fruhwald[2], A. Fahrleitner-Pammer[2], A.L. Clark[1], A. Rigby[1]. *[1]University of Hull, Hull, United Kingdom; [2]University Clinic of Internal Medicine, Graz, Austria*

Background: Both NT-proBNP and big-endothelin (Big-ET) predict morbidity and mortality in patients with heart failure and it is possible that prognostic accuracy may be improved by their combined use.
Objectives: To study the relationship between NT-proBNP and Big-ET and to evaluate the impact of NT-proBNP and Big-ET on mortality in heart failure.
Methods: Measurement of plasma concentrations of peptides was included as part of the standard assessment of patients with suspected heart failure referred to an out-patient clinic. Kaplan Meier survival curves were used to compare the predicted survival probabilities of the event of death between different tertiles of Big-ET and NT-proBNP levels. The overall comparison between different tertiles of Big-ET in each tertile of NT-proBNP was carried out by Log Rank test. Cox regression model was applied to find the important predictors of mortality. The relationship between NT-proBNP (pmol/L) and Big-ET was studied based on the value of correlation coefficient and the scatter plot. Log-transformation for both NT-proBNP and Big-ET was used through out the analysis. The end point was death within 2 years of assessment.
Results: Of 1233 patients, 724 (59%) were men. Median age was 72 (IQR 64-78), 295 (24%) patients were in NYHA class III/IV and 335 (27%) died within 2 years. The analysis showed that there was not a strong linear relationship between Big-ET and NT-proBNT in log-transformed format (ρ=0.38). Within the middle NT-proBNP tertile (37-189 pmol/L) there was a statistically significant difference between different tertiles of Big-ET (low (0-0.2]; middle (0.2-0.3] and high (>0.3)) ($\chi 2$=19.449, $p<0.001$) for mortality; similar results were found within the highest tertile of NT-proBNP (>189 pmol/L) ($\chi 2$=9.303, p=0.01). Both NT-proBNP and Big-ET predicted outcome on univariate analysis but only NT-proBNP was a significant predictor of mortality in Cox multivariate regression analysis ($p<0.001$). There was evidence of non-linear relationships between plasma concentrations of peptides and outcome. Patients in the mid-tertile of big-ET had a better outcome than patients with higher or lower levels in patients who also had elevated NT-proBNP.
Conclusions: Big-ET and NT-proBNP are both important predictors of mortality but NT-proBNP is stronger. However, in non-linear models Big-ET adds prognostic information to NT-proBNP.

P812 Interleukin-1beta induces myocardial systolic dysfunction in the mouse through a PI3K-gamma dependent pathway

B.W. Van Tassell, I.M. Seropian, J.L. Harrington, A.C. Menna, A.W. Scharf, A. Varma, R. Robati, F.N. Salloum, A. Abbate. *Virginia Commonwealth University, Richmond, United States of America*

Purpose: Myocardial dysfunction is a common clinical feature in sepsis and septic shock, associated with extremely high mortality rates. Interleukin-1 (IL-1) has been identified has a soluble cardiodepressant factor in patients with sepsis. We hereby present the results of an investigation in the mouse in vivo in which exogenous IL-1 was given and the effects on systolic function were determined in presence and absence of specific inhibitors.
Methods: Adult male mice were injected with recombinant murine IL-1β (3 μg/kg) and left ventricular (LV) fractional shortening, ejection fraction, stroke volume and cardiac output were measured at baseline and 4 hours after injection. Anakinra was used to inhibit IL-1β binding to its membrane receptor, whereas several inhibitory peptides were used to determine the signaling pathway downstream of the IL-1 receptor.
Results: IL-1β induced a transient reduction in LV fractional shortening, ejection fraction and stroke volume 4 hours after administration (all P values <0.001 vs baseline). Anakinra 1 mg/kg prevented IL-1β induced changes (all $P<0.05$ vs IL-1β alone). Inhibition of MyD88 dimer formation or IRAK 4/1 phosphorylation blocked IL-1 effects on LV systolic function ($P<0.05$). Similarly, inhibition of the PI3K-γ using 2 different inhibitors (AS605240 and TG100115) prevented IL-1 induced systolic dysfunction ($P<0.05$), whereas inhibition of PLC, COX-2, and NOS failed to prevent the reduction in LV systolic function. Similar results were obtained with silencing RNA technique for IL-1 receptor I, MyD88 and PI3K-γ.



Conclusions: IL-1 alone is sufficient to induce a septic cardiomyopathy phenotype in the mouse through a MyD88/IRAK pathway leading to PI3K-γ activation. The identification of these targets may lead to a novel treatment of septic cardiomyopathy.

P813 Post-operative B-type natriuretic peptide predicts mortality after gastrointestinal surgery

T. Cahill, P. Bowes, E. Duncan, E. Drye, S. Sen, S. Reshamwalla, C. Andrew, M. Ward, A. Bakhai. *Barnet & Chase Farm Hospitals NHS Trust, London, United Kingdom*

Purpose: Cardiac complications are a cause of significant morbidity and mortality in patients undergoing major non-cardiac surgery. Measurement of cardiac biomarkers in the perioperative period may help with diagnosis and identification of patients at risk. The aim of this study was to assess the prognostic value of post-operative B-type natriuretic peptide (BNP) level after major gastrointestinal surgery.
Methods: Between October 2007 and June 2008 99 consecutive patients undergoing elective or emergency major abdominal surgery for lower gastrointestinal or colorectal pathology were recruited. Patients were evaluated for perioperative cardiac risk according to the Lee Revised Cardiac Risk Index. ECGs and troponin I were recorded before and after surgery to identify myocardial injury and infarction. A single post-operative BNP level was measured 12-48 hours following surgery and prognostic value evaluated for all-cause mortality over a 3 month follow-up period.
Results: Mean post-operative BNP level was 240pg/ml. There were three non-fatal myocardial infarctions following surgery (3%), but 35 (35%) of patients had biochemical evidence of myocardial injury (post-operative troponin I $\geq$ 0.03ng/ml). Ten patients died over the three month follow-up period – nine of these following emergency surgery. Within the emergency population, post-operative BNP $\geq$ 400pg/ml identified patients with an odds ratio of death within 90 days of surgery of 15.2 (95% CI 3.06 –75.5, $p < 0.01$). The elective population had a low mortality, but elevated post-operative BNP at a threshold of $\geq$ 300pg/ml was associated with myocardial injury (OR 5.31, 95% CI 1.24 – 23.0, p = 0.02). The Lee Revised Cardiac Risk Index was not predictive of BNP or troponin elevation, myocardial infarction, or death for either the elective or emergency group.
Conclusions: A single BNP value in the early post-operative phase identifies patients at increased risk of death following major emergency gastrointestinal surgery.

P814 Combination of plasma cardiac troponin I and NT-proBNP for predicting mortality in patients with chronic heart failure

T. Tsutamoto, C. Kawahara, K. Nishiyama, T. Yamaji, T. Yamamoto, M. Fujii, M. Horie. *Shiga University of Medical Science, Otsu, Japan*

Background: Brain natriuretic peptide (BNP) is a well-established biomarker in patients with chronic heart failure (CHF). Other biomarkers such as cardiac troponin (cTnI or cTnT) have several limitations due to the sensitivity of the assay system.
Methods: To compare the prognostic value of cTnT (Roche Elecsys, lower limit of detection=0.01ng/mL), cTnI (Centaur TnI-Ultra, Siemens, lower limit of detection=0.006 ng/mL), brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) in the same population of CHF. Patients with recent (within 3 months) ischemic heart disease and patients with high creatinine (>2.5 mg/dL) were excluded. We measured hemodynamic parameters and plasma levels of cTnT, cTnI, BNP and NT-proBNP in 258 consecutive patients with CHF (mean EF=34%) and then prospectively followed-up for a mean period of 2.6years. In both assays of cTnT and cTnI, the lowest concentration at which the coefficient of variation was <10% were 0.03 ng/mL, respectively. Therfore, in the present study, a positive cTnT or cTnI test was defined as a level of 0.03 ng/mL or higher.
Results: During the long-term follow up, 20 patients had cardiac death. In 258 CHF patiens, serum cTnT were detectable (>0.03 ng/mL) in 34 patients (13%) and serum cTnI were detectable (>0.03 ng/mL) in 112 patients (43%), suggesting that the assay for cTnI were more sensitive than the assay for cTnT. The hazard ratio of patients with cTnT positive was 3.2 (95% confidence interval,1.14-9.0) compared to those with cTnT negative for mortality (p=0.027) and the hazard ratio of patients with cTnI positive was 4.7 (95% confidence interval,1.72-13.1) compared to those with cTnI negative for mortality (p=0.0027). On stepwise multivariate analyses, high plasma NT-proBNP (>627 pg/mL, p=0.006) and cTnI positive (p=0.013) were independent significant prognostic predictors but not cTnT positive. The hazard ratio of patients with high plasma NT-proBNP (>627 pg/mL) and cTnI positive was 5.74 (95% confidence interval, 2.33-14.28, p<0.0001) compared to those with low NT-proBNP (<627 pg/mL) or cTnI negative (<0.03 ng/mL) for mortality.
Conclusions: These results indicate that the combination of cTnI by a sensitive assay and NT-proBNP are useful for predicting mortality in patients with CHF.

P815 Differential cardiac autonomic modulation in different variants of Takotsubo cardiomyopathy

H. Bonnemeier, J. Ortak, C. Burgdorf, B. Weidtmann, M. Reppel. *Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany*

Introduction: Recently, a new variant of the transient left ventricular apical ballooning (AB)syndrome with only midventricular affection was described, suggestive for a shared pathophysiologic etiology. As in midventricular ballooning (MB) the apical segment is spared, only etiologies not related to an epicardial coronary artery distribution can be supported. Thus we hypothesized that differences in regional autonomic modulation may play a role in the genesis of these syndromes.
Methods: We prospectively enrolled 37 consecutive patients with transient left ventricular dysfunction syndrome. AB was diagnosed in 27 (73%), MB in 10 (27%) patients. Non-linear indices of heart rate dynamics [Detrended fluctuation analysis (DFA); power-law-slope (PLS)], traditional time and frequency parameters of heart rate variability (HRV), as well as deceleration capacity (DC) were determined from 24-hour-Holter-ECGs, recorded on the third day after hospital admission.
Results: There were no significant differences in baseline clinical characteristics. Mean RR-interval was higher in AB patients (908±118 vs. 835±104ms, p<0.05). There were no differences regarding parameters of time domain HRV, except higher values of SDNNi in AB patients (46.6±22 vs. 40.8±12ms; p<0.05). In frequency domain, LF and LF/HF-ratio were higher in MB patients (LF/HF-ratio 1.28±0.6 vs. 1.69±0.9, p<0.01). MB patients exhibited lower values for DC (5.98±1.4 vs. 4.55±1.4, p<0.01) and PLS (-1.13±0.15 vs. -1.27±0.18, p<0.01), and higher values for DFA-α1 (0.991±0.12 vs. 1.094±0.07) compared to AB patients.
Conclusions: This is the first study to show that there are significant differences in cardiac autonomic modulation and fractal organization of heart rate dynamics between AB and MB syndromes. Patients with MB exhibit stronger fractal correlations of short- and long-term heart rate dynamics, and lower levels of tonic parasympathetic nervous activity. Thus, the interplay between right and left cardiac autonomic nervous modulation and differences in bilateral sympathetic coactivation may be an underlying pathophysiological mechanism for AB and MB syndromes.

P816 Adjusting for clinical covariates improves the ability of BNP to distinguish cardiac from non-cardiac dyspnea

A.D. Michaels[1], R. Rogers[1], G. Stoddard[1], T. Green[1], S.P. Collins[2], W.F. Peacock[3], P. Clopton[4], A.D. Maisel[4], R. Nowak[5], J. Stehlik[1] on behalf of HEARD-IT. [1]*University of Utah, Salt Lake City, United States of America;* [2]*University of Cincinnati, Cincinnati, United States of America;* [3]*Cleveland Clinic Foundation, Cleveland, United States of America;* [4]*San Diego VA Medical Center, San Diego, United States of America;* [5]*Henry Ford Health System, Detroit, United States of America*

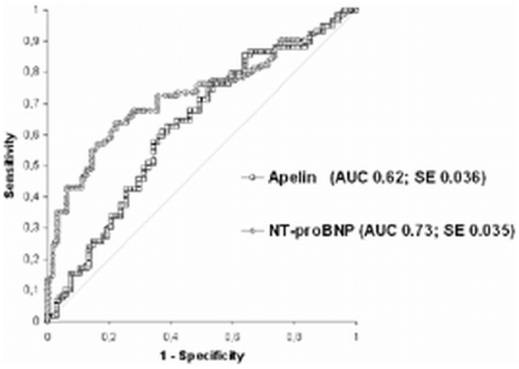
Purpose: Certain clinical covariates affect brain natriuretic peptide (BNP) levels independently of clinical heart failure (HF). We created a model that adjusts BNP levels for specific clinical covariates to improve the ability of this biomarker to distinguish cardiac from non-cardiac dyspnea in the emergency room (ER).
Methods: The HEARD-IT study is a multicenter, prospective cohort study of the diagnostic utility of acoustic cardiography in the ER. Patients over 40 years of age who presented to the ER with dyspnea were eligible. Exclusion criteria were creatinine clearance <15 mL/min and obvious non-cardiac cause of dyspnea. Two cardiologists independently adjudicated the criterion standard diagnosis of clinical HF by review of medical records through discharge from the ER or hospitalization. Using logistic regression, we developed a model that adjusts BNP for pertinent clinical covariates. The diagnostic ability of BNP alone for clinical HF as a cause of dyspnea was compared to that of the adjusted BNP model.
Results: Of 1076 patients meeting inclusion criteria, 741 pts who had BNP assays performed, did not have an elevated troponin, and had complete data form the sample for this analysis. The mean age was 66±13 years, 46% were female, 50% were African-American, and 46% were Caucasian. Clinical HF was the cause of dyspnea in 49% of patients. The clinical covariates age, gender, ethnicity, body mass index, and serum blood urea nitrogen and creatinine affected BNP levels independently of clinical HF. The model adjusting BNP for these covariates improved the discrimination between cardiac and non-cardiac dyspnea as compared to BNP alone (area under receiver operator characteristic curve

0.947 vs. 0.931, p=0.006). A net 15 of 116 (13%) patients without heart failure but with unadjusted BNP values >100 pg/mL were reclassified as not having HF with the adjusted BNP model. The net reclassification improvement, a new metric of model performance, was 4.0% for those without HF (p=0.01) as compared to the conventional BNP cutoff value of 100 pg/mL.
Conclusions: Adjusting BNP for important clinical covariates improves the ability of this biomarker to more accurately "rule-out" clinical HF as a cause of dyspnea in the ER setting. After validation, development of a clinical calculator could make this approach more clinically facile.

P817 Usefulness of Apelin measurement in identification of subclinical LV dysfunction in essential hypertension

W. Kosmala, T. Kotwica, M. Przewlocka-Kosmala, W. Mazurek.
Wroclaw Medical University, Wroclaw, Poland

LV dysfunction is a common complication of hypertension (HT), affecting long-term prognosis. Apelin – a novel endogenous peptide, possibly being involved in the pathophysiology of heart failure, might be employed as a diagnostic tool in patients with LV function abnormalities.We sought to investigate the utility of plasma apelin in the detection of LV dysfunction and to compare its discriminatory value to NT-proBNP - a laboratory gold standard in HT patients.
Methods: We studied 232 pts (age 58±11 yrs) with essential HT. The control group encompassed 76 age-matched healthy volunteers. Each subject underwent plasma apelin and NT-proBNP assessment and echo study with measurement of LV deformation indices reflecting systolic (strain and peak systolic strain rate) and diastolic function (peak early diastolic strain rate). LV dysfunction was defined as 2 standard deviations less than the mean normal values of strain and/or peak early diastolic strain rate in the controls (>18% and 1.80 1/s, respectively).
Results: LV dysfunction was found in 93 pts. The abilities of apelin and NT-proBNP to detect LV dysfunction were estimated in ROC analysis which revealed greater AUC for NT-pro-BNP than for apelin (p<0.02, Figure). Positive predictive value for apelin <180 pg/ml was 72% and for NT-proBNP >1100 pg/ml -90%. Negative predictive value for apelin >320 pg/ml was 75% and for NT-proBNP <400 pg/ml - 76%. Combined use of apelin >320 pg/ml and NT-proBNP <400 pg/ml increased negative predictive value to 88%.



Conclusion: In pts with essential HT (1) apelin is inferior to NT-proBNP in the identification of subclinical LV dysfunction; (2) using the combination of apelin and NT-proBNP improves the negative predictive value of these biomarkers suggesting the absence of LV function abnormalities.

P818 Angiotensin 1-7 acute myocardial effects and their modulation by the endocardial endothelium

P.M. Castro-Chaves, M. Pintalhao, R. Fontes-Carvalho, R. Cerqueira, A.F. Leite-Moreira. *Faculdade Medicina do Porto, Porto, Portugal*

Angiotensin 1-7 (Ang1-7) is a bioactive heptapeptide of the renin-angiotensin system. Its cardiovascular actions have recently acquired growing relevance, mainly due to its counter-regulatory actions in the angiotensin cascade. The aim of the present study was to evaluate the actions of angiotensin 1-7 on myocardial function.
Right ventricular rabbit papillary muscles were immersed in a modified Krebs-Ringer solution (1.8mM Ca^{2+}; 35°C) and electrically stimulated (0.6Hz). Increasing concentrations of Ang1-7 (10-9–10-5M) were added in the following conditions (1) baseline with intact endocardial endothelium (EE) (n=10); (2) after the selective removal of the EE with Triton X-100 (1s, 0.01%; n=8); (3) with intact EE in the presence of the Mas receptor antagonist A779 (10-5M; n=6), the AT1 receptor antagonist ZD-7155 (10-5M; n=8) or the nitric oxide synthesis inhibitor NG-nitro-L-arginine (L-NA; 10-5M; n=8). Evaluated parameters: active tension (AT), maximal velocity of increasing and decreasing tension (dT/dtmax and dT/dtmin, respectively), muscle peak shortening (PS), velocity of contraction (dL/dtmax), relaxation velocity (dL/dtmin) and time to half relaxation (tHR). The results are presented as mean±standard error (p<0.05).
Concerning the effects of Ang1-7 on contractility, we observed a significant decrease in AT, dT/dtmax, PS and dL/dtmax, maximal for the concentration of 10-5M, of -11.2±4.3%, -8.4±3.5%, -5.3±3.1% and -5.1±2.8%, respectively. There was no change on relaxation parameters namely on dT/dtmin or dL/dtmin. Time to half relaxation was significantly decreased with a maximal effect again at Ang1-7 concentration of 10-5M, which induced a shortening of -4.4±1.3%. Ang1-7 effects on myocardial properties were abolished after selective EE removal and in the presence of the Mas receptor antagonist or L-NA. The presence of ZD-7155 did not change these effects.
In conclusion, in this animal species, Ang1-7 through its binding to Mas receptor induces a negative inotropic effect modulated by the EE and nitric oxide and independent of AT1 receptors activation. These results are in favour of a counter-regulatory role of Ang1-7 in the acute modulation of myocardial function, with opposite actions to those observed with angiotensin II, the main effector of renin-angiotensin system. As the effects described in the present work were influenced by the endocardial endothelium, they may be disrupted in situations associated to endothelial dysfunction, as in heart failure or myocardial ischemia.

P819 Restoration of adrenal GRK2-mediated catecholamine production is an underlying mechanism for reduction of sympathetic activation by exercise training in heart failure

G. Rengo[1], A. Lymperopoulos[2], C. Zincarelli[2], M. Marchese[3], A. Rengo[3], E. Avallone[3], A. Filippelli[4], N. Ferrara[5], W.J. Koch[2], D. Leosco[3]. *[1]Fondazione Salvatore Maugeri, IRCCS, Telese Terme (Bn), Italy; [2]Thomas Jefferson University, Philadelphia, United States of America; [3]Azienda Ospedaliera Universitaria Federico II, Naples, Italy; [4]Secound University of Naples, Naples, Italy; [5]Università del Molise, Campobasso, Italy*

Background: Exercise training has been reported to exert beneficial effects on cardiac function and to reduce morbidity and mortality of chronic heart failure (HF). Augmented sympathetic nervous system (SNS) activity, leading to elevated circulating catecholamine (CA) levels, is a hallmark of chronic HF that significantly aggravates this disease. Exercise training has been shown to also reduce SNS overactivity in HF but the underlying mechanism(s) for this remain unidentified. We recently reported that adrenal G-protein coupled receptor kinase-2 (GRK2), an enzyme that regulates the sympatho-inhibitory α2-adrenoceptors (α2-ARs) present in the CA-producing adrenal medulla, is up-regulated in HF contributing to the chronically elevated CA levels and SNS activity of the disease. In the present study, we tested whether exercise training can affect the adrenal GRK2-α2-AR-CA production axis in the context of HF.
Methods and results: For this purpose, HF male Sprague-Dawley rats [4 weeks post-myocardial infarction (MI)] were randomized to a 10-week-long exercise training or sedentary regimen. As additional control group we included 8 sham-operated sedentary rats. At the end of this 10-week period, echocardiography revealed significant amelioration of cardiac diameters induced by exercise training. Invasive in vivo hemodynamic evaluation showed improvement of βAR-stimulated contractility in trained rats compared to controls (HF untrained). Plasma circulating CA levels were found increased in HF sedentary rats compared to sham, as expected, whereas exercise training was capable of normalizing them. The mRNA levels of several hypertrophy/remodeling related genes (Collagen-1, Transforming Growth Factor-β, Atrial Natriuretic Factor, Brain Natriuretic Peptide), whose expression was increased in HF sedentary rat hearts, were significantly lowered by exercise training. Training was also able to normalize cardiac and adrenal (72+5% reduction vs. HF untrained, n=5) GRK2 protein levels, that are normally increased in HF. Importantly, this latter finding was accompanied by a restoration of α2-AR number in the plasma membranes of adrenal glands after exercise training in HF animals.
Conclusions: These results suggest that exercise training restores the adrenal GRK2-α2-AR-CA production axis, and this might be part of the mechanism whereby this therapeutic modality normalizes sympathetic overdrive and impedes worsening of the failing heart.

P820 The arterial vasodilator action of apelin is abolished in heart failure

J.R. Dalzell[1], J.P. Rocchiccioli[1], N. Padmanabhan[2], R.C. Myles[1], C.E. Jackson[1], A. Rankin[1], M. Dunne[1], G.L. Smith[1], M.C. Petrie[3], J.J.V. Mcmurray[1]. *[1]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [2]Western Infirmary, Glasgow, United Kingdom; [3]Scottish National Advanced Heart Failure Unit, Golden Jubilee National Hospital, Glasgow, United Kingdom*

Purpose: The novel peptide apelin (AP) is the endogenous ligand for the G protein-coupled APJ receptor and both are ubiquitously expressed throughout the cardiovascular system. AP has vasodilator and inotropic actions and is also involved in fluid-volume homeostasis. These properties suggest AP could be of significance in heart failure (HF). We compared the vasodilator action of AP in mesenteric arteries (MAs) from rabbits with and without HF.
Methods: MAs were obtained from healthy control (26 vessels/13 rabbits) and HF (14/5) male New Zealand white rabbits. HF was induced by left anterior descending coronary artery ligation. Mean ejection fraction of the HF rabbits was 41.4 (SEM 1.72)%. 3mm segments of MA were isolated and mounted on a 4-channel myograph under physiological conditions for isometric tension recording. Contrac-

tile response was tested with high-potassium depolarization and norepinephrine (NE) 10μmol/L and endothelial integrity by relaxation with acetylcholine 3 μmol/L. Vessels without intact endothelium were discarded. Following pre-constriction with NE, cumulative concentration-response curves (CCRCs) were constructed for pyr1-apelin-13 (3×10^{-9}M - 3×10^{-5}M).
Results: AP produced concentration-dependent relaxation in MAs from healthy rabbits with 46 (SEM 9.2)% at maximum concentration of 3x10-5M. AP-mediated vasodilatation was abolished in MAs from rabbits with HF with -1.7 (SEM 3.3)% relaxation at maximum concentration (p=0.006) (See figure).

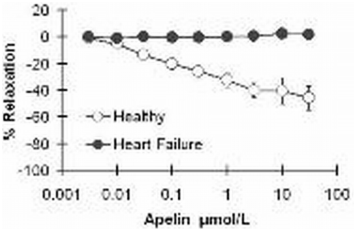


Figure 1

Conclusion: AP-mediated vasodilatation is abolished in untreated HF. The loss of the vasodilator response to AP may be due to a general diminution of nitric oxide/cGMP-mediated vasodilation in HF or a specific apelin-APJ system abnormality such as APJ receptor downregulation. Restoration of AP-mediated vasodilatation may be beneficial in HF.

P821 A potential pathophysiological role for serum soluble ST2 in post-infarction ventricular and infarct remodelling

R.A.P. Weir[1], A.M. Miller[2], S. Clements[1], T. Steedman[1], J.M.C. Connell[3], I.B. Macinnes[2], H.J. Dargie[1], J.J.V. Mcmurray[1].
[1]Western Infirmary, Glasgow, United Kingdom; [2]Glasgow Biomedical Research Centre, Glasgow, United Kingdom; [3]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom

Background: Serum concentrations of the interleukin-1 receptor family member ST2 are elevated early after acute myocardial infarction (AMI) and are associated with lower pre-discharge left ventricular ejection fraction (LVEF) and adverse cardiovascular outcomes. To date, the relationship between ST2 and serial change in left ventricular (LV) function following AMI has not been characterised.
Methods: ST2 levels were measured in serum from 100 patients (mean age 58.9±12.0 years, 77% male) admitted with AMI with resultant LV systolic dysfunction, at baseline, 12 and 24 weeks. Patients underwent cardiac magnetic resonance imaging and measurement of plasma N-terminal pro-brain natriuretic peptide (NTproBNP), norepinephrine and aldosterone at each time-point.
Results: Median ST2 decreased from 263.3 pg/mL at baseline to 140.0 pg/mL at 24 weeks ($p<0.001$) – Figure 1. ST2 correlated significantly with LVEF at baseline (r=-0.30, p=0.002) and 24 weeks (r=-0.23, p=0.026); change in ST2 correlated with change in LV end-diastolic volume index (r=-0.24, p=0.023). ST2 was positively associated with infarct volume index at baseline (r=0.26, p=0.005) and 24 weeks (r=0.22, p=0.037), and with change in infarct volume index (r=-0.28, p=0.001). ST2 was significantly higher in those with greater infarct transmurality and endocardial extent, and in the presence of microvascular obstruction. ST2 correlated significantly with norepinephrine and aldosterone, but not with NTproBNP.

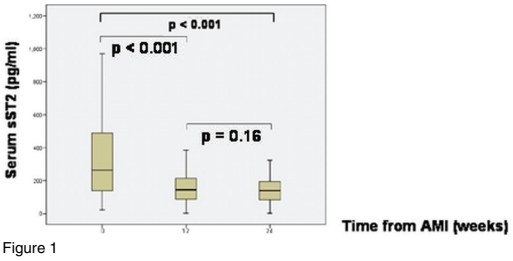


Figure 1

Conclusions: Measurement of ST2 early after AMI assists in the prediction of medium-term LV functional recovery. Novel relationships were observed between ST2, infarct magnitude/evolution and aldosterone, which may suggest a potential pathophysiological role for ST2 in ventricular and infarct remodeling after AMI.

P822 Plasma aldosterone as predictor of myocardial fibrosis in paucisymptomatic patients with nonischemic cardiomyopathy patients

P.G. Masci[1], A. Barison[2], G. Vergaro[1], G.D. Aquaro[1], M. Fontana[1], M. Lombardi[1], C. Passino[3], M. Emdin[3]. *[1]Fondazione G Monasterio/Instituto di Fisiologia Clinica, Pisa, Italy; [2]Ospedale Cisanello, Pisa, Italy; [3]Scuola Superiore Sant'Anna, Pisa, Italy*

Objectives: In patients with nonischemic cardiomyopathy (NICM), sustained neurohormonal activation promotes progressive loss of cardiomyocytes, replacement fibrosis and adverse left ventricular (LV) remodelling. Delayed enhancement (DE) magnetic resonance imaging (MRI) allows to detect gross myocardial fibrosis and to identify high-risk NICM patients. We aimed to investigate the neurohormonal determinants of DE extent in NICM patients with mild heart failure.
Methods: we prospectively studied 52 NICM patients (34 male, 58±14 years) with no or mild symptoms (NYHA class I-II) and on optimal medical treatment by the assay of creatinine, troponin I and neurohormones, and by contrast-enhanced MRI. Steady-state free-precession imaging was used to determine LV volumes, mass and ejection-fraction. DE was automatically quantified on late post-contrast segmented inversion-recovery gradient-echo images, and its extent was expressed as percentage of LV mass.
Results: Mean LV end-diastolic, end-systolic volume indexes and ejection-fraction were 135±46 ml/m^2, 91±42 ml/m^2 and 33±11% (range 16-50%), respectively. DE was detected in 23 (43%) patients and its extent was 9.1±7.2% of LV mass. At univariate analysis the plasma levels of troponin I (r=0.49, P=0.006), NT-proBNP (r=0.36, P=0.034), aldosterone (r=0.30, P=0.028), LV end-systolic index (r=0.30, P=0.035) and LV ejection-fraction (r= -0.32, P=0.024) were related with DE extent whereas no correlation was observed with age, LV end-diastolic volume index, creatinine, epinephrine, norepinephrine levels and renin activity. After adjustment for LV ejection-fraction, troponin I, NT-proBNP, the aldosterone level (median, interquartile range: 130.45 pg/ml, 139.38 pg/ml) was the only predictor of the DE extent (B=0.49, P=0.017).
Conclusion: Aldosterone level is the only predictor of the extent of myocardial fibrosis in paucisymptomatic NICM patients. This finding suggests the potential benefit of early treatment with antialdosteronic agents in this subset of patients.

P823 Sex differences in novel cardiovascular biomarkers and implications for diagnosis of acute heart failure

L.B. Daniels[1], S. Cammarata[1], P. Clopton[2], S.D. Anker[3], R. Christenson[4], C. Muller[5], R. Nowak[6], W.F. Peacock[7], A. Wu[8], A.S. Maisel[1]. *[1]Veterans Affairs San Diego Healthcare System and University of California, San Diego, San Diego, United States of America; [2]Veterans Affairs San Diego Health Care System, San Diego, United States of America; [3]Charite - Campus Virchow-Klinikum, Berlin, Germany; [4]University of Maryland School of Medicine, Baltimore, United States of America; [5]University Hospital Basel, Basel, Switzerland; [6]Henry Ford Health System, Detroit, United States of America; [7]Cleveland Clinic, Cleveland, United States of America; [8]University of California, San Francisco, San Francisco, United States of America*

Background: Understanding sex differences in baseline biomarker levels may help elucidate differences in diagnostic accuracy of various disease states. We studied sex differences in levels of novel cardiovascular prohormone fragments and their impact on heart failure (HF) diagnosis.
Methods: The Biomarkers in Acute Heart Failure (BACH) Trial was a prospective, 15-center international study of 1641 patients who presented to the Emergency Department (ED) with dyspnea and who had blood drawn on arrival for analysis of novel biomarkers. The final diagnosis, which was adjudicated by 2 independent cardiologists, was HF in 568 patients (34.6%).
Results: Men (n=859, 52%) were more likely to have a final diagnosis of HF than women (62% vs. 38%, $p<0.001$). Among patients without acute HF, men had significantly higher levels of all markers compared to women; among patients with acute HF, MR-proANP and CT-proAVP levels were significantly higher in men (Table). Diagnostic performance of each biomarker was nearly equivalent between sexes, with MR-proANP having the highest area under the receiver operator characteristic curve (AUC) in both men and women. There were no statistically significant interactions between sex and HF diagnosis.

	No Heart Failure			Heart Failure			AUC	
	Men	Women	p	Men	Women	p	Men	Women
CT-proET (pmol/L)	73	66	<0.001	149	140	0.16	0.814	0.838
MR-proADM (nmol/L)	0.72	0.67	0.032	1.39	1.41	0.86	0.796	0.819
MR-proANP (pmol/L)	98	80	0.003	452	371	0.002	0.901	0.889
CT-proAVP (pmol/L)	11	8	<0.001	29	22	0.025	0.704	0.712

Conclusion: Despite higher levels of novel prohormone biomarkers in men than in women, diagnostic performance in the setting of acute dyspnea is similar in both sexes.

P824 The chromogranins A and B are regulated differently in the myocardium and circulation during heart failure development; complimentary cardiac biomarkers?

H. Rosjo[1], C. Husberg[2], M.B. Dahl[1], M. Stridsberg[3], I. Sjaastad[2], A.V. Finsen[4], C.R. Carlson[2], E. Oie[4], T. Omland[5], G. Christensen[2]. *[1]Dep of Medicine, Akershus University Hospital, Lorenskog, Norway; [2]Institute for Experimental Medical Research, Oslo University Hospital, Ullevaal, Oslo, Norway; [3]Dep of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden; [4]Research Institute for Internal Medicine, Oslo University Hospital, Rikshospital, Oslo, Norway; [5]Faculty Division Akershus University Hospital, University of Oslo, Oslo, Norway*

Purpose: The chromogranins A and B (CgA and CgB) have recently been found to be closely associated with cardiac disease. CgA may serve as a cardiac biomarker independently predicting mortality in heart failure (HF) patients, and CgB was found to modulate development of myocardial hypertrophy in vitro. However, whether CgB is regulated in the myocardium and circulation during HF, and possibly in a similar fashion as CgA, is currently unknown.
Methods: In a post-myocardial infarction (MI) HF mouse model, animals were evaluated by echocardiography before being sacrificed one week post-MI. Gene expression was measured by qRT-PCR and protein levels by Western blotting and radioimmunoassay (RIA). Localization of chromogranin production was assessed by immunohistochemistry. Circulating chromogranin levels were measured with RIA in 80 HF patients recruited mainly from an ambulatory HF clinic and 20 age- and gender-matched healthy control subjects.
Results: CgB production was clearly upregulated in the left ventricle (LV) of HF animals compared to sham animals with a 5.2 fold increase in gene expression ($p<0.001$), and a 110% and 70% increase in protein levels in the non-infarcted and infarcted part, respectively. CgB mRNA levels in HF animals correlated with animal lung weights (r=0.74, p=0.04). CgB production was unaltered in other tissues investigated, indicating that the myocardium may contribute to circulating CgB levels in HF. CgA gene expression was also upregulated in LV tissue of HF animals (4.8 fold increase, p=0.015), however, there was no significant correlation between myocardial CgA and CgB mRNA levels in neither sham (r=0.57, p=0.14) nor HF animals (r=0.35, p=0.36). By immunohistochemistry we localized production of the chromogranins to cardiomyocytes. Circulating levels of CgB were increased in patients with HF of mainly moderate severity compared to controls (1.69 ± 0.03 vs. 1.52 ± 0.05 nmol/L, p=0.007), and levels increased according to NYHA functional class (test for trend: p=0.03), while CgA levels were not clearly regulated (7.44 ± 0.74 vs. 4.70 ± 0.30 nmol/L, p=0.10). Circulating levels of the chromogranins were only modestly correlated in HF patients (r=0.31, p=0.005), and CgB had superior diagnostic accuracy for diagnosing HF compared to CgA (ROC-AUC 0.70 vs. 0.61).
Conclusion: Myocardial production and circulating concentrations of CgB are increased in proportion to disease severity during HF development. CgB is regulated differently than CgA, another granin protein and established cardiac biomarker, suggesting that the chromogranins may reflect different biological processes in HF.

P825 The utility of cardiac biomarkers in early detection of cardiotoxicity anthracycline-induced

C. Mandric[1], A.G. Dimitriu[1], I. Miron[1], I. Dumitriu[2], B. Gurzu[2], M. Mihaila[3], A. Covic[3]. *[1]St.Mary Children Hospital, Iasi, Romania; [2]University of Medicine and Pharmacy, Iasi, Romania; [3]"C.I. Parhon" University Hospital, Iasi, Romania*

Background: Cardiotoxicity of the anthracyclines (AN) used in therapy of childhood cancer justifies the attention granted for precocious diagnosis and for monitoring,in order to reduce this new cardiovascular risk factor.
Objectives: Early detection of cardiotoxicity chemotherapy by specific biomarkers:cTnI (cardiac troponin I)and BNP (B-type natriuretic peptide) and to confirm IECA efficacy in the treatment of cardiotoxicity AN-induced.
Methods: 27 patients aged between 3-18; Patient evaluation: history and physical; electrocardiogram (EKG); chest X-ray, 2D/Doppler echocardiography (echo), cardiac biomarkers- BN,cTnI,ALAT,CPK.Patients were divided into 3 subgroups (A, B, C): A - 11 new cases of cancer; B - 10 children with subclinical cardiotoxicity echo revealed, in which the cardioprotector treatment–enalapril was applied; C - 6 children with chemotherapeutic protocol completed, no cardioprotector treatment introduced. The evaluation was made baseline (at the beginning of the study) and periodically. The interval between measurements was established in accordance to particularities of the studied subgroup.
Results: Clinical manifestations: heart failure (1), untypical clinic manifestation (mild dyspnea, fatigue, asthenia, palpitations) - (15); echo suggestive modifications for cardiotoxicity: 6 cases: diastolic dysfunction- 5cases/systolic dysfunction of the left ventricle (LV) 1case; EKG changes: insignificant (5 cases). High values of plasma BNP (cut-off value of 100 pg/mL) were noticed in 11 patients (4 cases: between 100-200 pg/ml and 7 cases: >200 pg/mL). cTnI values obtained: all cases were situated under the cut-off value of 0.04ng/mL. Increased values of plasma BNP was positive correlated with cumulative dose administered of AN and chemotherapeutic protocol followed. All children on cardioprotector treatment had normal values of BNP and cTnI. At the patients in which high values of plasmatic BNP were initially found (after the first cytostatic administered), later were seen changes of echo parameters of the LV function. In subgroup B, values of plasma BNP and cTnI were in normal limits. We couldn't establish a significant correlation between the high values of ASAT, CK obtained only in several cases and plasma BNP (>100pg/mL) or echo modification revealed in our study.
Conclusions: Our findings demonstrated that modification of plasma BNP appear much earlier compare with echo changes. No modification of serum cTnI was obtained in our study. The use of serial plasma BNP determinations and echo studies may be an useful and sensitive predictor of high-risk patients for cardiotoxicity AN-induced.

P826 Predictive value of serum aldosterone levels on long term clinical outcomes in japanese patients

K. Inoue, N. Makita, K. Matsuo, Y. Shiono, A. Matsuo, H. Fujita, M. Kitamura. *Kyoto Second Red Cross Hospital, Kyoto, Japan*

Background: Recently, It was reported higher aldosterone levels were predictors of mortality risk in patients with heart failure (HF) or myocardial infarction (MI), and mineralocorticoid receptor blockade improves survival. Despite a large number of experimental and clinical investigations on aldosterone, the prognostic significance of aldosterone in the Japanese subjects of cardiovascular outpatient clinic remains unknown.
Methods: Serum levels of aldosterone were quantified in a prospective cohort study of 739 consecutive Japanese outpatient clinic patients (425 men, 314 women, age 70.1 ± 12.6). The subjects were divided into two groups of elevated aldosterone group (group A) and non-elevated aldosterone group (group N) according to the median value of baseline aldosterone for data analysis. The primary end point of the study was cardiac death. The secondary end point was defined as death from any cause, stroke, new onset atrial fibrillation, MI and HF required hospitalizatione.
Results: The median value of baseline aldosterone was 105 mg/L in all patients. During a median follow-up of 653 days (interquartile range, 314 to 1098), 24 patients died (3.3% mortality rate). Patients of group A (n=375) with higher serum levels of aldosterone (≥105 pg/ml) had a significantly higher incidence of cardiac death, as compared to those of group N (n= 364) with lower serum levels of aldsoternoe (3.5% vs. 0.3%, p=0.0014). Although the mean age of the group A was higher than those of the group N, there was no significant difference of all cause mortality among 2 groups (3.7% vs. 2.7%). The incidence of new onset atrial fibrillation was remarkably higher in the group A than in the group N (3.5% vs. 0.3%, p=0.0014). While the group A had a tendency of higher stroke and MI events rate compared to the group N, it was not significant. The frequency of hospitalization for worsening HF was equal between two groups (2.7% vs. 2.7%). Multivariate analysis showed that elevation of aldosterone and New York Heart Association functional class were independently associated with cardiac death. Aldosterone were independent predictors of increased cardiac death risk in Cox regression analyses adjusted for age, sex, body mass index, C-reactive protein, white blood cell count, brain natriuretic peptide, sodium, eGFR, diabetes and hypercholesterolemia. The hazard ratio for higher versus lower group of aldosterone was 2.291 (95% CI, 1.25 to 3.81; p =0.018).
Conclusions: In Japanese outpatient clinic patients, higher serum levels of aldosterone was independent predictors of increased risk of cardiac death and atrial fibrillation.

P827 N-terminal fragment of proBNP is a marker of risk for right ventricular dysfunction and cardiac complications in thalassemia major

A. Pepe[1], L. Zyw[2], A. Meloni[1], C. Passino[2], A. Agazio[2], V. Positano[1], F. Fabrizio[1], M.A. Romeo[3], M. Lombardi[1], M. Emdin[2]. *[1]MRI Lab, Institute of Clinical Physiology, "G Monasterio" Foundation, Pisa, Italy; [2]Cardiovascular Medicine, "G Monasterio" Foundation, Pisa, Italy; [3]Thalassemia Unit, Pediatric Department, University of Catania, Catania, Italy*

Purpose: Cardiac complications are the main cause of morbidity and mortality in thalassemia major (TM). In particular, thalassemic cardiomyopathy include forms with right involvement difficult to detect by usual approach, whereas early diagnosis could permit early treatment and improvement in prognosis. Plasma N-terminal fragment of proBNP (NT-proBNP) concentration holds a known value in asymptomatic cardiac patients, too, but its usefulness in the management of TM has not been fully investigated. Aim of our study was to assess both diagnostic and prognostic role of NT-proBNP in a large prospective cohort of TM patients, evaluated by cardiovascular magnetic resonance (CMR).
Methods: 176 TM patients (age 30 ± 9 years, 54% females) underwent consecutively CMR (1.5 T) and blood sampling for plasma assay of NT-proBNP (ECLIA method). Myocardial iron overload was assessed using a multislice multiecho T2* approach. Cine sequences were obtained to quantify biventricular morphological and functional parameters. Myocardial fibrosis was evaluated by late gadolinium-enhanced acquisitions.
Results: NT-proBNP was associated positively with right ventricular (RV) end systolic volume (r = 0.2, P=0.045) and negatively with RV ejection fraction (EF) (r= - 0.2, P=0.001). The fibrosis group showed significantly higher NT-proBNP values vs the no-fibrosis group (median, 25th-75th percentile 171, 67-330 ng/l vs 71, 32-134; p=0.038). No correlation was observed between NT-proBNP levels and myocardial iron overload. Patients with cardiac complications (heart failure, arrhythmias, pulmonary hypertension) showed higher NT-proBNP, as compared

to patients without complications (108, 58-183 vs 64, 40-110; p=0.003). Considering abnormal NT-proBNP values (> 157 ng/L), odds ratio for RV dysfunction (EF < 49%) was 15 (3-80, OR 95%CI), and for cardiac complications 3 (1.1-7.8 OR 95%CI).
Conclusions: In TM patients NT-proBNP was significantly associated with RV global systolic function and presence of myocardial fibrosis. Abnormal NT-proBNP significantly predicts RV global systolic dysfunction and cardiac complications. These data suggest a clinical role for NT-pro-BNP assay in the anaemic TM population.

P828 Sequential measurements of emerging neurohormones in chronic heart failure

S. Neuhold[1], M. Huelsmann[1], G. Strunk[2], J. Struck[3], C. Adlbrecht[1], M. Elhenicky[1], R. Pacher[1]. *[1]Medical University of Vienna, Vienna, Austria; [2]University of Economics and Business Administration, Vienna, Austria; [3]B.R.A.H.M.S. AG, Hennigsdorf, Germany*

Background: Serial measurements of neurohormones have been shown to improve prognostication in the setting of acute heart failure (HF), or chronic HF without therapeutic intervention. We investigated the predictive accuracy of serial measurements of emerging neurohormones in a cohort of chronic HF patients while significantly increasing HF specific therapy.
Methods: In this prospective study we included 181 patients with chronic systolic HF after an episode of hospitalization for of worsening HF. Subsequently, HF therapy was continuously increased in the outpatient setting. We determined copeptin, midregional pro-adrenomedullin, C-terminal endothelin-1 precursor fragment, and midregional pro-atrial natriuretic peptide before and after optimization of HF therapy. The endpoint was all-cause mortality at 24 months.
Results: ACE/ARB and beta-blockers were increased significantly (p<0.0001 for both). In a stepwise Cox regression analysis adjusted for age, gender, and GFR, baseline levels of the neurohormones studied were stronger predictors of outcome than values after therapeutic intervention or relative change. Copeptin baseline hazard ratio (HR): 1,926, 95% confidence interval (CI): 1.233-3,007, p< 0,004; MR-proADM baseline HR: 2,788, CI: 1.297-5.995, p<0,009; MR-proANP baseline HR: 2.046,CI: 1.136-3.686, p<0,017; CT-proET baseline HR: 2,239, CI:1.133-4.425,p<0,025.
Conclusion: In pharmacologically unstable chronic HF patients, baseline values of neurohormones were the strongest predictors of outcome. To reap the full prognostic benefit of repeat measurements, a time window has to be defined including the point at which neurohormones have reached a new steady state after therapeutic intervention.

P829 Reliability of NT-pro BNP kinetics and left ventricular inotropic reserve at beta adrenergic stimulation in assessing prognosis in dilated cardiomyopathy

F. Parthenakis, A.P. Patrianakos, E.A. Zacharis, E. Nyktari, D. Arfanakis, D. Hatziiliadou, I. Saloustros, C. Goudis, P.E. Vardas.
Cardiology Dept. Heraklion University Hospital, Heraklion, Greece

Purpose: Brain Natriuretic Peptide (BNP) and Left Ventricular (LV) inotropic reserve have incremental prognostic value in dilated cardiomyopathy (DCM).This study evaluated the value of changes in plasma NT- pro BNP levels and the presence of inotropic reserve during low dose Dobutamine Stress Echocardiography (DSE) for predicting adverse outcomes in patients with DCM.
Methods: Forty three patients (31 men and 12 women, 60,8±9,6 years) with idiopathic DCM, left ventricular ejection fraction (LVEF) 31,9±7,2% and NYHA functional class III-IV underwent low dose DSE. Their NT-pro BNP levels (pg/ml) were measured before and 60 minutes after low dose DSE, wall motion score index (WMSI) was quantified during DSE and cardiopulmonary exercise testing was carried out afterwards to determine maximal oxygen uptake (peak VO2). Patients were followed up for 40 months for adverse clinical events such as hospitalization or death from worsening heart failure, sudden cardiac death and heart transplantation (Tx).
Results: Based on the WMSI changes during low dose DSE, two groups of patients were identified: Group I in which WMSI decreased >25% and Group II in which there was either no change or a ≤25% decrease in WMSI. Although baseline values of NT-pro BNP did not differ among the groups (0,745±0,356 pg/ml), the NT-pro BNP kinetics after beta adrenergic stimulation differed significantly with a considerable decrease (-10,7±12%) of NT-pro BNP levels in group I and a distinct increase in Group II (+2,4±11,2%), 60 minutes after low dose DSE, respectively. Likewise patients in group I exhibited greater peak VO2 values compared with patients in group II (20,2±3,3 vs 17,8±3,1 ml/min/kg, p=0,05). Adverse clinical events were observed in 12 patients (3 in group I vs 9 in group II). Among the variables associated with an increased hazard of clinical endpoints Kaplan Meyers analysis showed that the reduction of WMSI>25% during low DSE was the most important prognostic factor for adverse events during long term follow up of DCM patients.
Conclusion: T-pro BNP changes during DSE can predict the presence of inotropic reserve in patients with DCM. Among the different variables studied ie NT-pro BNP dynamic changes after beta adrenergic stimulation, peak VO2 and the presence of inotropic reserve, the latter seems to represent the most valuable prognostic factor of long term adverse outcomes in DCM patients.

MISCELLANEOUS

P830 The relationship between the long pentraxin 3 and B-type natriuretic peptide in patients admitted with acute coronary syndromes

T. Brugger-Andersen[1], V. Ponitz[1], F. Kontny[2], H. Staines[3], H. Grundt[4], K. Miyamoto[5], C. Miyazawa[5], T. Matsuura[5], M. Sagara[5], D.W.T. Nilsen[1]. *[1]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway; [2]Department of Cardiology, Volvat Medical Center, Oslo, Norway; [3]Sigma Statistical Services, Balmullo, United Kingdom; [4]Department of Medicine, Stavanger University Hospital, Stavanger, Norway; [5]Perseus Proteomics Inc., Tokyo, Japan*

Background: Long pentraxin 3 (PTX3) is a recently identified member of the pentraxin protein family, and elevated plasma levels are found in the acute coronary syndromes (ACS). B-type natriuretic peptide (BNP) is a well known marker of left ventricular dysfunction and heart failure, and it provides prognostic information in patients with ACS. The aim of this study was to assess the relationship between PTX3 and BNP during the first four days of hospitalization in patients admitted with ACS.
Methods: PTX3 was measured in EDTA plasma with a new, high-sensitive ELISA methodology (PPMX, Tokyo, Japan). BNP was analysed in EDTA plasma using the Microparticle Enzyme Immunoassay (MEIA) Abbott AxSYM®. The blood samples were taken on admission and after four days in 358 patients. The study cohort was also divided into subgroups according to their index diagnosis; ST-elevation myocardial infarction (STEMI) or non ST-elevation myocardial infarction (NSTEMI).
Results: The plasma concentrations of PTX3 and BNP increased from day 1 to day 4 for the total group, STEMI and NSTEMI subgroups (Table). PTX3 and BNP were correlated to each other for the total group, STEMI and NSTEMI subgroups at admission (R= 0.334 (p<0.001), R= 0.340 (p<0.001) and R = 0.322 (p<0.001), respectively), and on day 4 (R= 0.526 (p<0.001), R=0.511 (p<0.001) and R= 0.552 (p<0.001), respectively).

Table1. PTX3 and BNP following hospitalization in TnT positive (>0.05 ng/mL) chest pain patients

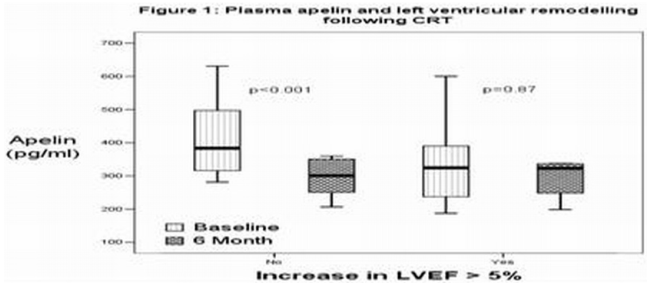
	Admission Median marker values (interquartile range)	Day 4 Median marker values (interquartile range)	Wilcoxon paired test p-value
PTX3 (ng/mL)			
Total group (n=358)	6.95 (4.35 – 11.30)	7.83 (5.61 – 11.20)	0.014
STEMI (n=l92)	6.54 (4.07 – 9.69)	7.69 (5.71 – 10.92)	0.012
NSTEMI (n=166)	7.12 (4.62 – 12.50)	8.00 (5.41 – 11.78)	0.251
BNP (pg/mL)			
Total group (n=358)	133.0 (43.0 – 416.0)	194.0 (80.0 – 499.0)	<0.001
STEMI (n=l92)	57.0 (30.0 – 210.0)	169.0 (85.5 – 348.3)	<0.001
NSTEMI (n=166)	204.5 (65.0 – 507.5)	229.0 (74.0 – 616.0)	0.025

Conclusion: PTX3 and BNP levels increase significantly from day 1 to day 4 and are strongly correlated for patients admitted with ACS.

P831 The effect of cardiac resynchronisation therapy on plasma apelin

B. Chandrasekaran[1], R. Sharma[2], J. Donovan[2], J. Stirrup[2], K. Wechalekar[2], J. Hooper[2], S.R. Underwood[1], M.R. Cowie[1], T. Mcdonagh[2]. *[1]Imperial College London, London, United Kingdom; [2]Royal Brompton Hospital, London, United Kingdom*

Purpose: Apelin is a novel, endogenous, inotropic, vasodilator peptide which acts on the APJ receptor. It is reduced in plasma of patients with heart failure and increased in myocardial tissue with favourable left ventricular (LV) remodelling. The effect of cardiac resynchronisation therapy (CRT) on plasma apelin was investigated in a homogenous population of patients with advanced heart failure.
Methods: 21 patients with an LV ejection fraction (EF) < 35% on radionuclide ventriculography (RNV), QRS > 150ms and NYHA class III on maximally tolerated pharmacological therapy underwent CRT implantation. Evaluation at baseline and after 6 months of CRT included a 6 minute walk test (6MWT), Minnesota living with heart failure questionnaires (MLWHF), plasma Brain natriuretic peptide (BNP) and plasma apelin.
Results: At 6 months LVEF increased (22%±1.6 to 27%±2.4, p<0.003), 6MWT



improved (251m±14.3 to 325m±22.4, p<0.0001) and MLWHF score decreased (48±3.5 to 28±3.3, p<0.0001). BNP (323pg/ml±60.8 to 262pg/ml±78.8, p=0.35) and apelin (360pg/ml±27.2 to 320pg/ml±23.4, p=0.3) did not change significantly. LV remodelling, defined as an increase of >5% in LVEF, was observed in 13 patients (mean increase 9.2%±0.8). There was no significant change in plasma apelin in those that remodelled however in the 8 patients who did not remodel there was a significant decrease in apelin (figure 1).

Conclusion: An improvement in LV function with CRT attenuates a reduction in plasma apelin. Apelin may play a protective role in human heart failure by preventing the onset of adverse LV remodelling.

P832 The preserved autonomic functions can avoid the development of heart failure symptoms in patients with left ventricular systolic dysfunction

S.A. Kocaman, G. Tacoy, M. Ozdemir, S.K. Acikgoz, A. Cengel. *Gazi University School of Medicine, Ankara, Turkey*

Background: Autonomic dysfunction is an important marker of prognosis in heart failure (HF) and may determine the symptoms and progression of HF. The aim of this study was to investigate whether preserved autonomic functions assessed by heart rate variability (HRV) analyses is independently related with absence of HF symptoms in patients with reduced systolic function.

Methods: Fifty patients with left ventricular ejection fraction (EF) below 40% were enrolled. The patients were divided into two groups according to their HF symptomatic status as Group 1 (NYHA functional class < II) and Group 2 (NYHA functional class ≥ II). Plasma C-reactive protein (CRP), N-terminal proB-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters and HRV indices were measured while the patients were clinically stable in each group. Factors associated with the development of HF symptoms were assessed by using multivariate regression analysis.

Results: Baseline clinical characteristics and left ventricular EF were similar in the two groups. Serum CRP (7.8±18 vs 15±21 mg/L, p= 0.011) and NT-proBNP levels (1249±1083 vs 1935±1088 pg/mL, p = 0.020) were significantly higher in group 2. The HRV parameters (SDNN, 122±42 vs 78±57 ms, p =0.001; SDNNi, 70±46 vs 36±41 ms, p <0.001; Triangular index (TI), 32±14 vs 17±12, p<0.001) were also significantly depressed in Group 2. When multivariate analysis was performed, only HRV indices of autonomic function were significantly associated with the symptomatic status (SDNN, OR: 0.983, 95% CI: 0.969-0.998, p= 0.03; SDNNi, OR: 0.969, 95% CI: 0.947-0.992, p = 0.008; TI, OR: 0.905, 95% CI: 0.844-0.971, p = 0.005).

Conclusion: Preserved autonomic functions were shown to be independently associated with absence of HF symptoms and can avoid the development of HF symptoms in patients with left ventricular systolic dysfunction.

P833 Benefits of catheter ablation of atrial flutter in patients with heart failure and structural heart disease

K.L. Leow[1], S.H. Ewe[1], L.W. Khin[1], K.L. Ho[1], Z.P. Ding[1], S.C. Chuah[1], B. Kwok[1], P.P. Goh[2], G. Leong[2], L.F. Hsu[1]. *[1]National Heart Centre, Singapore, Singapore; [2]Changi General Hospital, Singapore, Singapore*

Introduction: Patients with left ventricular (LV) dysfunction and structural heart disease are at increased risk of sudden death, the prevention of which requires an implantable cardiac defibrillator (ICD). Pharmacological treatment of atrial arrhythmias in these patients is difficult, with a high recurrence rate. We evaluated the outcome of atrial flutter (AFL) ablation in patients with moderate to severe LV dysfunction.

Methods: Patients with AFL presenting in NYHA Class II-III heart failure, and LVEF≤40% were included. Radiofrequency ablation of the cavotricuspid isthmus was performed using either an irrigated-tip or 8mm-tip catheter with the endpoint of bidirectional conduction block of the isthmus. LV function was assessed by transthoracic echocardiography before, and 6 to 12 months after ablation.

Results: 29 patients (27 male, age 60±11 years) with AFL of 12±33 weeks' duration were studied, including 1 awaiting cardiac transplantation. Structural heart disease, including ischemic and valvular disease, was present in 24 (83%). 17 (59%) had undergone a previous electrical or pharmacological cardioversion attempt, with recurrence despite maintenance on amiodarone in 15 (52%). The ablation procedure was performed in 50±32 minutes with 17±10 minutes of fluoroscopy time and without complications. Over 27±16 months' follow-up, 2 (7%) had recurrence of AFL necessitating a second procedure. However atrial fibrillation (AF) was subsequently observed in 14 (48%), of whom only 4 were persistent AF. Despite this, symptoms and LV function improved significantly (table) with LVEF improving to >40% in 17 and to >50% in 10, eliminating the need for ICD, while cardiac transplantation was deemed not necessary for the patient awaiting transplant.

Table 1

	Pre-Abalation	Post-Ablation	P-value
LVEF (%)	25±9	41±18	<0.0001
LVEDD (mm)	59±12	58±11	<0.743
LVESD (mm)	50±12	44±16	<0.009
NYHA CLASS	2.5±0.5	1.3±0.5	<0.0001

Conclusion: Catheter ablation of AFL can be performed rapidly and safely in patients with LV dysfunction and structural heart disease, leading to significant improvements in LV function and symptoms. It should be offered as primary therapy in this high-risk subgroup of patients.

P834 Impact of a heart failure management program on hospital readmission and functional status of patients with advanced heart failure

A. Khan, S.S. Kassim, M. O'Sullivan, K. Daly, J. Crowley. *University College Hospital Galway, Galway, Ireland*

Background: Heart failure is a major public health problem. Despite advanced pharmacological interventions, hospital readmission rates and morbidity remain high.

Objectives: To assess the impact of a comprehensive heart failure nurse led management program on heart failure patients.

Methods: Over a 2 year period, 125 patients with advanced heart failure (NYHA functional status II and III) were referred to the heart failure unit. Out of these, 72 patients with a mean ejection fraction of 30% were included in the study and their charts were analysed for 6 months pre and post referral. Demographics, changes in the functional status, readmission rate for cardiovascular problems, biochemical profile and changes in medications were documented. Hospital costs were estimated for in-patient stay and heart failure unit hours.

Results: During the 6 months pre referral, there were 40 admissions resulting in 190 bed days (2.63 days per patient) including 52 CCU days. Post referral, there were 9 hospital admissions for 45 bed days (0.62 days per patient), including 5 CCU days (90% reduction). Functional status improvement from NYHA III to II was noted in 24 (33%) patients. The rate of Ace-inhibitor and Beta locker up titration was 4 fold and 5 fold respectively, post referral, with 38 patients achieving maximum recommended doses. The heart failure nurse spent a total of 142.67 hrs (1.98 hrs per patient).The cost of pre referral treatment was E64890 while post referral in patient as well as heart failure nurse treatment cost was E15607. The estimated savings in the costs was E49284 (E684.5 per patient) in the 6 months follow up.

Conclusion: A Specialist heart failure unit is cost effective and allows proficient up titration of essential disease modifying medications and decreases subsequent hospital readmissions. Therefore, specialist heart failure units should be an integral part of all hospitals.

P835 Functional mitral regurgitation is a main determinant of adverse outcome in patients with heart failure due to non-ischemic dilated cardiomyopathy

C. Bergamini, A. Rossi, M. Cicoira, M. Toniolo, L. Zanolla, C. Vassanelli. *University of Verona, Verona, Italy*

Introduction: ischemic mitral regurgitation has been recently demonstrated to carry important prognostic informations in patients with left ventricular dysfunction due to coronary artery disease. There is no information regarding the prognostic role of functional mitral regurgitation in patients with non-ischemic dilated cardiomyopathy.

Methods: patients with stable heart failure due to non-ischemic dilated cardiomyopathy were prospectively enrolled. All patients underwent a comprehensive echocardiographic assessment. Left ventricular diastolic (LVD), systolic (LVS) diameters and and left atrial diameter (LAD) were measured and normalized by body surface area (BSA). Ejection fraction (EF) was measured. Restrictive mitral filling (RMP) was defined as E/A >2 or E/A >1 with E wave deceleration time <140 msec. Mitral regurgitant volume (RV) was calculated by means of proximal isovelocity surface area method. End points of the study were death or hospitalization due to worsening heart failure.

Results: 80 patients (mean age 61±9 years; 82% male) were enrolled. 10 patients reached the end points of the study. At univariate Cox analysis, the echocardiographic variables associated with the outcome were: EF (HR 0.84 95% CI 0.75 0.94; p=0.002), RMP (HR 5.2 95% CI 1.4 19.7; p=0.01), RV (HR 1.046 95% CI 1.02 1.07; p=0.0005) and LVS/BSA (HR 1.2 95% CI 1.02 1.4; p=0.03). At multivariate analysis RV remained the only variable independently associated with the outcome (p=0.04). Results did not change when LVS/BSA substituted EF in the model. Receiving operator characteristics analysis documented that, in identifying patients with adverse outcome, the area under the curve of RV, was 0.84±0.06 (95% CI 0.74 0.91) and the best cut off value for RV was 28 ml (sensitivity 80%-95% CI 44 97 and specificity 87%-95% CI 77 94). Patients with RV <28 had a survival rate of 95% after 6 years from the index echocardiogram compared with 22% in those with RV >28 (longrank 23; p<0.0001).

Conclusions: in patients with non-ischemic dilated cardiomyopathy, RV was a main predictor of death or hospitalization due to worsening heart failure.

P836 Secondary hyperparathyroidism and disturbances of calcium and phosphorus metabolism are associated with decreased cardiac and renal function and poor prognosis in chronic heart failure

E.V. Reznik[1], G.E. Gendlin[1], G.I. Storozhakov[1], V.M. Guschina[1], V.M. Volinkina[1], I.I. Baranich[2], M.E. Tursheva[2], A.V. Melekhov[1] on behalf of Academician Storozhakov's Group. *[1]Russian State Medical University, Moscow, Russian Federation; [2]12 Moscow's Clinical Hospital, Moscow, Russian Federation*

Background, aim: Abnormalities of calcium and phosphorus metabolism are important prognostic factors in chronic kidney diseases, which are common occurrence in chronic heart failure (CHF). Experimental studies of aldosteronism and clinical findings give the evidences that secondary hyperparathyroidism is a covariant of CHF. Our aim was to estimate parathyroid hormone (PTH), calcium and phosphorus status and their relationship with renal, cardiac function and prognosis in CHF pts.
Methods: 80 CHF outpatients I-III NYHA class without renal, endocrine, autoimmune, oncological, inflammatory bowel and bone diseases were included [median (interquartile range): age 62 (58-70) years; left ventricular ejection fraction (LVEF, Simpson) 36.6 (32.8-38.8)%, 96.6% males]. We estimated serum intact PTH, phosphorus and calcium corrected for albumin, microalbuminuria (immunoenzymatic assay), glomerular filtration rate (GFR, MDRD), retrospectively and prospectively collected clinical and laboratory data. All pts were stable on optimal medical therapy during 3 months before enrollment.
Results: PTH [110.74 (69.6-144.7) pg/ml] was elevated (>62 pg/ml) in 77.8% patients. GFR was >90 ml/min/1.73m^2 in 10.3%, 60-90 in 62.1%, 30-59 in 27.6%, microalbuminuria in 44.8% of pts. Hypocalcaemia (<8.6 mg/dl) was revealed in 48.3%, hypercalcaemia (>10.3 mg/dl) in 3.4%, hypophosphatemia (<0.81 mmol/l) in 10.3%, hyperphosphatemia (>1.58 mmol/l) in 6.8% of pts. Subjects with hyperparathyroidism compared to others had decreased LV EF [34.3 (30.2-28.1) vs 41.1 (36.4-44.9)%, p=0.038], GFR [63.9 (56.8-75.9) vs 84.5 (80.3-88.3) ml/min/1.73m^2, p=0.003], elevated urinary albumin excretion (15 (8.1-24) vs 5.6 (4-17.6) mg/l, p=0.044) and prolonged CHF duration (60 (52-69) vs 41 (24-42) months, p=0.049). PTH level was not associate with age, serum calcium, phosphorus, NYHA class, spironolactone and furosemide doses. Serum calcium correlated with LV end diastolic volume r=0.41, p=0.04. Serum phosphorus and calcium-phosphorus product correlated with urinary albumin excretion r=0.6, p=0.007 and r=0.61, p=0.009 at the beginning of follow-up. Cumulative proportion surviving was significantly less in group with calcium-phosphorus products higher median 33.1 (27.8-38.6) mg2/dl2 (p=0.006, Cox's F-test). After adjusting for age, weight, echocardiography parameters, GFR, only elevated calcium-phosphorus product was associated with all-cause mortality. In conclusion, hyperparathyroidism and disturbances of calcium and phosphorus metabolism are common, related with renal and cardiac dysfunction and poor prognosis in CHF pts.

P837 Urocortin-2 induced decrease in myocardial stiffness - contribution of PKA and PKC

C. Bras-Silva, M. Almeida, A.P. Fontes-Sousa, A.F. Leite-Moreira. *Faculdade Medicina do Porto, Porto, Portugal*

Purpose: The urocortin (Ucn) peptides Ucn1, Ucn2, and Ucn3 are recently isolated members of the corticotropin-releasing factor (CRF) family. It was previously demonstrated that Ucn2 acutely decreases myocardial stiffness. Several studies have shown that protein kinases, especially protein kinase (PK) A and PKC are involved in the regulation of myocardial stiffness. In the present study it was our goal to study the role of PKA and PKC in the Ucn2 induced decrease in myocardial stiffness.
Methods: The effects of increasing concentrations of Ucn2 (10-10 to 10-6M) were evaluated in right ventricular papillary muscles isolated from male New Zealand White rabbits (Krebs-Ringer: 1,8mM CaCl2, 35°C), in the presence and in the absence of: (i) PKA inhibitor (H89, 10-6M, n=9) and (ii) PKC inhibitor (Chelerythrine, 10-5M, n=9). Reported parameters include passive tension (PT; mN/mm^2) and muscle length (L; L/Lmax). Only significant results (mean±SEM, p<0.05) are given, expressed as % change from baseline.
Results: Ucn2 induced a concentration-dependent increase in resting muscle length up to 1.012±0.004 L/Lmax at the highest concentration. Correcting muscle length to its initial value resulted in a 29,6±8,9% decrease of PT, indicating a decrease in muscle stiffness. This effect was however attenuated in the presence of either PKA or PKC inhibitor. Ucn2 (10-6M) induced an increase in resting muscle length of 1,005±0,002 L/Lmax, in the presence of H89, and of 1,006±0,002 L/Lmax in the presence of Chelerythrine, corresponding to a decrease of PT of only 11,0±4,0%, and 13,3±6,4%, respectively.
Conclusions: The present study demonstrated that the physiologic adaptation mechanism induced by Ucn2, that may allow the heart to reach the same diastolic volume with up to 30% lower filling pressures, is dependent on PKA and PKC activation. These findings reinforce the relevance of Ucn2 in the pathophysiology of heart diseases and provide new elements for the comprehension of diastolic function regulation.

P838 Utility of end-diastolic strain rate for evaluation of end diastolic pressure

T. Ishizu, Y. Seo, T. Machino, M. Yamamoto, R. Kawamura, R. Kawano, K. Aonuma. *University of Tsukuba, Tsukuba, Japan*

Background: Increased chamber stiffness and elevated left ventricular end diastolic pressure (LVEDP) are central hemodynamic property in the diastolic heart failure. The speckle tracking imaging (STI) technique allows the non-invasive measurement of myocardial strain rate. We assessed the hypothesis that LV end-diastolic strain rate during atrial contraction may reflect LV passive compliance.
Methods: Doppler echocardiographic examinations with STI were performed in 50 consecutive patients who were underwent cardiac catheterization. We measured inner-, mid- and outer- myocardial peak circumferential strains rate (CSR), total wall radial strain rate (RSR) during atrial contraction using a newly developed STI software (Toshiba Medical Systems). Wall stress was calculated as formula: 0.334 × LVEDP × LVDd/Wall Thickness (1 + Wall Thickness/LVDd).
Results: LVEDP was significantly correlated with E/A ratio (r=0.30, p=0.043), E/e'(r=0.32, p=0.037), inner CSR (r=0.45, p=0.001) and total RSR (r=0.29, p=0.041). Inner-CSR was also significantly correlated with wall stress (r=0.54, p<0.001), and log-BNP (r=0.51, p=0.002). In a multiple regression analysis, Inner-CSR, LV mass, and LV volume change by atrial contraction were identified as significant determinants of LVEDP (r=0.69, p=0.009, p=0.022, p=0.008, respectively) after adjusting for LVEF and E/A ratio.
Conclusion: Endocardial circumferential deformation rate during atrial contraction reflects LV end -diastolic wall stress and LVEDP. Then, strain rate analysis with STI could be the non-invasive useful tool to assess LV passive compliance.

P839 Device monitoring of heart failure

J. Porterfield[1], L.M. Porterfield[1], S.L. Beau[2], R. Corbisiero[3], G.S. Greer[4], C. Love[5], F. Garcia[6], R. Kawasaki[7]. *[1]The University of Tennessee, Memphis, United States of America; [2]Arkansas Heart Hospital, Little Rock, United States of America; [3]Deborah Heart and Lung Center, Browns Mills, United States of America; [4]Baptist Health Medical Center, Little Rock, United States of America; [5]Ohio State Univ. Medical Center, Columbus, United States of America; [6]Hospital of the Univ. of PA, Philadelphia, United States of America; [7]Midwest Heart Foundation, Lombard, United States of America*

Purpose: Pulmonary edema (PE) is associated with fluid accumulation in the lungs. Fluid retention in the lungs leads to a decrease in impedance measured across the thorax. Device-based impedance measurements have been used to detect fluid retention prior to hospitalization. However, studies have reported a high false positive detection rate, reducing the clinical utility of these algorithms. The objective of this study was to develop and test a new multi-vector impedance based algorithm that reliably tracks PE events.
Methods: We prospectively studied patients with implanted CRT-Ds in 23 US centers. All patients were enrolled within 2 weeks of device implant. Data included daily patient diaries which documented weight and cardiac symptoms. Medical records were reviewed from ER visits hospitalizations as were blood work and chest x-ray(s). Six-vector impedance data was collected automatically by the CRT-Ds every 30 minutes during ER visits/hospitalizations and every 2 hours at all other times. A new PE tracking algorithm was developed and cross-validated using a combination of vectors. Changes in impedance during the first 30 days of lead implant was considered non-physiological and due to lead maturation.
Results: There were 75 patients (69% male), mean age 66±12 years with a LVEF 23±6% and QRS 149±25ms. The average follow-up was 7.5 months. A total of 21 major PE events were analyzed (18 cardiogenic, 3 non-cardiogenic). The algorithm showed a 71.4% sensitivity, 98.5% duration specificity, and 0.56 false positives detections per pt.-year.
Conclusions: This multi-vector impedance algorithm was effective in tracking PE events in this patient population. The favorably high specificity and low frequency of false positives make this algorithm valuable as a tool in aiding with diagnosis and appropriate treatment of the patients with PE. An expanded trial will prospectively evaluate the performance of this algorithm in a larger population over an extended time.

P840 Prevalence and implications of donor-transmitted coronary allograft vasculopathy on outcomes of heart transplant recipients

R. Estevez Loureiro, M.G. Crespo-Leiro, R.A. Calvino-Santos, M.J. Paniagua-Martin, J.M. Vazquez-Rodriguez, J. Salgado-Fernandez, N. Vazquez-Gonzalez, J.A. Rodriguez-Fernandez, J.J. Cuenca-Castillo, A. Castro-Beiras. *Complejo Hospitalario Universitario A Coruña, La Coruña, Spain*

Objectives: To determine the prevalence of donor-transmitted coronary allograft vasculopathy (DTCAV) among our heart transplant (HT) patients, and its influence on the risk of major adverse cardiovascular events (MACE).
Methods: Prospective analysis of patients who underwent HT in our centre between January 2000 and December 2007, excluding those who died in the first month post-HT and those from whom no coronary angiogram was obtained in

the first 6 months post-HT. Donor and recipient data were obtained from our institutional records. The criterion for DTCAV was angiographic visualization of at least one lesion with lumen stenosis of at least 50%, or intravascular ultrasonographic (IVUS) detection of a mean intimal thickness $\geq$ 5mm. Death, myocardial infarction/unstable angina, coronary revascularization and admission due to heart failure (excluding acute rejection) were regarded as MACE.
Results: The study group comprised 174 patients (83% men; mean age 52 years (SD 14 years); 66 (37%) with an IVUS evaluation. Mean donor age was 40 years (SD 14 years, range 2-73 years). DTCAV was detected by angiography in 7 patients (4%) and by IVUS in 35 (20%; 53% of those with an IVUS evaluation). On average, grafts with DTCAV came from older donors (53 (SD 6) vs. 39 (SD14) years, $p \leq 0.001$). Four patients underwent percutaneous revascularization during coronary angiography; these patients suffered no MACE during a mean 38 months' follow-up (SD 14 months). Among patients studied with IVUS (mean follow-up 35 (SD 19) months), only 9 (13%) suffered MACE without significant differences between groups (17% in IVUS-detected DTCAV vs. 10% in IVUS-absent DTCAV, p=0.650); and a Cox regression analysis with adjustment for relevant confounders confirmed that IVUS-detected DTCAV was not a predictor of MACE (hazard ratio 1.44, 95% confidence interval 0.31-6.75).
Conclusions: Angiographically detected DTCAV is rare among our patients (prevalence 4%), and if responded to adequately with percutaneous revascularization the 3-year outcome appears to be favourable. About half our patients have IVUS-detected DTCAV, but this condition is not associated with increased risk of MACE. The risk of DTCAV should not constitute cause for not transplanting from older donors.

P841 Corticoids withdrawal one year after heart transplantation. Experience in 265 patients

T. Garcia-Camarero, M.F. Llano Cardenal, L. Fernandez-Friera, M. Cobo Belaustegui, A. Canteli Alvarez, C. Castrillo Bustamante, V. Exposito Garcia, F. Gonzalez Vilchez, J.A. Vazquez De Prada Tife.
Hospital Universitario Marques de Valdecilla, Santander, Spain

Background: Conventional immunosuppression after Heart Transplantation (HTx) is based on triple therapy (a calcineurin inhibitor, an antimetabolite and steroids). To avoid side effects, mid-term withdrawal of corticosteroids has been proposed. Although there is a body of encouraging experience, the majority of HTx groups do not seem to feel confident with this approach. Actually, as revealed by the last (2008) ISHLT registry report, 63% of patients remain on corticosteroids after the first year of Htx, and this figure has remained unchanged from 2004 to 2006. We present our experience with a cohort of 325 HTx in which prednisone withdrawal was attempted.
Methods: In 325 patients >1 year after HTx on conventional triple therapy, an attempt to prednisone withdrawal was considered clinically reasonable, given a stable situation and no history of rejection or other contraindications. Therefore, prednisone was tapered to complete withdrawal in a 4-6 month period. We scheduled a close clinical and echocardiographic follow-up, without routine biopsies.
Results: Prednisone withdrawal was accomplished in 265 (82%) of patients 34+23 months after HTx (Interquartile range (IQR) 7-155 months; median 26). The follow up period has been 81+44 months (IQR 1-188 months; median 80). In 77 (29%) of patients, prednisone reintroduction was eventually decided at an average of 60+42 months after withdrawal (IQR 1-158; median 59). The main reasons for prednisone reintroduction were acute rejection (48%) and immunosuppressive regimen readjustment (30%). In 16 patients, a further prednisone withdrawal attempt was finally successful. Therefore, from the initial cohort of 265 patients, permanent prednisone withdrawal was finally achieved in 204, indicating a success rate of 77%. Actuarial survival for the whole cohort (intention to withdraw) was 91% at 5 years and 82% at 10 years. The cumulative mortality from rejection was 2.6% over the follow-up period.
Conclusions: Our experience illustrates that it is possible to successfully withdraw corticosteroids in a substantial number of patients one year after HTx. This approach does not translate into an increased mortality related to rejection. Therefore, this strategy should be routinely attempted in the appropriate clinical setting in order to avoid the well known secondary effects of chronic corticosteroid therapy.

P842 Heart failure-induced skeletal myopathy is associated with mitochondrial dysfunction

A. Schrepper, M. Schwarzer, P. Amorim, F.W. Mohr, T. Doenst.
Herzzentrum der Universitaet Leipzig, Leipzig, Germany

Background: Skeletal myopathy is often associated with heart failure. The mechanism for this association is not fully clear. In heart failure, mitochondrial dysfunction has been suggested as a cause for dysfunction, but in skeletal muscle non-mitochondrial mechanisms are being discussed. Oxidative skeletal muscle shares many similarities with heart muscle.
Objective: To test, that respiratory capacity of cardiac and oxidative skeletal but not glycolytic skeletal muscle is impaired in heart failure.
Methods: Heart failure was induced in rats by 20 weeks of aortic banding. Cardiac function was assessed by echocardiography. Mitochondrial subpopulations (interfibrillar IFM and subsarcolemmal SSM) were isolated with differential centrifugation and respiratory capacity (state 3) was assessed with different substrates using a Clark electrode in heart muscle, oxidative (gastrocnemius) and glycolytic (soleus) skeletal muscles.
Results: Twenty weeks of pressure overload caused reductions in fractional shortening (53±8% vs. 75±6%; p<0,05), LV dilatation (LVEDD 9,9±0,6 vs. 7,6±0,3; p<0,05) and dyspnoea. State 3 of cardiac mitochondria was reduced in IFM (natomsO/min/mg protein: glutamate 239±64 vs. 503±91, palmitoylcarnitine 241±27 vs. 521±83 and pyruvate 198±14 vs. 615±107; p<0,05). In skeletal muscle, both types of muscle mitochondria demonstrated reduced respiratory capacity (glutamate: gastrocnemius IFM 74,6±16,1 vs. 152±20, SSM 98,4±13,6 vs. 219±41; soleus 54,4±13,3 vs. 104±21; p<0,05). ADP/O was not different to control in all muscle types (e.g., heart muscle: glutamate 2,3±0,1 vs. 2,3±0,2).
Conclusion: Heart failure associated skeletal myopathy goes along with mitochondrial respiratory defects irrespective of the metabolic muscle type. The similarity of the findings in heart and skeletal muscle suggests a common regulatory mechanism for the observed dysfunction, which appears to be independent of workload.

P843 Extracellular matrix in Tako-Tsubo cardiomyopathy: a potential cause for structural defects and myocardial dysfunction

H.M. Nef[1], H. Moellmann[1], C.B. Behrens[2], S. Voss[1], C. Troidl[2], S. Kostin[3], P. Hilpert[2], M. Weber[1], C.W. Hamm[1], A. Elsaesser[4].
[1]Kerckhoff Klinik GmbH, Bad Nauheim, Germany; [2]Franz-Groedel-Institut der Kerckhoff-Klinik GmbH, Bad Nauheim, Germany; [3]Max-Planck-Institut fuer Herz und Lungenforschung, Bad Nauheim, Germany; [4]Klinikum Oldenburg, Oldenburg, Germany

Background: Catecholamine-triggered effects play a pivotalrole in the pathogenesis of Tako-Tsubo Cardiomyopathy (TTC). Initial studies showed that the extracellular matrix (ECM) is altered and transformation of ECM mediatorsis present. The structure and composition of the ECM is an essential parameterfor the maintenance of cardiac function. Therefore, the aim of our study was to characterize alterations of ECM and their underlying molecular mechanisms and stimuli in TTC.
Methods: In total, 12 patients in who TTC was diagnosed were included into the study. Left ventricular myocardialbiopsies were obtained from all patients in the acute phase of TTC (acute) and after functional recovery (Rec, 12±4 days). An intraindividual comparison of the samples was performed. Additionally, serial blood samples were taken every 24 hours. Quantitative RT-PCR and Western blot analysis were performed to detect the expression of transforming-growth-factor-β (TGF-β), osteopontin (OPN) and tissue-inhibitors-of-metalloproteinases (TIMPs) 3 and 4. The activity of matrix metalloproteinases (MMPs) 2 and 9 was analyzed with quantitative zymography. Quantitative analysis of fibronectin, collagen 1 and 3, CD31, connective tissue growth factor (CTGF), vimentin and α-smooth muscle actin was performed by immunohistochemistry. Serum level of angiotensin-II (Ang-II) was measured with a competitive ELISA.
Results: In the acute phase of TTC, asignificant increase of collagen1, fibronectin and myofibroblasts was evident. Capillary density significantly decreased (Acute: 78±3/mm^2, Rec: 100±10/mm^2). The pro-fibrotic mediators TGF-β, CTGF and OPN were upregulated in the acute phase. Accordingly, the protein amount of TGF-β(Acute: 0.63±0.03, Rec: 0.40±0.06), CTGF (Acute: 5.59±0.12, Rec: 6.54±0.18) and OPN (Acute: 0.63±0.03, Rec: 0.40±0.06) was significantly increased. MMP-2 activity (Acute: 0.35±0.01, Rec: 0.39±0.09) and MMP-9 activity (Acute: 0.51±0.09, Rec: 0.84±0.08) was decreased in the acute phase. Expression of TIMP-3 (Acute: 1.30±0.04, Rec: 0.7±0.11) and TIMP-4 (Acute: 1.38±0.05, Rec: 0.53±0.22) showed a significant increase. Increased serumlevels of Ang-II were detected in the acute phase of TTC.
Conclusion: TTC is associated with alterations of globular as well as fibrillar ECM components and a decreased capillary density in the myocardium. These rapid changes in the acute phase of TTC are the result of a disturbed MMP/TIMP-ratio and an enhanced influence of catecholamine-sensitive, pro-fibrotic mediators (TGF-β, Ang-II, CTGF). Thus, a modified ECM homeostasis might play a pivotal role in the development of cardiac dysfunction in TTC.

P844 Echocardiographic predictors of mortality change with aging in patients with chronic heart failure due to reduced systolic function

G. Bajraktari[1], P. Fontanive[2], S. Elezi[1], V. Berisha[1], A.M. Napoli[2], F.L. Dini[2]. *[1]Service of Cardiology, University Clinical Centre of Kosova, Prishtina, Kosovo UNMIK; [2]Unità Operativa Malattie Cardiovascolari 2, Ospedale Santa Chiara, Pisa, Italy*

Background and Aim: In previous studies several clinic, echocardiographic and biochemical predictors for cardiac events have been shown in patients with chronic heart failure (HF). However, the effect of aging in these predictors is unclear. The aim of our study was to assess the effect of age in these predictors in patients with chronic HF due to left ventricular (LV) systolic dysfunction.
Methods: This study included 698 consecutive patients (age 70±11 years) with chronic HF due to reduced LV systolic function (LV ejection fraction <45%). A complete M-mode, two-dimensional and Doppler echocardiographic study was performed in all patients. LV restrictive filling pattern was defined by a mitral E

wave deceleration time <150 ms. All-cause mortality was the major end point. Patients were followed-up for 38±18 months.
Results: Mean LV ejection fraction was 33±9%. Multivariate analysis identified advanced NYHA class (OR=1.78, 95% CI 1.25-2.54; P=0.002), reduced LV ejection fraction (OR=0.95, 95% CI 0.92-0.97; P=0.001), LV restrictive filling pattern (OR=2.22, 95% CI 1.31-3.76; P=0.003) and older age (OR=1.03, 95% CI 1.00-1.05; P=0.024) as independent correlates of mortality. These independent correlates changed with the aging: in the younger tertile (26-66 years) LV ejection fraction (OR=0.94, 95% CI 0.88-1.00; P=0.049) emerged as the single best predictor, in the middle tertile (67-75 years) LV restrictive filling pattern was the best (OR=3.30, 95% CI 1.34-8.13; P=0.009), whereas in the older tertile (76-98 years) again LV ejection fraction (OR=0.94, 95% CI 0.89-0.98; P=0.007) became the only correlate of mortality in these patients.
Conclusions: In patients with chronic HF, older age, high NYHA class, low LV ejection fraction and presence of LV restrictive filling pattern were independent correlates of the mortality. Predictors of all-cause mortality changed with age and LV restrictive filling pattern emerged as the single best predictor in the intermediate range of 67-75 years.

P845 The effect of transient changes in laboratory parameters on distant mortality of patients hospitalized for heart failure

K. Kaminski[1], K.M. Goode[2], J. Zhang[2], A.L. Clark[2], J.G.F. Cleland[2]. *[1]Medical University of Bialystok, Bialystok, Poland; [2]Department of Academic Cardiology, University of Hull, Hull, United Kingdom*

Several simple laboratory variables may be used to predict prognosis in patients hospitalised with heart failure (HF). However, whether their changes during hospitalization are transient and return to pre-decompensation levels or whether they persist has not been studied. The prognostic significance of transient, compared to persistent changes has also not been studied.
Aim: -To investigate the effect of transient changes of simple laboratory parameters on prognosis in patients hospitalized due to HF.
Patients with HF and a left ventricular systolic dysfunction who were assessed as out-patients in the 6 months prior to an admission with HF were included in this analysis. Serum urea, creatinine, sodium, albumin were measured at the baseline outpatient visit (baseline), during hospitalisation (admission, maximal change, discharge) and within the following 6 months. Measures of renal function were expressed as absolute values and as a ratio of baseline values. Statistical analysis was performed using ANOVA with the correction for repeated measures where necessary, Kaplan-Meier survival analysis with Cox' F-test and receiver operating characteristic curves (ROC).
223 patients were included (age 74 years, 27% women). During hospitalization 32 patients (14.3%) died and were excluded from this analysis. Patients were followed up for approximately 4 years (range 31 - 1500, median 912 days). During long-term follow-up 111 patients (58.1%) died. They were older (75±9 vs 72±11), had lower ejection fraction (30±11% vs 35±10%) and higher baseline values of urea (12.6±8.1 mmol/L vs 9.9±5.6 mmol/L), creatinine (161±70 umol/L vs 132±54 umol/L) and lower albumin (35.5±4.4 vs 36.7±3.6 g/L). Patients who died were characterized by more pronounced maximal in-hospital increase in urea (ANOVA: F(2, 378)=3.55, p=0.029) and better post-discharge recovery of albumin (ANOVA: F(2, 360)=6.52, p=0.002).
Survival analyses showed that transient increases in serum urea during hospitalisation was associated with a worse prognosis. Albumin, urea and creatinine measured at baseline predicted long-term mortality (c-statistics 0.603 CI 0.522-0.685, 0.612 CI 0.53-0.693 and 0.644 CI 0.606-0.762 respectively). However, compared to pre-admission values, only the maximal relative increase of urea compared to baseline, provided additional predictive value (c 0.594 CI 0.51-0.68).
Conclusions: Abnormal baseline results of albumin, urea and creatinine indicate a worse long term prognosis for patients with chronic heart failure. Moreover, a transient increase in serum urea but not in other parameters is associated with increased long term mortality.

P846 Lack of association between albuminuria and outcome in patients with heart failure

K. Damman, T. Jaarsma, A.A. Voors, G. Navis, H.L. Hillege, D.J. Van Veldhuisen. *University Medical Center, Groningen, Netherlands*

Purpose: The presence of micro and macro-albuminuria is associated with impaired survival and morbidity in the general population and different patient populations. However, there is no data about the association between the presence of albuminuria and outcome in patients with heart failure (HF).
Methods: The Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH) included 1023 HF patients after hospitalisation for HF. In a substudy, including 272 patients, morning spot urine samples were obtained and urinary albumin excretion (UAE) was determined. Estimated glomerular filtration rate (eGFR) was calculated using the sMDRD formula. The primary outcome was a composite of all-cause mortality and heart failure admissions.
Results: Mean age was 72 years, and 65% was male. Median UAE was 15 (7-54) mg/L, while the mean eGFR was 55 mL/min/1.73m^2. At baseline, 29% and 6% of patients had micro- or macroalbuminuria, respectively. UAE showed no relationship with eGFR (r = 0.04, P = 0.56). In 18 months follow up, 148 (54%) of patients reached the primary endpoint. Figure 1 shows the survival curves for albuminuria. UAE did not show any relationship with the primary outcome: hazard ratio 1.06 (0.83 – 1.35), P =0.64. There was no interaction between UAE and eGFR with outcome.

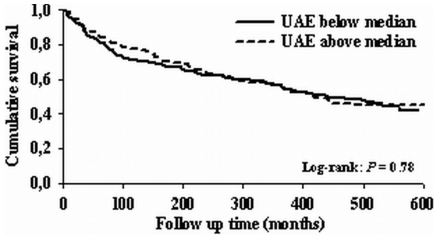


Figure 1: UAE and Outcome

Conclusion: Both micro and macroalbuminuria are prevalent in patients with HF, but their presence is not associated with impaired prognosis in these patients.

P847 Mortality predictors in patients with dilated cardiomyopathy in the current era: relevance of chagas disease

M.C. Pereira Nunes[1], M.M. M Barbosa[2], A.L.P. Ribeiro[1], L.M.A. Fenelon[2], M.M.P. Filho[1], L.C. Calazans[1], M.O.C. Rocha[1]. *[1]Postgraduate Course of Tropical Medicine, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil; [2]ECOCENTER, Hospital Socor, Belo Horizonte, Brazil*

Objectives: The purpose of this study was to identify mortality risk factors in patients with HF secondary to Chagas and idiopathic dilated cardiomyopathy and to determine the prognostic value of identifying Chagas disease as an underlying cause of dilated cardiomyopathy.
Background: Previous studies to investigate the influence of Chagas disease on mortality in patients with heart failure (HF) are limited by heterogeneity of patient populations.
Methods: We evaluated the outcome of 287 patients with HF secondary to dilated cardiomyopathies. Patients were grouped into two categories according to the underlying cause: dilated cardiomyopathy due to Chagas disease (224 patients) and idiopathic dilated cardiomyopathy (63). The end points were death and cardiac transplantation. A predictive model was developed considering the number of risk factors of each patient.
Results: Over a mean follow-up of 39.5 months, 102 patients died and nine patients underwent cardiac transplantation. In multivariable Cox proportional-hazards analysis, NYHA functional class, LV ejection fraction, RV function and LA volume remained predictors of adverse outcomes. Chagas cardiomyopathy as HF etiology was also independently associated with a poor prognosis (hazard ratio 2.41; 95% confidence interval, 1.24 - 4.68; p=0.009), after adjustment for other parameters predictors of outcome in HF.
Conclusions: The identification of the etiology of HF has prognostic importance, primarily for patients with Chagas cardiomyopathy. Chagas dilated cardiomyopathy was associated with worse survival when compared to idiopathic dilated cardiomyopathy, independent of clinical factors and echocardiographic parameters of poor prognosis in HF. A prediction model including risk factors was shown to be useful in stratifying risk categories in patients with dilated cardiomyopathy.

P848 Medical therapy fails to restore optimal functional capacity in heart failure patients with atrial fibrillation

E. Cronin, M. Carey, A. Headon, S. Fall, V. Maher. *Adelaide and Meath Hospital, Dublin, Ireland*

Purpose: Heart failure is associated with impaired functional capacity due to ischaemia, anaemia, hypertension and arrhythmia. However functional capacity may be improved with medical therapy. Whether medical therapy can restore functional capacity to a similar degree in those with atrial fibrillation (AF) as those in sinus rhythm (SR) is unknown.
Methods: We retrospectively investigated a group of 248 out-patients with heart failure, 98 with chronic AF and 150 patients in SR. Trans-thoracic echocardiography and assessment of New York Heart Association (NYHA) functional class was performed in all patients. Six minute walk tests (6MWT) were performed at baseline and after establishment of optimal medical therapy in each patient. Variables assessed included left ventricular ejection fraction (LVEF), NYHA class, 6MWT performance and change in 6MWT following medical therapy.
Results: Patients with AF were older and more often male (table 1). Patients with AF had reduced functional capacity at baseline compared to those in SR despite similar LVEF. Optimal medical therapy improved 6MWT times equally in those with AF and SR. However, final 6MWT distances after optimal medical therapy were still significantly lower in those with AF.
Conclusions: Our data suggest that in patients with heart failure, functional capacity continues to be significantly impaired in those with AF compared with those in SR, despite medical therapy. Further investigation of the effect of restoration of

Table 1. Patient demographics, NYHA class, LVEF, baseline and final 6MWT distances

	N (% female)	Age (years)	Baseline LVEF (%)	NYHA class	Change 6MWT (m)	Final 6MWT (m)
AF	98 (19)	68.4±1.3	42.7±2.5	1.92±0.1	14±8	377±20
SR	150 (30)	61.9±1.0	39.2±1.87	1.59±0.1	16±5	440±13
Significance		p<0.05	ns	p<0.001	ns	p<0.01

sinus rhythm is warranted in these patients in an effort to improve their functional capacity.

P849 Left ventricular assist devices improve autonomic imbalance in patients with severe heart failure

A. Gardiwal, H. Oswald, T. Koenig, U. Luesebrink, G. Klein. *Medizinische Hochschule Hannover, Hannover, Germany*

Left ventricular assist devices (LVAD) are an effective therapeutic option for end-stage heart failure (HF). Reduced heart rate variability (HRV) as a result of autonomic derangement is evident in chronic heart failure and several studies have established the independent prognostic value of HRV in chronic heart failure. In the present study we investigated, if autonomic function was restored in patients after LVAD implantation with persistent severely depressed left ventricular function.

Ambulatory ECG recordings were collected in heart failure patients with LVAD on top of optimal medical therapy (n=8) und age-matched heart failure patients on optimal medical therapy without LVAD (n=7). Severely depressed left ventricular function (ejection fraction <30%) was documented in all patients on echocardiography or angiography. Analysis for heart rate variability revealed reduced SDNN (67±4ms), SDANN (56±4ms) and triangular index (18±1) in heart failure patients on optimal medical therapy. However patients with LVAD demonstrated a restoration in heart rate variability with normal SDNN (108±9ms), SDANN (103±8ms) and triangular index (29±2). Compared to patients without LVAD this difference was statistically significant (p<0.01).

Autonomic imbalance indicated by severely reduced heart rate variability is restored after LVAD implantation in end-stage heart failure patients.

SURGERY

P850 Myocardial assistance by cell therapy associated with collagen

J.C. Trainini, J.C. Chachques, N. Lago, J. Herreros, J. Bordone, J.L. Barisani, J. Mouras, A. Christen, M. Redruello, O. Masoli. *Hospital Presidente Perón, Buenos Aires, Argentina*

Background: We evaluated the feasibility and safety of cell therapy associated with a cell-seeded collagen scaffold grafted onto ventricles.

Methods: In 22 consecutive patients presenting with myocardial scars and indication for coronary bypass surgery, bone marrow cells were implanted associated to revascularization surgery with left mammary artery. The patients were distributed in two groups. Group I: 12 patients (53.75±10.76 years). At the end of surgery the implantation of the bone marrow cell was performed (34±8.6 injections, 5.1±1.7 ml, 202±11x106 cells, CD34+ 0.7%). Group II: 10 patients (56.1±7.63 years), 15.7±4.5 ml of bone marrow cells (716±324x106 cells, CD34+ 1.2%) was implanted. The 40% of volume was injected into the scar (21.5±7.5 injections) and the 60% was utilized for seeded the collagen matrix.

Results: There was any related adverse events (follow-up 357±162 and 297±128 days respectively). In Group I, the NYHA functional class improved from 2.4±0.5 to 1.1±0.3 (p<0.0001), the left ventricle ejection fraction improved from 24.8±6.0% to 36.3±13.4% (p=0.003) and the left ventricular diastolic diameter progressed from 63.5±9.2 mm to 60.5±9.1 mm (p=ns). In Group II, the functional class improve from 2.5±0.7 to 1.2±0.4 (p<0.0001), the ejection fraction from 31.6±14.9% to 39.3±18.4% (p=0.01) and the diastolic diameter progressed from 63.2±8.7 mm to 60.2±9.7 mm (p=0.02).

Conclusions: Autologous intramyocardial injection of mononuclear bone marrow cells and fixation of a cell seeded matrix onto the epicardium is a feasible and safe procedure. The cell-seeded collagen matrix increase the functional capacity, limiting ventricular remodeling and improving diastolic function.

P851 NT-pro-BNP is an important predictor of major morbidity following surgical ventricular restoration

A. Ballotta[1], A. Kunkl[1], H. El Baghdady[1], F. Bettini[1], M. Ranucci[1], M. Di Donato[1], E. Bossone[2], L. Menicanti[1], S. Castelvecchio[1], R.H. Metha[3]. *[1]IRCCS Policlinico San Donato, San Donato Milanese 20097 Milano, Italy; [2]Divisione di Cardiologia Ospedale di Cava de'Tirreni-Costa d'Amalfi, Salerno, Italy; [3]Duke Clinical Research Institute, Durham, United States of America*

Background: The prognostic significance of preoperative (pre-op) NT-pro-BNP levels in patients (pts) undergoing surgical ventricular restoration-(SVR) of left ventricle remains less known.

Methods: We evaluated 45 pts undergoing SVR (2/2005-4/2006). NT-pro-BNP was determined a day before SVR and from post-op day 0 to 5. Major morbidity (MM) was defined according to STS criteria as at least one of the following: ventilation >48 hrs; stroke; acute renal failure; reoperation; or mediastinitis. The association of pre-op NT-pro-BNP with peri-op outcomes was assessed using multivariable logistic regression analysis. Receiver operating characteristic (ROC) curve was used to test its discrimination power.

Results: Major morbidity occurred in 20-pts (44%) with only 1 death within 30 days of SVR. The mean pre-op NT-pro-BNP was 4.6 fold higher in pts with MM than in those without it (3170±3024 vs 684±517 pg/ml, p=0.007). On multivariate analysis, pre-op NT-pro-BNP was an independent correlate of MM even after adjusting for baseline confounding, particularly, age, ejection fraction and EUROSCORE (p=0.031). Furthermore, pre-op NT-pro-BNP had a high discrimination power on ROC analysis (area under the curve 0.84), with a value of 1300 pg/mL having 73% sensitivity and 88% specificity for MM.

Conclusions: Pre-op NT-pro-BNP determination may be of value in stratifying the risk for peri-op MM in pts undergoing SVR. Influence of this biomarker on long-term outcomes of these pts needs to be studied in future.

P852 Mid- term reverse remodelling of left ventricular geometry after left ventricular reconstruction - MRI study

C. Alexandrescu, F. Civaia, L. Iacuzio, F. Montiglio, V. Dor. *Centre Cardio Thoracique de Monaco, Monte- Carlo, Monaco*

Purpose: Left ventricular reconstruction (LVR) has been demonstrated to improve the morphologic structure and function of the heart in patients in patients with heart failure.

The Cine MRI is a well- validated technique for assessment of left ventricular function and it is not limited by geometric assumptions needed for quantification of EF and LV volumes in echocardiography.

The aim of this study was to investigate the mid-term changes of LV geometry and function after LVR by MRI

Methods: 77 consecutive patients (mean age 64.6±11.5 years) with severe ischemic cardiomyopathy in advanced heart failure stage (EF < 30% or ESVol indexed >60 ml/m^2) were enrolled between July 2002 and November 2007.

They underwent LVR by endoventricular patch. CABG was performed using as many arterial grafts as possible, aiming at complete revascularization.

They underwent cine MRI within the week before the operation, one month after the operation (immediate postoperative stage), and at least one year after the intervention (late postoperative stage). MRI studies were performed using a standard Siemens1.5T system. Planned on the diastolic two- and four-chamber images, the heart was covered from base to apex with imaging levels in the short-axis orientation. For analysis the epi- and endocardial borders were outlined manually and the computer measured the enclosed surface areas. These were used to establish EDVol, ESVol, stroke volume, ejection fraction.All values were indexed.

Results: The left ventricle end-diastolic volume index (LVEDVol I) were significantly reduced immediately after the operation and unchanged in the late postoperative stage (129±46 ml/m^2 versus 83±22ml/ml/m^2, p< 0.001, versus 82±21 ml/m^2, p=0.76). Also left ventricle end- systolic volume index (LVESVol I) decreased immediately after the operation and remained almost unchanged at the late postoperative follow-up. (95±41 ml/m^2 versus 51±18ml/m^2, p<0.001 versus 47±18 ml/m^2, p=0.18) The EF was significantly increased immediately after the operation (EF presurgery=26%, to EF early postsurgery 40%, p < 0.001) and continued increasing thereafter almost in a linear fashion (EF late postsurgery 44%, p=0.001)

Conclusion: This data demonstrates the ability of MRI to report a various aspects of the LV reverse remodelling process after LVR. Our current results confirm that LV reverse remodelling is present at mid-term follow-up in the patients with advanced heart failure.

P853 Levosimendan pre-treatment in critically ill patients undergoing cardiac surgery is associated with better post-operative outcome

P. Cattaneo, M. Baravelli, A. Rossi, M. Romano, D. Imperiale, C. Anza'. *Division of Cardiology and Intensive Cardiopulmonary Rehabilitation, IRCCS Multimedica Holding, Cast, Castellanza, Italy*

Background and Purpose: Levosimendan is a new calcium sensitizer that enhances the contractile force of the myocardium and exhibits additional vasodilating properties. Although previous clinical trials in patients with decompensated heart failure and myocardial ischaemia show that levosimendan improves haemodynamic performance and potentially ameliorates symptoms and quality of life, little attention has been paid to its effects as a cardioprotective agent during cardiac surgery. The aim of our study was to evaluate the effect of perioperative infusion of levosimendan in cardiac surgery patients with low preoperative ejection fraction.

Patients and Methods: 43 patients (mean age 68±8,8, 6 women) with a low preoperative ejection fraction (EF 21,9±3,5%) were randomly assigned to two different administration modalities of levosimendan: infusion start before cardiopulmonary bypass (16 patients, Group A) and at the end of cardiopulmonary bypass (27 patients, Group B). Levosimendan was infused at a rate of 0,1 microg/kg/min

without loading dose for a period of at least 24 h to a maximum of 48 h. Haemodynamic parameters were obtained at baseline and at 2, 6, 24 and 48 h after start of infusion.
Results: Levosimendan was well tolerated with identical efficacy in both groups in improving haemodynamic performance: increase of stroke volume, cardiac index, and left ventricular ejection fraction by echo study, de-escalation of traditional inotropes, subtraction of IABP. Haemodynamic changes exerted by levosimendan persisted up to 48 h. Interestingly, both intensive care unit and hospital stay were significantly shortened in patients of Group A compared to patients of Group B; 10 patients in Group B (7 for irreversible cardiac failure, 1 for multiorgan failure, 1 for cerebral stroke, 1 for septic shock) and 1 patient in Group A (irreversible cardiac failure) died in hospital within 30 days of surgery (p=0,03). At six months and one year follow up, 2 patients died in Group B for irreversible cardiac failure and none in Group A (p= 0,01).
Conclusion: Levosimendan is a promising inotropic agent in the therapeutic management of low cardiac output syndrome during and after open-heart surgery. Our results demonstrate the superiority of the early infusion (before the start of cardiopulmonary bypass) as shown by improved in-hospital outcome and one year survival.

P854 Ischemia-associated changes in the atrial and ventricular myocardium during coronary artery bypass grafting with the use of cardiopulmonary bypass

W.T. Ruifrok, B.D. Westenbrink, R.A. De Boer, I.J. Den Hamer, M.E. Erasmus, H.E. Mungroop, A.H. Epema, A.A. Voors, D.J. Van Veldhuisen, W.H. Van Gilst. *University Medical Center, Groningen, Netherlands*

Purpose: we aimed to study whether the use of cardiopulmonary bypass and cardioplegic arrest during coronary artery bypass graft (CABG) surgery causes ischemia-reperfusion related changes in atrial and ventricular tissue, with increased number of apoptotic cells.
Methods: during CABG surgery with cardiopulmonary bypass and cardioplegic arrest (n=10), biopsies were taken from the right atrial appendage and left ventricular anterior wall before initiation of cardiopulmonary bypass and after aortic cross clamp release. Change in number of apoptotic cells (number of caspase-3 positive cells), expression of erythropoietin receptor, and markers of myocardial ischemia and renal function were assessed.
Results: cardiopulmonary bypass was associated with a transient small, but important increase in CK (1091±374%; $p<0.01$), CK-MB (128±38%; $p<0.05$), Troponin-T (102±13%; $p<0.01$) and NT-proBNP (1308±372%; $p<0.01$) levels. A higher number of apoptotic cells was found in the ventricular biopsies taken after aortic cross clamp release compared to the biopsies taken before initiation of cardiopulmonary bypass (5.3±0.6 vs. 14.0±1.5 cells/microscopic field, $p<0.01$). The number of apoptotic cells in the atrial appendage was not altered during cardiopulmonary bypass. Correlation between the duration of aortic cross clamp time and the change in apoptotic cells in the left ventricular wall showed a trend (r of 0.58, p=0.08). Erythropoietin receptor protein expression in atrial tissue went from 0.19±0.06 (baseline), to 0.27±0.10 (prior cardiopulmonary bypass), to 0.31±0.13 (after aortic cross clamp release) (p=0.36).
Conclusions: CABG surgery with cardiopulmonary bypass and cardioplegic arrest is associated with an elevated rate of apoptosis in ventricular tissue, but not in atrial tissue. Furthermore, the association between aortic cross clamp time and number of apoptotic cells in the ventricle suggests a relationship between the severity of the ischemic burden and the tissue damage. Ventricular tissue may be more sensitive to detect changes than atrial tissue, and may be more useful to investigate the protective effects of therapeutic intervention.

P855 Enlarged heart size and postoperative heart functioning are associated with intraoperative microembolic load in cardiac surgery patients

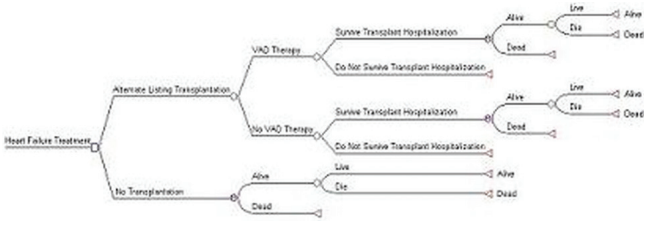
E.Z. Golukhova, L.A. Bockeria, A.G. Polunina, N.P. Lefterova, K.V. Shumkov, S.V. Zhuravleva on behalf of Bakoulev Scientific Center for Cardiovascular Surgery RAMS. *Bakoulev Scientific Center for Cardiovascular Surgery RAMS, Moscow, Russian Federation*

Purpose: The present study was purposed to determine if routine echocardiographic evaluation may be of value in identifying patients at risk for extensive microembolic load during cardiac surgery. Postoperative echocardiography data were also explored.
Methods: Overall, 66 patients agreed to participate in the study. Transthoracic echocardiography was performed in 2-3 days before surgery, on the first day after surgery and before discharge. Thirty six patients underwent open heart surgery – single valve (either mitral or aortic) replacement and thirty patients had on-pump coronary surgery. The protocols of anesthesia, perfusion and surgical techniques were standardized. A 2-MHz Transcranial Doppler system was used for continuous bilateral monitoring of middle cerebral artery (MCA) blood flow. Microemboli were registered intraoperatively as transient signals with intensity of >5dB higher than background noise.
Results: Left heart size (left atrium size, end-systole and end-diastole left ventricle sizes) significantly and positively correlated with intraoperative microembolic load (rs=0.32- 0.45, ps<0.05). Regression analysis demonstrated that the association between enlarged cardiac chambers and more extensive microembolic load was partially mediated by longer cardiopulmonary bypass (CPB) in patients with enlarged chambers. However, the association between heart size and microemboli was stronger in comparison with CPB effects, because other unknown factors associated with enlarged heart were also of importance. In contrast to preoperative data, postoperative ejection fraction and stroke volume negatively correlated with microembolic load (rs=0.27 - 0.36, ps<0.05). The latter correlations were stronger in open heart surgery patients (rs=-0,44-0,61, ps< 0,01), however, they had the same direction in the coronary surgery group (rs=-0,23-0,40, ps< 0,25). Regression analysis confirmed the association between postoperative ejection fraction and microembolic load to be independent of type of surgery, CPB duration and heart size.
Conclusions: Enlarged cardiac chambers are a risk factor for elevated microembolic load during on-pump surgery. The emergence of significant association between heart functioning characteristics in postoperative period and magnitude of intraoperative microembolic load evidenced that microemboli may damage myocardium with a consequent decrease of ejection fraction and stroke volume

P856 Alternate listing transplantation is a cost-effective treatment for end-stage heart failure patients

M. Russo[1], K. Hong[2], J. Chen[1], M. Argenziano[1], R. Davies[1], D. Ascheim[2], A. Moskowitz[2], A. Gelijns[2], M. Oz[1], Y. Naka[1]. [1]*Columbia University Medical Center, New York, United States of America;* [2]*Mount Sinai Hospital, New York, United States of America*

Purpose: The purpose of this study was to evaluate the cost-effectiveness of Alternate Listing Transplantation (ALT) strategies, where "high-risk" recipients are considered candidates for "marginal" donor (MD) organs.
Methods: A Markov model (Figure) was developed using published cost data and UNOS data (OHT ≥18 yo, listed 1/99 to 12/07) to determine the ICER of ALT candidates (Table) who received MD hearts (age>55yo, EF<45%, DM w/PVD, CRF or CVA, hep C+, donor:recipient wt <0.7, IV drug or cocaine use) compared to ALT candidates who died on the waiting list. Analysis was stratified by high-risk characteristic (HR) and probabilistic sensitivity analysis performed.



Cost Effectiveness Model

Results: see Table.

Study population and ICERs

	ALT		No Transplant		ICER	LL 95% CI	UL 95% CI
	N	% Total	N	% Total	$/Life-yr	$/Life-yr	$/Life-yr
Age > 65yo	394	43	410	36	67,647	63,567	72,113
Re-transplantation	78	8	317	28	80,007	76,019	82,748
Amyloidosis	20	2	32	3	82,988	80,227	89,389
DM w/PVD, CVA, CRF	101	11	137	12	88,588	83,387	92,505
eGFR < 33 mL/min	133	14	131	12	126,727	117,697	140,138
>1 High Risk Characteristic	193	21	110	10	135,998	129,812	147,883
Total	919	100	1137	100	86,346	83,453	90,527

ICER = incremental cost effectiveness ratio.

Conclusion: Our estimates suggest ALT strategies are within the boundaries of society's willingness to pay for an additional year of life. However, patient selection criteria will be important to keeping this strategy cost-effective.

P857 LV reverse remodelling in patients with idiopathic dilated cardiomyopathy undergoing restrictive mitral annuloplasty with and without cardiac support device

A. Ciarka, J. Braun, V. Delgado, E.E. Van Der Wall, M.J. Schalij, R. Klautz, J.J. Bax, N. Van De Veire. *Leiden University Medical Center, Leiden, Netherlands*

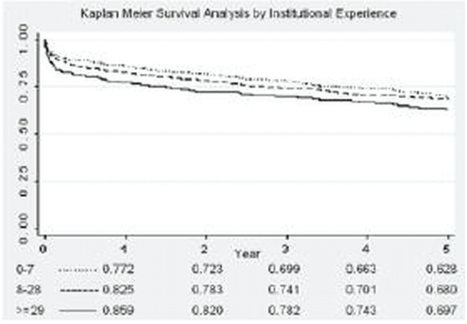
Background: Functional MR is frequently observed in patients with idiopathic dilated cardiomyopathy (DCM). Restrictive mitral annuloplasty is a recommended treatment in patients with ischemic cardiomyopathy, who undergo coronary bypass grafting, but little is known about the results of restrictive mitral annuloplasty and cardiac support device (CSD) in idiopathic DCM. We wanted to investigate the amount of LV reverse remodelling and recurrence of MR in patients with idiopathic DCM undergoing restrictive annuloplasty with and without CSD (CorCap).
Methods: We have included 69 patients with idiopathic DCM, aged 60±12 yrs, who underwent restrictive mitral annuloplasty alone (n=28) or combined with CSD (n=41). Patients underwent echocardiographic evaluation before operation, before discharge from hospital (6.8±4.4 days) and at long term follow up (2.5±1.6

yrs). Clinical status (survivors and non survivors) was assessed at 4±2 yrs from intervention.
Results: Before the intervention the patients presented with dilated left ventricle (LVEDD 67±9 mm), dilated left atrium (46±8 mm) and decreased EF (27±9%). Before the intervention 12, 65 and 23% of patients presented with MR grade 2, 3 and 4, respectively. Four patients died preoperatively (6%), while 21 patients died at long term follow up (32%). No difference was found in LVEDV, LVESV, EF and degree of MR in survivors and non survivors. All patients presented with MR<2 at the discharge, while at long term follow-up 16 patients (10% of survivors) presented with MR ≥ 2. LVEDV in comparison with pre intervention value, decreased at discharge and during long term follow up (182±73 vs. 163±70 vs. 153±78 ml, p<0.001, respectively) and similar changes were noted for LVESV (132±64 vs. 123±65 vs. 107±69 ml, p<0.001). Decrease in LVEDV and LVESV were more marked in patients with mitral annuloplasty and CSD in comparison with patients, who underwent the annuloplasty alone. At discharge, the same percentage of patients in group with and without CSD presented with LV reverse remodelling (40 vs. 43% respectively, p=ns), while at long term follow up more patients with CSD in comparison with patients without CSD presented with LV reverse remodelling (81 vs. 48%, p=0.02). There was a trend towards less recurrence of MR gr ≥2 at long term follow up in patients with CSD in comparison with those who did not receive CSD (28 vs. 8%, p=0.08).
Conclusions: Restrictive mitral annuloplasty combined with CSD is an efficient treatment of functional MR in patients with idiopathic DCM. CSD provide an extra benefit in terms of LV reverse remodelling in this group of patients.

P858 Institutional experience with bridge-to-transplant recipients predicts post-transplantation outcomes

M. Russo[1], K. Hong[2], J. Chen[1], E. Rose[2], Y. Naka[1], A. Gelijns[2].
[1]Columbia University Medical Center, New York, United States of America; [2]Mount Sinai Hospital, New York, United States of America

Purpose: To determine the relationship between post-heart transplant outcomes in recipients bridged-to-transplantation (BTT) with a left ventricular assist device (LVAD) and institutional experience (IE) with BTT recipients.
Methods: UNOS provided de-identified patient-level data. The study population included BTT recipients between 1/1/95 and 12/31/06 (n=4,271). At each center, BTT recipients were ordered based on date of transplant. The primary outcome was post-heart transplant graft survival at 1 year (PTGS1Y). Multivariable regression assessed the relationship between IE and PTGS1Y. ROC curves and stratum-specific likelihood ratios (SSLR) were generated to determine PTGS1Y at various thresholds for IE. Because UNOS began uniformly recording data regarding BTT status in 1995, centers (n=14) with > 3 BTT recipients (n=1,222) in 1995 were excluded from the analysis.
Results: In multivariable regression, IE with BTT was associated with PTGS1Y (OR=0.992, 0.987-0.998; p= 0.012). In threshold analysis, 3 discrete risk strata for IE were identified: 1st-7th (SSLR=1.39, 1.17-1.66), 8th-28th (1.00, 0.89-1.11), and ≥ 29th (0.81, 0.70-0.94). Actuarial PTGS1Y by IE strata for 1st-7th, 8th-28th, and ≥29th was 77.2% (73.3%-80.6%), 82.5% (80.2%-84.6%), and 85.9% (83.5%-87.9%), respectively (Figure). Among centers performing heart transplants between 1995 and 2006, 50.1% performed with ≤7 BTT recipients and 78.2% had ≤28.



Survival by Institutional Experience

Conclusion: Post-transplant outcomes among BTT recipients improved with increasing institutional experience with BTT recipients. Outcomes were significantly better after a center's 28th BTT recipient. During the study period, the vast majority of transplants did not meet this threshold. Therefore, outcomes after BTT should be expected to continue to improve as IE increases.

P859 Poor quality of life reflects impaired diastolic function in chronic heart failure patients

C. Chrysohoou, G. Metallinos, S. Athanasopoulou, C. Kastorini, S. Brili, J. Barbetseas, A. Aggelis, C. Pitsavos, C. Stefanadis.
University of Athens, Athens, Greece

Introduction: Many studies have revealed a link between depression and poor quality of life with the development and progression of heart failure. Additionally, echocardiographic indices of diastolic function have shown to reflect the progression of heart failure and to correlate with the clinical presentation of those patients. The purpose of this study was to evaluate the relationship between echocardiographic markers of systolic and diastolic function with depression and quality of life status of patients with chronic compensated heart failure.
Methods: We enrolled 178 consecutive patients (mean age 59±11 years old) with chronic compensated heart failure, due to ischemic or dilated cardiomyopathy, NYHA classification II-III, under optimal medical treatment. Echocardiographic assessment was performed in all patients. Left atrial kinetic energy (LAKE), an index of left atrial function, was calculated using the equation 1/2 × LASV × 1.06 × Amv2; where LASV is left atrial systolic volume. Furthermore tissue Doppler imaging of the systolic and diastolic waves of mitral and triscupid annulus (Smv, Emv and Stv, respectively) were also measured. The ratio E of the transmitral diastolic filling velocity to Emv was also calculated. Additionally, using a detailed questionnaire, we recorded lifestyle information, including medical treatment, and we evaluated depression status using Zung Self-rating Depression Scale and quality of life status using the Minnesota Living with Heart Failure Questionnaire.
Results: Linear regression analysis revealed that Minessota scale of quality of life was inversely correlated with Stv (b=-1.932, p=0.032) and positively correlated with LAKE (b=6.42, p=0.05), after controlling for sex, age, body weight, creatinine and hemoglobulin levels). Furthermore, zung depression scale was positively correlated with the ratio E/Emv (b=1.581, p=0.001) and inversely correlated with Stv (b=0.918, p=0.05), after controlling for the same aforementioned cofounders.
Conclusion: The presence of poor quality of life seems to accompany more impaired right ventricular systolic function and left ventricular diastolic dysfunction, presenting with higher left ventricular filling pressure and impaired left atrial function. This relationship may represent a mechanism beyond inflammation that links poor quality of life with adverse clinical outcome

P860 Clinical outcome of cardiac contractility modulation in patients with drug-refractory chronic heart failure

C. Schukro, M. Wolzt, G. Stix, T. Pezawas, J. Kastner, H. Schmidinger.
Medical University of Vienna, Vienna, Austria

Purpose: Intermittent non-excitatory electrical stimulation delivered during absolute myocardial refractoriness results in cardiac contractility modulation (CCM) with improvement of impaired ventricular function. Thus, CCM became a therapeutic alternative in patients with drug-refractory chronic heart failure, especially in those not eligible for cardiac resynchronisation therapy (CRT). We analysed the clinical outcome of the use of CCM in this collective.
Methods: Between November 2001 and December 2008, we implanted CCM devices in 36 patients with advanced drug-refractory chronic heart failure - i.e. NYHA-class III and left ventricular ejection fraction (LVEF) <35% - including 2 patients with heart transplantation and 2 patients non-responsive to CRT. Final analysis included 25 patients (all male; age at implantation: 64.1±7.5 years) with daily stimulation only. 21 patients also had an implantable cardioverter-defibrillator (ICD).
Results: Within a clinical follow-up period of 2.4±2.0 years, mean NYHA-class improved slightly to 2.7±0.8. Mean LVEF at the last follow-up was 26±11%. Incidence of device related complications was low: lead-reposition and infection of device loge in one patient respectively. All-cause mortality in patients with CCM was 40% (10 of 25 patients), with a one-year mortality of 20%. Causes were cardiogenic shock (3 patients), arrhythmic and non-cardiac death (2 patients respectively), while cause of death remained unknown in 3 patients.
Conclusions: Cardiac contractility modulation is able to improve the symptoms of advanced drug-refractory chronic heart failure. In this collective, a high all-cause mortality first reflects the end-stage character of the underlying heart failure.

P861 Ultrafiltration reduces the hospitalization rate of inotrope-depended end-stage heart failure patients

E. Repasos[1], J. Terrovitis[1], E. Grapsa[1], E. Kaldara[1], F. Katsaros[1], L. Katsaros[1], N. Diakos[1], E. Tseliou[1], I. Pozios[1], J. Nanas[2].
[1]University of Athens, Athens, Greece; [2]3rd Cardiology Dept. University of Athens, School of Medicine, Athens, Greece

Purpose: End stage heart failure is often resistant to treatment and patients have to be frequently hospitalized. Ultrafiltration is an alternative therapeutic modality for these patients. We examined the effect of the combination of ultrafiltration with intermittent inotrope infusions on hospitalization rate.
Methods: Thirty-six consecutive patients with end-stage heart failure and low cardiac output, refractory to optimal medical treatment, were included in this study. Patients were assigned in two groups based on their renal function and response to diuretics. Eighteen patients (Group 1) were treated with continuous inotrope infusions up to three days followed by weekly intermittent 8-hour infusions. Eighteen patients (Group 2) with severe deterioration of renal function and resistance to diuretics were treated with intermittent inotrope infusions and ultrafiltration as a temporary or permanent measure.
Results: Baseline characteristics were almost similar in the two groups. NYHA class 3,5 vs 3,7, age 55±12 years vs 62±11 years, left ventricular ejection fraction 21,8%±6% vs 25%±9,4%, mean right atrial pressure 14,3±5,4mmHg

vs 18±6,7mmHg, mean pulmonary capillary wedge pressure 29,6±6,9mmHg vs 26±5,6mmHg, serum Na 135,8±5,5mEq/lt vs 132,9±5,9mEq/lt, hemoglobin 12,1±2,8 vs 11,3±1,1g/dl, cardiac index 1,7±0,3 vs 1,8±0,3lt/min/m^2, brain natriuretic peptide 1639±1474pg/ml vs 2237±1369pg/ml, (P=ns for all comparisons, for groups 1 and 2 respectively). Serum creatinine was significantly elevated in group 2 patients, 3,1±1,6mg/dl vs 1,6±0,8mg/dl (P=0.004).
The composite end point of death, readmission or LVAD implantation occurred 50 times in group 1 vs 26 times in group 2 (p=0,014), while the total number of readmissions were 36 in group 1 vs 14 in group 2 (p=0,008). There was no difference in the composite end point of death or LVAD implantation between the two groups (12 vs 14, p=0,65)
Conclusions: The addition of ultrafiltration on the treatment of inotrope-depended end-stage heart failure patients results in significantly fewer readmissions, in comparison to the use of intermittent inotrope infusions alone.

OUTCOME IN HYPERTENSION

P862 Evaluation of arterial blood pressure and cardiovascular structure and function in women with previous preeclampsia

M. Salvetti[1], F. Prefumo[2], A. Paini[1], G. Gatti[2], E. Belotti[1], C. Agabiti Rosei[1], C. Aggiusti[1], E. Agabiti Rosei[1], T. Frusca[2], M.L. Muiesan[1].
[1]Department of Internal Medicine, University of Brescia, Brescia, Italy; [2]Department of Obstetrics and Ginaecology, University of Brescia, Brescia, Italy

Background: it has been reported that women with a history of preeclampsia (PE) may have an increased risk for cardiovascular events or chronic kidney disease in later life. Most studies analysed the prevalence of cardiovascular risk factors or the occurrence of CV events in the long term (9-14 years after delivery). Very few data are available on the time course of blood pressure (BP) increase and of cardiovascular target organ damage development in these patients.
The aim of the study was to evaluate arterial blood pressure and cardiovascular structural changes in patients with a previous first pregnancy complicated by preeclampsia as compared to subjects with a previous first uncomplicated pregnancy, 2 years after delivery.
Methods: 15 women with previous PE (defined as SAP≥140 and/or DAP≥90 mmHg and proteinuria > 0.3 gr/24h) and 15 women with a previous uncomplicated pregnancy, matched for demographic and anthropometric variables, underwent a follow up visit 30±7 months after delivery. In all patients echocardiography (Mono-bidimensional + conventional and tissue Doppler analysis) was performed for the evaluation of left ventricular structure and function.
Results: The two groups were comparable for age, weight, BMI and duration of follow up. Mean age was 36±10 years, gestational age at diagnosis of PE was 29.6±2.6 W. Systolic BP was similar in the two groups, while diastolic BP was significantly higher in patients with previous preeclampsia (114±10 vs 112±7 mmHg, p n.s and 67±8 vs 72±6 mmHg, p<0.05). Left ventricular (LV) mass index and relative wall thickness were not different in the two groups (24.5±7 vs 26±5 gr/h2.7 and 0.27±0.03 vs 0.26±0.03, respectively, p n.s), as were indices of LV systolic function. Left atrial diameter was significantly greater in patients with previous PE (3.3±0.3 vs 3.0±0.3, p< 0.05). The ratio of mitral annular E velocity (Em) to annular A velocity (Am) was significantly lower in PE (1.7±0.5 vs 2.1±0.5 respectively, p< 0.05) and the ratio of transmitral E velocity (E) to annular E velocity (Em), a reliable marker of LV filling pressures, was significantly higher in patients with previous PE in comparison to controls (7.01±1.3 vs 6.2±1.0 respectively, p< 0.05).
Conclusion: our findings suggest that, in patients with previous PE, an early increase in BP values may be observed associated with structural and functional changes of diastolic filling and relaxation indexes. These results may give further insights into the mechanisms underlying the increased CV risk observed in subjects with previous preeclampsia

P863 Impact of stroke volume on cardiovascular events in hypertensive patients with electrocardiographic left ventricular hypertrophy. A LIFE substudy

M.T. Lonnebakken[1], E. Gerdts[1], K. Boman[2], K. Wachtell[3], B. Dahlof[4], R.B. Devereux[5]. *[1]Haukeland University Hospital and University of Bergen, Bergen, Norway; [2]Skeleftaa County Hospital and Umeaa University Hospital, Umeaa, Sweden; [3]Rigshospitalet, Copenhagen, Denmark; [4]Sahlgrenska University Hospital, Gothenburg, Sweden; [5]Weill Cornell Medical Center, New York, United States of America*

Background: Left ventricular (LV) geometric patterns carry different cardiovascular (CV) risk in hypertensive patients with electrocardiographic LV hypertrophy. We hypothesized that this difference may be mediated by different stroke volume (SV).
Methods: To test this hypothesis, the association between LV SV and combined CV death, stroke and myocardial infarction, the pre-specified primary study endpoint, was assessed in Cox regression analysis using data from baseline and annual follow-up visits in 939 patients during 4.8 years of randomized losartan- or atenolol-based treatment in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) echocardiography substudy.
Results: During follow-up, a total of 105 primary end-points occurred. At baseline, lower LV SV was associated with smaller body size, female gender, lower LV mass, higher relative wall thickness and more concentric LV geometry (all p<0.01). In time-varying multivariable Cox-regression analysis, lower in-treatment LV SV was independently associated with higher risk of CV events (HR 1.55 per 1 SD lower SV [1.25-1.91] p<0.001) while no significant associations with in-treatment concentric geometry nor systolic blood pressure were found (Table).

Variable	Hazard ratio	95% Confidence interval	p
Stroke volume* (per 1 SD lower)	1.55	1.25-1.91	<0.001
Relative wall thickness*	1.42	0.71-2.84	0.325
LV mass index* (per 1 SD higher)	1.34	1.14-1.57	<0.001
Systolic blood pressure* (per 1 SD lower)	1.22	0.99-1.49	0.061
Randomized losartan treatment	1.08	0.73-1.61	0.692
Framingham risk score at baseline	1.05	1.03-1.07	<0.001

*In treatment levels.

Conclusion: In hypertensive patients with electrocardiographic LV hypertrophy participating in the LIFE echocardiography substudy, the relation between LV geometry and prognosis is partly explained by lower SV predicting higher risk of CV events.

P864 Plasma concentration of soluble TNF receptors type I and 2 and left ventricular mass in essential hypertension

M. Rivera Otero[1], E. Rosello-Lleti[1], J.R. Gonzalez Juanatey[2], P. Morillas[3], T. Lozano[4], P. Orosa[5], L. Martinez Dolz[1], A. Jordan[6], M. Portoles[1], V. Bertomeu[3]. *[1]Hospital La Fe, Valencia, Spain; [2]Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [3]Hospital Universitario de San Juan, Alicante, Spain; [4]Hospital Marina Baixa, Villajoyosa, Spain; [5]Hospital Francisco De Borja, Gandia, Spain; [6]Hospital General Universitario de Alicante, Alicante, Spain*

Purpose: Previous studies on the relationship between left ventricular hypertrophy (LVH) and inflammatory markers in essential hypertension (HT) are limited. We sought to assess the association and predictive role of sTNF-R1 and sTNF-R2 plasma levels with LVH in a group of patients with HT. We assessed the hypothesis that inflammation is an independent risk factor for high blood pressure, as consequence inflammatory cytokines could be related with LVH.
Methods: We studied 251 hypertensive patients (142 with LVH and 109 without LVH), referred from eleven hospitals, and 45 control subjects. A routine physical examination, laboratory analysis and echo-Doppler study were performed. Plasma TNF soluble receptor type 1 (sTNF-R1) and type 2 (sTNF-R2) were centrally determined. Results were expressed in pg/ml.
Results: Hypertensive patients had higher inflammatory sTNF-R1 and sTNF-R2 levels than control group (p<0.0001), and LVH patients showed the highest levels. Plasma concentrations of cytokines were significantly correlated with LVMI (sTNF-R1, r=0.38, p<0.0001 and sTNF-R2, r=0.24, p<0.0001). Receiver operating characteristic (ROC) curves were performed to analyse the capability of sTNF-R1 and sTNF-R2 for detecting LVH in our patients. Both cytokine concentrations obtained a significant area under the curve (AUC), plasma sTNF-R1 had an AUC, 0.71±0.03 and sTNF-R2, 0.63±0.04, p<0.0001. Then, a multivariate linear regression analysis was used to test the independent predictive power of cytokines (sTNF-R1, sTNF-R2), age, gender, known HT duration, systolic blood pressure, glomerular filtration rate, body mass index, ejection fraction, mitral flow propagation velocity (Vp) and treatment on LVMI in this group of patients. The best model included sTNF-R1 (p<0.01), known HT duration (p<0.05), body mass index (p<0.001), Vp (p<0.001) and glomerular filtration rate (p<0.05) as independent factors, accounting for an r^2 of 0.60 (p<0.0001). Finally, prevalence of LVH was increased in the group of patients with higher cytokine levels, and logistic regression analysis showed that sTNF-R1 (odds ratio=2.59, CI 95% of 1.14 - 5.87) was independent predictor of LVH.
Conclusions: sTNF-R1 and sTNF-R2 were significantly correlated with left ventricular mass index in HT. Plasma TNF soluble receptor type 1 was diagnostic and predictor factor of LVH in patients with essential hypertension.

P865 (W) Isolated systolic hypertension in patients with asymptomatic aortic stenosis (a SEAS substudy)

A.E. Rieck[1], D. Cramariuc[2], E.M. Staal[3], B.P. Lund[1], E. Gerdts[2]. *[1]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; [2]Department of Heart disease, Haukaland University Hospital and Institute of Medicine, University of, Bergen, Norway; [3]Stavanger University Hospital and Institute of Medicine, University of Bergen, Stavanger, Norway*

Background: Isolated systolic hypertension (ISH) and aortic stenosis (AS) are both associated with left ventricular (LV) hypertrophy and higher risk of cardiovascular advents. Less is known about patients with combined ISH and asymptomatic AS.
Design and methods: Baseline blood pressures and echocardiographic LV structure was assessed in 1719 patients with asymptomatic AS randomized in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study. LV hypertrophy was

defined as LV mass/$m^{2.7}$ $\geq$46.7/$m^{2.7}$ in women and $\geq$ 49.2mg/$m^{2.7}$ in men. ISH was defined as systolic blood pressure $\geq$140 mmHg and diastolic blood pressure $<$90 mm Hg (n=670) measured at baseline, and was compared to the rest of the patients (n=1049) including 489 patients with non-ISH hypertension.
Results: ISH patients were older, included more women, had more often aortic regurgitation, a history of hypertension and received more often antihypertensive treatment, while severity of AS and body mass index did not differ between the groups. ISH patients also had lower systemic arterial compliance, larger LV mass index and a higher prevalence of LV hypertrophy, mostly of eccentric type. LV ejection fraction did not differ between the groups. In logistic regression, ISH was independently associated with higher age, lower systemic arterial compliance and higher prevalence of LV hypertrophy and aortic regurgitation (Table). In a similar model replacing LV hypertrophy with LV geometry using normal geometry as reference, only eccentric hypertrophy was associated with ISH (Odds ratio 1.48, 95% confidence interval 1.13-1.93, p$<$0.05)

Associations of ISH in asymptomatic AS

Variables	Odds ratio	95% Confidence Intervals	Sign.
Aortic regurgitation	1.55	1.24-1.93	$<$0.001
Age (1 SD change)	1.46	1.30-1.64	$<$0.001
Treatment of hypertension	1.35	0.86-2.01	0.18
Left ventricular hypertrophy	1.32	1.05-1.67	$<$0.05
History of hypertension	0.98	0.63-1.5	0.92
Transaortic maximum velocity (1 SD change)	0.98	0.88-1.09	0.67
Systemic arterial compliance (1 SD change)	0.67	0.59-0.76	$<$0.001

Conclusion: In asymptomatic AS, ISH may be a marker of more advanced cardiovascular disease.

P866 Association of pulse pressure with new-onset atrial fibrillation in hypertensive patients with ECG left ventricular hypertrophy: the LIFE study

I. Ariansen[1], A.C. Larstorp[1], K. Wachtell[2], M. Hecht Olsen[3], H. Ibsen[4], R.B. Devereux[5], P.M. Okin[5], S.E. Kjeldsen[1], B. Dahlof[6] on behalf of the LIFE Study Group. *[1]Dept of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway; [2]Department of Cardiology, The Heart Center, Rigshospitalet, University of Copenhagen, Copnhagen, Denmark; [3]Dept of Internal Medicine, Glostrup University Hospital, Copenhagen, Denmark; [4]Division of Cardiology, Holbaek Hospital, Holbaek, Denmark; [5]Greenberg Division of Cardiology, Weill Cornell Medical College, New York, United States of America; [6]Dept of Internal Medicine, Sahlgrenska University Hospital/Ostra, Gothenburg, Sweden*

Objective: Atrial fibrillation (AF) is associated with increased cardiovascular events, and the incidence of new-onset AF is increased by hypertension. Antihypertensive treatment reduces new-onset AF, and treatment with the angiotensin receptor blocker losartan is more effective than the beta-1 selective blocker atenolol in this respect. To assess whether arterial stiffening influences the risk of developing AF, we examined whether pulse pressure predicted new-onset AF in the Losartan Intervention For Endpoint reduction in Hypertension (LIFE) study, independent of mean arterial pressure as time-varying covariates.
Methods: In LIFE, a double-blinded, randomized, parallel-group study, 9,193 hypertensive patients (46% men; mean age 67 yrs, blood pressure 174/98 mmHg after placebo run-in) with ECG-documented left ventricular hypertrophy (LVH), randomized to once daily losartan- or atenolol-based antihypertensive therapy were followed for a mean of 4.9 years. At baseline 8,831 patients had neither a history of AF nor AF by ECG Minnesota coding, and were at risk of developing this condition during the study.
Results: ECG confirmed new-onset AF in 353 patients. Univariate Cox analyses showed that time-varying heart rate, systolic blood pressure and pulse pressure as well as baseline Cornell product ECG LVH, weight, height, total cholesterol, urine albumin/creatinine ratio, age, male gender, Caucasian ethnicity, prior congestive heart failure and Framingham risk score significantly predicted subsequent new AF. Multivariate Cox regression analyses showed that time-varying pulse pressure or systolic blood pressure, age, male gender, treatment allocation, time-varying heart rate and time-varying ECG LVH independently predicted new-onset AF. Pulse pressure was an equally strong predictor of new onset AF as systolic blood pressure (HR [95% CI] 1.13 [1.05-1.22] per 10 mmHg, p = 0.001 vs. 1.10 [1.04-1.17] per 10 mmHg, p = 0.002). The mean arterial blood pressure did not reach significance as predictor of new-onset AF in the univariate (HR 1.10 [0.99, 1.22] per 10 mmHg, p=0.064) or in the multivariate (HR 1.10 [0.99, 1.21] per 10 mmHg, p=0.066) Cox analyses.
Conclusions: After taking into account effects of age, gender, heart rate and ECG LVH, pulse pressure was more strongly associated than mean arterial pressure with subsequent new AF in hypertensive patients with ECG LVH. Systolic blood pressure and pulse pressure were equally strong predictors of new onset AF in this model.

P867 Beta thalassemia minor and cardiovascular risk in hypertensives

G. Vyssoulis[1], E. Karpanou[2], S.-M. Kyvelou[1], V. Tzamou[1], D. Adamopoulos[1], G. Theodosiadis[1], A. Triantafyllou[1], D. Cokkinos[2], C. Stefanadis[1]. *[1]Hippokration General Hospital of Athens, Athens, Greece; [2]Onassis Cardiac Surgery Center, Athens, Greece*

Purpose: Recently, has been hypothesized that thalassemia minor could afford some protection against cerebrovascular accidents. The aim of the study was to investigate the effect of b-thalassemia minor on cardiovascular risk in hypertensive patients.
Materials and Methods: We studied 19270 consecutive patients (10258 men and 9012 women) with a mean age of 57 years with uncomplicated essential hypertension. After a fortnight wash-out period (42%) patients were evaluated with medical history, full laboratory and clinical examinations. Patients were classified in two groups according to the presence (1.6%) or not of the b thalassemia trait.
Results: Hypertensives with b-thalassemia minor did not differ in age, gender, diabetes and blood pressure, but they had better (p$<$0.0001) lipidemic profile (LDL cholesterol 122 vs 147 mg/dL, ApoB/ApoA1 0.72 vs 0.88) and thrombogenesity (fibrinogen 297 vs 317 mg/dL, PAI-1 2.61 vs 2.73 UI/mL) and lower (p$<$0.0001) incidence of LV hypertrophy (33.4 vs 49.9%) and metabolic syndrome (24.1 vs 37.4%). Although they did not differ in body mass index (28.34 vs 28.25 kg/m^2 p=NS) they had significantly (p$<$0.0001) lower waist to hip ratio (0.85 vs 0.88) and lower incidence of central obesity (39.3 vs 60.6%).
Conclusions: Hypertensive patients with b-thalassemia minor have lower cardiovascular risk. This maybe mediated through lower incidence of visceral obesity.

P868 Diagnostic value of 99mTc-tetrofosmin myocardial perfusion SPECT in hypertensives with ischemic-like ST segment changes

A. Kisko, M. Vereb, J. Kmec, J. Cencarik, P. Gazdic, R. Spratek. *Reimanus Polyclinic, Cardiology clinic, Reiman University hospital, Presov, Slovak Republic*

Purpose: patients (pts) with hypertension frequently complain of chest pain and exhibit ischemic-like ST segment changes on stress electrocardiography (SECG) with normal coronary angiography (CA). The aim of the study was to assess the accuracy of 99mTc-tetrofosmin myocardial perfusion SPECT (MPS) in these pts for detecting ischemia.
Methods: since October 2006, we studied 248 hypertensives with left ventricular hypertrophy (LVH), angina-like chest pain, preserved left ventricle systolic function, with no history of myocardial infarction, coronary revascularization or diabetes mellitus. Each of them underwent a standard exercise (bicycle ergometry) or pharmacological (dipyridamole 0.84 mg/kg) stress testing. In 48 pts (19,4%, 28 males, age 48-75 years, mean 61.6+12.4) it showed a positive result (80 ms from the J point ST-segment depression $>$1,0mm). MPS and CA – a gold standard for detecting coronary artery disease ($>$50% narrowing of at least one epicardial artery) were performed in each case.
Results: CA revealed significant coronary lesions in 20 pts (41.7%) and was normal in 28 pts (58.3%). MPS showed to be positive in 27 pts (56.3%) and negative in 21 pts (43.7%), sensitivity 100%, specificity 75%, diagnostic accuracy 85%, positive predictive value 74%, negative predictive value 100%.
Conclusions: hypertensives with LVH can be affected with angina for significant epicardial coronary stenosis or microvascular disease with normal CA. SECG is positive in both conditions. In our group of pts we found the high sensitivity and good specificity and diagnostic accuracy of MPS in detecting ischemia. We recommend MPS in hypertensives with LVH and ischemic-like ST segment changes on SECG, because when negative, it excludes significant epicardial lesions and should be considered as a predictor of microvascular disease.

P869 Enhanced prognostic significance of chronic kidney disease estimated according to creatinine clearance formula for major cardiovascular events in hypertension: a Greek 6-year follow-up study

D. Tsiachris, C. Tsioufis, E. Vezali, K. Dimitriadis, A. Agelis, D. Roussos, D. Syrseloudis, E. Andrikou, I. Kallikazaros, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: We assessed the comparative prognostic role of chronic kidney disease (CKD) for major CV events defined according to glomerular filtration rate (GFR) or creatinine clearance (CrCl) in a prospective observational study in Greek hypertensives.
Methods: We followed-up 1652 hypertensives (mean age 54.3 years, 696 males, office BP=147/93 mmHg) free of CV disease for a mean period of 6 years. Five major risk factors [age $>$65, gender, current smoking, diabetes mellitus (DM) and dyslipidemia (LDL$>$160mg/dl)] were evaluated at baseline along with the presence of CKD defined either according to MDRD-estimated GFR between 15 and 59 ml/min/1.73m^2 or based on estimated CrCl between 15 and 59 ml/min (by using Cockroft-Gault formula). End-points of interest were the incidence of coronary artery disease (CAD), stroke, all cause mortality and their composite.
Results: The prevalence of CKD according to Cockroft-Gault formula was lower

than the one based on estimated GFR (8.8% vs. 13.3%). At the end of follow up, CAD was the most prevalent (5.2%), followed by stroke (5%) and total mortality (3.1%). In univariate Cox regression analysis, age>65 (HR 2.53, p<0.001), male gender (HR 1.97, p=0.004), DM (HR 4.01, p<0.001) and the presence of CKD, based either on GFR (HR 1.91, p=0.039) or CrCl estimation (HR 2.67, p=0.003) were correlated with the incidence of CAD. In multivariate analysis, CKD based only on estimated CrCl (adjHR 2.34, p=0.018) along with age>65, male gender and DM remained independents prognosticator of CAD. In addition, age>65 (HR 5.98, p<0.001) and CKD based either on estimated CrCl (HR 3.56, p<0.001 and or estimated GFR (HR 1.91, p=0.048) were associated with the incidence of stroke. In multivariate analysis, only CrCl-estimated CKD (adjHR 2.17, p=0.029) and age>65 was a predictor of stroke. Finally, age>65 (HR 4.65, p<0.001), male gender (HR 1.34, p=0.041), DM (HR 2.00, p=0.001) and CKD based either on estimated CrCl (HR 3.42, p<0.001) or estimated GFR (HR 1.96, p=0.001) were correlated with the composite end-point. In multivariate analysis, apart from age and sex, CKD based on estimated CrCl (adjHR 2.31, p<0.001) and on GFR (adjHR 1.55, p=0.045) were independent predictors of the composite end-point.

Conclusions: In hypertensive subjects free of CV disease, CKD estimated according to CrCl formula, although less prevalent than estimation based on GFR, contains enhanced predictive significance for major CV events.

P870 Left ventricular mass regression and remodeling assessed by echocardiography after percutaneous transluminal renal angioplasty with brachytherapy of renal arteries guided by intravascular ultrasound

T. Niklewski, A. Lekston, K. Wilczek, M. Gasior, T. Zebik, M. Zebala, L. Polonski. *Slaskie Centrum Chorob Serca, Zabrze, Poland*

Purpose: The aim of our study was to evaluate the influence of intravascular brachytherapy (IVBT) procedure performed after percutaneous transluminal renal angioplasty (PTRA) controlled with intravascular ultrasound (IVUS) on left ventricular function, mass regression and type of LV hypertrophy (LVH) in long term observation.

Methods: 59 patients (pts.) aged 51,6±8 years with severe hypertension complicating renal artery atherosclerotic stenosis, were successfully treated with PTRA and randomised to Group I (PTRA alone) and group II (PTRA followed by IVBT). Subsequent IVBT with PARIS® catheter and Nucletron™ system for peripheral areries was performed and PTRA was optimised with IVUS study. Follow-up effect was assessed with IVUS and quantitative angiography (QCA.). LV mass and functional parameters before PTRA and 12 months follow up weres analyzed in echocardiographic examination with reference to different type of procedure

Results: In both analyzed groups elevated left ventricular mass index (LVMI) was observed (p=0,94). No significant differences in IVS to LVPW ratio, relative LV wall thickness, volume parameters and LVEF among both groups were found. In 12 months follow up study the values of LVMI and IVS to LVPW ratio were significantly lower (p=0,021) and (p=0,004) in PTRA+IVBT group in comparison to PTRA alone group. Analysis of left ventricular geometry and type of hypertrophy revealed marked reduction of concentric LVH in follow up in IVBT group (before 19 (61,3%) in follow up 13 (41,9%)). Control stenosis was significantly different 33,9±11,7% in group I and 25,5±12,3% in group II (p=0,0096). Control stenosis was 33,9±11,7% in group I and 25,5±12,3% in group II (p=0,0096). Also minimal lumen area (MLA) was significantly larger in group II than in group I 15,6±5,4 vs 11,9±4,4 (p= 0.0053). In IVUS examination late loss of MLD was 1,09±0,68 and 0,57±0,68mm in group I and II respectively (p= 0,006).

Conclusion: Echocardiographic analysis comparing several LV parameters in PTRA alone and PTRA + IVBT groups revealed that PTRA and brachytherapy was associated with better control of blood pressure and LV mass regression, especially concentric hypertrophy in long term observation. Both IVUS and QCA data provided that IVBT of renal arteries is safe an effective method in prevention of restenosis in long term observation after PTRA. IVUS is useful method of optimalisation the procedure and assessment of early results and long term effect after precutaneous renal angioplasty.

P871 Evolution of stroke and cardiovascular mortality risk in a hypertensive population in Belgium: results of one year follow-up in the Belgica Stroke study

P. Van Der Niepen on behalf of the BELGICA-STROKE committee. *Free University Brussels, Brussels, Belgium*

Purpose: evaluation of the impact of the use of a systemic tool for the calculation of the Framingham stroke risk and the SCORE cardiovascular mortality risk one year after its implementation.

Methods: multicenter prospective study in primary care in Belgium. Hypertensive patients of 40 years or older were recruited by their general practitioner. An online tool was made available to the physicians. Patients were followed up for up to 30 months.

Results: 15744 patients were included, of which 8690 completed 4 visits. The patients who did not complete 4 visits did not differ clinically from the patients who completed 4 visits. The Framingham stroke risk could be calculated for 6315 patients; the SCORE risk calculation (primary prevention) was available for 3434 patients. The Framingham stroke risk and the SCORE risk were reduced significantly after one year. Blood pressure and cholesterol were better controlled after one year, both contributing to the reduction in the calculated risk.

Evolution during the first year

	# patients	Visit 1	Visit 2	Visit 3	Visit 4	p
Framingham stroke risk	6315					
Mean (SD)	6315	19.2 (12.8)	18.1 (14.1)	17.6 (13.8)	17.4 (13.8)	
Median (range)	6315	16 (2-88)	13 (2-88)	13 (1-84)	13 (1-88)	<0.001
Age, years (mean (SD))	6398	68.6 (8.4)				
Male sex (%)	6398	51.4				
SBP, mmHg (mean ((SD))	6398	153.9 (12.9)	142.0 (13.9)	139.9 (13.9)	138.8 (13.8)	
SBP, mmHg (median)	6398	150	140	140	140	<0.001
Smoker %	6398	16.8	16.6	16.4	16.3	<0.001
Score risk	3434					
Mean (SD)	3434	6.0 (5.4)			4.4 (4.1)	
Median (range)	3548	4.4 (0.2-47.1)			3.1 (0.1-46.3)	<0.001
Age, years (mean (SD))	3548	60.1 (8.7)				
Male sex (%)	3548	51.7%				
SBP, mmHg (mean (SD))	3548	154.8 (12.7)	141.7 (13.8)	139.5 (13.3)	138.7 (13.7)	
SBP, mmHg (median)	3548	150	140	140	140	<0.001
Smoker (%)	3548	21.2	21.0	20.8	20.6	
Total cholesterol mg/dL (mean ((SD))	3548	218.0 (39.3)			209.4 (36.9)	

SBP = systolic blood pressure.

P872 Does pulsatile component of blood pressure explain CV risk associated with age ?

P. Jankowski[1], D. Czarnecka[1], K. Styczkiewicz[1], M. Brzozowska-Kiszka[1], M. Kloch-Badelek[1], J. Wilinski[1], L. Bryniarski[1], D. Debicka-Dabrowska[1], D. Dudek[2], K. Kawecka-Jaszcz[1] on behalf of ABPS Study Group. *[1]I Dept of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow, Poland; [2]II Dept of Cardiology Jagiellonian University Medical College, Krakow, Poland*

Objectives: Age is a major cardiovascular (CV) risk factor. Relative (represented by pulsatility) as well as absolute (pulse pressure [PP]) changes of central blood pressure (BP) were shown to predict CV complications in coronary patients.

Aim: We hypothesized that pulsatile component of BP can explain CV risk associated with age.

Methods: The study group consisted of 548 patients (443 men and 105 women; mean age: 57.9±9.6 years; mean EF: 56.1±11.0%) undergoing PCI (n=354), CABG (n=191) or both (n=3). Demographic and clinical information as well as invasive ascending aortic BP were obtained at baseline. Duration of follow-up was 53.3±17.1 months. The end point was defined as: CV death, myocardial infarction (MI) or stroke. We defined pulsatility as the ratio of PP to mean BP and pulsatility index as the ratio of PP to diastolic BP. Cox proportional hazard regression analysis was used to assess independent predictors of event-free survival.

Results: CV death or MI or stroke occurred in 66 (12.0%) patients. Hazard ratios for 10-years increase in age are shown in the table. Among all BP-derived indices only pulsatility (increase per 0.1: HR 1.29 [95% CI 1.07-1.56]) and pulsatility index (increase per 0.1: 1.17 [1.06-1.29]), but not systolic, diastolic, mean or pulse pressure, were related to the risk of the end point when adjusted for age.

HRs for 10-years increase in age

	Hazard ratio (95% CI)
Univariate analysis	1.30 (1.01-1.68)
Multivariate analysis*	1.39 (1.03-1.86)
Additional adjustments for:	
Systolic blood pressure	1.39 (1.03-1.88)
Diastolic blood pressure	1.34 (1.00-1.80)
Mean blood pressure	1.39 (1.04-1.87)
Pulse pressure	1.30 (1.05-1.78)
Pulsatility	1.19 (0.87-1.63)
Pulsatility index	1.18 (0.86-1.61)

*Age, sex, LV ejection fraction, extent of coronary atherosclerosis, NYHA class, heart rate, creatinine level, risk factors and treatment are included in the model.

Conclusion: Pulsatile component of BP (represented by pulsatility and pulsatility index) may at least partly explain CV risk associated with age in coronary patients.

P873 Effect of aortic pulse and fractional pulse pressures on early patency of sapheneous vein grafts

S. Cayli[1], G. Cagirci[2], Y. Balbay[1], R. Atak[1], O. Maden[1], S. Aydogdu[1]. *[1]Turkiye Yuksek Ihtisas Hospital, Ankara, Turkey; [2]Ministry of Health Diskapi Yildirim Beyazit Research and Educational Hospital, Ankara, Turkey*

Background: Coronary artery bypass grafting has a mortality benefit compared to medical therapy in some patient groups, such as those with left main or left anterior descending coronary artery disease, and those with left ventricular dysfunction. Therefore, patency of grafts, especially sapheneous grafts, is an important

issue. Aortic pulse and fractional pulse pressures are strong and independent indicators of the risk of atherosclerosis. We studied whether there was any negative effect of increased aortic pulse and fractional pulse pressures on saphenous vein graft (SVG) patency in the short term.
Methods: We evaluated aortic pulse and fractional pulse pressures of patients with occluded and patent SVGs, and investigated the relation between the two groups. One hundred and twenty-six patients with occluded SVGs with a mean age of 65.9±8.9 years and 114 patients with patent SVGs with a mean age of 66.9±8.6 years were studied consecutively. Aortic systolic and diastolic pressures were measured, and mean, pulse, and fractional pulse pressures (aortic pulse pressure/mean pressure) were calculated.
Results: Aortic pulse and fractional pulse pressures were significantly higher in the occluded SVG group than in the patent SVG group (58±19 and 48±13 mmHg, P=0.001; 0.59±0.16 and 0.50±0.10, P<0.001, respectively). In addition, a cut-off value of 50 mmHg and 0.52 for aortic pulse and fractional pulse pressures were determined, respectively. Increased aortic pulse (>50 mmHg) and fractional pulse (>0.52) pressures were present in 54.0 and 58.7% of patients in group 1 and 28.1 and 33.3% of patients in group 2, respectively (P=0.004 and P=0.005, respectively). Having increased aortic pulse and fractional pulse pressures increased the risk of SVG occlusion by 3.00 and 2.85-folds, respectively. The multiple-adjusted odds ratio of the risk of SVG occlusion was 6.86 (95% confidence interval 2.14-21.96) and 4.76 (95% confidence interval 1.58-14.30) for the higher aortic pulse and fractional pulse pressure levels compared with lower levels, respectively.
Conclusion: Increased ascending aorta pulse and fractional pulse pressures have a significant and independent negative effect on the fate of SVGs.

P874 Evolution of cerebrovascular risk, blood pressure and lipid parameters in hypertensive coronary patients in the prospective BELGICA-STROKE study

P. Van De Borne on behalf of the BELGICA-STROKE committee. *Erasme University Hospital, Brussels, Belgium*

Purpose: To evaluate the evolution of cerebrovascular accident (CVA) risk, blood pressure (BP) and lipid parameters in the hypertensive population with coronary heart disease (CHD) included in the BELGICA-STROKE prospective study.
Methods: Patients were recruited by their General Practitioner, an online CVA risk management tool was made available to the physician. Patients were followed up for up to 8 visits (4-monthly intervals).
Results: 2939 of 15744 patients had CHD. 1660 CHD patients completed only 4 visits (group A), 694 completed 8 visits (group B).The CVA risk, systolic and diastolic BP, TC and LDL-C were reduced at visit 4. Group B achieved further reductions of all parameters, TC and LDL-C reductions were significant (table). The patients finishing at 4 visits had significant higher systolic BP, diastolic BP, LDL-C (p<0.001, p=0.001; p=0.004 resp.) compared with patients finishing 8 visits.
Conclusion: CVA risk score, hypertension control and lipid management were improved. A larger number of GP/patient contacts is associated with an improved lipid control, probably reflecting enhanced motivation of both physician and patient. The CHD patient stays nevertheless at very high risk for CVA.

P875 Arterial compliance vs arterial distensibility as a determinant of outcome

B.A. Haluska, L. Jeffriess, S.G. Carlier, T.H. Marwick. *The University of Queensland, Brisbane, Australia*

Background: Arterial distensibility and pulse wave velocity have been shown to predict outcome in pts at risk of cadiovascular disease. Total arterial compliance (TAC) is a measure of arterial function that reflects the entire systemic circulation but few data exist regarding the relationship of TAC to outcome. We sought to compare TAC and distensibility in a large, primary prevention group of patients with varying degrees of CV risk.
Methods: We studied 719 primary prevention pts (373 men; age 55± 11) who had TAC assessed between April 2001 and February 2008. Clinical data were obtained and TAC was calculated by the pulse-pressure method from applanation tonometry and Doppler echocardiography. Distensibility coefficient (DC) was measured from high-resolution imaging of the carotid arteries. Clinical data were obtained by patient history. Kaplan Meier curves and log rank test were used to assess survival and event-free survival and Cox regression analysis was performed to determine correlates of outcome.
Results: The expected risk on clinical grounds was 17±11%. There were 42 deaths (6%) and 114 hospital admissions (16%) over a median follow-up of 5 years. The independent correlates of mortality (model chi-square 61; p<0.0001) were DBP, DM, number of risk factors and TAC, but not DC (Table 1). The independent correlates of event-free survival were age > 60 (HR 1.92; p=0.05) and TAC (HR 0.15; p<0.0001).

Table 1

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age > 60	4.42	2.26-8.63	<0.0001			
Gender	2.67	1.34-5.32	0.005			
DBP	0.95	0.92-0.97	<0.0001	0.90	0.82-0.98	0.02
TAC-PPM	0.47	0.24-0.91	0.02	0.004	0.00-0.20	0.006
DC	0.37	0.15-0.92	0.03			
HTN	3.09	1.30-7.35	0.01			
DM	0.83	0.44-1.55	0.55	0.03	0.001-0.21	0.002
# risk factors	1.32	0.98-1.79	0.06	7.89	2.29-27.17	0.001

Conclusions: Measurement of total arterial compliance is feasible, independently correlates with death and event-free survival and appears superior to distensibility measurements in patients at risk.

P877 Functional characterization of the coronary microcirculation by myocardial contrast echocardiography in arterial hypertensive heart disease

J. Coucello[1], L. Soares[2], J. Azevedo[1], L.C. Bronze Carvalho[1], A. Aleixo[1]. *[1]Unicard-Hospital Francisco Xavier, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal; [2]Hospital Barlavento, Portimão, Portugal*

In early phases of arterial hypertensive disease (HTD), coronary microcirculation (CM) can be already affected, because of vascular remodelling associated with left ventricular (LV) myocardial hypertrophy (H). Myocardial contrast echocardiography (MCE) has the capacity to evaluate CM. Our aim was to characterize CM through MCE in HTD clinical scenario. MCE was performed in 60 HTD patients (pts). From the calculation of the relative wall thickness (RWT) and LV mass index (LVMI-g/m^2), different forms of LVH were identified by transthoracic echocardiography according to the ASE recommendations: 15 pts without both LV remodelling (R) and LVH (R–H–), 15 pts with R and without H (R+H–), 15 pts without R and with H (R–H+), and 15 pts with both R and H (R+H+). HTD pts with diabetes mellitus, hyperlipidemia and coronary artery disease were excluded. MCE was performed with a Sequoia 512 Acuson ultrasound equipment, 4 MHz probe. The MCE agent was Optison (Mallinckrodt, USA), in a 2.5ml/min infusion rate; hyperaemia was provoked with intravenous adenosine 140 μg/kg/min infusion. With a quantitative DataPro software for imaging analysis, the waveform was displayed by the exponential function Y = A (1 – e –βt). From this formula, was derived both myocardial blood flow (MBF) under basal (bas) condition and after adenosine induced hyperaemia (adn) as well as myocardial coronary flow reserve (MFR), corresponding to the ratio between MBF under hyperaemia versus basal conditions.
Results: The MFR values suffered a significant reduction among the different LV geometric forms of HTD. These values are mainly dependent on the reduction of β and A values during hyperaemia. In R+H+ there is a significant β reduction (p<0.05) in comparison with R–H– and R+H– groups. The next table depicts our results (Ø p<0.05).

	β bas/adn ratio	A bas/adn ratio	MFR
R–H+	0.06/0.97	0.078/0.18	2.3
R+H–	0.95/0.96	0.075/0.15	2.0
R–H+	0.95/0.88	0.070/0.14	1.9
R+H+	0.93/0.76	0.058/0.09	1.3Ø

Conclusion: In early phases of HTD, a clear reduction of MFR was already observed by MCE, and registered an inverse correlation with LVMI. We described the MFR reduction of regional CM more dependent on LV RWT and without LVMI increase.

Abstract P874 – Table 1. Evolution for group A and group B

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Group A	ˆCVA score (n=1176)	29.9 (14.4)	29.5* (17.1)	28.5* (16.6)	28.6** (16.6)				
	ˆˆSBP (n=1660)	152.1 (12.6)	140.0* (14.0)	137.8*(13.9)	136.6* (13.5)				
	ˆˆˆDBP (n=1660)	85.7 (9.4)	80.7* (8.5)	79.7* (8.1)	79.0* (8.0)				
	†TC (n=1660)	198.2 (42.3)			191.2* (38.3)				
	‡LDL-C (n=1556)	114.8 (37.5)			108.4* (35.4)				
Group B	ˆCVA score (n=489)	30.6 (15.1)	30.2*** (17.5)	28.7* (16.7)	28.8 (17.1)	28.5 (16.8)	27.6° (16.7)	27.4 (16.7)	27.3 (16.6)
	ˆˆSBP (n=694)	152.3 (12.4)	140.7* (14.4)	138.1* (14.2)	137.0°° (13.5)	136.8 (14.7)	135.4§ (14.8)	134.7 (14.0)	134.1 (13.9)
	ˆˆˆDBP (n=694)	85.9 (9.6)	80.3* (8.9)	79.6 (8.4)	78.7§§ (802)	78.5 (8.2)	78.2 (8.4)	77.7 (8.3)	77.2 (8.4)
	†TC (n=694)	198.4 (41.7)			192.6* (39.2)				188.1* (36.6)
	‡LDL-C (n=656)	116.1 (36.2)			109.8* (36.0)				105.6* (32.3)

ˆCVA score = mean (SD) Framingham CVA risk score in percentage; ˆˆSBP = mean (SD) systolic blood pressure in mmHg; ˆˆˆDBP = mean (SD) diastolic blood pressure in mmHG, †TC= mean (SD) total cholesterol in mg/dL; ‡LDL-C = mean (SD) low density lipoprotein cholesterol in mg/dL; *p=0.001; **p=0.005; ***p=0.002; °p=0.008; °°p=0.018; §p=0.003; §§p=0.037 (comparisons with previous value).

P878 Cardiovascular risk in treated hypertensive patients and circadian blood pressure variation

T.H. Gialernios[1], A. Triantafyllou[1], K. Gialernios[1], S. Kougialis[1], M. Lambropoulou[1], H. Skopelitis[1], E. Logothetis[1], E. Kouskouni[1], A. Polydorou[2]. *[1]3rd Hospital of IKA Cardiology Department, Athens, Greece, Athens, Greece; [2]Evangelismos General Hospital of Athens, Athens, Greece*

Background: The prognostic relevance of cicardian blood pressure (BP) variations in treated hypertensive patients is not yet clear. The aim of this study was to evaluate the prognostic impact of cicardian BP patterns in treated hypertension.
Methods: We studied 1272 treated hypertensive subjects. Among these 388 had a dipper BP pattern (systolic and diastolic nighttime BP reduction >10% and <20%), 745 had a nondipper BP pattern (systolic and/or diastolic nighttime BP reuction <10%), and 399 had an extreme-dipper BP pattern (systolic and/or diastolic nighttime reduction BP reduction >20%)
Results: During the follow-up (3.2±1.9 y), 98 cardiovascular events occurred. The event rate per 100 patients-years was 0.81, 1.53 and 1.62 in dipper, nondipper and extreme dippers patients,respectively. Event-free survivals was significantly different among the groups (P=0.001). After adjustment for various covariates, including 24h BP and drug therapy, Cox regression analysis showed that cardiovascular risk was significantly higher in nondipper patients (nondipper versus dipper, relative risk 1.51, 95% confidence interval [CI] 1.03-2.67, P=0.03) and in extreme-dipper patients (extreme-dipper vs dipper, relative risk 1.9, 95% CI 1.1-4.14, P=0.02).
Conclusions: This study demonstrates that treated hypertensive patients with a nondipper or extreme-dipper cicardian BP pattern show higher cardiovascular risk than those with a dipper BP pattern. Cicardian BP pattern infuences cardiovascular outcome in treated hypertension and its evaluation allows a better prognostic stratification and may suggest a more appropriate pharmacological management.

P879 Left ventricular diastolic dysfunction reflects reduced exercise tolerance in newly diagnosed essential hypertensives

D. Chatzis, C. Tsioufis, D. Tsiachris, C. Thomopoulos, E. Stefanadi, D. Syrseloudis, C. Papastasinos, A. Michaelides, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: Left ventricular (LV) diastolic dysfunction, an established confounder of heart failure with preserved ejection fraction, and decreased exercise tolerance are both correlated with adverse cardiovascular prognosis. We sought to investigate the plausible interrelationship of these parameters in the setting of essential hypertension (EH).
Methods: 160 consecutive patients (aged 52±8 years) with newly discovered and untreated stage I – II EH underwent a negative for myocardial ischemia, maximal treadmill exercise testing and were classified based on the amount of metabolic equivalents achieved as fit (METS>10.5 ml/kg/min, N=80) and unfit (METS≤10.5 ml/kg/min, N=80). All the participants underwent 24hour ambulatory blood pressure (BP) monitoring and complete echocardiographic study including LV diastolic function evaluation by means of pulsed tissue Doppler Imaging (TDI), averaging diastolic mitral annular velocities (Em, Am) from 4 separate sites of measurement (LV lateral, septal, anterior and inferior wall).
Results: Unfit hypertensives, compared to the fit ones, were older (by 6 years, p<0.001), had greater 24hour pulse pressure (PP) (by 3.1 mmHg, p=0.005) and lower prevalence of male gender (by 28%, p<0.001). The two groups did not differ with respect to metabolic profile, as well as office systolic and diastolic BP. Similarly, LV mass index as well as left atrial diameter and volume index were not different between the two groups. In contrast unfit hypertensives, compared to their fit counterparts, exhibited higher LV filling pressures as reflected by greater E/Em ratio (by 1.7, p=0.001) and impaired LV relaxation as reflected by lower Em/Am ratio (by 0.11, p=0.014). In the entire study population the amount of achieved METS was related to age (r=-0.366), gender (r=0.393), Em/Am ratio (r=0.333), E/Em ratio (r=-0.307) (p<0.001 for all cases) and to 24hour PP (r=-0.227, p=0.005).
Conclusions: In untreated, newly diagnosed subjects with EH, the diminished exercise tolerance is interrelated with increased ambulatory pulsatile load, impairment of LV relaxation and augmented LV end-diastolic pressures. These associations may further elucidate the prognostic role of the decreased exercise capacity in the clinical setting of hypertension.

P880 High intraluminal pressure reduces angiotensin II-induced tachyphylaxis in arterioles by increasing the functional availability of AT1 receptors

A. Koller[1], Z.S. Bagi[2]. *[1]Dept of Physiol, New York Med Coll, USA and Dept of Pathophysilogy, Pécs And Valhalla, Hungary; [2]Dept of Physiol, New York Med Coll, USA, Valhalla, Ny, United States of America*

There are several forms of hypertension, in which the elevated peripheral vascular resistance is not due the up-regulation of the systemic renin angiotensin system (RAS). Yet, many clinical trials have shown that angiotensin converting enzyme (ACE) inhibitors or type 1 Ang II (AT1) receptor blockers efficiently reduce blood pressure and prevent vascular complications almost in all forms of hypertension. Previously we found that high intraluminal pressure leads to production of reactive oxygen species (ROS) and also upregulates several components of the renin-angiotensin system in the wall of small arteries. We hypothesized that acute exposure of arterioles to high intraluminal pressure in vitro, via increasing ROS production, enhances the functional availability of AT1 receptors, resulting in sustained constrictions. In arterioles (~180 μm) isolated from rat skeletal muscle Ang II elicited dose-dependent constrictions, which decreased significantly by the second application (max.: from 59±4% to 26±5%, at 10^{-8} M, p<0.05), in the presence of 80 mmHg of intraluminal pressure. In contrast, if the arterioles were exposed to high intraluminal pressure (160 mmHg, for 30 min) Ang II-induced constrictions remained substantial upon the second application (max.: 51±3% at 10^{-8} M). In the presence of Tiron and PEG-catalase, known to reduce the level of superoxide anion and hydrogen peroxide (H2O2), second applications of Ang II evoked similarly reduced constrictions, even after high pressure exposure (29±4% at 10-8 M). Furthermore, when arterioles were exposed to H2O2 (for 30 min, 10-7 M, at normal, 80 mmHg pressure), Ang II-induced constrictions remained substantial upon second applications (59±5% at 10-8 M). These findings suggest that high pressure, likely via inducing H2O2 production increases the functional availability of AT1 receptors and thus enhances Ang II-induced arteriolar constrictions. In conclusion, we propose a novel pathophysiological mechanism by which high intraluminal pressure, (independent of the circulating and tissue levels of Ang II) - via increased production of H2O2 - augments the functional availability of AT1 receptors, a mechanism which may operate in every form of hypertension or disease states associated with oxidative stress. Also, we propose that the level of intraluminal pressure - even in the physiological range - continuously modulates the functional availability AT1 receptors.

YOUNG INVESTIGATORS' AWARDS SESSION: POPULATION SCIENCES

882 The NSAID diclofenac increases cardiovascular risk among young and healthy individuals after short treatment duration: a nationwide study

E. Fosbol[1], G.H. Gislason[2], L. Kober[2], C. Torp-Pedersen[1]. *[1]University Hospital Gentofte, Copenhagen, Denmark; [2]Rigshospitalet (The Heart Centre), Copenhagen, Denmark*

Purpose: Diclofenac is a widely used non-steroidal anti-inflammatory drug (NSAID) in the general population and has been linked to increased cardiovascular risk. We analysed the effect of duration of diclofenac treatment on cardiovascular risk in healthy young individuals.
Methods: By individual-level-linkage of nationwide administrative registers; we identified a young (age<40 years) cohort of individuals without hospitalizations five years prior to first prescription claim of NSAID and without claimed drug prescriptions for selected concomitant medication two years previously. The risk of death or myocardial infarction associated with duration of diclofenac treatment was estimated by time-dependent Cox proportional hazard analysis. Treatment duration was stratified as follows: less than seven, seven to 14, 14-30, 30-90, and over 90 days of treatment.
Results: The entire Danish population aged 10 years or more consisted of 4,614,807 individuals on January 1, 1997. Of these; 525,656 individuals were included in the study. During the study period, a total of 76,675 (15%) used diclofenac and 202 individuals experienced an event during treatment with the drug. Compared to no use of NSAID; diclofenac treatment raised the risk of death or myocardial infarction significantly after less than 7 days and the risk persisted later on (see Figure).

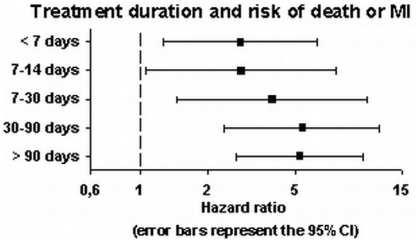


Figure: The Cox analysis

Conclusions: Diclofenac raised the risk of death or myocardial infarction from the initial face of treatment in young and healthy individuals and the risk persisted during long-term treatment. Diclofenac may constitute a major public health issue as it is used widely in the general population and should be used with caution in all individuals.

883 Usefulness of triglycerides-to-HDL ratio to predict the first coronary event in active male workers: a case-control study

A. Cordero[1], E. Andres[2], B. Ordonez[2], M. Leon[2], E. Alegria[2], E. Luengo[2], I. Pascual[2], F. Civeira[2], M. Pocovi[2], J.A. Casasnovas[2].
[1]*Hospital Universitario de San Juan, Alicante, Spain;* [2]*Clinica Universitaria de Navarra, Pamplona, Spain*

Introduction: Overweight and obesity potentiate the development of other cardiovascular risk factors and atherosclerotic events although some doubts have recently aroused. We evaluated the predictive value of a surrogate maker of insulin resistance, the triglyceride-to-HDL (TG/HDL) ratio, for the incidence of a first coronary event in male workers with the hypothesis that TG/HDL ratio would identify a high-risk subset of patients within those that would be classfied as overweight or obese.
Methods: Case-control study of active subjects collected from a single factor through their annual health examination and medical reports. Cases included myocardial infarction, unstable angina or inducible ischemic detected through ECG abnormalities.
Results: The study was conducted in 208 cases and 2080 controls, with mean age 49.9 (49.6-50.2) years. General characteristics of cases and controls were well matched. TG/HDL ratio was significantly higher in cases compared to controls in all categories of BMI (Figure 1). Overweight (OR: 1.47) and obesity (OR: 1.75) showed a non-significant trend to higher risk of coronary events. Stratification of the sample by categories of (BMI) revealed an increasing prevalence of cases and mean TG/HDL in each category of BMI. Multivariate analysis, adjusted by smoking, demonstrated that TG/HDL increased significantly the risk of a first coronary event (OR: 1.47; 95% CI 1.26-1.71) as well as LDL values (OR: 1.01; 95% CI 1.005-1.012); nonetheless, metabolic syndrome (OR: 1.76; 95% CI 0.94-3.30) and hypertension (OR: 1.50; 95% CI 0.81-2.79) did not reach statistical significance. TG/HDL ratio was associated to first coronary event in all categories of BMI.

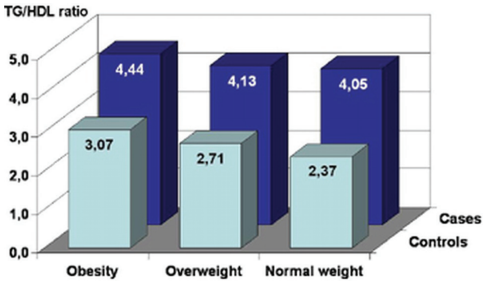


Figure 1

Conclusion: TG/HDL ratio has a high predictive value of a first coronary event regardless of BMI.

884 Ten-year risk of cancer mortality according to lipid levels and use of lipid-lowering drugs in the French general population

E. Berard[1], V. Bongard[1], P. Amouyel[2], D. Arveiler[3], J. Dallongeville[2], A. Wagner[3], D. Cottel[2], B. Haas[3], J.B. Ruidavets[1], J. Ferrieres[4].
[1]*Department of Epidemiology, INSERM U558, Toulouse University School of Medicine, Toulouse, France;* [2]*Department of Epidemiology and Public Health, INSERM U744, Pasteur Institute of Lille, Lille, France;* [3]*Department of Epidemiology and Public Health, EA 3430, University of Strasbourg, Medical Faculty, Strasbourg, France;* [4]*Department of Cardiology B and Department of Epidemiology, INSERM U558, Toulouse University Hospital, Toulouse, France*

Purpose: The beneficial effect of lipid-lowering drugs on cardiovascular morbidity and mortality is perfectly established, but long term safety data remain scarce. However, such information is particularly warranted in primary prevention where drug prescriptions are generally initiated for a long period of time. The aim of this study was to assess 10-year risk of cancer mortality according to blood lipid levels and lipid-lowering drug exposure, in the French general population.
Methods: Our analysis was based on the Third French MONICA Cross-sectional survey on cardiovascular risk factors (1995-1996). Participants were randomly recruited from the general population of three French areas and were aged 35-64 years. Subjects with a history of cancer at baseline were excluded from the analysis. Vital status and cause of mortality were obtained 10 years after inclusion. Assessment of determinants of cancer mortality was based on multivariable Cox modelling.
Results: There were 3262 participants and 177 deaths were recorded over the 10-year period (78 due to a cancer). The sample was mainly composed of subjects in primary cardiovascular prevention (96%) and comprised 64% of normolipidemic, 25% of untreated dyslipidemic (i.e. total cholesterol $\geq$6.5 mmol/L or triglycerides $\geq$3.5 mmol/L) and 11% of dyslipidemic subjects treated with a lipid-lowering drug (4% statin, 6% fibrate and 1% other hypolipidemic drug). After adjustment for centre, age, smoking, gamma-glutamyl transpeptidase and mean corpuscular volume, which were all significantly associated with cancer mortality, the hazard ratio (HR) for cancer mortality in subjects with non HDL-cholesterol $<$3.5 mmol/L was 2.83 [95% confidence interval: 1.73-4.62]. The adjusted HR in subjects with HDL-cholesterol $<$0.90 mmol/L was 2.87 [1.63-5.06]. The adjusted HR in subjects on lipid-lowering drug as compared to untreated subjects was 0.31 [0.11-0.85].
Conclusion: In this cohort mainly composed of primary prevention subjects, low HDL- and low non HDL-cholesterol levels were associated with increased cancer mortality, whereas risk of cancer death was reduced in users of lipid-lowering drugs. This suggests that the impact of low cholesterol on cancer risk may be different in subjects with spontaneously low levels and in those for whom cholesterol is lowered by lipid-lowering drugs.

885 Italian smoking regulation decreased hospital admissions for acute coronary events:effect modification by age and day of the week

F. Barone Adesi, L. Vizzini, F. Merletti, L. Richiardi. *University of Turin, Turin, Italy*

Purpose: Recent studies have shown a reduction of hospital admissions for cardiovascular diseases after the introduction of laws banning smoking in public places. We used the hospital discharge records of Piedmont, an Italian region with 4.3 million inhabitants, to estimate changes in admissions for acute coronary events during the first 30 months after the introduction (January 2005) of a national smoking ban.
Methods: Rates of admission for acute coronary events (ICD9: 410-411) in Piedmont from January 2001 to June 2007 were analysed using Poisson regression models allowing for long term trends and seasonality. Standard methods for interrupted time-series were adopted to assess the role of immediate and gradual effects of the smoking ban. The immediate effects were analyzed including a dummy variable in the model, while gradual effects were studied testing the change in the underlying trend after the introduction of the ban. Effect modification by age and day of the week was investigated in the assumption that exposure to passive smoking in public places was stronger among young people and during weekends.
Results: A 7% reduction of hospital admissions for acute coronary events among persons aged less than 70 was evident after the introduction of the ban (Rate Ratio [RR], 0.94; 95% Confidence Interval [CI], 0.90-0.97). No effect was found among persons aged at least 70 (RR 1.00; 95%CI 0.97-1.03). The effect of the ban was considerably stronger during weekends (Rate Ratio, 0.87; 95% confidence interval, 0.80–0.93) than in the other days of the week (Rate Ratio, 0.96; 95% confidence interval, 0.92–1.00). The observed reduction in the number of admissions for acute coronary events started in the same month in which the ban came into effect and remained evident for the entire study period. No change (p: 0.51) in the underlying trend was found, suggesting that most of the reduction came into effect immediately after the introduction of the ban.
Conclusions: The results of this study, carried out on a large population, suggests that smoke-free policies may result in a short-term reduction in admissions for acute coronary events. This is further supported by the finding that the effect was stronger among young people and during weekends. Consequences for public health are relevant.

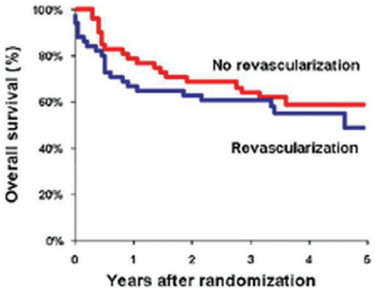
YOUNG INVESTIGATORS' AWARDS SESSION: CLINICAL SCIENCE

887 Long-term outcome of a randomized trial of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery

O. Schouten[1], J.P. Van Kuijk[1], W.J. Flu[1], H. Boersma[1], T.A. Winkel[1], S.E. Hoeks[1], H.J.M. Verhagen[2], Y.R.B.M. Van Gestel[1], J.J. Bax[3], D. Poldermans[4]. [1]*Erasmus, Rotterdam, Netherlands;* [2]*Erasmus MC, Rotterdam, Netherlands;* [3]*Leiden University Medical Center, Leiden, Netherlands;* [4]*Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Background: Prophylactic coronary revascularization in vascular surgery patients with extensive coronary artery disease is not associated with an improved immediate postoperative outcome. However, the potential long-term benefit remains unknown.
Aim: To assess the long-term benefit of prophylactic coronary revascularization in very high-risk cardiac patients
Methods: Of 1880 patients scheduled for major vascular surgery, 430 had $\geq$3 risk factors ($>$ 70 yrs, angina pectoris, MI, heart failure, stroke, diabetes, and renal failure). All underwent cardiac testing using dobutamine echocardiography or nuclear stress imaging. Those with extensive stress-induced ischemia ($>$ 5 segments or $>$ 3 walls) were randomly assigned for best medical treatment only (n=52) or additional revascularization+best medical treatment (n=49). Of these 24% had 2-vessel disease, 67% 3-vessel disease and 8% left main disease.
Results: After 2.8 years survival was 64% for patients randomized to no preoperative revascularization versus 61% for patients assigned to preoperative revascularization (HR 1.18, 95%CI 0.63-2.19, p=0.61). The survival free of death, nonfatal MI, and coronary revascularization was similar in both groups: 49% and 42%

respectively for patients allocated to medical treatment or coronary revascularization (HR 1.51, 95% CI 0.89-2.57, p=0.13). Only 2 patients assigned to medical treatment required coronary revascularization during follow-up. Also in patients who survived the first 30 days after surgery there was no benefit of revascularization on cardiac events (HR 1.35, 95% CI 0.72-2.52, p=0.36).



Conclusion: Preoperative coronary revascularization in high-risk patients undergoing major vascular surgery is not associated with an improved postoperative or long-term outcome compared to best medical treatment.

888 A variant at chromosome 9p21 is associated with recurrent myocardial infarction after acute coronary syndrome: the GRACE genetics study

I. Buysschaert[1], K. Carruthers[2], D. Dunbar[2], E. Rietzschel[3], A. Belmans[4], T. De Meyer[3], A. Budaj[5], F. Van De Werf[4], D. Lambrechts[1], K.A.A. Fox[2]. *[1]VIB - KULeuven, Leuven, Belgium; [2]The University of Edinburgh, Edinburgh, United Kingdom; [3]University of Ghent, Ghent, Belgium; [4]Catholic University of Leuven (KULeuven), Leuven, Belgium; [5]Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland*

Purpose: Recent genetic studies identified the common variant rs1333049 on chromosome 9p21 as a major susceptibility locus for coronary artery disease and acute myocardial infarction (MI), however, the impact of this variant on recurrent MI and plaque rupture events is yet unknown.
Methods: 3,247 patients with acute coronary syndrome (ACS), prospectively followed for 6 months and enrolled in the Global Registry of Acute Coronary Events (GRACE) program in 3 distinct populations (UK, Belgium and Poland), and 3,004 and 2,467 healthy controls from the UK and Belgium, were genotyped for rs1333049. We analysed the association of rs1333049 with (i) primary ACS and (ii) recurrent MI status within 6 months.
Results: Consistent with previous studies, the at-risk C-allele of rs1333049 was uniformly associated with ACS, with a pooled odds ratio of 1.21 (CI=1.10-1.32; P=4.6x10-5). Most interestingly, following a first ACS, the C-allele was significantly and independently associated with recurrent MI, with a multivariable-adjusted hazard ratio of 1.48 (CI=1.00-2.19; P=0.048; Table 1 and Figure 1).

Table 1

rs1333049 Genotype	No Recurrent MI N (%)	Recurrent MI N (%)	Multivariable-adjusted HR (95% CI)	P value
CC+GC	2077 (74.9%)	139 (81.8%)	1.48 (1.00 - 2.19)	0.048
GG	695 (25.1%)	31 (18.2%)	Reference	

Analyzed by Cox proportional hazard model. CI denotes confidence interval; HR, hazard ratio.

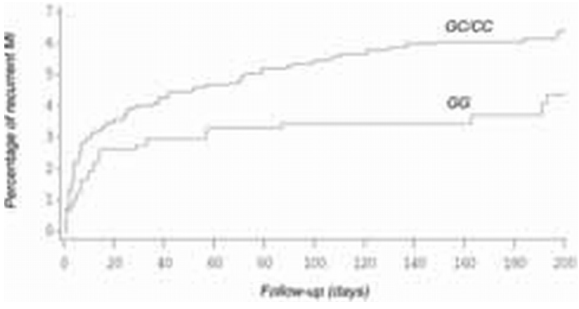


Figure 1

Conclusions: The 9p21 variant confers a risk not only for a first, but also for subsequent recurrent acute coronary events, suggesting that 9p21 is also implicated in plaque rupture.

889 Circulating Factor Seven Activating Protease (FSAP) is associated with clinical outcome in acute coronary syndrome, but not with complexity of coronary artery disease

M. Parahuleva[1], C. Neuhof[1], H. Hoelschermann[2], H. Tillmanns[1], A. Erdogan[1], S. Kanse[3]. *[1]Universitaetsklinikum Giessen und Marburg GmbH, Giessen, Germany; [2]2Department of Internal Medicine, Division of Cardiology and Angiology, Hochtaunus Kliniken gGmbH, Bad Homburg, Germany; [3]University of Giessen, Institute of Biochemistry, Giessen, Germany*

Introduction: There are many indications for a relationship between FSAP and the progression of atherosclerosis and the development of associated clinical events. FSAP is present in unstable lesions and is a risk factor for atherosclerosis. It is not known if circulating FSAP concentration or its activity is related in any way to the development and progression of coronary artery disease (CAD). The present study was performed (i) to examine the relation between plasma concentration and activity of FSAP and clinical instability or complexity of CAD and (ii) to investigate the FSAP expression in monocytes and activated platelets in patients with CAD.
Methods: 545 sequential patients with CAD brought to the university hospital comprised the study group. Circulating FSAP concentration and activity as well as FSAP expression in monocytes and activated platelets were assessed in patients with acute coronary syndrome (ACS), unstable angina (UA), stable angina (SA) and were compared to control non-coronary subjects. Coronary angiography was performed and the extension of coronary disease was defined as one, two or three vessel disease.
Results: The median FSAP concentration in control non-coronary subjects (1.05 PEU/ml, range 0.85–1.19 PEU/ml) were significantly different from those in patients with SA (1.13 PEU/ml, range 0.93–1.30 PEU/ml, $p < 0.01$). In the group of patients with UA, the median FSAP concentrations (1.31 PEU/ml, range 1.02–1.40 PEU/ml) were significantly higher than those in the control group ($p < 0.001$) or the group with SA. In the group of patients with ACS, the median FSAP concentrations (1.64 PEU/ml, range 1.28–2.09 PEU/ml) were also significantly higher than those in the control group ($p < 0.001$) or the group with SA ($p < 0.01$). There was no association between the extension of coronary disease and the FSAP levels and activity. Among patients elevated FSAP levels indicated a significantly increased risk of death or nonfatal myocardial infarction during six months of follow-up (adjusted hazard ratio as compared with patients with low levels of FSAP, 2.75; 95% confidence interval; p=0.001) Furthermore, there were no significant changes in the FSAP expression in monocytes and activated platelets in both group, CAD and control non-coronary subjects.
Conclusions: Plasma FSAP level and activity were increased in patients with ACS. Plasma FSAP levels was an independent prognostic marker for future cardiovascular events, suggesting its potential role in risk stratification and clinical management of stable CAD, but FSAP does not predict either the extension or the complexity of coronary disease.

890 Association of outcome with left ventricular parameters measured by two- and three-dimensional echocardiography

C. Jenkins, T. Stanton, T.H. Marwick. *The University of Queensland, Brisbane, Australia*

Objectives: Left ventricular end-systolic volume (LVESV) measured by 2-dimensional echocardiography (2DE) is an important correlate of survival. Real-time three-dimensional echo (3DE) has addressed some of the limitations of 2DE. In this study, we sought whether 3DE was more predictive of outcome than 2DE.
Methods: We studied 535 patients undergoing LV assessment with 2DE and 3DE in 2003 and 2004. 3DE images were gathered over 4 cardiac cycles using a matrix array transducer and measurements were performed off-line. Follow-up (cardiac admission, incident heart failure and atrial fibrillation and all-cause mortality) was obtained over 4.8±0.4 years in 461 of 504 patients with images suitable for measurement (92%).
Results: There were 48 events (10%) including 34 deaths. Larger LVESV and lower EF were associated with worse outcome, but 3DE was a stronger correlate of survival than 2DE (figures). In a stepwise Cox regression analysis, the addition of 2DE-ESV increased the association of clinical variables (renal disease, cardiomyopathy, myocardial infarction and age) with outcome (model χ^2=5.9,

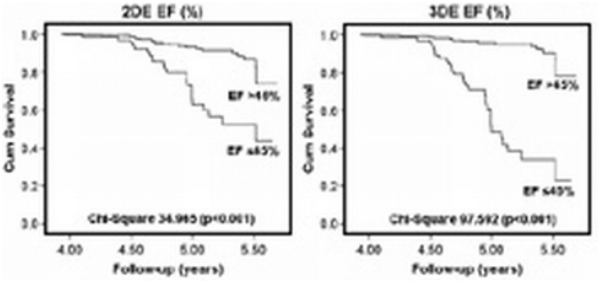


Figure 1. Survival curves for EF% for 2DE and 3ED

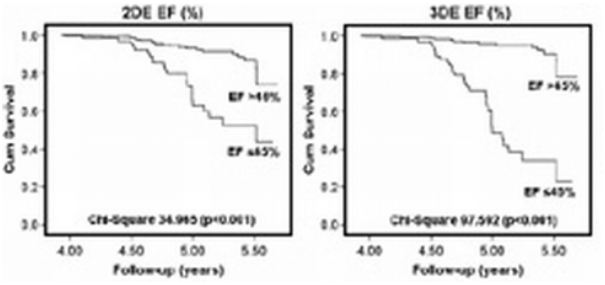


Figure 2. Survival curves for ESV ml for 2DE and 3ED

p=0.015), but 3D-ESV increased the strength of association (χ^2=7.5, p=0.006). Similarly, the incremental value of 2DE-EF (χ^2=15.9, p<0.001) was exceeded by 3DE-EF (χ^2=21.2, p<0.001).

Conclusions: In this outcome study, 3DE measurements of ESV and EF showed a stronger prediction of outcomes than 2DE. 3DE now appears to be the measurement of choice for when LV volumes and EF are sought to guide management decisions.

YOUNG INVESTIGATORS' AWARDS SESSION: THROMBOSIS

892 Despite similar cholesterol removing abilities, recombinant HDL-Milano exerts greater anti-inflammatory properties than wild type-HDL

B. Ibanez[1], G. Cimmino[1], C. Giannarelli[1], A. Pinero[1], C.G. Santos-Gallego[1], G. Vilahur[2], V. Fuster[1], L. Badimon[2], J.J. Badimon[1]. *[1]Mount Sinai Hospital, New York, United States of America; [2]Hospital de Sant Pau, Barcelona, Spain*

Background: Recombinant HDL-apoA-IMilano (HDLMilano) has been shown to regress and stabilize atherosclerotic plaques. However there is a significant controversy on whether its antiatherogenic activity is superior to that of wild-type HDL (HDLwt). We have compared the effect of HDLMilano in plaque volume, reverse-cholesterol-transport (RCT) and inflammation in comparison with HDLwt.

Methods: Atherosclerotic rabbits (n=15) received 2 infusions, 4 days apart, of HDLMilano (75 mg/kg of apoA-IMilano), HDLwt (75 mg/kg of apoA-Iwt) or placebo. Changes in plaque volume were assessed by magnetic resonance imaging studies performed pre- and post-treatments.

Lipid content in aortas and livers and expression of proteins involved in RCT (ABCA-1 and SR-BI) were assessed to evaluate the effect on RCT.

Inflammation and oxidative stress (both at atherosclerotic plaque and systemic levels), were evaluated by western blot and lipid peroxidation products respectively. Gelatinase activity (MMP-2) was evaluated by zymography. Activated marophages were quantified by RAM-11-peroxidase immunostaining.

Results: All 3 groups showed similar plaque volume pre-treatment. Both forms of HDL induced a similar degree of plaque regression as compared with placebo (-4.4% and -2.3% vs. pre-Rx in HDLMilano and HDLwt respectively, p<0.001 and p=0.009). The two groups receiving HDL treatment showed reduced lipid deposition in aorta and liver. Concomitantly, expression of aortic ABCA-1 and hepatic SR-BI, was significantly higher in both groups receiving HDL as compared to placebo, but no different among them.

HDLMilano resulted in a higher anti-inflammatory activity than HDLwt: reduced protein levels of COX-2, MCP-1 and Caspase-3, decreased MMP-2 activity, and lower local and systemic oxidative stress.

On histology, a 50% and 25% reduction in RAM-11+ cells was observed in the HDLMilano and HDLwt groups respectively (p<0.01 and p=0.08 vs. placebo; p<0.05 for the comparison between both forms of HDL). Compared to placebo, the smooth muscle cell-to-macrophage ratio (histological marker of plaque stability) was 2.3-fold and 1.5 higher in the aortas of the HDLMilano and HDLwt-treated animals (p<0.001 and p<0.05 vs. placebo respectively). Again, the smooth muscle cell-to-macrophage ratio was significantly higher in the HDLMilano group than in the HDLwt (p<0.01).

Conclusions: Despite having a similar effect on reverse cholesterol transport and plaque regression, HDLMilano exerts greater anti-inflammatory and plaque stabilizing properties than HDL wild type. These effects support the use of HDLMilano as a promising therapeutic approach for high risk patients.

893 Composition of a single atherosclerotic plaque predicts systemic cardiovascular outcome

W. Peeters[1], W.E. Hellings[2], D.P.V. De Kleijn[1], J.P.P.M. De Vries[3], F.L. Moll[2], G. Pasterkamp[1] on behalf of Athero-Express. *[1]Experimental Cardiology Laboratory, Utrecht, Netherlands; [2]Dept. of Vascular Surgery, UMCU, Utrecht, Netherlands; [3]Dept. of Vascular Surgery, St Antonius Hospital, Nieuwegein, Netherlands*

Objectives: It is a major challenge to identify patients at high risk for primary and secondary manifestations of cardiovascular disease. The composition of atherosclerotic plaques is thought to be a determinant of future cardiovascular events. However, prospective studies have not been performed to test the hypothesis that atherosclerotic plaque composition is associated with the occurrence of vascular events during follow-up.

Methods: Consecutive patients who underwent carotid endarterectomy between April 1, 2002 and March 11, 2008 were included in this study of the Athero-Express biobank. Endarterectomy specimens were subjected to histological examination. Patients underwent clinical follow-up yearly, up to 3 years after carotid endarterectomy. The primary outcome was defined as the composite of vascular event (vascular death, non-fatal stroke, non-fatal myocardial infarction) and vascular intervention.

Results: During a mean follow-up of 2.3 years, 196 of 818 patients (24%) reached the primary outcome. Patients whose excised carotid plaque revealed presence of plaque hemorrhage demonstrated 30.6% risk of the primary outcome compared to 17.2% in patients without plaque hemorrhage (hazard ratio [HR] with 95% confidence interval = 1.7 [1.2-2.5]). Increased presence of intraplaque vessel formation was associated with a 30% risk of primary outcome compared to 23.8% in patients with decreased or no vessel formation within the plaque (HR = 1.4 [1.1-1.9]). Plaque macrophage infiltration (HR = 1.1 [0.8-1.5]), large lipid core (HR = 1.1 [0.7-1.6]), calcifications (HR=1.1 [0.8-1.5]), collagen (HR = 0.9 [0.7-1.3]) and smooth muscle cell infiltration (HR = 1.3[0.9-1.8]) were not associated with outcome. Local plaque hemorrhage and the presence of increased intraplaque vessel formation were independently related to clinical outcome and were independent of recognized clinical risk factors and medication use.

Conclusions: Plaque hemorrhage and increased vessel density in local carotid plaque are independently associated with an increased risk of future cardiovascular events. For clinical perspectives, this is the first study demonstrating that the histological composition of a single atherosclerotic plaque contains prognostic information about systemic cardiovascular outcome.

894 Higher stent thrombosis rate after coronary stenting in patients on dual antiplatelet treatment and concomitant treatment with proton pump inhibitors

N. Sarafoff, D. Sibbing, U. Sonntag, S. Schulz, A. Schoemig, A. Kastrati. *Deutsches Herzzentrum Muenchen, Munich, Germany*

Purpose: Clopidogrel is a prodrug that is converted via the hepatic cytochrome P450 system into its active thiol metabolite. Evidence is accumulating that proton pump inhibitors (PPI) do inhibit this enzymatic pathway and may therefore attenuate the antiplatelet effect of clopidogrel.

Methods: This is a retrospective analysis of prospectively enrolled and followed patients who received dual antiplatelet treatment with aspirin and clopidogrel after drug eluting stent placement. Outcomes were compared according to the prescription of PPIs at discharge. The primary endpoint was the incidence of definite stent thrombosis (ST) at 30 days. Secondary endpoints were death and myocardial infarction (MI).

Results: The study population included 2025 randomly selected patients of our PCI database. 435 patients (21.4%) received a PPI at discharge. Patients receiving PPIs were significantly older (69.2 vs.66.2 years p<0.001), had worse left ventricular ejection fraction (50.6% vs. 54.2%, p<0.001) and more previous MI (37.5% vs.27.8%. p<0.001) compared to patients without PPI treatment. PPI patients had significantly more ST (1.6 vs.0.3% p=0.002) and an increased mortality (1.8 vs. 0.7% p=0.04) at 30 days compared to patients without a PPI. There was a trend towards an increased incidence of MI in PPI patients (3.0 vs. 1.7%, p=0.08).

30 day follow up	PPI, n=435 (%)	no PPI, n=1590 (%)	p value
Stent thrombosis	7 (1.6)	5 (0.3)	0.002
Death	8 (1.8)	12 (0.7)	0.04
Myocardial infarction	13 (3.0)	27 (1.7)	0.08

Conclusion: Concomitant treatment with a PPI in patients under dual antiplatelet treatment after coronary stenting is associated with higher rates of stent thrombosis and an increased mortality. Whether concomitant PPI treatment is an independent predictor for the occurrence of ischemic events and whether a significant association exists for all PPIs in general warrants further investigation in larger study populations.

895 Strong decrease of the clopidogrel antiplatelet effect with esomeprazole, but not with ranitidine and recovering of the antiplatelet effect by doubling the dosage of clopidogrel

P. Moceri, L. Drogoul, E. Ferrari. *CHU de Nice - Hopital Pasteur, Nice, France*

Aims: We set out to study the impact of esomeprazole (PPI) and ranitidine (H2RA) on the antiplatelet action of clopidogrel and aspirin. We also evaluated the influence of doubling the dosage of clopidogrel in association with the PPI.

Background: Persistent high platelet reactivity although clopidogrel treatment is correlated with a poorer cardiovascular prognosis. This clopidogrel "resistance" may be due to a drug-drug interaction. Omeprazole, a PPI, has been incrimi-

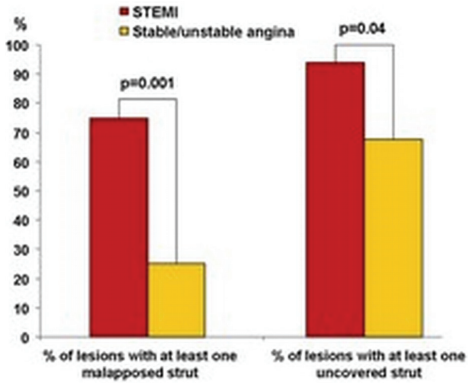
nated in this type of resistance. However, little is known about esomeprazole and ranitidine.
Methods: In a prospective cross-over study, we tested platelet reactivity to clopidogrel and aspirin with VerifyNow (Accumetrics Inc., San Diego- USA) in 4 therapeutic stages, each lasting 7 days: T1: low dose aspirin 160mg and clopidogrel 75 mg, T2: same treatment plus esomeprazole 20 mg, T3: T2 + 75 mg clopidogrel and T4: T1 + ranitidine 150 mg. Results are expressed in PRU for clopidogrel, ARU for aspirin.
Twenty-one patients with stable coronary artery disease were included.
Results: Among the 21 patients, esomeprazole 20 mg/day dramatically decreased the clopidogrel effect with a 32±24% loss in PRU % ($p < 0.001$), with no change in aspirin response. The association of esomeprazole with clopidogrel increased 8-fold the prevalence of low responders to clopidogrel as defined by a PRU < 20%.The loss of clopidogrel response due to esomeprazole was reversed by increasing the clopidogrel dosage to 150 mg or by esomeprazole withdrawal. Ranitidine did not modify the anti-platelet effects of clopidogrel and aspirin.
Conclusion: Our study shows a strong negative clopidogrel/esomeprazole interaction. Doubling the dosage of clopidogrel allowed us to recover the initial anti-platelet effect of clopidogrel. Ranitidine did not affect clopidogrel or aspirin efficacy.

YOUNG INVESTIGATORS' AWARDS SESSION: CORONARY PATHOPHYSIOLOGY AND MICROCIRCULATION

897 Incomplete stent apposition and delayed tissue coverage are more frequent in drug eluting stents implanted during primary percutaneous coronary intervention for ST elevation myocardial infarction

N. Gonzalo Lopez, P. Barlis, P.W. Serruys, H.M. Garcia-Garcia, Y. Onuma, J. Ligthart, E. Regar. *Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Background: ISA and the absence of strut endothelialization might be linked to stent thrombosis. DES implanted for STEMI may have higher risk of thrombosis.
Objective: To compare the frequency of incomplete stent apposition (ISA) and struts not covered by tissue at long term follow-up (as assessed by optical coherence tomography, OCT) in drug-eluting stents (DES) implanted during primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) vs DES implanted for unstable and stable angina.
Methods: Consecutive patients in whom OCT was performed at least 6 month following DES implantation were included in the study. Stent struts were classified based on the presence or absence of ISA and tissue coverage.
Results: Forty-seven lesions in 43 patients (1356 frames, 10140 struts) were analyzed (48.9% stable angina, 17% unstable angina, 34% STEMI). Median follow up time was 9 (range 7-72) months. DES implanted during primary PCI presented ISA more often than DES implanted in stable/unstable angina patients (75% vs 25.8% p=0.001). The frequency of uncovered struts was also higher in the STEMI group (93.8% vs 67.7% p=0.048). On multivariate analysis, DES implantation in STEMI was the only independent predictor of ISA (OR 9.8, 95%CI 2.4-40.4 p=0.002) and presence of uncovered struts at follow-up (OR 9.5 95%CI 1.0-90.3 p=0.049).



Conclusions: DES implanted for STEMI had higher frequency of incompletely apposed struts and uncovered struts as assessed by OCT at follow up. DES implantation during primary PCI in STEMI was an independent predictor of ISA and presence of uncovered struts at follow-up.

898 Independent and additive predictive value of total cholesterol content of erythrocyte membranes with regard to coronary artery disease clinical presentation

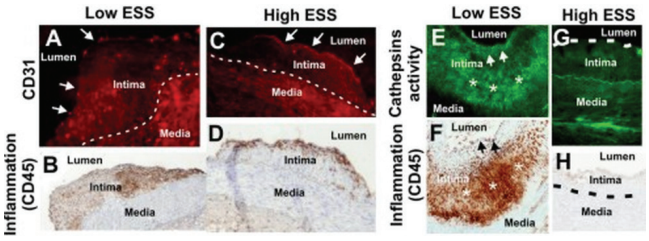
G. Chalikias[1], D.N. Tziakas[1], D. Stakos[1], I. Tentes[1], D. Papazoglou[1], A. Thomaidi[1], S. Manousakis[1], A. Grapsa[1], J.C. Kaski[2], H. Boudoulas[3]. *[1]Democritus University Thrace, Alexandroupolis, Greece; [2]St George's Healthcare NHS Trust, London, United Kingdom; [3]Biomedical Research Foundation, Athens, Greece*

Purpose: A new mechanism for clinical instability in coronary artery disease (CAD) has been proposed where erythrocytes could play an active role in atherosclerotic plaque growth and rupture. Clinical studies showed increased total cholesterol levels in the membrane of circulating erythrocytes (CEM) in acute coronary syndrome (ACS) patients compared to patients with chronic stable angina (CSA). In order to assess the incremental value of a novel biomarker like CEM in distinguishing clinical quiescence (CSA) and instability (ACS) in CAD, it should be demonstrated that improves the discriminating accuracy of an available model that incorporates several known markers that are increased in ACS. Therefore, we investigated the independent and incremental discriminating value of CEM along with N-terminal propeptide of BNP (NT-proBNP), high sensitivity C-reactive protein (hs CRP), myeloperoxidase (MPO) and apolipoprotein B (apoB) with regard to CAD clinical presentation.
Methods: Consecutive angina patients were prospectively assessed; 252 had CSA (195 men, 62±9 years) and 267 had ACS (213 men, 62±10 years).
Results: Simple logistic regression models showed that all biomarkers could distinguish ACS, nevertheless CEM with greater potency (OR 9.26 95%CI 6.31-13.59, $p<0.001$). Multiple logistic regression models after adjustment for all the variables that were different between the 2 groups as well as for other biomarkers showed that CEM continued to be a significant and an independent predictor of ACS (OR 22.27 95%CI 10.63-46.67, $p<0.001$). An increment of the c-statistic was also shown when CEM levels were incorporated in the predictive model (including traditional vascular risk factors and new well established biomarkers i.e. hs CRP, MPO, apoB and NT-proBNP).
COCNLUSIONS
The present study showed that CEM levels are associated with clinical instability in CAD patients in an independent and incremental manner. Our findings endorse previous findings from our group suggesting that in the clinical setting, erythrocytes reaching the plaque via intraplaque haemorrhage or neovessel extravasation represent a source of atheromatous plaque vulnerability.

899 Augmented expression of extracellular matrix-degrading enzymes by low Endothelial Shear Stress (ESS) promotes the formation of coronary atheromata with thin fibrous caps

Y.S. Chatzizisis[1], A.B. Baker[2], G.K. Sukhova[1], R. Beigel[2], M. Jonas[2], A.U. Coskun[1], P. Libby[1], C.L. Feldman[1], P.H. Stone[1], E.R. Edelman[1]. *[1]Brigham and Women's Hospital, Boston, United States of America; [2]Massachussets Insitute of Technology, Cambridge, United States of America*

Purpose: The mechanisms that determine the generation of coronary thin capped atheromata remain unknown. We tested the hypothesis that low ESS augments the expression of matrix degrading proteases and promotes the formation of thin-capped atheromata.
Methods & results: In 12 diabetic, hyperlipidemic swine 3D reconstruction of the coronary arteries was performed at wk 23. ESS was calculated in plaque-free segments (n=142). The segments were identified in the harvested coronary arteries (n=31) at wk 30 and analyzed by histopathology, PCR and in situ zymography. Segments with low ESS at wk 23 showed enhanced endothelial cell retention, lipid accumulation and inflammation ($p<0.05$, Fig A-D). In these lesions augmented mRNA expression of MMP 9, 12, and cathepsins K, L, S relative to their inhibitors TIMP 1, 2 and cystatin C resulted in increased elastolytic activity ($p<0.05$, Fig E-H). Intimal mRNA expression and activity of these enzymes correlated with the severity of internal elastic lamina (IEL) fragmentation and media thinning ($r>0.3$, $p<0.05$). To identify the hemodynamic and molecular determinants of the evolution of early lesions to plaques with thin cap, we focused on similarly sized lesions at intermediate stage of development. Lesions were classified as either small atheromata with thin fibrous cap or atheromata without fibrous cap. Compared to atheromata without cap, plaques with thin caps developed in regions with lower preceding ESS and were characterized by intense lipid and inflammatory cell accumulation, enhanced activity of proteases and severe IEL fragmentation ($p<0.05$, Fig E, F).



Conclusion: Low ESS induces intimal inflammation, production of matrix degrading enzymes, IEL fragmentation and ultimately evolution of an early plaque to a thin-capped atheroma.

900 Natural course of lipid-rich plaques assessed with combination of intra-vascular ultrasound and optical coherence tomography

K. Ishibashi, S. Takarada, T. Tanimoto, H. Kitabata, T. Kubo, K. Hirata, N. Nakamura, M. Mizukoshi, T. Imanishi, T. Akasaka. *Wakayama Medical University, Wakayama, Japan*

Purpose: Identification of coronary lesions with morphological characteristic of "rupture-prone plaques" is not sufficient. The purpose of this study to examine the natural history of non-culprit lipid-rich plaques in patients with non-ST elevated acute coronary syndrome (NSTEACS).
Methods: Consecutive 80 patients with NSTEACS who underwent percutaneous coronary intervention (PCI) were enrolled. We assessed the volume change of residual non-culprit lipid-rich plaques and the change of the corresponding fibrous cap thickness (FCT) by use of intra-vascular ultrasound (IVUS) and optical coherence tomography (OCT), respectively, at baseline and after 9-months.
Results: From the analysis study of natural history, the change in total atheroma volume (TAV) of lipid-rich plaques was 0.42±0.6% and the change in the corresponding FCT was 14±12% during 9 months follow-up periods. Percent change in TAV showed a significant positive correlation with percent LDL/HDL ratio reduction ($R=0.37$, $P<0.01$). In contrast, the change in FCT demonstrated no correlation with LDL/HDL ratio level, but had a significant positive correlation with percent change in high sensitive CRP ($R=0.39$, $P<0.01$). And between TAV and FCT changes, no significant correlation was observed. Furthermore, in a multivariable analysis including age, sex, diabetes mellitus, hypertension, several concomitant drugs, only statin-use was the independent predictor for changing well-stabilized plaques, which obtained both TAV reduction and FCT increase.
Conclusion: The change in TAV and in FCT of coronary plaques during 9-months was related to the two different independent factor (reduction rate of LDL-C and high sensitive CRP, respectively). Furthermore, lipid lowering therapy by use of statin has a potential to stabilize them by both plaque reduction and fibrous cap thickening.

YOUNG INVESTIGATORS' AWARDS SESSION: BASIC SCIENCE

902 Lack of cardiomyocyte PPARgamma leads to myocardial inflammation resulting in cardiac insulin resistance

E. Caglayan[1], K. Mueller-Wellensiek[1], M. Kreissl[2], D. Stout[3], H. Schelbert[3], W.A. Hsueh[4], S. Rosenkranz[1]. *[1]Uniklinik Köln - Herzzentrum, Cologne, Germany; [2]Medizinische Universitaetsklinik Wuerzburg, Wurzburg, Germany; [3]UCLA, Los Angeles, United States of America; [4]The Methodist Hospital System, Houston, United States of America*

Heart failure is a deadly condition and remains a severe health care problem in the industrialized countries. Insulin resistance predicts the incidence of congestive heart failure independently of established risk factors including diabetes. The myocardial expression of the ligand-activated nuclear hormone receptor PPARγ has been shown to be decreased in patients with terminal heart failure. However, the pathogenetic role of cardiomyocyte PPARγ in this process remains largely unknown.
We have previously demonstrated that PPARγ is expressed in cardiomyocytes and plays a role in cardiomyocyte hypertrophy. Using the Cre-lox P system we generated mice with a cardiomyocyte specific deletion of PPARγ (cPPARγ-/-). Littermate mice (WT) were used as controls throughout the study.
cPPARγ-/- showed a cardiac pro-inflammatory milieu with an increased myocardial expression of the macrophage marker CD68 and the pro-inflammatory molecule osteopontin compared to WT mice. Using small animal positron emisson tomography (microPET) technology, we measured cardiac 18F-DG uptake before and after prior subcutaneous insulin (2 IU/kg*BW) injection. Insulin significantly increased cardiac 18F-DG uptake in WT ($p<0.02$), but not in cPPARγ-/-. At the cellular level, insulin-stimulated glucose uptake was reduced in cardiomyocytes isolated from adult cPPARγ-/-. Despite this observed myocardial insulin resistance in cPPARγ-/-, whole body insulin sensitivity was not altered as evaluated by oral glucose tolerance and intraperitoneal insulin sensitivity testing. Western blot analysis revealed attenuated myocardial insulin-stimulated protein kinase B (Akt/PKB) and Akt substrate (AS-160) phosphorylation, as well as attenuated glucose transporter 4 (GLUT4) translocation to the plasma membrane 20 minutes after insulin injection in cPPARγ-/-. However, tyrosine phosphorylation of the insulin receptor was unaffected, suggesting enhanced inhibitory IRS-1 serine phosphorylation in cPPARγ-/-.
We hypothesized that an anti-inflammatory treatment might reverse the insulin resistant phenotype of cPPARγ-/-. Indeed, administering acetyl salicylic acid (30mg/mouse*day) for 4 days reversed the alterations seen in the insulin signaling pathway.
These results suggest that 1) Lack of PPARγ in the cardiomyocyte leads to myocardial inflammation. 2) Cardiomyocyte PPARγ regulates insulin-mediated cardiac glucose uptake 3) Anti-inflammatory treatment reverses cardiac insulin resistance caused by lack of cardiomyocyte PPARγ.

903 Atrial fibrillation leads to electrical remodelling of Na currents. Role of INa inhibition by ranolazine on arrhythmias and contractility

S. Sossalla[1], B. Kallmeyer[1], S. Wagner[1], U. Maurer[1], G. Hasenfuss[1], L. Belardinelli[2], L.S. Maier[1]. *[1]University of Goettingen, Goettingen, Germany; [2]CV Therapeutics, Palo Alto, United States of America*

Atrial fibrillation (AF) is the most common sustained arrhythmia. Electrical remodelling during AF is associated with alterations in Ca^{2+} and K^+ currents leading to reduced action potential duration. It remains unclear whether Na^+ currents (INa) are also altered in AF. Especially the late component of INa (late INa), which persists throughout the whole action potential and induces Na^+ and Ca^{2+} overload (via reverse mode Na^+/Ca^{2+} exchanger, NCX) in heart failure and ischemia, has never been investigated. Therefore, we studied changes in INa and potential beneficial effects of INa inhibition using ranolazine (Ran) on arrhythmias and contractility in human atrial myocardium.
Human atrial myoyctes were isolated from 70 patients with sinus rhythm (SR) and from 20 patients with chronic AF. Patch-clamp experiments revealed significantly reduced peak INa density by ~16% in AF vs. SR which was accompanied by ~26% lower expression of Nav1.5 ($P<0.05$). In contrast, late INa was significantly increased in myocytes from AF atria by ~17%. Ran (10 μM) reduced late INa by ~60% ($P<0.05$) in myocytes from patients with AF but only by ~18% ($P<0.05$) in myocytes from SR atria. Interestingly, peak INa was concentration and frequency-dependent inhibited (e.g. the higher the pacing rate the stronger peak INa inhibition) in SR cells but only slightly in AF.
Proarrhythmic activity was elicited in isometrically contracting atrial muscles exposed to 30 nM isoprenaline- or high Ca^{2+} which was significantly reversed by Ran (7 out of 7 and 5 out of 6). Increasing pacing rates from 0.5, 1, 2, and 3 Hz were associated with increases in diastolic tension that could be significantly reduced by Ran (e.g. 3 Hz: Ran 3.2±0.6 vs. vehicle 4.6±0.9 mN/mm^2) similar to our previous findings of reduced diastolic dysfunction by Ran in end-stage failing ventricular myocardium. Moreover, ouabaine induced time to contracture was significantly prolonged in the presence of Ran.
In summary, our results show for the first time that Na^+ channels may contribute to arrhythmias and contractile remodelling in human AF. Inhibition of INa using Ran had beneficial antiarrhythmic and contractile effects. Therefore, Ran appears to be a promising new treatment option for patients with atrial rhythm disturbances and diastolic dysfunction and should be further investigated in vivo.

904 c-kit+/cd45- cardiac stem cells generate polygonal stromal cells and secrete myxoid matrix in atrial myxomas

D. Torella[1], G.M. Ellison[2], C. Vicinanza[1], V. Galuppo[1], I. Mendicino[1], I. Aquila[1], M. Torella[3], M. Cotrufo[3], C. Indolfi[1], B. Nadal-Ginard[4]. *[1]Magna Graecia' Universita Degli Studi di Catanzaro, Catanzaro, Italy; [2]Liverpool John Moores University, Liverpool, United Kingdom; [3]Second University of Naples, Naples, Italy; [4]Coretherapix, Madrid, Spain*

Purpose: Myxomas, the most common primary tumor of the heart, usually develop in the atria and consist of a myxoid matrix composed of an acid-mucopolysaccharide-rich stroma with polygonal stromal cells scattered throughout the matrix. These benign tumors, despite their rarity, continue to generate interest because of their clinical presentation and uncertain histogenesis. The heterogeneous cell differentiation within cardiac myxomas postulates their origin from a mesenchymal-like pluripotent stem cell or an endothelial/neuronal progenitor cell. We recently reported the presence within cardiac myxomas of c-kit+ cardiac stem and progenitor cells (CSCs). The objective of this study was to assess whether CSCs give rise to myxoma stromal cells and secrete the typical myxoid matrix.
Methods: We examined 11 left and 2 right atrial polypoid myxomas (weight, 7 to 68 g) from 11 female and 2 male patients (47 to 65 years old) obtained as myocardial samples during cardiac surgery. Myxoma samples were divided to be processed for immunohistochemical studies or digested by enzymatic technique to isolate c-kit+ cells by MACS sorting. Human c-kit+ CSCs isolated from healthy atrial tissue were used as controls.
Results: All the tumors showed the typical histological features of cardiac atrial myxoma with polygonal cells positive for the myxoma tumor-cell marker, calretinin, dispersed in an abundant myxoid matrix. Immunohistochemistry and confocal microscopy imaging detected myxoma cells positive for c-kit. Most of these c-kit+ cells were also CD45+/tryptase+, representing cardiac mast cells. More importantly, the c-kit+/CD45- cardiac myxoma cells expressed stemness and cardiac progenitor cell markers, Oct-4, Nkx2.5 and Isl-1. Some of these c-kit+/CD45- myxoma cells expressed calretinin, representing myxoma stromal precursor cells. Elisa, HPLC and western blot analysis of the supernatant media from primary cultures of atrial myxoma-derived c-kit+/CD45- cells demonstrated that these cells secrete large amounts of chondroitin-6-sulfate and hyaluronic acid, the main disaccharide units of glycosaminoglycans composing the gelatinous matrix of cardiac myxoma in vivo. Finally, c-kit+/CD45- cardiac myxoma cells have self-renewing and clonogenic capacity while exhibit an abortive cardiac differentiation potential when compared to normal adult human CSCs.

Conclusions: c-kit+/CD45- CSCs generate polygonal stromal cells and secrete the typical myxoid matrix in atrial myxomas. Thus, c-kit+/CD45- cardiac stem cells seem to fulfil the criteria of tumor-initiating cells in atrial myxoma.

905 Impaired elastin function increases features of plaque instability in ApoE-deficient mice

J.L. Van Herck[1], G.R.Y. De Meyer[2], W. Martinet[2], H. Bult[2], C.J. Vrints[1], A.G. Herman[2]. *[1]University Hospital of Antwerp (Edegem), Edegem, Belgium; [2]University of Antwerp (Wilrijk), Wilrijk, Belgium*

Purpose: Decreased vascular compliance has been associated with an increased cardiovascular risk. Here, we investigated the effect of an impaired elastin function on the composition of the atherosclerotic plaque.
Methods: Mice with a mutation (C1039G+/-) of the fibrillin-1 gene, which leads to fragmentation of the elastic fibers, were cross-bred with ApoE-/- mice. ApoE-/- and ApoE-/-C1039G+/- mice were fed a Western-type diet for 10 weeks (early atherosclerosis) or 20 weeks (advanced atherosclerosis) (n=10 in each group). To evaluate the effect of an impaired elastin function on plaque stability, the number of buried fibrous caps was counted. The mechanical properties of the aorta were deduced from the wall stress – distension curves.
Results: The proximal part of the ascending aorta in ApoE-/-C1039G+/- mice showed an increased vascular stiffness during distension. At the level of the aortic valves, plaque area increased 1.5 fold and 2.1 fold in ApoE-/-C1039G+/- mice after 10 and 20 weeks of Western-type diet, respectively. Early and advanced plaques of ApoE-/-C1039G+/- mice showed an increased phospho-smad 2/3 positivity, indicative of increased TGF-β activity. In early plaques, increased TGF-β activity was associated with an increased apoptosis of smooth muscle cells, a decrease in collagen content (63±3% for ApoE-/- mice, 48±3% for ApoE-/-C1039G+/- mice; $p<0.001$), an enlargement of the necrotic core (13±2% for ApoE-/- mice, 24±3% for ApoE-/-C1039G+/- mice; $p<0.01$) and an increase in macrophages (9±1% for ApoE-/- mice, 15±1% for ApoE-/-C1039G+/- mice; $p<0.001$). After 20 weeks of Western-type diet, the number of buried fibrous caps was increased in advanced lesions of ApoE-/-C1039G+/- mice, not only at the level of the aortic valves (n=0.5±0.2 for ApoE-/- mice, n=1.7±0.2 for ApoE-/-C1039G+/- mice; $p<0.01$), but also in the brachiocephalic artery (n=1.4±0.3 for ApoE-/- mice, n=3.2±0.5 for ApoE-/-C1039G+/- mice; $p<0.01$) and in the upper, middle and lower thoracic aorta (n=0.2±0.1, 0.1±0.1 and 0.5±0.2 for ApoE-/- mice, respectively; n=1.7±0.3, 1.1±0.3 and 1.9±0.3 for ApoE-/-C1039G+/- mice, respectively; $p<0.01$).
Conclusion: Our results indicate that fragmentation of the elastic fibers leads to increased vascular stiffness, which promotes features of increased multifocal plaque instability.

RISKS FOR CARDIOVASCULAR DISEASE – NEW INSIGHTS

976 Systemic vascular dysfunction in children conceived by assisted reproductive technologies

S.F. Rimoldi[1], T. Stuber[2], S.F. De Marchi[1], S. Garcin[3], H. Duplain[3], M. Germond[4], C. Sartori[3], U. Scherrer[3], Y. Allemann[1]. *[1]Swiss Cardiovascular Center Bern, University Hospital Bern, Bern, Switzerland; [2]Imperial College Healthcare NHS Trust, St.Mary's Hospital, London, United Kingdom; [3]Department of Internal Medicine, CHUV, Lausanne, [4]Centre de Procréation Médicalement Assistée, Lausanne, Switzerland*

Objectives: Environmental influences acting early in life predispose to cardiovascular disease in adulthood. Assisted reproductive technologies (ART) have allowed millions of infertile couples to have children. ART involves the manipulation of early embryos at a time when they may be particularly vulnerable to external disturbances. Accordingly, ART has been found to modulate the epigenome. The safety of ART for long-term health is, therefore, of utmost importance, but there is little information. We recently showed that children born after ART display vascular dysfunction at high altitude, a condition known to facilitate the detection of endothelial dysfunction. We wondered whether a similar dysfunction was also present under normoxic conditions.
Methods: 65 healthy singletons born from ART (mean age 11.1±2.4y, 27 girls) and 57 age-, sex- and body weight-matched controls (11.9±2.3y, 30 girls) were studied al low altitude (Bern, 540m). We assessed the flow-mediated endothelium-dependent vasodilation (FMD) of the brachial artery, its endothelium-independent vasodilation (glycerin trinitrate, 250 μg) and pulse wave velocity (PWV), a proxy of arterial stiffness. 8-isoprostaglandin F2-alpha (8-iPF2a) plasma concentration was measured as a proxy of oxidative stress.
Results: The major new finding was that children born after ART displayed marked systemic vascular dysfunction under normoxia: FMD was 20% smaller (6.7±1.6 vs. 8.6±1.7%, $P<0.0001$, Figure) and PWV significantly faster (10.0±2.7 vs. 8.3±1.8 m/sec, $P<0.0001$) in children born after ART. This vascular dysfunction was not related to a structural vasculopathy, since endothelium-independent vasodilation was similar (13.5±2.3 vs. 13.9±2.5%, P=0.38) in both groups; nor was it related to dyslipidemia or altered glucose homeostasis, since lipid, glucose and insulin plasma concentration, as well as the insulin resistance index (HOMA) and glucose tolerance were comparable in both groups. In contrast, 8-iPF2a was significantly higher in children born after ART than in controls (83.4±41.5 vs. 55.1±28.2 pg/ml, P=0.0008).
Conclusions: ART predispose the offspring to systemic vascular dysfunction that is possibly related to increased oxidative stress. The magnitude of this dysfunction is similar to what has been reported in children with type 1 diabetes. We hypothesize that this predispose them to premature cardiovascular disease and speculate that epigenetic mechanisms may cause vascular dysfunction in offsping of ART.

977 Impact of behavioural and biologic cardiovascular risk factors on the relationship between stature and all-cause mortality: 8-years follow-up study in a cohort of Chilean adults

E. Koch[1], T. Romero[2], C. Romero[1], M. Paredes[3], L. Manriquez[4], M. Bravo[1], D. Sandoval[1], C. Roman[3], A. Taylor[3] on behalf of Tha San Francisco Project Research Team. *[1]Department of Family Medicine, Faculty of Medicine, University of Chile, Santiago, Chile; [2]Sharp Health Care, San Diego, United States of America; [3]Health Center of Mostazal, San Francisco De Mostazal, Chile; [4]Department of Cardiology, Internal Medicine Service, Regional Hospital, Rancagua, Chile*

Background: Several prospective studies in developed countries have demonstrated that short stature is a risk factor for cardiovascular disease and mortality. The association persists after adjusting for other traditional cardiovascular risk factors (CRF). However, in Latin American developing societies there is a paucity of information on this matter.
Aim: To test the impact of behavioural and biological CRF on the relationship between short stature and all-cause mortality in a cohort of Chilean adults.
Methods: A prospective study was carried out in Chile using a weighted random sample of 11,600 apparently healthy subjects aged 30-89 years followed during eight years. Body height (population quartiles by gender using the median as reference) was established at the onset of the study along with behavioural (alcohol consumption, smoking status, obesity, education and income level) and biologic CRF (hypertension, diabetes, lipids, and family history of cardiovascular disease). To test different causal pathways, relative risks of all-cause mortality were estimated using age- and sex- adjusted Cox regression models: model 1 adjusted for behavioural CRF; model 2 adjusted for biologic CRF and model 3 adjusted for all CRF.
Results: Height groups in women were <155 cm (median), 155-159 cm and >159 cm. In men height groups were <167 cm (median), 167-172 cm and >172 cm. After the follow-up period, 694 weighted cases of mortality were observed - 38% cardiovascular, 24% cancer, 17% respiratory and 20% miscellaneous. A graded inverse association between stature and risk of all-cause mortality was observed which persisted after adjustment for behavioural and biological CRF (Table). The tallest group had a 48% lower risk of mortality compared with the shortest group.

Table 1. Relative Risk with 95% condifdence intervals

Height group	Crude risk	Age- and sex- adjusted risk	Model 1	Model 2	Model 3
Shortest	1.0	1.0	1.0	1.0	1.0
Middle	0.46	0.68	0.66	0.74	0.71
	(0.38-0.56)	(0.56-0.84)	(0.54-0.81)	(0.60-0.91)	(0.57-0.87)
Tallest	0.22	0.58	0.55	0.54	0.52
	(0.17-0.29)	(0.44-0.76)	(0.42-0.74)	(0.41-0.71)	(0.39-0.69)

Conclusion: These data corroborate the hypothesis that stature is inversely related to all-cause mortality in Chilean adults independently of traditional CRF. Height may partly be an early exposure measure to adverse circumstances in childhood providing a plausible hypothesis to explain the inverse association with adulthood mortality.

978 A smoking ban in public places may reduce the incidence of acute coronary syndrome among non-smoking men

T. Gudnason, T. Viktorsson, K. Andersen. *Landspitali University Hospital, Reykjavik, Iceland*

Introduction: Secondary smoking is known to have deleterious health effects. Several studies have shown a decline in the incidence of myocardial infarction following smoking bans in public places. Legislation was recently passed in Iceland prohibiting smoking in public places. We investigated whether there were differences in the incidence of acute coronary syndrome (ACS) among the non-smoking population in the country before compared to after the ban. To our knowledge the possible effect of such legislation on the incidence of ACS among non-smokers has not previously been investigated. The hypothesis was that a decrease would be seen in the incidence of ACS.
Material and methods: Nationwide data was gathered prospectively on all non-smoking patients who underwent coronary angiography for ACS during the 5 months immediately prior to and following the smoking ban. Current smokers were excluded. ACS was defined as: clinical symptoms of unstable coronary artery disease (chest pain at rest) as well as at least one of the following 1) elevated cardiac enzymes, 2) ischemic changes on the EKG at rest, or 3) an abnormal exercise stress test during the same unstable episode.

Results: During the 10 month study period coronary angiography was performed on 1439 patients for any indication in the country, 378 of them fulfilled the criteria to be included in the study. Of these, 281 were male and 97 female ($p<0.01$). Baseline and demographic characteristics were similar for the groups included prior to vs. following the ban. Women were 24% vs. 28%, hypertensive's were 54% vs. 65%, former smokers were 65% vs. 67%, 57% vs. 56% were on statin therapy, and 16% vs. 16% had diabetes before and after the ban, respectively (p=ns for all). Among men a 21% reduction of the ACS incidence was seen during the 5 months following (n=124), compared to the 5 months prior to (n=157) the ban ($p<0.05$). In the total population a trend was seen towards a 20% reduction in ACS (p=0.08). No effect was seen among women (0.5%, p=ns).
Conclusions: A significant 21% reduction in the incidence of ACS was seen among men, but not among women, after a smoking ban in public places became effective on the 1st of June 2007. This is in concordance with prior studies on myocardial infarction, and theories that tobacco smoke increases the risk of plaque rupture and atherothrombosis. The gender difference is unexplained but might be due to fewer vulnerable plaques in the coronary arteries of women exposed to secondary smoking. Further research is needed on the relationship between secondary smoking and ACS in men and women.

979 The impact of achieving risk factor targets on CVD events in a community-based study

E. Zomer[1], D. Liew[2], A. Owen[1], D. Magliano[3], C. Reid[1]. *[1]Monash University, Melbourne, Australia; [2]The University of Melbourne, Melbourne, Australia; [3]Baker IDI Heart and Diabetes Institute, Melbourne, Australia*

Purpose: There remains much scope for the prevention of cardiovascular disease (CVD). This study sought to compare the preventable burden of CVD attributable to various risk factors in the Australian population.
Methods: Individual-level data was collected from 8874 participants of the Australian Diabetes, Obesity and Lifestyle (AusDiab) study aged 30 to 74 years of age with no history of CVD. Each subjects five-year risk of CVD (CHD: MI, CHD death, angina, coronary insufficiency; plus stroke, congestive heart failure and peripheral vascular disease) was estimated by applying a Framingham equation. An epidemiological model was used to estimate the 'baseline' number of CVD events arising from the cohort over 5 years, and the number of events that would be prevented if each subject's modifiable risk factors were reduced to target levels. Modifiable risk factors included systolic blood pressure, total cholesterol, HDL-C and smoking; their respective target levels are specified in Table 1. Potential savings were also estimated. The annual cost of CVD per person (AUD$4172) was drawn from Access Economics.
Results: The mean (SD) age of the modeled subjects was 49.0 (11.4) years; 44% were male. The proportions of the cohort with risk factors 'outside' of target ranges were: SBP 23%; TC 57%; HDL-C 11% and smoking 16.2%.

Number of preventable events after 5 yrs

Age group	Risk factor and target level				
	SBP*	TC†	HDL‡	0% smoking	All risk factors at target levels
All ages	56.04	77.65	9.80	51.90	175.71
	(55.23-56.86)	(75.68-79.62)	(9.70-9.90)	(51.34-52.46)	(170.55-180.88)
	$584,080	$810,411	$102,214	$541,317	$1,832,551
30-39	0.433	1.78	0.65	4.74	6.78
	(0.43-0.44)	(1.74-1.82)	(0.64-0.66)	(4.68-4.80)	(6.60-6.97)
	$4172	$18,774	$7301	$49,021	$70,924
40-49	3.50	9.15	2.22	12.97	25.00
	(3.46-3.54)	(8.92-9.38)	(2.20-2.23)	(12.84-13.10)	(24.27-25.70)
	$36,505	$95,956	$22,946	$135,590	$260,750
50-59	12.33	21.14	2.92	18.07	48.60
	(12.12-12.52)	(20.58-21.71)	(2.89-2.95)	(17.91-18.23)	(47.13-50.08)
	$128,289	$220,073	$30,247	$188,783	$506,898
60-69	23.35	27.65	2.73	12.33	59.56
	(22.91-23.80)	(26.95-28.34)	(2.71-2.76)	(12.25-12.42)	(57.84-61.28)
	$244,062	$288,911	$28,161	$128,289	$621,628
≥70	16.43	17.94	1.29	3.79	35.78
	(16.10-16.77)	(17.52-18.36)	(1.28-1.30)	(3.77-3.81)	(34.83-36.73)
	$171,052	$186,697	$13,559	$39,634	$373,394

*SBP<130 mmHg for those with dm and/or LVH, 140 mmHg for all others; †TC <4 mmol/L (156 mg/dL) for high-risk individuals (dm, LVH, 5-year CVD risk >15%, metabolic syndrome and 5-year CVD risk 10-15%) individuals, <5.5 mmol/L (214.5 mg/dL) for all others; ‡HDL-C>1 mmol/L (39 mg/dL).

Conclusions: Targeting smoking appears to be the most effective CVD preventive strategy in Australia. Among those aged 50 years and above, high systolic blood pressure and total cholesterol are also contributing to significant disease burden.

980 Underestimation of the importance of isolated systolic hypertension in older people

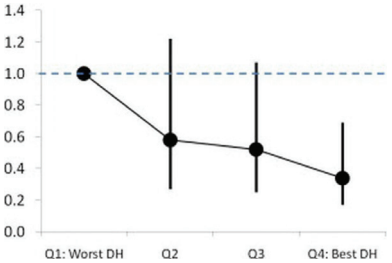
R. Clarke, J.R. Emberson. *Clinical Trial Service Unit, Oxford, United Kingdom*

Purpose: While blood pressure is continuously related to risk of vascular disease, the relevance of isolated systolic hypertension (ISH) for mortality from ischaemic heart disease (IHD) and all vascular causes of death (CVD) in older people is still uncertain. We examined the prevalence of ISH and other categories of hypertension and their association with IHD and CVD mortality in a cohort study of older people.
Methods: In a 8 year follow-up of 5280 men (mean age 77 yr) who were examined in 1997 and previously participated in the 1970 study of London Civil Servants, blood pressure was measured twice after 5 minutes in the seated position. The analyses were carried out before and after excluding men with a prior history of cardiovascular disease or use of blood pressure lowering treatment. Blood pressure was considered "normal" if SBP<140 and DBP <90mmHg. ISH was classified as "mild" if SBP was 140-159, and DBP <90mmHg and "moderate" if SBP was 160+ and DBP <90mmHg.
Results: Among all men, one third had a prior diagnosis of hypertension, one third took blood pressure lowering medication, but two thirds had evidence of either hypertension (i.e. SBP 140+ or DBP 90+ mmHg) or ISH at re-survey (30% had mild ISH and 12% had moderate ISH). In the 3014 with no prior history of CVD and not taking blood pressure lowering drugs, there were 181 IHD deaths and 431 CVD deaths. Compared with men with normal blood pressure, men with any evidence of either hypertension or ISH had 1.80-fold (95%CI: 1.29-2.53) higher IHD mortality and 1.40-fold (1.14-1.72) higher CVD mortality. The strength of the associations of IHD and of CVD mortality with blood pressure increased with increasing severity of hypertension and with the presence of additional CVD risk factors. Mild and moderate ISH were associated, respectively, with a 1.63 (1.11-2.39) and 2.33-fold (1.47-3.69) higher IHD mortality, and a 1.16 (0.90-1.48) and 1.85-fold (1.38-2.47) higher CVD mortality when compared with men with normal blood pressure.
Conclusions: In this study of older men, there was substantial under-diagnosis and under-treatment of hypertension and these men had greatly elevated risks of vascular mortality.

981 Mediterranean dietary habits predict prognosis in post-MI patients: results of the GOSPEL study

P. Giannuzzi[1], R. Marchioli[2], P.L. Temporelli[1], M. Gattone[1], R.M. Marfisi[2], R. Griffo[3], S. Urbinati[4], A.P. Maggioni[5], L. Tavazzi[6], D. Vanuzzo[7] on behalf of GOSPEL Investigators. *[1]Istituto Scientifico - Fondazione Salvatore Maugeri IRCCS, Veruno, Italy; [2]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [3]Azienda Ospedaliera G. Salvini, Passirana, Italy; [4]Ospedale Bellaria, Bologna, Italy; [5]Associazione Nazionale Medici Cardiologi Ospedalieri Research Centre, Florence, Italy; [6]GVM Hospitals of Care and Research, Cotignola, Italy; [7]Centro per la Prevenzione Cardiovascolare, Udine, Italy*

Aims: To assess the benefit of adopting correct Mediterranean dietary habits (MDH) in patients following a post-MI cardiac rehabilitation program (CRP) in the Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction (GOSPEL) trial performed in 78 Italian cardiac rehabilitation centers.
Methods: We used prospectively ascertained information among 3,233 patients enrolled in GOSPEL, a randomized trial with prospective, open-label, blinded end point evaluation (PROBE) design and testing the efficacy of long-term, reinforced, multifactorial educational and behavioral CRP vs. usual care for CRP after MI. MDH were assessed with a simple, self-administered frequency questionnaire collecting information on selected food indicators. To build a dietary score (DS), intake of fresh and cooked vegetables, fruit, fish, olive oil were taken as indicators of MDH. The association between the DS in quartiles (Q1-Q4) and the cumulative primary endpoint (EP) including cardiovascular death, nonfatal stroke and MI was assessed. Risk was evaluated using Cox proportional hazards adjusted for potential confounders and with time-varying covariates to update information on MDH, level of physical activity, and medical treatments at clinical visits which were performed biannually. Indicator variables were used for missing data on baseline covariates; values were otherwise carried forward for missing time-varying covariates.
Results: 128 (4%) EP were observed during 3 years of follow-up. The proportion of EP was 5.1% and 3.7% in Q1 vs. Q4. The risk of EP was reduced by 66% (95%CI 0.17-0.69, P=0.0025) when we compared the highest and lowest quartiles (Q4 vs. Q1) of DS (Figure).



Conclusions: To maintain correct MDH habits during follow-up is an important prognostic determinant in post-MI CRP.

TOO MANY RISK FACTORS FOR CARDIOVASCULAR DISEASE?

983 Association between anthropometric obesity measures and coronary artery disease - a cross-sectional survey of 16,657 subjects from 444 Polish cities

B. Kaess[1], J. Jozwiak[2], W. Lukas[2], M. Mastej[3], A. Windak[4], W. Piwowarska[4], A. Tykarski[5], K. Rygiel[2], N. Samani[6], M. Tomaszewski[6] on behalf of Lipidogram study group. *[1]Universitaetklinikum Regensburg, Regensburg, Germany; [2]Medical University of Silesia, Zabrze, Poland; [3]Silesian Analytical Laboratories, Katowice, Poland; [4]Jagiellonian University Collegium Medicum, Krakow, Poland; [5]University of Medical Sciences, Poznan, Poland; [6]Glenfield Hospital, Leicester, United Kingdom*

Although obesity has been recognised as a risk factor of cardiovascular (CV) morbidity and mortality, it is not clear which anthropometric measure is the best surrogate of CV risk, in particular in Eastern European populations largely underrepresented in epidemiological surveys. Therefore, we evaluated associations between coronary artery disease (CAD) and 4 different measures of obesity; body mass index (BMI), waist circumference, waist/height and waist/height^2 in a sample representative of middle-age general population of Poland.

Methods: 16,657 patients (40.4% men; 20.8% CAD cases) recruited and phenotyped for CV risk factors by 700 primary care physicians in 444 cities throughout Poland were included in the analyses. Association between obesity measures and CAD were explored using receiver operating curves (ROC) and logistic regression analyses.

Results: 74.5% of study subjects were classified as overweight and 31.7% as obese, 39.8% satisfied the criteria of abdominal obesity. Both overweight and obesity were more prevalent in men than in women (80.9% vs. 70.2%, $p<0.001$, and 32.9% vs. 31.0%, p=0.01, respectively) and in patients with CAD than in controls (82.6% vs. 72.4%, $p>0.001$, and 39.1% vs. 29.8%, $p<0.001$, respectively). Abdominal obesity was more common in patients with CAD than in controls (50.2% vs. 37.0%, $p>0.001$) and less prevalent in men than women (27.7% vs. 47.9%, $p < 0.001$).

Univariate ROC analyses revealed that all 4 obesity measures were significant associates of CAD (all $p<0.001$). Waist/height^2 showed the strongest potential to discriminate between CAD patients and controls in the whole cohort and in both genders analysed separately. Consistently, age and sex-adjusted regression analyses confirmed a graded linear increase in risk of CAD for all 4 obesity measures - one standard deviation increase in BMI, waist, waist/height and waist/height^2 increased the odds of CAD by 1.23, 1.24, 1.26 1.27, respectively (all $p<0.001$). In models fully adjusted for other CV risk factors, waist/height^2 remained the strongest obesity correlate of CAD. Notably, in men only waist/height^2 was significantly associated with CAD in the fully adjusted model.

Conclusion: This cross-sectional study reveals an epidemic of overweight, obesity and abdominal obesity in a population sample from Eastern Europe. We also show consistently positive linear associations between all assessed measures of adiposity and CAD. Given that waist/height^2 is the strongest correlate of CAD in our study, we propose waist/height^2 as a novel clinically useful measure of obesity in assessment of CV risk.

984 Thirty novel biomarkers as predictors of clinically incident diabetes

V. Salomaa[1], A.S. Havulinna[1], T. Zeller[2], O. Saarela[1], K. Kuulasmaa[1], S. Blankenberg[2]. *[1]National Institute for Health and Welfare, Helsinki, Finland; [2]Johannes Gutenberg Universitaet, Mainz, Germany*

Background: The prevalence of diabetes is increasing in all western countries and its prevention has become a public health priority. However, the predictors of diabetes risk in middle-aged individuals are insufficiently known.

Aims: The aim of the present study was to evaluate the usefulness of thirty novel pathophysiological biomarkers in the prediction of diabetes risk over and above the traditional risk factors.

Materials and Methods: The study is based on the FINRISK 1997 cohort, which consists of the participants of a population-based risk factor survey carried out in five geographical areas in Finland. After excluding persons with clinically known diabetes at baseline, 7,931 men and women aged 25-74 years were included in the analyses. During the follow-up of almost 11 years, until the end of 2007, 395 new cases of clinically incident diabetes were observed. We calculated relative risk of diabetes separately for each biomarker and each sex using Cox proportional hazards models. Next, we evaluated the ability of novel biomarkers to improve the prediction of diabetes risk using ROC curves and C-statistics, integrated discrimination improvement, and net reclassification improvement. Finally, we combined the best predictors to construct a biomarker score.

Results: The biomarker score consisted of adiponectin, apolipoprotein B, C-reactive protein, ferritin and interleukin-1 receptor antagonist. After accounting for age, sex, study area, non-HDL cholesterol, HDL-cholesterol, triglycerides, body mass index, systolic blood pressure, smoking, family history of diabetes, history of CHD or stroke event, use of hypolipidemic or antihypertensive medications, this score still improved the C-statistics from 0.837 to 0.849 (p=0.001). Integrated discrimination improvement also was significant ($p<0.0001$) and the total net reclassification improvement was 6.9% (p=0.0029).

Conclusions: Novel biomarkers can significantly improve the prediction of diabetes risk over and above the traditional risk factors.

985 A consultation-based method is equal to SCORE and an extensive laboratory-based method in predicting risk of future cardiovascular disease

U. Petersson[1], C.J. Ostgren[1], L. Brudin[1], P.M. Nilsson[2]. *[1]Department of Medical and Health Sciences, Linköping University, Linkoping, Sweden; [2]Department of Clinical Sciences, Lund University, University Hospital, Malmö, Sweden*

Background: As cardiovascular disease (CVD) is one of the most common causes of mortality worldwide much interest has focused on reliable methods to predict cardiovascular risk.

Design: A cross-sectional, population-based screening study with 17 years' follow-up in southern Sweden.

Methods: We compared a non-laboratory, consultation-based risk assessment method consisting of gender, age, present smoking, diabetes and treated hypertension at baseline, measured blood pressure (systolic $\geq$140 or diastolic $\geq$90), waist/height ratio and family history of CVD (angina, myocardial infarction and stroke), to SCORE and a third model including several laboratory analyses, respectively, in predicting CVD risk. The study included clinical baseline data on 689 subjects aged 40-59 years without CVD. Blood samples were analyzed for blood glucose, serum lipids, insulin, IGF-I, IGFBP-1, CRP, ADMA and SDMA. During 17 years the incidence of total CVD (first event) and death was registered.

Results: A non-laboratory-based risk assessment model, including variables easily obtained during one consultation visit to a general practitioner (GP), predicted cardiovascular events as accurately, hazard ratio (HR) 2.72; (CI 95% 2.18-3.39, $p<0.001$), as the established SCORE algorithm, HR 2.73; (CI 95% 2.10-3.55, $p<0.001$), that requires laboratory testing. Furthermore, adding a combination of sophisticated laboratory measurements covering lipids, inflammation and endothelial dysfunction, did not confer any additional value to the prediction of CVD risk, HR 2.72; (CI 95% 2.19-3.37, $p<0.001$). The c-statistics (ROC-curves) for the consultation model against SCORE and the extended model were: 0.794; (CI 95% 0.762-0.823), 0.767; (CI 95% 0.733-0.798, p=0.12) and 0.806; (CI 95% 0.774-0.835,p=0.55), respectively.

Conclusions: A risk algorithm based on non-laboratory data from a single primary care consultation predicted long-term cardiovascular risk as accurately as either SCORE or an elaborate laboratorybased method in a defined middle-aged population.

986 Cardiovascular risk prediction in an Australian population: the old versus the new Framingham equation

E. Zomer[1], A. Owen[1], D. Magliano[2], C. Reid[1], D. Liew[3]. *[1]Monash University, Melbourne, Australia; [2]Baker IDI Heart and Diabetes Institute, Melbourne, Australia; [3]The University of Melbourne, Melbourne, Australia*

Purpose: Multivariable risk prediction equations allow for identification of individual's cardiovascular risk (CV) and can be applied to different populations. Those borne from the Framingham Heart Study remain the most well-established and widely used. In February 2008, a new Framingham risk equation was published. We sought to determine differences between the most commonly used Framingham equation from 1991 and the 2008 version via their application to a contemporary Australian population.

Methods: The two risk equations were applied to 8976 subjects aged 30 to 74 years and free of cardiovascular disease from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Differences in mean risk scores were analyzed via 3-way ANOVA and Bonferroni post-hoc analysis.

Results: Compared to the 1991 equation, mean CV risk scores derived from the 2008 equation increased from 1 to 13% and 1 to 8% among males and females, respectively. The differences were statistically significant across all age-groups for both males and females, $p<0.001$

Mean CV risk scores

Age group	Male		Female	
	1991	2008	1991	2008
30-34	2.28	3.35	0.27	1.49
35-39	3.84	5.23	0.96	2.46
40-44	6.52	8.19	1.90	3.29
45-49	8.83	11.54	3.58	4.94
50-54	11.88	16.09	5.92	7.87
55-59	15.56	21.69	7.97	10.48
60-64	19.59	28.00	10.33	13.84
65-69	23.71	34.10	12.92	18.54
70-74	27.80	40.54	15.94	23.84
All	12.00	16.66	5.61	8.13

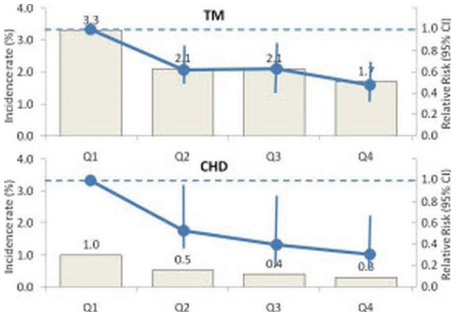
Conclusions: Previous Framingham equations have been suggested to overpredict CV risk in low-risk populations and under-predict risk in high-risk groups. The latest Framingham equation (based on data from the same era as previous equations), does not address this issue as it systemically predicts higher risks

than the most popular previous equation. This study highlights the need to validate CV risk prediction equations using population-specific outcome data.

987 Prognostic ability of a simple dietary score in cohort of 12,513 patients at high risk of cardiovascular risk followed by 860 Italian GPs: preliminary analysis of the risk & prevention trial

M.G. Silletta[1], R. Marchioli[1], F. Avanzini[2], V. Caimi[3], I. Marzona[2], R. Pioggiarella[1], M.C. Roncaglioni[2], M. Scarano[1], G. Tognoni[1], M. Tombesi[3] on behalf of R&P and RIACE Investigators. *[1]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [2]The Mario Negri Institute for Pharmacological Research, Milan, Italy; [3]CSeRMEG Centro Studi e Ricerca in Medicina Generale, Monza, Italy*

Aims: Dietary habits are strong determinants of cardiovascular (CV) risk. To assess the association of dietary habits with CV risk, we analyzed the database of Risk&Prevention (ReP), an ongoing trial aimed at testing the effect of 1 g daily of n-3 PUFA on top of optimization of CV risk management in a general population of 12,513 outpatients at high CV risk of CV, but without prior myocardial infarction followed by 860 GPs.
Methods: Dietary habits were assessed by means of a simple, self-administered frequency questionnaire collecting information on selected food indicators. To build up a comprehensive dietary score (DS), the intake of vegetables, fruit, fish, olive oil from one side and of butter and salami on the other side were taken as positive and negative indicators of correct dietary habits at baseline and after 12 months, respectively. The association between the dietary score in quartiles (Q1-Q4) and total (TM) and CV mortality (CVM), CV death plus nonfatal MI and stroke (MACE), total coronary heart disease (CHD), was assessed. Cox proportional models adjusted for potential confounders were fitted.
Results: The DS predicted significantly the risk of TM, CVM, MACE, and CHD (Figure). By comparing Q4 (best) with Q1 (worst) dietary habits, we found lower risks of TM (0.48, 0.34-0.66, P<0.001), CVM (0.44, 0.27-0.73, P<0.001), MACE (0.67, 0.49-0.91, P<0.001), CHD (0.31, 0.15-0.62, P<0.001).



Conclusions: A simple dietary questionnaire on food indicators can be easily used in general practice and allows to classify subjects according to a dietary score which is associated with prognosis after allowing for potential confounders.

988 Identifying novel predictors of 30-day mortality for acute coronary syndromes: diagnosis differential and the Myocardial Ischaemia National Audit Project (MINAP)

E.A. Metcalfe, C.P. Gale, B.A. Cattle, A.D. Simms, R.M. West, P.D. Baxter. *University of Leeds, Leeds, United Kingdom*

Purpose: To develop ACS risk models that discriminate short-term mortality using novel predictors from an extensive observational ACS database.
Methods: Using the MINAP database we identified 81,811 patients admitted to all acute hospitals (n=228) with an ACS in England and Wales between 01/01/06 to 31/12/06. Manual and automated generalized linear modelling (taking into consideration collinearity, interaction terms and Mote Carlo multiple imputation for missing data) was used to generate models for ACS subgroups, and random effects and mixed models used to account for the hieracharical structure of the data. Confusion matrices compared performance of the models which were validated against a later MINAP cohort.
Results: Males=64%. Mean age (SD)=69.3 (13.9) years, systolic BP =139.1 (29.4) mmHg, heart rate = 82.8 (24.8) bpm. 30-day mortality rate = 8.4% and 1-year mortality rate =19.9%. Significant predictors of 30-day mortality were heart rate, systolic blood pressure, age, high IMD score, prior use of ACE inhibitors, initial ECG and aspirin use. The diagnosis differential was a novel and highly significant predictor (see Table 1) of early mortality with odds of 30-day mortality on average doubling with a missed NSTEACS (from 'other' initial diagnosis).
Conclusions: More sophisticated modelling strategies that incorporate the complex nature of the data structure enhance the predictive ability of ACS models. Novel predictors such as diagnosis differential have a significant effect on mortality, with patients admitted with an initial diagnosis of 'other' and final diagnosis of NSTEACS have up to 3 times the odds of 30-day death.

Table 1. Log odds ratios of ACS diagnosis differentials for 30-day mortality relative to an initial and final diagnosis of NSTEACS

Initial diagnosis vs final diagnosis		Estimate of log odds ratio	SE of log odds ratio	95% CI of odds ratio
NSTEACS	Other	-0.89	0.62	0.12 to 1.39
NSTEACS	STEMI	-0.89	0.73	0.10 to 1.72
Other	NSTEACS	0.68	0.19	1.35 to 2.86
Other	Other	0.22	0.36	0.62 to 2.53
Other	STEMI	0.21	0.74	0.29 to 5.26
STEMI	NSTEACS	-0.35	0.94	0.11 to 4.44
STEMI	Other	0.48	1.08	0.19 to 13.46
STEMI	STEMI	-1.26	0.73	0.07 to 1.19

HEART TRANSPLANTATION AND LEFT VENTRICULAR ASSIST DEVICES: AN EXPANDING HORIZON

1001 Heterotopic heart transplantation for congenital or acquired heart disease with elevated pulmonary vascular resistance: mid and long term hemodynamic results

A. Gamba, A. Vassileva, R. Fiocchi, R. Sebastiani, A. Iacovoni, A. Fontana, O. Valsecchi on behalf of Dipartimento Cardiovascolare, Centro Trapianti di Cuore, Diagnostica ed Interventistica Cardiovascolare. *Ospedali Riuniti di Bergamo, Bergamo, Italy*

Background and Purpose: Cardiac transplantation is a well defined therapy for end-stage heart failure. Right ventricular failure due to elevated pulmonary vascular resistance (PVR) is one of the major causes of mortality and morbidity after ortotopic heart transplantation. Aim of this study is to examine the results of heterotopic heart transplantation (HCT) in different type of congenital or acquired heart disease with ventricular dysfunction and high pulmonary vascular resistances
Methods: From July 1995 to August 2007 18 patients (9 males) with irreversible high PVR contraindicating an orthotopic transplantation have undergone heterotopic transplantation (HCT). The donor pulmonary artery anastomosed to the recipient right atrium. Recipients mean age at transplant was 31.7±19.39 years (range 8-65) and donors 24±15.9 yrs (range 7 - 57). Two cases had an post ischemic cardiomyopathy, 4 dilated cardiomyopathy, 7 restrictive, 1 post – chemotherapy, 1 mitral valvulopathy with "porcelain" left atrium, 2 aortic insufficiency and 1 transposition of great vessels with ventricular septal defect.
Indications to HCT have been based on the following parameters in presence of adequate pulmonary vasodilatation: PVRI >6 U m^2, transpulmonary gradient (TPG) >15 mm Hg, pulmonary artery systolic pressure> 60 mm Hg and / or mean >50 mm Hg. Mean value of systolic pulmonary pressure was 75 mmHg; mean TPG 23±8,8 mmHg; mean PVRI 12,5±3,7 U m^2
Results: One patient died early (30 days) for acute rejection and 5 late (after 3, 26, 44, 91,112 months) for respiratory complications, infection (2 cases), and multi-organ failure and acute rejection. In a case with restrictive cardiomyopathy the presence of native hypoplastic ventricle was contributory to death.
12 patients with an average period of observation of 61±40 months (range 12 - 132) are currently in NYHA Class I, with a normal effort tolerance and lead a normal life. In 9 cases, with observation period exceeding 10 months, periodic controls with right heart catheterization showed a progressive normalization of pulmonary pressures - mean systolic pulmonary pressure 29 mmHg, TPG 10 mmHg; PVRI 3.7 U x m^2
Conclusions: The results in the medium and long term in this patient's group confirm that the HCT can be considered a viable surgical solution for patients with high risk of congestive post-transplant right heart failure. Regardless of the pulmonary vascular resistance, the HCT has not been an additional risk factor compared to traditional orthotopic transplantation.

1002 Diabetic patients with good metabolic control have similar 1-year survival and morbidity after heart transplantation as non-diabetic patients

N. Antonio, M.J. Guimaraes, D. Prieto, J. Ferrao De Oliveira, M.J. Antunes. *University Hospital, Coimbra, Portugal*

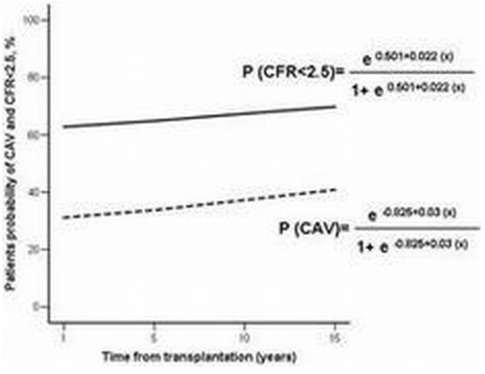
Background: Transplantation in diabetic patients remains controversial. The hyperglycemic effect of immunosuppressant steroid therapy further complicates the post-transplantation management of their disease and, perhaps, increases the incidence of post-transplantation infection, rejection and mortality.
Aims: To compare post-transplantation outcomes of survival and morbidity among recipients with and without diabetes mellitus.
Methods: Prospective observational study of 114 consecutive patients submitted to first heart transplantation between Nov03 and Jan08, who underwent 1-year follow-up. We divided them into two groups according to whether they had pre-transplantation diabetes (group 1) or not (group 2). Baseline variables and the development of complications were recorded. Logistic regression analysis was used to identify independent predictors of 1-year mortality.
Results: 33% of patients were diabetic before transplant. Diabetic patients were older (57±7 vs 51±13 years, p=0.003), with higher prevalence of hypertension (64 vs 17%, p=0.002), lower creatinine clearance (53.5±16.2 vs

63.0±21.8 ml/min, p=0.020) and higher C-reactive protein (2.4±0.4 vs 1.3±0.2 mg/dl, p=0.029) than non-diabetic. They tended to have higher body mass index (23.9±3.2 vs 23.5±2.8 kg/m^2, p=ns), more peripheral artery disease (21 vs 15%, p=ns), carotid artery disease (26 vs 14%, p=ns) and renal dysfunction (41 vs 24%, p=ns). Diabetic patients tended to be less frequently under tacrolimus than non diabetic patients (8% vs 17%, p=0.207). We found no significant differences in lipid profile between groups, either before transplant or at 1-year follow-up. Moreover, glycosylated hemoglobin and fasting glycemia were lower at 1-year than before heart transplantation (7.6±0.9 vs 6.5±1.0%, p=ns and 158.4±71.2 vs 134.2±45.3 mg/dl, p=0.039).There were no significant differences in rejection episodes (18 vs 25%, p=ns), infection (27 vs 34%, p=ns) or mortality (16 vs 7%, p=ns) at 1 year follow-up between diabetic and non-diabetic patients. By logistic regression analysis, the only predictor of 1-year mortality was a baseline creatinine >1.4 mg/dl (OR:6.36, CI95%: 1.12-36.04). Diabetes and impaired fasting glycemia before heart transplantation were not predictors of 1-year mortality.
Conclusions: This data suggests that diabetes is not associated with worse 1-year prognosis in heart transplant patients with good glucometabolic control. Therefore, diabetes should not be a contraindication to heart transplantation.

1003 Microvascular dysfunction preceeds epicardial coronary stenosis in heart transplant patients with cardiac allograft vasculopathy

E. Osto[1], F. Tona[1], A. Gambino[1], A. Maddalozzo[1], A.L.P. Caforio[1], R. Montisci[2], A. Ramondo[1], G. Gerosa[1], S. Iliceto[1]. [1]*University of Padova, Padova, Italy;* [2]*University of Cagliari, Cagliari, Italy*

Cardiac allograft vasculopathy (CAV) affects both epicardial coronary vessels and microvasculature. Coronary flow reserve (CFR) evaluation allows functional assessment of microvasculature in CAV patients (pts). This study was designed to assess either the presence or the risk of CAV and severe microvascular dysfunction (CFR<2.5) in relationship with time from heart transplantation (HT).
Methods: CFR was assessed in the left anterior descending coronary artery by contrast-enhanced transthoracic echocardiography (CE-TTE) in 119 HT pts (97 male, aged 50±12 years at HT), at 9±6 years post-HT. CAV was defined as any angiographic lesion ≥10%. Severe microvascular dysfunction was defined as CFR <2.5. The relationship between time from HT and CAV or microvascular dysfunction was evaluated by logistic regression.
Results: CAV was diagnosed in 74 pts (62%) (group A), 45 (38%) had no CAV (group B). Group A had lower CFR than group B (2.2±0.6 vs 3.1±0.7, p<0.0001). In 15 pts (20%) without CAV CFR was <2.5. At 5, 10 and 15 years from HT the probability of CFR<2.5 resulted higher than CAV probability (p<0.0001 for all comparisons). Figure shows the relationship among time from HT and probability of CAV and/or severe microvascular dysfunction (CFR<2.5) as continuous variables assessed with logistic regression model. In addition, a close correlation was observed between the presence of CAV and the evidence of CFR< 2.5 (chi square = 21, OR 6.4, p <0.0001).



Probability of CAV and microvasculopathy

Conclusions: In HT patients the risk of CAV and microvascular dysfunction increases with time from HT. The risk of severe microvascular dysfunction is higher than that of CAV. Finally, severe CFR impairment seems to preceed angiographic CAV onset.

1004 Mechanical circulatory support in patients of advanced age

T. Drews, T. Krabatsch, E. Potapov, M. Pasic, Y. Weng, R. Hetzer. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Purpose: During recent years the non-pulsatile ventricular assist devices have been increasingly used for long-term mechanical circulatory support (MCS). We present the results of support with ventricular assist devices in patients of advanced age.
Methods: Of 236 patients, 122 were on pulsatile (78 Berlin-Heart Excor, 18 CardioWest, 4 Lion Heart, 18 Novacor, 3 HeartMate I) and 114 on non-pulsatile MCS (67 Berlin Heart Incor, 19 DeBakey, 14 HeartMate II, 8 DuraHeart, 6 Jarvik 2000), implanted between June 1991 and January 2009 at a mean age of 65±3.6 (range 60-80.5) years.
Results: In the pulsatile group mean support time was 128 (range 1-1836) days, in the non-pulsatile group 211 (range 1-1306) days. In the first group 16 patients (13%) were supported for more than 6 months, 10 (8.2%) for more than 1 year and 6 (5%) for more than 2 years. In the second group 42 patients (37%) were supported for more than 6 months, 23 (20%) for more than 1 year and 6 (5%) for more than 2 years. In the first group 14 patients received heart transplantation, 6 patients still have a device and 3 patients have been weaned; one patient died due to device failure (CardioWest). In the non-pulsatile group 27 patients are still on support, 7 patients received transplantation and 3 patients were weaned; 5 pump exchanges were performed for device failure (3 for technical failure, 2 for thrombosis).
Conclusions: Although both types of devices can be used for extended periods of time, elderly patients have a significantly higher survival rate with the non-pulsatile systems, as the surgical procedure is less invasive and less anticoagulation is required. These systems enable elderly patients to enjoy additional years of life in their familiar environment.

1005 Main predictors of long-term cardiac stability after explantation of ventricular assist devices in patients with unloading-induced myocardial recovery

M. Dandel, Y. Weng, M. Pasic, H. Siniawski, H.B. Lehmkuhl, T. Drews, T. Krabatsch, E. Potapov, C. Knosalla, R. Hetzer. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Background: During ventricular unloading, cardiac recovery which allows ventricular assist device (VAD) removal is possible. However, very few patients with chronic heart failure (HF) have been weaned from VADs, most of them only during the past 5 years. Thus, long-term (> 5 years) outcome data after VAD removal are few. Now that our patient cohort with post-weaning stability for > 5 years has become larger, we focused our attention on these patients, in order to obtain useful information for future weaning decisions.
Methods: Among the 84 patients weaned from VADs since 3/1995 we selected for this study only patients (n = 36) who were weaned ≥ 5 years ago, before 9/2003. We evaluated echocardiographic and hemodynamic data obtained before VAD implantation and during pre-explantation "off-pump" trials, HF duration before VAD implantation, duration of mechanical support, and stability of unloading-induced cardiac recovery before and early after VAD explantation.
Results: Of 36 evaluated patients, 33 (91.7%) had non-ischemic cardiomyopathy and only 3 patients had ischemic cardiomyopathy. The vast majority, i.e. 34 (94.4%) of 36 patients, had LVADs Only 2 patients had BVADs. Post-weaning 5- and 10-year survival without transplantation or the necessity of another VAD implantation was 76.5% and 70.6.%, respectively. Post-weaning survival for ≥ 13 years with the native heart was reached by 3 patients. During the first 5 post-weaning years, HF recurred in 13 (36.1%) patients (one received another LVAD, other 9 underwent HTx and 3 patients died). Patients with ≥ 5 years stability were younger, their history of HF and recovery time during unloading were shorter and pre-weaning LV assessment revealed higher LVEF, less sphericity, and higher end-diastolic relative wall thicknesses. For LVEF ≥ 45% at end-diastolic diameter ≤ 55mm the predictive value for ≥5 year cardiac stability was 88.9%. Time course of LVEF during the first 6 post-weaning months also appeared predictive for long-term stability. History of HF >5 years and pre-weaning instability of unloading-induced cardiac recovery appeared predictive for HF recurrence.
Conclusions: Weaning from VADs can be successful for >13 years even in patients with chronic heart failure and incomplete cardiac recovery. Pre-explantation echocardiographic data obtained in off pump trials, stability of unloading-induced recovery, duration of HF before VAD insertion and duration of VAD support allow identification of patients with the potential to remain stable for >5 years. LVEF time course during the first 6 post-weaning months facilitates the prognostic assessment.

1006 Two-year outcome with the LVAD Impella LP2.5 compared to IABP for patients with cardiogenic shock by myocardial infarction: longterm follow-up of a randomized trial (ISAR-SHOCK)

M. Seyfarth[1], D. Sibbing[1], T. Gloeck[1], L. Bott-Fluegel[2], I. Bauer[2], A. Kastrati[1], A. Schomig[2]. [1]*Deutsches Herzzentrum Muenchen, Munich, Germany;* [2]*Technische Universitaet Muenchen, Munich, Germany*

Background: In the ISAR-SHOCK trial, 26 patients with cardiogenic shock (CS) caused by myocardial infarction were randomly assigned to the left ventricular assist device (LVAD) Impella LP2.5 (Abiomed Europe GmbH, Aachen, Germany) or an intraaortic ballon counterpulsation (IABP). The primary endpoint (change of the cardiac index from baseline to 30 minutes after implantation) was significantly different in both groups with an improved hemodynamic state in patients allocated to the LVAD (Δ CI = 0.49±0.46 L/min/m^2; IABP: Δ CI = 0.11±0.31 L/min/m^2; P=0.02). Overall 30-day mortality was 46% in both groups. The aim of the present study is to assess whether a clinical benefit from treatment with the LVAD Impella LP2.5 in patients with CS is observable at 2 years after randomization.
Methods: The design and results of the initial study has been previously de-

scribed (JACC 2008;52:1584-8). All surviving patients are planned to be evaluated at 2 years. Cardiac function is assessed by echocardiography. The left ventricular ejection fraction is measured to evaluate intraindividually the effect of the assigned device on the improvement of cardiac function after 2 years. Neurologic outcome is measured by the five-point Pittsburgh cerebral-performance category. Complex organ dysfunction scores (MODS and SOFA) are used to evaluate clinical outcome.
Results: Follow-up of all patients will be completed in June 2009. Outcomes will be compared between the 2 study groups and results will be presented at the meeting.

AORTIC DISSECTION: THERAPEUTIC CHALLENGES

1007 Long-term outcome of aortic dissection with patent false lumen. Clinical and imaging predictors of poor prognosis

G. Teixido, A. Evangelista, A. Ribera, I. Ferreira, H. Cuellar, V. Pineda, J. Rodriguez-Palomares, T. Gonzalez-Alujas, P. Mahia, D. Garcia-Dorado. *Hospital Universitario Vall d'Hebron, Barcelona, Spain*

Aims: To define clinical and imaging predictors of long-term outcome of aortic dissection (AD) with persistent patent false lumen in descending aorta.
Methods: In 140 consecutive patients with patent false lumen aortic dissection (AD), 84 surgically-treated type A and 56 medically-treated type B, clinical and imaging (TEE, CT and MRI) follow-up at 3, 5 months and yearly after acute AD was performed. Median follow-up was 6.8 y, interquartile interval range from (3.3-9.8y).
Results: The maximum rate of increase in aortic diameter per year was greater in type B than type A (2.9 + 2.5 mm vs 1.9 + 2.9 mm; $p< 0.05$). 22 patients required surgical (n=7) or endovascular (n=15) treatment owing to severe aorta dilatation, impending rupture and/or peripheral ischaemia. 38 died during follow-up, 25 suddenly. Rate of aortic complications (sudden death or need for surgical/endovascular treatment) at 3,5 and 10 years was 8% (95% CI:4-14), 20% (95% CI:14-29) and 42% (95% CI 32-53), respectively. Independent predictors of an increased risk of aortic complications were: type B syndrome (HR: 2.3, 95% CI:1.1-4.9), Marfan syndrome, (HR: 4.5, 95% CI: 1.4-14.1), baseline maximum diameter (HR for each 5 mm increase: 1.4, 95% CI:1.3-1.8), entry tear size (HR for each 1 mm increase 1.1, 95% CI: 1.0-1.2) and location (HR for a proximal location: 6.0, 95% CI: 2.7-13.4) and partial false lumen thrombosis (HR: 3.5, 95% CI: 1.4-9.2).
Conclusion: Predictors of severe complications in AD with patent false lumen were essentially defined by imaging techniques. In addition to Marfan syndrome, baseline maximum diameter, proximal location and size of entry tear, and partial false lumen thrombosis were predictors of poor prognosis.

1008 Ulcerlike lesions in intramutral haematoma. Long-term follow-up and management implications

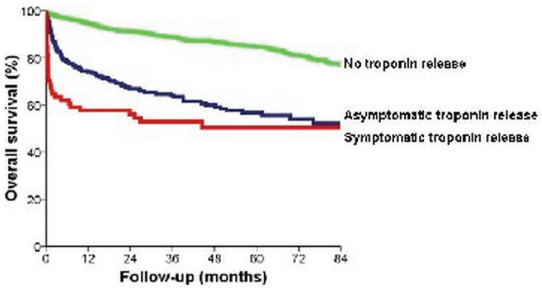
Z. Gomez Bosch, A.E. Evangelista, H.C. Cuellar, T.G.A. Gonzalez-Alujas, J.R.P. Rodriguez Palomares, G.T. Teixidor, P.M. Mahia, A.D. Dugoni, M.T. Thomas, D.G.D. Garcia-Dorado. *Hospital Universitario Vall d'Hebron, Barcelona, Spain*

Ulcerlike lesions (UL) have been considered a predictor of severe complications in the evolution of intramural haematoma (IMH) and are often managed by surgical/endovascular treatment.
Purpose: To investigate the natural history of newly developed UL in arch or descending aorta in patients with IMH.
Methods: In 26 of 82 patients with IMH, UL was identified in acute phase or during the first year of follow-up. Patients were followed up clinically and by CT/MR at 3, 6 months and annually thereafter. Mean follow-up was 5.2 (1-10y). Medical treatment was recommended except when UL was located in ascending aorta or had signs of impending aortic rupture, severe or rapid enlargement or persistent pain.
Results: UL were located in aortic arch (3), proximal descending aorta (13), in mediun segment (5) and in distal segment (8). UL size ranged from 4 mm to 17mm. In 3 patients more than one UL was present.
In 7 patients (27%) UL dissapeared at 1-3 y, in 9 (35%) remained stable, in 5 (19%) enlarged slightly, and 5 (19%) evolved to saccular aneurysm or pseudoaneurysm formation. Enlargement was less than 3mm/y in all cases except 1 (7mm/y). No patients died during follow-up and in only in 2 cases non-urgent endovascular therapy was indicated owing to severe enlargement of pseudoaneurysm formation (at 1and 3 y follow-up).
Conclusion: Most ulcerlike lesions in descending aorta are asymptomatic and dissapear or do not enlarge. In about one-fourth of cases lesions progress to aneurysm or pseudoaneurysm formation but with slow progressive enlargement. Therefore conservative approach suffices in most cases but close CT/MR follow-up is mandatory.

1009 Asymptomatic postoperative troponin release is associated with poor long-term outcome after vascular surgery

O. Schouten[1], T.A. Winkel[1], W.J. Flu[1], S.E. Hoeks[1], Y.R.B.M. Van Gestel[1], D. Goei[1], J.P. Van Kuijk[1], J.J. Bax[2], D. Poldermans[1]. *[1]Erasmus MC, Rotterdam, Netherlands; [2]Leiden University Medical Center, Leiden, Netherlands*

Background: Cardiac troponin T (cTnT) release is a sensitive marker for myocardial injury and occurs frequently after vascular surgery. However, the prognosis of cTnT elevations without clinical symptoms and/or new electrocardiographic changes (asymptomatic cTnT release) is unknown.
Aim: To assess the long-term prognosis of vascular surgery patients who experience perioperative asymptomatic cTnT release.
Methods: A total of 1545 patients undergoing elective major vascular surgery were enrolled. Baseline characteristics and medication were noted. Routine sampling of cTnT and ECG recording was performed on day 1, 3, and 7 after surgery and at the day of discharge. Elevated cTnT was defined as serum concentrations $\geq$ 0.01 ng/ml. The mean follow-up was 3.7 years and mortality was noted.
Results: A total of 213 (14%) patients experienced asymptomatic cTnT release, median 0.08 ng/ml (IQR 0.04-0.20 ng/ml), while 71 (5%) patients had symptomatic cTnT release. During follow-up 304 patients (20%) died. Mortality was higher in patients with asymptomatic cTnT release compared to patients without cTnT release (13% vs. 40%; $p<0.001$, figure). After adjustment for risk factors, the association between asymptomatic elevated cTnT levels and increased late mortality persisted (adjusted HR 2.3; 95% CI 1.8-3.0) and risk increased with higher cTnT levels (HR 1.64 for every 0.10 ng/ml increase, p=0.02). Elevated cTnT had prognostic value irrespective of baseline creatinine value or worsening of renal function after surgery.



Conclusions: Asymptomatic cTnT release, without clinical symptoms or new ECG changes, is associated with an increased long-term mortality in patients undergoing vascular surgery.

1010 Differences in the long-term evolution of aortic dissection and intramural haematoma types B

G. Teixido, A. Evangelista, I. Ferreira, A. Ribera, J. Rodriguez, T. Gonzalez-Alujas, A. Salas, A. Dugoni, M. Thomas, D. Garcia-Dorado. *Hospital Universitario Vall d'Hebron, Barcelona, Spain*

Purpose: To assess differences in the long-term evolution of medically treated type B aortic dissection (AD) and intramural haematoma (IMH) patients.
Methods: One hundred and twenty-one consecutive patients discharged after a first episode of type B acute aortic sindrome, 87 AD and 65 IMH were studied. IMH patients were older than AD (67$\pm$10y vs 58$\pm$12y; $p<0.001$). Patients were followed-up clinically and by CT/MR at 3, 6 months and annually thereafter to assess aortic diameter progression and the incidence of overall death and severe aortic related events defined as sudden death or need of endovascular/surgical therapy. Mean follow-up was 6.7 years (IQI: 4-9.6y). Outcome determinants were assessed by proporcional Cox multivariable modelling.
Results: Annual increase in descending aorta diameter was similar in both groups (2.9$\pm$2.5 mm/y vs 2.8$\pm$6.6 mm/y). Unadjusted ten-years cumulative survival was similar for both types of syndrome 0.60 (95% CI 0.44-0.73) for IMH and 0.54 (0.36-0.68) for AD; p=0.66. However, unadjusted ten-years cumulative survival free of aortic related events was higher for IMH 0.72 (0.56-0.83) vs 0.47 (0.32-0.60); $p<0.01$. Adjusting for baseline clinical and demographic variables, the risk of both aortic related events and overall mortality was higher for AD [HR 1.9 (1.01-3.56) and 1.86 (0.92-3.74), respectively.
Conclusions: Patients with AD and IMH types B present similar unadjusted long-term global survival. Nevertheless, AD is associated to higher risk of sudden death and the need of surgical/endovascular treatment.

1011 Hybrid approach to type A aortic dissection: use of a new multibranched Dacron graft to obtain a fixed Elephant trunk for second endovascular stage

G.P.E. Esposito, C.S. Sacra, R.A.P. Pennetta, K.V.F. Vaziri Farahani, S.B. Bichi, A.M.C. Cricco, L.S. Specchia, N.C. Corvaja. *Citta' di Lecce Hospital, Lecce, Italy*

Introduction: The purpose of this report is to evaluate mid-term result after hybrid two stage repair of extensive type A Aortic Dissection (A. D.) using a new multibranched Dacron graft (Lupiae graft).
We perform ascending aorta and arch replacement with debranching of epiaortic vessels in order to obtain a "fixed" elephant trunk of adequate length (3-5 cm) to be used as optimal proximal landing zone for a second (2-3 weeks later) endovascular stage which will cover the dissected descending aorta stimulating the thrombosis of distal false lumen.
Methods: From March 2006 to July 2008 24 patients with extensive type A A.D. underwent ascending aorta and aortic arch replacement with debranching of epiaortic vessels. Operation were performed with moderate hypotermic cardiopulmonary bypass, antegrade cerebral perfusion with open distal aortic anastomosis. There was 1 (4.16%) post operative death. All the survived patients (23) were treated with a second stage endovascular stent graft implantation in the dissected descending thoracic aorta.
Results: Hospital mortality was 1/24 (4.16%) owing to multiple organ failure. Overall actuarial survival is 92.08±7.92% with 100% freedom from reoperation. The residual false lumen in the thoracic aorta was thrombosed completely in 35% and partially in 15% of survived patients.
Conclusions: Immediate and mid-term results in two stage treatment of extensive type A A.D. demonstrate that the use in the first surgical stage of a new multibranched Dacron graft to replace ascending aorta and aortic arch with debranching of epiaortic vessels permit to obtain a "fixed" elephant trunk which can be easily used as proximal landing zone in the second stage trans-femoral endovascular stent graft implantation. Further experience and longer follow-up to validate these preliminary results is warranted.

1012 Outome of patients suffering from acute Stanfort type B aortic dissection: A retrospective single center analysis of 136 patients

J. Garbade[1], M. Jenniches[1], R. Battellini[1], M. Borger[1], D. Scheinert[2], M. Gutberlet[3], T. Walther[1], F.W. Mohr[1]. *[1]Herzzentrum der Universität Leipzig, Herzchirurgie, Leipzig, Germany; [2]Herzzentrum der Universität Leipzig, Angiologie, Leipzig, Germany; [3]Herzzentrum der Universität Leipzig, Radiologie, Leipzig, Germany*

Objectives: Acute uncomplicated Stanford type B aortic dissection (TBAD) is optimally managed with medical treatment. However, surgery and endovascular intervention are occasionally indicated, particularly when end-organ ischemia develops. The purpose of this study was to therefore assess the perioperative and long-term outcomes of medical, interventional and surgical management of acute TBAD.
Methods: A total of 136 consecutive patients (96 men) with acute TBAD treated at our institution between 2000 and 2008 were identified and analysed. Of these patients, 84 were treated medically (Group A, median age: 65, interquartile range (IQR): 34-90), 46 patients received endovascular repair (Group B, median age: 65, IQR 23-83) and 6 patients underwent surgical management (Group C, median age: 61, IQR 44-69).
Clinical data including presentation variables, early complications and mortality, and long-term reintervention and mortality were retrospectively collected and examined. Follow up was obtained on 98% of survivors and averaged 669 days (median 467 days, IQR 218 – 715).
Results: There were no significant differences in age, gender, BMI or comorbidities between the three groups. In group B we found the highest rate of ruptures (n=6) and impending ruptures (n=23). Indications for surgery were impending rupture with malperfusion (n=3) and rupture (n=3).
The maximal diameter of aortic dissection was significantly higher in group C (mean: 50.7mm, IQR: 32-82), than in group B (mean: 42.9mm, IQR: 20-80) and group A (mean: 40.5, IQR: 23-66). The mean duration from the time of onset to therapy was 1.0 days (IQR: 0.45-1.54) for group A, 3.0 days (IQR: 0.57-5.42) for group B (p=0.014 vs. group A), and immediately for group C. The acute (30 days) and long-term mortality were 8.9% and 16.9% (group A), 22.1% and 39.6% (group B), and 33.3% in group C. No patient died in group C after 30 days. The rate of reintervention (stent or surgery) was significantly higher in group A (group A 84/22 vs. group B 46/7; p=0.049, and group C 6/1). The complication rate (stroke and paraplegia, renal failure, and disturbance of cardiac rhythm) were higher in groups A and B.
Conclusion: Medical, interventional and surgical management for acute TABD produced acceptable results with good survival. Although stent implantation and surgery were reserved for patients with complications of TABD, results were very good for both treatment modalities. Randomized prospective trials should be performed to determine if stent implantation or surgery is beneficial in complicated TABD patients.

A GLOBAL PERSPECTIVE ON HYPERTENSION

1013 Association of candidate gene polymorphisms with chronic kidney disease in Japanese individuals with hypertension

K. Kato[1], T. Yoshida[2], Y. Yamada[1], K. Yokoi[3], M. Oguri[3], K. Yajima[3], T. Fujimaki[3], T. Hibino[3], G. Kimura[4], T. Murohara[5]. *[1]Department of Human Functional Genomics, Life Science Research Center, Mie University, Tsu, Japan; [2]Department of Cardiology, Inabe General Hospital, Inabe, Japan; [3]Department of Cardiovascular Medicine Gifu Prefectural Tajimi Hospital, Tajimi, Japan; [4]Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medi, Nagoya, Japan; [5]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Although hypertension has been recognized as a risk factor for chronic kidney disease (CKD), genetic factors for predisposition to CKD in individuals with hypertension remain largely unknown. The purpose of the present study was to identify genetic variants that confer susceptibility to CKD among individuals with hypertension. The study population comprised 3696 Japanese individuals with hypertension (2265 men, 1431 women), including 1257 subjects (789 men, 468 women) with CKD [estimated glomerular filtration rate (eGFR) $<$ 60 mL min–1 1.73m–2] and 2439 controls (1476 men, 963 women; eGFR $\geq$ 60 mL min–1 1.73m–2). The genotypes for 30 polymorphisms of 26 candidate genes were determined. An initial screen of allele frequencies by the chi-square test revealed that eight polymorphisms were significantly (false discovery rate $<$ 0.05) associated with the prevalence of CKD in hypertensive individuals. Subsequent multivariable logistic regression analysis with adjustment for covariates as well as a stepwise forward selection procedure revealed that the T/C (Val591Ala) polymorphism of APOB (rs679899), the –681C/G polymorphism of PPARG (rs10865710), the T/C (Cys1367Arg) polymorphism of WRN (rs1346044), the –850C/T polymorphism of TNF (rs1799724), the –219G/T polymorphism of APOE (rs405509), the C/T polymorphism of PTGS1 (rs883484), and the 41A/G (Glu14Gly) polymorphism of ACAT2 (rs9658625) were significantly ($P < 0.05$) associated with the prevalence of CKD. Our results suggest that APOB, WRN, ACAT2, APOE, PPARG, TNF, and PTGS1 are susceptibility loci for CKD among Japanese individuals with hypertension. Determination of the genotypes for these polymorphisms may prove informative for assessment of genetic risk for CKD among such individuals.

1014 The importance of anthropometric indices in the prediction of 5-year incidence of hypertension in apparently healthy individuals: the ATTICA Study

C. Chrysohoou[1], D. Panagiotakos[2], C. Pitsavos[1], J. Skoumas[1], J. Lentzas[1], A. Katinioti[1], C. Masoura[1], A. Zeibekis[1], L. Papadimitriou[1], C. Stefanadis[1] on behalf of ATTICA study. *[1]University of Athens, Athens, Greece; [2]Harokopio University, Athens, Greece*

Objective: To evaluate the role of anthropometric indices in the 5-year incidence of hypertension, in a sample of cardiovascular disease-free adults.
Methods: 1514 men and 1528 women ($>$18 years) without any clinical evidence of cardiovascular disease, living in Attica area, Greece, were enrolled in the ATTICA study from May 2001 to December 2002. In 2006, the 5-year follow-up was performed. Hypertension was defined as systolic/diastolic blood pressure measurements $>$ 140/90 mmHg or use of anti-hypertensive treatment. Weight, height, waist and hip circumferences, as well as body mass index and waist-to-height and waist-to-hip ratio were tested in relation to the development of hypertension.
Results: During 2001-2006, 86 men and 102 women were diagnosed as having hypertension. Thus, annual incidence rate is 2.86 per 100 men and 2.68 per 100 women. From the anthropometric indices, waist, and hip circumferences, BMI, weight and waist-to-height ratio were associated with the development of hypertension, while hip and waist-to-hip ratio were not associated. Particularly, for every 1 cm difference in baseline measurements of waist a 2% higher risk of hypertension was observed; while abnormal waist at baseline examination was associated with 1.92-times (95%CI 1.35 to 2.77) higher risk of hypertension, in both genders. Moreover, presence of obesity at baseline examination was associated with a 2.4-fold (95% CI 1.62-3.79) of the risk of hypertension. All the aforementioned relationships were independent from age, sex, and various other confounders, while the model that contained waist had the best diagnostic ability, followed by BMI, hip circumference and weight.
Conclusions: Among various anthropometric measurements that showed a significant association with hypertension incidence, waist circumference was the best predictor. The latter finding may lead to new pathophysiological mechanisms for the development of hypertension.

1015 Impact of alcohol and smoking habits on the risk of new-onset atrial fibrillation in hypertensive patients with ecg left ventricular hypertrophy: the life study

I. Ariansen[1], K. Wachtell[2], M. Hecht Olsen[3], H. Ibsen[4], R.B. Devereux[5], P.M. Okin[5], S.E. Kjeldsen[1], B. Dahlof[6] on behalf of the LIFE Study Group. *[1]Dept of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway; [2]Department of Cardiology, The Heart Center, Rigshospitalet, University of Copenhagen, Copnhagen, Denmark; [3]Dept of Internal Medicine, Glostrup University Hospital, Copenhagen, Denmark; [4]Division of Cardiology, Holbaek Hospital, Holbaek, Denmark; [5]Weill Cornell Medical College, New York, United States of America; [6]Dept of Internal Medicine, Sahlgrenska University Hospital/Ostra, Gothenburg, Sweden*

Objective: Atrial fibrillation (AF) is associated with increased cardiovascular events and the incidence of new-onset AF is increased by hypertension. Antihypertensive treatment reduces new-onset AF and treatment with the angiotensin receptor blocker losartan is more effective than the beta-1 selective blocker atenolol in this respect. However, it is unclear how smoking and alcohol intake influence the risk of new AF during treatment which we assessed in the Losartan Intervention For Endpoint reduction in Hypertension (LIFE) study.
Methods: In LIFE, a double-blinded, randomized, parallel-group study, 9,193 hypertensive patients (46% men; mean age 67 yrs, average blood pressure 174/98 mmHg after placebo run-in) with ECG-documented left ventricular hypertrophy (LVH), randomized to once daily losartan- or atenolol-based antihypertensive therapy were followed for a mean of 4.9 years. At baseline 8,831 patients had neither a history of AF nor AF by ECG Minnesota coding, and were thus at risk of developing this condition during the study.
Results: ECG confirmed new-onset AF in 353 patients. New-onset AF occurred in 5.7% (n = 20) of patients with alcohol intake $>$ 10 units/week vs. 3.9% (n = 333) patients with lower or no alcohol intake. Univariate Cox analyses showed that time-varying heart rate and systolic blood pressure, and baseline Cornell product ECG LVH, weight, height, total cholesterol, urine albumin/creatinine ratio, age, male gender, Caucasian ethnicity, prior congestive heart failure and Framingham risk score significantly predicted subsequent new AF. Intake of alcohol $>$10 units/week was predictive of AF in univariate Cox analysis, HR (95% CI) 1.6 (1.0, 2.5) p=0.042. Multivariate Cox regression analyses showed that age, male gender, time-varying systolic blood pressure, time-varying Cornell voltage-duration, time-varying heart rate, treatment allocation, and intake of alcohol $>$10 units/week (HR 1.8 (1.2, 2.9), p = 0.009) independently predicted new-onset AF. Trend for impact of smoking was cancelled out in the Cox multivariate analyses, and there was no significant interaction between high alcohol intake and smoking.
Conclusions: High intake of alcohol was associated with an increased risk of new-onset AF maybe due to volume changes or to direct toxic effects on the left atrium. However, smoking habits did not influence the risk of new-onset AF in these hypertensive patients with ECG LVH.

1016 Rural residence and higher level of physical activity lessen the probability of hypertension in the Africans. Results from the Vitaraa study

D. Lemogoum[1], P.H. Van De Borne[1], J.R. M'buyamba[2], J.J. Pik[3], M. Leeman[1], J. Toto Moukouo[4], J.P. Degaute[1] on behalf of VITARAA study investigators. *[1]ULB-Erasme Hospital, Brussels, Belgium; [2]Kinshasa school of Medecine, University of University, Kinshasa, Democratic Republic of Congo; [3]Centre Hospitalier Clermont D'Oise, Clermont Oise, France; [4]Clinique des Fleures, Douala, Cameroon*

Purpose: We investigated the prevalence of cardiovascular risk factors among adult Cameroonians and assessed determinants of hypertension.
Methods: Trained nurses visited at home a random sample of urban and rural Cameroonians aged 15 years or more and obtained anthropometric data, lifestyle habits, history of cardiovascular (CV) disease and use of medication for chronic diseases. They measured sitting blood pressure (BP) twice using an electronic device. We averaged the two measurements for analysis. Casual plasma glucose and lipid concentrations were also determined. Hypertension and diabetes were self-report diagnoses or, repectively, a BP $\geq$140/90mmHg and a casual glycaemia $\geq$200mg/dL. We compared the prevalence in the two settings and modeled the probability of hypertension in a stepwise logistic regression analysis.
Results: The prevalence of hypertension among people aged 20 years or more (n=2221) was 31.7%: 25.4% in rural and 36.4% in urban dwellers (P$<$0.0001). Rural (32.4% vs 19.3%; P$<$0.0001) and urban (38.6% vs 34,0%; P=0.09) women had higher prevalences than men. Rural Cameroonians had lower prevalence of diabetes (3.5% vs 5.6%; P=0.002), obesity (15.9% vs 24.1%; P$<$0.0001), smoking (1.2% vs 2.0%; p=0.023), and hypercholesterolaemia (2% vs 7.7%; P$<$0.0001), but greater proportion of subjects reporting higher level of physical activity (6.4% vs 5.6%; P=0.004), and consumption of legumes (28.9% vs 18.7%; P$<$0.0001) and fruits (35.3% vs 23.8%; P$<$0.0001). In the logistic model, the probability of hypertension increased with age (Odds ratio for age $\geq$55 years: 3.63; 95% confidence interval: 2.92-4.51; P$<$0.0001), diabetes (present vs absent 1.93; 1.24-3.01; P =0.004), obesity (present vs absent 1.34; 1.02-1.74; P =0.033), central obesity (present vs absent 1.41; 1.10-1.79; P =0.006) and legumes consumption (1.30; 1.13-1.49; P =0.0002); it was lower for rural residence (0.61; 0.49-0.76; P $<$0.0001), higher level of physical activity (0.81; 0.71-0.92; P =0.0011) and higher consumption of fruits (O.89; 0.78-1.001; P= 0.072).
Conclusion: Our data indicate that cardiovascular risk factors are rather common in adult Africans. However, living in rural environment with increased level of physical activity and high fruits intake lessen the prevalence of hypertension partly linked to epidemic of overweight.

1017 Blood pressure control and cardiovascular risk profile of hypertensive patients in central and east European countries: results of the BP-care study

G. Grassi[1], R. Cifkova[2], S. Erdine[3], S. Laurent[4], K. Narkiewicz[5], J. Redon[6], M. Viigimaa[7], G. Seravalle[8], G. Mancia[1]. *[1]Clinica medica, Univ. Milano Bicocca, Monza, Italy; [2]Inst Clinic and Exper Medicine, Prague, Czech Republic; [3]Dept Cardiology, Univ Istanbul, Istanbul, Turkey; [4]Dept Pharmacology and INSERM U970, Paris, France; [5]Dept Hypertension and Diabetology, Univ Gdansk, Gdansk, Poland; [6]Hypertension Clinic, Univ Valencia, Valencia, Spain; [7]Centre of Cardiology, North Estonia Medical Centre, Tallin, Estonia; [8]S.Luca Hpt- Istituto Auxologico Italiano, Milan, Italy*

Purpose: Limited information is available on the association between hypertension and other cardiovascular (CV) risk factors as well as on blood pressure (BP) control in Central and East European countries, i.e. in a geographic area characterized by a high prevalence of CV disease.
Methods: In 2007 a survey in 7923 hypertensives followed by general practitioners or specialists was carried out in Albania (n=463), Belarus (n=3219), Bosnia (n=812), Czech Republic (n=539), Latvia (n=437), Romania (n=491), Serbia (n=502), Slovakia (n=1360) and Ukraine (n=100). CV risk assessment was based on clinical history, sitting BP (3 measurements) and target organ damage (TOD) assessment.
Results: Patients had a mean ($\pm$SEM) age of 59.2$\pm$0.1 years and the majority of them (83.5%) were followed by specialists mainly working in the hospital (67.6%). Average clinic BP was 149.3$\pm$1.5/88.8$\pm$1.0 mmHg. The most common concomitant CV risk factors were hypercholesterolemia ($>$200 mg/dl, 59.3%), history of coronary heart disease (50.7%), metabolic syndrome (40.4%), obesity (39.5%), diabetes (23.7%), smoking (15.1%), previous stroke (11.5%) and renal failure (creat clear $<$60ml/min, 2.5%). About 70% of patients displayed a very high risk profile (ESH/ESC Guidelines). EKG was performed in 99% of patients, echocardiography in 65%, carotid ultrasonography in 24%, fundoscopy in 68% and microalbuminuria in 10%. ABPM was performed in about $\frac{1}{4}$ of the patients. Despite the presence of antihypertensive drug treatment in almost all patients (87.0% was on combination treatment), BP control ($<$140/90 mmHg) was achieved in only 27.1%. BP control was 1) variable among countries, 2) worse for systolic than for diastolic BP, 3) better in patients followed by specialists than by general practitioners 4) unrelated to patients'age and 5) more unsatisfactory in high risk, diabetic, CHD and renal failure patients. The most frequently used drugs (monotherapy or combination) were ACEIs (70.0%), β-blockers (57.0%), calcium antagonists (51.2%), diuretics (45.8%)and ARBs (13.0%). Drug treatment included lipid-lowering (54.4%) and antiplatelet (66.6%) agents.
Conclusions: Thus BP control rates in Central and East European countries are low (particularly for systolic) and do not differ from that seen in Western Europe. It also shows that 1) BP control is even more unsatisfactory in very high CV risk patients, whose prevalence is elevated, 2) TOD assessment is quite common, except for microalbuminuria and 3) combination drug treatment is frequently used.

1018 Cardiovascular risk factor management in Australian general practice

E. Heeley[1], D. Peiris[1], A. Weekes[2], C. Morgan[2], A. Cass[1], C. Anderson[1], A. Patel[1], J. Chalmers[1]. *[1]The George Institute for International Health, Sydney, Australia; [2]Servier laboratories, Melbourne, Australia*

Purpose: General practitioners (GPs) play a pivotal role in the primary and secondary prevention of cardiovascular (CV) disease, and this can be maximised when management is targeted towards those at highest absolute risk of experiencing a CV event. We aimed to determine the proportion of people in primary care whose CV risk is being treated according to current Australian guidelines.
Methods: The Australian HypErtension and Absolute Risk sTudy (AusHEART) was a nationally representative, cluster-stratified, cross-sectional survey among 322 general practitioners (GPs). Each GP was asked to collect data on CV risk factors and their management in 15 to 20 consecutive patients (age $\geq$55 years) who presented between May and June, 2008. GPs and patients were asked to estimate 5 year CV risk, which was categorised as low ($<$10%), medium (10-15%), high risk ($\geq$15%) or established CVD and then compared to a central calculated estimate based on submitted data and Framingham risk equation incorporating recommended adjustments from the Heart Foundation Hypertension Management Guidelines for General Practitioners 2004.
Results: Among a total of 5352 patients registered to 322 GPs (out of 534 GPs selected, 60% response rate), the centrally calculated frequencies of 'low' ($<$10%), 'medium' (10-15%) and 'high' ($\geq$15%) 5-year risk of a CV event were 19%, 8%, 34%, respectively. A further 37% had established CV disease and 2% had insufficient information for Framingham-based risk estimation. In high risk patients, only 45% of those with established CV disease and 23% of those without established CVD were prescribed the combination of BP-lowering, statin and anti-platelet therapy. Treatment based on single risk factor guidelines was bet-

ter, with only 28% of patients with a BP ≥140/90mmHg not prescribed BP lowering, although 63% of patients with elevated lipid levels (LDL > 2.0mmol/l in established CVD and >2.5mmol/l otherwise) were not prescribed lipid lowering therapy. GPs provided an estimate of CV risk for 89% of patients. This agreed with the centrally estimated category in only 34% of patients (kappa 0.14-slight agreement).Overall GPs tended to underestimate risk. Patients generally overestimated their risk with only 35% agreeing with the centrally calculated estimate (kappa 0.05, slight agreement).

Conclusions: These data re-affirm that high CV risk patients are substantially under-treated. A single, national CV risk assessment tool and management guideline may be a necessary first step in addressing an important evidence-practice gap.

PATHOPHYSIOLOGY OF HYPERTENSION

1019 CaMK4 participates in the settings of the hypertensive phenotype: a human genome wide analysis supported by animal model

G. Santulli[1], M. Illario[2], G.L. Palumbo[1], D. Sorriento[1], E. Cipolletta[1], V. Trimarco[3], C. Del Giudice[1], M. Ciccarelli[4], B. Trimarco[1], G. Iaccarino[1]. *[1]Dept of Clinical Medicine - Federico II University, Naples, Italy; [2]Dept. of Biology and Cellular & Molecular Biology - Federico II University, Naples, Italy; [3]Dept. of Neuroscience - Federico II University, Naples, Italy; [4]Thomas Jefferson University, Philadelphia, United States of America*

Background: Calcium/calmodulin-dependent protein kinase 4 (CaMK4) belongs to the CaMK family and is expressed in selected cellular types, where it regulates calcium-dependent signaling. In particular, we demonstrated the presence of CaMK4 in the endothelium but not in smooth muscle cells, suggesting a yet undisclosed role for this kinase in the regulation of vascular function through the endothelium. Furthermore, a recent Genome-Wide Analysis showed an association between diastolic blood pressure (BP) and the rs10491334 T/C Single Nucleotide Polymorphism (SNP) of human CaMK4 gene.

Methods: To evaluate in vivo the role of CaMK4 in blood pressure regulation, we characterized the cardiovascular phenotype of mice with deletion of this gene (CaMK4-/-, n=14). As control, we used CaMK4+/+ littermates C57/Bl6 mice (WT, n=12). We performed an ultrasound (US, VeVo, Visualsonic) cardiac evaluation and an invasive (Millar) arterial BP measurement. Furthermore, endothelial function was assessed on ex vivo aortic rings preparations, pre-constricted with phenylephrine (1 μM) and treated (0.1 nM to 0.1 μM) with Acetylcholine (Ach), Isoproterenol (Iso) and Nitroprusside (Np).

Results: CaMK4-/- presented BP levels (Systolic BP 124±0.8 mmHg, Diastolic BP 90±0.3 mmHg) significantly higher (ANOVA, $p < 0.05$) than WT (Systolic BP 110±0.7, Diastolic BP 81±0.3 mmHg). Interestingly, the increase in BP levels paralleled the development of cardiac hypertrophy (Heart weight/body ratio: 5.5±0.3 in CaMK4-/- vs 4.24±0.2 in WT; Heart weight/tibia lenght: 7.4±0.4 in CaMK4-/- vs 5.7±0.3 in WT; ANOVA, $p<0.05$), with worsening of US assessed cardiac function (Telediastolic Diameter 4.2±0.3 in CaMK4 vs 3.3±0.4 in WT; Shortening Fraction 0.36±0.06 in CaMK4 vs 0.42±0.04 in WT; $p<0.05$,ANOVA). Vascular reactivity of CaMK4-/- was altered according to a hypertensive phenotype. In particular, endothelium-dependent vasorelaxation to Ach (CaMK4-/- % max vasodilation: 86.3±0.05 vs WT 66.2±0.03) and to low doses of Iso (CaMK4-/- % max vasodilation: 75.8±0.07 vs WT 44.2±0.05) were attenuated (ANOVA, $p<0.05$), while no differences were observed in endothelium independent vasorelaxant response to Np.

Conclusions: The altered endothelium-dependent vasorelaxation in CaMK4 -/- suggests that CaMK4 regulates vascular reactivity and participates in BP homeostasis. We hypothesize that the loss of CaMK4 at the endothelial level causes a reduction in NO production. This could be the underlying mechanism for the association in humans of CaMK4 gene polymorphism and essential hypertension.

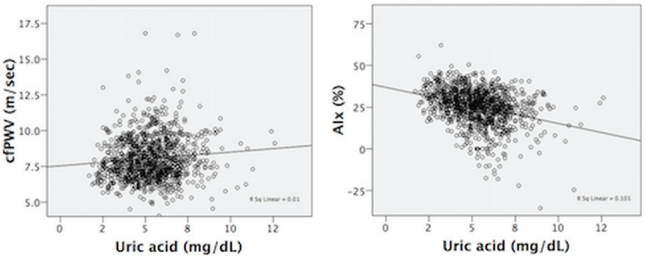
1020 Uric acid: arterial friend or foe? Linking urate levels with arterial stiffness and wave reflections in never-treated hypertension

P. Xaplanteris, C. Vlachopoulos, G. Vyssoulis, K. Aznaouridis, I. Dima, K. Baou, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: We evaluated the relationship between uric acid (UA), arterial stiffness and wave reflections in newly diagnosed hypertensives naïve to medications by measuring carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx).

Methods: 1100 never treated hypertensives were studied. Blood pressure was measured using a sphygmomanometer. cfPWV was calculated using a validated non-invasive device; AIx by applanation tonometry. The correlations were examined by Spearman's rank correlation. Multiple stepwise linear regression analyses with cfPWV and AIx as the dependent variables were carried out to determine the variables independently associated with arterial elastic properties.

Results: UA levels correlated with cfPWV (r=0.095,P=0.002), AIx (r=-0.32, $P<0.001$), male gender (r=0.541, $P<0.001$), age (r=-0.07, P=0.02), presence of the metabolic syndrome (r=0.242,$P<0.001$), body mass index (r=0.338, $P<0.001$), diastolic blood pressure (r=0.06, P=0.046), creatinine (r=0.415, $P<0.001$), glucose (r=0.22, $P<0.001$), cholesterol (r=0.07,P=0.02), triglycerides (r=0.335,$P<0.001$), HDL-C (r=-0.385, $P<0.001$) and LDL-C (r=0.109,$P<0.001$). Two stepwise multivariable linear regression models were examined, with UA as independent variable and cfPWV (model 1) or AIx (model 2) as dependent variables. After adjusting for confounders, a positive association of cfPWV with UA was observed (β=0.052, P=0.04) in model 1; a negative association of AIx with UA was observed (β=-0.114, $P<0.001$) in model 2.



UA and cfPWV, AIx correlations

Conclusions: This is the first study to show that in never-treated hypertensives exists a positive correlation of UA and arterial stiffness, whereas the correlation with wave reflections is negative: as UA levels increase, cfPWV increases and AIx decreases. The mechanisms underlying these relationships remain unknown.

1021 Valsartan was effective in dyslipidemic patients: a sub-analysis of JIKEI heart study

K. Ikewaki[1], M. Shimizu[2], M. Yoshimura[3], B. Dahlof[4], S. Mochizuki[5]. *[1]Division of anti-aging, Department of Internal Medicine,National Defense Medical College, Tokorozawa, Japan; [2]Division of Cardiology, Department of Internal Medicine, Jikei University School of Medicine, Kashiwa, Japan; [3]Division of Cardiology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [4]Institute of Medicine, Department of Emergency and Cardiovascular Medicine, Sahlgrenska University H, Göteborg, Sweden; [5]Musashino University Medical Center, Musashino University, Tokyo, Japan*

Purpose: Hypertension and dyslipidemia are major risk factors for coronary heart disease (CHD), whereby synergistically accelerating atherosclerosis. Among therapies available today, angiotensin receptor blocker (ARB) for the former and statin for the latter have been established to prevent CHD. However, it is not clear whether ARB is effective in dyslipidemic patients who are likely to be under statin treatment. We therefore performed a post-hoc analysis to investigate the effects of valsartan, ARB, on cardiovascular outcomes in dyslipidemic patients in JIKEI heart study.

Methods: JIKEI heart study is a randomized, open-label, blinded endpoint morbidity-mortality study where valsartan, as compared with non-ARB treatment, significantly reduced cardiovascular events by 39% (Lancet 369:1431, 2007). Dyslipidemia was defined as either under lipid-lowering treatment or LDL-C ≥ 140 mg/dl and/or HDL-C<40 mg/dl and/or TG ≥ 150 mg/dl. We examined subgroups depending on the presence/absence of dyslipidemia.

Results: Among participants of JIKEI heart study, 72% of patients were found to be dyslipidmic and statin comprised 90% of lipid-lowering medication. Baseline characteristics as well as follow-up blood pressure did not differ between valsartan groups (n=416 without, n=1125 with dyslipidemia) and non-ARB groups (n=447 without, n=1093 with dyslipidemia). Primary composite endpoints of cardiovascular morbidity and mortality were 49% fewer in dyslipidemic valsartan group as compared with non-ARB counterpart (95% CI 0.37-0.70). Whereas, the primary endpoint did not differ between non-dyslipidemic two groups (16% fewer in ARB group, CI 0.60-1.53).

Conclusions: The present sub-analysis demonstrated that valsartan treatment was particularly effective in patients at high risk such as dyslipidemic & hypertensive patients, indicating that valsartan, together with statin, exerts synergistic cardio-protective functions.

1022 Genetic polymorphism A1675G on type 2 angiotensin receptor increases cardiovascular risk in hypertensive individuals: effects on inflammatory mechanisms

N. Koumallos, D. Tousoulis, C. Antoniades, A. Miliou, A. Antonopoulos, D. Mentzikof, K. Marinou, K. Toutouzas, E. Kallikazarou, C. Stefanadis. *University of Athens, Athens, Greece*

Purpose: Evidence suggests that there is a balance between angiotensin II effects on proatherogenic constitutive type 1, and antiatherogenic inducible type 2 (AT2R) receptors. The AT2R gene is located on chromosome X, and the biological effect of a newly described polymorphism (A1675G) in this gene is unclear. We examined the impact of A1675G polymorphism on AT2R, on the risk for coronary atherosclerosis, and its effect on the expression of proatherogenic inflammatory molecules.

Methods: The study population consisted of 437 males: 155 with coronary artery disease (111 with hypertension) and 282 healthy age-matched controls (121 with hypertension). The presence of A1675G polymorphism on AT2R gene (located in chromosome X) was determined by PCR. Serum levels of C-reactive protein, fibrinogen, interleukin-6 (IL-6) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured in all the participants.
Results: The frequency of the A allele was similar among healthy individuals (41.8% 118/282) and CAD patients (47.7%, 74/155, p=NS). However the presence of the A allele was more frequent in hypertensives with CAD (55%, 59/107) than in hypertensives without CAD (35.8%, 43/120, p<0.01). Importantly, the A allele was associated with increased risk for CAD among hypertensive individuals (OR: 2.201[95%CI: 1.291-3.752], p=0.004), an effect which was not seen among normotensive subjects (p=NS). Importantly, the presence of the A allele was also associated with significantly higher levels of CRP (mean[25th-95th percentile]: A:3.52[1.98-6.08] vs G:1.18[0.66-1.71] mg/ml, p=0.0001), fibrinogen (A:407[347-513] vs G:369[320-416] mg/dl, p=0.001), IL-6 (A:1.55[3.63-5.40] vs G:0.99[0.51-2.46] pg/ml, p=0.002), and sVCAM-1 (A:702[648-925] vs G:621[476-799] ng/ml, p=0.03).
Conclusions: Genetic polymorphism A1675G on AT2R affects systemic inflammatory mechanisms, since the presence of the A allele is associated with higher levels of CRP, fibrinogen, IL-6 and sVCAM-1. In addition, the A allele is associated with elevated cardiovascular risk among hypertensive individuals.

1023 Endothelin-1 pathway during methionine-induced homocysteinemia, mediates endothelial dysfunction in hypertensive individuals

G. Bouras, D. Tousoulis, C. Antoniades, K. Marinou, A. Antonopoulos, N. Papageorgiou, E. Stefanadi, G. Latsios, C. Tentolouris, C. Stefanadis. *University of Athens, Athens, Greece*

Purpose: Endothelin-1 (ET-1) is a key regulator of arterial blood pressure in humans, and homocysteinemia is associated with increased oxidative stress. It is still unclear whether homocysteine-induced oxidative stress is implicated in the regulation of ET-1 expression. We examined the impact of acute homocysteinemia on endothelial function in hypertensive patients and healthy individuals, and the potential role of ET-1.
Methods: In this double-blind placebo controlled study, 35 hypertensive subjects and 30 healthy volunteers underwent methionine-loading (100mg met/kg BW) after they received vitamins C (2g) plus E (800IU) (16 hypertensives (HTN+vit) and 15 healthy (C+vit)) or placebo (18 hypertensives (HTN+placebo) and 15 healthy (C+placebo)). Endothelial function was evaluated by gauge-strain plethysmography (to determine endothelium dependent dilation (EDD)), at baseline and 4 hours post loading (4hPML). ET-1 and lipid hydroperoxides (per-ox) levels were measured by ELISA.
Results: Homocysteine was similarly increased in both hypertensives (by 22.2±1.26μM p<0.0001) and healthy controls (by 23.2±2.22 μM, p<0.0001), and was not affected by pre-treatment with antioxidants. EDD was significantly decreased in HTN+placebo (75.4±11.5 to 51.6±7.3%, p<0.05) and C+placebo (96.7±9.6 to 52.2±6.5%, p<0.0001), while antioxidant treatment did not prevent this effect in either HTN+vit (76.4±8.8 to 53.7±7.8%, p<0.01) or C+vit (86.6±10.5 to 41.1±6.3%, p<0.001). Importantly, ET-1 was increased 4hPMLonly in hypertensive individuals (HTN+placebo: 1.09±0.3 to 1.40±0.4pg/ml, p<0.05) an effect not prevented by antioxidants (HTN+vit: 0.82±0.08 to 1.1±0.09pg/ml p<0.01). Per-ox were significantly decreased in the HTN+vit (170[65-368] to 148[98-372]pg/ml, p<0.05) but not in the HTN-placebo (170[65-268] to 148[98-372]pg/ml, p=NS). No effect of methionone-loading was observed on ET-1 levels in healthy individuals (C+placebo: 1.96±0.84 to 1.87±0.77pg/ml and C+vit: 3.59±1.35 to 2.84±1.15pg/ml, p=NS).
Conclusions: Experimental homocysteinemia rapidly blunts endothelial function in both hypertensive subjects and healthy individuals. The rapid elevation of ET-1 levels observed only in hypertensives, suggests that the ET-1 may be the key mediator of homocysteine-induced endothelial dysfunction, independently of oxidative stress status.

1024 Effects of continuous positive airway pressure therapy on sympathovagal balance and arterial stiffness in obstructive sleep apnea

K. Shiina, H. Tomiyama, H. Saruhara, K. Kato, Y. Hashimura, C. Matsumoto, M. Yoshida, Y. Usui, Y. Takata, A. Yamashina. *Tokyo Medical University, Tokyo, Japan*

Background: Increased arterial stiffness and sympathovagal imbalance are noted in patients with obstructive sleep apnea (OSA). Continuous positive airway pressure therapy (CPAP) can have beneficial effects in such cases. However, it is not clear whether the improvement of sympathovagal balance by CPAP is directly related to the reduction of arterial stiffness, independent of changes in blood pressure.
Methods: In 50 consecutive eligible patients with OSA in whom CPAP was conducted (apnea-hypopnea index > 20/hour), the measurements of brachial-ankle pulse wave velocity (baPWV), heart rate variability (HRV), baroreceptor sensitivity (BRS), plasma levels of C-reactive protein (CRP) and endothelial function assessed by changes in forearm blood flow before and after reactive hyperemia (END) were conducted before and after 3 months of CPAP therapy.
Results: Of the 50 patients, 38 had good CPAP compliance. In the CPAP good compliance group, CPAP therapy decreased baPWV, low frequency (LF)/high frequency (HF) ratio in HRV, CRP and HR, and increased BRS significantly. Furthermore, in this group, the changes in baPWV by CPAP therapy had significantly correlated with those in LF/HF ratio and mean blood pressure (MBP), but not those in BRS, CRP and END. Multivariate linear regression analysis demonstrated that the changes in baPWV had a significant positive relationship with those in LF/HF (beta = 0.15, p=0.01), independent of those in MBP.

Results of Univariate Linear Regression

	CPAP Good compliance group		CPAP Poor compliance group		Entire Cohort	
Variable	r	p-value	r	p-value	r	p-value
perLF	0.20	0.22	0.27	0.39	0.23	0.14
perHF	-0.14	0.38	0.26	0.41	0.001	0.99
perLF/HF	0.40	0.01	0.26	0.41	0.33	0.02
perBRS	-0.088	0.58	-0.27	0.38	-0.13	0.41
perMBP	0.62	<0.01	0.86	0.00	0.66	0.00
perHR	0.24	0.14	0.04	0.88	0.12	0.42
perEND	-0.02	0.90	0.11	0.71	-0.001	0.99
perCRP	0.133	0.43	0.17	0.60	0.13	0.42

per = percent changes before and after 3 months of CPAP therapy.

Conclusions: The improvement of sympathovagal balance by CPAP may directly reduce stiffness of central to middle-sized arteries independently of the changes in MBP and vascular endothelial status.

NEUROHORMONES AND HEART FAILURE: THE SEARCH GOES ON!

1095 Serial measurements of natriuretic peptides are predictive of not-high-dose anthracycline-induced cardiotoxicity in a 1-year follow-up

S. Romano[1], G. Stifano[1], V. Procaccini[1], M. Mancini[2], S. Fratini[1], E. Ricevuto[2], C. Ficorella[2], M. Penco[1]. [1]*Cardiology, University of L'Aquila, L'Aquila, Italy;* [2]*Oncology, University of L'Aquila, L'Aquila, Italy*

Background: Biohumoral markers may be useful in early detection of subjects at high risk of developing cardiotoxicity. There are few studies considering natriuretic peptides in not-high-dose chemotherapy.
Aim: To evaluate the possibility of early detection of high-risk pts by serial assessment of N-terminal Brain Natriuretic Peptide (NT-proBNP) in breast cancer pts undergoing not-high-dose chemotherapy.
Methods: We studied 72 pts treated with anthracycline. NT-pro-BNP and cardiac Troponine I (c-TnI) were evaluated before each drug administration and 24 hours after. Left ventricular (LV) function (End-diastolic, End-sistolic Volumes - EDV ESV, and Ejection Fraction - EF) was assessed by echocardiography at baseline, every two cycle of chemotherapy and after 3, 6 and 12 months follow up.
Results: NT-proBNP and C-TnI values were normal at baseline in all pts. Serial samples showed normal values of NT-proBNP in 10 pts (Group A), temporary alterations (increase at 24 hours and then decrease to normal values) in 38 pts (Group B), while in 24 pts (Group C) NT-proBNP abnormalities were persistent. Only one pt showed an increase of C-TnI. LV function did not show significant alterations in Group A and B, whether Group C showed a decrease of EF and an increase in EDV and ESV, statistically significant in the examination performed at the end of chemotherapy (p<0.05), and more evident in the 1st-year control (p<0.01) (see Table).
Conclusions: Serial evaluation of NT-pro-BNP may be an useful tool, more than c-TnI or single samples of NT-pro-BNP, in early identifying pts at high risk of cardiotoxicity, among those treated with not-high-dose chemotherapy.

Abstract 1095 – Table 1. LV volumes and EF during 1-year follow-up

	EF (%)			ESV (ml/m^2)			EDV (ml/m^2)		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
Baseline	63.8±2.9	63.5±6.5	65.5±4.6	27.8±2.3	27.1±7.1	23±5.9	78.1±2.8	77.8±9.8	65.8±11.4
End of chemotherapy	64.6±2.8	64.1±5.7	61.7±4.3*	27.5±2.5	26.9±7.5	28.4±6.7*	77.7±4.2	77.3±8.4	71.6±11.9*
3 month follow-up	64.8±3.1	64.4±5.2	60,1±4.2*	26.9±2.5	29.6±6.5	28.7±5.2**	77.3±2.5	77.9±8.1	72.3±10.5*
6 month follow-up	64.8±3.1	64.2±5.2	58.6±4.5**	26.8±2.9	27.1±7.1	29.3±6.7**	77.5±2.6	76.9±9.9	72.9±11.6**
1 year follow-up	65.2±3.4	64.3±5.1	56.3±4.8**	26.9±3.1	26.7±6.9	30.1±6.8**	77.5±2.1	77.5±10.5	74.4±12.7**

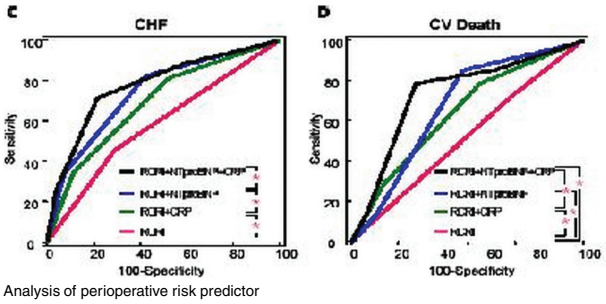
*p<0.05; **p<0.01.

1096 Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in noncardiac surgery

E.S. Jeon[1], D.K. Cho[2], Y.B. Song[1], J.Y. Hahn[1], S.H. Choi[1], J.H. Choi[1], H.C. Gwon[1], D.K. Kim[1], S.H. Lee[1], J.K. Oh[3]. [1]*Samsung Medical Center, Seoul, Korea, Republic of;* [2]*Hanmaeum General Hospital, Jeju, Korea, Republic of;* [3]*Mayo Clinic College of Medicine, Rochester, United States of America*

Background: A simple and strongly predictive non-invasive test for perioperative cardiovascular event is clinically warranted. We hypothesized that preoperative N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) predict perioperative major cardiovascular event (PMCE) independent of traditional clinical risks.

Methods and Results: In a prospective cohort of 2054 elective noncardiac surgery patients, predictive power of NT-proBNP, CRP, and baseline Revised Cardiac Risk Index (RCRI) for the risk of PMCE (myocardial infarction, heart failure, or cardiovascular death) were evaluated. Optimal cutoff values were derived from receiver operating characteristic curve (ROC) analysis. A total of 290 patients (14.1%) had a PMCE. Each increasing quartile of NT-proBNP or CRP level was associated with a greater risk of PMCE even after adjustment for traditional clinical risk factors (NT-proBNP: relative risk [RR] of highest quartile versus lowest quartile = 5.2 (95% confidence interval [CI], 3.8-6.8, P<0.001), CRP: RR = 3.7 (95% CI, 2.6-4.9, P<0.001)). Both NT-proBNP (cutoff = 301 ng/L) and CRP (cutoff = 3.4 mg/L) predicted PMCE better than RCRI (cutoff = 2) by ROC analysis (P<0.001). Moreover, the predictive power of RCRI (adjusted RR = 1.5, 95% CI, 1.2-1.9) could be improved significantly by addition of CRP and NT-proBNP to RCRI (adjusted RR=4.6, 95% CI, 3.7-5.5) (P<0.001).



Analysis of perioperative risk predictor

Conclusions: High preoperative NT-proBNP or CRP is a strong and independent predictor of perioperative major cardiovascular event in non-cardiac surgery. The predictive power of current clinical risk evaluation system would be strengthened by incorporation of these biomarkers.

1097 BNP-guided heart failure therapy: a meta-analysis of randomized control trials

P. Porapakkham, P.L. Porapakkham, H. Zimmet, B. Billah, H. Krum. *Monash University, Melbourne, Australia*

Aim: The use of plasma levels of B-type natriuretic peptides (BNP) to guide management of patients with chronic heart failure (CHF) has been investigated in a number of randomized control trials (RCTs). Based on individual RCTs, the benefits of this treatment approach has been uncertain. We therefore performed a meta-analysis to examine the effect of BNP-guided drug therapy on all cause mortality, all cause hospitalization and survival free of any hospitalization in these patients.

Methods: RCTs were identified by systematic search of manuscripts, abstracts and databases. Eligible RCTs were those that enrolled more than 20 patients and involved comparison of BNP-guided drug therapy vs usual clinical care of the CHF patient in an outpatient setting.

Results: Six trials, with a total of 1131 patients and mean duration of 15 (3-18) months, met the specified criteria. Overall, there was a significantly lower risk of all cause mortality (Table) in the BNP-guided therapy group compared with control. In the sub-group of patients < 75 years all-cause mortality was also significantly lower in the BNP-guided group. However, there was no reduction in mortality with BNP-guided therapy in patients > 75 years. The risk of all-cause hospitalization and survival free of any hospitalization was not significantly different between groups. The additional percentage of patients achieving target dose of ACE inhibitors and beta-blockers was 21% and 22% in the BNP-group and 11.7% and 12.5% in the control group, respectively.

Event	Number of Pts	Risk Ratio	95% CI	P value for significance
All cause Mortality	1,131	0.74	0.59-0.93	0.009
All cause Mortality in < 75 yrs	319	0.52	0.33-0.82	0.005
All cause Mortality in >75 yrs	417	0.94	0.71-1.25	0.694
All cause Hospitalization	330	0.82	0.64-1.05	0.121
Survival free of any hospitalization	559	1.07	0.85-1.34	0.583

Conclusion: BNP-guided therapy reduces all-cause mortality in patients with CHF when compared to usual clinical care, especially in pts < 75 yrs. A component of this survival effect may be due to increased utilisation of agents proven to decrease mortality. However, there does not appear to be a reduction in all-cause hospitalization or increase in survival free of hospitalization using this approach.

1098 Emergency department short term mortality in acute heart failure: results of the international BACH trial

W.F. Peacock[1], R. Nowak[2], S.X. Neath[3], R. Christenson[4], P. Clopton[5], S. Disomma[6], S.D. Anker[7], A. Maisel[5], G. Filippatos[8], M. Mockel[7]. [1]*Cleveland Clinic, Cleveland, United States of America;* [2]*Henry Ford Health System, Detroit, United States of America;* [3]*University of California, San Diego, United States of America;* [4]*University of Maryland School of Medicine, Baltimore, United States of America;* [5]*University of California, VA medical center, San Diego, United States of America;* [6]*La Sapienza Universita, Rome, Italy;* [7]*Charite - Campus Virchow-Klinikum, Berlin, Germany;* [8]*Evangelismos General Hospital of Athens, Athens, Greece*

Objectives: Emergency physicians have few tools providing objective accurate prediction of short term mortality risk in patients presenting to the ED with acute heart failure (AHF). Our purpose was to describe the accuracy of candidate markers for predicting short term death rates in ED patients presenting with AHF.

Methods: The Biomarkers in ACute Heart failure (BACH) trial was a prospective, 15-center, international study of patients presenting to the ED with non-traumatic dyspnea. All investigational marker values were blinded, with the exception of natriuretic peptides which, when used clinically, were at the discretion of the treating emergency physician and employed the local hospital reference range. For all markers in the analyses below, including natriuretic peptides, a core lab was utilized. Gold standard diagnoses were determined by 2 cardiologists reviewing all data available 90 days post ED visit.

Results: Of the 1641 BACH patients, 568 (34.6%) had a gold standard diagnosis of AHF, 52% were male, and 36% had a prior history of HF. Overall, 20 (3.5%) died by 14 days, and 65 (11.4%) were dead by 90 days. Mortality prediction is described by C- statistic; all p values <0.05, EXCEPT when noted by * where p=NS.

AHF mortality prediction by markers

	AHF mortality presented as C statistic		
	90 day	30 day	14 day
BNP	0.596	0.552*	0.512*
NTproBNP	0.654	0.636	0.585*
Procalcitonin	0.633	0.696	0.625
Endothelin	0.655	0.705	0.682
A type natriuretic peptide	0.644	0.630	0.589*
Arginine vasopressin (AVP)	0.660	0.735	0.773
Adrenomedullin (ADM)	0.669	0.732	0.720
AVP + ADM	0.681	0.764	0.784

Conclusions: Both arginine vasopressin and adrenomedullin, alone and in combination, demonstrate superior short term mortality prognostic ability when compared to natriuretic peptides and the other evaluated markers. Objective determination of mortality risk may provide opportunities to improve emergency department AHF decision making and consequent clinical outcomes.

1099 Plasma renin activity retains a strong prognostic value in patients with chronic HF, independent of ACE inhibitor or beta-blocker therapy. Data from the Valsartan Heart Failure (Val-HeFT) trial

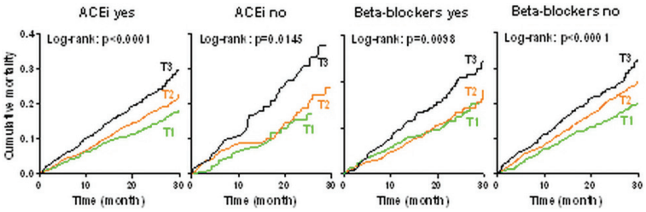
S. Masson[1], S. Solomon[2], L. Angelici[1], R. Latini[1], I.S. Anand[3], M. Prescott[4], A.P. Maggioni[5], G. Tognoni[6], J.N. Cohn[7] on behalf of Val-HeFT Investigators. [1]*The Mario Negri Institute for Pharmacological Research, Milan, Italy;* [2]*Brigham and Women's Hospital, Boston, United States of America;* [3]*Minneapolis VA Medical Center, Minneapolis, United States of America;* [4]*Novartis Pharmaceutical Corporation, East Hanover, United States of America;* [5]*Associazione Nazionale Medici Cardiologi Ospedalieri, Florence, Italy;* [6]*Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy;* [7]*University of Minnesota, Minneapolis, United States of America*

Purpose: Both ACE inhibitors (ACEi) and beta-blockers (BB) improve outcome in patients with chronic HF but have opposite effects on the secretion of renin. Given the possibility of direct renin inhibition, we evaluated whether plasma renin activity (PRA) retains prognostic value in patients with chronic HF who are getting ACEi and have reflex increase in PRA.

Methods: PRA was measured at baseline in 4,291 patients with chronic and symptomatic HF enrolled in Val-HeFT. Determinants of elevated levels of log (PRA) were identified with multivariable linear regression. The association between PRA and all cause mortality was assessed as a function of ACEi and/or BB prescriptions in multivariate Cox models including significant clinical risk factors and NT-proBNP.

Results: PRA was higher in patients on ACEi (5.85 [0.01-323] ng/mL/h, median [min-max]) than in those without ACEi (1.57 [0.01-73]), and lower in those on BB (3.89 [0.01-163]) than not on BB (6.21 [0.01-323]). Mortality increased progressively across deciles of PRA in the overall population (p<0.0001), and across tertiles of PRA in patients on, or not on ACEi or BB (p<0.05, Figure).

In multivariable Cox models, log (PRA) was associated with mortality in patients on (p=0.0005) or not on ACEi (p=0.01). PRA remained an independent marker of death in patients with recommended (n=1890) or lower than recommended doses of ACEi (n=2068) or in those on ACEi and with (n=1415) or without BB (n=2563).



Kaplan-Meier curves by tertiles of PRA

Conclusions: PRA is a powerful prognostic marker of death over a wide range of concentrations in patients with chronic HF. Prescription of ACEi and/or BB does not influence this relationship. This suggests that the increase in PRA is related to risk and raises the possibility that blocking at this step might be useful.

1100 Osteoprotegerin predicts long-term all-cause mortality in patients with chronic heart failure

T. Ueland[1], P. Aukrust[1], J. Kjekshus[1], J. Hulte[2], M. Lindberg[3], J. Wikstrand[2], L. Gullestad[1]. [1]*National University Hospital, Oslo, Norway;* [2]*Sahlgrenska University Hospital, Gothenburg, Sweden;* [3]*AstraZeneca, Mölndal, Sweden*

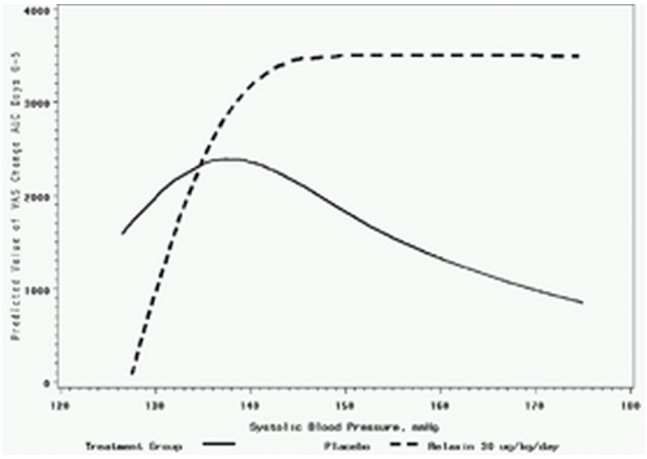
Purpose: Numerousreports confirm a pathogenic role for tumor necrosis factor (TNF)α in thedevelopment and progression of heart failure (HF).We have shown thatosteoprotegerin (OPG), a member of the TNF superfamily, may be implicated inthe pathogenesis of HF and that OPG levels are predictive of survival in patients withpost-infarction HF. However, prognostic data in patients with chronic HF arelacking.
Methods: The importance of plasma OPGas a risk factor for the primary endpoint (cardiovascular death, nonfatalmyocardial infarction, nonfatal stroke; events, n=411) and for all-causemortality (events, n=424) was investigated in a total of 1464 patients at least60 years of age [mean age 72±7 (SD), 341 (23%) women], in NYHA class II-IV, with ischaemic systolic HF receiving optimal pharmacologicaltherapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) population, randomly assigned to receive 10 mg rosuvastatin or placebopr day and followed for a median 32.8 months.
Results: OPG was strongly related to age, and patients in Tertile 1of OPG were at much lower risk than in those in Tertile 3. In multi-variableanalyses, OPG as a continuous variable, added no clear significant predictiveinformation for the risk estimation of the primary endpoint, beyond demographic,clinical and biochemical variables (left ventricular ejection fraction, NYHAclass, age, body mass index, diabetes, sex, intermittent claudication, heartrate, serum creatinine and apoA1), [HR1.05 (1.00-1.10), p=0.058]. However, OPG added independent predictiveinformation for all-cause mortality [HR 1.09 (1.04-1.14), p<0.001]. The primaryendpoint and total mortality were reduced by rosuvastatin in Tertile 1 of OPG [OPG<5420pg/ml;Cox adjusted HR 0.67 (0.45-0.99), p= 0.047, and 0.65 (0.43-0.98), p=0.038,respectively], but not in Tertile 2 or 3, interactionby treatment comparing the three OPG Tertiles showed p=0.076.
Conclusion: Circulating OPG is predictive of all-causemortality in patients with advanced chronic systolic HF of ischemic aetiologyindependently of conventional risk markers.

NEW DRUGS AND THERAPEUTIC STRATEGIES IN HEART FAILURE

1101 Increased symptom-improvement with the novel vasodilator, relaxin, in Acute Heart Failure (AHF) patients with elevated blood pressure. Results from the Pre-RELAX-AHF study

J.R. Teerlink[1], M. Metra[2], A.A. Voors[3], G.M. Felker[4], P. Ponikowski[5], G.S. Filippatos[6], B.H. Greenberg[7], S.L. Teichman[8], B.D. Weatherley[9], G. Cotter[9] on behalf of the Pre-RELAX-AHF Investigators. [1]*University of California, San Francisco, San Francisco, United States of America;* [2]*University of Brescia, Brescia, Italy;* [3]*University Medical Center, Groningen, Netherlands;* [4]*Duke Clinical Research Institute, Durham, United States of America;* [5]*Military Hospital, Department of Health Sciences, Medical University, Wroclaw, Poland;* [6]*University of Athens, Athens, Greece;* [7]*University of California, San Diego, San Diego, United States of America;* [8]*Corthera, Inc., San Mateo, United States of America;* [9]*Momentum-Research Inc., Durham, United States of America*

Current ESC guidelines recommend vasodilators for patients admitted with AHF and systolic blood pressure (SBP) >110 mmHg. However, to-date limited information is available on the interaction between vasodilator therapy in providing symptom relief and the initial blood pressure. Recent data from prospective randomized studies (REVIVE, VERITAS) suggest that there may be an important interaction between efficacy and SBP.
Methods: Pre-RELAX-AHF enrolled 234 patients with symptomatic AHF (moderate-severe dyspnea), systolic BP (SBP)>125mmHg, and mild-moderate renal impairment during the first 16 hours of admission (median 7 hours) and randomized them to 4 doses of IV relaxin or placebo given for 48 hours. We modeled the effect of the most efficacious dose (30 mcg/kg/d, n=42; dashed line) compared to placebo (n=61;solid line) on improvement in dyspnea (mean change in AUC of visual analog scale through 5 days; VAS; 0-100mm) according to baseline SBP using restricted cubic splines and analysis of variance.
Results: There was a markedly significant interaction between baseline BP and treatment effect (p=0.009). Patients with SBP>135 mmHg had greater improvements in dyspnea with relaxin therapy compared to placebo (Figure). However, a tendency to a better response to placebo was noted with an initial SBP <130, although the confidence intervals are exceptionally wide and overlapping due to the relatively few patients with SBP<130.

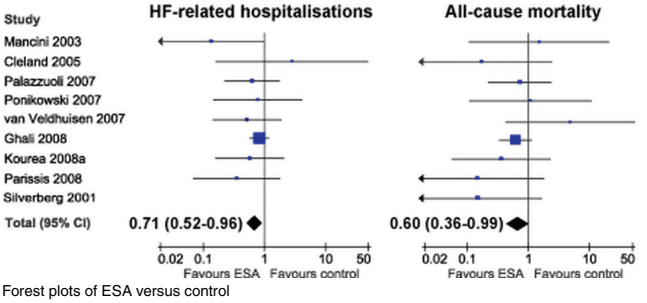


Conclusions: Relaxin markedly improved dyspnea in patients with SBP>130mmHg, representing over half of the population of patients admitted with AHF. The results of this analysis suggest a dramatic predictive effect of the initial blood pressure on subsequent symptom improvement when treated with vasodilators, such as relaxin.

1102 Eythropoietin for anaemia in heart failure: a meta-analysis of exercise tolerance, symptoms and clinical outcome improvement

D. Kotecha[1], K. Ngo[2], J. Walters[2], L. Manzano[3], A. Palazzuoli[4], D.J. Van Veldhuisen[5], M. Flather[1]. [1]*Royal Brompton Hospital, London, United Kingdom;* [2]*University of Tasmania, Hobart, Australia;* [3]*Hospital Universitario Ramon y Cajal, Madrid, Spain;* [4]*Le Scotte Hospital, Siena, Italy;* [5]*University Medical Center, Groningen, Netherlands*

Purpose: Anaemia in heart failure (HF) is both common (12-55%) and associated with worse symptoms and increased mortality. Erythropoiesis-stimulating agents (ESA) have been studied in several small randomised controlled trials (RCTs) but definitive evaluation and clinical guidance is required.
Methods: An extensive search strategy using MEDLINE, EMBASE, clinical trial registries, reference lists and author communication identified 11 RCTs with 793 participants comparing ESA with control. Published and additionally requested data were meta-analysed as part of a submitted Cochrane review (CD007613). Fixed and random-effects models were used depending on statistical heterogeneity, which was substantial for a number of outcomes.
Results: ESA treatment significantly improved exercise duration by 96.8 sec (5.2-188.4, p=0.04) and 6-minute walk distance by 69.3 metres (17.0-121.7, p=0.009) compared to control. Benefit was also noted in terms of peak VO2 (+2.29



Forest plots of ESA versus control

mL/kg/min, p=0.007), NYHA class (-0.73, p<0.001), ejection fraction (+5.8%, p<0.001), B-type natriuretic peptide (-236.6 pg/mL, p<0.001) and quality-of-life indicators with a mean increase in haemoglobin of 2 g/dL. There was no associated increase in adverse events with ESA therapy and a suggestion of lower mortality and hospitalisations (see figure), although the number of events was limited. Overall quality of studies was moderate with 9 studies being placebo-controlled but only 5 double-blinded.

Conclusion: Meta-analysis of small RCTs to-date suggests that ESA treatment can improve exercise tolerance, reduce symptoms and have benefits on clinical outcomes in anaemic HF patients. Confirmation requires well-designed studies with careful attention to dose, attained haemoglobin level and associated iron therapy.

1103 Combined therapy with angiotensin receptor antagonists and ACE inhibitors versus standard therapy in patients with heart failure: a meta-analysis of randomized controlled trials

A.J. Nordmann[1], A. Kuenzli[1], H.C. Bucher[1], I. Anand[2], G. Arutiunov[3], L.C. Kum[4], R. Mckelvie[5], R. Afzal[5], M. White[6]. *[1]University Hospital Basel, Basel, Switzerland; [2]University of Minnesota, Minneapolis, United States of America; [3]Russian State Medical University, Moscow, Russian Federation; [4]Prince of Wales Hospital, Hong Kong, China, People's Republic of; [5]McMaster University, Hamilton, Canada; [6]Montreal Heart Institute, Montreal, Canada*

Purpose: To compare the effects of combination therapy with angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors versus standard therapy in patients with congestive heart failure.

Methods: We searched MEDLINE, EMBASE, PASCAL, the Cochrane Central Register of Controlled Trials (all from their inception to August 2008), reference lists, and contacted experts to identify all randomized controlled trials of ARBs and ACE inhibitors compared to standard therapy in patients with heart failure reporting mortality and rehospitalization outcomes having a follow-up of at least 6 months. Two investigators independently searched and abstracted studies.

Results: Eight trials including a total of 18'061 patients fulfilled our inclusion criteria. There was no difference between patients treated with combination therapy and standard therapy for overall mortality, hospitalization for any reason, fatal or nonfatal MI. Combination therapy was, however, associated with fewer hospital admissions for heart failure (RR 0.81, 95%CI 0.72-0.91), although there was significant heterogeneity across trials (p-value for heterogeneity = 0.04; I2 = 57% [95%CI 0-83%]). Patients treated with combination therapy had a higher risk of worsening renal function and symptomatic hypotension, and their trial medications were more often permanently discontinued.

Conclusions: Combination therapy with ARBs and ACE inhibitors does not reduce overall mortality or myocardial infarction in patients with congestive heart failure when compared to standard therapy, but reduces heart failure related hospitalizations. This benefit must be weighed against the higher risk of adverse events.

1104 Time course analysis of the effect of n-3 PUFA on fatal and non fatal arrhythmias in heart failure: secondary results of the GISSI-HF trial

R. Marchioli[1], M.P. Aldegheri[2], L. Borghese[3], M.G. Franzosi[4], R. Latini[4], R.M. Marfisi[1], A.P. Maggioni[5], G.L. Nicolosi[6], G. Tognoni[1], L. Tavazzi[7] on behalf of GISSI-Heart Failure Investigators. *[1]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [2]Ospedale Mater Salutis, Legnago, Italy; [3]Ospedale de Gironcoli, Conegliano Veneto, Italy; [4]The Mario Negri Institute for Pharmacological Research, Milan, Italy; [5]Centro Studi ANMCO, Firenze, Italy; [6]Azienda Ospedaliera S. Maria Degli Angeli, Pordenone, Italy; [7]GVM Hospitals of Care and Research, Cotignola, Italy*

Aims: GISSI-Heart Failure (HF) showed n-3 polyunsaturated fatty acids (PUFA) decreasing absolute mortality by 1.8% during a median 4-year follow-up (FUP). At variance with GISSI-Prevenzione in post-MI, survival curves diverged after 2 years. We assessed the time-course benefit of PUFA on fatal arrhythmias (FA), hospitalization from ventricular arrhythmias (HVA), and their combination (major arrhythmias, MA) in HF.

Methods: GISSI-HF was a double-blind, placebo-controlled trial testing 1 g/d PUFA in 6975 HF pts with NYHA class II-IV. Analyses were intention-to-treat. Cox proportional models adjusted for clinical variables unbalanced at baseline were fitted. To assess when the curves started to diverge, data were left-censored at times 0, 6, 12, and 24 months. To assess whether the amount of relative risk reduction (RRR) increased during FUP, data were right-censored every 6 months until study end.

Results: Total deaths, FA, HVA, and MA were recorded in 1969, 578, 228, and 775 patients. Absolute risk reduction of FA was 0.9%, i.e., 50% of the total benefit of PUFA on mortality. PUFA decreased significantly MA by 17% (0.83, 0.72-0.95, P=0.009). Survival curves for FA, HVA, and MA diverged early and continued to separate during FUP. As to MA, RRR were 16%, 13%, 13%, and 17% when we right-censored data at 12, 24, 30, and study end. Figures present the effect of n-3 PUFA on MA during the whole study as well as after left-censoring data at 6, 12, and 24 months and show the divergence of the curves by using multiple starting time points for the analysis.

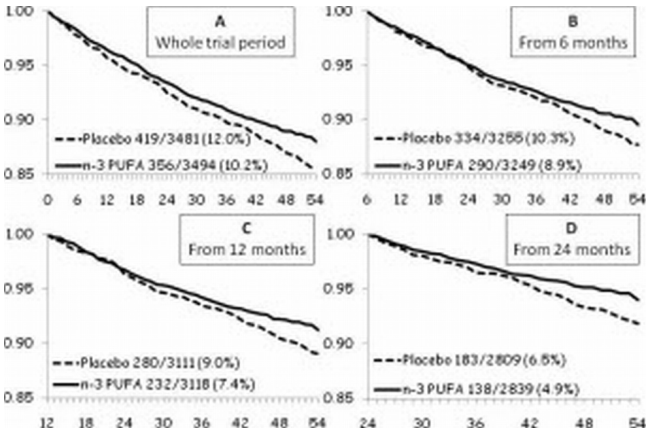


Figure 1

Conclusions: n-3 PUFA significantly decreased arrhythmias in HF patients and this effect contributed importantly to the clinical benefit.

1105 Safety and tolerability profile of aliskiren added to optimized therapy in elderly and very elderly patients with heart failure

S.D. Solomon[1], J.J. Mcmurray[2], A.P. Maggioni[3], R. Latini[4], B.A. Smith[5], C. Bush[5], D.L. Keefe[5], B. Pitt[6] on behalf of ALOFT Investigators. *[1]Brigham and Women's Hospital, Boston, United States of America; [2]Western Infirmary, Glasgow, United Kingdom; [3]Associazione Nazionale Medici Cardiologi Ospedalieri, Florence, Italy; [4]The Mario Negri Institute for Pharmacological Research, Milan, Italy; [5]Novartis Pharmaceuticals Corporation, East Hanover, United States of America; [6]University of Michigan Medical School, Ann Arbor, United States of America*

Background: Elderly (≥65 years) or very elderly (≥75 years) patients with heart failure (HF) are at greater risk of renal adverse events than younger HF patients. This subgroup analysis of the ALiskiren Observation of heart Failure Treatment (ALOFT) study evaluated the tolerability of the direct renin inhibitor aliskiren (ALI) added to standard therapy in elderly or very elderly patients with chronic stable HF.

Methods: Patients ≥18 years with NYHA class II-IV HF, prior/current hypertension and plasma B-type natriuretic peptide (BNP) >100 pg/mL were randomized to 12 wks' double-blind treatment with ALI 150 mg or placebo (PBO) once daily added to an ACE inhibitor or angiotensin receptor blocker and beta-blocker.

Results: Of the 302 patients enrolled, 212 (70.2%) were ≥65 years; 85 (28.1%) were ≥75 years. There were no notable differences between ALI and PBO in rates of laboratory abnormalities or predefined adverse events (AEs) across age subgroups (Table). ALI lowered BNP (% geometric mean change [95% CI]) from baseline to wk 12 by 20% [-1, 36], 39% [23, 51] and 42% [21, 57] in patients aged <65, ≥65 and ≥75 years, respectively.

Laboratory abnormality	<65 years		65-75 years		≥75 years	
	ALI (n=49)	PBO (n=40)	ALI (n=65)	PBO (n=61)	ALI (n=42)	PBO (n=43)
Blood urea nitrogen >14.28 mmol/L	3 (6.1)	4 (10.0)	6 (9.2)	5 (8.2)	4 (9.5)	6 (14.0)
Creatinine >176.8 μmol/L	4 (8.2)	0	3 (4.6)	3 (4.9)	4 (9.5)	5 (11.6)
Potassium <3.5 mmol/L	1 (2.0)	4 (10.0)	0	1 (1.6)	1 (2.4)	2 (4.7)
>5.5 mmol/L	4 (8.2)	3 (7.5)	4 (6.2)	7 (11.5)	5 (11.9)	2 (4.7)
≥6.0 mmol/L	2 (4.1)	2 (5.0)	1 (1.5)	3 (4.9)	0	1 (2.3)
Renal dysfunction	0	0	3 (4.6)	1 (1.6)	0	1 (2.3)
Symptomatic hypotension	1 (2.0)	1 (2.4)	3 (4.6)	1 (1.6)	1 (2.4)	0
Hyperkalemia	5 (10.2)	2 (4.9)	1 (1.5)	3 (4.8)	4 (9.5)	2 (4.7)

Data are number (%) of patients with clinically significant laboratory abnormalities or predefined adverse events at any time during the study. ALI, aliskiren; PBO, placebo.

Conclusions: Adding aliskiren to standard therapy was not associated with clinically significant increases in rates of laboratory abnormalities or predefined AEs, and reduced plasma BNP effectively in elderly or very elderly patients with HF.

1106 Thyroid hormone, amiodarone therapy and prognosis in chronic heart failure

M. Coceani[1], S. Molinaro[2], M. Scalese[2], C. Carpeggiani[2], A. L'Abbate[3], G. Iervasi[2], A. Pingitore[2]. *[1]Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [2]CNR Istituto di Fisiologia Clinica, Pisa, Italy; [3]Scuola Superiore Sant'Anna, Pisa, Italy*

Purpose: The safety of amiodarone in chronic heart failure (CHF) remains uncertain. Amiodarone interferes with thyroid hormone metabolism by inhibiting the peripheral conversion of thyroxine into triiodothyronine (T3). Pathologically reduced serum levels of T3 - the so called "low T3 syndrome" (LT3) - are associated with

increased mortality in CHF. The aim of the study was to examine the relationship between thyroid hormone status, amiodarone therapy, and outcome in CHF.
Methods: Two thousand three hundred forty-four patients (median age 68 years, 73% male) with systolic CHF (50% ischaemic in origin, median ejection fraction at echocardiography 43%) and free of overt hyper- and hypothyroidism were enrolled in the study. The population was then divided into four groups according to thyroid hormone profile and therapy with amiodarone: group 1 (LT3 and amiodarone therapy, n=126), group 2 (isolated amiodarone therapy, n=74), group 3 (isolated LT3, n=682), group 4 (controls, n=1462).
Results: Kaplan-Meier curves showed, after a median follow-up of 30 months (interquartile range 14-47 months), increased total and cardiac mortality in groups 1 (30% and 20%, respectively), 2 (23%, 11%), and 3 (22%, 12%) compared to group 4 (9%, 4%; for total mortality log-rank 69.8, $p<0.0001$; for cardiac mortality log-rank 55.4, $p<0.0001$). At multivariate analysis (see Table 1), survival was reduced in groups 1 and 3 compared to group 4. Group 2, instead, had a similar mortality to group 4.

Table 1. Total and cardiac mortality

	Group 1	Group 2	Group 3	Group 4
Total mortality (HR and 95% CI)	1.58 (1.08-2.31)	1.29 (0.77-2.31)	1.96 (1.55-2.50)	1
	p=0.019	p=NS	p<0.001	
Cardiac mortality (HR and 95% CI)	1.98 (1.21-3.24)	1.06 (0.48-2.35)	2.22 (1.59-3.10)	1
	p=0.007	p=NS	p<0.001	

Multivariate analysis adjusted for age, diabetes mellitus, history of myocardial infarction, serum creatinine, left ventricular ejection fraction, beta blocker therapy, and digoxin therapy.

Conclusions: LT3 exerts an adverse impact on prognosis in CHF, even among patients taking amiodarone. Conversely, amiodarone does not protect against LT3-associated mortality and does not confer a survival advantage in patients with normal T3 levels. Whether the observed lack of benefit of amiodarone therapy in CHF is linked to a reduction in T3 levels should be assessed in future studies.

CLINICAL ELECTROCARDIOGRAM REVISITED: NEW OBSERVATIONS, NEW CHALLENGES

1107 Prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome screening

L. Ferreira Santos[1], E. Correia[1], B. Rodrigues[1], R. Faria[1], L. Nunes[1], A. Costa[1], J. Lopes Carvalho[1], C. Henriques[2], A. Matos[2], J. Oliveira Santos[1]. *[1]Hospital São Teotónio, Viseu, Portugal; [2]Escola Superior de Tecnologia de Viseu, Instituto Politécnico de Viseu, Viseu, Portugal*

Introduction: All family members of patients with Brugada syndrome (BS) should be screened. Fluctuations between the diagnostic and non-diagnostic basal ECG pattern in patients with BS are known, but systematic studies are still lacking.
Objectives: Prospectively evaluate the spontaneous changes between diagnostic and non-diagnostic ECG patterns in a family screened for BS.
Methods and Results: 129 family members possibly affected plus the index case (mean age 25,22±16,64) were screened with two ECG with an interval of six mouths. The ECGs were analysed for the presence of coved type (type 1), saddleback type (type 2 and 3) or no changes (normal). Only coved-type ECG pattern with more than 2 mm ST-segment elevation (type 1) in at least two right precordial leads was defined as diagnostic, and type 2 or 3 were only considered suggestive. The first ECG made six (4,6%) diagnostics and the second 11 (8,5%), but only three of them maintained the diagnostic in the two ECG's. So, the two separated ECGs revealed 14 (10,8%) elements (eight males) with a type 1, five with type 2 and three with type 3. Patients with basal diagnostic ECG were older (37,43±11,07) than elements with non spontaneous diagnostic ECG (23,74±16,63) (p=0,001). All 43 relatives aged under 16 years had normal basal ECG. No significant gender difference was found among relatives with or without diagnostic ECG. Body mass index (BMI) was significantly lower in those with diagnostic plus suggestive ECG when compared with the others (21,3±2,7 against 23,9±2,9) (p=0,003). Additionally, logistic regression revealed that age and BMI are significant predictors of diagnostic ECG pattern.
Among the 14 relatives with diagnostic, eleven (79%) exhibited one non-diagnostic ECG and six (43%) one normal ECG. Out of the 22 elements with a suggestive or a diagnostic ECG, ten (45%) had the other ECG classified as normal. We found significant difference between the percentages of diagnoses with only the first ECG against two serial ECG. Among patients with diagnostic, no significant differences were found in age, gender and BMI between patients with or without fluctuations from diagnostic to non-diagnostic ECG or otherwise.
Conclusion: Spontaneous phenotypic manifestation of BS was more frequent in older elements, absent in children and related with low BMI. Characteristic ECG manifestations were intermittent in more than $\frac{3}{4}$ of the affected elements. The prevalence of fluctuations between diagnostic and non-diagnostic ECG may have an implication on the correct phenotyping in family screening so several ECG and drug challenging are mandatory.

1108 High prevalence of early repolarization in the German general population

M.F. Sinner[1], W. Reinhard[2], B.M. Beckmann[1], E. Martens[1], M. Grassl[2], C. Meisinger[3], A. Peters[3], S. Perz[4], C. Hengstenberg[2], S. Kaab[1]. *[1]Klinikum der Universitaet Muenchen, Munich, Germany; [2]Universitaetklinikum Regensburg, Regensburg, Germany; [3]Helmholtz Zentrum Munich; Institute of Epidemiology, Neuherberg, Germany; [4]Helmholtz Zentrum Munich, Institute of Biological and Medical Imaging, Neuherberg, Germany*

Background: The electrocardiogram (ECG) is used to decipher signatures predicting the risk for malign arrhythmias leading to sudden cardiac death. The signature early repolarization (ER) recently received great attention, when it was shown to be strongly associated with fatal ventricular arrhythmias. However, the prevalence of ER in the general population remains unclear. We thus intended to determine this prevalence in the population-based WHO/MONICA survey.
Methods: The WHO/MONICA survey S1 is a population-based study conducted in Augsburg, Germany, and two adjacent counties in 1984/85. It comprises of 4.022 men and women aged 25-74 years who were identified through the registration office being representative for the German general population. All subjects received a digital 12-lead resting ECG recording (Siemens Bioset). According to previous descriptions, ER was defined as a J-point elevation of at least 0.1 mV in at least two leads of I, II, III, aVL, aVF, V4, V5 or V6. Morphologically, ER had to occur either as a notch following the QRS complex or as slurring of the descending section of the QRS complex fading into the ST segment. We analyzed 1.026 randomly selected ECGs, being representative for the entire study population concerning age and sex. All selected ECGs were evaluated by two independent cardiologists. In case of discrepant findings, a final decision was made by consensus between the two and a third expert cardiologist/electrophysiologist.
Results: We analyzed 1026 individuals (519 men and 507 women). The mean age was 46.44±11.22 years for men and 45.26±11.33 years for women. In this population-based study cohort, the typical ER signature occurred in 359 of 1026 ECGs, corresponding to a prevalence of 35.0%. This prevalence was 37.8% for males and 32.1% for females. Individuals with an ER signature tended to be slightly older (47.16±11.30 years vs. 45.15±11.22 years).
Conclusion: With 35.0%, the prevalence of ER in the German general population exceeded that seen in the case group of a recently described sudden cardiac death sample. The importance of this finding remains to be elucidated especially in the context of associated cardiac morbidity and mortality. Further studies clarifying the impact of ER on these issues are warranted.

1109 Mode of onset in idiopathic ventricular fibrillation; early repolarization-J wave syndrome vs. Brugada syndrome

G.B. Nam, E.S. Jin, K.J. Choi, Y.H. Kim. *Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of*

Background: Idiopathic ventricular fibrillation occurring in patients with background early repolarization and transient augmentation of J waves (IVF-ER-J) has been described. The present study evaluates the mode of VF initiation in patients with IVF-ER-J compared with those with typical Brugada syndrome (BrS).
Methods: The mode of the onset and the coupling intervals of the PVCs initiating VF episodes were analyzed in patients with BrS (n=8) or IVF-ER-J (n=11) who experienced sudden cardiac death/syncope or repeat ICD shocks.
Results: From a total of 50 patients with VF in the absence of structural heart diseases, 11 patients showed background ER in the resting ECGs. Among the 11 patients with IVF-ER-J, 5 presented with electrical storm (ES, more than 3 recurrent VF episodes/day). The 5 ES patients displayed a prominent but transient accentuation of J waves across the precordial and limb leads prior to development of ES. VF episodes were more commonly initiated by PVCs with a short-long-short (SLS) sequence in IVF-ER ES (42/58, 72.4%) than in BrS patients (13/86, 15.1%, $p<0.01$). Coupling intervals were significantly shorter in the IVF-ER-J patients as compared with those with BrS (307±53ms vs. 409±101ms, $p<0.01$).
Conclusion: Short-long-short sequence and PVCs with short coupling intervals were more frequently observed in patients with IVF-ER-J compared with those with BrS. This unique pause-dependent mode of initiation could potentially be applied in prevention of VF episodes in patients with IVF-ER-J.

1110 Outcome of individuals with an electrocardiogram of coved-type ST-segment elevation in a single right precordial lead

S. Richter[1], A. Sarkozy[1], T. Boussy[1], S. Henkens[1], G. Paparella[1], G.B. Chierchia[1], R. Brugada[2], J. Brugada[3], P. Brugada[1]. *[1]Heart Rhythm Management Centre, Cardiovascular Centre, Free University of Brussels (VUB), Brussels, Belgium; [2]Cardiovascular Genetics Center, University of Girona, Girona, Spain; [3]Arrhythmia Section, Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain*

Purpose: According to the diagnostic consensus criteria, the electrocardiographic diagnosis of Brugada syndrome requires coved-type $\geq$ 2 mm ST-segment elevation in $>$ 1 right precordial lead (RPL) V1-V3 in the presence or absence of a sodium-channel blocker. However, this consensus has not been evaluated.
Methods: We included 186 individuals from a single-center Brugada registry who had documented spontaneous and/or drug-induced electrocardiograms of coved-

type ≥ 2 mm ST-segment elevation in at least 1 RPL. Clinical characteristics and outcome were compared between subjects with ECGs displaying only 1 diagnostic RPL and Brugada patients fulfilling the proposed diagnostic ECG criteria.
Results: Among the study population, 126 subjects (68%) fulfilled the diagnostic ECG criteria for Brugada syndrome. Sixty subjects (32%) had only electrocardiograms with 1 single RPL displaying a diagnostic coved-type ST-segment elevation, either lead V1 or V2. There were no significant differences in clinical characteristics and outcome between case subjects with only single-lead coved-type electrocardiograms and Brugada patients with ECGs displaying ≥ 2 diagnostic RPLs. Mayor arrhythmic events occurred with the same frequency (8%) in both groups during > 5-year follow-up. The figure shows the Kaplan-Meier estimate of arrhythmic event-free survival according to the electrocardiographic presentation (log-rank 0.79).

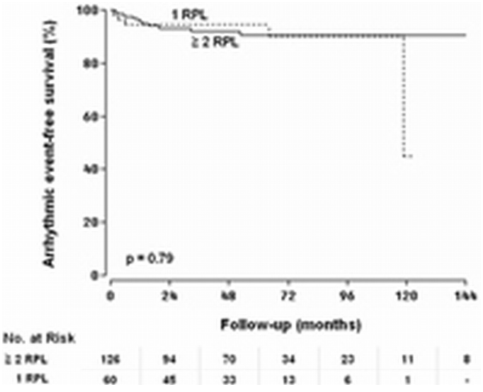


Figure 1

Conclusions: Individuals with electrocardiograms displaying only 1 diagnostic RPL have a similar clinical profile and arrhythmic risk as Brugada patients with ECGs displaying ≥ 2 diagnostic RPLs. Revision of the diagnostic consensus criteria should be considered.

1111 Electrocardiographic differentiation of stress induced cardiomyopathy and acute myocarditis

H.W.P. Park, Y.J.H. Hong, J.H.K. Kim, Y.K.A. Ahn, M.H.J. Jeong, J.G.C. Cho, J.C.P. Park, J.C.K. Kang. *Chonnam National University Hospital, Gwangju, Korea, Republic of*

Objectives: Stress induced cardiomyopathy and acute myocarditis usually show very similar clinical presentation such as chest pain, dyspnea, electrocardiographic abnormalities, elevation of cardiac markers. Early diagnosis is important because stress induced cardiomyopathy is usually recovered with supportive treatment but myocarditis may results in fatal outcome. This study was done to investigate the role electrocardiography in differentiation of these diseases.
Methods: We reviewed the medical record of 27 patients with stress induced cardiomyopathy (M:F=5:22, 66±12 years) and 36 with acute myocarditis (M:F=23:13, 46±13 years). Both of them underwent coronary angiogram and showed insignificant stenosis. Echocardiography revealed apical ballooning in stress induced cardiomyopathy or compatible findings with acute myocarditis.
Results: Stress induced cardiomyopathy was more common in women and myocarditis in men (p<0.001). Sinus cycle length, PR interval, QRS width were not different between the 2 groups. QT and QTc interval were longer in group I than in group II (454±74ms vs. 396±56ms, 519±78ms vs. 441±44ms, p=0.001, <0.001, respectively). Q wave was present in 22.2% and only at chest leads in group I but in 25.0% at both limb, chest leads in group II. There were no differences in ST elevation (25.9% vs. 27.8%) or ST depression (3.7% vs. 13.9% in group II) (p=0.388). Ventricular tachycardia/fibrillation occurred in 3.7% in group I and 12.9% in group II but it was not statistically significant. Atrioventricular block higher than Mobitz type II was observed in 1 patient in each group. T wave inversion (88.9% vs. 51.6%, p=0.001) and giant negative T wave were observed more frequently in group II than group I (55.5% vs. 0%, p<0.001). Both QTc interval >480 ms and giant negative T wave had sensitivity 51.9%, specificity 100%, positive predictive value 100%, negative predictive value 74% in stress induced cardiomyopathy.
Conclusions: QTc interval >480 ms and giant negative T wave are considered useful in differential diagnosis of stress induced cardiomyopathy and acute myocarditis

1112 Prevalence of the early repolarization aspect in a healthy women population

U. Vinsonneau, A. Brondex, C. Vergez-Larrouget, L. Leroy, A. Lecoat, A. Vigneau-Vinsonneau, S. Geneau De La Marliere, G. Quiniou. *french military hospital, Brest, France*

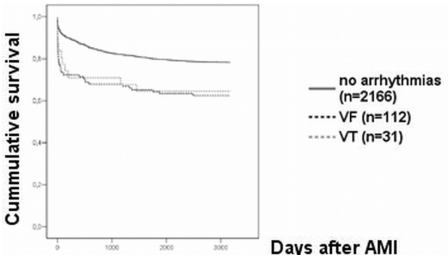
Introduction: Early repolarization aspect (ERA) is a common electrocardiographic finding that is generally considered to be benign. It has been recently reported a series of more than 30 patients resuscitated from ventricular fibrillation associated with the aspect of ERA. However, the prevalence of ERA in healthy women population has not been precisely evaluated. The aim of the present study is to evaluate the prevalence of ERA in normal women population incorporated in French navy.
Methods: Candidates (male or female) for incorporation in the French Navy or already members of the institution have a complete examination including a cardiac workup with history taking, physical examination, electrocardiogram (ECG) and when necessary echocardiogram. ECG of 128 women examinated for this medical workup were selected. These 128 ECG were blindly and separately reviewed by 2 cardiologists. An ERA was diagnosed when a slurring of the terminal part of QRS associated with an elevation of ST segment or when a definite J wave (amplitude > 0.05 mV for 0.03 sec) was registered. In case of discordance between the 2 cardiologists either a consensus was found or this ECG was considered normal to exclude from ERA controversial tracings and to collect only "true" cases.
Results: Majority of the 128 subjects were young (mean age 30.2 years, standard deviation 9.6 years), with the largest proportion in the age range 17-29 years (107/128; 87% of the study sample). Individuals > 30 years representing only 13% of the study population (22/128). Among the 128 women, 22/128 had an ERA (17.2%). ERA was more frequent in very young women aged 17-29 years (19/107, 17.7%) than older women 30-49 (3/22, 14.3%), but this difference is not statistically significant (P=0.5).
Conclusion: The early repolarization aspect is a common finding in normal women population without overt heart disease.

HOW TO PREDICT THE PROGNOSIS IN VENTRICULAR TACHYARRHYTHMIAS

1113 Long-term outcome of patients with ventricular tachycardia and ventricular fibrillation within 48 hours of acute myocardial infarction

H. Bonnemeier, D. Rzepka, A. Heinke, D. Heckmann, M. Reppel, H. Schunkert. *Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany*

Introduction: Recent data of smaller studies suggested that ventricular tachycardia (VT) and fibrillation (VF) within 48 hours of acute myocardial infarction (AMI) is a predictor for long-term mortality even in patients with interventional and adjuvant medical state-of-the-art therapy. We therefore studied the incidence and outcomes of such arrhythmias in a large patient population in a university hospital setting.
Methods: We investigated a total of 2319 consecutive patients with AMI undergoing primary angiography/-plasty (age 66±12y; 29% females; 37% STEMI; 41% anterior AMI; 24% diabetes; CKmax 1151±1291 U/l; PCI 85%). The incidence of VF and sustained VT was documented within 48 hours after admission.
Results: A total of 143 patients with malignant ventricular arrhythmias were identified in the subacute phase of AMI [VF 112 patients (4.8%); VT 31 patients (1.4%)]. Kaplan-Meier survival analysis revealed a significant higher short- and long-term mortality in patients with both, VT and patients with VF. Total mortality during follow-up was 21.7% for patients without arrhythmias, 37.5% for patients with VF, and 35.5% for patients with VT.



Conclusions: Despite early invasive strategies, inhospital malignant ventricular arrhythmias are associated with higher short- and long-term mortality rates after AMI, also when occurring during 48 hours after hospitalization. Better therapies are needed to improve outcomes of these arrhythmias.

1114 Non-invasive identification of ventricular tachycardia related conducting channels with MRI in patients with chronic myocardial infarction: a case-control study

E. Perez-David[1], R. Del Castillo[1], L. Atea[1], A. Arenal[1], E. Arbelo[2], V. Celorrio[1], I. Gomez Anta[1], J. Lafuente[1], J. Bermejo[1], F. Fernandez Aviles[1]. *[1]Hospital General Universitario Gregorio Maranon, Madrid, Spain; [2]Hospital Universitario De Gran Canaria "Dr. Negrin", Las Palmas de Gran Canaria, Spain*

Purpose: In patients with prior myocardial infarction (MI), intra-scar surviving

fibers may create conducting channels (CC) which are the substrate of most sustained monomorphic ventricular tachycardias (SMVT). Non invasive identification of CC could facillitate the ablation procedure. The aim of this study was to assess the capability of contrast-enhanced MRI (ce-MRI) for detecting intrascar CC in patients with chronic MI.
Method: Ce-MRI and left ventricular electroanatomic voltage maps (CARTO®) were obtained in 19 patients (p) with chronic myocardial infarction referred for VT ablation. CMR studies were performed with a 1.5 T Unit (Philips Intera®), including SSFP sequences in standard views and late enhancement 10 minutes after injecting 0.02 mmol/kg of gadolinium contrast (Omniscan®) with 3D T1-TFE acquisition. Postprocessing of images included quantitation of total infarct size divided in core and grey zone (>3 SDs and 2 to 3 SDs above remote normal myocardium, respectively), and signal intensity-guided detection of CC. CC was defined as an intrascar grey zone connected with normal myocardium in two different points. Endocardial voltage maps were analyzed with different voltage levels of scar definition to identify CCs. Pace, activation and entrainment mapping were used to establish the relationship between CCs and VTs. A control group of 19 p with chronic MI matched for age, sex, MI location and LV ejection fraction was selected for comparison.
Results: 19 p (67±8 years, LVEF 34±10%) with clinical SMVT (cycle length 344±58 ms) were studied. 16p had chronic inferior MI and 3p had chronic anterior MI. ceMRI identified CC in 17p (89%), endocardial in 13p and meso-epicardial in 4p. In 5 p several independent CC were observed. 3 CC were observed in the anterior wall, 3 in the infero-lateral and 16 in the inferior. Voltage maps identified a VT-related CC in all patients when the voltage scar definition was 0.39±0.34 mV. Concordance in location between CARTO and MRI existed in 17p (89%). In the control group, complete CC were observed in 3p and incomplete CC (i.e. connected to normal myocardium in only one point) in 5p. The incidence of complete CC was significantly lower in the control group compared to VT group (89% vs 16%, $p<0.05$).
Conclusions: ce-MRI may be useful to non-invasively identify VT-related CC. Good concordance was found between ce-MRI and CARTO findings. This information could be used for VT substrate ablation in patients with chronic MI, especially in non-inducible VT.

1115 Prognostic value of three-dimensional electroanatomic voltage mapping in patients with arrhythmias of right ventricular origin

M. Bevilacqua[1], M. Silvano[1], L. Leoni[1], F. Migliore[1], A. Zorzi[1], C. Basso[2], G. Buja[1], G. Thiene[2], S. Iliceto[1], D. Corrado[1].
[1]Department of cardiac, thoracic and vascular sciences, University of Padua, Padua, Italy; [2]Department of medical-diagnostic sciences, University of Padua, Padua, Italy

Background: Endocardial voltage mapping (EVM) by CARTO system offers the potential to accurately identify the presence, location and extent of right ventricular (RV) low-voltage regions (i.e. electroanatomic scars) which may represent the substrate of life-threatening RV ventricular tachyarrhythmias. This study prospectively evaluated the prognostic value of RV electroanatomic scar in a cohort of patients presenting clinically with arrhythmias of RV origin.
Methods: The study population comprised 109 consecutive patients (73 men and 36 women; mean age 36±14 years) with a left bundle branch block pattern ventricular arrhythmia, such as sustained ventricular tachycardia (VT) in 21, non sustained VT in 64, frequent and/or ripetitive premature ventricular beats in 94 patients. All patients underwent detailed clinical evaluation and high density RV EVM by sampling multiregional RV bipolar electrograms (197±23 sampled points) to identify RV electroanatomic scars (defined as low-amplitude areas with bipolar electrogram <0.5 mV).
Results: Electroanatomic scars were found in 54 patients (49%), affecting 20.4±13% (range 2.6% to 49.8%) of the RV free wall. The presence of electroanatomic scar significantly correlated with a positive family history ($p<0.001$), late potentials on SAECG ($p<0.001$), and RV dilatation/dysfunction ($p<0.001$). During a mean follow-up period of 49±13 months, 25 of 109 patients (23%) experienced malignant arrhythmic events such as sudden death in 2, cardiac arrest due to ventricular fibrillation in 4, appropriate ICD intervention in 7, and instable VT leading to syncope in 12. Unexplained syncope ($p<0.001$) and electroanatomic scar ($p<0.001$) were significantly associated with the arrhythmic events. Among patients with an abnormal RV EVM, those who experienced arrhythmic events during follow-up had a significantly greater percentage of electroanatomic scar (27.4±10.5% vs 16±12.3%, $p<0.001$). After adjustement for age, family history, VT, and RV dilatation/dysfunction, unexplained syncope (OR=15.9, 95%CI=4.1-61.8; $p<0.001$) and RV electroanatomic scars (OR=9.28, 95% CI=2.0-42.7; p=0.004) remained independent predictors of malignant arrhythmic outcome.
Conclusions: Electroanatomic scars were found in approximately half of patients with significant arrhythmias of right ventricular origin. There was a significant correlation between electroanatomic scar extent and incidence of arrhythmic events during follow-up. Electroanatomic scar, unlike RV dilatation/dysfunction, was an independent predictor of malignant arrhythmic outcome.

1116 Myocardial mechanical dispersion in long QT syndrome identifies individuals with high risk for cardiac arrhythmias

K.H. Haugaa[1], T. Edvardsen[1], T.P. Leren[2], O.A. Smiseth[1], J.P. Amlie[1].
[1]Rikshospitalet University Hospital and University of Oslo, Oslo, Norway; [2]Rikshospitalet University Hospital, Oslo, Norway

Purpose: Long QT syndrome (LQTS) predisposes to life-threatening ventricular arrhythmias. Prolonged action potentials in LQTS may cause prolonged myocardial contraction which can be assessed by strain echocardiography. We hypothesized that heterogeneity in myocardial contraction duration measured as myocardial mechanical dispersion can serve as a risk marker in LQTS patients.
Methods: We included 87 genotyped LQTS mutation carriers and 20 healthy control subjects. 45 mutations carriers had a history of cardiac arrest or syncope and 42 were asymptomatic. Myocardial contraction duration was assessed as time to peak strain. Standard deviation of contraction duration from the 6 basal LV segments was calculated as a marker of mechanical dispersion.
Results: Contraction duration was prolonged in LQTS mutation carriers compared to healthy controls (430±50 vs. 370±40ms, $p<0.001$) and in symptomatic compared to asymptomatic carriers (440±50 vs. 410±40ms, p=0.001). The longest contraction duration was predominantly localized in the interventricular septum in symptomatic mutation carriers (p=0.02). Mechanical dispersion was more pronounced in symptomatic mutation carriers compared to asymptomatic (67±22 vs. 34±15ms, $p<0.001$). The figure shows representative strain traces from a healthy individual with homogeneous contraction duration and a LQTS-patient with mechanical dispersion. Mechanical dispersion was better related to severe arrhythmia than QTc (AUC by ROC analysis 0.92 (95%CI 0.86-0.98) vs. 0.73 (95%CI 0.62-0.83)).

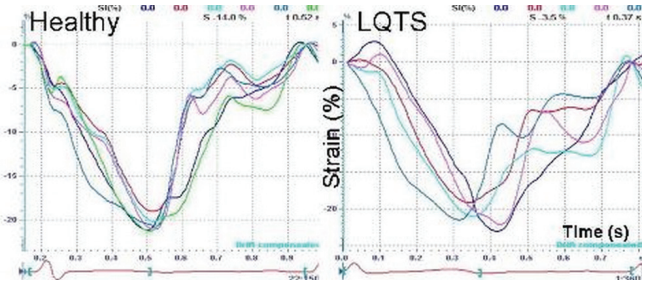


Figure 1

Conclusions: Mechanical dispersion of myocardial contraction assessed by strain echocardiography was increased in LQTS mutation carriers and was superior to QTc in identifying those with cardiac events.

1117 Electrophysiologic-guided quinidine therapy in brugada syndrome: an alternative to ICD therapy

D. Fourey, A. Glick, R. Rosso, Y. Michowitch, S. Viskin, B. Belhassen.
Sorasky University Hospital, Tel Aviv, Israel

Introduction: Implantation of an ICD is usually recommended for patients with Brugada syndrome who have inducible ventricular fibrillation (VF) during electrophysiologic studies (EPS). We have proposed EPS-guided therapy with quinidine and here we report our long-term experience with this approach.
Methods: During a 10-year period, we studied 68 pts with Brugada syndrome (88% males, aged 20-85 years). All pts had a type 1 Brugada-ECG observed spontaneously (n=19) or following flecainide infusion (n=49). Clinical presentation included cardiac arrest in 6 patients and syncope in 25 patients whereas and 37 patients were asymptomatic. Our EPS protocol included single, double and triple ventricular extrastimulation (VES) delivered from 2 right ventricular sites (apex and outflow tract) at 2 basic cycle lengths (600 and 400msec). However, it differed from standard protocols by the use of 1) a stimulus current at 5-fold diastolic threshold (but always < 3mA) and 2) repetition of VES at the shortest coupling intervals that captured the ventricle (10 times for double and 5 times for triple VES).
Results: VF was induced in 47 (69%) pts. Inducibility rates were 100%, 75% and 62% for patients presenting with cardiac arrest, syncope, or no symptoms, respectively. EPS-guided quinidine therapy was attempted in 43/47 (91%) patients with inducible VF and was effective for preventing VF re-induction in 38 (88%) of 43 patients. Long-term therapy consisted of EPS-guided quinidine in 26 patients and implantable defibrillator (ICD) in 16 patients with inducible VF. During a mean follow-up period of 52 months (range 3 to 128 months), all patients remained free of arrhythmic events and only one died (of cancer).
Conclusions: VF inducibility is high in pts with Brugada syndrome during EPS using an aggressive PVS protocol. Quinidine is very effective for preventing VF re-induction at EPS and may reduce the number of ICD implantations without compromising patient safety.

1118 Integration of MRI derived 3D scar maps with electroanatomical mapping during catheter ablation of scar-related ventricular tachycardia late after myocardial infarction

A.P. Wijnmaalen, R.J. Van Der Geest, H.J. Siebelink, L. Kroft, J.J. Bax, J.H.C. Reiber, M.J. Schalij, K. Zeppenfeld. *Leiden University Medical Center, Leiden, Netherlands*

Purpose: The current used gold standard to guide substrate based ablation of scar-related ventricular tachycardia (VT) relies on electroanatomical endocardial and epicardial voltage mapping (EAM) using a cut-off value of 1.5mV to define normal myocardium. Integration of the complex 3-dimensional (3D) scar geometry derived from contrast enhanced magnetic resonance imaging (CE-MRI) with EAM may provide supplementary substrate information. This study aimed to assess the relation between bipolar electrogram voltages and scar characteristics defined by CE-MRI.
Methods: 15 patients (14 male, 64±9yr) referred for RFCA of VT late after myocardial infarction underwent CE-MRI using a 1.5 T MRI system. Endocardial contours of the CE-MRI were used to create 3D surface meshes of the left ventricle (LV), the aortic cusps and the left main (LM) origin. Bipolar endocardial EAM of the LV and aortic cusps were obtained and the LM location was marked. Registration of the MRI derived scar maps and electroanatomical voltage maps was performed using the LM as landmark and the CARTO surface registration algorithm during the ablation procedure. The mapping point coordinates were used to superimpose bipolar voltages on the corresponding CE-MRI slice using the reversed registration matrix. CE defined scar was categorized by transmurality and signal intensity. Infarct core was defined as myocardium with a signal intensity (SI) ≥50% of the maximum SI, infarct border zone was defined as myocardium with SI≥35% and SI<50% of the maximum SI of the CE-MRI.
Results: The average number of LV EAM points was 258±42. Merging of MRI derived scar maps with voltage maps was successful in all patients with an average registration error of 3.8±0.6mm. The mean bipolar voltages decreased with increasing signal intensity and with scar transmurality. A mean bipolar voltage of <1.5mV was only found in areas with a transmural core infarct as defined by CE MRI.
Conclusions: Integration of MRI derived scar maps with EAM during VT ablation is feasible and accurate. CE-MRI identifies intramural and non-transmural scar undetected by EAM according to currently used voltage criteria and may provide important supplementary substrate information.

DIASTOLIC DYSFUNCTION: CAN IT BE BETTER UNDERSTOOD?

1123 Reduced cardiac performance and exercise capacity due to exercise-induced diastolic dysfunction in HFNEF. Bicycle exercise 3D echocardiography

M. Kasner[1], R. Gaub[1], D. Sinning[1], J. Lober[1], D. Westermann[1], D. Milicic[2], H.-P. Schultheiss[1], C. Tschoepe[1]. *[1]Charite - Campus Benjamin Franklin, Berlin, Germany; [2]University of Zagreb School of Medicine, Zagreb, Croatia*

Evaluating diastolic dysfunction in patients with suspected heart failure induced symptoms despite normal EF (HFNEF) is complex, in particular when LV filling index E/E' reveal borderline results (E/E': 8-15). Stress echocardiography with accurate 3D volume analysis may clarify the status of cardiac dysfunction in these patients. Therefore we investigated changes in E/E' and cardiac performance at exercise in a HFNEF population with borderline E/E' results at rest using bicycle exercise 3D echocardiography (3DE).
Methods: Mitral flow and tissue Doppler; and full-volume analysis obtained by 3DE recordings are performed at rest and during bicycle exercise (25W/2min) in 62 HFNEF patients with suggested diastolic dysfunction characterised by E/E' 8-15 and compared with 14 age/sex-adjusted controls. End-diastolic pressure-volume relationship (EDPVR) was determined as a ratio of estimated end-diastolic pressure (EDP=0,44xE/E'+6,7) and measured end-diastolic volume (LVEDV).
Results: There were no significant differences in LVEDV, stroke volume (SV), cardiac output (CO), LVEF (62+9 vs. 63+5%) at rest between both groups. 39/62 (62%) of HFNEF patients with borderline E/E' developed significantly an increased filling index E/E' (12+4 to 18.5+9) and EDPVR (0.17+0.05 to 0.30+0.19 mmHg/ml) at maximal exercise level whereas controls showed no significant changes (E/E': 5.6+0.8 to 6.8+1.8; EDPVR: 0.08+0.03 to 0.10+0.06 mmHg/ml). Controls responded furthermore with an increase in LVEDV (mean LVEDV: +10%) and SV (+32%). In contrast, patients with increased LV EDPVR could not expand their LVEDV (mean LVEDV: - 9%) and SV, which was was associated with a reduced exercise capacity (95+33 vs. 203+65 Wat, p<0.05) and elevated NT-proBNP levels (282+224 vs. 46+24 pg/ml, p<0.05). Other 23 of 62 (38%) patients did not further elevate their LV filling pressures and EDPVR at exercise and showed a cardiac performance similar to controls.
Conclusion: Heart failure patients with normal EF and only borderline LV filling index at rest who revealed impaired EDPVR during exercise showed lower cardiac performance associated with exercise induced symptoms. Bicycle exercise 3DE can identify impaired EDPVR and reduced cardiac performance in HFNEF.

1124 Advanced left ventricular diastolic dysfunction is associated with longitudinal systolic impairment in patients with systemic hypertension

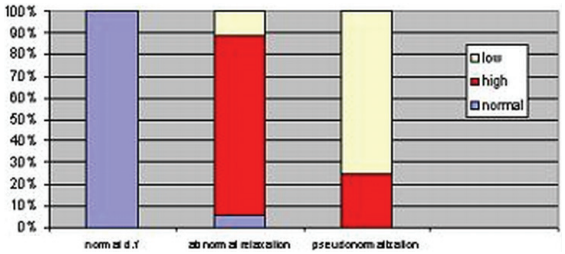
F.L. Dini[1], M. Ciavarella[2], E. De Marco[3], C. De Gregorio[4], L. Badano[5], V. Di Bello[1], S. Gallina[6], P.N. Marino[7], S. Mondillo[8], M. Galderisi[9]. *[1]Azienda Ospedaliero - Universitaria Pisana, Pisa, Italy; [2]Policlinico di Roma Umberto Primo, Rome, Italy; [3]Policlinico Gemelli, Roma, Italy; [4]Policlinico Universitario, Messina, Italy; [5]Ospedale Santa Maria della Misericordia, Udine, Italy; [6]Universita G. D'Annunzio, Chieti, Italy; [7]Azienda Ospedaliera Maggiore Della Carita, Novara, Italy; [8]Policlinico Santa Maria Alle Scotte, Siena, Italy; [9]Azienda Ospedaliera Universitaria Federico II, Naples, Italy*

Background: In patients with arterial hypertension, left ventricular (LV) diastolic function progressively deteriorates with the advance of LV hypertrophy (LVH). However, prevalence of advanced diastolic dysfunction (DD) and its relationship with LVH and longitudinal systolic function is not known. Pulsed Tissue Doppler (TD) imaging may provide useful information on both diastolic function and longitudinal systolic function in patients with hypertension.
Aim: To assess prevalence of patterns of LV geometry and LV longitudinal indices in hypertensive patients with advanced TD-assessed DD enrolled in the SPHERE (multicentre proSPective study of ecHocardiography in hypERtEnsion) project of the Working Group on Echocardiography of the Italian Society of Cardiology.
Methods: An M-mode and two-dimensional echocardiographic study was carried out in 1,294 hypertensive patients enrolled in 15 Italian cardiology centres. All patients had a LV ejection fraction (EF) ≥50% and no history of heart failure or coronary artery disease. They were divided into four groups: (1) HTN-N: normal LV geometry, (2) HTN-CR: concentric remodelling, (3) HTN-EH: eccentric hypertrophy and (4) HTN-CH: concentric hypertrophy. Mitral annular plane systolic excursion (MAPSE) was measured at the septal and lateral sites of the mitral annulus. TD longitudinal velocities were recorded with the sample volume placed at the junction of septal and lateral LV wall with the mitral annulus. Analysis was performed for peak systolic myocardial velocity (Sm) and peak early diastolic velocity (Em). Advanced DD was defined by an the ratio of mitral to myocardial early velocities (E/Em) >15.
Results: Mean LV EF was 63±7%. Forty-seven patients (3.9%) exhibited advanced DD. Among them, prevalence of HTN-CH was 34% followed by HTN-CR (30%), HTN-N (23%) and HTN-EH (13%). LV EF and midwall shortening were not different between patients with or without DD. Systolic indices of LV longitudinal function were more compromised in patients with advanced DD with respect to those without DD (MAPSE at septal site was 12.7±3.3 mm vs 13.9±3.3 mm, p =0.019; MAPSE at lateral site was 14.1±3.0 mm vs 15.2±3.1 mm, p=0.019; Sm at septal site was 7.1±1.3 cm/sec vs 9.8±3.2, p <0.0001, Sm at lateral site was 7.6±1.7 cm/sec vs 10.7±3.9 cm/sec, p <0.0001).
Conclusion: Hypertensive patients with advanced DD exhibited an association between elevated prevalence of LV concentric geometry (hypertrophy or remodeling) and a compromised LV longitudinal function.

1125 Relation between desmin remodeling and cardiac diastolic dysfunction

A. Pawlak[1], E. Czarnowska[2], A.I. Gziut[1], J. Rzezak[1], R.J. Gil[3]. *[1]Central Clinical Hospital MSW i A, Warsaw, Poland; [2]Department of Pathology The Children' Memorial Health Institute, Warsaw, Poland; [3]Institute of Experimental and Clinical Medicine Polish Academy of Science, Warsaw, Poland*

Background: Desmin (DES) as one of major stress-bearing element in the sarcomere and intercalated disc is an important determinant of cardiomyocyte function. However DES disturbances have been noticed in various heart diseases their relation with diastolic function (DD) of left ventricle (LV) is still not clear. Aim: Evaluation of DES expression in cardiomyocytes depending on stage of DD of LV.
Material and methods: Endomyocardial tissue samples of RV wall were obtained from 27 pts (92,6% of males, mean age 45.4±14.1 years). Clinical symptoms of HF and LVEF<45% was observed in 24 pts and ventricular arrhythmia in 4 pts. During Echo examinations (Philips iE33) DD of LV (by parameters: E/A, DT, IVRT, tissue Doppler) were evaluated. Three gr of pts were defined according to DD: (I)-4 pts with normal diastolic function, (II)–18 pts with abnormal relaxation, (III)–4 pts with pseudonormalization. DES expression and localization were investigated in histological section by immunohistochemical method using antibody anti-desmin (DAKO).



Relation between desmin & diastolic dys

Results: Pts with normal diastolic function had a appropriate DES expression (100%).
In cardiomiocytes of pts gr II DES expression was in 15 pts (83%) high and normally localized or in granular form, 2 pts (11%) low in sarcomeres and 1pt (6%) normal. In gr III cardiomyocytes in all pts presented abnormal DES expression (1 (25%) – high in granular form and 3 (75%) abnormally low).
Conclusions: Obtained results suggest abnormalities of DES expression as marker of haemodynamic dysfunction. Abnormal localization and expression of DES in cardiomyocytes carries direct impact on diastolic function of LV. The low expression of DES in cardiomyocytes in immunohistochemical assay is associated with the worst pattern of filing LV-pseudonormalization.

1126 Echocardiographic diagnosis of diastolic dysfunction: E/e is superior to complex algorithms in predicting a clinical impairment in exercise capacity

A. Kockskaemper[1], H. Post[1], S. Kleta[2], R. Wachter[2], L. Binder[2], B. Pieske[1] on behalf of Competence network heart failure. [1]*Medical University of Graz, Graz, Austria;* [2]*University Medicine Göttingen, Göttingen, Germany*

Purpose: Diastolic dysfunction (diaDF) is characterized by elevated left ventricular end-diastolic pressure (LVEDP). To date, there is no standardized procedure for the echocardiographic (echo) diagnosis of diaDF. Recently, a strong correlation between E/e' and LVEDP was demonstrated. Therefore, we evaluated the predictive value of published echo diagnostic schemes compared to E/e' alone with regard to a 6-Minute-Walk-Test (6MWT) and NTproBNP in patients with presumed diaDF.
Methods: Inclusion criteria were at least one cardiovascular risk factor, sinus rhythm and an ejection fraction >50% (n=1038, 44% male, 64.9±0.2yrs). A 6MWT, NTproBNP and echo analysis of systolic and diastolic function (diaF) was assessed. Patients were classified according to 2 published schemes (Abhayaratna et al., Heart 2006:92 (A) and Bursi et al., JAMA 2006:296 (B)) and E/e' (E/e'<8, 8-15, >15) into 3 groups of diaF: Dia0–normal, Dia1–mild, Dia2–moderate/severe DF. Within each classification, values of 6MWT and NTproBNP were compared between the different degrees of diaF (1-way-ANOVA, Tukey's post-hoc Test, *p<0.05 vs Dia0).
Results: According to the schemes of (A) and (B) 10% of patients could not be classified (n.c.). The remaining patients were classified as follows: (A/B): Dia0: 46/40%, Dia1: 18/21%, Dia2: 26/29%. When E/e' was used, all patients were classifiable (Dia0: 40%, Dia1: 52%, Dia2: 8%). Prediction of 6MWT (Fig.1) and NTproBNP by E/e' was superior to the schemes of (A) and (B).

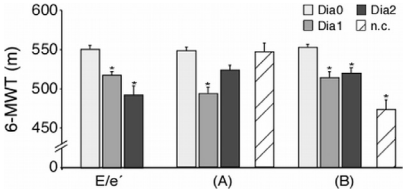


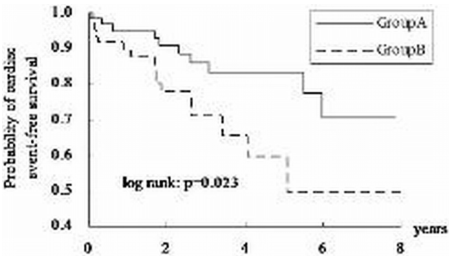
Figure 1

Conclusions: Classification of diaF according to E/e' allows to assign all patients to a group of diaF and has a better predictive value with regard to 6MWT and NTproBNP than more complex diagnostic algorithms. These results suggest that assessment of E/e' alone is sufficient to detect the clinically relevant aspects of diaDF.

1127 Pressure half-time as an independent predictor of prognosis in patients with nonischemic dilated cardiomyopathy

A. Hirashiki[1], H. Izawa[2], T. Okumura[1], K. Ohshima[1], M. Sakakibara[1], H. Funahashi[1], M. Yokota[3], T. Murohara[1]. [1]*Nagoya University Graduate School of Medicine, Nagoya, Japan;* [2]*Fujita Health University, Banbuntanehotokukai Hospital, Nagoya, Japan;* [3]*School of Dentistry, Aichi-Gakuin University, Nagoya, Japan*

Purpose: The purpose of this study was to evaluate left ventricular (LV) isovolumic relaxation in comparison with other parameters as a potential prognostic marker in NDCM patients.
Methods: A total of 165 NDCM patients was evaluated for hemodynamic parameters including measurement of LV pressure by cardiac catheterization. The maximal first derivative of LV pressure and the pressure half-time (T1/2) were determined as indices of contractility and LV isovolumic relaxation, respectively. The patients were followed up for a mean of 5.2 years. The ability of T1/2 to distinguish between cardiac events (hospitalization for heart failure or cardiac death) and noncardiac events was assessed by receiver-operator characteristic (ROC) analysis.
Results: The mean age and LV ejection fraction of the subjects were 50±12 years and 39.6±12.3%, respectively. The area under the ROC curve with respect to cardiac events within 3 years was 0.684 for T1/2. On the basis of this analysis, the patients were divided into two groups, consisting of 84 individuals with a T1/2 of ≤40 ms (group A) and 81 individuals with a T1/2 of >40 ms (group B). Kaplan-Meier analysis revealed that the probability of cardiac event–free survival was significantly higher in group A than in group B (P = 0.023). Stepwise multivariate analysis of hemodynamic parameters revealed that T1/2 was the most significant independent predictor of cardiac events (odds ratio, 1.071; 95% confidence interval, 1.025 to 1.119).



Kaplan-Meire curve of cardiac events

Conclusions: Pressure half-time was a significant independent predictor of cardiac events in patients with NDCM. Impairment of LV isovolumic relaxation might contribute to cardiac events to a greater extent than systolic dysfunction, even in patients with nonischemic systolic dysfunction.

1128 Inhibition of the endogenous proteasome-system impairs cardiac diastolic function

C. Wohlert[1], J. Herrmann[2], D. Loeffler[2], L. Lerman[2], R. Erbel[1], A. Lerman[2]. [1]*Universitaetsklinik Duisburg-Essen, Essen, Germany;* [2]*Mayo Clinic and College of Medicine, Rochester,Mn, United States of America*

Background: Diastolic dysfunction is an important mechanism leading up to heart failure, often attributed to "stiffening of the ventricles" secondary to compositional changes with increase in left ventricular mass. The proteasome fulfills an important role in endogenous protein quality control and prevents the intracellular accumulation of proteins. Hence, proteasome inhibition could lead to compositional changes of the myocardium structure with impairment in diastolic function.
Methods: Three-month-old, female pigs were kept on normal (N, n=5) or atherogenic diet (HC; daily dietary load of 2% cholesterol, 15% lard, n=5) with or without biweekly subcutaneous injection of peptide-boronate type proteasome inhibitor MLN273 at a dose of 0.08 mg/kg (N+PSI, n=5; HC+PSI, n=5).To assure an adequate degree of proteasome inhibition an in-vivo serum-proteasome activity assay was performed. After 11 weeks the in-vivo-EBCT-analysis of cardiac function and structure was accomplished.
Results: As shown in Table 1.

Table 1

Values are mean ± SD	Normal	HC	N+PSI	HC=PSI
Left Ventricular-Ejection fraction [%]	52.74±8.8	55.51±3.97	46.42±11.77	38.38±3.49**/$
Early diastolic filling (E) [ml/s]	154±16.1	143.59±40.85	115.86±19.02	137.71±4.64
Late diastolic filling (A) [ml/s]	85.56±14.0	50.95±10.76**	34.12±7.43**/$	23.36±2.48**/$
E/A-Ratio	1.82±0.1	2.81±0.59**	3.50±0.89**/$	5.95±0.70*
Left Ventricular muscle mass (LVMM) [g]	106±16.4	126.63±15.72	183.07±24.15**/$	171.25±33.85**/$

*p<0.05 vs. all other groups, **p<0.05 vs. N, $p<0.05 vs. HC, $$p<0.05 vs. HC+PSI.

Conclusion: Chronic proteasome inhibition results in an increased left-ventricular mass and a restrictive filling pattern. Hence, the current study supports a role for the endogenous proteasome and related protein quality mechanisms for cardiac structure and function including diastology.

BLOOD, KIDNEY AND THE HEART: NEW LINKS

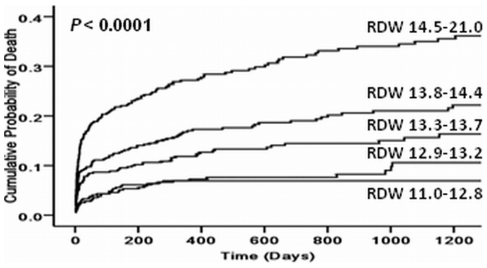
1145 Red blood cell distribution width and mortality after acute myocardial infarction

D. Aronson, M. Kapeliovich, R. Beyar, H. Hammerman, S. Dabbah. *Rambam Health Care Campus, Haifa, Israel*

Background: Increased red blood cell distribution width (RDW), a measure of the variability in size of the circulating erythrocytes, has been shown to be associated with adverse outcomes in patients (pts) with heart failure and with coronary disease. However, there is no information regarding the prognostic significance of RDW in the acute phase of acute myocardial infarction (AMI).
Methods: We performed a post hoc analysis of data from a prospective study. Baseline RDW was measured in 2095 pts admitted with AMI and followed for a median of 19 months. We used Cox proportional hazards models to examine the association between quintiles of RDW and all-cause mortality, adjusting for

the Global Registry of Acute Coronary Events (GRACE) risk score and baseline hemoglobin.

Results: During the follow up period 362 pts died. There was a graded positive association between increased RDW and mortality across quintiles of RDW (Figure). In a Cox model, the adjusted hazard ratios (HRs) of pts with RDW in the 2nd, 3rd, 4th and 5th RDW quintile compared with pts in the 1st quintile were 1.0 [95% CI, 0.6 to 1.7], 1.5 [95% CI, 1.0-2.3], 1.9 [95% CI, 1.2 to 2.9] and 2.7 [95% CI, 1.8 to 4.0], respectively (P for trend < 0.0001). The association between increased RDW and mortality remained highly significant in sensitivity analyses stratified based on anemia (Hb < 12 g/dl in women and Hb < 13 g/dl in men). Compared with pts in the first RDW quintile, the adjusted HRs for death was 3.1 in pts without anemia (95% CI 1.5 to 6.2) and 2.6 in pts with anemia (95% CI 1.6 to 4.2).



Conclusions: There is a graded independent relation between increased RDW and the risk of death in pts with AMI. RDW provides incremental information in pts with and without anemia.

1146 Early stage chronic kidney disease is associated with coronary spastic angina

S. Koga[1], S. Ikeda[1], T. Yasunaga[1], T. Nakata[1], M. Takeno[1], Y. Koide[1], S. Kohno[2], K. Maemura[1]. *[1]Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [2]Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan*

Objectives: Chronic kidney disease (CKD) is associated with the morbidity and mortality of obstructive coronary artery disease through atherosclerotic processes. CKD is also related to endothelial dysfunction, which is considered a proatherosclerotic condition, and a key factor for coronary vasospasm. However, the relationship between CKD and coronary vasospasm has not been elucidated. The aim of this study was to investigate whether CKD is associated with coronary spastic angina (CSA).

Methods: We evaluated 127 patients (mean age 60±12 years) who underwent coronary angiography with intracoronary acetylcholine or ergonovine provocation test. Coronary spastic angina was defined as total or subtotal coronary vasoconstriction with chest pain and ischemic ST segment changes on electrocardiography after provocation that were resolved by an intracoronary injection of isosorbide dinitrate, and the absence of organic coronary stenosis. Kidney function was determined by the estimated glomerular filtration rate (eGFR). An eGFR of < 60 mL/min/1.73m^2 was defined as CKD, and ≥ 90 mL/min/1.73m^2 as a normal eGFR. The relative risk for CSA among confounding factors including age, male gender, hypertension, dyslipidemia, diabetes mellitus, obesity, smoking and eGFR was estimated using logistic regression analysis.

Results: Fifty-three and 74 patients with and without CSA, respectively were recruited from our in-patient clinic. Age and proportion of smokers, hypertension, diabetes mellitus, and obesity did not differ between the two groups. The proportion of male gender and dyslipidemia was higher among the patients with, than without CSA (72 vs. 46%, p = 0.004, and 49 vs. 31%, p = 0.040). Patients with CSA had significantly decreased eGFR (70.4±14.8 vs. 79.2±17.1 mL/min/1.73m^2, p = 0.003), a higher prevalence of CKD (25 vs. 11%, p = 0.040), and a lower proportion of normal eGFR (8 vs. 26%, p = 0.009) than those without CSA. Logistic regression analysis showed that independent risk factors for CSA were male gender (OR, 3.938; 95%CI, 1.725 to 8.988) and eGFR per 10 mL/min/1.73m^2 increase (OR, 0.658; 95%CI, 0.506 to 0.857).

Conclusions: A lower eGFR is associated with an increased prevalence of CSA, suggesting that early stage CKD is related to a relatively initial stage of atherosclerosis. Management for CKD might lower the incidence of CSA.

1147 Effect of anemia in high-risk subgroups of patients with myocardial infarction treated with primary coronary intervention

T. Kurek, R. Lenarczyk, J. Kowalczyk, A. Swiatkowski, O. Kowalski, J. Stabryla-Deska, G. Honisz, A. Lekston, Z. Kalarus, T. Kukulski. *Slaskie Centrum Chorob Serca, Zabrze, Poland*

Background: The significance of anemia in acute myocardial infarction (AMI) patients treated with percutaneous coronary intervention (PCI) remains controversial. The aim of study was to evaluate the impact of anemia on short- and long-term prognosis in patients with AMI treated with PCI, including high-risk subgroups.

Methods and results: The study group consisted of 1497 consecutive patients with AMI treated in acute phase with PCI. Anemia was defined using World Health Organization criteria (hemoglobin level <13g/dL for men and <12g/dL for women). Study population was divided into 2 major groups: patients with anemia (n = 248, 16.6%) and without anemia (n = 1249, 83.4%) and 6 subgroups: diabetic patients, with impaired renal function, aged >70 years, with left ventricular dysfunction, with incomplete revascularization (ICR) and patients with multivessel disease (MVD). Comparative analysis was performed between both groups within the whole population and within particular subgroups. Significantly higher 30-day (13.2% vs. 7.3%), 1-year (20.5% vs. 11.3%) and total mortality rates (24.1% vs.12.7%; all P<0.05) were observed in the anemic group. Multivariate analysis identified anemia as an independent predictor of any-cause death in the whole population during the observation period (covariate-adjusted HR 1.46, ±95% CI 1.31-1.61; P <0.05). Anemia was significantly associated with excessive long-term mortality in MVD group (adjusted HR 1.54, ±95% CI 1.34-1.74) and in ICR group (HR 1.67, both P<0.05).

Conclusion: Anemia on admission in AMI patients treated in acute phase with PCI is independently associated with increasing short- and long-term mortality, especially in subgroups with ICR and MVD.

1148 Impact of anemia and reduced left ventricular ejection fraction on in-hospital outcome of acute coronary syndromes. Euro Heart Survey ACS III registry (2006-2008)

W. Wojakowski[1], M. Tendera[1], M. Tubaro[2], M. Gierlotka[3], H. Bueno[4], B. Lindahl[5], M. Hochadel[6], Y. Hasin[7], J.P. Bassand[8], A.K. Gitt[6]. *[1]Slaski Uniwersytet Medyczny w Katowicach, Katowice, Poland; [2]Ospedale San Filippo Neri, Rome, Italy; [3]Slaskie Centrum Chorob Serca, Zabrze, Poland; [4]Hospital General Universitario Gregorio Maranon, Madrid, Spain; [5]Uppsala University Hospital, Uppsala, Sweden; [6]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [7]Poria Medical Center, Tiberias, Israel; [8]CHU de Besancon - Hopital Jean Minjoz, Besancon, France*

Aim: Aim of the study was to examine the impact of anemia and reduced left ventricular ejection fraction (LVEF) on in-hospital outcome of patients with acute coronary syndromes (ACS).

Methods: Euro Heart Survey on Acute Coronary Syndromes included 21872 patients (66.6% males) admitted across Europe in 2006-2008 with ACS [35.1% NSTEMI, 24.4% unstable angina, 40.5% STEMI/LBBB MI].

Results: LVEF was normal in 51.7% pts, moderately reduced (31-50%) in 40.4%, severely (≤30%) reduced in 7.9% of pts. Anemia (Hb <14 g/dL in males, <12 g/dL in females) was diagnosed in 2462 (19.2%) pts. Patients with reduced LVEF and anemia had higher prevalence of co-morbidities (diabetes, chronic renal failure, history of stroke, myocardial infarction and revascularization) in comparison to patients with normal LVEF and no anemia.

Patients with anemia were more frequently taking aspirin (40.1-42.5% vs. 28.6-31.9%, p<0.01), clopidogrel (12.1-15.1 vs. 6.6-7.1%, p<0.01), oral anticoagulants (4.9-9 vs. 2.8%, p<0.01) and ACEI/ARB (45-46.6 vs. 33.7-35.2%, p<0.01) prior to hospitalization than patients without anemia. Patients with anemia were less frequently discharged on aspirin (90.2-91.6% vs. 94.7-95.5%, p<0.01) and clopidogrel (62.9-66.5 vs. 71-75%, P<0.01).

Outcome	Normal LVEF		Reduced LVEF		P-value*
	No anemia	Anemia	No anemia	Anemia	
Mild heart failure (%)	6.2	10.6	17.3	23.7	<0.01
Pulmonary oedema (%)	0.6	2.3	4.6	9.7	<0.01
Cardiogenic shock (%)	0.5	0.6	4.3	7.4	<0.01
Bleeding (%)	3.4	7.2	5.1	9	<0.01
Major bleeding (%)	2.5	3.1	3.3	4.8	<0.01
Reinfarction (%)	1.2	1.4	2.1	3.0	<0.01
Stroke (%)	0.4	0.2	0.8	1.3	<0.01
In-hospital mortality (%)	0.7	0.6	4.8	7.7	<0.01

*χ^2 or Kruskal-Wallis.

Conclusion: Approximately 48% of patients with ACS have reduced LVEF and 20% present with anemia. Presence of reduced LVEF and anemia confers particularly high risk of MACE and in-hospital mortality.

1149 Estimation of renal function in acute coronary syndromes: MDRD or Cockcroft-Gault?

S. Nabais, A. Gaspar, S. Rocha, S. Ribeiro, P. Azevedo, J. Costa, M. Alvares Pereira, A. Correia. *Sao Marcos Hospital, Braga, Portugal*

Background: Renal function is an important predictor of adverse events in patients (pts) with acute coronary syndromes (ACS), and can be estimated by Cockcroft-Gault (C-G) and Modification of Diet in Renal Disease (MDRD) equations. This study aimed to determine which equation better predicts mortality in ACS pts.

Methods: We analyzed 1985 pts with an ACS consecutively admitted to a Coronary Care Unit over 5 years. Admission creatinine was used to estimate glomerular filtration rate (GFR, ml/min), and pts were classified as having no/mild

(GFR≥60), moderate (GFR 30-59), or severe (GFR<30) renal dysfunction (RD) using the 2 equations.
Results: There was a good correlation between C-G and MDRD estimates of GFR (r=0.87, p<0.0001), although the C-G formula calculated a lower median (interquartile range [IQR]) GFR (83.1 [57.6, 110.7] vs. 86.1 [64.0, 105.2] ml/min). When classifying pts into the 3 different GFR categories using the 2 equations, agreement was 86% (Table). Six-month mortality was similar in the 2 renal function classifications: 39.6% (C-G) vs 37.3% (MDRD) for GFR <30 ml/min (p=0.8); 19.9% (C-G) vs 23.6% (MDRD) for GFR 30-59 ml/min (p=0.2); 5.0% (C-G) vs 6.0% (MDRD) for GFR ≥60 ml/min (p=0.3). Among pts with "moderate RD agreement by C-G and MDRD" (n=258), "moderate RD by MDRD only" (n=46), and "moderate RD by C-G only" (n=175), 6-month mortality was 22.6%, 13.3%, and 15.2% (p>0.05 for all comparisons), and in-hospital TIMI major bleeding occurred in 4.7%, 0.0% and 2.1% of pts (p>0.05), respectively. The area under the receiver operator characteristic curve was significantly larger for predicting 6-month mortality with the C-G equation (0.78 [0.76-0.80] vs 0.76 [0.74-0.78]; p=0.002); both were superior to creatinine alone (0.72 [0.70-0.74]; p<0.001 for both C-G and MDRD).

Agreement between C-G and MDRD equations

GFR (MDRD), ml/min/1.73m^2	C-G, ml/min			
	<30 (n=104)	30-59 (n=442)	≥60 (n=1439)	All (n=1985)
<30 (n=69)	60 (3.0%)	9 (0.5%)	0 (0.0%)	69 (3.5%)
30-59 (n=347)	43 (2.2%)	258 (13.0%)	46 (2.3%)	347 (17.5%)
≥60 (n=1569)	1 (0.1%)	175 (8.8%)	1393 (70.2%)	1569 (79.0%)
All (n=1985)	104 (5.2%)	442 (22.3%)	1439 (72.5%)	

Conclusions: The C-G equation is slightly superior to the MDRD equation for predicting 6-month mortality in ACS pts, although differences between equations are minor.

1150 Glucose and creatinine as risk factors in patients with acute myocardial infarction: importance and interactions

M.D. Andrade, J.C. Nicolau, L.M. Baracioli, R.R.C.V. Giraldez, C.V. Serrano, R.C. Moraes, F.G. Lima, M. Franken, K.D. Rosa, C.C.F. Fernades. *Heart Institute (InCor) - University of Sao Paulo Medical School, Sao Paulo, Brazil*

Purpose: Baseline hyperglycemia and high creatinine are both important risk factors for mortality in acute myocardial infarction (MI). However, the relationship between them is poorly studied.
Methods: We analyzed 1451 patients (median age 64 y.o., 72.7% males) with MI included prospectively in a dedicated databank. The role of glucose and creatinine levels as risk factors for mortality, and the correlation between both variables, were evaluated initially by univariate analyses. Sequentially, 2 multivariable regression models were developed, respectively with in-hospital mortality and creatinine levels as dependent variables. In both models, the results were adjusted for 13 baseline variables as age, gender, history of heart failure or diabetes, ST-elevation or non-ST-elevation MI, and heart rate.
Results: 1) The mean ± SD values for patients that died or survived the in-hospital phase were as follows: for glucose, 169.6±96.3 mg/dL vs. 136.8±67.4 mg/dL (P<0.001); for creatinine, 1.67±1.19 mg/dL vs. 1.31±0.48 mg/dL (P<0.001). 2) The correlation between glucose and creatnine levels was significant, with a P-value of 0.002; 3) In the adjusted models, the following variables correlated significantly and independently with in-hospital mortality: age (t-value=7.37, P<0.001], creatinine (t-value=5.38, P<0.001), glucose (t-value=4.1, P<0.001), history of heart failure (t-value=2.88, P=0.004), and ST-elevation MI (t-value=2.04, P=0.041); on the other hand, the following variables correlated significantly and independently with creatinine levels: age (t-value=7.15, P<0.001), male gender (t-value=7.03, P<0.001), history of heart failure (t-value=4.56, P<0.001) and arterial hypertension (t-value=2.74, P=0.006), glucose (t-value=2.77, P=0.006) and heart rate (t-value=1.97, P=0.049). History of diabetes correlated significantly with creatinine levels only in univariate analysis, but not in the adjusted model.
Conclusion: Higher levels of glucose and/or creatinine are associated with worse prognosis in MI patients and, at the same time, the levels of both variables are significantly correlated with each other. Different mechanisms could be involved in this relationship, and should be tested in future studies.

INFLAMMATION AND MICROVASCULAR DAMAGE: FROM CELLS TO HUMANS

1151 Genetic loci influencing C-reactive protein levels and risk of coronary heart disease: a Mendelian Randomisation experiment in 130,000 people

J.C. Chambers, P. Elliot, J. Sehmi, J.S. Kooner on behalf of The Genetics of CRP and CHD Investigators. *Imperial College London, London, United Kingdom*

Background: Plasma levels of C-reactive protein (CRP) are independently associated with risk of coronary heart disease (CHD). Whether the relationship of CRP with CHD is causal, or whether CRP is simply an "innocent bystander" of the inflammatory disease process, is unknown.
Methods: We first carried out a genome-wide association (n=17,967) and replication study (n=14,747) to identify genetic loci associated with plasma CRP concentrations. At each locus, we selected the most closely associated ('top-ranking') SNP for testing against CHD among 14,377 CHD cases and 32,069 controls. For the CRP locus, we then carried out a Mendelian randomisation experiment and meta-analysis with published studies, providing data for 28, 421 cases and 101,173 controls. We compared the size of effect with that predicted from an updated meta-analysis of the epidemiologic data on the CRP-CHD association.
Results: Genetic variants in the CRP, LEPR, IL6R, HNF1A and APOE-CI-CII loci were strongly associated with differences in CRP levels. There was no association between rs7553007 and other variants in the CRP locus with CHD risk. Overall, our Mendelian randomisation study meta-analysis of the association of variants in the CRP locus and CHD gave OR 1.00 (95% CI 0.97 to 1.02). This compares with predicted association from the epidemiologic studies of OR 0.95 (0.95 to 0.96, P<0.001) per 20% lower CRP. Polymorphisms in LEPR (rs6700896), IL6R (rs4537545) and APOE-CI-CII (rs4420638) were associated with risk of CHD (P<0.002 and P<0.001).
Conclusions: We found no association of variants in the CRP locus and CHD, arguing against an important causal role for CRP in atherosclerosis. We identify LEPR and IL6R as putative new susceptibility loci for CHD.

1152 Toll-Like Receptor-4 (TLR-4) and Monocyte Chemoattractant Protein-1 (MCP-1) play a key role in myocardial remodelling after acute myocardial infarction

G. Vilahur, X. Duran, L. Badimon. *Barcelona Cardiovascular Research Center, CSIC-ICCC, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Purpose: Myocardial infarction is associated with an acute inflammatory response, a key element on cardiac remodelling. However, the understanding of the inflammatory pathways triggered upon reperfusion is limited and controversial. We sought to evaluate the effects of flow restoration on myocardial death and inflammatory cardiac-related mechanisms over time.
Methods: Pigs (N=36) were subjected to a closed-chest 90 min mid-LAD occlusive balloon inflation followed by 2.5h, 1, 3, 6, and 21 days post-reperfusion (R). At sacrifice, tissue from ischemic myocardium was obtained for molecular analysis of: 1) the toll-like receptor (TLR)-4, its downstream transcription factor NF-kB (involved in inflammatory and death-related responses) and pro-inflammatory cytokine IL-6; 2) MCP-1, Cox-2, and modified-CRP expression; and, 3) pro-apoptotic Bax and truncated-caspase-3. Histopathological assessment of the inflammatory infiltrate was also performed. Cardiac function (LVEF by echocardiography), infarct size (necrotic area), and Tn-I and CKMB/CK levels were also evaluated.
Results: Reperfusion acutely induces genes of the TLR-4 pathway in the heart (i.e., TLR-4, NF-kB, and IL-6). However, whereas TLR-4 remains high up to 21 days post-R, NF-kB and IL-6 returns to basal values at day 1. Reperfusion also stimulates cardiac MCP-1 and cox-2 expression. Cox-2 returns to basal values at day-1 whereas MCP-1 declines gradually and reaches a basal plateau 21 days post-R. Accordingly, the inflammatory infiltrate reaches a 30-fold increase 6-days post-R and no inflammatory infiltrate is detected 21-days post-R. In the ischemic region, modified-CRP protein expression is already highly detected during ischemia and remains high up to day 3. LVEF was consistently reduced 90-min after AMI in all animals (74%±2% vs 46%±3%; p<0.05 vs. basal) but gradually improves at 21 days (6-8% absolute improvement; p<0.05 vs post-AMI). Necrotic cell death, Tn-I, and CKMB/total CK reach a peak 1 day post-R (34% LV) and gradually reduces 3 days post-R (6% absolute decrease vs. day-1) whereas Bax and truncated-caspase-3 remain high up to 6-days post-R.
Conclusions: Reperfusion triggers a cardiac inflammatory response that progresses up to one-week after MI and likely enhances cardiomyocyte apoptosis. In addition, immune inflammatory response through the cardiac receptor TLR-4 contributes to post-infarct cardiac remodelling.

1153 C-reactive protein inhibits endothelial cell migration via upregulation of pten

S. Goetze, C. Schneeweiss, M. Roser. *Deutsches Herzzentrum Berlin, Berlin, Germany*

C-reactive protein (CRP) is a pluripotent mediator of inflammation and is present at sites of vascular injury and in atherosclerotic lesions. CRP stimulates endothelial cell adhesion molecule expression and monocyte migration, thereby contributing to the development and progression of vascular lesion formation. In addition, chronic exposure to CRP is known to inhibit endothelial cell (EC) migration, however, the cellular mechanisms involved are not completely understood. To elucidate the chemotactic signaling pathways that are affected, migration experiments were performed using a transwell chamber migration assay. VEGF (20 ng/ml, 5 h incubation)-induced migration of human umbilical vein EC was significantly inhibited in cells that were pretreated with CRP (10 ug/ml) for 24 h (92% inhibition vs control, p<0.05). EC migration in response to VEGF is known to require

activation of the Akt/eNOS- and the ERK1/2 pathway. We therefore investigated the longterm effects of CRP on these signaling events. Immunoblotting with phosphospecific antibodies revealed a rapid and transient activation/phosphorylation of the protein kinase Akt within 20 minutes after stimulation with VEGF, that was inhibited by 86% in EC that were pretreated with CRP (10 mg/dl, 24 h, $p<0.05$). Also, VEGF-induced phosphorylation of eNOS downstream of Akt was significantly inhibited in CRP-treated EC. In contrast, CRP-pretreatment did not affect VEGF-induced phosphorylation of ERK1/2. Interestingly, stimulation of EC with CRP for 16-24 h induced the prominent expression of the lipid phosphatase PTEN (max. 3.4-fold at 24 h; $p<0.05$), which functions as a negative regulator of PI3K–>Akt signaling. The observed time course for CRP-mediated PTEN upregulation corresponds to the exposure time needed for inhibition of Akt-phosphorylation and migration and may therefore constitute a potential mechanism by which CRP inhibits inducible Akt phosphorylation and EC migration.

1154 Improved ventricular remodeling after acute myocardial infarction in transgenic mice lacking the IL-1 receptor type I

A. Abbate, F. Salloum, L. Smithson, A. Varma, I. Seropian, N.N. Hoke, V. Chau, B.W. Van Tassell. *Virginia Commonwealth University, Richmond, United States of America*

Purpose: Healing after acute myocardial infarction (AMI) and cardiac remodeling after AMI are characterized by an intense inflammatory response within the myocardium. Interleukin-1β (IL-1β) is a potent pro-inflammatory mediator with local and systemic effects. The current study examines the characteristics of post-AMI cardiac remodeling in genetically engineered mice lacking the gene encoding for the IL-1 type I receptor, the only signaling membrane receptor for IL-1β (IL-1R1-/- mice).

Methods: Four IL-1R1-/- mice 6 age-matched wild-type (WT) mice with the same genetic background underwent surgical coronary artery ligation, and were allowed to recover for 7 days. Three additional IL-1R1-/- mice and WT mice underwent sham operation. All animals underwent transthoracic echocardiography before surgery and at day 7. Cardiomyocyte apoptosis were measured using detection of DNA fragmentation (Apoptag).

Results: At baseline, IL-1R1-/- mice had smaller body weight than WT (23±2 vs 29±3, $P<0.001$), but similar cardiac dimensions and function. Seven days after AMI, IL-1R1-/-mice showed a more favorable cardiac remodeling pattern characterized by smaller end-diastolic and end-systolic diameters (EDD and ESD, respectively), and a significantly greater fractional shortening vs WT mice [Figure 1]. An average of 4 aneurysmatic segments were seen in the IL-1R1-/- mice vs 2 segment in the WT mouse (p=0.031). IL-1R1-/- mice also had a significantly lower rate of cardiomyocyte apoptosis in the peri-infarct myocardium compared to WT mice (0.1±0% vs 0.7±0.3%, p0.05).

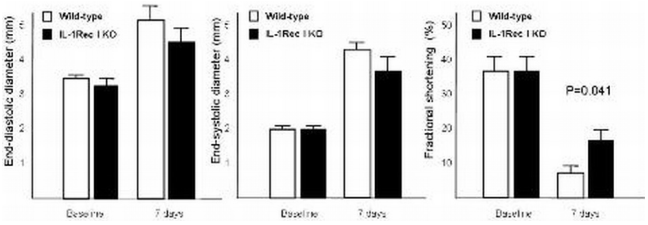


Figure 1

Conclusion: The study shows that lack of IL-1 signaling post-AMI is associated with a more favorable remodeling. This sets the stage for studies testing IL-1 blocking therapeutics in AMI in order to prevent heart failure.

1155 Levels of endothelial progenitor cells are increased in thrombectomy-aspirated blood of ST-elevation myocardial infarction patients and correlate with microvascular damage

I. Porto[1], G.L. De Maria[1], L.M. Biasucci[1], L. Di Vito[1], A.M. Leone[1], A. Tritarelli[1], G. Di Rocco[1], A. Paglia[1], M.C. Capogrossi[2], F. Crea[1]. *[1]Catholic University of the Sacred Heart, Rome, Italy; [2]Istituto Dermopatico dell'Immacolata, Rome, Italy*

Purpose: Endothelial progenitor cells (EPCs) are bone marrow derived elements mobilized by ischemic stimuli involved in the repair processes after myocardial infarction. We assessed whether a difference in levels of EPCs can be detected between intracoronary and peripheral blood soon after the onset of ST elevation myocardial infarction (STEMI). Wealso assessed the correlation of EPCs with angiographic indexes of revascularisation

Methods: Twenty four STEMI patients undergoing primary percutaneous coronary intervention (pPCI) were included. Aortic blood samples from the guiding catheter and intracoronary, translesional blood aspirate from thrombectomy device were sequentially drawn at the beginning of pPCI to measure EPCs (CD34+/KDR+/CD45-) by flow cytometry. Haematocrit (HTC) and white blood cells count (WBC) were measured both in intracoronary and peripheral blood. TIMI flow grade, corrected TIMI frame count (cTFC), and Myocardial Blush Grade (MBG) were measured after PCI to assess revascularisation efficacy.

Results: EPCs levels (expressed as %, number of cells per total number of cytometric events) were higher in intracoronary 0.08% (0.05-0.19 IQR, $p<0.001$) than in peripheral blood 0.02% (0.01-0.06 IQR). Intracoronary and peripheral blood did not differ both in terms of Htc (42% IQR 33-43 vs 39% IQR 33-41, p=0.7) and WBC (11260 IQR 10615-13765 vs 11170 IQR 10270-12760, p=0.7), confirming the existence of a true intracoronary-peripheral EPCs gradient. Only intracoronary EPCs levels were related to revascularisation index, resulting higher in MBG0/1 class 0.07% (0.04-0.17 IQR, overall ANOVA p=0.05, p=0.01 for linear trend) than in MBG2 class 0.06% (0.04-0.16 p=ns) and MBG3 class 0.05% (0.02-0.16, p=0.05). No correlation were found with other revascularisation indexes.

Conclusions: Our data show that a rapid intracoronary EPCs recruitment takes place in the earlier phases after STEMI onset. This recruitment is inversely related to post-PCI MBG suggesting that EPC are recruited in the culprit artery in attempt to overcome ongoing microvascular dysfunction.

1156 Myocardial ischemia/reperfusion injury in murine cardiac allografts: Erythropoietin inhibits leukocyte adhesion without affecting coronary microcirculatory dysfunction

R. Schramm, S. Kirsch, H.J. Schaefers, Y. Harder, M.D. Menger. *Universitaetsklinikum der Saarlandes, Homburg, Germany*

This study was meant to analyze the effect of erythropoietin (Epo) on microcirculatory dysfunction and inflammation in murine cardiac allografts.

Balb C mouse hearts were transplanted into C57BL/6 mice after 3-hour cold ischemia. Epo was given i.p. in recipients at 2 hours before reperfusion (n=6), while controls received saline only (n=6). The subepicardial microcirculation was assessed by intravital fluorescence microscopy (IVM) at 1, 3 and 6 hours of reperfusion.

In controls, subepicardial capillary blood flow velocities and functional capillary densities (FCD) decreased during reperfusion from 0.34±0.04 mm/s and 351±73 cm/cm^2 to 0.30±0.01 mm/s and 239±41 cm/cm^2, however not significantly. Capillary diameters and venular blood flow characteristics showed no significant changes over time, ranging between 4.5 and 5.5 μm as well as 0.76 and 0.96 mm/s. Epo-treatment had no effect on coronary microhemodynamics. Postischemic inflammation was characterized by augmented microvascular leakage ranging between 71 and 99% throughout the entire observation period. This was comparable between controls and Epo-treated mice. During reperfusion, control allografts showed decreasing numbers of rolling leukocytes and increasing numbers of firmly attached leukocytes from 64±16 cells/min and 238±84 cells/mm^2 to 19±16 cells/min and 479±154 cells/mm^2 ($P>0.05$). Capillary leukocyte plugging remained stationary over time in controls with 5.7±0.4 cells/HPF at 1h and 5.0±0.5 cells/HPF at 6h of reperfusion. Epo-treatment did not alter leukocyte rolling interactions. In contrast, firm leukocyte arrest in postcapillary venules was inhibited by Epo-treatment, resulting in 84±34 cells/mm^2 at 6h of reperfusion ($P<0.05$). Epo-treatment also reduced capillary leukocyte plugging to 3.6±0.3, 2.6±0.3 and 3.0±1.3 cells/HPF at 1, 3 and 6h of reperfusion ($P<0.05$). Rejection was not affected by erythropoietin. These are the first data on microcirculatory dysfunction and inflammation in murine cardiac allografts assessed by IVM. We demonstrate that non-hematopoietic treatment with Epo exerts anti-inflammatory effects, reducing leukocyte-coronary endothelium adhesive interactions, without affecting microhemodynamics.

CLINICAL AND GENETIC MARKERS IN CARDIOMYOPATHIES

1208 Long-term outcome of patients with end-stage idiopathic dilated cardiomyopathy and evidence for autoantibodies against beta-1 adrenoceptors after immunoglobulin adsorbtion therapy

M. Dandel[1], G. Wallukat[2], H.B. Lehmkuhl[1], A. Englert[1], R. Hetzer[1]. *[1]Deutsches Herzzentrum Berlin, Berlin, Germany; [2]Max-Delbrueck-Centrum fuer Molekulare Medizin, Berlin, Germany*

Background: After our promising results obtained in the late 1990s in a prospective study, which showed that for idiopathic dilated cardiomyopathy (IDCM) associated with serum autoantibodies against β1-adrenoceptors (β1-AABs), immunoadsorbtion (IMA) is superior to standard medical therapy we continued to use IMA for IDCM treatment. Now, after > 13 years of experience we assessed the safety and long-term efficacy of IMA in IDCM patients referred for heart transplantation (HTx).

Methods: To provide a follow-up of ≥ 5 years, we evaluated only patients with end-stage IDCM (LVEF < 30%) associated with evidence of β1-AABs (> 3.0 laboratory units) who underwent IMA for AAB removal before 5/2003. IMA, performed on 5 consecutive days, was accompanied by close monitoring of serum IgG and β1-AAB levels. For unselective IMA we used columns with polyclonal anti-human immunoglobulin antibodies produced in sheep. Specific IMA (selective β1-AABs removal) was performed on peptide-columns.

Results: A total of 104 IDCM patients fulfilled the criteria for evaluation. IMA was well tolerated by all patients without any complication. Unselective IMA was performed in 88 patients between 5/1995-5/2003. Survival without HTx or the necessity of ventricular assist device (VAD) implantation was reached at 3 years and 5 years by 77.3% and 69.3% of these patients, respectively. Of t 88 patients, 69 (78.4%) showed 6 months after IMA significant ($p<0.01$) decrease in LV diameters and improvement of LVEF (increase from 23.6±5% to 30.7±7%). Of 54 patients who underwent unselective IMA ≥10 years ago, 27 (50%) survived for ≥8 years without HTx or VADs and 4 patients have already reached 13 years of cardiac stability after IMA. Selective β1-AAB removal by specific IMA was performed between 8/2000-5/2003in 16 patients. Of these, 9 (56.3%) showed lower LV diameters and improvement of LVEF (from 23.5±5% to 31.8±6%), at the f6 months ollow-up echo-check ($p < 0.05$). At 5 years after specific IMA, 81.3% survived without HTx or VAD implantation. Stable cardiac improvement for ≥5 years after IMA appeared not related to patients' age, duration of disease or differences in LV size and LVEF. Early reappearance of β1-AABs after IMA was shown in 9 (8.6%) of 104 patients and were always associated with cardiac worsening.
Conclusions: In a high proportion of IDCM patients with severe LV dysfunction, the use of IMA allows evident and long-term stable improvement of cardiac function which can delay patients' listing for HTx for many years. Removal of β1-AABs by unselective IMA showed no therapeutic disadvantages in comparison to selective β1-AAB removal.

1209 Genotype-fenotype correlation in ARVC patients carrying a causative mutation of the different disease genes encoding for desmosome components

I. Rigato[1], B. Bauce[2], A. Rampazzo[3], A.K. Steriotis[1], E. Mazzotti[1], C. Basso[1], G.A. Danieli[3], G. Thiene[1], A. Nava[2]. [1]*Department of Medico- Diagnostic Sciences and Special Therapies, Padua, Italy;* [2]*Department of Cardio-Thoracic and Vascular Sciences, University of Padua, Padua, Italy;* [3]*Department of Biology, University of Padua, Padua, Italy*

Background: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited disorder characterized by fibrofatty replacement of cardiomyocites. Autosomal dominant pattern of inheritance and variable penetrance is proven, although recessive forms exist. Disease-causing mutations have been identified in genes encoding for components of the desmosome. Available genotype-phenotype correlation studies analysed the phenotypic features associated with mutations of a single disease-gene.
Purpose: we sought to provide a detailed analysis of the genotype-phenotype correlation in subjects carrying a causative mutation of the different disease-genes encoding for desmosome components (Plakophillin2-PKP2, Desmoglein2-DSG2, Desmoplakin-DSP, Multiple mutations-MM).
Methods: a total of 38 families (257 patients-128 women and 129 men- mean age at first evaluation 35±18 years) affected by ARVC and in whom mutations of a known ARVC-gene has been identified were analysed. The study population was divided into 4 groups according to the disease-gene. The instrumental and clinical features detected at first and at last examination were compared. Clinical evaluation included a detailed personal and family history, 12- lead ECG, signal-averaged ECG, two-dimensional echocardiography, 24-hour ambulatory ECG monitoring. In selected cases a cardiac magnetic resonance with gadolinium injection was performed.
Results: a total of 170 patients were found to carry a mutation in a desmosomal gene (DSP=59, PKP2= 46, DGS2=37,MM=22). A total of 48% of patients fulfilled the ARVC diagnostic criteria (M/F 2,8/1). Analysis of clinical and instrumental data showed a greater extent of the disease in PKP2 and MM groups, defined as larger right ventricular dimensions and more frequent left ventricular involvement. During follow- up patients carrying a DSP mutation showed a greater progression of the disease, with particular regard to the left ventricle. Nonetheless, survival analysis didn't show a significant difference of major events among patients carrying distinct genes mutations.
Conclusions: patients affected by ARVC seem to be characterized by gene-specific clinical features, with particular regard to right ventricular dilatation and left ventricular involvement. Nevertheless the prognosis is not different among mutation carriers of different genes. Thus the genetic characterization does not appear to have a role on therapeutic strategy and patients risk stratification. Finally, the wide spectrum of clinical expression in subjects carrying the same mutation suggests a possible role of modulating factors.

1210 Noncompaction Cardiomyopathy; mutation spectrum, distribution of disease genes and implications for diagnostic strategies

Y.M. Hoedemaekers[1], K. Caliskan[2], M. Van Tienhoven[1], M. Michels[2], F.J. Ten Cate[2], D.F. Majoor Krakauer[1], D. Dooijes[1]. [1]*Erasmus MC Dept. of Clinical Genetics, Rotterdam, Netherlands;* [2]*Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Background: Noncompaction cardiomyopathy (NCCM) is characterised by an excessively thickened endocardial layer with deep intertrabecular recesses. Cardiac symptoms include heart failure, lethal arrhythmias and/or thrombo-embolic complications. NCCM is genetically heterogeneous, predominantly autosomal dominantly inherited. To contribute to a genetic classification 17 different genes associated with cardiomyopathy were completely analysed in a cohort of 56 NCCM patients.
Methods: DNA analysis of the genes β-Myosin Heavy Chain (MYH7), Myosin Binding Protein C (MYBPC3), cardiac Troponin C (TNNC1), Troponin T (TNNT2) Troponin I (TNNI3) and α-Actin (ACTC1), cardiac-regulatory Myosin Light Chain (MYL2), cardiac-essential Myosin Light Chain (MYL3), α-Tropomyosin (TPM1), Cypher/Zasp (LDB3), Cysteine- and Glycine-rich Protein (CSRP3), Theletonin (TCAP), Calsequestrin (CASQ2), Calreticulin (CALR3), Phospholamban (PLN), Taffazin (TAZ) and Lamin A/C (LMNA) was performed.
Results: Twenty-nine mutations were identified in the genes MYH7 (11), MYBPC3 (4), TNNT2 (3), TNNI3 (1), TPM1 (2), ACTC1 (1), CASQ2 (2), PLN (1), TAZ (1), LDB3 (2) and LMNA (1) in 23 probands (41%). Eighteen probands had a single mutation, four had two and one had three mutations.
Conclusion: We identified the MYBPC3, TNNI3, TPM1, PLN and CASQ2 genes as new NCCM genes. PLN and CASQ2 are the first Calcium-handling genes to be associated with NCCM. In 41% of the NCCM patients we found a mutation in sarcomere, Z-disc, Calcium-handling or other cardiomyopathy genes. This warrants molecular analysis of these genes in NCCM. The identification of the genetic cause for cardiomyopathy facilitates family study and allows accurate identification of relatives at risk of developing cardiomyopathy. Genetically, NCCM is part of a continuous pathophysiological spectrum including hypertrophic, dilated and restrictive cardiomyopathy.

1211 Late gadolinium-enhanced CMR predicts atrial fibrillation in hypertrophic cardiomyopathy: Implications for a new proposed risk scale

F. Marin Ortuno[1], A. Garcia-Honrubia[2], X. Fernandez[3], M.J. Oliva[1], J. Gonzalez[1], V. Climent[2], G. De La Morena[1], R. Soler[3], M. Valdes[1], L. Monserrat[3]. [1]*Hospital Universitario Virgen de la Arrixaca, Murcia, Murcia, Spain;* [2]*Hospital General Universitario de Alicante, Alicante, Spain;* [3]*Instituto Universitario de Ciencias de la Salud, A Coruna, Spain*

Hypertrophic cardiomyopathy (HCM) is characterised by myocardial hypertrophy, myocyte disarray and interstitial remodelling; increased myocardial collagen can be non-invasively assessed by late gadolinium-enhancement (LGE) using CMR imaging. Few studies have focussed on identifying the predictors of AF development in HCM. Importantly, the prognosis is poor amongst these patients with an increased risk for heart failure, stroke/thromboembolism and life-threatening arrhythmias. Thus, the detection of patients at high risk for developing AF may be extremely useful in proposing preventive measures and treatment strategies. Given that interstitial fibrosis is one of the most important underlying mechanisms in the development of atrial fibrillation (AF), the aim of the present study was to assess the prognostic implications of LGE in AF development in a cohort of patients with HCM. Indeed, it has been demonstrated, LV fibrosis is more severe in patients with HCM and AF. Additionally, we propose a risk scale for predicting AF development.
Methods: Two hundred and forty-four patients (50.5±14.9 years; 169 males) with HCM in sinus rhythm were included. Peripheral bolus injection of Gadolinium-DTPA (0.2mmol/kg) was administered and late contrast-enhanced images were acquired using a segmented inversion-recovery sequence. A complete follow-up was performed in all patients (789±456 days).
Results: 142 patients (58.2%) showed LGE. During follow-up, 35 patients (14.3%) developed AF. In the univariate Cox analysis, AF development was associated with LGE (mild HR 3.79, 95%CI:1.12-12.85; p=0.032 and severe enhancement HR 4.77, 95%CI:1.57-14.48; p=0.006) On a multivariate Cox analysis, AF development was associated with previous AF (HR 9.08, 95%CI:3.41-24.17; $p<0.001$), presence of obstruction (HR 2.46, 95% CI:1.02-5.92; p=0.043), enlarged left atrial diameter (HR 2.32, 95%CI:1.08-4.96; p=0.031) and LGE (mild HR 3.79, 95%CI:1.12-12.85; p=0.032 and severe HR 4.77, 95%CI:1.57-14.48; p=0.006). Using these four variables, giving 1 point to enlarged left atrial diameter, 1 point to presence of obstruction, 2 points to mild LGE, 3 to severe LGE, and 4 points to previous AF, we constructed a risk scale for predicting AF. This proposed risk scale was associated with the development of AF on multivariate analysis (log rank test $p< 0.001$).
Conclusions: LGE is independently associated with AF development, even after adjusting by different confounding variables. A more extensive LGE increases the risk of AF. We proposed a novel simple risk scale for identifying HCM patients at risk of developing AF.

1212 Prevalence of double or compound heterozigosity in a consecutive series of genotyped patients with hypertrophic cardiomyopathy

M. Tagliani, M. Pasotti, A. Serio, F.I. Gambarin, M. Grasso, N. Marziliano, A. Pilotto, S. Ghio, L. Scelsi, E. Arbustini. *IRCCS Fondazione Policlinico San Matteo, Pavia, Italy*

Background: Hypertrophic cardiomyopathy (HCM) is a primary disease of the sarcomere, with considerable genetic heterogeneity and variability in phenotypic expression. The prevalence of double or compound heterozigosity is currently matter of controversy. Phenocopies clinically mimic HCM.
Purpose: we aimed at determining the prevalence of double or compound heterozigosity in a consecutive series of genotyped patients diagnosed with HCM.

Methods: The clinical series consists of 149 unrelated probands diagnosed with HCM and 244 genotyped relatives. HCM was diagnosed according to the WHO criteria. Both probands and relatives underwent genetic testing after genetic counselling and written consent. MYH7, MYBPC3, TNNT2, TNNI3, tCAP, MYL2, TPM1, MYH6, MYL3, MYO6, and MYOZ2 were routinely screened while LAMP2, PRKAG2 and mtDNA were screened in the presence of specific clinical markers or family data. Provisional mutations are not included. Patients with Anderson-Fabry disease were excluded.
Results: Of 393 genotyped individuals, 283 were affected and 110 healthy carriers. The mean age of affected members was significantly higher compared to those of the healthy carriers (34.4±16.3 versus 27.4±15.2 years, p=0.003). The molecular genetic analysis identified a pathologic mutation in one of the following disease genes: MYH7 (n=102, 27%), MYBPC3 (n=179, 45%), TNNT2 (n=25, 6%), TNNI3 (n=22, 6%), LAMP2 (n=3, 0.5%), PRKAG2 (n=3, 0.5%), tCAP (n=8, 2%), MYOZ2 (n=2, 1%), mtDNA (n=16, 4%). Moreover, 33 patients (8%) carried a compound or double heterozigosity (double MYBPC3: n=16; MYH7 plus MYBPC3: n=8; MYH7 plus double MYBPC3: n=1; MYH7 plus mtDNA: n=6; tCAP plus mtDNA: n=2). After 90±70 months 62 (16%) affected HCM patients had one of the following events: CHF death while awaiting for HTx (n=11); HTx (n=18); appropriate ICD intervention plus HTx (n=4); sudden cardiac death (SCD)or appropriate ICD intervention (n=29). Among the 33 patients with double or compound heterozigosity, 31 were affected and 2 were young healthy carriers (respectively 13 and 15 years of age). After a mean follow-up of 60±34 months (p=0.002), we observed 11 (33%) events (SCD: n=2; CHF death: n=1; HTx: n=5; appropriate ICD intervention: n=2; appropriate ICD intervention plus HTx: n=1). None of the mutated individuals without phenotype had cardiac events.
Conclusions: in our experience the prevalence of double or compound heterozigosity is 8%. The clinical outcome of affected HCM patients with double or compound heterozigosity is characterised by an higher rate of adverse events in a shorter period of time.

1213 Prognostic value of a systematic familial screening in idiopathic dilated cardiomyopathy. The experience of trieste heart muscle disease

M. Moretti[1], M. Merlo[1], G. Barbati[1], G. Sabbadini[2], L. Mestroni[3], F. Brun[1], A. Di Lenarda[4], G. Sinagra[1] on behalf of Heart Muscle Disease Study Group. *[1]Cardiovascular Department, "Ospedali Riuniti" and University, Trieste, Italy; [2]Depatment of Internal Medicine-Geriatrics, "Ospedali Riuniti" and University, Trieste, Italy; [3]Cardiovascular Center, University of Colorado, Denver, United States of America; [4]Cardiovascular Center, Azienda per i Servizi Sanitari (A.S.S.) n 1, Trieste, Italy*

Purpose: Familial screening of idiopathic dilated cardiomyopathy (IDCM) patients allows an early diagnosis of the disease in family members. It is unclear if familial dilated cardiomyopathy (FDC) has a different long-term outcome with respect to the sporadic IDC. The aim of this study was to compare long-term prognosis in FDC with respect to sporadic forms in order to assess the role of familial screening in IDC patients (pts).
Methods: We analysed 637 pts with IDC consecutively enrolled in the Trieste Heart Muscle Disease Registry from 1988 to 2007. We compared proband and non-proband FDC patients (NP-FDC) with a sample of sporadic forms, randomly matched by year of enrolment and sex (2:1), the matching procedure was done in order to increase the efficiency of comparisons.
Results: FDC were 130 (20%), 82 (63%) were probands. The familial screening effectively diagnosed IDCM in 48 (7.5%) non-proband FDC patients. With respect to the random sample of 164 sporadic patients, probands-FDC did not show difference in baseline clinical findings and long-term outcome. On the contrary, with respect to the random sample of 96 sporadic patients, NP-FDC pts were younger (40±16 vs 47±13 years, p=0.002), less severely symptomatic (NYHA class III-IV 8% vs 28%, p=0.006), had lower end diastolic diameter (62±12 vs 67±9 mm, p=0.006), higher left ventricular ejection fraction (35±10 vs 30±9, p=0.005), lower prevalence of LBBB (10% vs 37%, p=0.001), and were less frequently treated (ACE-inhibitors 75% vs 96%, p<0.001; beta-blockers 65% vs 79%; p=0.06; diuretics 37% vs 68% p=0.001). The survival free from heart transplant at 2, 5 and 10 years of follow-up was respectively 93, 91 and 82% in NP-FDC versus 86, 76 and 62% of sporadic forms (p=0.04). No difference was observed in the rate of sudden death or life threatening arrhythmias.
Conclusions: FDC represented 20% of our population. Probands did not show significant differences as compared to sporadic IDCM. Familial screening of IDC patients allowed early recognition and treatment of 48 (7.5%) NP-FDC with improved long-term outcome. If prognosis could be further improved by early tailored treatment in all patients has to be proved. Our data emphasise the importance of familial screening in all IDC patients.

CALCIUM STORES IN TIME AND SPACE

1238 CPVT related RYR2 mutation:impact of an arrhythmogenic disorder on the mechanical properties of myocardium. Insights from a transgenic mouse model

R. Coppini[1], C. Ferrantini[1], F. Stillitano[1], S. Priori[2], C. Poggesi[1], E. Cerbai[1]. *[1]University of Florence, Florence, Italy; [2]Fondazione Salvatore Maugeri, Pavia, Italy*

Mutant RyR2 responsible for CPVT can trigger, on stress and exercise, catecholaminergic induced-ventricular arrhythmias and sudden death.Defective RyR2, ubiquitously expressed in the heart, is responsible for sarcoplasmic reticulum dysfunction that may lead to atrial and ventricular contractile changes also detectable under basal conditions.Left atrial and right ventricular trabeculae (trab.) were dissected from control (WT) and heterozygous transgenic mice (HE) carrying one of the most common CPVT-related RyR2 mutations (R4496C). Preparations underwent various stimulation protocols, including pause-delayed and premature stimuli while isometric tension was recorded. For intracellular Ca^{2+} transients (CaT) and electrophysiological recordings ventricular and atrial myocytes (MC) were isolated. Perfusing solution's $[Ca^{2+}]$ was 2mM.
In HE MC maximum post-rest increase in the amplitude of CaT was reduced compared to WT (139±7% vs 209±8%, $p<0.01$, in ventricular MC). Maximum post-rest potentiation of isometric tension was lower in HE than in WT trab. (eg, 152±20% vs 290±43%, $p<0.05$, in atrial trab.) and was reached at shorter rest-intervals in HE preparations. Isoproterenol-induced positive inotropic responses were less pronounced in HE vs. WT trab. CaT showed a slightly positive amplitude-frequency relationship in WT MC but a negative relationship in RM MC (3hz/1hz CaT amplitude: 110±3% vs 90±4%, $p<0.01$, in ventricular MC). These results seem consistent with the "leaky phenotype" of mutant RyR2. Electrical refractoriness, action potential duration, calcium current characteristics (density, activation, inactivation, restitution at 1hz) were the same in HE and WT MC. Nevertheless in HE MC restitution of CaT amplitude was significantly faster than in WT (Time to 63% of Basal CaT: 180±11ms vs 280±27ms, $p<0.01$). Similarly in HE trab. restitution of isometric tension was faster than in WT (Time to 63% Basal Force: 196±19ms vs 349±47ms, $p<0.05$). Isoproterenol accelerated mechanical restitution of all types of trab. and CaT amplitude restitution of MC, but did not abolish the difference between HE and WT preparations. No significant differences in CaT upstroke/decay rates and no different kinetics of force development and relaxation were found. Therefore secondary alterations (eg Phospholamban Hyperphosphorilation) seem to be unlikely. Decreasing extracellular Ca concentration (to 1mM) renders mechanical restitution slower in HE trab. abolishing the differences. A faster recovery from refractoriness of the mutant RyR2 may be responsible for these findings and may depend on an increased sensitivity of the channel to luminal calcium concentration.

1239 nNOS gene disruption reduces the diastolic calcium leak from the ryanodine receptor: implications for excitation-contraction coupling in heart failure

G.B.S. Lim, M.H. Zhang, Y.H. Zhang, B. Casadei. *University of Oxford, Oxford, United Kingdom*

Increased diastolic Ca^{2+} leak from the ryanodine receptor (RyR2), possibly due to hyperphosphorylation, has been proposed to deplete sarcoplasmic reticulum (SR) Ca^{2+} content and thus cause impaired contractility in heart failure. Although nitric oxide (NO) and superoxide donors have been shown to modulate the open probability of reconstituted RyR2, the effect of endogenous NO and superoxide on RyR2 function in vivo remains uncertain. Using an established method, we measured RyR2 leak in left ventricular myocytes isolated from nNOS knock-out (KO) mice and their wild-type (WT) littermates.
To investigate the relationship between SR Ca^{2+} content and RyR2 leak, we altered the former by varying $[Ca^{2+}]_o$. The rise in both SR Ca^{2+} content and $[Ca^{2+}]_i$ transient amplitude in response to increasing $[Ca^{2+}]_o$ was greater in WT than KO myocytes, suggesting that nNOS gene disruption impairs SR Ca^{2+} loading (in agreement with reduced phospholamban phosphorylation in these mice). At the highest SR Ca^{2+} content, the RyR2 leak was significantly larger in WT than KO myocytes (fura-2 fluorescence ratio F365/F380 = 0.240±0.05 vs. 0.124±0.03; n = 9, 10; P = 0.02).
Superoxide production measured by lucigenin-enhanced chemiluminescence was higher in KO compared to WT hearts at 2 mM $[Ca^{2+}]_o$, but was significantly decreased in both genotypes by higher $[Ca^{2+}]_o$. Interestingly, neither preincubation and perfusion with 100 μM oxypurinol (to inhibit xanthine oxidoreductase) nor with 100 μM apocynin (to inhibit NADPH oxidases) had a significant effect on the leak – load relationship in either genotype.
However, western blot analysis showed that the lower RyR2 leak – SR load relationship in the KO was associated with decreased RyR2 phosphorylation at both serine-2809 and serine-2030, consistent with the previously reported increased protein phosphatase activity in the KO myocardium.
In summary, our data indicate that (1) nNOS-derived NO increases RyR2 leak (possibly by increasing channel phosphorylation), particularly at high SR Ca^{2+} contents; (2) Ca^{2+} mediated stimulation of nNOS activity in the myocardium may prevent SR Ca^{2+} overload through both a NO mediated increase in RyR2 leak

and the previously observed reduction in Ca^{2+} influx via the L-type Ca^{2+} channel. These findings suggest that nNOS overexpression in the failing myocardium may be an adaptive mechanism aimed at preventing myocardial oxidative damage and disruption of Ca^{2+} homeostasis.

1240 Role of the cytosolic adenosine level in the regulation of calcium release from the sarcoplasmic reticulum in human atrial myocytes

A. Llach[1], C.E. Molina[1], J. Fernandes[1], J. Montiel[1], J. Cinca[1], L. Hove-Madsen[2]. *[1]Hospital de Sant Pau, Barcelona, Spain; [2]Centro de Investigación Cardiovascular CSIC-ICCC, Barcelona, Spain*

Purpose: Selective activation of adenosine A2A receptors (A2AR) has been shown to promote spontaneous calcium release in human atrial myocytes. It is, however, not known how the endogenous adenosine level affects intracellular calcium handling, and the purpose of the present study was to investigate how manipulation of the cytosolic adenosine level modulates spontaneous calcium release in isolated human atrial myocytes.
Methods: Human atrial myocytes were subjected to ruptured patch-clamp technique and 30 μM adenosine was infused into the cell through the patch pipette. To follow the rise in the cytosolic adenosine level after patch-break, 50 μM Fluo-4 was added to the standard pipette solution. Confocal calcium images were acquired at a frame rate of 100 Hz with a fast resonance scanning confocal microscope, and ionic currents were recorded simultaneously.
Results: With the membrane potential clamped at -80 mV, the rise in baseline fluorescence was fit with a sigmoidal equation (y=A/(1+exp-((x-xo)/B))) where A is the maximal fluorescence, B is a slope factor and xo is the time where half-maximal fluorescence is reached. Fitting of 12 individual experiments gave a plateau of 0.85±0.13 a.u. and a time to half-maximum of 13.4±1.6 min. Infusion of adenosine initially induced numerous calcium sparks and mini-waves whereas longer infusion primarily produced large calcium waves that propagated throughout the entire cell and were associated with a transient inward Na-Ca exchange current. On average, the appearance of the first large calcium wave above the baseline wave frequency occurred 17.6±9.7 min. after patch break, corresponding to a cytosolic adenosine concentration of 13.96±4.97 μM (n=8). Infusion of adenosine containing (n=8) and adenosine free solutions (n=4) had opposite and significantly different effects ($p<0.05$, one-way ANOVA) on the frequency of calcium waves, indicating that the endogenous adenosine level is sufficient to activate spontaneous SR calcium release. Moreover, pharmacological inhibition of the A2AR eliminated the stimulatory effect of adenosine, confirming that the A2AR activation is responsible for the promotion of spontaneous calcium release.
Conclusions: We conclude that the endogenous adenosine level can account for A2AR-mediated spontaneous SR calcium release at baseline, and that elevation of cytosolic adenosine levels above baseline strongly promote abnormal SR calcium release. These results emphasize the physiological importance of endogenous adenosine levels and A2ARs in the regulation of SR calcium release in human atrial myocytes.

1241 Chronic mechanical unloading of rat hearts disrupts local calcium-induced calcium release in isolated cardiomyocytes

C. Terracciano[1], A. Al-Masri[2], U. Siedlecka[1], G.K. Soppa[1], M. Navaratnarajah[1], S. Hadjiphilippou[1], M. Ibrahim[1], M.H. Yacoub[1]. *[1]Imperial College London, London, United Kingdom; [2]King Saud University, Riyadh, Saudi Arabia*

Purpose: Left-ventricular assist devices (LVADs) have an established role in sustaining the circulation of patients with severe heart failure awaiting cardiac transplantation. However, prolonged mechanical unloading using LVADs can cause contractile dysfunction and arrhythmias. Deranged cellular Ca^{2+} homeostasis may be responsible for these changes. In this study we investigated the consequences of mechanical unloading on the local Ca^{2+}-induced Ca^{2+} release (CICR) process, which plays a crucial role in systolic and diastolic function and has been closely associated with the pathophysiology of heart failure including arrhythmogenesis.
Methods: LV unloading was induced in rat hearts by heterotopic abdominal transplantation for 4 weeks. Studies were performed on cardiomyocytes isolated from the unloaded hearts using confocal microscopy. Cell and t-tubular compartment volumes were measured using the fluorescent dye Di-8-Anepps. Cytoplasmic [Ca^{2+}] was monitored using fluo-4 AM and Ca^{2+} sparks, spontaneous local sarcoplasmic reticulum (SR) Ca^{2+} release events, were measured. Synchronicity of CICR from the SR was calculated as the variance of time-to-peak of Ca^{2+} transients measured at each x pixel during line scanning.
Results: The volume of cardiomyocytes isolated from unloaded hearts (UN) was decreased by 56.5% compared to the cardiomyocytes from control hearts (C) (UN: 19190±779 mm^3, n=90 vs. C: 44120±2042 mm^3, n=59, $p<0.001$) without differences in the relative volume of the t-tubular compartment (% of Di-8-Anepps stained area: UN: 42.5±0.8%, n=90 vs. C: 42.2±1.0%, n=59, p=NS). In UN cells there was a significantly higher Ca^{2+} spark frequency (UN: 3.7±0.8 spark/sec, n=47 vs. C: 0.9±0.2 spark/sec, n=45, $p<0.01$). Moreover, in UN cardiomyocytes Ca^{2+} spark width and duration were increased (width: UN: 3.3±0.06 mm, n=410 vs. C: 2.7±0.04 mm, n=149, $p<0.001$; duration: UN: 25.9±0.8 ms, n=410 vs. C: 14.8±0.4 ms, n=149, $p<0.001$), while Ca^{2+} spark peak was decreased (UN: 1.5±0.01 F/Fo, n=410 vs. C: 1.7±0.02 F/Fo, n=149, $p<0.001$). The variance of time-to-peak of Ca^{2+} transients was significantly increased in UN cardiomyocytes (UN: 227.4±24.9 ms^2, n=42 vs. C: 157.8±18.0 ms^2, n=40, $p<0.05$), suggesting that the synchronicity of Ca^{2+} release during the Ca^{2+} transient was disrupted.
Conclusions: Our study shows that prolonged mechanical unloading leads to reduction in cardiomyocyte size with alterations in the process of local SR Ca^{2+} induced Ca^{2+} release, which may contribute to the changes in myocardial function and arrhythmias after prolonged treatment with left ventricular assist devices.

1242 Nuclear envelope and nucleoplasmic reticulum in cardiac myocytes act as functional calcium stores to regulate nucleoplasmic calcium concentration

M. Khafaga[1], T. Mittler[1], G. Leitinger[2], S. Jaeger[2], M. Asgarzoei[3], L. Seidlmayer[3], S. Walther[1], H. Maechler[4], B. Pieske[1], J. Kockskaemper[1]. *[1]Division of Cardiology, Medical University of Graz, Graz, Austria; [2]Core Facility Ultrastructure Analysis, Center for Medical Research (ZMF), Medical University of Graz, Graz, Austria; [3]University Medicine Göttingen, Göttingen, Germany; [4]Division of Cardiac Surgery, Medical University of Graz, Graz, Austria*

Purpose: Nucleoplasmic calcium concentration ([Ca]) in cardiac myocytes regulates transcription and may be involved in remodelling processes. How nucleoplasmic [Ca] is regulated is unknown. We thus characterized perinuclear Ca stores in cardiac myocytes and evaluated their contribution to the regulation of nucleoplasmic [Ca] transients.
Methods: Perinuclear Ca stores in isolated atrial and ventricular myocytes from rabbit and mouse hearts were visualized using confocal imaging and staining with the high affinity Ca indicator Fluo-4/AM (8 μM, 30-60 min) or the low affinity Ca indicators, Mag-Fluo-4/AM (10 μM, 30-60 min) and Fluo-5N/AM (10 μM, 120-150 min), respectively. Human atrial trabeculae were used for electron microscopic analysis of perinuclear structures and immunogold labelling of IP3 receptors. Nucleoplasmic and cytoplasmic [Ca] transients (CaTs) were recorded simultaneously using fast, 2D confocal microscopy in electrically-stimulated atrial myocytes loaded with Fluo-4/AM (8 μM, 20 min).
Results: Atrial myocytes were mono-nucleated, whereas ventricular myocytes were bi-nucleated. In resting atrial and ventricular myocytes, staining of perinuclear Ca stores with Fluo-4, Mag-Fluo-4 or Fluo-5N revealed a prominent nuclear envelope and tubular structures traversing the nucleus, i.e. the nucleoplasmic reticulum. In atrial myocytes, nuclei (n=11) measured 11.2±0.7 μm in length and 4.1±0.3 μm in width and exhibited 3.9±0.4 tubules per nucleus. Ventricular myocyte nuclei (n=88) measured 13.9±0.3 μm in length and 4.9±0.1 μm in width and exhibited 5.8±0.2 tubules per nucleus. Rapid application of caffeine (20 mM, n=7) reversibly abolished Mag-Fluo-4 fluorescence of nuclear envelope and nucleoplasmic reticulum. Electron microscopy (n=5 atrial trabeculae) showed direct connections between the sarcoplasmic reticulum and the nuclear envelope as well as invaginations of the nuclear envelope into the nucleoplasm. IP3 receptors were observed both in the nuclear envelope as well as in the nucleoplasmic reticulum. In electrically-stimulated atrial myocytes (n=8), endothelin-1-induced IP3 signalling caused selective increases of nucleoplasmic CaTs.
Conclusions: Atrial and ventricular myocytes from animal and human hearts contain nuclear envelope and nucleoplasmic reticulum as functional perinuclear Ca stores that can be depleted by caffeine exposure and that may control local [Ca] in the nucleoplasm via IP3 receptor-induced Ca release.

1243 Stimulation of the calcium receptor: A new positive inotropic intervention of the post-ischemic heart

R. Schreckenberg, Y. Abdallah, K.D. Schlueter. *Universitaet Giessen Physiologisches Institut, Giessen, Germany*

Background: Acute heart failure as a result of a myocardial infarction is characterized by a critical drop in blood pressure and cardiac output. At present, pharmacologic therapies for acutely decompensated heart failure include Dobutamine, Adrenaline or calcium sensitizer. The major potential disadvantages of these drugs are the induction of arrhythmias and the acceleration of the heart rate. An imbalance of the polyamine metabolism in post-ischemic myocytes leads to an accumulation of putrescine, a physiological agonist of the Calcium Receptor (CR). The aim of this study was to investigate the potential of CR stimulation as a positive inotropic principle using isolated cardiomyocytes and isolated perfused hearts.
Methods: CR was stimulated by putrescine (Put, 1μM) or gadolinium (Gd, 200nM), NPS (10 μM) was used for blocking the receptor. Ventricular cardiomyocytes were isolated from adult rats, paced at different frequencies and cell shortening was monitored. The alteration of cytosolic calcium was measured using fura-2AM as fluorophore. Results of these experiments were transferred to the Langendorff heart. Isolated perfused hearts were subjected to 45 min no-flow ischemia and 120 min reperfusion. Myocardial function was evaluated by continuous assessment of left ventricular developed pressure and heart rate.
Results: After incubation with Put cell shortening and shortening dynamics of isolated myocytes increased frequency-dependent by 7.5% (1.0Hz) and 12.0% (2.0Hz), (n=62, $p<0,05$), Gd improved cell shortening by 13.0% (1,0 Hz) and 22.5% (2Hz), (n=62, $p<0,05$). Simultaneous, both agonists induced a rise in sys-

tolic calcium up to 23% whereas the diastolic calcium remains unchanged. The improved calcium transient could be suppressed by the receptor blocker NPS and the IP3 inhibitor Xestospongin D. An improvement of the relaxation velocity was accompanied by an acceleration of the calcium sequestration. Treatment with Put also improved functional performance in normoxic hearts by 32% (Gd: 31%) and in post-ischemic hearts by 23% (Gd: 26%). Both agonists did not affect the enddiastolic pressure. Early perfusion with NPS blocks cardioprotective effects of Put/Gd in normoxic and post-ischemic hearts.
Conclusion: Stimulation of the myocardial CR induces an IP3-dependent release of calcium from the sarcoplasmatic reticulum. This mechanism improves contractile activity without any effects on the diastolic relaxation.

DAMAGE LIMITATION: VASCULAR REGENERATION AND REPAIR

1244 A switch between arterial regeneration or chronic inflammation regulated by myeloid notch signaling

A. Limbourg[1], C. Napp[1], L. Hu[1], J. Larmann[1], M. Meier[1], R.H. Adams[2], G. Theilmeier[1], H. Drexler[1], F.P. Limbourg[1].
[1]Medizinische Hochschule Hannover, Hannover, Germany; [2]MPI for Molecular Biomedicine, Münster, Germany

Circulating cells, described as endothelial progenitor cells (EPC), play an important role in vascular regeneration, but their definitive identity and functional role remains unclear. Endothelial Notch signaling controls is thought to control many aspects of arterial homeostasis. Here we show an essential function of non-vascular Notch in regulating the balance between arterial regeneration and inflammation.
Results: Analysis of human EPC derived from peripheral blood mononuclear cells revealed a myeloid, CXCR4+ cell type co-expressing endothelial markers. Cell-fate tracking of pre-labeled CD14+ monocytes unequivocally demonstrated monocytic origin of EPC. Genetic or pharmacological inhibition of Notch signaling switched EPC to macrophages with strongly reduced CXCR4, but increased macrophage marker expression and increased ROS production. Time lapse videos of co-cultures demonstrated a specific, CXCR4-dependent interaction of EPC with EC, which promoted EC migration resulting in enhanced closure of injured EC monolayers (2,1-fold vs ctl, $p < 0,01$) and which was absent in Notch-deficient macrophages.
In vivo endothelial regeneration after carotid injury in mice occurred from pre-existing endothelium without EPC incorporation or differentiation, as shown by genetic labeling of pre-existing endothelium and subsequent transplantation of unlabeled bone marrow followed by carotid injury. Near-infrared fluorescence molecular tomography (FMT) demonstrated specific, CXCR4-dependent EPC homing to injured endothelium, which was completely absent in Notch-deficient macrophages. Consequently, EPC transfer strongly enhanced re-endothelialization (3,2-fold compared to control mice, $p < 0,01$), which was severely impaired after Notch or CXCR4 inhibition.
Furthermore, EPC transplantation after hind limb ischemia (HLI) strongly enhanced limb perfusion by perfusion-weighted magnetic resonance imaging and enhanced artery growth by histologic analysis and wholemount angiography, while reducing leukocyte infiltration, tissue necrosis (35% reduction vs ctl, $p< 0.01$) and fibrosis and scarring when compared to controls. In contrast, Notch-deficient macrophages caused a further reduction in limb perfusion compared to controls and induced severe and ongoing inflammation by endogenous leukocytes, which increased necrosis (32% increase vs ctl, $p<0.01$) and fibrosis. As a result, EPC treatment for HLI led to a near complete rescue of the ischemic hind limbs (95% recovery), while treatment with Notch-deficient macrophages worsened the clinical outcome (60% autoamputation, 40% necrosis) compared to control.

1245 A biological self assembling amphiphilic peptide enhances Endothelial Progenitor Cells growth and paracrine release

R. Di Stefano[1], M.C. Barsotti[1], A. Magera[1], H. Hosseinkhani[2], F. Chiellini[3], D. Dinucci[3], M. Alderighi[4], R. Solaro[4], A. Balbarini[1].
[1]Cardiac, Thoracic and Vascular Department, University of Pisa, Pisa, Italy; [2]International Center for young Scientists-National Inst. For Material Science, Tsukuba, Japan; [3]BIOLab-Dept. of Chemistry and Industrial Chemistry,University of Pisa, Pisa, Italy; [4]Dept. of Chemistry and Industrial Chemistry,University of Pisa, Pisa, Italy

Purpose: Autologous transplantation of endothelial progenitor cells (EPC) is a promising approach for revascularization of ischemic tissues, however strategies for in situ prolonged stay of the cells are needed. Peptide-amphiphiles (PA) are biocompatible molecules self-assembling with the potential of forming nanofibers when mixed with opposite charged solutions. PA can include sequences, such as arginine-glycine-aspartic acid (RGD), present in extracellular matrix (ECM). When injected together with growth factors or stem cells in experimental models, PA are able to induce a significant neovascularization and necrotic area reduction. Purpose of our work was: 1) to evaluate a PA containing the RGD sequence as potential scaffolds for EPC growth; 2) to compare 2-D and 3-D EPC culture; 3) to evaluate the paracrine factors release by EPC.
Methods: PA final chemical structure contained RGD and an alkyl tail. Gel was formed mixing PA (0.1%-1%-2%) with an endothelial medium with 5% FBS and growth factors containing CaCl2 (10–20-100 mM). Gel structure was analysed by atomic force microscopy (AFM). Mononuclear cells obtained from peripheral blood of healthy donors were seeded either on the surface (2-D) or inside the gel (3-D) and cultured for 1 week to obtain EPC. Fibronectin was used as a control. EPC viability was assessed by confocal microscopy (calcein-AM) and by conversion of a tetrazolium salt (WST-1). The release in the supernatant of a panel of 50 cytokines involved in inflammatory process and chemotaxis was evaluated by a multiplexable bead assay.
Results: PA had a native pH of 4.0 but gained solubility when pH=7.4 was reached. A gel was obtained when PA concentration was $\geq$ 1%, irrespectively from CaCl2 concentration. AFM analysis showed the presence of 3-D networks of nanofibers. No effect of CaCl2 concentration on EPC viability was observed. However, a higher viability was observed at PA concentration of 1% and in the 3-D seeding model (0.660 ± 0.140 a.u. vs. fibronectin: 0.311 ± 0.067, $p=0.05$). Interestingly, a significant release of chemokines involved in cell homing-recruitment (MIF, SDF 1, IL-8 and MCP-1) was obtained only with cells growths on 3D PA culture.
Conclusions: The 3-D gel formed by our PA containing RGD is a suitable scaffold for EPC growth and function with the potential to be used as injectable scaffold. The development of a class of self assembling PA created through molecular design and able to selectively release mediators involved in cell recruitment at sites of neo-vessels offers new possibilities in ischemic tissue regeneration.

1246 The transcription factor FoxP1 modulates vascular formation and endothelial proliferation and is upregulated in growing collateral arteries

S. Grundmann[1], R. Herpers[2], I.E. Hoefer[3], J. Sluijter[3], M.J. Goumans[3], M. Moser[1], C. Bode[1], S. Schulte-Merker[2], G. Pasterkamp[3], D.P.V. De Kleijn[3]. *[1]Universitaetsklinikum Freiburg, Freiburg im Breisgau, Germany; [2]Hubrecht Institute, Utrecht, Netherlands; [3]University Medical Center Utrecht, Utrecht, Netherlands*

Adaptive neovascularization (angiogenesis and arteriogenesis) in response to progressive vascular occlusive disease represents in parts a reactivation of embryonic pathways. We aimed to identify genes that are differentially expressed during adaptive collateral artery growth (arteriogenesis) in adult mammals (rabbits and mice). Functional effects of differentially expressed genes on vascular development were tested by morpholino mediated knockdown in zebrafish embryos.
Three days after femoral artery ligation, growing collateral arteries were isolated from New Zealand white rabbits, mRNA was extracted, converted to cDNA and subjected to subtractive hybridization and suppression PCR against arteries from the sham-operated contralateral hindlimb. We found the rabbit ortholog of the forkhead box protein p1 to be upregulated in isolated growing collateral arteries at three days after surgery ([pg plasmid]collaterals: 4.2 ± 3.2; controls: 0.6 ± 0.8). Its increased expression during arteriogenesis was verified in mice as early as 24h after surgery, with a predominantly nuclear expression pattern in endothelial cells of collateral arteries.
Knockdown of foxp1 in flk:GFP transgenic fish resulted in a disruption of vascular formation, with a prominent negative effect on the truncal intersomitic vessels ([missing or incomplete vessels] Wildtype: 0 ± 0, Morphants: 12 ± 3). SiRNA-mediated knock down (KD) of foxp1 in cultured endothelial cells demonstrated a significantly reduced proliferation (BrdU-incorporation [relative values] KD: 0.14 ± 0.02; controls: 0.36 ± 0.06), migration (distance [pixel]: KD: 1.43 ± 0.69; control: 2.35 ± 0.83) and tube formation activity in the matrigel assay (total tube length [pixel]: KD: 2101 ± 620; control: 7871 ± 1510), whereas overexpression of foxp1 had a stimulatory effect.
Our results for the first implicate a modulating function of the transcription factor foxp1 in embryonic vasculogenesis and adaptive neovascularization in the adult. The target genes regulated by foxp1 are currently under investigation.

1247 Positioning of transgenic endothelial cells to injured mouse carotid artery by magnetic nanoparticles

U.M. Becher, A. Hofmann, D. Wenzel, B.K. Fleischmann, G. Nickenig, A. Pfeifer. *Universitaetsklinikum Bonn, Bonn, Germany*

Purpose: Our aim was to position superparamagnetic endothelial cells to the denuded common carotid artery (CCA) in mice. Here, we used magnetic nanoparticles (MNPs) to combine cell transduction and positioning in the vascular system under clinically relevant, non-permissive conditions in vivo.
Methods and Results: For this purpose, we labeled human umbilical vein endothelial cells (HUVECs) with MNPs. HUVECs (40,000 cells) were transduced with MNPs coupled to a HIV-derived lentiviral vector (LV) carrying a CMV promoter-driven eGFP expression cassette. LV/MNP transgenic cells exhibited superparamagnetic behavior and were efficiently retained by magnetic fields in vitro. In order to evaluate the feasibility of positioning in the vascular system in vivo, we used an injury model of the mouse carotid artery. MNP-labeled, transgenic HUVECs (LV/MNP) were infused via the external carotid artery, while small magnets were positioned at the CCA. In parallel, control experiments were performed under the same conditions, but without placing a magnet to the CCA. Retention of MNP-labeled, transgenic HUVECs were analyzed by fluores-

cence stereomicroscopy and histology. Fluorescence imaging revealed eGFP-expression at the injured vessel wall in the presence of magnets. Histological analysis corroborated the presence of MNP-labeled, eGFP-expressing cells at the site of the magnetic gradient field. In contrast, in the control mice application of MNP-labeled cells in the absence of a magnetic field did not result in retention of cells. Furthermore, in the untreated vessel no GFP fluorescence was observed. In summary the application of external magnetic fields significantly changed biodistribution of LV/MNP transgenic endothelial cells in an injury model of the mouse carotid artery. The magnetic interactions were strong enough to position MNP-containing endothelial cells at the intima of the CCA under physiological flow in vivo.

Conclusion: Taken together, MNPs can be used to target endothelial cells to distinct areas of a blood vessel by magnetic forces. Magnetic positioning of transgenic cells via nanomagnetic particles has high relevance for regenerative medicine, because cell replacement therapies require efficient seeding.

1248 Protein Kinase A (PKA) plays a key-role in late ischemic preconditioning-induced protection of endothelial cells from apoptosis

A. Bellis, D. Castaldo, V. Trimarco, M.G. Monti, B. Trimarco, C. Morisco.
Azienda Ospedaliera Universitaria Federico II, Naples, Italy

Objective: Ischemic Preconditioning (PC) is a physiologic and protective mechanism of tissues against ischemia/reperfusion injury. We have recently demonstrated that our PC-protocol is able to protect bovine aortic endothelial cells (BAECs) from hypoxia-evoked apoptosis and to induce nitric oxide (NO) production. Protein kinase A (PKA) and B (Akt) are two serine/threonine kinases implicated in NO synthesis and with protective properties in cardiomyocytes. Therefore, it seems reasonable that these kinases are implicated in survival mechanisms mediated by PC in endothelial cells.

Aim of the Study: To analyze involvement and role of PKA- and phosphatidilinositol-3-kinase (PI3K)/Akt pathway in PC.

Methods and Results: PC was induced by exposing bAECs to three cycles of 15 minutes of hypoxia (incubation in hypoxic chamber) followed by 15 minutes of reoxygenation. First, we evaluated activation of PKA and Akt through phosphorylation assay of kemptide (a specific substrate of PKA) and Akt phosphorylation, respectively. The activity of both kinases was present in early and late phase of PC. Since protection by late PC is longer, we assessed hypoxia (12 hours)-induced cell mortality in this phase, following administration of PKA (H89) and PI3K (LY294002) inhibitors, through staining with Propidium Iodide (necrosis detection) and Annexin V (apoptosis detection). Cell pretreatment with H89 and LY294002 affected cytoprotective effect of PC. Consistently, overexpression of PKA and Akt dominant negative mutants increased apoptosis in late preconditioned cells. Furthermore, Bad, a protein which plays an anti-apoptotic role when phosphorylated in serine 112 and 136 by PKA and Akt respectively, was activated in both phases of PC. Then, to verify whether PKA and Akt interact or not during late PC, we evaluated activation of Akt in presence of above mentioned inhibitors. Akt phosphorylation was inhibited by H89 and blunted by LY294002, allowing to speculate that Akt activation is dependent by PKA and, partially, by PI3K. In effects, we found that PKA physically interacts with phosphorylated form of Akt during both phases of PC and that Akt is selectively bound by an antibody recognizing phosphorylated substrates of PKA.

Conclusions: The cross-talk between PKA and Akt protects endothelial cells from apoptosis in late phase of ischemic preconditioning.

1249 The protective effect of T-cadherin on vascular endothelial cells under endoplasmic reticulum stress

E. Kyriakakis[1], M. Philippova[1], M.B. Joshi[1], V. Bochkov[2], P. Erne[3], T.J. Resink[1]. *[1]University Hospital Basel, Basel, Switzerland; [2]Medical University of Vienna, Vienna, Austria; [3]Cantonal Hospital Luzern, Luzern, Switzerland*

Purpose: Endothelial dysfunction plays a key role in the pathogenesis of atherosclerosis. T-cadherin, an atypical GPI-anchored member of the cadherin superfamily is upregulated in atherosclerotic lesions. Grp78 is a key mediator of endoplasmic reticulum (ER) stress, which activates UPR (unfolded protein-response) in order to re-establish normal ER function. Uncontrolled UPR contributes to apoptosis of vascular cells and progression of atherosclerosis. In endothelial cells a small fraction of Grp78 is located on the cell surface where it co-associates with T-cadherin. This suggests some role for T-cadherinin ER stress responses. Here we investigate the ability of T-cadherin to influence UPR signaling and endothelial cell survival during ER stress.

Methods: Human umbilical vein endothelial cells (HUVEC) and human microvascularcell line (HMEC-1) were treated for up to 24 hours with a variety of ER stress-inducing agents, including thapsigargin (1 μM), DTT (1 mM), brefeldinA (5 μg/ml), tunicamycin (3 μg/ml), calcium ionophore A23187 (2 μM) andhomocysteine (15 mM). Immunoblotting and quantitative RT-PCR were used to evaluate modulation of T-cadherin expression during ER stress, and changes inexpression of UPR signaling molecules such as Grp78, ATF3, TRB3 and phospho-eIF2α. Silencing and overexpression ofT-cadherin in endothelial cells was achieved using viral vectors.

Results: Treatment of HUVEC and HMEC-1 with the different ER stress-inducing agents increased mRNA and protein levels of T-cadherin within 2-4 hours; thereafter levels declined. Levels of phospho-eIF2α increased within 3 hours and remained stably elevated for up to 12 hours. Grp78 levels were elevated within 6 hours and thereafter continued to further increase for up to 12 hours. Total caspases activity increased after 12 hours of exposure to ER stress-inducing agents. Overexpression of T-cadherin attenuatedthe ER stress-induced increase in levels of phospho-eIF2α and Grp78and lowered the levels of active caspases. In contrast, silencing T-cadherin amplifiedER stress-induced increases in levels of phospho-eIF2α, Grp78 and caspasesactivity.

Conclusions: T-cadherin seems to be involved in ER stress responses of endothelial cells since it is elevated early following induction of ER stress. Our data supportthat T-cadherin upregulation may function to protect from adverse outcomes (e.g. apoptosis) of ER stress. The role of surface Grp78 and/or Grp78/T-cadherin complexin protection of vascular cells from ER stress has to be evaluated.

CARDIOVASCULAR MAGNETIC RESONANCE: A NEW WINDOW ON ISCHAEMIC HEART DISEASE

1250 The prognostic impact on identification of silent myocardial ischaemia and unrecognized myocardial infarction by cardiac magnetic resonance imaging in diabetic patients

C.W.S. Chan[1], S.C.W. Cheung[2], J. Ho[2], S. Ho[2], M. Sun[2], W.K. Tso[2], S. Lee[1], H.F. Tse[1]. *[1]Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China; [2]Department of Radiology, Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Previous studies have shown that silent myocardial infarctions (MI) are prevalent among diabetic patients and its presence signified long term morbidity and mortality. Cardiac magnetic resonance imaging (CMR) provides comprehensive assessment in myocardial perfusion reserve and characterization of myocardial scar by delay contrast imaging (DHE).

Purpose: We hypothesize that CMR perfusion study and identification of silent MI have roles in risk stratification and prognostic significance in diabetic patients.

Methods and Results: Totally 170 clinical indicated diabetic patients underwent CMR adenosine perfusion and DHE. CMR imaging and follow-up were successful in 164 patients (M: F= 101:63). Cox regression analyses were performed to associate the presence of myocardial ischemia by positive adenosine perfusion study and DHE with major cardiovascular events (MACE), including death, acute MI, new congestive heart failure or unstable angina, stroke and significant ventricular arrhythmias between the study groups Vs control group (n=114 vs n=50) respectively. At a median follow-up of 26 months, positive myocardial perfusion defect and DHE was presence in 32% (36 of 114 patients) and 26% (30 of 114 patients) experienced MACE respectively. The presence of DHE was associated with a 3.5 fold hazards increase for MACE (hazard ratio, 3.5; p=0.01). The presence of perfusion defect was associated with a 2.5 fold hazards increase for MACE (hazard ratio, 3.1; p=0.04). Adjusted with other clinical risk factors, left ventricular ejection fraction and myocardial perfusion imaging, DHE was the strongest multivariable predictor of the development of MACE.

Conclusion: CMR adenosine myocardial imaging and DHE for the identification of silent MI provide incremental value in the prognostication of diabetic patients.

1251 Predicting late myocardial recovery during the hyperacute phase of ST-elevation myocardial infarction by contrast-enhanced magnetic resonance imaging

E. Larose, J. Rodes-Cabau, P. Pibarot, S. Rinfret, C.M. Nguyen, J.-P. Dery, O. Gleeton, L. Roy, R. Delarochelliere, O.F. Bertrand. *Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada*

Purpose: Predicting poor outcomes at the earliest possible time during ST-elevation myocardial infarction (STEMI) is desirable.

Methods: 99 patients with STEMI were studied by contrast-enhanced magnetic resonance imaging (CE-MRI) at the earliest possible time after primary angioplasty ($<$12h, median 4.6h) and after infarct healing at 6 months. Very early predictors of late systolic dysfunction were determined.

Results: 25% of patients with left ventricular dysfunction (ejection fraction, LVEF $<$50%) during STEMI recovered at 6 months, while 27% of those with preserved function during STEMI developed late LV dysfunction. Late gadolinium enhancement (LGE) volume showed stronger association to percent change in LVEF than "no reflow" or transmural LGE (p=0.02). Multivariable analysis identified LVEF ($p<0.0001$) and LGE ($p<0.0001$) as the only parameters during STEMI that maintained independent association with 6-month change in LVEF. Multivariable logistic regression identified LGE volume during STEMI as the best predictor of late LV dysfunction (OR 1.34, p=0.005 –best-fit– and OR 1.36, p=0.03 –adjusted for traditional predictors). A LGE cutoff of 18 mL/m^2 or 30% of LV during STEMI correctly classified 89% of patients for late LV dysfunction. LGE volume during STEMI (AUC=0.92) provided incremental benefit predicting 6-month LV dysfunction beyond infarct territory, pain-to-balloon time, maximum CKMB rise, presence of Q waves, and LVEF during STEMI ($p\leq0.03$ for all, Figure).

Conclusion: During STEMI, LGE volume provides the strongest association and incremental predictive value for late systolic dysfunction. Identifying patients at

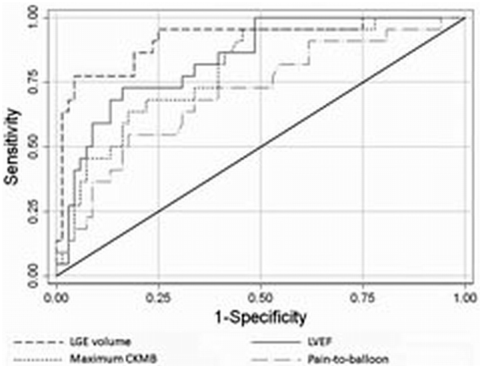


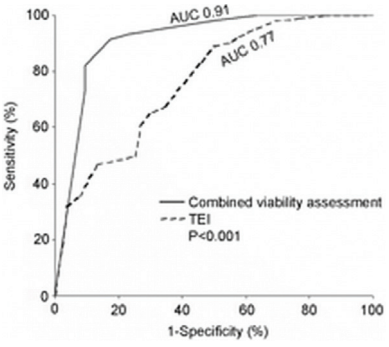
Figure 1

risk for late cardiac dysfunction during STEMI may allow earlier implementation of prognosis-altering therapies in those likely to benefit most.

1252 Prediction of improvement of myocardial function after recanalisation of a chronic total coronary occlusion: usefulness of combined viability assessment using cardiac magnetic resonance imaging

S.W.M. Kirschbaum[1], A. Rossi[2], H. Boersma[1], T. Springeling[1], M. Van Den Ent[1], G.P. Krestin[2], D. Duncker[1], P.W. Serruys[1], P.J. Feyter[1], R.J.M. Van Geuns[1]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]Erasmus MC, Rotterdam, Netherlands*

Purpose: To improve the diagnostic accuracy of pre treatment cardiac magnetic resonance imaging (CMR) for the prediction of improvement of myocardial function after percutaneous coronary intervention (PCI) of a chronic total coronary occlusion (CTO).
Methods: We studied patients with successful PCI (42/71) and with unsuccessful (29/71) PCI of a CTO. Segmental wall thickening (SWT) was quantified before and after PCI. Before PCI, using CMR, 5 viability parameters were evaluated: transmural extent of infarction (TEI), contractile reserve during dobutamine, end diastolic wall thickness, unenhanced rim thickness and SWT of the unenhanced rim (SWTur). Diagnostic accuracy for these parameters and for combined viability assessment for improvement in myocardial function was determined. ROC curve analysis was performed.
Results: Mean SWT improved significantly in patients with successful PCI (16±19% to 39±35%; $p<0.0001$) and did not improve in patients with unsuccessful PCI (19±21% to 21±25%; p=0.54). (figure 1)TEI<50% demonstrated a sensitivity of 89% (95% CI 81-94) and a specificity of 50%(95% CI 36-64) for the prediction of improvement of myocardial function after PCI. Multivariate analysis showed incremental predictive value for the combination of contractile reserve, SWTur and TEI. ROC curve analysis showed that combined viability assessment was superior to TEI (figure 1) with a sensitivity of 92%(95% CI 82-97) and specificity of 83%(95% CI 70-91).



Receiver Operator Curve

Conclusion: Successful PCI for a CTO has a beneficial effect on myocardial function that can be predicted by pre-treatment CMR with a high diagnostic accuracy using combined viability assessment. This may be useful for the selection of patients in which improvement of myocardial function by PCI of a CTO is desired.

1253 Clinical correlates of myocardial salvage index in acute ST-segment elevation myocardial infarction: a cardiac magnetic resonance imaging study

P.G. Masci[1], J. Ganame[2], E. Strata[1], G.D. Aquaro[1], W. Desmet[2], V. Valenti[3], S. Dymarkowski[2], M. Lombardi[1], F. Van De Wef[2], J. Bogaert[2]. *[1]Fondazione G Monasterio/Instituto di Fisiologia Clinica, Pisa, Italy; [2]University Hospital Gasthuisberg, Leuven, Belgium; [3]Ospedale Sant'Andrea - Università La Sapienza, Roma, Italy*

Background: In acute myocardial infarct (MI) patients, cardiac magnetic resonance imaging (MRI) allows to assess the extent of area-at-risk and MI size using T2-weighted and delayed enhancement (DE) imaging, respectively. Combining these measurements, the myocardial salvage can be determined albeit its clinical significance has not been adequately investigated.
Methods: MRI was performed in 137 patients with reperfused ST-segment-elevation MI at 1-week and 4-month. Left ventricular (LV) volumes, mass and ejection-fraction were determined by cine MRI. T2-weighted imaging was used to quantify the area-at-risk whereas MI size was measured on DE imaging. Myocardial salvage index was defined as extent of area-at-risk size minus MI size divided by extent of area-at-risk. MI size and area-at-risk were expressed as percentage of LV mass. In 55 patients, the degree of ST-segment-elevation 1 hour after the beginning of reperfusion treatment was also calculated.
Results: The extent of the area-at-risk was significantly larger than MI size (32±15% vs 18±13%, $P<0.0001$), yielding a myocardial salvage index of 0.46±0.24. A strong linear correlation was observed between MI size and area-at-risk size ($r=0.84$, $P<0.0001$). At multivariate analysis after adjustament for age, area-at-risk size, LV ejection-fraction, infarct transmurality, microvascular obstruction extent, infarct location (anterior vs nonanterior MI) and time-to-reperfusion treatment, the myocardial salvage index was a major and independent determinant of changes in LV end-systolic volume between the acute and chronic phase (B= -0.48, P=0.004), and was independently related to the degree of early ST-segment-elevation resolution (B=0.55, P=0.001).
Conclusion: Myocardial salvage index can be obtained in patients with reperfused MI by combining T2-weighted and DE imaging. This parameter correlates closely with early ST-segment-elevation resolution and is a major and independent determinant of LV remodeling.

1254 Troponin elevation and delayed gadolinium enhancement (DGE) in patients post-percutaneous coronary intervention (PCI)

S. Watkins[1], R. Mcgeoch[1], M.-J. Mclaughlin[1], T. Steedman[1], J. Lyne[2], I. Ford[3], H.J. Dargie[1], K.G. Oldroyd[1]. *[1]Western Infirmary, Glasgow, United Kingdom; [2]Royal Brompton Hospital, London, United Kingdom; [3]University of Glasgow, Glasgow, United Kingdom*

Purpose: Minor elevations in troponin are common following PCI and are thought to be due to myocardial necrosis secondary to side branch occlusion and distal embolisation of atherosclerotic debris. The extent of myocardial necrosis due to any cause can be visualised by cardiac MRI (CMR) using DGE imaging. A previous study in patients undergoing complex PCI showed that troponin elevation correlated with mass of DGE. The present study aimed to assess this relationship in an unselected group of patients with angina and less complex coronary disease.
Methods: Fifty-five patients with angina scheduled for coronary angiography underwent CMR in the preceding week (Siemens Sonata 1.5T). Cine scans to assess left ventricular ejection fraction (LVEF) were performed (TrueFISP sequence) followed by the administration of gadolinium (Omniscan, GE Healthcare) at a dose of 0.1mmol/kg. Short and long axis images for DGE (TurboFLASH sequence) were acquired through the entire LV. Images were analysed offline by two blinded observers and the LVEF and mass of DGE were calculated and averaged. PCI was performed using standard techniques and quantitative coronary angiography (QCA) was performed offline on the culprit vessel. Troponin I was measured 24 hours post-PCI and repeat CMR scanning was performed at 24 hours and 4 weeks.
Results:-Elevated troponin I was found in 41 (79%) of 52 patients who had their results recorded. The median troponin I was 0.57μg/L (SD=2.0, Range <0.04 – 13.1) and this correlated with increasing lesion length ($r=0.6$, $p<0.0001$) and total stent length ($r=0.37$, $p=0.02$). No significant correlations were found with any other QCA parameters. Fifty-four (98%) patients attended for the 24 hour CMR scan and 51 (93%) for the 4 week scan. New DGE was found in 10 (19%) patients at 24 hours post-PCI and 8 (16%) at 4 weeks. The mean increase in DGE was 1.24g (95% CI – 0.61 to 1.87) at 24 hours and 0.81g (95% CI – 0.48 to 1.14) at 4 weeks. No significant correlation was found between troponin I and the change in mass of DGE at 24 hours ($r=0.25$, $p=0.07$) or 4 weeks post-PCI ($r=-0.19$, $p=0.2$). There was a significant increase in LVEF from 66.7% pre-PCI to 71.9% at 24 hours ($p<0.0001$) and 69.6% at 4 weeks post-PCI ($p<0.0001$).
Conclusions: Troponin release post-PCI is common and related to lesion and stent length. Troponin in unselected patients does not correlate with the occurrence of new DGE differing from a previous study of selected patients with more complex disease and greater troponin elevations. Despite the release of troponin and the development of new DGE, PCI resulted in a significant increase in LVEF.

1255 European Cardiovascular Magnetic Resonance (EuroCMR) registry - Results of the German pilot phase

O. Bruder[1], T. Dill[2], V. Hombach[3], J. Schulz-Menger[4], E. Nagel[5], M. Lombardi[6], A.C. Van Rossum[7], A. Wagner[8], J. Schwitter[9], H. Mahrholdt[10] on behalf of Working Group on Cardiovascular Magnetic Resonance of the ESC. *[1]Department of Cardiology and Angiology, Elisabeth Hospital, Essen, Germany; [2]Kerckhoff Klinik GmbH, Bad Nauheim, Germany; [3]Department of Internal Medicine II, Cardiology, University of Ulm, Ulm, Germany; [4]Franz-Volhard-Klinik, Charite Campus Buch, Berlin, Germany; [5]Division of Imaging Sciences, King's College, London, United Kingdom; [6]Clinical Physiology Institute/G. Monasterio Foundation, Pisa, Italy; [7]VU University Medical Center, Amsterdam, Netherlands; [8]Duke Cardiovascular Magnetic Resonance Centre, Duke University, Durham, United States of America; [9]Clinic of Cardiology and Cardiac MR Centre, University of Zurich, Zurich, Switzerland; [10]Robert Bosch Medical Centre, Stuttgart, Germany*

Purpose: Cardiovascular magnetic resonance (CMR) has a broad range of clinical applications and is increasingly used in daily clinical practice in many European countries. During its German pilot phase the EuroCMR registry sought to evaluate indications, image quality, safety and impact on patient management of clinical routine CMR imaging in a large number of cases.
Methods: Multicenter registry with consecutive enrolment of patients scanned in 20 German CMR centres using web based online case record forms.
Results: 11040 consecutive patients were enrolled from April 2007 to January 2009 (64% male, median age 60 years [quartiles 47 - 70]). Eighty-eight percent of patients received a gadolinium based contrast agent. Twenty-one percent of patients underwent adenosine perfusion, and 11% high-dose dobutamine stress CMR. The most important indications are workup of myocarditis and cardiomyopathies (32%), risk stratification in suspected CAD/Ischemia (31%), as well as assessment of myocardial viability (15%). Image quality was found to be good or excellent in 90.1%, moderate in 8%, and inadequate in less than 2% of cases. Severe complications occurred in a minority of patients (0.05%) only, and were all associated with stress testing. No patient died during or due to the CMR procedure.
In nearly two thirds of patients (62%), CMR findings resulted in a change of patient management. Importantly, in 16% of cases the final diagnosis based on CMR was different to the diagnosis before CMR, leading to a complete change in patient management. In more than 86% of cases CMR was capable of satisfying all imaging needs so that no further imaging procedure was required after completion of CMR.
Conclusion: CMR is frequently performed in daily clinical practice. The most important indications are work-up of myocarditis and cardiomyopathies, risk stratification in suspected CAD/Ischemia, and assessment of myocardial viability. CMR imaging as used in the centres of the pilot registry is a safe procedure, has diagnostic image quality in 98% of cases, and its results have strong impact on patient management.

CARDIAC COMPUTED TOMOGRAPHY: FROM MOLECULES TO CLINICS

1256 Computed tomography with N1177 can identify ruptured atherosclerotic plaques in rabbit model of atherosclerosis

J.L. Van Herck[1], G.R.Y. De Meyer[2], W. Martinet[2], R.A. Salgado[1], B. Shivalkar[1], H. Bult[2], A.G. Herman[2], C.J. Vrints[1]. *[1]University Hospital of Antwerp (Edegem), Edegem, Belgium; [2]University of Antwerp (Wilrijk), Wilrijk, Belgium*

Purpose: Most acute coronary syndromes are caused by rupture of atherosclerotic plaques. N1177 is an iodinated contrast agent that is taken up by macrophages. The aim of this study was to investigate whether computed tomography (CT) with N1177 can differentiate between ruptured and non-ruptured plaques.
Methods: The effect of N1177 on J774 macrophages was investigated in vitro. For in vivo experiments, 6 rabbits were fed a cholesterol-supplemented diet (0.3%) for 15 months. In 3 rabbits mechanical plaque rupture was induced by retrograde pull-back of an embolic protection device through the entire aorta. Subsequently, CT-imaging of the aorta was performed before and 2 hours after intravenous injection of N1177.
Results: In vitro, the viability of J774 macrophages was not affected by treatment with N1177 (concentration range 0 to 2.5 mg/ml) for 24 h or 48 h. Treatment of J774 macrophages with N1177 did not induce expression of the inflammatory cytokines TNF-α or IL-6. After incubation with fluorescently labelled E. coli, the mean fluorescence was not different between control- and N1177-treated macrophages, indicating that N1177 did not influence the phagocytosis capacity of J774 macrophages. In vivo, N1177 had no effect on the density of non-ruptured plaques (35.0$\pm$4.3 HU before injection versus 37.6$\pm$4.4 HU 2 h after injection of N1177; $p>0.05$). However, after induction of mechanical plaque rupture, the density of the atherosclerotic plaques increased from 40.0$\pm$4.2 HU before injection to 75.9$\pm$5.1 HU 2 h after injection of N1177 ($p<0.001$).
Conclusion: Our results indicate that N1177 is a safe contrast agent that can identify ruptured atherosclerotic plaques.

1257 Is there a correlation between coronary artery plaque burden assessed by cardiac CT and serum levels of inflammatory biomarkers for the detection of coronary atherosclerosis?

J. Rixe, A. Rolf, A. Koch, H. Nef, H. Moellmann, H. Steiger, D. Erkapic, C.W. Hamm, T. Dill. *Kerckhoff Klinik GmbH, Bad Nauheim, Germany*

Background: The role of inflammation for atherosclerosis is well established, but data emphasizing the correlation of plaque burden to serum levels of biomarkers are missing. Since Computed Tomography (CT) is the only non–invasive technique that permits the detection of coronary plaques, we sought to investigate the relation between coronary plaque burden assessed by Dual Source-CT (DSCT) and the serum levels of inflammatory markers.
Methods: 145 patients (90 male, mean age 53$\pm$11y) with suspected Coronary Artery Disease underwent DSCT (Siemens Somatom Definition). Serum levels of Myeloperoxidase (MPO), Troponin T (TnT), N–terminal pro–BNP (ntBNP) and High Sensitivity–CRP (hsCRP) were determined. CT data sets were assessed with a dedicated software (Siemens Circulation). Coronary plaque burden was evaluated calculating total plaque volumes and plaque composition (calcified, mixed, non-calcified) using curved multiplanar reconstructions.
Results: Serum levels for all subgroups are given in table 1. Standard deviations were high for all biomarkers, but patients with plaque had significantly higher serum levels than patients without plaque, except for TnT. Among patients with coronary plaque, there were no statistical significant differences in serum concentrations of any biomarker except for hsCRP, that reached the lowest serum level in patients with calcified plaque (1.9$\pm$1.8 mg/l) and the highest for those with non–calcified plaque, respectively (5.2$\pm$9.4 mg/l, $p < 0.05$ if compared to other subgroups).

Table 1

	n	MPO (pmol/l)	TnT (ng/ml)	ntBNP (pg/ml)	hsCRP (mg/l)
All Patients	145 (100%)	231.6±271.2	0.013±0.064	71.3±106.4	2.7±4.6
No plaque in DSCT	54 (37.2%)	179.3±141.4	0.003±0.005	46.2±38.1	1.9±1.7
Plaque in DSCT	91 (62.8%)	247.2±298.7	0.019±0.08	89.1±125.98	2.9±5.4
Calcified plaque	37 (25.5%)	253.5±286.3	0.03±0.12	92.3±145.3	1.9±1.8
Non-calcified plaque	11 (7.6%)	248.4±200.2	0.02±0.02	37.2±39.7	5.2±9.4
Mixed plaque	43 (29.7%)	223.6±251.6	0.013±0.03	101.1±118.3	2.5±2.3

Conclusion: The presence of coronary plaque in cardiac CT is related to an increase of serum levels of MPO, ntBNP and hsCRP, but not of TnT. For different plaque compositions, serum concentrations of cardiac biomarkers do not differ significantly, except for hsCRP, that achieves highest serum levels in patients with non – calcified plaque.

1258 Coronary CT angiographic screening of subclinical coronary atherosclerosis in patients with acute stroke

Y.E. Yoon, K.H. Jeon, E.J. Chun, S.I. Choi, H.J. Bae, J.W. Suh, D.J. Choi, C.H. Kim, H.J. Chang. *Seoul National University, Seoul, Korea, Republic of*

Background: The prognosis of patients with cerebrovascular disease (CVD) is critically influenced by coronary artery disease (CAD). The identification of CAD in stroke patients could allow more effective, targeted, and cost-effective treatment. However, there are no data available on the incidence and severity of CAD in patients with CVD and no history of a coronary event. In the present study, we prospectively investigated the incidence of subclinical CAD in patients with acute stroke using coronary CT angiography (CCTA) and compared to results with conventional risk stratification algorithm.
Method: One-hundred ninety consecutive patients with acute ischemic stroke or transient ischemic attack (TIA) (63$\pm$12 years, male 56%) were included during the period from May, 2007 to January, 2008. Patients with a history of angina, myocardial infarction and revascularization were excluded. Patients underwent CCTA, using 64 slice multi-detector CT and carotid MR angiography (MRA). The presence and severity of stenosis for each arterial segments were determined on CCTA and MRA. Using Framinghm risk scoring (FRS), we calculated a 10-year risk for coronary events on all patients.
Results: Atherosclerotic plaques were identified in 112 (59%) individuals, 32 (17%) subjects had significant ($\geq$50%) diameter stenosis, and of those, 8 (4%) had severe ($\geq$75%) stenosis: single-vessel CAD in 69% of patients, 2-vessel CAD in 22%, and 3-vessel CAD in 9%. When patients were stratified by their 10-year risk for coronary events, only 8 (25%) of patients with significant stenosis on CCTA were classified into high risk ($>$20%), and 21 (66%) of patients with significant stenosis on CTA showed no luminal narrowing on carotid MRA.
Conclusions: Subclinical CAD, oftenly associated with CVD was effectively identified using CCTA. In a population of CVD without history of a coronary event, conventional risk stratification algorithm and carotid MRA showed a limited value to identify patients at risk. An active investigation of CAD using CCTA might be considered in CVD patients in order to plan optimal, comprehensive management.

1259 Multislice computed tomography coronary angiography predicts long-term outcome in patients with suspected coronary artery disease

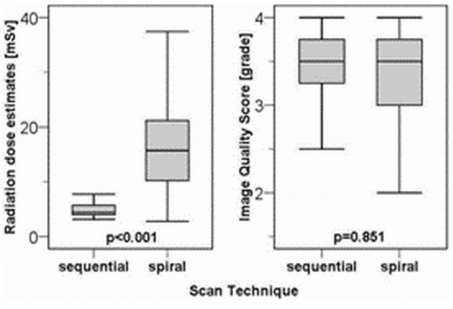
M. Pasowicz, T. Miszalski-Jamka, P. Klimeczek, R. Banys, M. Krupinski, K. Bury, K. Nycz, M. Lada, B. Laskowicz. *Center for Diagnosis, Prevention and Telemedicine, John Paul II Hospital, Krakow, Poland*

Purpose: The aim of the study was to assess the long-term prognostic value of multislice computed tomography (MSCT) in patients with suspected coronary artery disease (CAD).
Methods: Clinical and MSCT data were analyzed in consecutive patients scheduled for MSCT coronary angiography due to suspicion of obstructive CAD. MSCT was performed using 16-slice and 64-slice MSCT systems (Somatom Sensation 16 and 64 Cardiac, Siemens, Erlangen, Germany). MSCT angiograms were assessed for the presence, luminal narrowing severity, location, and type (non-calcified, mixed or calcified) of coronary atherosclerotic plaques. A 17-segment model of coronary arteries was used for analysis. 494 patients (259 males, 235 females, mean age 58.2±9.8 years) were followed for 1308±318 days. Cardiac events (cardiac death, nonfatal myocardial infarction (MI), late revascularisation (>3 months)) were related to clinical and MSCT data. The Cox proportional-hazards model was applied in a stepwise forward fashion to identify univariate and multivariate predictors of outcome. Each variable's risk was expressed by a hazard ratio (HR) with a 95% confidence interval (CI). Event-free survival was estimated by the Kaplan-Meier method and compared between groups by the log-rank test.
Results: Coronary plaques were found in 339 patients. Cardiac events occurred in 40 patients (9 cardiac deaths, 8 MIs and 27 late revascularisations). Age>60 years (HR 2.23; 95%CI:1.18-4.19;p=0.013), diabetes mellitus (HR 2.18; 95%CI:1.00-4.73;p=0.049), presence of a plaque (HR 4.44; 95%CI 1.58-12.48;p=0.005), presence of an obstructive plaque (HR 4.59; 95%CI:2.40-8.76;p<0.001), number of segments with any plaque(s) (HR 1.28 per segment; 95%CI:1.17-1.39;p<0.001), with noncalcified plaque(s) (HR 1.55 per segment; 95%CI:1.26-1.91; p<0.001), with mixed plaque(s) (HR 1.59 per segment; 95%CI:1.30-1.95;p<0.001) and with calcified plaques (HR 1.15 per segment; 95%CI:1.03-1.28;p=0.01) demonstrated unadjusted association with adverse outcome. By multivariate analysis, the independent predictors of events were presence of any obstructive plaque (HR 2.9; 95%CI:1.48-5.66;p=0.002), number of segments with any plaque(s) (HR 1.23 per segment; 95%CI:1.09-1.37;p<0.001) and with noncalcified plaque(s) (HR 1.27 per segment; 95%CI:1.02 to 1.57; p=0.03). 5-year event free survival was 97% for normal coronary arteries, 93% for nonobstructive plaque(s) and 84% for obstructive plaque(s) (p<0.0001).
Conclusions: MSCT predicts outcome in patients with suspected CAD. This imaging modality may stratify patients into low, intermediate and high risk groups for adverse cardiac events.

1260 Impact of prospective ECG-triggered sequential scanning in coronary CT angiography on radiation dose and image quality: A subgroup analysis of the PROTECTION I study

B. Bischoff, T. Meyer, F. Hein, M. Hadamitzky, A. Will, S. Martinoff, J. Hausleiter. *Deutsches Herzzentrum Muenchen, Munich, Germany*

Background: One strategy for radiation dose reduction of coronary CT angiography (CCTA) is the use of a prospective ECG-triggered sequential scanning mode in patients with slow and stable heart rates. The international multicenter PROTECTION I (Prospective Multicenter Study OnRadiaTion Dose Estimates Of Cardiac CT Angiography IN Daily Practice) study was an observational trial to analyse radiation dose and image quality of CCTA. Aim of this pre-specified PROTECTION I subgroup analysis was to determine radiation dose and image quality of sequential technique in comparison to the standard spiral image acquisition.
Methods: For PROTECTION I, 50 world-wide study sites provided images and scan related data of all consecutive CCTAs performed during a 1 month period. Image quality was assessed in all 99 sequential scans and in 424 randomly selected spiral 64-slice CCTAs based on a 4-point image quality score (1: non-diagnostic – 4: excellent). Radiation dose estimates were derived from the dose-length-product (DLP) and a conversion factor (0.014 mSv mGy^{-1} cm^{-1}).
Results: The sequential scan mode was used in only 6% of all 1546 CCTAs performed on a 64-slice system. In patients scanned with the sequential mode, heart rate was significantly lower compared to patients with spiral image acquisition (56 vs. 63 min^{-1}; p<0.001). Although the sequential scan was associated with radiation dose reduction of 69%, there was no significant difference in diagnostic image quality between both groups (Figure).
Conclusion: The PROTECTION I study shows the high potential of the prospective ECG-triggered sequential scanning mode for radiation dose reduction without imparing image quality in coronary CT angiography in appropriate patients.



1261 Diagnostic accuracy of non-invasive coronary angiography with 320-slice dynamic volume computed tomography

A. Nasis[1], M.C. Leung[1], P.R. Antonis[1], J.D. Cameron[1], I.T. Meredith[1], W.S. Moir[1], S.A. Hope[1], J.M. Troupis[2], M.P. Crossett[2], S.K. Seneviratne[1]. *[1]MonashHeart, Melbourne, Australia; [2]Monash Medical Centre, Melbourne, Australia*

Purpose: Multislice CT coronary angiography (CTCA) is currently widely used in the detection of coronary atherosclerosis, with its main strength being the exclusion of significant coronary stenoses. There is no data assessing the diagnostic accuracy of the latest 320-slice dynamic volume CTCA system, which has the advantage of imaging the entire coronary tree in a single heart beat, potentially reducing artefact. We sought to determine the diagnostic accuracy of 320-slice CTCA, using invasive coronary angiography (ICA) as the gold standard.
Methods: Forty-one sequential patients (26 male, mean age 64±14 years) with suspected coronary artery disease who underwent both 320-slice CTCA (320 x 0.5mm slice collimation, 0.35s gantry rotation time, 0.35-0.70s scan time, 75ml contrast at flow rate 6 mL/s) and ICA within 45 days were included in the analysis. Patients with prior PCI or CABG were excluded. ICA images were assessed by a single observer unaware of CTCA results. CTCA studies were assessed by consensus between two observers blinded to the results of ICA. All available coronary segments were included in the analysis, regardless of size. Lesions with >50% diameter stenoses by visual estimate were considered significant. Analysis was performed on a per-segment, per-vessel and per-patient basis.
Results: Twenty-five patients (61%), 42/169 vessels (25%) and 61/596 segments (10%) had at least one significant stenosis diagnosed on ICA. Mean heart rate was 64±6 during image acquisition, with 6 patients (15%) in atrial fibrillation. No patients were excluded because of impaired image quality. The diagnostic accuracy for detecting significant coronary stenoses is summarised in Table 1.

Table 1

	Sensitivity	Specificity	PPV	NPV
Per-patient	96% (78-99)	94% (67-99)	96% (77-99)	94% (67-99)
Per-vessel	76% (60-87)	97% (91-99)	89% (73-96)	93% (86-96)
Per-segment	74% (61-84)	98% (96-99)	80% (66-88)	97% (95-98)

PPV = positive predictive value; NPV = negative predictive value; 95% confidence intervals in brackets.

Conclusions: 320-slice dynamic volume CTCA provides high diagnostic accuracy in the diagnosis of coronary artery disease, particularly in the exclusion of significant stenoses across all coronary segments, regardless of size.

POSTER SESSION 2

MODERATED POSTERS 1
CLINICAL AND GENETIC ASPECTS OF CARDIOMYOPATHIES

P1262 Myocardial fibrosis as an independent predctor of atrial fibrillation in HCM. A cardiovascular magnetic resonance study

R. O'Hanlon[1], C. Bucciarelli-Ducci[1], A. Grasso[1], R. Wage[1], J.C. Moon[2], D. Dawson[1], W.J. Mckenna[2], P. Elliott[2], D.J. Pennell[1], S.K. Prasad[1]. *[1]Royal Brompton Hospital, London, United Kingdom; [2]The Heart Hospital, London, United Kingdom*

Introduction: Atrial fibrillation (AF) is the commonest arrhythmia in HCM, developing in approximately 20% of all cases, with an annual incidence of 1-3% per year. The risk of AF developing is 4-6 fold greater in HCM than in the general population. It is associated with increased risk of thromboembolism, heart failure and death. Myocardial fibrosis is an important risk factor for the development of AF. Cardiovascular magnetic resonance (CMR) is the gold standard to visualise replacement myocardial fibrosis in vivo. Aim:To determine if the presence of myocardial fibrosis is an independent predictor of AF in patients with HCM.
Methods: Between 2001 and 2005, 126 HCM patients underwent CMR. Oucome clinical data, cardiac events, and investigations were collected prospectively. The severity of mitral regurgitation, left atrial indexed volumes, LV mass and ejection fraction were noted. The median duration of follow up was 1076 days. CMR volumes, mass, and ejection fraction were analysed using customised software (CMRTools, London). Myocardial fibrosis was assessed using standard late enhancement techniques with gadolinium-DTPA contrast agent. The amount of fibrosis was quantified from sequential short axis slices using customised software

(MASS, Medis, Leiden). The total amount of fibrosis was expressed as a percentage per segment, as a total in grams, and as a percentage of the total left ventricular mass. A Cox proportional hazard model was applied to correlate the incidence of new onset AF with the presence of myocardial fibrosis.
Results: Of 126 patients, 87 (69%) had detectable myocardial fibrosis. In those with myocardial fibrosis, the incidence of new onset AF over the follow up period was 21% vs 5% for those without (p=0.033). The presence of myocardial fibrosis was associated with an 8-fold increased risk of the development of AF (HR 8.45; CI 1.12-65.53; p=0.038). Multivariate analysis demonstrated that fibrosis remained an independent predictor of AF regardless of mitral regurgitant severity, ejection fraction, indexed LV mass, and LA indexed volumes.
Conclusion: The presence of LV myocardial fibrosis in HCM is an independent predictor of the development of new-onset AF over a median of approximately three years. This may have important implications for risk stratification, patient monitoring, decision to anticoagulate, and maintenance of sinus rhythm in this population. Potential mechanisms may be associated diastolic dysfunction resulting in changes to atrial architecture. LV changes may also reflect increased atrial fibrosis but that is more difficult to detect with present techniques.

P1263 Primary malignant tumors of the heart: which treatment?

C. Lestuzzi[1], F. Santini[2], A. De Paoli[3], S. Frustaci[4], E. Viel[1], M. Telesca[2], L. Tartuferi[1], V. Canzonieri[5], A. Mazzucco[2], N. Meneguzzo[1]. [1]*Cardiology, Centro di Riferimento Oncologico, National Cancer Institute, Aviano (Pn), Italy;* [2]*Division of Cardiac Surgery-Università di Verona, Verona, Italy;* [3]*Radiation Therapy, Centro di Riferimento Oncologico, National Cancer Institute, Aviano (Pn), Italy;* [4]*Oncology, Centro di riferimento Oncologico, National Cancer Institute, Aviano (Pn), Italy;* [5]*Pathology, Centro di Riferimento Oncologico, National Cancer Institute, Aviano (Pn), Italy*

Purpose: There is no definite therapy for primary malignant tumors of the heart (PMTH), and only single case reports or small series have been described. We report the follow-up (FU) of 14 PMTH treated with surgery (Surg), chemotherapy (CT) or radiotherapy (RT) both conformational (CRT) or intensity-modulated (IMRT) or a combination of these treatments.
Methods: The clinical records of 14 patients (pts) aged 24-71 (mean 38,6) with PMTH treated at our institutions were reviewed, evaluating the outcome at the last available follow-up. Tumors were: 13 sarcomas (5 leiomio, 3 myxo, 2 angio, 1 rhabdomio, 1 schwannoma, 1 malignant fibrous hystiocitoma), 1 lymphoma; they were localized in the left (6) or right (2) or both atria (3), right ventricle (1) or pulmonary artery (2). Two had distant metastases. Surg was radical in 4 pts, non radical or simple biopsy in 10. Pts undergoing CT and/or RT had a regular echocardiographic FU. The FU of the tumor was based on echocardiography, Computed Tomography and/or Magnetic Resonance imaging.
Results: Radical SURG was followed by adjuvant (A) RT in 1 case, by CT in 1; 2 pts had no A therapy. The pts without radical Surg received CT alone in 5 cases, CT and RT in 4, no therapy in one. Drug used were Epiadriamicin/Ifosfamide in 7 cases, poliCT in 4; RT doses ranged from 40 to 59 Gy. Mild left ventricular dysfunction (LVD) observed in half of the pts treated by CT and/or RT, but it never led to congestive heart failure. Four pts with relapse and one with residual tumor after CT had redo radical SURG; among the five, one died at Surg, the other survived and had A CT (3 pts) or A RT (1 pt). At last follow-up 8 pts had died of progressive or metastatic disease after 4-48 (mean 18) months, 5 are alive in complete remission (CR) at 9, 10, 24, 62 months and 12 years respectively after first SURG. The shorter survival was observed in pts treated with SURG alone (one relapsed and died after 4 months) or CT alone (6,8,9 and 10 months respectively). The longer disease-free survival was obtained in pts treated with radical SURG plus A CT and/or RT or, when radical Surg was technically impossible, by combined CT and RT
Conclusions: PMTH have usually a poor prognosis, but a integrated treatment ideally including radical surgery, CT and RT may prolong survival and even lead to complete remission. CRT and IMRT seems to be effective and, reducing the radiation burden on the heart, is usually well tolerated, even if associated with the potentially cardiotoxic anthracycline CT, at least on the medium-term period, even if a longer FU is necessary.

P1265 Diagnostic contribute of left ventricular endomyocardial biopsy in patients with clinical phenotype of hypertrophic cardiomyopathy

C. Chimenti[1], A. Cioppa[2], R. Verardo[1], M. Rossi[1], M. Agrusta[2], M.A. Russo[1], P. Rubino[2], A. Frustaci[1]. [1]*La Sapienza Universita, Rome, Italy;* [2]*Montevergine Cardiology Clinic, Mercogliano, Italy*

Purpose: The definition of hypertrophic cardiomyopathy includes heterogenous entities with different treatment options and prognosis. Non invasive imaging techniques are often inadequate for a differential diagnosis while the role of endomyocardial biopsy is still debated. The purpose of the present study is to determine whether left ventricular endomyocardial biopsy (LVEMB) may have a role for the histologic differentiation of patients with clinical phenotype of hypertrophic cardiomyopathy.
Methods: From January 1988 to May 2008, 139 consecutive patients (91 M, 48 F, mean age 44.2±15.9 ys) with unexplained left ventricular hypertrophy (maximal wall thickness $\geq$ 15 mm) and normal or elevated QRS voltages, underwent cardiac catheterisation, coronary angiography and LVEMB. Family history without histological diagnosis was present in 15% of cases. Endomyocardial samples ($\geq$ 4 specimens per patient, $\geq$ 3 mm^2 each) were processed for histology, histochemistry and transmission electron microscopy.
Results: LVEMB was diagnostic in all cases. Histology showed severely hypertrophied cardiomyocytes, often in disarray, consistent with hypertrophic cardiomyopathy in 114 patients (82%). In 17 patients (12.2%) histology showed a myocardial storage disease presenting as primary cardiomyopathy, consisting in Fabry disease in 13 patients (9.3%), and in glycogen-storage disease in 4 (2.9%), due to acid maltase deficiency in 1 case, LAMP2 mutation in 1 and PRKAG2 mutation in 1. In 8 patients (5.8%) a myocardial infiltrative disease, consisting in amyloidosis (5 cases,3.6%) hemochromatosis (2 cases, 1.4%), and sarcoidosis (1 case, 0.7%) was diagnosed. The procedure had non fatal low rate complications (vasovagal reaction to arterial puncture in 2%, local bleeding in 1%, systemic embolization with transient brain ischemia in 0,7%).
Conclusions: LVEMB recognises unpredictable specific histologic changes in up to 18% of patients with clinical phenotype of hypertrophic cardiomyopathy. Particularly for storage and infiltrative diseases specific therapy may modify patients' clinical outcome.

P1266 Short- and long-term prognosis of Tako-tsubo cardiomyopathy in the Italian Multicenter Registry

M. Previtali[1], A. Repetto[1], R. Camporotondo[1], P. Faggiano[2], E. Baldini[3], R. Citro[4], D. Bovelli[5], G. Pasquetto[6], E. Bossone[7], C. Klersy[1] on behalf of Italian Multicenter Registry. [1]*IRCCS Pol. S.Matteo Università di Pavia, Pavia, Italy;* [2]*Spedali Civili Università di Brescia, Brescia, Italy;* [3]*Ospedale Civile, Legnano, Italy;* [4]*Ospedale S.Luca, Vallo Della Lucania (Sa), Italy;* [5]*Ospedale S.Maria, Terni, Italy;* [6]*Ospedale Civile, Mirano (Ve), Italy;* [7]*Ospedale Costa d'Amalfi, Cava Dei Tirreni (Sa), Italy*

Purpose: Tako-tsubo cardiomyopathy (TTC) is a recently described syndrome whose aetiology and prognosis remains to be defined. The aim of the study was to assess the short- and long-term prognosis of TTC and its determinants in a large population of pts included in the Italian Multicenter Registry.
Methods: From 2003 to 2008, 125 pts with TTC were prospectively identified and followed up
(F-U) for a median time of 13 months (p25-p75, 7-25 months) in 14 Italian centers. The diagnosis of TTC was based on these criteria: 1) acute symptoms associated with ST-T changes; 2) normal or $<$50% diseased coronary arteries; 3) reversible apical or midventricular wall motion abnormalities (WMA); 4) absence of diseases known to produce TTC-like WMA. Events considered included cardiac death and major cardiac complications during hospitalization and death from any cause, major complications and recurrences of TTC during
F-U. Predictors of short- and long-term prognosis were evaluated by univariate and multivariate logistic regression model and Cox analysis.
Results: The population included 122 women (97%), mean age was 67±11 years; risk factors included hypertension in 59%, hypercholesterolemia in 45%, diabetes in 7% and smoking in 22% of pts; a triggering event was identified in 64%. Chest pain was present in 88% and dyspnoea in 22%. Admission ECG showed ST-elevation in 42% and negative T waves in 38%; 82% of pts showed apical and 18% midventricular WMA; acute LV ejection fraction (EF) was 42±9%; significant ($>$2/4+) mitral regurgitation (MR) was present in 7%. Mean troponine I levels were 5±13 ng/ml. During hospitalization no pt died and 25 (20%) had major complications (LV failure and shock in 11 pts, major ventricular and supraventricular arrhythmias in 9, LV thrombosis in 5). In a multivariate logistic regression model dyspnoea at presentation (OR 3.0, 95%CI: 1,1-8,3), acute MR (OR 2.95, 95%CI: 0.67-12.8) and 2-D echo WM score index (OR 2.8, 95%CI: 0.79-9.82) were significant predictors of short-term prognosis. During F-U, 11 events (9%) occurred (1 non-cardiac death, 1 LV failure, 3 recurrences of TTC, 6 supraventricular arrhythmias). At multivariate Cox analysis no significant predictor of long-term prognosis was identified owing to the small number of events.
Conclusions: 1) During the acute phase TTC is characterized by a significant rate of complications but no death; 2) Dyspnoea at admission, major MR and extent of WMA are significant predictors of short-term prognosis; 3) In our population long-term prognosis of TTC is very good, with no cardiac death and a low incidence of recurrences.

P1267 Tissue determinants of ECG abnormalities in arrhythmogenic right ventricular cardiomyopathy: a study performed by cardiac contrast-enhanced magnetic resonance

M. Perazzolo Marra[1], B. Bauce[1], A.K. Steriotis[1], F. Corbetti[2], I. Rigato[1], E. Mazzotti[1], D. Corrado[1], L. Cacciavillani[1], C. Basso[3], A. Nava[1]. [1]*Department of Cardio, Thoracic and Vascular Sciences, Univerisity of Padua, Padua, Italy;* [2]*Service of Radiology, University of Padua Medical School, Padua, Italy;* [3]*Department of Medic-Diagnostic Sciences and Special Therapies, University of Padua Medical School, Padua, Italy*

Introduction: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is characterized by myocardial necrosis and by fibro-fatty replacement. This pathologic process constitutes the basis for the ECG abnormalities used

for diagnostic criteria. Contrast-enhanced cardiac magnetic resonance (CE-MR) allows a clear visualization of right (RV) and left ventricular (LV) of fat and fibrosis replacement. Aim: To evaluate the relationship between traditional ECG in ARVC/D and tissue impairment detected by CE-MR.
Methods: thirty ARVC/D patients affected by a moderate or severe form of the disease were evaluated. The following ECG parameters were analysed: RV conduction delay, right bundle branch block (BBDX), ST-segment elevation in V1-V2, negative T waves, epsilon wave. CE-MR images were analyzed in long-axis short axis and RV two-chamber views after intravenous injection of 0.02 mmol/kg of Gd-DTPA. Diagnosis of ARVC/D was based upon the Task Force criteria.
Results: Among the 30 ARVC/D patients (mean age 36±15 yrs, range 16 to 72), 20 (66,5%) were males. An abnormal ECG was found in 86% pts. A BBDX was found in 3 (10%) pts, an inferior Q wave in 5 (16,7%); ST-segment elevation V1-V2 in 8 (26,7%), a negative T wave on V1-V3 in 8 (26,7%) and a negative T wave beyond V3 in 8 (26,7%). Moreover, a minority of pts showed negative T wave in lateral (6,7%) and inferior (16,7%) leads. Epsilon wave was described in only 3 (10%) pts and in 13 (43,3%) were also defined positive SAECG. Statistical analysis demonstrated a strong correlation between RV fatty infiltration and inferior Q waves ($p<0,001$), whereas RV thinning was more common in pts with negative T wave in V1-V3 (p=0,015). Left ventricular dilatation/dysfunction was related to presence of inferior Q waves (p=0,032), ST-segment elevation in V1-V2 (p= 0,035) and negatives T waves beyond V3 (p=0,023). Moreover, ST-segment elevation was also related to LV fatty infiltration (p=0,031) and LV delayed enhancement (p=0,014). Finally, there was a strong correlation between presence of epsilon wave and LV fatty replacement (p=0,024). SAECG were more common in patients with LV delayed enhancement on anterior wall (p=0,03). Multivariate analysis confirmed the association between negative T waves beyond V3 and LV dilatation/dysfunction (p=0,043, O.R. 10,5; I.C. 1,07-102,47).
Conclusion: The typical ECG features usually found in pts affected by ARVC/D reflect the presence of a pathologic morphological and tissue substrates detectable with CE-MR. Thus a careful evaluation of ECG parameters can provide important data for diagnosis and assessment of ARVC extent.

P1268 Long-term outcome of percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy

L. Faber[1], D. Welge[1], H. Seggewiss[2], D. Hering[1], O. Oldenburg[1], D. Horstkotte[1]. [1]*Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany;* [2]*Leopoldina Krankenhaus, Schweinfurt, Germany*

Introduction and methods: To define the value of septal ablation (PTSMA) as compared to surgical myectomy, we analyzed the long-term outcome of the first 347 consecutive patients (pts., mean age: 54±15 years) treated with PTSMA for symptomatic hypertrophic obstructive cardiomyopathy (HOCM) between 1996 and 2005. Data were acquired by outpatient examination in our own institution or by phone contact with the pts.' local cardiologist. Pts. who could not be traced neither personally nor via their local physician or their health insurance company were considered "lost" to follow-up.
Results: During in-hospital stay following intervention, 4 pts. (1%) died. Mean CK rise was 534±258 U/l. A DDD-pacemaker (DDD-PM) had to be implanted in 26 pts. (7%) for PTSMA-induced AV conduction problems.
Follow-up was 98% complete (n=345). During follow-up (58±30 [range: 3-131] months), 26 pts. (8%) died, 10 of these (3%) from non-cardiac, and 16 (5%) from cardiovascular causes. Survival was 93% at 5 years, and 90% at 10 years. A re-intervention for significant residual or recurrent outflow obstruction (LVOTO) was necessary in 27 pts. (8%; re-PTSMA: 18 pts.; myectomy: 9 pts). These cases included, at their last follow-up visit 308 pts. (89%) were in functional class I or II. There were 6 additional DDD-PM implantations (2%) and 12 (4%) ICD implantations (3 for secondary, 9 for primary prevention of sudden cardiac death) in our pt. cohort. The most frequent clinical problem was atrial fibrillation which occurred in 40 pts. (12%), and which was refractory to rhythm control attempts in 24 pts. (7%).
Conclusions: During long-term follow up following PTSMA, a persistent clinical improvement was observed. A second intervention (surgical or catheter-based) was needed in about 10%. Atrial fibrillation was a frequent problem. A total mortality rate of 26/347 (7%) or 1.7%/pt.-year, including all procedure-related deaths, compares favourably with the natural course of this pt. group with severe disease, and seems to be equivalent to post-myectomy data.

P1269 Genotype-to-phenotype correlations in dilated and hypertrophic cardiomyopathy: initial results from the German Heart Failure Network

S. Waldmueller[1], G. Gelbrich[2], P. Binner[1], M. Loeffler[2], H. Schunkert[3], T. Scheffold[1] on behalf of German Heart Failure Network. [1]*University of Witten/Herdecke, Dortmund, Germany;* [2]*Institute for medical informatics, statistics and epidemiology, Leipzig, Germany;* [3]*University Hospital Schleswig-Holstein, Luebeck, Germany*

Purpose: A major goal of the German Heart Failure Network was to unravel novel genotype-to-phenotype correlations in patients suffering from either dilated or hypertrophic cardiomyopathy. These correlations may be of prognostic value and could provide a base for phenotype-guided molecular genetic testing.
Methods: A total of 178 HCM and 651 DCM patients were genotyped by conventional sequencing of the genes MYH7 and MYBPC3. Two-dimensional echocardiography was performed in parasternal M-mode recordings. In addition, all DCM patients underwent left heart catheterization according to national standard protocols.
Results: Among the HCM patients, 73 had at least one putative disease causing mutation in MYH7 or in MYBPC3 and 90 had no suspicious variant at all in these two genes (herein referred to as "mut-"). Mutation-positive patients were younger than those with no mutation detected at the time of examination (49±16 vs 57±15 years, P=0.001) and at the time of first diagnosis of heart failure (37±17 vs 50±16 years, $P<0.001$). Mutation-positive patients more frequently had a pacemaker or defibrillator implanted (n=24, 33% vs n=15, 17%, P=0.018) and more often had a history of septum myectomy (n=8, 11% vs n=2, 2%, P=0.044). The end-systolic left atrial to end-diastolic left vetricular diameter ratio was 1.10±0.26 in mutation-positive patients compared to 0.98±0.21 in those patients with no mutation detected (P=0.002). This increase was moderate in patients with a single MYH7 mutation (1.13±0.25, P=0.006 vs mut-) and higher in patients with a single premature termination codon (caused by nonsense or frameshift mutations) in MYBPC3 (1.26±0.25, $P<0.001$ vs mut-, P=0.058 vs single MYH7), but it was not present in patients with mutations not belonging to either of these subgroups (0.98±0.21, P=0.964 vs mut-). Upon examination of the DCM patients, no significant phenotypic difference was observed between patients with (n=80) and without (n=491) mutations. However, the ratio of nonsense and frameshift vs missense mutations in MYBPC3 was found to be reduced in DCM patients as compared to HCM patients (0/33, 0% vs 16/30, 53%, $P\leq0.001$).
Conclusions: The data presented here suggest that the presence of a mutation in either MYH7 or MYBPC3 is a negative predictor of the outcome of HCM, but not DCM. Mutations leading to a premature termination codon in MYBPC3 appear to predispose to HCM, rather than to DCM, and are associated with a larger relative size of the left atrium than other types of mutations.

MODERATED POSTERS 2
ACUTE CORONARY SYNDROMES – PITFALLS AND DILEMNIAS

P1271 Abciximab vs placebo in patients without ST-elevation acute myocardial infarction undergoing non emergent percutaneous coronary interventions: an updated meta-analysis of randomised trials

G. Ferrante[1], F. Andreotti[1], G. Niccoli[1], G. Liuzzo[1], R.A. Montone[1], N. Cosentino[1], P. Barlis[2], D. Locca[3], A.G. Rebuzzi[1], F. Crea[1]. [1]*Università Cattolica del Sacro Cuore, Rome, Italy;* [2]*The Northern Hospital, Victoria, Australia;* [3]*The London Chest Hospital, London, United Kingdom*

Purpose: We aimed at assessing the long term benefit of abciximab administration compared to placebo as adjuvant therapy in patients without ST elevation acute myocardial infarction (STEMI), undergoing non emergent percutaneous coronary interventions (PCI).
Methods: We performed a meta-analysis of ten randomised trials that compared intravenous administration of abciximab vs placebo in patients without STEMI undergoing non emergent PCI. Death, myocardial infarction (MI), target vessel revascularization (TVR) or target lesion revascularization (TLR), at 6 to 12 months follow up (FU), and the safety endpoint of major bleeding were assessed. Binary outcomes were combined with DerSimonian and Laird method according to a random effect model, and the risk of events was expressed as relative risk (RR) with 95% Confidence Interval (CI). Publication bias was assessed with the use of Peter's test. A random effect metaregression evaluated the effect of the patient's risk profile (expressed as logarithm odds of MI in the control group) on the odds ratio of MI (expressed as logarithm) associated with abciximab administration.
Results: A total of 10529 patients were included. FU duration was 6 months in 4 studies and 12 months in 6 studies. No publication bias was detected for each endpoint. Abciximab was associated with a significant reduction of the risk of MI [RR 0.72, 95%CI (0.59-0.88), p= 0.001] and with no significant difference in the risk of death [RR 0.86, 95%CI (0.69-1.08), p=0.19], TVR/TLR [RR 0.94, 95%CI (0.87-1.02), p=0.15] and major bleeding [RR 1.04, 95%CI (0.71-1.52), p= 0.86] compared to placebo. At metaregression analysis, increasing patient's risk profile was associated with a higher benefit of abciximab, in terms of reduction of odds ratio of MI [b -0.56, 95% CI (-0.96, -0.17), p=0.005].
Conclusions: In patients without acute STEMI, undergoing non emergent PCI, abciximab is associated with nearly 30% risk reduction of MI at 6 to 12 months FU, with no significant reduction in the risk of death or TVR, and no increase in the risk of major bleeding. The benefit of abciximab, in terms of MI risk reduction, increases linearly with increasing patient's risk profile.

P1272 More than three simultaneous antithrombotic drugs: no benefit, just higher bleeding risk. Metaanalysis of nine randomized trials

R. Petr, P. Widimsky, Z. Motovska. *University hospital Kralovske Vinohrady, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic*

Background: Bleeding complications are increasingly recognized as important negative prognostic factor in patients with acute coronary syndromes, especially when they undergo intervention (CAG/PCI/CABG). The number and dosages of various antithrombotic drugs used are the key factors influencing the likelihood of the bleeding complications. The aim of this metaanalysis is to investigate these factors in details.
Methods: With the Medline (Web of Science) search system 64 randomized clinical trials focused on either anticoagulation or antiplatelet therapy of acute coronary syndromes (including trials focused on PCI in ACS) were found. From these, 9 trials were selected for further analysis – these were trials using aspirin and thienopyridine in both groups. The total number of antithrombotic drugs used in each group could be clearly analyzed from the manuscript. These 9 trials enrolled alltogether 15 860 patients with ST-elevation or non-ST-elevation acute coronary syndromes (including unstable angina). For the purpose of this metaanalysis, the patients were divided into two groups:
Group A: patients in whom 3 antithrombotic drugs were used during the hospital stay.
Group B: patients in whom 4 antithrombotic drugs were used during the hospital stay.
Typical example of group A treatment: ASA + clopidogrel + heparin (or bivalirudin)
Typical example of group B treatment: ASA + clopidogrel + GPIIbIIIa inhibitor + heparin (or enoxaparin).
Patient baseline characteristics in both groups did not differ significantly.
Results: see table.

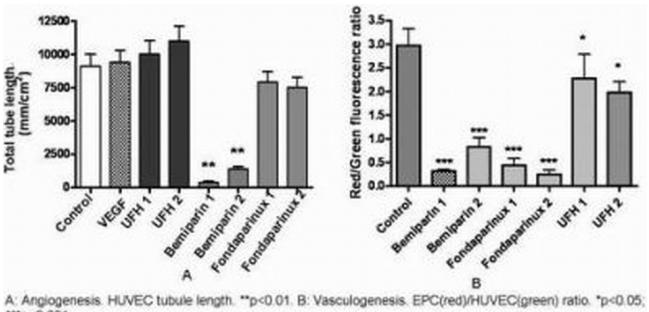
	3 antithrombotic drugs	4 antithrombotic drugs
N	7740	8120
30-day mortality	1,67%	1,61%
Major bleeding complications	2,61%	4,36%
(Re-)infarction	4,82%	4,33%

Conclusions: The simultaneous use of more than 3 antithrombotic drugs increased the risk of bleeding complications without modifying the risk of death, (re-)infarction or stroke.

P1273 Beyond the anticoagulant activity: different effect of glyco-anticoagulants and oligosaccharides on angiogenesis and vasculogenesis

R. Di Stefano[1], M.C. Barsotti[1], E. Da Pozzo[2], S. Bendinelli[2], C. Martini[2], A. Balbarini[1]. *[1]Cardiac, Thoracic and Vascular Department - University of Pisa, Pisa, Italy; [2]Department of Psychiatry, Pharmacology, Neurobiology and Biotechnology - University of Pisa, Pisa, Italy*

Purpose: Anticoagulants are used to reduce complications after acute coronary syndrome. The effects of these drugs on angiogenesis and vasculogenesis, with an important role in plaque destabilization, are not known. Our aim was to test the effect of Bemiparin (B), the low molecular weight heparin with the lowest MW (3600 Da) and the highest anti-FXa/anti-FIIa activity ratio (8:1), and of the synthetic pentasaccharide Fondaparinux (F), a FXa inhibitor, on vasculogenesis and angiogenesis, mediated by endothelial progenitor cells (EPC) and mature endothelial cells (HUVEC), as compared to unfractionated heparin (UFH).
Methods: HUVEC or EPC were treated for 24 h with B (0.01-5 I.U./ml), UFH (0.01-5 I.U./ml) or F (0.0005-0.05 mg/ml) before assay for cell viability (MTS), proliferation (BrdU) and in vitro angiogenesis (matrigel) and vasculogenesis (EPC incorporation on matrigel). Drug doses were chosen as the ones used in clinical practice. For angiogenesis, HUVEC were detached and seeded on matrigel. After 20 h, tubule network was quantified. For vasculogenesis, EPC were detached, stained with DiI and seeded on matrigel together with HUVEC. Incorporation of EPC in the tubules was quantified after 20 h.



A: Angiogenesis. HUVEC tubule length. **p<0.01. B: Vasculogenesis. EPC(red)/HUVEC(green) ratio. *p<0.05; ***p<0.001

In vitro angiogenesis and vasculogenesis

Results: Viability was significantly reduced by the three anticoagulants only at the highest concentration ($p<0.01$); proliferation was not affected. B resulted in a significant reduction of angiogenesis (Fig.1A), while UFH and F had no significant effect. The three drugs significantly decreased vasculogenesis (Fig.1B), with a less relevant effect of UFH.
Conclusions: This is the first report of anticoagulants effect on vasculogenesis. Among the glyco-anticoagulants, B was the only one to show an effect on both angiogenesis and vasculogenesis, while oligosaccharide affected only vasculogenesis.

P1274 Combined results and long-term follow-up in NORVIT and WENBIT with 6837 coronary artery disease patients: Homocysteine-lowering B-vitamin treatment does not prevent major cardiovascular events

M. Ebbing[1], K.H. Bonaa[2], J.E. Nordrehaug[1], P.M. Ueland[3], E. Arnesen[2], H. Refsum[4], I. Njolstad[2], D.W. Nilsen[5], K. Rasmussen[6], O. Nygard[1]. *[1]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; [2]Institute of Community Medicine, University of Tromsø, Tromsø, Norway; [3]Institute of Medicine, University of Bergen, Bergen, Norway; [4]Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [5]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway; [6]Department of Heart Disease, University Hospital of North Norway, Tromsø, Norway*

Objectives: Observational studies have reported associations between circulating total homocysteine (tHcy) concentration and risk of cardiovascular disease. Oral administration of folic acid and vitamin B12 can lower plasma tHcy levels. Our purpose was to assess the effects of homocysteine-lowering treatment in the Norwegian Vitamin Trial (NORVIT) and the Western Norway B-vitamin Intervention Trial (WENBIT) by combined analyses of trial results and long-time follow-up of the two study populations.
Methods: A total of 6837 patients, 76.5% male, mean (SD) age 62.3 (11.0) years, with acute myocardial infarction (AMI) or angiographically verified coronary artery disease, were included between December, 1998 and April, 2004. They were randomly assigned to four groups receiving daily oral treatment with 1) folic acid (0.8 mg)/vitamin B12 (0.4 mg)/vitamin B6 (40 mg), 2) folic acid/vitamin B12, 3) vitamin B6 alone or 4) placebo. Otherwise, they were given conventional medical treatment. The primary end point during the intervention was a composite of AMI, thromboembolic stroke or cardiovascular death. The end point during long-time follow-up was cardiovascular death. Estimates of the hazard ratios (HR) and 95% confidence intervals (CI) were obtained using Cox proportional hazard regression with adjustment for trial.
Results: By 1 to 2 months after randomization, plasma tHcy concentration was lowered by median 25% in the groups receiving folic acid/vitamin B12. During intrial follow-up of median 39 months, the primary end point was experienced by 533 (15.6%) of participants receiving folic acid/vitamin B12 versus 503 (14.7%) of those not receiving such treatment (HR, 1.07; 95% CI, 0.95 to 1.21; P=0.25). The incidence of the separate end points of AMI and thromboembolic stroke did not differ among the groups. During extended long-time follow-up of median 74 months from randomization until September, 2007, a total of 571 (8.4%) of participants died from cardiovascular disease. There was no difference in cardiovascular mortality between groups that had received folic acid/vitamin B12 or not (HR, 1.10; 95% CI, 0.94 to 1.3; P=0.24).
Conclusions: The combined results and long-time follow-up in two large randomized clinical trials with coronary artery disease patients in Norway, are consistent with no beneficial effects of treatment with folic acid/vitamin B12 on major cardiovascular events during intervention or on cardiovascular death during long-time follow-up. Use of homocysteine-lowering B-vitamin supplements as secondary prevention in such patients is not justified.

P1275 Clinical evaluation plus Nt-proBNP versus exercise testing for decision making in acute chest pain of uncertain origin

E. Santas[1], J. Sanchis[1], X. Bosch[2], V. Bodi[1], J. Nunez[1], A. Doltra[2], M. Heras[2], L. Mainar[1], E. Bragulat[2], A. Llacer[1]. *[1]Hospital Clinic Universitari. Universitat de València, Valencia, Spain; [2]Hospital Clínic. Universitat de Barcelona, Barcelona, Spain*

Purpose: Exercise testing constitutes the usual tool for decision making in chest pain units. This policy implies logistic constrains and around 40% of the patients can not exercise.
Methods: We conducted a prospective, randomized study on patients presenting to the emergency department with chest pain of uncertain origin (with no ischemic ECG changes or troponin elevation). A total of 320 patients (160 per study arm) were enrolled. Patients were randomized to either the usual management, involving early (<24 hours) exercise testing, or the new strategy combining Nt-proBNP and a previous validated clinical risk score (including the variables typical chest pain, ≥2 episodes in <24 hours, age ≥67, diabetes and prior coronary angioplasty) without exercise testing. Patients with clinical risk score ≥3 points as well as those patients with risk score <3 but with Nt-proBNP >110 ng/L were directly hospitalized. On the other hand, patients with both clinical risk score <3 and Nt-proBNP <110 ng/L were directly discharged. The primary outcome was

the hospitalization at the day of the index episode. Secondary end points were death, myocardial infarction, readmission by unstable angina or post-discharge revascularization at 6-12 months.
Results: Clinical characteristics were similar in both arms, including the clinical risk score. A total of 50 (31%) patients were discharged at the day of the index episode using the usual management in comparison with 70 (42%) in the new strategy (p=0.03). There were no differences in death or myocardial infarction (n=11, 6.9% vs n=6, 3.8%, p=0.3) or any event (n=13, 8.1% vs n=16, 10%, p=0.7) during follow up. Revascularizations at the index episode were more frequent with the usual management (n=29, 18.1% vs n=13, 8.1%; p=0.01), although the new strategy was associated with a higher rate of planned post-discharge revascularizations (n=8, 5% vs n=1, 0.6%, p=0.04) indicated in the ambulatory setting.
Conclusions: In patients with chest pain of uncertain origin, a strategy combining clinical history and Nt-proBNP, without exercise testing, is simpler and reduce initial emergency hospitalizations in comparison with the usual strategy involving exercise testing. This saving of hospitalizations at the index episode did not increase events during follow up, albeit some patients required late revascularizations planned in the ambulatory setting.

P1276 Beneficial effect of preinfarction angina on in-hospital outcome in patients with acute myocardial infarction

Y. Pak, E. Lykasova, V. Todosiychuk, V. Kuznetsov. *Tyumen Cardiology Center, Tyumen, Russian Federation*

Background: It has been reported that preinfarction angina (PA) occurring shortly before the onset of acute myocardial infarction (AMI) is associated with reduced infarct size, improved left ventricular (LV) function and a favorable outcome after infarction. However scientific evidence about the effects of PA on in-hospital outcome of AMI is open to question. The aim of our study was to assess the relationship between PA and in-hospital outcome of AMI.
Methods: We have studied prospectively 145 patients with AMI. Typical angina within 48 hours preceding AMI was present in 72 patients (group PA) and absent in 73 patients (group non-PA).
Results: In group PA the prevalence of the in-hospital complications were significantly lower (14.0% vs 24.0%, p=0.006). There was a trend toward less in-hospital death (p=0.07) and ventricular fibrillation (p=0.1) in group PA versus group non-PA. The incidence of severe congestive heart failure was significantly lower in group PA (1.0% vs 8.0%, p=0.01). The extent of LV wall motion abnormalities was diminished (28.4±0.9% vs 35.0±1.4%, p=0.0001), LV ejection fraction was higher (41.3±0.1% vs 38.7±0.7%, p=0.02) in group PA. LV aneurysm and LV thrombus were less prevalent in group PA (4.8% vs 13.1%, p=0.01; 2.0% vs 6.9%, p=0.04, respectively). Maximal creatine kinase was significantly lower in group PA (1370.0±105.4 U/l vs 1769.8±119.8 U/l, p=0.01). Logistic regression analysis showed that the absence of PA was the significant independent predictor for LV aneurysm (odds ratio 3.3; 95% confidence interval 1.3–8.5; p=0.016).
Conclusions: Patients with PA occurring within 48 hours of AMI have better in-hospital outcome and less extensive myocardial injury than patients without PA.

P1277 Is there an influence of age on the results of percutaneous coronary interventions (PCI) in patients with non ST-elevation acute coronary syndromes (NSTE-ACS)? Results from the ALKK PCI registry

R. Zahn[1], M. Hochadel[2], U. Zeymer[1], H. Darius[3], S. Kerber[4], S. Kerber[5], K.E. Hauptmann[6], J. Senges[2], H. Mudra[7] on behalf of ALKK study group. *[1]Klinikum der Stadt Herzzentrum Ludwigshafen, Ludwigshafen am Rhein, Germany; [2]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [3]Vivantes Klinikum Am Urban, Berlin, Germany; [4]Klinikum, Bad Neustadt, Germany; [5]Klinikum der Stadt, Bad Neustadt, Germany; [6]Krankenhaus der Barmherzigen Brüder, Trier, Germany; [7]Klinikum Neuperlach, München, Germany*

Background: Advanced age is an important independent predictor of higher complication rates in most invasive procedures. However, there are little data on the age distribution and its influence on outcomes in patients presenting with non ST-elevation acute coronary syndromes (NSTE-ACS) undergoing percutaneous coronary interventions (PCI).
Methods: We analysed data from the prospective ALKK PCI Registry.
Results: In 2006 7824 PCIs in 7579 patients presenting with NSTE-ACS were performed at 42 hospitals. Mean age of the patients was 67.2 years, with a range of 19.9-95.0 years. 43.8% of patients were >70 years old, 13.6% > 80 years and 0.4% > 90 years. Patient characteristics depending on age as well as clinical events in these patients are shown in the table.

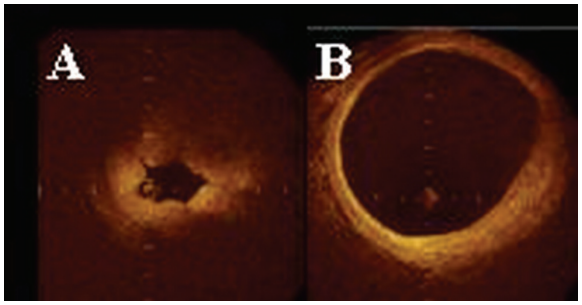
	All	>70y	>80y	>90y	P for trend
Female gender	30.7%	41.7%	50.9%	61.8%	<0.001
Prior PCI	29.8%	31.5%	29.1%	8.8%	0.013
Prior CABG	12.0%	15.0%	13.3%	0	<0.001
Cardiogenic shock	1.1%	1.3%	1.4%	0	0.247
Renal failure	16.1%	25.7%	32.1%	40.6%	<0.001
Diabetes mellitus	24.8%	28.3%	25.7%	18.2%	<0.001
Hospital events					
All cause death	1.6%	2.4%	2.0%	0	<0.001
Stroke/TIA	0.2%	0.2%	0.2%	0	0.486
Myocardial infarction	0.5%	0.5%	0.5%	0	0.970

Conclusions: Almost half of the patients undergoing PCI for NSTE-ACS are older than 70 years and 13.6% are already older than 80 years. In-hospital death rate, but not the rate of stroke/TIA or myocardial infarction is related to advanced age.

P1278 Coronary artery spasm in unstable angina pectoris: assessment of plaque morphology and dynamic state of vasoconstriction by optical coherence tomography

M. Mizukoshi, A. Tanaka, S. Takarada, H. Kitabata, T. Tanimoto, K. Hirata, K. Komukai, K. Ishibashi, T. Imanishi, T. Akasaka. *Wakayama Medical University, Wakayama, Japan*

Background: Intravascular ultrasound studies have suggested that the plaque morphology of spasm coronary arteries might be related to the pathogenesis of variant angina. However, the influence on unstable angina pectoris (UAP) remains unclear. Optical coherence tomography (OCT) is a high-resolution imaging modality and allows us to analyze tissue characteristics in detail. In this study, we assessed dynamic state of vasoconstriction and plaque morphology at the spasm sites in patients with UAP by OCT.
Methods: Fifty patients with UAP were enrolled. Nine of these patients had coronary spasm. OCT examinations were performed at the spasm sites during coronary spasm and after intracoronary injection of nitroglycerin.
Results: OCT findings were as follows: mild intimal thickening (0.130~0.180mm) with erosion, 3 patients (33.3%); lipid-rich plaque with rupture, 1 patient (11.1%); and eccentric fibro-fatty plaque, 5 patients (55.5%). In 5 patients with fibro-fatty plaque, there were more intensity-attenuated areas in the plaques, which correspond to necrotic core or hemorrhage. More accumulation of erythrocytes and macrophages was observed in the specimen of the plaque obtained by directional coronary atherectomy. OCT examinations revealed dynamic state of spasm. Circumferential vasoconstriction occurred equally regardless of the plaque burden. The constriction changed the morphology of the intima. The surface of the intima was folded, whereas the media got thick without making folds.



A: during spasm, B: relief from spasm

Conclusions: Tissue characteristics at coronary spasm sites had the potential for the progression of plaque vulnerability. Furthermore, the dynamic state of coronary spasm could lead to intimal injury. Coronary spasm might play an important role on the onset and/or progression of acute coronary syndrome.

SCREENING OF CORONARY ARTERY DISEASE

P1280 Relationship between carotid and femoral intima-media thickness and symptomatic coronary atherosclerosis

A. Mirek, W. Ruminski. *Wyszynski Hospital, Department of Cardiology, Lublin, Poland*

Background: The gaol of the study was to investigate the thesis whether the estimation of the extent of coronary atherosclerosis is possible based on ultrasonographic measuring intima-media thickness of common carotid (IMTC) and femoral arteries (IMTF).
Methods: 206 patients with angina pectoris underwent coronary angiography. The mean age was 61±10 years. Every patients underwent ultrasound imaging of the peripheral arteries in order to assess the intima-media thickness (IMT). Obstructive coronary artery disease (CAD) was defined as the exsistence of a stenosis > 50% of the lumen diameter of at least one major coronary vessel. The severity of CAD was estimated by the number of diseased vessels (Vesell score). We also calculated Gensini's and Extent score. Atherosclerosis risk factors and body mass index (BMI) were analyzed.
Results: In patients with significant CAD, IMTF value was statistically higher than in patients without CAD (p=0.001). Univariate analysis of logistic regression showed that the most powerful risk factors for the presence of significant CAD were as follows: male sex (p=0.0001), age (p=0.003), BMI (p=0.003), IMTF (p=0.03). The best model of the independent risk factors of obstructive CAD consisted of age, BMI and male sex. ROC analysis showed that the sensitivity

and specificity of IMTC and IMTF for the prognosis of obstructive CAD were low (<70%). IMTC values were significantly higher in patients with three vessel disease than in patients without CAD and with lesions in one or two vessels. IMTF values were only significantly higher in patients with three vessel disease than in patients without CAD. IMTC and IMTF values were significantly but weakly correlated with the coronary scores; the correlation coefficients were r=0.26 and 0.25 with Vessel and Gensini score, and r=0.25 and 0.20 with Extent score, respectively ($p<0.01$ for each). Multivariate analysis was used to assess whether risk factors and IMT affected CAD. The best multivariate model for predicting severity of CAD included male sex, age, diabetes mellitus. The addition of IMTC did not improve this model.

Conclusions: Although IMT is significantly correlated with extent of CAD, the relationship is weak. The measurement of IMT is not clinically useful because it was not specific or sensitive enough to identify patients with or without significant CAD. We proved also that IMTC is a weaker marker of progression of coronary atherosclerosis in comparison with cardiovascular risk factors.

P1281 Comparison of IVUS and QCA in patients presenting with atypical chest pain, inconclusive stress testing and significant lesions detected by MDCT-64

G.B. Pedrazzini[1], I. D'Angeli[1], F. Faletra[1], C. Klersy[2], E. Pasotti[1], T. Moccetti[1], A. Auricchio[1]. [1]*Fondazione Cardiocentro Ticino, Lugano, Switzerland;* [2]*Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

Backgroud: Although angiography is the gold standard for coronary imaging, several previous studies have documented the ability of multi-slice computed tomography (MDCT) to quantify the degree of coronary artery stenosis (CAS) and to assess dimensions and characteristics of coronary plaques. We assessed the diagnostic accuracy of MSCT in comparison with catheter-based angiography (QCA) and intravascular ultrasound (IVUS). We also evaluated the impact of coronary artery remodelling, measured by MSCT and IVUS, to the angiographic visualization of coronary stenosis.

Methods: After MDCT scan demonstrated significant CAS, 55 patients with stable angina (48 men and 7 women, mean age 63.5±9.7 years), underwent QCA and IVUS at the time of cardiac catheterization. 109 plaques in the major coronary vessels, with stenosis degree >50%, were obtained. Coronary artery angiography and intravascular ultrasound with motorized pullback at the velocity of 0.5 mm/s were performed. Correlations of vessel obstruction (lumen area stenosis, LAS), lumen cross-sectional area (L-CSA), plaque cross-sectional area (P-CSA), as well as, plaque volume (PV) and remodelling index (RI) for MSCT and IVUS and LAS and L-CSA for MSCT, QCA and IVUS were determined by calculating the Lin coefficient. For all measurements Pearson's r was evaluated. Bland-Altman correlation analysis was determined too.

Results: MSCT and IVUS yield similar results for plaque area (LAS r=0.881, $p<0.0001$; L-CSA r=0.904, $p\leq0.0001$; P-CSA r=0.907, $p<0.05$), plaque volume (r=0.986, p=0.046) and the remodelling index (r=0.800, p=0.256). QCA understimates coronary lesions compared to MSCT (LAS: r=0.443, $p<0.05$; L-CSA r=0.484, $p<0.05$) and IVUS (LAS r=0.473, $p<0.05$, L-CSA r=0.5000, $p<0.05$). Positive coronary artery remodelling was present in 69/109 (63%) plaques, with a mean remodelling index of 1.21±0.3.

Conclusions: Our data show that 64-slice CT can reliably detect and measure the severity of stenosis and it is best correlated to IVUS rather than quantitative coronary angiography. Positive coronary plaque remodeling might also be present in clinical stable setting and is associated with angiographically underestimation of stenosis degree.

P1282 Abnormal coronary vasoreaction in patients with suspected CAD but normal coronary arteries (ACOVA study)

P.E. Ong, A. Athanasiadis, G. Meinhardt, S. Hill, H. Mahrholdt, U. Sechtem. *Robert-Bosch Krankenhaus, Stuttgart, Germany*

Background: Angina pectoris and dyspnea are the cardinal symptoms in patients with suspected coronary artery disease (CAD). Risk stratification often leads to non-invasive examinations such as exercise-stress-testing. However, despite a high pre-test-probability coronary angiography reveals no significant CAD in up to 50% of patients. An alternative explanation of the patients' symptoms is an abnormal epicardial and/or microvascular vasoreaction (Spasm). Therefore the aim of this study was to determine the frequency of an abnormal coronary vasoreaction in patients with suspected CAD but normal coronaries by intracoronary acetylcholine provocation (ACH-test).

Methods and results: In this prospective study between 11/2007 and 11/2008 376 patients were included (inclusion criteria: LVEF>50%, creatinine <1,4mg/dl, no coronary angiography before, no valvular heart disease, no cardiomyopathy). In 173 patients (46%) coronary angiography revealed significant CAD. Normal or near normal coronary arteries (plaques <20%) were found in the remaining 203 patients (54%). Written informed consent for the ACH-test was obtained from all patients with normal coronaries. The test was performed in 173 of 203 patients (85%). Abnormal epicardial vasoreaction was defined as a significant reduction of the coronary diameter to ≤25% in comparison to the relaxed state after nitroglycerine i.c. together with a reproduction of the reported symptoms. Abnormal microvascular vasoreaction was defined as reproduction of the reported symptoms together with ischemic ECG-changes but without significant epicardial vasoreaction. ACH-testing showed an abnormal coronary vasoreaction in 66% of the patients tested (n=115). In 54 patients (47%) it was localised epicardially whereas it was localised on the microvascular level in 61 patients (53%). Statistical analysis showed that a pathologic ACH-test was significantly more frequent in women than in men (n=81, p=0.007). Furthermore there was a trend towards a higher prevalence of a microvascular vasoreaction in women (n=47, p=0.074).

Conclusions: In this prospective study coronary angiography revealed no significant CAD in more than 50% of all patients. However intracoronary acetylcholine provocation revealed an abnormal coronary vasoreaction in 2/3 of the patients. These findings suggest a cardiac origin of the patients' symptoms and have important implications on prognosis and medical therapy of these patients.

P1283 Diagnostic power of different pretest algorithms in patients with chest pain

M. Elkheyr, N. Houe, O. May. *Region Hospital Herning, Herning, Denmark*

Current guidelines recommend that the diagnostic approach in patients with chest pain and suspected coronary artery disease (CAD) should be based on risk stratification using pretest algorithms, but there is no consensus on which risk level or algorithm to use.

Purpose: To compare the diagnostic power at different risk levels of different pretest algorithms.

Methods: Clinical data regarding age, gender and angina type according to Diamond were prospectively registered in an exercise test database. These data were supplemented with data from patient files and the laboratory database. Significant CAD was defined as a luminal diameter reduction of at least 50% at coronary angiography (CA) as judged by the operator. The pretest probability of CAD was computed according to the ESC guideline (ESC, escardio.org), Diamond (Diam1, JACC 83;1:574; Diam2, Am Heart J 81;102:189) and Morise (Mori1 and Mori2, Am Heart J 95;130:267). A score defined by Morise was also calculated (Mori3, JACC 03;42:842). The diagnostic power of these risk estimations against CA were compared using receiver operating characteristic (ROC) curves. A higher area under the curve (AUC) indicates a more valid test. The prevalence of CAD at different levels of calculated risks are also given.

Results: 207 persons with a CA were included, the overall prevalence of CAD was 41%. The AUC in the ROC-analyses were for ESC 0.67, Diam1 0.65, Diam2 0.68, Mori1 0.75, Mori2 0.75 and Mori3 0.65. The frequency of CAD at high, intermediate and low risk levels defined by 90 and 10% were for ESC 62%, 34% and 8%, Diam1 54%, 29%, and 17%, Diam2 62%, 33% and 18%, Mori1 100%, 39% and 0% and Mori2 100%, 36% and 11%. Defining the risk levels at 80 and 20%, resulted in frequencies of CAD for ESC at 63%, 36% and 20%, Diam1 44%, 36% and 20%, Diam2 54%, 39% and 21%, Mori1 83%, 40% and 10% and for Mori2 80%, 35% and 15%. If the levels were defined by 70 and 30%, the frequencies of CAD were for ESC 51%, 44% and 25%, Diam1 49%, 34% and 22%, Diam2 50%, 46% and 24%, Mori1 71%, 41% and 18% and Mori2 73%, 36% and 19%.

Conclusion: The algorithms developed by Morise resulted in the largest diagnostic power. We suggest that patients with a pretest probability > 70% calculated be one of these algorithms could go directly to CA.

P1284 Prognostic power of different pretest algorithms regarding major cardiovascular events in patients with chest pain

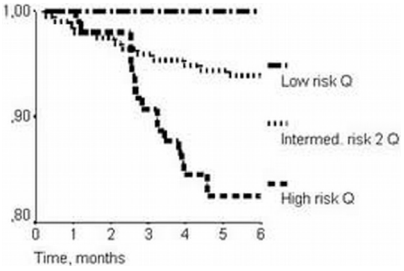
N. Houe, M. Elkheyr, O. May. *Region Hospital Herning, Herning, Denmark*

Current guidelines recommend that the diagnostic approach in patients with chest pain and suspected coronary artery disease (CAD) should be based on risk stratification using pretest algorithms, but there is no consensus on which algorithm to use.

Purpose: To compare different pretest algorithms with regard to their short term prognostic power in patients with suspected CAD.

Methods: Clinical data regarding age, gender and angina type according to Diamond were prospectively registered in an exercise test database and supplemented with data from patient files and the laboratory database. A major cardiovascular event (MACE) was defined as revascularization, acute coronary syndrome (ACS) or death based on data drawn from the patient administrative system. The pretest probability of CAD was computed according to the ESC guideline (ESC, escardio.org), Diamond (Diam1, JACC 83;1:574; Diam2, Am Heart J 81;102:189) and Morise (Mori1 and Mori2, Am Heart J 95;130:267). A score defined by Morise was also calculated (Mori3, JACC 03;42:842). The prognostic power of these risk estimates were assessed in Cox regression analyses. We computed the relative risk (RR) of having a MACE within 6 months for patients in the upper quartile compared to the lower quartile.

Results: 728 persons were included and 47 had an event within 6 months, 45 revascularization, 35 ACS and 18 death. The RR was for ESC 59.1 (p=0,009), Diam1 15.2 (p=0.0002), Diam2 32.9 (p=0.006), Mori1 72.3 (p=0.01), Mori2 72.4 (p=0.03) and Mori3 15.5 (p=0.007). The effect on survival to a first MACE is shown for Mori2 in the figure.



Survival to MACE for Mori2 (see text)

Conclusion: The largest prognostic power was found for the algorithms developed by Morise (Mori1 and Mori2). We suggest that one of these algorithms is used when the diagnostic approach is chosen for patients with chest pain.

P1285 Dual-source CT angiography versus exercise ECG for assessment of stable chest pain in a population with low disease prevalence

K. Nieman, T. Galema, A. Weustink, A. Moelker, L. Neefjes, N. Mollet, P. Musters, R. De Visser, P. De Feyter. *Erasmus MC, Rotterdam, Netherlands*

Purpose: evaluate the diagnostic performance of CT coronary angiography (CTA) in comparison to exercise ECG (XECG), to detect coronary artery disease (CAD) in a low-prevalence population.
Methods: 471 consecutive patients (227 female; 56±10 yrs) visited a fast-track chest pain clinic and underwent both XECG and dual-source 64-slice CTA (Siemens Definition, Forchheim, Germany). Cycle ergometer XECG was performed, and analyzed using standardized criteria. Quantitative catheter angiography (QCA) was performed in 98 (21%) patients, 59 (13%) were revascularized. QCA with a ≥50% or ≥70% diameter stenosis cutoff was used as reference.
Results: XECG was not performed in 48 (10%), non-diagnostic in 140 (30%), normal in 190 (40%) and abnormal in 93 (20%) patients. CTA was not performed in 16 (3%), non-interpretable in 3 (1%), negative in 312 (66%), and positive in 140 (30%). Negative CTAs (312) were confirmed by normal XECGs in 138/182 (76%), while 44/182 (24%) XECG was abnormal. QCA was performed in 17/312 (5%) patients with a negative CTA, revealing stenosis in 2 (one positive XECG). Positive CTAs were confirmed by abnormal XECGs in 47/92 (51%), of whom 23/25 (92%) had positive QCAs. Positive CTAs were contradicted by normal XECGs in 45/92 (49%), in whom still 10/23 (43%) QCAs were abnormal, but only 4/23 (17%) severely. For not performed or nonconclusive XECGs, CTA was positive in 48/188 (26%), with 22/32 69% QCAs abnormal, while negative in 130/188, 1/7 QCAs abnormal. The sensitivity of CTA to detect ≥50% CAD was higher, while the specificity of XECG was higher for both moderate or severe stenosis by QCA ($P<0.05$, table). Quantitative CTA overestimated stenosis severity: 6±21% (R=0.71).

Stenosis detection by CTA and XECG

	QCA	Excl (%)	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)
CTA	≥50%	2 (2)	96 (86-99)	37 (23-53)	67 (55-77)	88 (62-98)
XECG	≥50%	39 (39)	71 (52-84)	76 (54-90)	80 (61-92)	66 (46-81)
CTA	≥70%	2 (2)	96 (80-100)	24 (14-36)	34 (24-46)	94 (69-100)
XECG	≥70%	39 (39)	80 (56-93)	64 (47-78)	53 (35-71)	86 (67-95)

Performance per patient (N=98) without exclusions (excl). Reference: QCA ≥50% or ≥70% diameter stenosis in ≥1 vessel. Predictive value (PV).

Conclusion: Compared to XECG, CTA can be performed and interpreted in more patients, and has a higher sensitivity but lower specificty to detect CAD ($P<0.05$). CT was negative in the majority, making ischemia or significant CAD on QCA unlikely.

P1286 A review of outcome of patients with chest pain in rapid access chest pain clinic. A district general hospital experience

M. Batra, P. Batra. *Leighton Hospital, Crewe, United Kingdom*

Aim: The aim of our study was to review our local practice of risk stratification of patients of chest pain in Rapid access chest pain clinic and to correlate the results of coronary angiograms with the findings of Exercise tolerance tests.
Methods: We reviewed case notes of 2286 patients referred to Rapid Access Chest Pain Clinic from April 2002 to March 2008. All exercise tolerance tests were carried out with a Quinton-450 treadmill utilising the full Bruce protocol. Exercise tolerance tests (ETT) were graded as follows:
Strongly positive test – clinically AND electrically positive at <6 minutes
Positive – clinically AND/OR electrically positive at >6 minutes
Equivocal test – electrical minor changes at >6 minutes and reverted to recovery within 1 minute. Negative – clinically and electrically negative at achievement of maximum heart rate
Suboptimal – No significant changes on ECG but patient did not achieve maximum heart rate.
All the patients were followed up for one year and results of ETT and coronary angiography were compared.
Results: The average age of patients was 72 years. On comparing the results of exercise tolerance tests with coronary angiographies, it was found that majority of patients with strongly positive ETT at <6 minutes had severe coronary artery disease as compared to patients with equivocal tests and submaximal tests.

Results of ETT (N)	Left main stem disease	Triple vessel disease	Double vessel disease	Single vessel disease	Minor Coronary disease	Normal coronaries
Strongly positive test (518)	11.7%	40.2%	36.1%	11.5%	None	0.5%
Positive test (465)	6%	17.4%	33.2%	14.4%	23%	6%
Equivocal test (243)	None	None	7.4%	25.5%	24.6%	42.4%
Submaximal tests (250)	None	2.4%	12.4%	33.2%	8%	59.2%

Conclusions: This study highlights that the 6- minute exercise criteria on ETT can be utilized to recognise the strata of patients who require cardiac catheterisation. By using this risk stratification with 6 minute test, the waiting times of those patients requiring urgent cardiac catheterisation can be reduced. If specialist cardiac nurses and technicians can offer a protocol driven assessment of these patients then rapid access clinics can become a more practical approach for their accurate and timely management. A standardized database should be created which includes final diagnosis and time to procedure.

P1287 Genetic variability of fibrinogen a-chain gene defines fibrinogen levels between healthy individuals and patients with documented atherosclerosis: effects on prothrombotic profile

N. Papageorgiou, D. Tousoulis, G. Hatzis, A. Miliou, C. Antoniades, M. Kozanitou, A. Giolis, C. Tentolouris, E. Bosinakou, C. Stefanadis. *1st Cardiology Unit Hippokration Hospital Athens, Athens, Greece*

Purpose: Fibrinogen plays an key role in atherogenesis. A genetic polymorphism on fibrinogen a-chain, the G58A, has been associated with fibrinogen levels in healthy individuals, but its effect on patients with coronary artery disease (CAD) is still unknown. In the present study we examined the impact of this polymorphism on fibrinogen levels and its relation to the prothrombotic profile.
Methods: The study population consisted of 230 subjects, 179 of which with angiographically documented CAD and the rest with angiographically documented absence of any significant coronary stenoses. The G58A polymorphism was detected by Polymerase Chain Reaction (PCR) and appropriate restriction enzymes. Fibrinogen levels were measured by a nephelometric method, while other factors of thrombosis such as plasma levels of D-dimers, factors V, X, plasminogen were measured by standard coagulometry techniques.
Results: The genotype distribution was GG: 39.6%, AG: 40.2%, AA: 20.2% and GG: 37.3%, AG: 49.0%, AA: 13.7% for CAD patients and healthy individuals respectively. Among the three genotypes there was no significant difference in fibrinogen levels of CAD patients (128.6±32.4 vs 115.8±29.5 vs 127.8±33.4 mg/dl, p=NS for all). Patients with CAD had significantly higher levels of fibrinogen than healthy individuals regarding to the G58A polymorphism (456.3±131.2 vs 385.3±102.0 mg/dl, $p<0.001$). In addition, there were significant differences fibrinogen levels between the same genotypes of the two populations (CAD vs healthy, AA: 477.5±123.1 vs 386.8±62.7, GG: 452.4±146.3 vs 374.8±114.0, AG: 449.1±119.3 vs 393.6±104.0 mg/dl $p<0.05$ for all). Similarly, d-dimers levels were significantly higher in the CAD than healthy subjects regarding to the G58A polymorphism (555.8±628.7 vs 360.3±336.7 mg/L). On the contrary, levels of thrombotic markers did not differ significantly between CAD and healthy individuals: fV (124.0±31.8 vs 115.0±25.1%), fX (94.2±23.2 vs 90.3±18.7%), plasminogen (109.5±19.0 vs 107.7±14.7 u/ml) p=NS for all.
Conclusions: Genetic polymorphism G58A on fibrinogen a-chain gene fails to affect the prothrombotic profile as healthy subjects and CAD patients presented with no differences on specific markers. On the contrary, it turns to be effective on fibrinogen levels implying a potential mechanism which promotes atherosclerosis.

P1288 Can BNP and Troponin T predict coronary artery disease and mortality in patients with chronic kidney disease at initiation of renal replacement therapy ?

A. Tanaka, Y. Suzuki, K. Miki, N. Yasuda, T. Hirai, N. Suzuki, H. Asada, T. Tanaka. *Okazaki city hospital, Okazaki, Japan*

Background: Some studies reported that troponin T (TnT) and brain natriuretic peptide (BNP) were associated with adverse outcomes in hemodialysis patients. However, examination at initiation of renal replacement therapy has not been systematically studied. We evaluated the relation between cardiac biomakers (BNP, TnT, and the other) and coronary artery disease (CAD) in the patients with chronic kidney disease (CKD) at the initiation of renal replacement therapy, besides followed up their clinical outcomes.
Methods: 119 patients with CKD initiated renal replacement therapy from July 2006 to August 2008 were enrolled. Some examinated data including BNP, TnT, adrenomedullin, and high-sensitivity C-reactive protein were measured just be-

fore the first dialysis session. We examined stress myocardial scintigraphy and coronary angiography (CAG) except for their rejection or having reasons not to be done. CAD was defined as the presence of at least one stenosis>50% of a coronary artery with CAG performed before or newly. Cardiovascular morbidity and mortality were assessed until September 2008.
Results: 28 patients were diagnosed as CAD (15 previously, 13 newly)(group C),and 53 patients were not (group N). BNP and TnT levels in group C were significantly higher than in group N (1254±1792 vs 312±286 pg/ml; p=0.003, 0.32±0.70 vs 0.12±0.22 ng/ml; p<0.005, respectively). Adrenomedullin level in group C tended to be higher than in group N, and high-sensitivity C-reactive protein level had no significant differences between two groups. Mean follow-up term was 262±223 days. All cause mortality and cardiovascular composite endpoint (death, myocardial infarction, coronary revasucularization, cerebrovascular disease; cerebral bleeding or cerebral infarction) in groupC was higher than in groupN (p<0.005 and p<0.000001, respectively).
Conclusions: We showed that BNP and TropT might predict coronary artery disease in patients with chronic kidney disease at initiation of renal replacement therapy, and patients with CAD had higher mortality and morbidity. We should treat for CKD patients with high BNP or TnT level more carefully.

P1289 Prognostic value of C-reactive protein in subjects with no apparent heart disease but daily-life silent myocardial ischemia

M.R. Mouridsen, T. Intzilakis, Z. Binici, O.W. Nielsen, A. Sajadieh.
Bispebjerg Hospital, Copenhagen, Denmark

Background: Silent myocardial ischemia (SMI) in subjects without known heart disease is generally associated with a poor prognosis, but false positive findings are common, and risk stratification usually necessary.
Aims: The aim of this study was to evaluate the prognostic value of CRP and traditional Framingham risk score in subjects with SMI. The aim was also to uncover whether measurement of CRP provides added information over and above what is available with existing assessments.
Methods: 678 healthy men and women between 55 and 75 years of age with no history of cardiovascular disease or stroke were included in the study. All were tested with fasting laboratory testing inclusive high sensitive CRP and 48-hour ambulatory ECG monitoring. The median follow-up time was 76 months. An adverse outcome was defined as death or myocardial infarction.
Results: The 48-hour ambulatory ECG monitoring revealed, that 77 subjects (11.4%) had SMI. Adverse events occurred in 26% of the subjects with SMI and 14% of the subjects without SMI (p = 0,005). The median value of CRP was 2.5 μg/ml. Stratification with CRP showed, that SMI had a poor prognosis in the group with elevated CRP above 2.5 μg/ml (HR = 3.52, 95% CI: 1.78-6.95, p = 0.0003). In the group with SMI and low level of CRP, there was no significant increase in events compared to the reference group without SMI (HR = 1.24, 95% CI: 0.47-3.29, p = 0.66). Stratification with Framingham risk score showed, that SMI predicted poor outcome in subjects with a Framingham score of more than 10% per 10 year, but not in the group with lower risk score.
Conclusions: In apparently healthy subjects low level of CRP < 2.5 μg/ml selected a low-risk subgroup, despite the present of SMI. In subjects with SMI, CRP yields prognostic information beyond traditional risk factors. CRP, therefore, must be considered as a potential prognostic biomarker and a guide in decision-making when dealing with patients with SMI.

P1290 Is spot urinary albumin or albumin to creatinine ratio more useful for predicting coronary artery disease?

E. Ural, T. Kilic, F. Aygun, U. Bildirici, G. Oner, M. Cekmen, D. Ural.
Kocaeli University Medical Faculty, Kocaeli, Turkey

Purpose: The aim of this study is to investigate predicting utilities of urinary albumin concentration (UAC) and urinary albumin to creatinine ratio (UACR) in detecting coronary artery disease (CAD).
Methods: A total of 118 consecutive patients (mean age=59±10) undergoing diagnostic coronary angiography were included to the study. Random spot urine specimens were taken at the first morning before the procedure. UAC and urinary creatinine concentration were measured. The UACR was calculated. Angiograms were scored using the method of Gensini. The clinical parameters, UAC and UACR were compared between subjects with and without CAD. Correlations between Gensini score with UAC and UACR were were examined. Factors predicting CAD were evaluated by multivariate analysis.
Results: The clinical and laboratory characteristics of patients with and without CAD were presented in Table 1. Patients with CAD had significantly higher UACRs and UACs than patients without CAD (Table 1). A positive correlation was found between Gensini score and UACR (R=0.2, p=0.01) whereas not with UAC. In the multivariate analysis adjusted for well known CAD risk factors, only UACR continued to be a significant parameter for predicting CAD (OR=1.3, CI=1.0–1.5, p=0.006).

Table 1. Clinical and laboratory characteristics of patients with and without angiographically documented coronary artery disease

Parameter	CAD (–) (n=30)	CAD (+) (n=88)	P
Age	55±10	59±10	0.06
Male gender	16 (53%)	66 (75%)	0.02
Hypertension	23 (77%)	56 (64%)	0.2
Diabetes	6 (20%)	21 (24%)	0.6
Smoking	13 (43%)	41 (47%)	0.8
Family history of CAD	8 (27%)	32 (36%)	0,3
Systolic blood pressure	134±18	134±22	0.6
HDL	46±12	43±12	0.2
LDL	113±34	112±40	0.6
UAC, mg/L	0.56±0.50	1.15±1.13	0.01
UACR, mg/g	4.77±3.28	9.17±7.38	0.009

Conclusion: Our preliminary results suggest that UACR is more useful marker than UAC for predicting CAD among patients undergoing diagnostic coronary angiography.

P1291 Clinical assessment of ischemia modified albumin and heart- fatty acid binding protein in early diagnosis of non ST elevation acute coronary syndrome in emergency department

S. Charpentier[1], J.L. Ducasse[1], M. Cournot[2], F. Maupas-Schwalm[3], M. Elbaz[3], H. Juchet[3], D. Lauque[1]. *[1]CHU Toulouse, Hôpital Purpan, Toulouse, France; [2]Centre Hospitalier du Val d'Ariège, Foix, France; [3]CHU de Toulouse - Hopital de Rangueil, Toulouse, France*

Purpose: Diagnosis of acute coronary syndrome (ACS) in patients admitted in emergency department (ED) is often difficult. H-Fatty Acid Binding Protein (h-FABP and Ischemia Modified Albumin (IMA) have been recently evaluated for the detection of myocardial infarction. The aim of the study was to analyse the diagnostic accuracy and the clinical usefulness of h-FABP and IMA for non ST segment elevation ACS diagnosis in ED.
Methods: A prospective 11 month observational study was carried out. Consecutive patients admitted to a 32000 visits university ED were eligible. Inclusion criteria were: chest pain within 12 hours of ED presentation and clinical suspicion of ACS. Patients were excluded if they were younger than 18 years old, had an ST elevation on a 12-lead ECG, or a previous severe renal impairment. Biomarkers were measured on admission: CardioDetect® for h-FABP qualitative detection (threshold of 7ng/ml) and ACB test for IMA. Physicians in ED were blinded to markers results. Patients were classified as having ACS by two independent physicians (kappa=0.71). Performance of biomarkers for ACS diagnosis was studied for each markers and clinical utility was assessed by performing multivariate analysis, area under the curve (AUC) calculation for accuracy, and reporting operating characteristics with 95% confidence intervals.
Results: Out of the 677 eligible patients who were recruited, non-ST elevation ACS was diagnosed in 185 patients (27.3%). IMA was not predictive of ACS diagnosis (p=0.208) with an AUC of 0.54. H-FABP was a statistically significant predictor of ACS diagnosis (odds ratio 4.7 95%CI 2.4-9.0); the sensitivity was only 13.5% (95%CI 10.9-16.1) and specificity 96.8% (95%CI 95.4-98.1). In addition to a predictive model that included the usual diagnostic tools for ACS management, h-FABP added no significant incremental information (p=0.40).
Conclusion: In a large cohort of patients IMA and h-FABP provided no valuable information for ACS diagnosis on admission.

P1292 Asymmetric dimethylarginine (ADMA) levels correlate with the angiographic extent of coronary artery disease in patients with stable angina and/or abnormal stress test

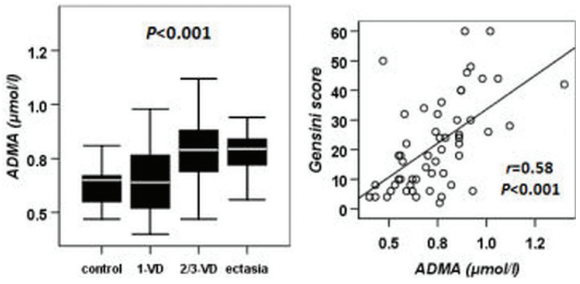
N. Ioakeimidis, C. Vlachopoulos, D. Terentes-Printzios, K. Baou, G. Antoniou, P. Xaplanteris, G. Lazaros, G. Roussakis, C. Aggeli, C. Stefanadis.
Hippokration General Hospital of Athens, Athens, Greece

Purpose: Increased levels of asymmetric dimethylarginine (ADMA) are asso-

Abstract P1289 – Table 1. Cox regression analyses

	All included subjects		Subjects with 10-year Framingham risk > 10%	
	Unadjusted	Adjusted for traditional risk factors	Unadjusted	Adjusted for traditional risk factors
CRP < 2,5 and no SMI	1	1	1	1
CRP ≥ 2,5 and no SMI	HR=2,30 (95% CI: 1,47-3,60) p=0,0003	HR=1,94 (95% CI: 1,22-3,10) p=0,005	HR=2,20 (95% CI: 1,36-3,55) p=0,001	HR=1,87 (95% CI: 1,15-3,02) p=0,011
CRP < 2,5 and SMI present	HR=2,12 (95% CI 0,93-4,85) p=0,076	HR=1,24 (95% CI: 0,47-3,29) p=0,66	HR=1,67 (95% CI: 0,58-4,81) p=0,43	HR=1,09 (95% CI: 0,37-3,20) p=0,87
CRP ≥ 2,5 and SMI present	HR=4,44 (95% CI: 2,30-8,57) p=0,0001	HR=3,52 (95% CI: 1,78-6,95) p=0,0003	HR=4,29 (95% CI: 2,15-8,58) p=0,0001	HR=3,26 (95% CI: 1,61-6,60) p=0,001

ciated with endothelial dysfunction and increased cardiovascular risk. The relationship between ADMA and extent of coronary artery disease (CAD) in patients with chest pain and/or abnormal stress test has not been fully elucidated.
Methods: Seventy six subjects (mean age, 58±9 years) with stable angina and/or stress echocardiography considered positive for myocardial ischemia were enrolled prospectively for coronary angiography. According to the angiographic findings they were divided into 4 groups: group A (no coronary stenoses >50%, n = 16), group B (1-vessel CAD, n = 20), group C (2/3-vessel CAD, n = 34) and group D (coronary ectasia, n=6). ADMA levels were measured with ELISA.
Results: ADMA concentrations were significantly higher in group C as compared to group A or B (left figure). This last relationship remained significant in multivariate analysis ($P<0.05$ by ANCOVA, post hoc $P<0.05$) after adjusting for age, blood pressure, lipids and blood glucose. Interestingly, when patients with 2/3 vessel CAD (group C) were compared with patients with coronary ectasia (group D), no significant differences were found in ADMA levels. ADMA level was also significantly correlated with extent of coronary atherosclerosis as assessed by modified Gensini's score (right figure). ROC curve analysis for the prediction of the presence of 2/3 vessel CAD showed that areas under the curve for ADMA level was 72% (95% CI: 60 to 83%) which (with a cutoff at 0.74 μmol/l) had a sensitivity of 75% (20 to 36%) and a specificity of 67% (96 to 100%).



ADMA and extent of CAD

Conclusion: Coronary angiographic findings correlate significantly with ADMA levels. This may reinforce the link between ADMA and increased cardiovascular risk.

P1293 Serum adiponectin, resistin and angiogenin as predictors of major adverse cardiac events (MACE) in 1-year follow-up of patients with stable, multivessel coronary artery disease

R. Krecki[1], J. Drozdz[1], P. Szczesniak[2], J.D. Kasprzak[1], P. Lipiec[1], K. Wierzbowska-Drabik[1], D. Orszulak-Michalak[2], M. Krzeminska-Pakula[1]. [1]*II Department of Cardiology Medical University, Lodz, Poland;* [2]*Medical University of Lodz, Department of Biopharmacy, Lodz, Poland*

Background and aim: Adipokines such as adiponectin and resistin, as well as novel angiogenesis factor - angiogenin are suggested to be associated with inflammation and atherosclerosis. The relationship between their levels and prognosis in high risk patients is, however, still unclear. The aim of this study was to evaluate the prognostic values of these adipokines in patients with stable, multivessel coronary artery disease (MCAD).
Methods: The study group comprised of 107 MCAD patients (80 males, mean age 63±8 years). 55 patients were surgically revascularized (CABG), whereas 52 weretreated conservative. Each patient had coronary angiography (mean Gensini score in the study group was 91, range 66-132) and a laboratory test panel related to biochemaical risk factors. Adiponectin, resistin and angiogenin plasma levels were measured at admission and after 1-year follow-up. MACE was defined as cardiac death, nonfatal myocardial infarction, stroke and hospitalization for angina or heart failure over 1-year period.
Results: After 1-year follow-up 9 (8%) patients died, all from cardiovascular reasons. 34 (32%) of patients experienced MACE. Predictors of MACE, revealed by univariate logistic regression analysis were: total cholesterol (p=0,01), LDL-cholesterol (p=0,009) and resistin (p=0,01) plasma levels. Total cholesterol concentration level ≥ 173 mg/dl was associated with 7-fold increase of MACE risk (OR 7,25; 95% CI, 1,59 – 32,97); LDL ≥ 93,5 mg/dl with 16-fold increase of MACE risk (OR 16,31; 95% CI, 2,84 – 93,84) and resistin ≥ 17,265 ng/ml with 13-fold increase of MACE risk (OR 13,5; 95% CI, 2,27 – 80,3). In multivariate analysis, medical treatment strategy (b 4,83; p=0,001), higher CCS class (b 3,22; p=0,004), resistin level (b 0,15; p=0,003) and higher Gensini score (b 0,023; p=0,03) were independent predictors of MACE.
Conclusion: In stable patients with multivessel coronary artery disease, high plasma resistin (as opposed to adiponectin or angiogenin) is a strong independent predictive factor for the occurrence of MACE over 1-year follow-up.

P1294 Multiple marker approach to risk stratification in patients with stable coronary artery disease

R. Schnabel[1], E. Lubos[1], P.S. Wild[1], T. Zeller[1], C.R. Sinning[1], T. Kempf[2], K. Wollert[2], K.J. Lackner[1], T.F. Munzel[1], S. Blankenberg[1]. [1]*Johannes Gutenberg Universitaet, Mainz, Germany;* [2]*Medizinische Hochschule Hannover, Hannover, Germany*

Background: Multiple biomarker approaches for risk prediction in coronary artery disease have remained inconsistent.
Methods and Results: We prospectively investigated 18 biomarkers reflecting inflammation (C-reactive protein, growth-differentiation factor (GDF)-15, procalcitonin, neopterin), oxidative stress (Cu/Zn-superoxidedismutase, myeloperoxidase), lipid metabolism (apolipoproteins AI, B100), renal function (cystatin C), cardiovascular function and remodeling (copeptin, C-terminal-pro-endothelin-1, mid-regional-pro-adrenomedullin (MR-proADM), midregional-pro-atrial natriuretic peptide (MR-pro-ANP), N-terminal-pro-B-type natriuretic peptide (Nt-proBNP), tissue-inhibitor of metalloproteinase), and metabolic processes (adiponectin, leptin, resistin) in 1781 stable angina patients in relation to non-fatal myocardial infarction and cardiovascular death (n=137). Risk scores were examined in a training and validation set.
Using Cox regression models and C-indices, the strongest association with outcome in the validation set was observed for MR-proADM, cystatin C, GDF-15, Nt-proBNP, and MR-proANP. The two scores obtained (1) from forward stepwise variable selection (Nt-proBNP and GDF-15; HR 1.46, 1.12-1.91; C-index 0.73), (2) through Lasso method (MR-proADM, MR-proANP, neopterin, GDF-15, Nt-proBNP; HR 1.43, 1.11-1.83; C-index 0.73), performed similar to the top five single markers. Each top single marker and the scores added incremental predictive information beyond the baseline model (all $p<0.0001$ by AUC for 3-year survival) and lead to substantial reclassification for prediction of cardiovascular outcomes.
Conclusions: Comparative analysis of 18 biomarkers revealed MR-proADM, cystatin C, GDF-15, and natriuretic peptides as the strongest predictors of cardiovascular outcome in stable angina. All five biomarkers offered incremental predictive ability over established risk factors as single markers or incorporated in scores.

P1295 Serum osteoprotegerin levels and long-term prognosis in patients with stable angina pectoris

E.R. Pedersen[1], T. Ueland[2], R. Seifert[3], H. Schartum-Hansen[1], P. Aukrust[2], M. Ebbing[1], G. Svingen[4], Ø. Bleie[3], J.E. Nordrehaug[1], O. Nygaard[1]. [1]*Institute of Medicine, University of Bergen, Bergen, Norway;* [2]*Research Institute for Internal Medicine, Rikshospitalet, University of Oslo, Oslo, Norway;* [3]*Department of Heart Disease, Haukeland University Hospital, Bergen, Norway;* [4]*Department of Medicine, Haraldsplass Hospital, Bergen, Norway*

Background and purpose: Osteoprotegerin is a member of the tumor necrosis factor superfamily, and has pleiotropic effects on bone metabolism, endocrine function and the immune system. Serum OPG levels are elevated in cardiovascular disease, and its synthesis within atherosclerotic plaques is hypothesised to be a response to plaque instability. Unstable plaques may, however, occur even in patients with clinically stable angina. We therefore assessed whether OPG predicts thromboembolic events and mortality in such patients.
Methods: Serum samples for OPG analysis were obtained from 1025 patients (mean (SD) age 62 (11) years, 72% men) who underwent elective coronary angiography for clinically stable angina. At inclusion, 443 patients (43%) had 1 or 2 vessel disease, whereas 352 (34%) had 3 vessel disease. OPG levels at baseline were related to the incidence of acute coronary thromboembolic events (fatal and nonfatal acute myocardial infarction (MI), acute hospitalisation for unstable angina pectoris and sudden cardiac death) and to all-cause mortality. Hazard ratios, HR (95% CI), were estimated using Cox regression.
Results: During a median follow-up of 72 months, 144 patients (14%) experienced an acute coronary thromboembolic event (CTE). A total of 116 patients (11%) died. In crude analysis, OPG predicted both CTE and all-cause mortality. For CTE the HR was 1.27 (1.09-1.47) per quartile increment and 2.03 (1.31-3.14) for decile 10 versus 1-9 of OPG level. For all-cause mortality the HR was 1.61 (1.35-1.92) per quartile increment and 3.38 (2.22-5.14) for decile 10 versus 1-9. Adjustment for age and gender attenuated the risk estimates. For CTE, the HR was 1.61 (1.01-2.56), and for all-cause mortality the HR was 2.02 (1.28-3.18) for decile 10 versus 1-9.
After additional adjustment for conventional risk factors (hypertension, smoking, diabetes mellitus, history of MI, ejection fraction and CRP levels), there was no significant association between OPG levels and CTE. Nor was there any significant trend over quartiles of OPG in relation to all-cause mortality. However, serum OPG was still a predictor of mortality among patients with levels above the 90th percentile; HR for decile 10 versus 1-9 was 1.87 (1.17-2.99).
Conclusion: In patients with stable angina pectoris, serum OPG is not an independent predictor of acute coronary thromboembolic events. OPG predicts long-term mortality, but this effect is mainly restricted to levels above the 90th percentile.

P1296 Severity of coronary atherosclerosis and platelets activity in patients with coronary artery disease

T. Pavlova[1], D. Duplyakov[2], G. Saveleva[1], V. Polyakov[1], S. Khokhlunov[2]. [1]*Samara State Medical University, Samara, Russian Federation;* [2]*Samara Regional Cardiology Dispensary, Samara, Russian Federation*

Aim: To investigate the relationship between the severity of atherosclerosis in coronary arteries and platelets activity in patients with CAD.
Methods: 89 patients (78M/11F, aver.age 48,2±2,1 yrs) with coronary artery disease (CAD) confirmed by coronary angiography and stress testing were divided on three groups according to the number of affected vessels. Group 1 consisted of 12 pts (6M/6F, aver.age 42,3±3,7 yrs) with one-vessel disease, group 2 consisted of 36 pts (32M/4F, aver.age 49,1±5,3 yrs) with double-vessel disease and group 3 consisted of 41 pts (40M/1F, aver.age 52,4±2,9 yrs) with tripple-vessel disease. Among 89 patients 67% survived AMI, hypertension was observed in 7,4% pts, and diabetes in 7,4%. 37 patients (26M/11F, aver.age 46,9±3,1 yrs) without overt CAD comprised the reference group.
Intravascular platelet's activation was analyzed by original morpho-functional method. Dispersion analysis was used to find the correlation between the numbers of affected coronary arteries and platelets activation.
Results: Pts with one-vessel disease had 23,3% activated forms of platelets (reference level ≤18,1%), whereas pts with double-vessel lesions – 31,6%, and triple-vessel coronary injury – 36,7% ($p<0,01$). Small platelet aggregates (< 3 platelets) were observed in 5,8% of pts with one-vessel disease (reference level < 3,7%), in 8,2% of pts with double-vessel disease, and in 10,8% of pts with triple-vessel disease ($p<0,01$). Large platelet aggregates (>4 platelets) were observed in 0,19% of pts with one-vessel disease (reference level < 0,1%), in 0,42% of pts with double-vessel disease, and in 0,57% of pts with triple-vessel disease ($p<0,01$). According to dispersion analysis strong relationship was established between the severity of atherosclerosis in coronary arteries and platelets activity in our group of patients with CAD.
Conclusions: Severity of coronary atherosclerotic lesions has significant influence on platelets activity. The total number of affected coronary arteries is strongly associated with a quantity of activated platelets and platelet aggregates.

P1297 Relationships of serum angiogenin with biochemical risk factors and angiographic severity of multivessel coronary disease

R. Krecki[1], J. Drozdz[1], P. Szczesniak[2], J.D. Kasprzak[1], P. Lipiec[1], K. Wierzbowska-Drabik[1], D. Orszulak-Michalak[2], M. Krzeminska-Pakula[1]. [1]*II Department of Cardiology Medical University, Lodz, Poland;* [2]*Medical University of Lodz, Department of Biopharmacy, Lodz, Poland*

Background: Patients with advanced coronary artery disease have unfavorable prognosis. Therefore, early identification of this high-risk group is important.
Aim: To assess the utility of clinical, electrocardiographic and echocardiographic parameters, supported by novel atherogenesis markers as well as angiogenesis markers, to identify patients with a stable, multivessel coronary artery disease (MCAD).
Methods: The study group comprised 107 patients (pts; 80 males, mean age 63±8 years) suffering from MCAD and a control group of 15 patients (8 males, mean age 60±11 years – presenting with typical angina, positive exercise stress test but no hemodynamically significant coronary stenosis in angiogram). In each patient we characterized a biochemistry test panel including novel markers: angiogenin, resistin, adiponectin, interlukin (IL)-8 and tumor necrosis factor TNFα. Angiographic severity of CAD was expressed in Gensini score in all pts.
Results: Mean Gensini score in the study group was 91 (66-132). MCAD pts had more segmental contractility disorders, and left ventricular EF in this group was significantly lower than in the control group (45 vs. 55%, p=0.005). There were significant differences between MCAD patients and control groups with respect to serum levels of: hsCRP (2.8 vs. 1.4 mg/l, p=0.01), HDL-cholesterol (45 vs. 54 mg/dl, p=0.04), LDL cholesterol (102 vs. 95 mg/dl, p=0.04), NTproBNP (392 vs. 151 pg/ml, p=0.008) and a marker of angiogenetic activity, angiogenin (414 vs. 275 ng/ml, p=0.02), However, no significant differences were found between MCAD and control group with respect to serum level of adiponectin (8.08 vs. 7.82μg/ml), resistin (17.5 vs. 21ng/ml), IL-8 (20.7 vs. 26.8pg/ml) and TNFα (4.1 vs. 4.3pg/ml). Angiogenin tended to be higher in patients with higher Gensini scores (p=0,06) but no influence of ejection fraction was noted. Over 12-months of follow-up, a significant decrease in angiogenin level was observed in surgically treated as opposed to medically treated patient subgroups. Serum level of angiogenin correlated positively with NTproBNP (r=0,32; p=0,001), TNFalfa (r=0,027; p=0,005) and resistin (0,32; p=0,001).
Conclusions: Angiogenin is a novel marker of multivessel coronary disease showing a relationship with angiographic severity of the disease which becomes normalized in patients with successful revascularization therapy. This initial demonstration of diagnostic and prognostic potential of the marker warrants further studies on its practical utility and relationship to established clinical factors.

P1298 High-sensitive cardiac troponin I in patients with stable cardiovascular disease and indication for heart catheterisation

O. Schulz[1], M. Reinicke[1], G. Berghoefer[1], R. Bensch[1], J. Kraemer[1], I. Schimke[2], A.S. Jaffe[3]. [1]*Interventionelle Kardiologie Spandau, Berlin, Germany;* [2]*Charite - Campus Mitte, Humboldt-Universitaet, Berlin, Germany;* [3]*Mayo Clinic, Rochester, United States of America*

High-sensitive cardiac troponin assays have been developed to help detect more cardiac patients at risk. However, their role in the diagnostic workup and clinical decision-making for different diseases and scenarios has yet to be defined. We investigated whether a novel high-sensitive cardiac troponin I (hscTnI) is helpful in the diagnostic workup of 222 patients with stable cardiovascular diseases and indication for heart catheterisation. Blood was drawn for measurement of hscTnI with a pre-commercial assay after performance of echocardiography and stress-test before heart catheterisation. A follow-up of 1103±299days was performed by a questionnaire and phone calls.
Results: Very few patients were without some abnormality after evaluation. hscTnI was detectable in all patients (median (interquartile range) 6.20 (4.85; 8.25)ng/L). Patients with either coronary artery disease (defined as having coronary artery stenosis≥70%; n=103), with a B-type coronary lesion of ≥50% (n=74) or with a myocardial impairment (defined as left ventricular ejection fraction<50%, end-diastolic pressure ≥20mmHg or regional wall-motion abnormalities; n=98) had higher hscTnI values than patients without these characteristics: 15.29±42.78 vs 7.16±6.41; p=0.009, 13.91±33.34 vs 9.44±27.73; p=0.043, and 16.19±44.02 vs 6.77±4.34ng/L; p=0.002, respectively. Multivariable analysis revealed creatinine ($p<0.001$), systolic wall stress (p=0.004), the presence of myocardial impairment (p=0.049) as well as coronary artery stenosis ≥70% (p=0.050) as independent predictors of hscTnI-concentrations. 16.6% of patients showed values above the established 99th percentile (9.20ng/L) and those had a higher rate of hospitalisations during follow-up.
Summary: All stable cardiovascular patients had detectable hscTnI. Its concentration varied in relation to the underlying disease. hscTnI could not distinguish between individuals with chronic coronary heart disease and those with myocardial abnormalities suggesting that the clinical context of their use will be critical for the proper interpretation of abnormalities.

P1299 Pregnancy associated plasma protein A, a marker for outcome in patients with stable coronary heart disease

K.K. Iversen[1], P. Grande[2], P. Clemmesen[2], P. Winkel[3], C. Gluud[3], J. Kastrup[2] on behalf of The CLARICOR Trial Group. [1]*Hilleroed Hospital, Copenhagen, Denmark;* [2]*Rigshospitalet (The Heart Centre), Copenhagen, Denmark;* [3]*Clinical Trial Unit, Copenhagen, Denmark*

Purpose: In patients with stable coronary artery disease often both stable and unstable plaques are present. While a stable plaque evolves slowly and seldom results in acute coronary syndromes, the unstable plaque can suddenly rupture and make thrombosis and subsequently result in myocardial infarction and death. Identification of the unstable plaque can be difficult and biomarkers that could detect an unstable plaque could be of great value in identifying patients at risk for a coronary event. Pregnancy associated plasma protein-A (PAPP-A) has been identified in the unstable plaque and could potentially represent such a biomarker.
Method: The study was a substudy to the short-term clarithromycin versus placebo for patients with stable coronary heart disease (CLARICOR) trial. In CLARICOR patients a blood sample was drawn at trial entry. Blood samples were analysed for PAPP-A with a sandwich ELISA technique based on two monoclonal antibodies reacting with distinct epitopes on the PAPP-A molecule. PAPP-A values above the detection limit of the method (< 4 mIU/l) were considered elevated based on previously reported results from analysis of serum samples from 103 healthy blood donors. Information about death came from the Danish Central Civil Register, which records the vital status of all inhabitants.
Results: Of the 4372 patients included in the trial, samples for measurement of PAPP-A and follow-up data were available in 4243 patients (97%). There were no significant differences between patients included and not included in the analysis regarding background or effect variables. The mean follow-up from randomisation was 2.6 years. PAPP-A was measurable (i.e. ≥ 4 mIU/l) in 549 patients (12.9%). Among patients with elevated PAPP-A the mean value was 7.4 mIU/l (range 4.0 – 167.6 mIU/l). In bivariate analysis taking clarithromycin or placebo in consideration patients with measurable PAPP-A had significantly increased cardiac mortality (HR 2.52, 95% c.i. 1.82-3.49, $p<0.001$) and all-cause mortality (HR 2.42, 95% c.i. 1.91-3.05, $p<0.001$). In multivariate analysis where known risk factors (clarithromycin, age, sex, smoking, hypertension, previous myocardial infarction and diabetes) were included patients with measurable PAPP-A still had significantly increased cardiac mortality (HR 1.87, 95% c.i. 1.30-2.54, $p<0.001$) and all-cause mortality (HR 1.80, 95% c.i. 1.42-2.28, $p<0.001$). PAPP-A did not differ significantly in patients treated with clarithromycin or placebo.
Conclusion: PAPP-A seems to be a valuable marker for both cardiac mortality and all-course mortality in patients with stable coronary artery disease.

P1300 Correlation between carotid and coronary disease in patients with acute coronary disease

L. Franceschini, E. Zorzi, R. Abukaresh, M.P. Donataccio, N. Cicorella, E. Battaia, C. Vassanelli. *Presidio Ospedale Civile Maggiore, Verona, Italy*

Background: Aim of our study is to investigate, in pt with Acute Coronary Syndrome (ACS), the correlation between markers of carotid atherosclerosis assesed by ultrasound and coronary artery disease (CAD).
Methods: Our study included 784 patients (pt) (mean age 67.2±8.8 yrs) with ACS who performed both carotid ultrasound evaluation and coronary angiography from 1995 to 2005. The population was divided into 2 groups: one including pt with non significant CAD (nsCAD), the other one with a significant CAD (sCAD) (at least one lesion ≥ 50%) involving 1, 2 or 3 vessels. The IMT was measured with a 6-MHz probe at the posterior wall of the common left carotid artery 1 cm from the bulb. We considered Unstable Carotid Plaque (UCP) those with one or more of the following criteria: ulceration, irregular surface, presence of thrombus, echolucency, dishomogeneity of plaque; stable carotid plaques (SCP) were those characterized by homogeneity, echolucency and regular surface; "severe carotid stenosis" (SCS) were sub-occlusive lesions (greater than >70% and/or peak sistolic velocity ≥ 250 cm/sec).
Results: Mean IMT value was 1.0±0.16 mm. In the 16% of the cases (125 pt) was < 0.9 mm, in the 84% (659 pt) was >0.9mm. There were SCP in 602 pt (77%), UCP in 182 pt (23%). The angiografic study revealed a sCAD in the 94% of cases (735 pt), a nsCAD in the 6% of the cases (49 pt). Of those with sCAD, 125 pt (16%) had a monovessel (MV) disease, 239 pt (30%) had a bivessel (BV) disease, 371 pt (47%) had a trivessel (TV) disease. Pt with sCAD had a major IMT value than those with nsCAD (1±0.16 mm vs 0.94±0.15 mm, t = 2.27, p = 0.02). There was a strong association between IMT and the number of atherosclerotic coronary vessels involved in pt with ACS (IMT: 0.95±0.18 mm in MV, 0.99±0.16 mm in BV, 1.01±0.15 mm in TV, F = 6.53, p=0.0002). Carotid IMT is significantly linked to the presence and extension of coronary artery disease, over or under the cut point of 0.90 mm (p=0.003). There wasn't any association between UCP and CAD neither between UCP and the number of vessels involved. The presence of SCS was associated with the number of vessels involved but not with a sCAD (p=0.01, p=0.40). At the multivariate analysis the IMT resulted the best predictive factor of sCAD (p=0.041).
Conclusions: There is a significant correlation between the increased IMT and the severity of coronary disease for pt with ACS. This marker should be useful in the risk stratification and in diagnostic and therapeutic management of pt with ACS, especially in a very heterogeneous population such as NSTEMI.

NEW ADVANCES IN STEMI

P1301 CHADS2 score accurately predicts early and late mortality in patients presenting for STEMI

F. Beygui, O. Barthelemy, A. Bellemain-Appaix, J. Silvain, J.P. Collet, N. Vignolles, G. Montalescot. *Pitie-Salpetriere Hospital (AP-HP), Paris, France*

Purpose: Based on age and simple history data of patients, the CHADS2 score provides accurate assessment of the 1 year risk of stroke in the setting of atrial fibrillation. We assessed the hypothesis that the CHADS2 score may be as useful as more complex validated scores in the setting of STEMI.
Methods: We assessed CHADS2, TIMI and GRACE risk scores, in 697 consecutive patients admitted for STEMI within 24 hours of symptom onset. In-hospital and 1-year mortality rates were assessed according to the CHADS score (0 to 6). Low, intermediate and high risk patients were identified by different scores: <2, 2-3, >3 for CHADS; <4, 4-6, >6 for TIMI; <126, 126-154, > 154 for GRACE respectively. The concordance between scores was assessed using the kappa coefficient.
Results: The population was 63±14 years old and included 24% female, 43% hypertensive and 20% diabetic patients.
The cumulative in-hospital and 1-year mortality rates were 5.3% and 8.8% respectively.
Median (IQR) values were 1 (2), 3 (3) and 96 (47) for CHADS, TIMI and GRACE scores respectively.
A CHADS2 score increase of 1 point was associated with an OR of 2.2 (95%CI 1.7-2.9) for in-hospital mortality and, 2.1 (95%CI 1.6-2.7) for 1-year mortality (p<0.0001 for both).
The figure depicts in-hospital (A) and one year mortality (B) rates according to the different scores.
The concordance between the scores was highest between CHADS2 and GRACE (0.53) compared to other combinations (0.52 for TIMI and GRACE and 0.50 for CHADS and TIMI scores).
Conclusions: CHADS2 score at presentation is highly predictive of in-hospital and 1-year mortality after STEMI. The risk prediction by this simple score, purely clinical and available at first medical contact, is concordant with more sophisticated scores.

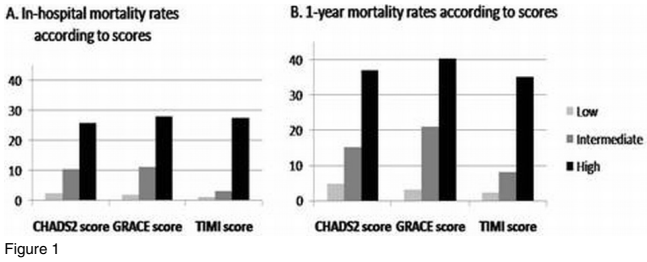


Figure 1

P1302 Microcalcifications in culprit lesions of patients with ST-elevation acute myocardial infarction are associated with osteopontin and C- reactive protein - a thrombectomy study

X. Li, M.C. Kramer, C.M. Van Der Loos, K.T. Koch, J.G.P. Tijssen, R.J. De Winter, A.C. Van Der Wal. *Academic Medical Center, Amsterdam, Netherlands*

Purpose: Coronary thrombectomy at the time of primary PCI is the treatment of choice for ST-elevation acute myocardial infarction (STEMI). The aspirated material contains plaque components and can be used for in vivo investigations on inflammatory biomarkers in culprit lesions (unstable plaques). Purpose of the present study is to describe (micro-) calcifications and its association with inflammatory biomarkers in thrombosuction material.
Method: Aspirated materials obtained from 460 patients who presented with STEMI were screened with Hematoxylin and Eosin stain for presence of thrombus and/or plaque fragments. Calcification was visualized with Alizarin stain. Size of calcifications was measured morphometrically. Co-localization was studied by means of immunostaining with anti-CD68 (macrophages), anti-CRP (C-reactive protein) and anti-Osteopontin (OPN) antibodies in immunodouble and triple stains.
Results: In a total of 460 thrombectomy specimens, measuring 3.9±2,8mm in diameter, 289 showed thrombus-only and 171 showed thrombus with plaque fragments. A total of 67 out of 171 (39%) plaque fragments contained microcalcifications. Ninety five percent of microcalcifications were smaller than 44 μm in diameter. Co-localization of the microcalcifications with macrophages, CRP and OPN immunostain, as well as association between microcalcifications and serum hsCRP are shown in table 1.

Table 1. Percentage of plaques positively stained with macrophages, CRP and OPN

	With calcification (N=52)	Without calcification (N=67)	P-value
Macrophages	93%	87%	0.38
CRP	85%	65%	0.009
OPN	98%	57%	<0.001
Serum hsCRP (mg/l, median, IQR)	3.9, 1.63-10.3	3.0, 1-7.55	0.14

IQR: Inter Quartile Range (25-75%).

Conclusions: Disperse microcalcifications in thrombectomy specimens from STEMI patients are co-localized with CRP and OPN. CRP and OPN are presently considered as powerful biomarkers of atherosclerotic cardiovascular risk. Microcalcifications can be detected with high resolution intravascular imaging, and such associations may be helpful in identifying patients with atherosclerotic plaques at risk for development acute coronary syndromes.

P1303 Early assessment of ST-segment resolution, residual ST-segment elevation and Q waves in relation to left ventricular function, size and extent of infarction, and microvascular injury in AMI

R. Nijveldt[1], P.A. Van Der Vleuten[2], A. Hirsch[3], A.M. Beek[1], R.A. Tio[2], J.G.P. Tijssen[3], J.J. Piek[3], A.C. Van Rossum[1], F. Zijlstra[2]. *[1]VU University Medical Center, Amsterdam, Netherlands; [2]University Medical Center Groningen, Groningen, Netherlands; [3]Academic Medical Center, Amsterdam, Netherlands*

Objectives: We investigated early electrocardiographic findings in relation to left ventricular (LV) function, extent and size of infarction, and microvascular injury in patients with acute myocardial infarction (MI) treated with percutaneous coronary intervention (PCI).
Background: ST-segment resolution and residual ST-segment elevation have been used for prognosis in acute MI, whereas Q waves are related to outcome in chronic MI. We hypothesized that the combination of these electrocardiographic measures early after primary PCI would enhance risk stratification.
Methods: A 12-lead electrocardiogram (ECG) was analyzed in 180 patients with a first acute ST-segment elevation MI, to assess ST-segment resolution, residual ST-segment elevation and number of Q waves acquired on admission and 1 hour after successful PCI. ECG findings were related to LV function, infarction and microvascular injury as assessed with cardiovascular magnetic resonance 4±2 days after reperfusion.
Results: Residual ST-segment elevation (β=-2.00,p=0.004) and the number of Q

waves (β=-1.46,p=0.01) were independent ECG predictors of LV ejection fraction. While the number of Q waves was the only independent predictor of infarct size (β=1.97, p<0.001) and transmural extent (β=0.59,p<0.001), residual ST-segment elevation was the only independent predictor of microvascular injury (OR 19.1 (2.4–154), p=0.005) in multivariable analyses. ST-segment resolution was not associated with LV function or infarction indices in multivariable analysis.
Conclusions: In patients after successful coronary intervention for acute MI, residual ST-segment elevation and the number of Q waves on the post-procedural ECG offer valuable complementary information on prediction of myocardial function and necrosis.

P1304 Impact of heterogeneity of human peripheral blood monocyte subsets on myocardial salvage in patients with primary acute myocardial infarction

H. Tsujioka, T. Imanishi, H. Ikejima, A. Kuroi, T. Tanimoto, H. Kitabata, S. Takarada, K. Hirata, A. Tanaka, T. Akasaka.
Wakayama Medical University, Wakayama, Japan

Background: In view of the heightened appreciation of the heterogeneity of circulating monocytes, we examined whether distinct monocyte subsets contribute in specific ways to myocardial salvage in patients with acute myocardial infarction (AMI).
Methods and Results: We studied 36 patients with primary AMI. Peripheral blood sampling was performed on days 1, 2, 3, 4, 5, 8, and 12 days after AMI onset. Two monocyte subsets (CD14+CD16- and CD14+CD16+) and chemokines receptors (C-C motif chemokine receptor 2 (CCR2) and C-X3-C motif chemokine receptor 1 (CX3CR1)) were measured by flow cytometry. Placental growth factor (PIGF) was measured by enzyme-linked immunoadsorbent assay. The extent of myocardial salvage 7 days after AMI was evaluated by cardiovascular magnetic resonance (CMR) imaging as the difference between myocardium at risk (T2-weighted hyperintense lesion) and myocardial necrosis (delayed gadolinium enhancement). CMR imaging was also performed six months after AMI. Circulating CD14+CD16- and CD14+CD16+ monocytes increased in AMI patients, peaking on days 3 and 5 after onset, respectively. As expected, CD14+CD16- and CD14+CD16+ monocytes were very closely associated with the expressions of CCR2 and CX3CR1, respectively. PIGF levels, which were found to peak on day 3 after AMI, were significantly associated with the peak levels of CD14+CD16- monocytes, but not of CD14+CD16+ monocytes. Importantly, the peak levels of CD14+CD16- monocytes, but not those of CD14+CD16+ monocytes, were significantly negatively associated with the extent of myocardial salvage. We also found that the peak levels of CD14+CD16- monocytes were negatively correlated with recovery of left ventricular (LV) ejection fraction 6 months after infarction.
Conclusions: The peak levels of CD14+CD16- monocytes affect both the extent of myocardial salvage and the recovery of LV function after AMI, indicating that the manipulation of monocyte heterogeneity could be a novel therapeutic target for salvaging ischemic damage.

P1305 Circulating cytochrome c is a new candidate biomarker of reperfusion injury in ST-segment elevation acute myocardial infarction

G. Marenzi[1], M. Giorgio[2], M. Trinei[2], M. Moltrasio[1], P. Ravagnani[1], D. Cardinale[2], F. Ciceri[3], A. Cavallero[1], C.M. Cipolla[2], A.L. Bartorelli[1]. *[1]Centro Cardiologico Monzino, Milan, Italy; [2]European Institute of Oncology, Milan, Italy; [3]San Raffaele Scientific Institute, Milan, Italy*

Purpose: In patients with ST-segment elevation acute myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI), abrupt reperfusion may induce myocardial injury and apoptotic cell death. Cytochrome c, a mitochondrial protein, upon reperfusion is released into the cytosol of infarcted cardiomyocytes and it may reach external fluid and circulating blood when cell rupture occurs. On these bases, cytochrome c might represent a potential peripheral biomarker of myocardial reperfusion-associated apoptosis. In this study, we investigated serum levels of cytochrome c in patients with STEMI undergoing primary PCI, a clinical setting in which sudden prolonged ischemia and abrupt therapeutic reperfusion are major critical features.
Methods: Plasma CK–MB mass and serum cytochrome c (ELISA method) were serially measured during hospitalization of 55 patients with STEMI undergoing primary PCI. We assessed angiographic (TIMI flow and myocardial blush grade [MBG]) and electrocardiographic signs of myocardial reperfusion.
Results: Cytochrome c transiently raised in all STEMI patients with a curve that paralleled that of CK-MB. A CK-MB peak value of 242±229 ng/ml was recorded at 13±5 hours from symptoms onset (9±5 hours from coronary revascularization), and a cyt c peak value of 1.71±1.76 ng/ml was recorded at 16±19 hours from symptoms onset (12±19 hours from coronary revascularization). A significant relationship was found between the peak values of the two biomarkers (R=0.35, P=0.01) and between the areas under the two curves (R=0.33; P=0.02). CK-MB peak value was significantly correlated with clinical features associated with infarct extension (ischemic time, early and late left ventricular ejection fraction, baseline TIMI flow, initial and post-procedural ST-segment elevation). Conversely, cytochrome c peak value was significantly correlated only with MBG. Similar relationships were found when the area under the curve, instead of the peak value of the two biomarkers, was considered. Patients with clinical signs of myocardial reperfusion injury (TIMI flow <3 or TIMI flow 3 and MBG 0 or 1 or ST resolution after the procedure <70%) had a significantly greater cytochrome c peak value than that of patients without reperfusion injury (2.3±2.3 ng/ml vs. 1.3±1.1 ng/ml; P=0.04).
Conclusions: Seruum cytochrome c is detectable in the early phase of STEMI treated with primary PCI and is associated with clinical signs of myocardial reperfusion injury.

PLATELETS AND CORONARY THROMBOSIS

P1306 Influence of mean platelet volume on post-procedural coronary flow and in-hospital and long term mortality in patients with stemi treated by primary PCI

M. Kucuk, A. Belgi Yildirim, I. Basarici. *Akdeniz University Faculty of Medicine, Antalya, Turkey*

Objectives: Infarct related artery (IRA) patency and the quality of the flow/myocardial reperfusion is an important prognostic determinant of STEMI. This study investigates the effect of mean platelet volume (MPV) on short and long term mortality in patients with STEMI treated by PCI. Moreover from an causative mechanistic point of view we utilized thrombolysis in myocardial infarction (TIMI) frame count (TFC) as an objective marker of post-procedural coronary flow in IRA and questioned any association with patients' admission MPV values.
Methods: We enrolled 188 of 215 consecutive patients fulfilling the inclusion and exclusion criteria. Patient medical files were reviewed, clinical and laboratory datas of index event were noted. Coronary angiography records of the primary PCI were analyzed and TFC calculations of IRA (adjusted for individual instantaneous heart rate during intervention) were performed. Follow-up data (18,3±7 months) were collected by evaluation of routine scheduled visits on patient medical files and by phone contact for patients without any follow-up visits.
Results: Mean age of the patients was 56.6±12 and 87.2% were men. Based on the mean MPV plus one standard deviation value (9.025 fl) of overall population two comparative groups (normal and high-MPV) were determined. Infarct localizations, multivessel disease rates, admission Killip classes and door to balon times were similar between two groups. Corrected IRA-TFC values were significantly longer in high-MPV group (19.12±8 vs. 24.48±12; p=0.015). This finding was consistent (19.03±8 vs. 23.72±11; p=0.015) when the analysis was repeated after restricting the analysis in patients (n=162) with procedural success. In-hospital mortality rate was increased in high-MPV group (10.3% vs. 1.3%; p=0.027). The long term mortality rate was also increased in the high-MPV group (19.2% vs. 1.3%; p=0.001). Additionally the major cardiovascular event rate (18.5% vs. 50%; p=0.000) in the long term follow-up was significantly higher in the high-MPV group than the normal-MVP group.
Conclusion: This study demonstrates that in-hospital and long term morbidity and mortality rates are higher in patients with high admission MPV. Also higher MPV values are associated with longer IRA-TFC which may be a explanatory factor for increased mortality in these patients. Therefore we suggest that admission MPV values can be a simple and beneficial prognostic marker to determine patients at high risk for impaired myocardial reperfusion and long term mortality after primary PCI in patients with STEMI.

P1307 Platelet reactivity assessed by flow cytometric VASP phosphorylation is an independent predictor of death and cardiovascular death in unselected patients undergoing PCI

S. El Ghannudi[1], P. Ohlmann[1], M.L. Wiesel[2], B. Radulescu[1], P. Bareiss[1], M. Chauvin[1], C. Gachet[2], O. Morel[1]. *[1]Hopital Civil de Strasbourg, Strasbourg, France; [2]U949 INSERM Etablissement français du sang Alsace, Strasbpurg, France*

Background: Impaired platelet responsiveness to clopidogrel is thought to be a determinant of cardiovascular events following percutaneous coronary angioplasty. The platelet VAsodilator Stimulated Phosphoprotein test (VASP) using flow cytometry is a new clinically practical platelet activation assay specific of the P2Y12 ADP receptor-pathway.
Methods: In a large cohort of unselected patients undergoing urgent or planned PCI (n = 300), we examined whether poor platelet response to clopidogrel assessed by VASP analysis after PCI could be a reliable marker of cardiovascular mortality during follow-up. After PCI, VASP analysis was performed at least 6 hours following a ≥ 300 mg bolus dose of clopidogrel or later (up to 72h). Poor platelet response to clopidogrel was defined as a VASP value > 69% (PPR+). This value corresponds to the mean value –2 SD measured in untreated patients. Patients were followed at least 6 months for the occurrence of death, cardiovascular death, non-fatal myocardial infarction, target vessel revascularisation, and stroke. Follow-up was completed in 280 patients.
Results: PPR+ was evidenced in 76/280 patients (27.1%). Mean cumulative dose of clopidogrel at time of sampling was equivalent between groups (PPR+: 619±1054 mg vs. PPR-: 556±478 mg; p=0.623). By univariate analysis, body weight, history of diabetes were associated with PPR+. At follow-up, all cause and cardiovascular mortality were higher in PPR+ patients (respectively: 9/76 (11.8%) vs 8/204 (3.9%); p=0.022 and 7/76 (9.2%) vs. 5/204 (2.5%); p=0.02). After ad-

justment for other parameters that affect mortality namely history of stroke, renal failure, PPR+ and history of stroke remained independent predictors of mortality. In conclusion, in unselected patients undergoing PCI, poor platelet responsiveness to clopidogrel (>69%) assessed by flow cytometric VASP phosphorylation is an independent predictor of death and cardiovascular death.

P1308 Effects of lower platelet aspirin and clopidogrel response on long-term outcomes in patients with acute STEMI

D. Milicic[1], D. Lovric[1], B. Skoric[1], J. Samardzic[1], I. Gornik[1], K. Narancic Skoric[2], I. Skorak[1], D. Puljevic[1]. *[1]University of Zagreb School of Medicine, Zagreb, Croatia; [2]University Hospital Merkur, Zagreb, Croatia*

Objective: Dual anti-platelet therapy with aspirin and clopidogrel has been a cornerstone of therapy in patients with acute ST-elevation myocardial infarction (STEMI) who undergo primary percutaneous coronary intervention (pPCI). However, some patients didn't respond as effectively to this therapy as others, an occurrence that was first named aspirin and clopidogrel resistance. Our objective was to define patients with suboptimal platelet response to this therapy by using a novel point-of-care method of multiple electrode aggregometry and investigate it's role on occurrence of major adverse cardiac events (MACE) and cardiac or cerebrovascular events (MACCE).
Methods: Aspirin and clopidogrel response was assessed in 87 consecutive patients with STEMI and successful pPCI. The patients were stratified into quartiles depending on the percentage reduction of arachidonic acid (AA) and ADP-induced platelet aggregation on 5th day after pPCI compared to baseline values determined before loading with aspirin and clopidogrel. Follow-up was done at 1 month, 6 months and 1 year. MACE was defined as a composite end-point of death, MI or need for additional revascularization, while MACCE included both MACE and stroke.
Results: Comparing incidence of MACE and MACCE at one year to the relative reduction of platelet aggregation induced by either AA or ADP showed that patients in the highest quartiles had significantly higher incidence of both MACE and MACCE (Table 1). Platelet reactivity was an independent risk factor regardless of age, sex, blood pressure, Killip class, ejection fraction, NT-pro BNP, troponin, creatinine and hemoglobin values.

Table 1

	Reduction in platelet aggregation with arachidonic acid			Reduction in platelet aggregation with ADP		
	1st quartile	2nd-4th quartile	P	1st quartile	2nd-4th quartile	P
No. of pts.	23	64		23	64	
No MACE	15	59	0.05	14	60	0.018
MACE	8	5	7	6		
No MACCE	15	58	0.012	14	59	0.033
MACCE	8	6	7	7		

Conclusion: The patients who underwent pPCI for STEMI and showed a suboptimal response to dual anti-platelet therapy had significantly higher incidence of MACE and MACCE within one year follow-up compared to the patients with an optimal response.

P1309 Comparative assessment of platelet P2Y12 signaling in type 2 diabetes mellitus versus non diabetic subjects

P. Capranzano, J.L. Ferreiro, D. Kodlipet, R. Alissa, A. Darlington, R.K. Charlton, B. Desai, L.A. Guzman, T.A. Bass, D.J. Angiolillo. *University of Florida-Shands Jacksonville, Jacksonville, United States of America*

Purpose: Numerous pharmacodynamic studies have shown that patients with diabetes mellitus (DM) have reduced clopidogrel-induced platelet P2Y12 inhibitory effects compared to non-DM. These functional data may explain why DM patients continue to have a high risk of ischemic events despite clopidogrel therapy. The mechanisms leading to reduced clopidogrel effects in DM patients remain poorly explored. We hypothesize that T2DM patients have upregulation of P2Y12 signaling. To support this hypothesis baseline P2Y12 signaling was compared in clopidogrel naïve patients with and without DM.
Methods: A total of 200 clopidogrel naïve patients on low-dose aspirin therapy were studied: 100 DM and 100 non-DM. The functional activity of the P2Y12 signaling pathway was determined by flow cytometric assessment of intraplatelet vasodilator-stimulated phosphoprotein phosphorylation (VASP-P). VASP-P levels after PGE1 (MFI PGE1) and PGE1 + ADP (MFI PGE1 + ADP) stimulation were measured as per standard protocols. The P2Y12 reactivity index (PRI) was derived from these parameters, whereas higher values are indicative of upregulation of this signaling pathway and viceversa. Results are reported as median and interquartile range (IQR).
Results: DM patients had significantly lower MFI PGE1 (median 22.5, IQR 17.9-28.6 vs median 25.9, IQR 21.9-30.3; p= 0.01) and MFI PGE1 + ADP (median 4.3, IQR 3.2-5.4 vs median 5.3, IQR 4.4-6.8, p<0.0001) compared to non-DM. Accordingly, the PRI was significantly higher in DM compared to non-DM (median 81.6, IQR 75.8-85.7 vs median 77.3. IQR 71.3-82.9, p=0.001). Similar significant differences between DM and non-DM were also observed in different subgroups according to sex, age and weight and concomitant cardiovascular risk factors.
Conclusions: The P2Y12 signaling pathway is upregulated in DM patients. These findings may explain why DM patients have reduced clopidogrel-induced platelet P2Y12 inhibitory effects and benefit from more potent P2Y12 inhibiting strategies.

P1310 Cangrelor inhibits the binding of clopidogrel and prasugrel active metabolites to the P2Y12 receptor

R. Buckland[1], H.M. Judge[1], A. Sugidachi[2], J.A. Jakubowski[3], R.F. Storey[1]. *[1]The University of Sheffield, Sheffield, United Kingdom; [2]Daiichi Sankyo Co.,Ltd., Tokyo, Japan; [3]Lilly Research Laboratories, Indianapolis, United States of America*

Cangrelor (Cang) is a reversible iv P2Y12 receptor antagonist being investigated for use during percutaneous coronary intervention (PCI). Most PCI patients will require subsequent treatment with oral P2Y12 inhibitors such as the thienopyridines clopidogrel (Clop) or the investigational drug prasugrel (Pras), which act via active metabolites (AM) that bind irreversibly to P2Y12. Recent studies suggest an interaction between the two types of drug. We investigated the influence of Cang on binding of Clop and Pras AM to P2Y12.
Whole blood from healthy volunteers was anticoagulated with hirudin. PRP was prepared and incubated with Cang (0-1000nM). P2Y12 blockade by Cang was confirmed in aliquots of PRP using a 33P-2MeSADP binding assay in the presence of a P2Y1 receptor antagonist, MRS2179; Cang 1000nM yielded 93.5±4% receptor blockade. PRP samples were then incubated in the presence or absence of Clop or Pras AM (3uM each) followed by washing steps to remove Cang and unbound AMs. P2Y12 blockade was then assessed by the 33P-2MeSADP assay. In the absence of AM, there was no difference in unblocked receptor number in samples incubated with Cang vs control confirming effective removal of Cang. In the absence of Cang, Clop and Pras AM yielded a high level of P2Y12 blockade but % blockade decreased with increasing concentration of Cang for both AMs (table).

Cang (nM)	% P2Y12 blockade Pras	% P2Y12 blockade Clop
0	97.9	93
10	95	56.1
100	38.5	8.7
1000	3.2	7

This study confirms that Cang bound to P2Y12 prevents the irreversible binding of both Clop and Pras AM and has important implications for the timing of administration of thienopyridines to Cang-treated patients.

P1311 Insufficient platelet aggregation inhibition by pre-hospital clopidogrel alone vs additional high dose Tirofiban in patients with acute STEMI undergoing primary PCI resulting in worse clinical outcome

J.J.J. Smit[1], J.W. Van Werkum[2], A.A.C.M. Heestermans[1], S. Postma[3], R.S. Hermanides[1], T. Dill[4], C. Hamm[4], E. Kolkman[3], J.M. Ten Berg[2], A.W.J. Van 't Hof[1]. *[1]Isala Klinieken, Zwolle, Netherlands; [2]St Antonius Hospital, Nieuwegein, Netherlands; [3]Diagram, Zwolle, Netherlands; [4]Kerckhoff Klinik GmbH, Bad Nauheim, Germany*

Purpose: Adequate platelet aggregation inhibition is of paramount importance in the treatment of acute coronary syndromes. It is unknown whether in the ambulance, given additional high dose (HD) Tirofiban on top of HD-clopidogrel results in more adequate inhibition of platelet aggregation and better clinical outcome after primary percutaneous coronary intervention (PCI). Furthermore, the optimal test-specific level of platelet aggregation inhibition resulting in better clinical outcome is also unknown.
Methods: The Ongoing in Tirofiban in Myocardial Infarction Evaluation trial is a prospective, international, multicenter, placebo controlled trial comparing early pre-hospital initiation of HD dose (25 μg/kg) Tirofiban to placebo on top among others 600mg clopidogrel in STEMI pts undergoing primary PCI. Platelet function was measured before PCI, after angiography using: adenosine diphosphate (ADP) induced platelet aggregation (Platelet Works), platelet function analyser (PFA)-100 (collagen-epinephrine: col-epi and collagen-ADP: col-ADP cartridge) and Fe-induced platelet aggregation (FIPA) in consecutive pts from 2 selected participating centres.
Results: From 1398 randomized pts, platelet inhibition data were available in 648 of the 964 pts. Platelet inhibition was measured at a median of 60 min after study medication administration. Platelet inhibition was more in tirofiban group as compared with placebo (means ±SD): Plateletworks 82±20% vs 39±24%, col-epi 283±33 s vs 158±84 s, col-ADP 282±41 s vs 88±50 s, FIPA 85%±18% vs 39%±24%, p<0.001 for all tests. Pts in the highest quartile of platelet inhibition, using as well Plateletworks as PFA-100 (col-epi and col-ADP) and FIPA had less residual ST segment deviation on the one hour post PCI ECG (primary endpoint of the trial; p=0.004, 0.001, 0.002, 0.001). There was a significant relationship between PFA-100 (col-epi and col-ADP) and major adverse events (mortality, target vessel revascularisation, myocardial infarction in 30 days; p=0.028, 0.035) and subacute thrombosis (p=0.009, 0.007).

Conclusions: Sixty minutes of pre-hospital treatment with clopidogrel and acetylsalicylic acid results in reduced platelet aggregation inhibition as compared to additional HD Tirofiban, which results in enhanced residual ST segment deviation one hour after PCI. Furthermore, PFA-100 bleeding time was related to major adverse events and subacute thrombosis. Therefore, this substudy confirms the results of the main findings of the On-TIME trial that clopidogrel alone is not enough, even at high dose and given well in advance of primary PCI.

P1312 Impact of platelet poor responsiveness to clopidogrel on cardiovascular outcome in type 2 Diabetes mellitus patients treated by percutaneous coronary angioplasty

S. El Ghannudi[1], P. Ohlmann[1], M.L. Wiesel[2], B. Radulescu[1], P. Bareiss[1], M. Chauvin[1], C. Gachet[2], O. Morel[1]. [1]*Hopital Civil de Strasbourg, Strasbourg, France;* [2]*U949 INSERM Etablissement français du sang Alsace, Strasbpurg, France*

Objectives: This study sought to determine the prognostic implication of platelet poor responsiveness to clopidogrel assessed by Vasodilator Stimulated Phosphoprotein test (VASP) in unselected type 2 Diabetes mellitus (T2DM) patients treated by percutaneous coronary angioplasty (PCI).
Background: T2DM patients have increased platelet reactivity compared with non diabetic patients (NDM). Whilst recent data have suggested that platelet poor responsiveness could be indicative of a worsened cardiovascular outcome, little is known about the specific prognostic implication of impaired platelet response to thienopyridine in T2DM. The platelet VAsodilator Stimulated Phosphoprotein test (VASP) using flow cytometry is a new clinically practical platelet activation assay specific of the P2Y12 ADP receptor-pathway.
Methods: Platelet response to clopidogrel was assessed by VASP analysis in 116 T2DM and 184 NDM patients treated by planned (23.9%) or urgent PCI (76.1%). After PCI, VASP analysis was performed at least 6 hours following a $\geq$ 300 mg bolus dose of clopidogrel or later (up to 72h). Platelet poor response to clopidogrel was defined as a platelet reactivity index (PRI) value $>$ 69% (PPR+). This value corresponds to the mean value–2 SD measured in untreated patients. Patients were followed for 6 months and MACE were recorded. Follow-up was completed in 280 patients.
Results: The PRI (%) was higher in T2DM patients (T2DM: 57.2$\pm$19.6% vs. NDM: 50.6$\pm$21.3%, p=0.008). Likewise, the number of PPR+ patients was higher in T2DM (41/115 (35.7%) vs. 39/180 (21.7%); p 0.011). However, at time of blood sampling, mean cumulative dose of clopidogrel was equivalent between groups (T2DM: 562$\pm$851 mg vs. NDM: 586$\pm$558 mg, p=0.793). In T2DM, no correlation between PRI, body weight, inflammatory status, HbA1c and glycemia levels could be evidenced. At 6 months follow-up, death occurred in 10 T2DM (9.1%) and 7 NDM (4%) (p = 0.121), cardiac death in 7 T2DM (6.4%) and 5 NDM (2.9%), non fatal myocardial infarction in 3 T2DM (2.8%), and 2 NDM (1.1%)(p = 0.377) patients. Among T2DM, death occurred in 7 (17%) PPR+ patients and in 3 PPR- patients (4.3%)(p = 0.033). InT2DM, PPR+ appeared a strong predictor of global and cardiovascular mortality (OR 4.87 CI 95% [1.18-20]; p = 0.028).
Conclusion: Unselected T2DM patients undergoing PCI have a greater prevalence of inadequate clopidogrel-induced antiplatelet effects assessed by VASP phosphorylation analysis. In T2DM, platelet poor response to clopidogrel appeared to be a strong predictor of 6 months global and cardiovascular mortality.

P1313 A double-blind and randomized study on the existence and prevention of a rebound phenomenon of platelet aggregation after cessation of clopidogrel treatment

D. Sibbing, J. Stegherr, J. Mehilli, S. Schulz, S. Braun, I. Graf, W. Vogt, A. Kastrati, N. Von Beckerath, A. Schomig. *Deutsches Herzzentrum München, München, Germany*

Purpose: Clinical studies have shown a clustering of thrombotic events in the period after discontinuation of clopidogrel. The hypothesis of a rebound phenomenon of platelet aggregation (PA) has been declared causative but its existence has never been confirmed. Tapering of clopidogrel over a certain period of time before stopping it completely, might provide a way to attenuate this supposed phenomenon. Thus, the goal of this study was to assess whether a rebound phenomenon exists and whether it can be attenuated by clopidogrel tapering.
Methods: Patients (n=69) on clopidogrel due to prior drug-eluting stent placement who were planned to stop clopidogrel were recruited in a double-blind randomized trial and were randomized to either receive a pre-specified tapering regimen (tapering group) of 4 weeks with discontinuation of clopidogrel thereafter or to continue clopidogrel for 4 more weeks with abrupt discontinuation thereafter (off group). ADP-induced PA was assessed with light transmission aggregometry (LTA) and multiple electrode aggregometry (MEA) at study inclusion and during a follow-up weekly at weeks 2-8. The primary endpoint was the maximal value of PA measured after complete clopidogrel cessation (weeks 5-8).
Results: Maximal PA values after complete cessation of clopidogrel were similar between both groups (*P=NS, see Figure 1). In the off group, a peaking of PA (rebound) in the time period after complete clopidogrel cessation with a significant decrease in the weeks afterwards was not observed (P$\geq$0.48, see Figure 1).

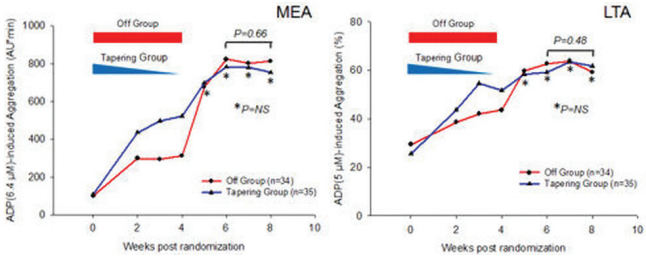


Figure 1

Conclusions: Tapering of clopidogrel does not result in lower PA values after complete clopidogrel cessation. The course of PA values after clopidogrel cessation provides no evidence for the existence of a rebound phenomenon of platelets after discontinuation of clopidogrel.

P1314 Levels of platelet microparticles are increased in thrombectomy-aspirated blood of ST-elevation myocardial infarction patients and correlate with thrombus burden of the culprit lesion

G.L. De Maria[1], I. Porto[1], L.M. Biasucci[1], L. Di Vito[1], G.P. Niccoli[1], F. Burzotta[1], A. Tritarelli[1], A. Paglia[1], M.C. Capogrossi[2], F. Crea[1]. [1]*Catholic University of the Sacred Heart, Rome, Italy;* [2]*Istituto Dermopatico dell'Immacolata, Rome, Italy*

Purpose: Microparticles (MPs) are fragments derived from activated platelets (CD31+/CD42+ PMPs) endothelial cells (CD31+/CD42- EMPs) or from apoptotic cells (CD31+/AnnexinV+ AMPs) and known to be increased in the context of acute coronary syndromes. We assessed whether a difference in levels of MPs could be detected between intracoronary and peripheral blood soon after the onset of ST elevation myocardial infarction (STEMI), and the correlation of MPs with angiographic indexes of revascularisation and thrombotic burden.
Methods: Sixteen STEMI patients undergoing primary percutaneous coronary intervention (pPCI) were included. Aortic blood samples from the guiding catheter and intracoronary, translesional blood aspirate from thrombectomy device were sequentially drawn at the beginning of pPCI to assess the three types of MPs by flow cytometry. Haematocrit (HTC) and white blood cells count (WBC) were measured both in intracoronary and peripheral blood. TIMI flow grade, corrected TIMI frame count (cTFC), and Myocardial Blush Grade (MBG) were measured after PCI to assess revascularisation efficacy, while Thrombus Score (TS), after initial guidewire passage was chosen as a measure of thrombotic burden.
Results: MPs (in MPs/μL) were significantly higher in intracoronary than in peripheral blood, being 5.3 (IQR 1.2-7.6) vs 1.5 (0.4-2.7), p =0.001 for AMPs, 17.2 (8.0-31.3) vs 6.8 (5.8-13.7), p=0.01 for EMPs, 92.8, (29.5-367.4) vs 16.9, (11.8-80.9) p = 0.001 for PMPs). Intracoronary and peripheral blood did not differ in terms of both HTC (42% IQR 33-43 vs 39% IQR 33-41, p=0.7) and WBC (11260 IQR 10615-13765 vs 11170 IQR 10270-12760, p=0.7), confirming the absence of concentration of the intracoronary blood. No significant correlation was observed between either circulating or intracoronary microparticles and TIMI flow grade, cTFC and MBG. Intracoronary and peripheral PMPs were strongly related to TS (r=0.7, p=0.003 for intracoronary PMPs and r=0.8, p$<$0.001 for peripheral PMPs).
Conclusions: Our data show for the first time that all the three types of MPs are higher in the culprit vessel than in peripheral blood during pPCI for STEMI, possibly as the result of a local production. The correlation of both systemic and intracoronary PMPs with TS suggests a pathophysiological link between systemic platelet activation, local intracoronary factors, and thrombus formation during acute myocardial infarction.

P1315 Does the continuous clopidogrel administration overcome the platelet poor response to the drug in patients with acute coronary syndrome and clopidogrel resistance?

K. Kalantzi[1], A. Dimitriou[2], H. Milionis[1], A. Tselepis[2], I. Goudevenos[1]. [1]*Department of Cardiology, Medical School, University of Ioannina, Ioannina, Greece;* [2]*Department of Chemistry, University of Ioannina, Ioannina, Greece*

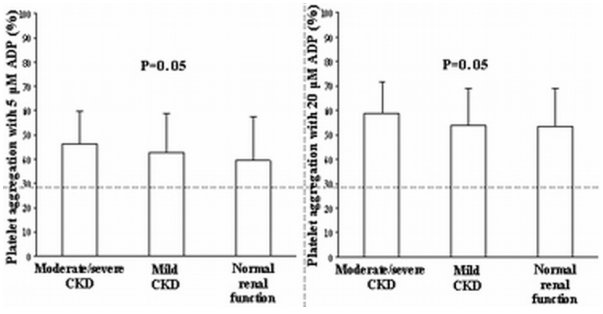
Purpose: Clopidogrel resistance plays a key role in ischemic recurrence in patients who underwent an acute coronary syndrome (ACS). Recent studies showed that the incidence of platelet poor response to clopidogrel ranged from 4-44%. We studied platelet aggregation response at baseline and follow-up in patients with ACS treated with clopidogrel and exhibiting adequate or poor response to clopidogrel.
Methods: Blood samples were obtained from 30 patients with recent ($<$24 hours) ACS within 24 hours of hospital admission before the administration of clopidogrel (baseline), 5 days later and 30 days after the admission. All patients had received clopidogrel (600 mg loading dose, followed by 75 mg per day). We studied ADP- induced platelet aggregation with aggregometry in platelet-rich-plasma

(PRP). Clopidogrel resistance was evaluated according to Vasolidator Stimulated Phosphoprotein (VASP) test with flow cytometry in whole blood.
Results: Nine of the 30 patients (33%) exhibited clopidogrel resistance according to the VASP test. VASP index was 1,00 (range 0,00- 6,77) for patients with clopidogrel resistance and 32 (range 21- 70) for patients with good response to clopidogrel. These patients presented with significantly lower inhibition of platelet aggregation to ADP (2.5 μM) at 5 days after drug administration (30% inhibition compared to the baseline values) versus (51% inhibition compared to the baseline values) observed in patients with good response to clopidogrel ($P<0.05$). Importantly, 30 days after continuous administration of clopidogrel, the inhibition of ADP-induced platelet aggregation in patients with clopidogrel resistance was 60% compared to the baseline values and it was similar to that observed in clopidogrel good responders (70% inhibition compared to the baseline values).
Conclusion: This is the first study suggesting that continuous drug administration for at least 30 days after the onset of the ACS, may significantly improve the platelet response to clopidogrel in patients exhibiting clopidogrel resistance. The mechanisms involved in this procedure need further investigation.

P1316 Impact of renal function on clopidogrel-induced antiplatelet effects in diabetes mellitus patients with coronary artery disease

D.J. Angiolillo[1], E. Bernardo[2], P. Capranzano[1], M. Sabate[2], P. Jimenez-Quevedo[2], F. Alfonso[2], R. Hernandez-Antolin[2], T.A. Bass[1], C. Macaya[2], A. Fernandez-Ortiz[2]. *[1]University of Florida-Shands Jacksonville, Jacksonville, United States of America; [2]Hospital Clinico San Carlos, Madrid, Spain*

Purpose: Chronic kidney disease (CKD) often occurs in diabetes mellitus (DM) patients. Recent findings have shown that clopidogrel does not have the same beneficial clinical effect in patients with mild or moderate CKD as it does in patients with normal renal function. It has been hypothesized that reduced clopidogrel responsiveness associated with CKD may explain these outcomes. However, if renal function is associated with variations in clopidogrel effects remains unexplored. The aim of the present study was to assess the impact of renal function on platelet function profiles in DM patients with coronary artery disease on treatment with clopidogrel.
Methods: A total of 230 patients with DM were studied. All patients were in the steady state phase (>1-month) of clopidogrel therapy (75mg/day). In addition, all patients were on aspirin 100mg/day. Patients were divided into three groups: creatinine clearance ≥90 mL/min (normal renal function), 60 to 90 mL/min (mild CKD), and <60 mL/min (moderate/severe CKD). The creatinine clearance was estimated using the Cockroft-Gault formula. Platelet aggregation was assessed by means of standard light transmittance aggregometry following stimuli with 5 and 20 microM adenosine diphosphate (ADP).
Results: Normal renal function, mild CKD, and moderate/severe CKD were observed in 70, 105, and 55 patients, respectively. Platelet aggregation increased with the severity of renal dysfunction (Figure). Patients with moderate/severe CKD had the highest degree of platelet aggregation following 5 microM ADP (46±13 vs 41±17; p=0.02) and 20 microM ADP (59±13 vs 54±15; p=0.01) stimuli.



Conclusions: Diminished renal function is associated with reduced clopidogrel-induced antiplatelet effects in DM patients with coronary artery disease.

P1317 Monitoring P2Y12 receptor inhibition with light transmission aggregometry: a comparison with vasodilator stimulated phosphoprotein phosphorylation assay

D. Aradi[1], A. Vorobcsuk[1], M. Tokes-Fuzesi[2], T. Magyarlaki[2], I.G. Horvath[1], A. Komocsi[1]. *[1]Heart Institute, University of Pécs, Pécs, Hungary; [2]Institute of Laboratory Medicine, University of Pécs, Pécs, Hungary*

Purpose: In patients on clopidogrel therapy, measuring ADP-stimulated late platelet aggregation has been hypothesized to be more appropriate in reflecting the efficacy of P2Y12 receptor inhibition than maximal aggregation since the latter might be influenced by the activation of the P2Y1 receptor. We aimed to compare different measures of light transmission aggregometry (LTA) with vasodilator stimulated phosphoprotein phosphorylation (VASP-PRI) to determine the most appropriate parameter of LTA for monitoring P2Y12 receptor inhibition.
Methods: Efficacy of clopidogrel therapy was measured in 89 clopidogrel-naïve stable angina patients in the setting of a double-blind, randomized clinical trial (NCT00638326). Samples for LTA and VASP assessments were drawn at 12-18 hours (T1) after receiving a 600-mg loading dose of clopidogrel and 25 days (T2) after the coronary intervention. ADP 5 μM-induced maximal aggregation (AG-Gmax), 6-minute late aggregation (AGGlate), disaggregation (disAGG) and area under the LTA curve (AUC) were compared to VASP-PRI. Receiver-operating characteristic (ROC) curves were used to test the predictive value of LTA parameters and to define their optimal cutoff values. Categorical agreement with VASP-defined normal and high platelet reactivity (HPR: VASP-PRI>50%) was analyzed with the k-statistic.
Results: The analysis of 169 measurements (T1: 89; T2: 80) showed significant, moderate-strength correlations between VASP-PRI and LTA parameters with AUC demonstrating the strongest relationship (Spearman's rho; AGGmax: r=0.48; AGGlate r=0.48; disAGG: r= -0.49; AUC: r=0.51). Bland-Altman plots showed that AGGlate, disAGG and AUC are underestimating the degree of P2Y12 receptor inhibition, particularly in cases of low platelet reactivity (VASP-PRI<50%). Based on the ROC analysis, LTA parameters were equivalent in predicting HPR (areas under the ROC curve: AGGmax: 0.76; AGGlate: 0.75; 1/disAGG: 0.75; AUC: 0.77). Using the optimal cutoff values to classify patients as normal or HPR, AGGlate showed the highest categorical agreement with VASP-PRI (AGGmax>32.9%: k=0.45; AGGlate>12.8%: k=0.53; disAGG<63.6%: k=0.51; AUC>96.5: k=0.48). When T1 and T2 measurements were analyzed separately, similar results were found.
Conclusions: When estimating the degree of P2Y12 receptor inhibition, 5 μM ADP-induced LTA parameters show moderate correlation with VASP-PRI without any benefit of AGGlate over the others. However, AGGlate might better reflect VASP-defined normal or high platelet reactivity based on the optimal cutoff values of the ROC curve.

P1318 Residual platelet activation: Too many methods for an accurate definition in clinical practice

F.J. Pastor-Perez[1], J. Rivera[2], J.A. Hurtado[1], L. Navarro[2], J.M. Ruiz-Nodar[3], V. Roldan[4], D. Hernandez-Romero[1], V. Vicente[2], M. Valdes[1], F. Marin Ortuno[1]. *[1]Hospital Universitario Virgen de la Arrixaca, Murcia, Murcia, Spain; [2]Centro Regional de Hemodonación, Murcia, Spain; [3]Hospital General Universitario de Alicante, Alicante, Spain; [4]Hospital Morales Meseguer, Murcia, Spain*

A high percentage of patients with symptomatic atherosclerosis will suffer from a serious vascular event despite antiplatelet therapy. It has been proposed different underlying mechanisms, but an incomplete platelet inhibition could take some significant influence. None of the platelet reactivity assays ex vivo is considered gold-standard for monitoring antiplatelet therapy. The objective of the present study was to explore the residual platelet function by 4 different laboratory assays in patients under dual antiplatelet therapy. Additionally, we explored the utility of these findings in a group of patients with late thrombosis of drug eluting stent.
Methods: We included 29 patients with drug eluting stent (14 with late thrombosis, and 15 without any event in the last 12 months), all of them under dual antiplatelet therapy and without any clinical instability in the last 6 weeks. These patients were compared with 45 healthy controls without antithrombotic therapy. We tested VASP phosphorylation by flow cytometry and PFA-100 (Col-Epi & Col-ADP) in whole blood. Light transmittance aggregometry (LTA) was assayed in non-adjusted platelet rich plasma with 1.6mM arachidonic acid (AA), 10μM ADP, 5.5μM epinephrine (E), 2μg/mL collagen (C), 1.25mg/mL ristocetin (R) or 25μM TRAP. Serum TxB2 level was determined by a commercial ELISA. Patients with results within the normality interval (mean from controls ±3SD) were considered as non-responders (NR). Agreement on %NR among assays was assessed with the κ statistic.
Results: All tests, except LTA-R, showed significant differences between patients and controls. Platelet reactivity in patients was highly variable (20-75% of normal values in different tests). %NR were: TxB2: 0%; LTA-AA, LTA-ADP, LTA-C and LTA-E <10%; VASP and Col-Epi: 50%; LTA-TRAP, LTA-R and Col-ADP >75%. Differences in platelet reactivity or %NR were not associated to thrombosis occurrence. Agreement on %NR among assays was low. Yet, agreement and κ value between LTA-ADP and VASP (52%,κ=0.15,p>0.05) significantly raised if non-response criteria was changed to residual response >60% (72%,κ=0.5,p<0.001).
Conclusions: Patients under dual antiplatelet therapy maintained a variable residual reactivity which did not correlate with the occurrence of stent thrombosis. %NR patients is highly test-specific and dependent on non-response criteria.

P1319 Clopidogrel administration significantly attenuates the platelet meditative inflammatory response on patients with acute coronary syndrome

K. Kalantzi[1], A. Dimitriou[2], H. Milionis[1], A. Tselepis[2], I. Goudevenos[1]. *[1]Department of Cardiology, Medical School, University of Ioannina, Ioannina, Greece; [2]Department of Chemistry, University of Ioannina, Ioannina, Greece*

Purpose: Platelets play a dominant role in thrombosis and inflammation that take

place in the development of atheromatic plaque. We sought to characterize the antithrombotic and inflammatory action of clopidogrel in patients with acute coronary syndromes (ACS).
Methods: Blood samples were obtained from 20 patients with recent (<24 hours) ACS within 24 hours of hospital admission before the administration of clopidogrel, 3-5 days later and 30 days after the admission. Six patients had clopidogrel resistance as evaluated by the Vasolidator Stimulated Phosphoprotein (VASP) test and were excluded. We studied platelet function and platelet-leucocytes interaction with aggregometry in platelet-rich-plasma (PRP) and flow cytometry in whole blood and PRP after ADP- and TRAP-14- induced platelet activation.
Results: Clopidogrel attenuated platelet aggregation to both ADP (2,5 μM) and TRAP-14 (10 μM) by 51% and 48% respectively at 3-5 days after the clopidogrel administration and 75% at 30 days after the clopidogrel administration. Furthermore, patients appeared with lower membrane expression of CD40L ($p<0,001$) in platelets, lower secretion of platelet-derived microparticles (PMPs) ($p<0,002$) and with significant reduction in platelet-monocyte ($p<0,002$) and platelet-neutrophils ($p<0,01$) interaction 5 days after the administration of clopidogrel in contrast with the values before the drug administration. In 30 days the above findings were amplified ($p<0,05$).
Conclusions: Clopidogrel exhibits antithrombotic actions by inhibiting platelet aggregation and anti-inflammatory actions by attenuating membrane expression of CD40L, PMPs secretion and platelet-leucocytes interaction. These effects may contribute to the clinical benefits of the drug in ACS.

P1320 Preoperative aspirin discontinuation and perioperative myocardial infarction in patients undergoing CABG procedure

D. Plicner, Z. Zietkiewicz, R. Stapor, B. Kapelak, A. Pazdan, I. Gorkiewicz-Kot, M. Sniezek-Maciejewska, A. Undas, J. Sadowski. *John Paul II Hospital, Krakow, Poland*

Objectives: Platelet activation and oxidative stress are involved in the pathogenesis of perioperative myocardial infarction (PMI) in patients undergoing CABG. Aspirin discontinuation increases platelet activation and therefore current recommendations state that aspirin should be maintained perioperatively in patients with high thrombotic risk.
Aims: To evaluate platelet activation and oxidative stress markers in relation to PMI in elective CABG patients who withdrew aspirin at least 10 days before the operation.
Methods: In elective CABG patients who self reported aspirin discontinuation at least 10 days before the operation – thromboxane B2 (TXB2), β-thromboglobulin (β-TG), 8-isoprostaglandin F 2α (8-iso PGF 2α) were measured in circulating blood at baseline and 5-7 days after procedure (after 4 doses of 150 mg/day aspirin). Exclusion criteria were other concomitant cardiac procedure, renal failure, cancer and use of anticoagulation or thienopyridienes.
Results: We studied 108 patients (M-85, F-23; mean age 64,9±8,1 y.) including 24 (22,2%) patients with off pump CABG. Baseline levels of TXB2, β-TG, and 8-iso PGF 2α were elevated and rose following surgery despite aspirin administration. 13 PMI patients (12%) including 3 deaths were identified within the first 7 postoperative days. The PMI patients showed higher levels of TXB2, β-TG, and 8-iso PGF 2α than the remainder. On multiple regression analysis including pre- and perioperative variables TXB2 and 8-iso PGF 2α levels were the independent predictors of PMI. Postoperative β-TG and 8-iso PGF 2α correlated with TXB2 (for both $p<0.0001$).
Conclusions: Preoperative aspirin discontinuation in CABG patients is associated with markedly increased TXB2 levels in early postoperative period, despite the early reintroduction of aspirin. This phenomenon is related to an increased risk for PMI and correlated with enhanced oxidative sress.

P1321 Pregnane X receptor (PXR) 6 base pair (bp) deletion has no impact on platelet function after a loading dose of 600 mg clopidogrel

J. Kaufmann, A. Koster, P. Stawowy, A. Mueller, T. Hauptmann, H. Meyborg, T. Berg, K. Graf, E. Fleck. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Background: One major mechanism of clopidogrel resistance seems to be the failure of clopidogrel, a prodrug, to be metabolically activated by hepatic cytochrome P450 (CYP), e.g. CYP2C19 and CYP3A4. Data published recently suggested that this mechanism may be due to functional variants in genes encoding nuclear pregnane X receptor (PXR) regulating the induction of the CYP3A4 isoenzyme. PXR is a member of the nuclear receptor superfamily and mediates the induction of the CYP3A4 gene in response to xenochemicals.
Purpose: The aim of this study was to determine whether the antiplatelet effect of a 600 mg loading-dose clopidogrel followed by a 75 mg maintenance-dose in patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) with stent implantation is influenced by 6 base pair (bp) deletion located in the intron 1 of the PXR gene and by CYP2C19 681G>A polymorphism.
Methods: Eighty patients (67 males, 13 females, 66.3±9.2 years) were included in the study. Platelet function was assessed by optical aggregometry (LTA) and vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis 21±2 h after admistration of the loading dose and after one month of maintenance-therapy respectively. Inhibition of platelet aggregation (IPA) was calculated in % with respect to baseline platelet reactivity. Genotyping was performed for CYP2C19 681G>A polymorphism and PXR 6 bp-deletion.
Results: Analysis showed a correlation of LTA (mean 43.7±3.4%) with VASP-analysis (PRI, mean 35.8±4%) ($r = 0.5$, $p < 0,001$). The IPA increased significantly after one month of maintenance-therapy ($p < 0,001$). The allele frequency of the PXR 6 bp-deletion variant was 64%. There was no difference in platelet reactivity between carriers of the deletion and noncarriers after clopidogrel intake (PRI: 43.6±4.5% (del) vs. 43.9±5.3 (wt), $p = 0.9$). Carriers of at least one CYP2C19 681G>A allele (32% of the study population) had a relative reduction in PRI of 36% after a 600 mg loading-dose ($p = 0,01$) and 43,8% after one month ($p < 0,001$) as compared with noncarriers. A significant increase in clopidogrel-response after one month could be measured in noncarriers ($p = 0,001$) but not in carriers ($p = 0,068$).
Conclusion: PXR 6 bp-deletion had no impact on platelet reactivity. In accordance with data published recently, carriers of the CYP2C19 681G>A loss-of-function polymorphism have an increased platelet-reactivity after clopidogrel intake. Furthermore, compared to carriers noncarriers have a significant increase in clopidogrel-response after one month of maintenance-therapie.

P1322 Increased whole blood platelet aggregation in coronary artery disease patients with a high platelet turnover

E.L. Grove[1], A.M. Hvas[2], S.B. Mortensen[1], S.B. Larsen[1], S.D. Kristensen[1]. *[1]Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark; [2]Centre for Haemophilia and Thrombosis, Aarhus University Hospital, Skejby, Aarhus, Denmark*

Purpose: Immature platelets reflect platelet production and turnover and may be more haemostatically active than mature platelets. Our objective was to evaluate the presence of immature platelets in patients with stable coronary artery disease (CAD) and to investigate the relationship between immature platelets and whole blood platelet aggregation.
Methods: We included 177 CAD patients, including 85 type 2 diabetics and 92 non-diabetics. Patients were stable with no cardiovascular events or revascularization procedures within the previous 12 months and received no other antiplatelet therapy than 75 mg of aspirin daily. Blood samples were drawn exactly one hour after aspirin ingestion. Flow cytometric determination of immature platelets was performed with a haematology analyzer and RNA fluorescent dyes. Serum levels of thrombopoietin, soluble P-selectin and thromboxane B2 were measured with ELISA. Whole blood platelet aggregation was determined using five different agonist concentrations: arachidonic acid (0.5 and 1.0 mM), ADP (10 μM) and collagen (1.0 and 2.0 μg/mL).
Results: Immature platelet levels did not differ between diabetics and non-diabetics but significantly correlated with platelet aggregation induced by all five agonists ($r=0.21$-0.36, $p=0.0057$ for arachidonic acid 0.5 mM, other p-values were < 0.0001) and with thrombopoietin levels ($r=-0.24$, $p=0.0014$) and P-selectin ($r=0.17$, $p=0.0276$). In diabetics, trombopoietin (37.6±16 vs 43.4±18 pg/mL, $p=0.0001$) and P-selectin levels (66.3±28 vs 77.8±25 ng/mL, $p=0.0049$) were increased. Arachidonic acid induced residual platelet aggregation was also higher in diabetics than in non-diabetics (0.5 mM: $p=0.0048$, 1.0 mM: $p=0.0090$) and, in diabetics, serum thromboxane B2 levels were less efficiently suppressed by aspirin (0.58 [0.4;0.6] vs 1.03 [0.5;2.2] ng/mL, $p<0.0001$).
Conclusions: Increased levels of immature platelets consistently correlated with increased platelet aggregation in whole blood. Aspirin seems to confer a biochemically less efficient inhibition of platelet aggregation in CAD patients with diabetes mellitus type 2. This may explain previous clinical findings of a reduced cardiovascular protection from aspirin in diabetics. Immature platelets may contribute to thrombus formation in patients with CAD and might increase the risk of cardiovascular events.

P1323 The formation of monocyte-platelet aggregates is independent of on-treatment residual agonists-inducible platelet reactivity

T. Gremmel, C.W. Kopp, D. Seidinger, R. Koppensteiner, S. Steiner, S. Panzer. *Medical University of Vienna, Vienna, Austria*

Purpose: Circulating monocyte-platelet aggregates (MPA) are a sensitive marker of in vivo platelet activation and patients with atherosclerotic vascular disease exhibit higher levels of MPA. Clopidogrel has been shown to reduce MPA formation in these patients to a greater extent than aspirin. However, response to clopidogrel and aspirin shows a wide variability, and patients with high on-treatment residual platelet reactivity are at an increased risk for adverse events after coronary stenting. We therefore investigated the association of MPA with on-treatment residual agonists'-inducible platelet aggregation in 125 patients on dual antiplatelet therapy after peripheral, coronary or carotid artery stenting.
Methods: MPA were characterized by co-expression of monocyte marker CD14 and platelet-specific markers (CD42b and CD62P) by whole-blood flow cytometry. Platelet reactivity was determined by light transmission aggregometry, the VerifyNow P2Y12 and aspirin assays, and the vasodilator-stimulated phosphoprotein phosphorylation assay. Cut-off values for residual platelet reactivity were defined according to quartiles of each assay.

Results: The extent of MPA formation showed no significant differences between patients without and with residual ADP-inducible platelet reactivity, and between individuals without and with residual arachidonic acid (AA)-inducible platelet reactivity. Even patients with combined on-treatment residual ADP- and AA-inducible platelet reactivity did not exhibit significantly higher levels of MPA than patients without any on-treatment residual platelet reactivity.
Conclusion: The formation of MPA is independent of on-treatment residual ADP- and AA-inducible platelet reactivity.

P1324 The impact of premature discontinuation of dual antiplatelet therapy on patients with second generation DES implantation

C. Patsa, K. Toutouzas, E. Tsiamis, C. Tsioufis, A. Synetos, A. Spanos, C. Liasidis, A. Androulakis, E. Stefanadi, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: The use of second generation drug eluting stent (DES) has dramatically diminished the restenosis rate as compared with bare metal stent, whereas the increase rate of thrombosis is still a concern after the discontinuation of dual antiplatelet therapy. In this prospective single-centred trial, we sought to demonstrate the safety of DES after premature interruption of the dual antiplatelet therapy due to severe medical reasons in patients (pts) with single vessel disease in the proximal segment of the left anterior descending artery (pLAD).
Methods: We enrolled 379 consecutive pts with everolimus- and zotarolimus-eluting stents implantation in pLAD. Of these, 331 pts received dual antiplatelet therapy for at least 12 months, and 48 pts interrupted dual antiplatelet therapy prior to 12 months due to the appearance of gastrointestinal haemorrhage. Patients with acute coronary syndrome and contraindications for long-term double antiplatelet therapy were excluded. All pts were scheduled to receive double antiplatelet therapy for at least 12 months. Major adverse cardiac events (MACE) were defined as: Death, non-fatal myocardial infarction (MI) and target lesion revascularization (TLR). The pts underwent either clinical or telephone follow-up. Stent thrombosis was also evaluated and classified according to the Academic Research Consortium (ARC) definition.
Results: Demographic and angiographic characteristics were similar between the 2 groups. There was no difference regarding the MACE between the 2 groups of pts (p=0.15) during the 14.80±5.70 months follow-up period. The rate of death was higher in pts with discontinuation without a statistically significant difference [1.20% pts without discontinuation versus 4.16% pts with discontinuation, p=0.16]. Non-fatal MI was also increased in the group with discontinuation (4.16%) as compared with the non-discontinuation group (0.90%), (p=0.12). The TLR rate was similar between the two cohorts [2.41% pts without discontinuation versus 2.08% pts with discontinuation, (p=0.99)]. Finally, the thrombosis rate was 1.20% in pts with non-discontinuation versus 2.08% in pts with discontinuation, (p=0.49).
Conclusion: In this prospective study, we noted that the premature discontinuation of the dual antiplatelet therapy did not affect the effectiveness and safety of second generation DES implantation in pts with an isolated pLAD lesion, although a non-statistical increase in myocardial infarction rate was observed. Large scale, randomised trials are necessary to draw a safe conclusion.

P1325 Cardiovascular death and nonfatal MI in ACS patients are predicted by residual latelet reactivity to ADP in the absence of CYP2C19*2 allele: beyond genetic screening

R. Marcucci, B. Giusti, A.M. Gori, R. Paniccia, C. Saracini, A. Vestri, C. Nanna, A. Cordisco, G.F. Gensini, R. Abbate. *Azienda Ospedaliero Universitaria Careggi, Florence, Italy*

Introduction: Residual Platelet Reactivity (RPR) by ADP has been found to be an independent predictor of ischemic events in patients with ACS undergoing PCI on dual antiplatelet treatment. CYP2C19*2 polymorphism affects the conversion of clopidogrel to the active drug and it was found to be associated with the risk of adverse events in patients on clopidogrel. We sought to evaluate if RPR is a predictor of ischemic events.in patients non-carriers of CYP2C19*2 allele.
Methods: We measured platelet function by 10micromol/L ADP platelet rich-plasma aggregation (PA) in 843 ACS patients within 24 hrs from PCI. All patients received 600 mg clopidogrel loading dose followed by 75 mg daily and aspirin 100-325 mg daily. RPR was defined in presence of 10 micromol/L ADP PA ≥70%.
Results: 257 patients were carriers of CYP2C19*2 allele (228 heterozygotes and 29 homozygotes) and 586 patients were identified as good –metabolizers of clopidogrel as non carriers of CYPC2C19*2 allele. Diabetes, advanced age, and reduced left ventricular systolic function were significantly associated with RPR in patients non-carriers of CYP2C19*2 allele. At a follow-up of 18 months, we found 28 (4.7%) nonfatal myocardial infarction and 13 (2.2%) cardiovascular deaths among the 586 patients non carriers of CYP2C19*2 allele. RPR was found to be significantly associated with the risk of both nonfatal myocardial infarction [OR: 2.6 (95%CI 1.1-6.2), p<0.001] and cardiovascular death [OR: 2.8 (95%CI 1.1-9.5), p<0.005]. These results were confirmed in a model adjusted for classical and procedural risk factors.
Conclusions: RPR to ADP is able to detect patients non carriers of CYPC2C19*2 allele at risk of 18-month cardiovascular death and nonfatal MI. This result demonstrated that CYPC2C19*2 polymorphism explains only a part of a complex biological entity - RPR to ADP - whose role in identifying high-risk patients is maintained even in the absence of the genetic polymorphism affecting clopidogrel metabolism. These data underline the need of the evaluation of both phenotype – RPR to ADP – and genotype in order to obtain the better identification of patients with ACS on clopidogrel treatment at risk of ischemic recurrences.

P1326 Comparison of antiplatelet effects of single versus twice daily dose of aspirin in diabetic coronary patients

F. Addad[1], S. Chouchene[2], Z. Dridi[1], T. Chakroun[2], R. Cheaito[1], M. Mahjoub[1], M. Hassine[1], M. Hassine[2], H. Thawaba[1], H. Gamra[1]. [1]*Department of cardiology A, Fattouma Bourguiba University Hospital, Monastir, Tunisia, Monastir, Tunisia;* [2]*Haematology laboratory Fattouma Bourguiba Hospital, Monastir, Tunisia*

Background: Patients with diabetes mellitus (DM) have a two- to fourfold increase in the risk for mortality and morbidity due to complications of cardiovascular disease. Therefore, adequate and effective antiplatelet treatment for patients with DM is vitally important. Objectives: In this prospective study, we compared the effects of aspirin 100 mg twice daily and a single dose of aspirin 100 mg/day on platelet function measuring by PFA-100 in patients with DM and coronary artery disease (CAD) whose platelet function was not adequately inhibited by aspirin 100 mg/day.
Patients and methods: The study population consisted of 23 patients with DM and CAD who had been taking 100 mg once daily (at midday) aspirin for at least one month before the enrollment. The mean age of the patients was 58.4±7.7 years, 9 pts (39.1%) were insulin-treated and 14 (60.9%) were treated by oral agents. The anti-platelet effect of aspirin was determined for each patient by measuring the collagen/epinephrine closure time (CT) using the PFA-100 assay at 2 P.M two hours after the last aspirin intake (CT1) and at the next morning at 8.00 A.M (CT2). If the CT2 exceeded 298s indicating an optimal platelet effect of aspirin during the 24-hour, the study was terminated. If not, the patients regimen was modified to 100 mg aspirin twice-daily (at midday and at 8 P.M.) for another ten days then the CT was again measured at 2 P.M. (CT3) and at the next morning at 8 A.M. (CT4). Closure time data were compared with the Wilcoxon test.
Results: Two hours after the last aspirin intake, mean CT1 was significant higher than the level of CT2 assessed the next morning (at 8 A.M.), 250.7±72.9s vs 192.6±81.7s (p=0.001), respectively. A statistically significant difference was observed between the prevalence of ASA non-responsiveness (closure time <16 0s) measured at 2 P.M. and at 8 A.M. (21.7% versus 43.5%, p=0.025, respectively). Of the initial 23 patients, only 7 (30.4%) had an optimal platelet-inhibitory effect (CT2 ≥ 298s) of therapy with aspirin 100 mg/day during 24 hour. In the remaining 16 patients (CT2<298 sec), the CT Consequently, 3 patients (18.8%) showed an optimal response to 100 mg aspirin twice-daily (CT4 ≥ 298s). The percentage of resistant patients detected two hours after aspirin intake decreased from 31.2% with 100 mg once daily to 6.2% with 100 mg twice-daily (p = 0.046). There were no hemorrhagic complications due to aspirin during this study
Conclusions: The ideal dose for aspirin doesn't exist. The majority of diabetic patients has not optimal protection with a single low dose of aspirin.

P1327 Differential expression of local versus systemic platelet-monocyte complexes in the circulation of patients with acute coronary syndrome

B. Majumder, M. Lowdell, C. Smith, R.D. Rakhit. *Royal Free Hospital, London, United Kingdom*

Purpose: Formation of platelet monocyte complexes (PMC), and their recruitment at the site of plaque disruption in the coronary artery, may play an important role in the pathogenesis of acute coronary syndrome (ACS). PMC mediate platelet dependant thrombogenesis and monocyte dependant inflammation. Previous studies have shown increased expression of PMC in the peripheral circulation of ACS patients. This study aimed to demonstrate direct evidence of local expression of PMC in the culprit coronary and whether differential expression exists between this and the systemic circulation.
Methods: Blood samples from femoral vein, aorta and culprit coronary artery were collected from ACS patients. Coronary samples distal to the culprit lesion were aspirated. Citrated blood samples were incubated with flurochrome conjugated monoclonal antibodies to CD 61 and CD 14 for 20 minutes at 4°C. Samples were fixed and erythrocytes lysed using FACS Lyse (BD UK Ltd) immediately prior to flow cytometry (FACS Calibur BD UK Ltd). Co-incident events were excluded by low flow rate acquisition (<900 events per seconds) and by limiting flight duration through the laser using the pulse width of the CD 61 fluorescence parameters of the light processing board. PMC were expressed as a percentage of the total monocyte population. In a control group PMC were also measured in the peripheral blood of 5 normal individuals.
Results: PMC were measured in 8 patients (6 male and 2 female) with a mean age 66.87±12.63 years presenting with ACS (STEMI and NSTEMI). Mean percentage PMC expression in the femoral vein, aorta and coronary artery was 12.6%±11.7, 8.0%±4.3 and 17.3%±8.0 respectively. The venous blood of ACS patients had a higher PMC expression than normal controls (12.6±11.7% vs

3.5±0.5%, p=0.06). Percentage PMC expression in ACS patients was significantly higher in the culprit coronary circulation compared to the aortic circulation with a difference of (9.3%±7.9), (95% confidence interval 2.7% to 15.9%, p=0.01) and non-significantly higher compared to the venous circulation (4.7%±11.7), (95% confidence interval -5.1 to 14.5%, p=0.29). Coronary PMC expression inversely correlated with pain to sampling time (r= -0.57).
Conclusion: Compared to the normal population, increased expression of PMC in the venous circulation of ACS is evidence of systemic platelet activation. Differential expression in the coronary circulation as compared to the aortic and systemic venous circulation suggests an important pathogenic role of PMC within the culprit coronary circulation in promoting thrombogenesis, inflammation and plaque instability.

P1328 Baseline platelet size is increased in patients developing stent thrombosis and predicts future residual platelet reactivity despite dual antiplatelet therapy. A case-control study

Z. Huczek, K.J. Filipiak, J. Kochman, M. Michalak, M. Roik, R. Piatkowski, M. Postula, G. Opolski. *Medical University of Warsaw, Warsaw, Poland*

Objectives: Data on objective pre-procedural factors predisposing for stent thrombosis (ST) and future poor responsiveness to platelet inhibitors are sparse. We sought to evaluate the predictive value of baseline platelet indices measured before emergent PCI for the occurrence of ST and future residual platelet reactivity despite antiplatelet therapy.
Methods: Hundred and eight patients were included in the present study: 36 consecutive ST cases and 72 matched controls. Platelet count (PLT), mean platelet volume (MPV), % of large platelets (LPLT) and platelet distribution width (PDW) obtained before stent implantation were retrieved from the department's data base. Additionally residual platelet reactivity specific to aspirin (aspirin reaction units–ARU) and clopidogrel (P2Y12 reaction units–PRU) was assessed prospectively with VerifyNow System after 30 days of dual antiplatelet treatment, both in ST cases and controls.
Results: Platelet size expressed as MPV and LPLT was significantly higher in ST cases compared with controls (10.4, 95% confidence intervals [CI], 10.1-10.8 vs. 9.7, CI, 9.5-9.9, P=0.0004 and 35.8, CI, 34.2-37.3 vs. 33.3, CI, 32.2-34.3, P=0.007, respectively). A strong positive correlation was found between MPV and residual platelet reactivity after treatment, both for ARU (r=0.66, P<0.0001) and PRU (r=0.55, P<0.0001). Similarly, higher LPLT at baseline was associated with higher ARU (r=0.47, P<0.0001) and PRU (r=0.38, P=0.0001) under antiplatelet inhibitors. There was a similar frequency of isolated aspirin (6.5% vs. 4.2%, P=0.636) or isolated clopidogrel poor responsiveness (28.1% vs. 19.4%, P=0.416) between ST cases and controls. However, dual poor responsiveness was diagnosed significantly more often in ST cases than in controls (19.6% vs. 1.4%, P=0.004).
Conclusions: Baseline platelet size is increased in patients developing ST after emergent PCI with stent implantation and correlate positively with residual platelet reactivity under aspirin and clopidogrel therapy. Dual poor responsiveness but not isolated aspirin or clopidogrel poor responsiveness appears to be associated with ST.

P1329 Detrimental effects of energy drink consumption on platelet and endothelial function

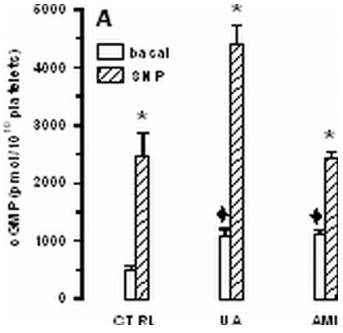
S. Willoughby, P. De Sciscio, A. Prabhu, R. Roberts-Thomson, C. Schultz, P. Sanders, M. Worthley. *University of Adelaide, Adelaide, Australia*

Background: The popularity of energy drinks continues to increase especially with young and middle aged subjects. Energy drink consumption has been anecdotally linked with sudden cardiac death, and more recently myocardial infarction; however possible mechanisms underlying this increased cardiovascular risk are poorly understood. We therefore tested the hypothesis that energy drink consumption alters platelet and endothelial function.
Methods and Results: 50 healthy volunteers (34 Male, aged 22±2 years) participated in the study. Platelet aggregation and endothelial function were tested before and 1 hour after the consumption of 1) 250ml (1 can) of a sugar-free energy drink containing caffeine, taurine and glucuronolactone or 2) 250ml carbonated water (control). Platelet function was assessed by ADP-induced (1 μmol/L) optical aggregometry in platelet-rich plasma. Endothelial function was assessed via changes in peripheral arterial tonometry and expressed as the reactive hyperemia index (RHI).
Compared to baseline values there was a highly significant increase in platelet aggregation following energy drink consumption, while no change was observed with control (Δ 13.7±3.7 vs Δ 0.3±0.8% aggregation, respectively, P<0.01). Similarly, RHI markedly decreased following energy drink consumption (Δ -0.33±0.13 vs Δ 0.07±0.12 RHI [control], P<0.05). Mean arterial pressure significantly increased following energy drink consumption compared to control (P<0.05). Heart rate was unaffected by energy drink consumption.
Conclusion: This study demonstrates that one hour following consumption of an energy drink there are objective cardiovascular changes characterized by increase in blood pressure, increase in platelet aggregation and impairment of endothelial function; all well described to be associated with adverse cardiovascular outcomes.

P1330 Altered nitric oxide/cGMP platelet signalling pathway in platelets from patients with acute coronary syndromes

M. Anselmino, L. Bergandi, P. Dalmasso, M. Cordero, C. Moiraghi, L. Ravera, D. Ghigo, G.P. Trevi, A. Bosia, S. Bergerone. *San Giovanni Battista Uinversity Hospital, Turin, Italy*

Purpose: To investigate the nitric oxide (NO)/cyclic GMP (cGMP) signalling pathway in platelets from patients with an acute coronary syndrome (ACS).
Methods: Markers of platelet activation (sP-selectin), inflammation (TNF-α and erythrosedimentation rate), thrombotic state (fibrinogen) and plaque disruption (HsCRP) were assessed in ten patients with unstable angina (UA), 14 with acute myocardial infarction (AMI) and 14 macthed healthy subjects. Western blot analysis of platelets homogenates were performed in basal conditions and stimulated by sodium nitroprusside (SNP) to assess cGMP levels. Serine phosphorylation in several proteins of the NO/cGMP signalling pathway (Akt1 protein kinase, eNOS) were measured in all patients.
Results: Markers of platelet activation, inflammation, thrombotic state and of plaque disruption (listed above) were significantly higher in UA and AMI patients compared to healthy controls. Basal levels of cGMP were significantly higher in platelets from patients presenting with UA (p<0.0001) and AMI (p<0.0001) compared to those from healthy controls (see Figure). Serine phosphorylation in Akt1 protein kinase and eNOS was more represented in platelets from UA (p=0.02 and p<0.001) and AMI (p<0.01 and p<0.0001 respectively) patients compared to controls. Platelets of patients with AMI disclosed a lack of cGMP increase (see Figure) and of VASP phosphorilation following SNP stimulation in comparison with healthy controls.



Conclusion: The present results support the hypothesis that the increased inflammatory state that often accompanies ACS may be responsible of platelet activation via the NO/cGMP pathway. Furthermore, platelets from AMI patients have shown more resistant to SNP stimulation.

P1331 Endothelial P-selectin expression and platelet consumption during sleep in obstructive sleep apnea

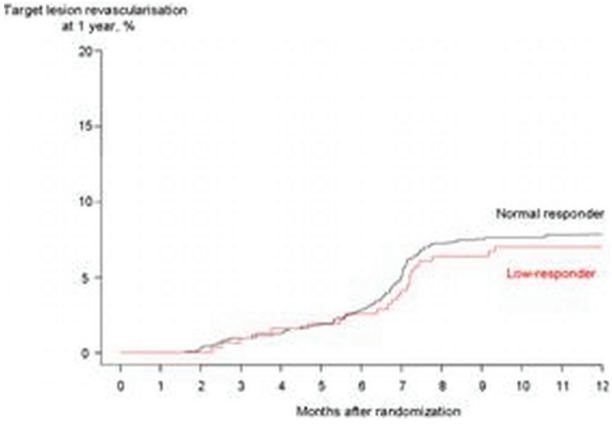
H. Maruyama, M. Satoh, S. Sakai, S. Kawano, N. Shimojo, K. Tajiri, K. Yasuda, S. Watanabe, K. Aonuma. *University of Tsukuba, Tsukuba, Japan*

Purpose: Patients with obstructive sleep apnea syndrome (OSA) are subject to increased morbidity and mortality from cerebrovascular and cardiovascular diseases associated with arterial thrombosis. However, the detailed mechanism underlying this relationship has not been clearly established. P-selectin (CD62P) is an adhesion molecule that is expressed on the membrane of activated endothelial cells and initiates thrombus formation via the rolling and attachment of platelets. Circulating microparticles derived from endothelial cells (EMPs) and from platelets (PMPs) are shed from the plasma membrane of these cells after stimulation. We aimed to clarify the relationship between the activated endothelium and platelet consumption during sleep in OSA patients.
Methods: We used flow-cytometry to count the CD41-positive PMPs and the P-selectin- and PECAM-1-expressing EMPs from the peripheral blood of 20 male subjects undergoing testing for suspected OSA. Blood samples were collected before and after polysomnography.
Results: The overnight decrease in platelet count (P<0.05), increase in PMPs (P<0.05), and increase in P-selectin-positive EMPs (P<0.01) correlated positively with the longest duration of apnea. The overnight increase in P-selectin-positive EMPs also correlated positively with the increase in PMPs (P<0.05), but not with urinary catecholamine or oxidative stress products.
Conclusions: This is the first report of platelet consumption and of the expression of P-selectin on the vascular endothelial surface of OSA patients during sleep. These findings suggest that activated endothelial cells expressing P-selectin initiate the aggregation and consumption of platelets. Severe hypoventilation–causing arterial hypoxia may augment the endothelial P-selectin expression.

P1332 Does platelet reactivity to clopidogrel effect restenosis after DES implantation ?

S. Schulz[1], D. Sibbing[1], T. Morath[1], N. Von Beckerath[1], J. Mehilli[1], R.A. Byrne[1], A. Schomig[2], A. Kastrati[1]. [1]*Deutsches Herzzentrum, Munich, Germany;* [2]*1. Medizinische Klinik, Klinikum rechts der Isar, Munich, Germany*

Does platelet reactivity to clopidogrel effect restenosis after DES implantation ?
Purpose: The aim of this study was to assess the impact of platelet reactivity to clopidogrel on the risk of angiographic and clinical restenosis after drug-eluting stent (DES) implantation.
Methods: Between February 2007 and April 2008, a total of 1.608 consecutive patients were enrolled in a study on the relation between platelet reactivity and outcomes after DES implantation. All patients received a loading dose of 600 mg clopidogrel. Blood samples for the assessment of ADP-induced platelet aggregation with multiplate electrode platelet aggregometry (MEA) were drawn directly prior to PCI and ≥ 2hours after loading. Clopidogrel low response was defined as upper quintile of MEA measurements. Accordingly, 323 patients (20%) were considered as non responders and 1.285 (80%) as normal responders. The primary endpoint of the present study was target lesion revascularization (TLR) at 1 year. Secondary endpoints included binary restenosis (BAR) and late lumen loss (LLL) at 6-8 months angiography.
Results: Results relative to stent thrombosis have already been presented/published. At 1 year, there was no difference in the TLR rate of low responders compared to normal responders (7,0% and 7,8%; p=0,609). There was also no difference in BAR (12% versus 15%; p=0,201) and LLL (0,30±0,64mm and 0,34±0,60mm; p=0,403) at follow-up angiography.

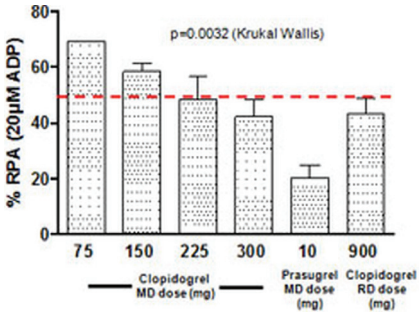


Conclusions: Low platelet responsiveness to clopidogrel, a known predictor of thrombotic complications after stenting, does not appear to have any significant impact on restenosis after DES implantation.

P1333 Can we override clopidogrel resistance?

J.-P. Collet, A. Pena, J.S. Hulot, J. Silvain, O. Barthelemy, F. Beygui, C. Funck-Brentano, G. Montalescot. *Pitie-Salpetriere Hospital (AP-HP), Paris, France*

Background: Stent thrombosis (ST) often leads to empiric modifications of antiplatelet treatments.
Aim: To describe a novel clinical approach using pharmacodynamic and genetic information to override clopidogrel resistance in ST.
Methods: Aspirin and clopidogrel pharmacodynamic responses were evaluated using light transmission aggregometry and the VerifyNowTM assay every 3weeks with established cut-off too define poor response. Genotyping was performed in all patients, testing the 2C19 alleles only.
Results: We report 7 cases of definite ST (median time from stent implantation to ST of 6 days IQ[4-8.5]). Only one patient had a poor response to aspirin and his daily maintenance dose (MD) was increased to 200 mg. All patients were resistant to 75mg and 150mg MD (figure 1). All but one patients were found to be carriers of the genetic variant 2C19*2 (5 heterozygous and 1 homozygous). To check compliance to treatment, a new loading dose of 900 mg of clopidogrel was also administered in 4 patients in whom residual platelet aggregation (RPA) was >50% (figure 1). Four hours after the load, two patients remained fully resistant. Clopidogrel MD was increased to 225 mg in all patients except one (prior stroke). Resistance to 225 mg MD was found in 4 out of 6 leading to an increase of the MD of clopidogrel to 300 mg. Two were still resistant and two had improved platelet inhibition but side effects (stomach discomfort and joint pain). Compassionate use of prasugrel was initiated at 10mg MD in these 4 patients and all had an optimal response.
Comments: A strategy of incremental increase of clopidogrel MD in patients cumulating clinical resistance (ST), biological resistance (RPA>50%) and a genetic profile of resistance is time consuming and little effective compared to a swith to prasugrel.



P1334 High platelet reactivity after clopidogrel correlates with the extent of coronary atherosclerosis and predicts peri-procedural outcome in patients with stable angina undergoing PCI

F. Mangiacapra[1], O. Muller[1], C. Trana[1], A. Ntalianis[1], W. Wijns[1], B. De Bruyne[1], G. Heyndrickx[1], J. Bartunek[1], G. Di Sciascio[2], E. Barbato[1]. [1]*Cardiovascular Center OLV Hospital, Aalst, Belgium;* [2]*Universita Campus Bio-Medico, Rome, Italy*

Purpose: Platelets are actively involved in vascular atherosclerosis. We tested the hypothesis that residual platelet reactivity after clopidogrel correlates with the extent and severity of coronary atherosclerosis in patients (pts) undergoing elective percutaneous coronary intervention (PCI).
Methods: We prospectively enrolled 338 pts undergoing uncomplicated PCI for stable angina, loaded with 600 mg clopidogrel. Platelet reactivity was assessed (12 hours after clopidogrel and before PCI) by measuring platelet reactivity unit (PRU) with VerifyNow P2Y12 assay. High platelet reactivity (HPR) was defined as PRU value ≥ 240. Presence of multi-vessel disease (MVD = stenosis > 50% in at least two major coronaries) and total stent length (TSL) were used as surrogate markers of atherosclerosis severity and extension.
Results: MVD pts showed significantly higher PRU compared to single vessel disease (SVD) pts (222±85 vs. 191±73; p<0.001). PRU progressively increased with number of stenotic coronaries (1-VD: 191±73; 2-VD: 220±88; 3-VD: 226±80; p=0.002). PRU was higher in the 3rd tertile compared with the 1st tertile of TSL (217±83 vs. 191±73; p=0.015). HPR was most frequently observed among MVD pts (40.5% vs. 21.6% in SVD pts, respectively; OR 2.47, 95% CI 1.53-3.98, p<0.001) and those in the 3rd tertile of TSL (35.8% vs. 22.2% 1st tertile; OR 1.96, 95% CI 1.07-3.57, p=0.028). A higher incidence of peri-procedural myocardial infarction (MI) was observed in pts with HPR (41.2% vs. 26.7% in pts without HPR; OR 1.92, 95% CI 1.18-3.13, p=0.008) and in those in the 3rd tertile of TSL (37.7% vs. 23.1% 1st tertile; OR 2.01, 95% CI 1.11-3.65, p=0.020). At multivariate analysis, HPR was the only independent predictor of peri-procedural MI (p=0.034).
Conclusions: Platelet reactivity after clopidogrel is significantly correlated with extent and severity of coronary atherosclerosis. HPR, more frequent in pts with MVD and higher TSL, is a strong predictor of peri-procedural MI.

CARDIOVASCULAR MAGNETIC RESONANCE ISCHAEMIC HEART DISEASE

P1335 Three years experience on the prediction of major adverse cardiac events in patients with suspected myocardial ischaemia by adenosine stress magnetic resonance imaging

W.S. Chan[1], S.C.W. Cheung[2], J. Ho[2], S. Ho[2], M. Sun[2], W.K. Tso[2], S. Lee[1], H.F. Tse[1]. [1]*Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China;* [2]*Department of Radiology, Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Nuclear myocardial perfusion imaging has been well proven its predictive value for the development of major adverse cardiac events (MACE) for decades. Though recent studies have shown the incremental value of cardiac magnetic resonance (CMR) myocardial perfusion imaging in the prediction of MACE, the long term outcome data is still insufficient. We hypothesized that adenosine CMR retains a high negative predictive value in development of coronary artery disease (CAD) or future adverse cardiac events at the mid-term follow up.
Methods: Adenosine stress CMR was performed on 449 consecutive patients who were referred for the suspicious of myocardial ischaemia. The CMR study protocol consists of assessment of myocardial function, adenosine and rest perfusion and DHE imaging. The patients were followed up during outpatient visits or contacted through telephone interview to identify the occurrence of MACE.
Results: Totally 430 patients with optimal image quality (M: F = 320:110; mean age=58±16; mean baseline TLCRF= 2.4±1) underwent rest and adenosine

stress CMR. With a follow up period of 41±10 months, there were 45 adverse event (34 patients underwent coronary percutaneous angioplasty due to unstable angina, 4 congestive heart failure and a 2 new MI) and 5 cardiovascular deaths. Adenosine perfusion abnormalities had 99% sensitivity and 87% specificity in detecting subsequent CAD and the most accurate component of the CMR examination in predicting events. Despite TLCRF and abnormal CMR can significantly predicting the prognostic outcome (p=0.04 Vs p=0.0001 respectively), multivariate analysis showed that the abnormal CMR was the strongest predictor of the event rate (adjusted hazard ratio 2.6 per 10% increase, p=0.01).
Conclusions: Adenosine CMR perfusion studies had retained a high negative predictive value in the low to moderate cardiac risk patients up to three years.

P1336 Complementary role of adenosine stress perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in prognostication of low to moderate cardiac risk patients

C.W.S. Chan[1], S.C.W. Cheung[2], J. Ho[2], S. Ho[2], M. Sun[2], W.K. Tso[2], S. Lee[1], H.F. Tse[1]. *[1]Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China; [2]Department of Radiology, Queen Mary Hospital, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Recent studies have shown the prognostic implication of cardiac magnetic resonance (CMR) perfusion imaging using stress agents in patients with suspected coronary artery disease (CAD). On the other hand, the CMR late enhancement imaging (DHE) have been proven to be the most sensitive method of identifying the presence of myocardial infarction (MI). We postulate that there is a complementary role of CMR perfusion imaging and DHE in prognostication of patients with suspected CAD.
Methods: CMR was performed on 520 consecutive patients who are presented initially with chest and suspicious of myocardial ischaemia and no previous history of MI. The CMR study protocol consists of assessment of myocardial function, adenosine and rest perfusion and DHE imaging. Ten patients were excluded due to suboptimal image quality. Patients were followed up during outpatient visits or contacted through telephone interview to determine the presence of MACE, including the incidence of significant CAD defined as coronary artery stenosis >50% on angiography, new myocardial infarction (MI), heart failure, unstable angina or cardiovascular death
Results: Totally 510 patients (M:F = 380:130); mean age 60±14; mean number of cardiac risk factors (= 2.3±1) underwent CMR. With a follow up period of 30±8months, there were adverse event (43 patients underwent coronary percutaneous angioplasty due to unstable angina, 3 new myocardial infarction, 4 cardiovascular deaths and 2 heart failure). Despite the number of cardiac risk factors and left ventricular systolic function, inducible myocardial perfusion defect was the strongest multivariate predictor to major adverse effect with 6-fold hazard increase to MACE ($p<0.0001$) and a 4-fold increase to cardiac death (p=0.04). Adjusted to the effects of reversible myocardial effects, DHE maintained a 3-fold adjusted hazards with MACE (adjusted HR 4.3, p=0.02).
Conclusion: In patients without history of MI, presence of adenosine inducible myocardial perfusion and DHE provided complementary incremental prognostic information in daily clinical practice.

P1337 Impact of infarct size on outcome in MADIT II patients assessed by contrast-enhanced CMR

C. Jensen[1], H.-C. Eberle[1], K. Nassenstein[2], T. Schlosser[2], B. Kuepper[1], C.K. Naber[1], G.V. Sabin[1], O. Bruder[1]. *[1]Elisabeth - Krankenhaus, Essen, Germany; [2]University Hospital Essen, University of Duisburg-Essen, Essen, Germany*

Purpose: Despite optimal medical treatment morbidity and mortality is still high in patients with chronic ischemic heart disease. Prophylactic implantation of a cardioverter/defibrillator (ICD) has been shown to reduce mortality in patients with chronic myocardial infarction and severely depressed left ventricular function meeting MADIT II criteria. However, the clinical course of the individual patient still remains unpredictable. Aim of this study was to investigate whether the extent of delayed enhancement assessed by contrast-enhanced cardiac magnetic resonance imaging (CMR) predicts adverse outcomes in MADIT II patients.
Methods: 59 Patients (56 males, age 65±9 years) with chronic ischemic heart disease and severely depressed LV function meeting MADIT II criteria were enrolled. CMR was performed on a 1.5 Tesla MR Scanner 5±1 days prior to ICD implantation for primary prevention of sudden cardiac death. The CMR protocol included steady-state free precession (SSFP) cine imaging for LV ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV) and myocardial mass (LVM) and single shot inversion-recovery SSFP imaging for delayed enhancement (DE) following injection of 0.15 mmol/kgBW gadoter acid. DE was calculated by the disc-summation method and expressed as percentage of left ventricular mass. Patients were prospectively followed for a composite end point of appropriate ICD shock, hospitalization for worsening heart failure and cardiac death.
Results: During 24±6 months follow-up an end point occurred in 20% (n=12) of patients. LV function and volume parameters showed no statistical significant difference between the group with and without events (EF 24.8±12.3% vs. 28.3±11.6 ml, p= 0.194; EDV 291.8±129.2 ml vs. 255.4±92.3 ml, p= 0.341; ESV 229.4±121.6ml vs. 188.4±83.3ml, p= 0.364; LVM 217.5±66.7g vs. 195.7±47.3g, p= 0.181). Though, patients with events had higher relative infarct mass compared to patients without (DE% 23.7±11.5% vs. 17.0±11.1%, p=0.044). Univariate analysis showed a statistically significant association between extensive relative infarct mass (>median) and occurrence of an event during follow-up (OR = 4.05, CI 0.97 - 16.90, $p<0.001$). Including age, EF, EDV, ESV and LVM into a stepwise cox regression model, the extent of the relative infarct mass remained independently related to outcome (p=0.002).
Conclusion: The extent of the relative infarct mass assessed by contrast-enhanced CMR predicts adverse outcomes in patients fulfilling MADIT II criteria and might allow for improved risk stratification and cost-control in this high risk population.

P1338 Mechanical dyssynchrony of peri-infarct zone during post myocardial-infarction remodeling

K.H. Schuleri, M. Centola, Y. Kobayashi, K.S. Evers, R. Evers, A.C. Lardo. *Johns Hopkins University, Baltimore, United States of America*

Purpose: Clinical studies using delayed enhanced magnetic resonance imaging (de-MRI) suggest the peri-infarct zone (PIZ) contains a mixture of viable and non-viable myocytes and is associated with greater susceptibility to ventricular tachycardia induction and adverse clinical outcomes. The purpose of this study was to investigate if changes in morphology over time lead to mechanical dyssynchrony of the myocardial segments within and around the peri-infarct zone.
Methods: Eight mini-pigs underwent coronary occlusion followed by reperfusion. Functional and de-MRI studies were performed prior and at five time points after MI induction. Custom signal density threshold algorithms based on the remote myocardium were applied to define the infarct core (IN) and PIZ region and Eulerian radial in-plane strain (Err) values were calculated in end-systole for IN, PIZ and remote myocardium.
Results: LVEDV increased from 34.7±2.2 ml to 47.8±3.0 ml (day 3 and day 90, respectively; $p<0.001$). The size of infarct scar expanded by 14% and thinned by 56% from day 3 to day 90 (p=0.004 and $p<0.001$, respectively). The PIZ mass changed form 1.18±0.17gram, to 0.58±0.06gram, to 0.46±0.3 gram and to 0.24±0.03 gram at day3, day 10, day 30 and day 90, respectively, parallel to the structural remodeling of the left ventricle. After the initial post-MI edema subsided the PIZ decreased further by 54% from day 10 to day 90 (p=0.04). At day 3 and day 30 the IN and PIZ segments showed opposing Err values (-0.18±0.06 and 0.04±0.09; p=0.003 and -0.08±0.09 and 0.05±0.1; p=0.01, respectively) consistent with mechanical dyssynchrony.
Conclusions: The PIZ is dynamic and decreases in volume following reperfused MI. Remodeling characteristics and regional myocardial dyssynchrony of the PIZ may provide mechanistic insights into the development of life-threatening arrhythmias and sudden cardiac death post-MI.

P1339 Myocardium at risk in STEMI - Validation of T2 edema imaging using magnetic resonance against the angiographic APPROACH-Score

G. Fuernau, V. Franke, I. Eitel, M. Gutberlet, G. Schuler, H. Thiele. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Background: The assessment of the area at risk with T2-weighted imaging using MRI is a relatively new method, which could be an interesting alternative in clinical studies in STEMI patients to analyse the effects of different therapies in revascularization. Purpose of this trial was to assess the area at risk and myocardial salvage by MRI and to compare it to the validated angiographic APPROACH-Score in a large consecutive patient cohort.
Methods: From November 2006 to February 2008 189 patients undergoing primary PCI in acute STEMI were enrolled. Myocardial salvage was assessed by MRI 2-4 days after primary PCI with measurement of the extension of myocardial edema in T2-weighted images and of infarct size with delayed enhancement imaging, both sequences covering the whole left ventricle. Angiographic scoring was done by use of the former validated APPROACH-Score. MRI measurements and angiographic scoring were done by blinded investigators.
Results: All images were assessable for measurements of the area at risk, infarct size and consecutively the myocardial salvage. The area at risk in the MRI-Studies showed a good correlation with the angiographic area at risk measured with the APPROACH-Score (r=0.858; $p<0.001$). However, as shown by Bland-Altman-analyses there was a certain bias towards an overestimation of the area at risk by MRI in comparison to angiographic scoring (36.5%LV vs. 27.8%LV, $p<0.001$). The infarct size measured by MRI was 18,2±11,6% LV. The calculated myocardial salvage was 18,3±11,8%LV. The time from symptom-onset to reperfusion had a significant impact on the myocardial salvage.
Conclusions: The measurement of the area at risk by MRI shows excellent correlation to the angiographic APPROACH-Score with slight overestimation. This might be explained by the former validation of the angiographic score by pathological studies mostly in human hearts without recent myocardial infarction, whereas acute edema represents also some kind of swelling at an early stage. Assessment of the myocardial salvage by MRI is therefore a promising tool for the assessment of myocardial salvage.

P1340 Determinants and clinical impact of myocardial salvage assessed by magnetic resonance imaging in patients with STEMI undergoing primary PCI

I. Eitel, G. Fuernau, M. Sareban, S. Desch, M. Gutberlet, G. Schuler, H. Thiele. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Purpose: Myocardial salvage is the hallmark of successful reperfusion therapy and results in improved prognosis. Cardiovascular magnetic resonance (CMR) can visualize the extent of the salvaged area at risk and may serve as an important therapeutic target. The time-to-reperfusion, electrocardiographic and angiographic parameters are also of prognostic relevance in STEMI patients. The purpose of this CMR study was the evaluation of predictors and the prognostic relevance of myocardial salvage in patients with STEMI undergoing primary PCI.
Methods: This study analyzed 230 consecutive STEMI patients (158 male (69%); mean age 65±12) reperfused by primary PCI within 12h after symptom onset. The following parameters were calculated using a 1.5 Tesla scanner: a) area at risk=volume edema/volume left ventricular mass; b) %infarct size=volume infarct/volume left ventricular mass; c) myocardial salvage index (MSI)=area at risk-infarct size/area at risk.
Reperfusion times, 90min STR, TIMI-flow grades pre and post PCI, TIMI risk score and multiple clinical parameters such as cardiovascular risk factors, Killip-class, and infarct location were also assessed. Clinical endpoints were major adverse cardiovascular events defined as a composite of death, reinfarction, and the occurrence of new congestive heart failure within 6 months after randomization
Results: The median time between index event and CMR was 4±6 days. In patients with pre PCI TIMI-flow 0-1 MSI was significantly higher in comparison to TIMI-flow 2-3 (44±24 versus 59±26; $p<0.001$). The extent of STR 90min after primary PCI correlated with MSI (r=0.238, $p<0.001$). Anterior MI MSI was higher with 56±26 versus 48±26 in inferior MI (p=0.02). In a stepwise multiple linear regression model the strongest predictors were pre PCI TIMI-flow, pain-to-balloon time, STR at 90min, infarct location, Killip class and previous MI. There was a significant inversely correlation of symptom duration and MSI (r-0.265, $p<0.001$). Patients with MSI ≥50 had a 6-month major adverse cardiac event rate of 3.5%, significantly less than the 19.7% of patients with MSI <50 ($p<0.001$).
Conclusions: In patients with reperfused STEMI, CMR visualizes both reversible and irreversible injury. This allows for quantifying the extent of the salvaged area after revascularization as a reliable clinical parameter with important prognostic relevance. Pre PCI TIMI-flow, pain-to-balloon time, STR at 90min, infarct location, Killip class and previous MI are the strongest predictors of MSI. This may explain why these clinical, angiographic and electrocardiographic measures are associated with survival.

P1341 Failure of 3Tesla MRI to assess the aetiology of acute chest pain with low troponin elevation in patients without significant angiographic coronary artery disease

I. Lafolie, L. Job, S. Tassan-Mangina, P. Nazeyrollas, C. Marcus, D. Metz. *CHU de Reims - Hopital Robert Debre, Reims, France*

Purpose: Cardiac MRI is currently considered as the gold standard to discriminate acute coronary syndrome (ACS) from myocarditis in the setting of acute chest pain and troponin elevation without angiographic coronary artery disease. We aimed to assess the contribution of 3T MRI in the subgroup of patients with low troponin rising.
Method: Patients admitted in hospital from 2006/01/01 to 2007/12/31 for chest pain associated with troponin elevation but without culprit lesion on coronary angiogram were included in a prospective registry. Twenty-two men and 17 women 45±17 years old, representing 2.7% of the 1814 patients who underwent a coronary angiogram for acute coronary syndrome (ACS) during the same period, underwent a 3T contrast-enhanced cardiac MRI including first-pass perfusion and delayed-enhancement sequences in order to determine the aetiology of the pain. The initial diagnosis was STEMI for 21 patients, NSTE-MI for the others. Thirty-four patients (87.5%) had a wall motion abnormality detected by transthoracic echocardiography. Mean troponin elevation was 14.3±18.7 ng/ml.
Results: MRI was helpful to assess the diagnosis for 25 patients (64.1%). Thirteen patients (33.3%; group 1) had a delayed subendocardial (n = 6) or transmural (n= 7) gadolinium hyperenhancement matching a coronary artery territory. Three of these patients had a first-pass myocardial perfusion defect in the same territory. The diagnosis of ACS was confirmed in this group and medical treatment continued according to guidelines. Seven patients (17.9%; group 2) showed no early defect but a non-segmental focal or diffuse subepicardial (n=4) or mid-wall (n=3) delayed enhancement, leading to the diagnosis of myocarditis. MRI was not conclusive for 5 patients (12.8%; group 3).
There was no significant difference in term of age, number of risk factors, initial ECG abnormalities between the groups. Patients of group 3 had a lower troponin elevation than groups 1 and 2 (5.9±6.1 ng/ml vs 18.2±17.9 ng/ml and 21.3±26.3 ng/ml respectively; p=0.029). MRI was not conclusive for 63% of patients with troponin concentration under 5 ng/ml.
Conclusion: 3T MRI was helpful to determine the final diagnosis in 2/3 of patients with acute chest pain and troponin elevation without significant coronary artery disease on angiography, but was not conclusive for most patients with troponin levels under 5 ng/ml.

P1342 Accuracy of magnetic resonance dual bolus quantitative myocardial perfusion for determining the myocardial area at risk in chronic coronary artery stenosis

M. Wu, J. Ganame, J. D'Hooge, K. Vermeulen, S. Dymarkowski, J. Bogaert, F. Rademakers, P. Claus. *Catholic University of Leuven (KULeuven), Leuven, Belgium*

Aims: While in acute infarct reperfusion magnetic resonance (MRI) edema imaging delineates the area at risk (AAR), in chronic coronary artery disease AAR quantification relies on perfusion (reserve). We determined the accuracy of dual bolus first pass MRI to quantitate myocardial blood flow (MBF), and delineate the AAR, in a preclinical porcine model.
Methods: Pigs underwent a copper-coated stent implantation (n=7) to induce a circumflex coronary stenosis or a sham operation (n=5). Dual-bolus first-pass 3T MRI was acquired at rest and during adenosine stress at basal, mid and apical levels. MBF was quantified with Fermi deconvolution in 12 segments per slice. As reference AAR was outlined with Evan's blue and segments were matched to MRI. The thresholds (TH) for stress and rest were given as a reduction in a number of standard deviations (SD) of either the global or segmental mean sham MBF. ROC analysis assessed area under the curve (AUC), sensitivity (sens) and specificity (spec).
Results: Mean coronary stenosis was 90% (range: 81-100%). Thirteen segments (5%) were excluded due to artifacts, resulting in 72 segments in and 167 outside the AAR. In sham, mean MBF increased from 0.50±0.08 ml/min/g at rest to 1.40±0.18 ml/min/g during stress and showed considerable segmental variation (Figure 1A). At rest global (TH: 0.2 SD, sens: 0.62, spec: 0.64) and segmental TH (TH: 0.1 SD, sens: 0.59, spec: 0.60) do not differ. Stress increases the accuracy ($p<0.0001$ vs rest) and segmental TH increases it further (segmental TH: 2.95, sens: 0.95, spec: 0.94; global TH: 1.65 SD, sens: 0.84, spec: 0.86; p=0.008 vs global) (Figure 1B).

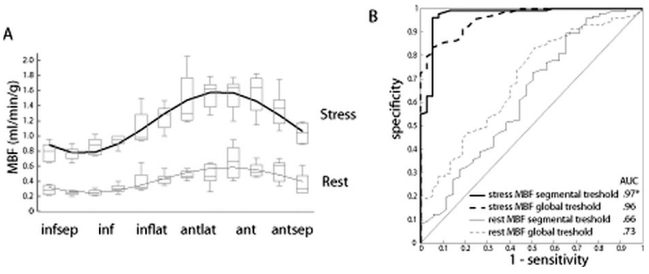


Figure 1

Conclusions: Quantitative stress perfusion MRI can identify the AAR accurately in chronic coronary disease. Considering the segmental variation in normal MBF increases the accuracy further.

P1343 Endothelin-1 release induced by reperfusion in patients with acute infarction as a predictor of no-reflow assessed by contrast-enhanced magnetic resonance imaging

H. Thiele, M. Nowak, I. Eitel, C. Stehl, V. Adams, L. Hlidebrand, G. Schuler. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Introduction: No-reflow after primary percutaneous coronary intervention (PCI) in acute ST-elevation myocardial infarction (STEMI) is associated with poor prognosis and the underlying mechanisms are not fully understood. Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor peptide and an important modulator of neutrophil function. ET-1 levels are elevated in the acute ischemic phase and enhanced ET-1 release might aggravate reperfusion injury by increasing microvascular vasoconstriction, triggering of inflammatory response and attenuation of antioxidant defence. Whether ET-1 may exert its detrimental effects by favouring the no-reflow phenomenon is still unknown. This study assessed the relationship between ET-1-release during reperfusion and occurrence of no-reflow (assessed by 3 different methods).
Methods: To investigate the extent of ET-1 we examined 128 consecutive patients undergoing primary PCI in STEMI within 12 h after symptom onset. ET-1 was assessed with an ELISA before and directly after successful primary PCI as percent change from baseline. No-reflow was assessed by use of three methods: 1) angiographic TIMI flow grade; 2) 90 min. ST-resolution (STR) after PCI; 3) microvascular obstruction (MVO) measured by delayed enhancement magnetic resonance imaging (MRI) within 2-4 days.
Results: After primary PCI, there was a significant increase of ET-1 (1.93±5.94%; $p<0.001$ vs baseline). Patients with TIMI-flow 0-2 after PCI had a 3-fold increase of ET-1 as compared to TIMI-3 patients (6.0±9.6% vs. 1.8±4.4%; p=0.01). Patients with no STR (<30%) had a significant higher increase in ET-1 than intermediate STR (70-30%) (7.0±8.3% vs. 1.3±6.4%; p=0.01) or complete (>70%) STR patients (1.4±4.6%; $p<0.001$). In patients with MVO the levels of ET-1 were significant higher than in patients without MVO (1.4±1.5% vs. 0.9±1.2%; $p<0.05$). Dividing patients into minor and major ET-1-increase (< versus > median) showed

significant better results after PCI as assessed by both STR (74.6±26.9% vs. 59.2±55.1%; $p<0.05$) and MVO (0.9±1.2% LV vs. 1.4±1.5% LV; $p<0.05$).
Conclusions: Reperfusion in STEMI results in a significant release of ET-1. The extent of ET-1 increase after PCI predicts no-reflow assessed by angiographic and electrocardiographic methods as well as measured by MVO. Therefore, ET-1 seems to be both an important parameter as well as a key mediator of no-reflow and reperfusion injury. The role of ET-1 antagonists warrants further investigation.

P1344 Scar size predicts ventricular tachyarrhythmias better than ejection fraction in primary prevention patients with ischemic cardiomyopathy

T.A. Meijers, S. De Haan, F. Afsharzada, A.M. Beek, A.C. Van Rossum, C.P. Allaart. *VU University Medical Center, Amsterdam, Netherlands*

Purpose: Ventricular tachycardias (VT) and ventricular fibrillation (VF) are a major cause of cardiac death in patients with cardiomyopathy, but risk stratification remains challenging. Presently, there is growing interest in extent of scar and heterogenic scar zone as predictors for VT/VF, since most electrical markers have shown to be of poor prognostic value. We investigated whether scar and its properties correlate with actual arrhythmic events.
Methods: All patients that underwent a cardiac MRI with delayed contrast enhancement and received an implantable cardioverter defibrillator (ICD) in the VUmc were included. MASS software was utilized to quantify left ventricle volume, myocardial mass, and amount of scar. Scar was defined as a signal intensity of 5 standard deviations (SD) and heterogenic zone as a signal intensity of 2SD to 5SD above normal remote myocardium. Information about VT/VF was obtained from the ICD's.
Results: 65 patients were included, 40 had ischemic cardiomyopathy, 33 of whom had primary prevention. Follow-up ranged from 1 to 3 years. Thirty patients experienced VT or VF. No predictors of VT/VF could be identified in this heterogenic group. However, in the subgroup of ischemic patients with primary prevention (N=33) scar mass, but not scar percentage, was significantly higher in patients with VT/VF than in those without (p=0.04). The EF was also correlated to the occurrence of VT/VF (p=0.05). Heterogenic zone was not shown to be a predictor (p=0.14). Multivariate analysis showed that absolute scar mass was the only significant predictor of VT/VF in this group.

Correlation between the presence of VT/VF and extent of scar, heterogenic zone mass and EF for the subgroup of ischemic patients with primary prevention

	Scar mass	Scar percentage	Heterogenic zone	Ejection fraction
VT/VF (n=10)	28.4 g	21.7%	15.7 g	20.3%
No VT/VF (n=23)	18.3 g	17.1%	10.7 g	25.3%
p-value	0.04	0.38	0.14	0.05

Conclusion: Absolute scar mass, but not scar percentage or heterogeneity, predicts VT or VF in a subgroup of ischemic patients with primary prevention. No predictors were found for the entire heterogenic group.

P1345 Adenosine-stress magnetic resonance imaging in patients with previous percutaneous intervention and coronary bypass graft

P. Bernhardt, J. Spiess, R. Gradinger, V. Hombach. *Universitaetsklinikum Ulm, Ulm, Germany*

Background: The combination of vasodilator induced stress perfusion and late Gadolinium enhancement (LGE) has established cardiac magnetic resonance imaging (CMR) for the diagnosis of myocardial ischemia. However, little is known about its ability to detect myocardial ischemia in patients previously treated by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). Aim of our study was to assess the accuracy of a combined CMR examination for the diagnosis of relevant coronary or bypass graft stenosis in latter mentioned patients.
Methods: We included 183 patients with suspected coronary artery disease (CAD), 67 who previously underwent PCI and 39 who previously underwent CABG into our stdy. All patients underwent adenosine-stress perfusion in a 1.5T CMR scanner after three minutes of adenosine infusion (140μg/kg/min) usint 0.1 mmol/kg Gadolinium-based contrast agent. Rest perfusion was performed with a second contrast bolus and LGE was acquired ten minutes after contrast administration.
CMR images were assessed visually using the 17-segments-model. A regional perfusion deficit during stress perfusion without LGE and rest perfusion deficit was defined as reversible ischemia. All patients underwent coronary angiography after CMR examination. A relevant stenosis was defined by QCA as luminal reduction ≥70% in a vessel with ≥2 mm diameter.
Results: Coronary angiography found a relevant coronary stenosis in 68 (37.2%) patients with suspected CAD, in 21 (31.3%) PCI patients and in 24 (61.5%) CABG patients. CMR detected relevant ischemia in 80 (43.7%) patients with suspected CAD, 24 (35.8%) PCI and 21 (53.8%) CABG patients. Accuracy values are shown in table 1.
Conclusion: The combination of CMR stress perfusion and LGE is suitable for detection of relevant myocardial ischemia in patients who previously were treated by PCI or CABG. However, diagnostic accuracy is reduced in patients with CABG. This could be due to different flow and perfusion kinetics. Furthermore, presented analysis method may insufficientyl consider collaterals and schanged perfusion territories.

Table 1. Accuracy values for the different patient groups

	Suspected CAD	PCI patients	CABG patients
Sensitivity	0.94	0.90	0.75
Specificity	0.86	0.89	0.80
Overall accuracy	0.89	0.90	0.77

P1346 High values of glycemia during PCI for STEMI influence intra myocardial hemorrhage lesions development identified by cardiac MRI

N. Amabile[1], A. Jacquier[2], A. Shuhaib[2], S. Armero[1], O. Com[1], F. Paganelli[1], G. Moulin[1]. [1]*AP-HM - Hopital Nord, Marseille, France;* [2]*AP-HM - Hopital de la Timone, Marseille, France*

Background: Intra myocardial hemorrhage lesions (IMH) are hardly identified in clinical current practice in patients with ST elevation myocardial infarction (STEMI).
Objectives: To determine incidence, predictive factor and prognosis value of IMH in STEMI using cardiac MRI techniques.
Methods: We consecutively screened for inclusion patients with STEMI treated within the first 12 hours of evolution by percutaneous coronary intervention (PCI) and transmural necrosis on cardiac MRI. Clinical, biological, EKG and angiographic parameters were assessed at baseline and after PCI. Glycemia was measured during the procedure. MRI was performed between day 4 and 8 after PCI. IMH lesions were identified on STIR-T2 images by the presence of a hyposignal within the core of the bright myocardium. Left ventricle ejection fraction (LVEF) was measured. Myocardial infarction (MI) and microvascular obstruction (MO) sizes, both expressed as percentage of LV mass, were determined on late gadolinium-enhanced images. All patients were clinically followed up after STEMI. Adverse cardiac events were defined as a composite of death +stroke + severe ventricular arrhythmias+ acute coronary syndrome +acute heart failure.
Results: n=85 patients were included and n=11 patients (13%) presented IMH lesions. There was no difference regarding demographic variables and treatment between the 2 groups. Initial TIMI flow (0.3±0.2 vs. 0.8±0.1) and 24h STsum regression on EKG (46±9 vs. 69±4%) were lower whereas per PCI glycemia values (9.8±0.7 vs. 7.5±0.3 mmol/L) were higher in IMH patients compared to the others ($p<0.05$ for all). The MI (27±4 vs. 16±1%) and MO (5.1±1.8 vs. 1.9±0.5%) extents were significantly larger in patients with IMH, whereas the LVEF was lower (40.7±1.3 vs. 48.3±1.4%/$p<0.05$ for all). Multivariate analysis revealed that per-PCI value of glycemia was an independent predictor of IMH development (RR=2.3 per mmol/L of glycemia, p=0.02). The incidence of adverse cardiac events was higher in the IMH group than in the no IMH group during the first year following STEMI (p=0.03, log-rank analysis). Cox regression analysis identified presence of IMH lesions on initial MRI as an independent predictor of poor clinical outcome (Relative Risk= 3.9, p=0.01).
Conclusion: IMH is a rare but severe finding in STEMI treated by PCI. IMH development is influenced by glycemia values and associated with a larger myocardial infarction and a worse clinical outcome. Identification of IMH by MRI could be useful to identify subjects with high-risk profile who could beneficiate from a more aggressive medical management.

P1347 Patterns of myocardial perfusion in the acute and chronic stage after infarction assessed by cardiac magnetic resonance

A. Mayr, M. Schocke, T. Trieb, K. Pedarnig, G. Klug, W. Jaschke, O. Pachinger, B. Metzler. *Innsbruck Medical University, Innsbruck, Austria*

Background: After successful revascularisation of the infarct-related coronary artery, perfusion at tissue level does not necessarily improve. The aim of the present study was to monitor the microvascular perfusion damage in the acute and chronic stage after myocardial infarction (MI) using first-pass dynamic MRI. Furthermore we compared improvement of myocardial microcirculation and function in infarcted with non-infarcted left midventricular segments over a 4 months period.
Methods: Cardiac MRI was performed in 46 consecutive patients (40 male, mean age 54.6±11.5 years) within 8 days after successful reperfused first acute MI and four months thereafter. First-pass images were obtained by using Turbo-FLASH sequence during a bolus injection of Gd-based contrast agent. Signal-to-time-intensity (STI) curves of 276 left mid-ventricular myocardial segments were generated. Furthermore, infarct volumes of corresponding segments were calculated from late enhancement in phase-sensitive IR-SSFP sequences. Parameters of regional left ventricular function were determined from short-axis cine MR sequences.
Results: STI curves correlate highly significantly with MI volumes (r= -0.57, r= -0.43 respectively; all $p\geq0.0001$) and with segmental wall thickening (SWT) of corresponding segments at baseline and follow-up scans. STI curves and SWT

differ highly significantly between segments with and without late enhancement at baseline and follow-up (all p≥0.002), presenting clear improvements at follow-up. In contrast, infarcted segments showing microvascular obstruction evidenced no significant recovery of STI.
Conclusion: Beyond epicardial artery patency, the assessment of myocardial perfusion and contractile function with the help of CMR appears to be a useful tool for estimating myocardial recovery after acute MI. Our data indicate a close relationship beween MI size and myocardial perfusion as well as function. The advantage of CMR is the ability to establish quantitative parameter that could help to determine prognosis and to monitor therapy effects.

P1348 Pitfall of stress myocardial perfusion MRI: late arrival of coronary flow in the inferior wall

K. Kitagawa[1], H. Sakuma[1], S. Kato[1], M. Ishida[1], M. Nagata[1], H. Miyagi[1], H. Nakajima[1], T. Kurita[2], Y. Ichikawa[2], K. Takeda[1]. *[1]Mie University Hospital, Tsu, Japan; [2]Matsusaka Central Hospital, Matsusaka, Japan*

Purpose: Previous studies demonstrated that stress myocardial perfusion MRI can detect obstructive coronary artery disease with high sensitivity and specificity. However, arrival of coronary flow to the area supplied by the right coronary artery (RCA) can be delayed compared to the left coronary artery because of longer epicardial course and/or slow flow due to vessel ectasia. The purpose of this study was to investigate the incidence of perfusion abnormality caused by late arrival of coronary flow in the inferior wall and to evaluate whether endo/epi ratio is useful for differentiating ischaemia and late arrival.
Methods: MRI reports of 960 stress perfusion MR studies performed between February 2006 and December 2008 were surveyed to find patients with stress-induced perfusion abnormality in the inferior wall. Stress perfusion MR images were obtained with 1.5T scanner using a saturation-recovery prepared steady-state free precession sequence with pharmacologic stress and bolus injection of gadolinium contrast medium (0.05mmol/kg, 4ml/s). Endo/epi ratios in the inferior wall and remote myocardium were measured based on signal intensity increase from baseline at the time of peak enhancement of epicardial myocardium.
Results: According to the MRI reports, perfusion abnormality suggestive ofmyocardial ischaemia in the inferior wall was detected in 89 patients by visual assessment. X-ray coronary angiography was performed in 24 of these patients (mean age, 68.8±8.6 years). Significant stenosis (≥ 75% diameter reduction) was present in the RCA in 12 patients (50%). The other patients had either normal coronary artery (n=5) or ectatic RCA (n=7). Endo/epi ratio in patients with significant stenosis decreased (0.85±0.09) in the inferior wall compared to remote (0.97±0.07, p<0.001), while no difference was observed in those without coronary stenosis (1.01±0.13 in the inferior wall vs 1.05±0.08 in remote, p=0.42). In addition, endo/epi ratio in the inferior wall in patients with stenosis was lower than that in those without (0.85±0.09 vs 1.01±0.13, p<0.002). With a threshold value of 0.96, endo/epi ratio can indicate perfusion abnormality caused by significant coronary artery stenosis with a sensitivity of 100% (12/12) and positive predictive values of 75% (12/16) in this study population.
Conclusions: Late arrival of coronary flow in the inferior wall is an important pitfall of stress myocardial perfusion MRI. Evaluation of endo/epi ratio was useful for differentiating ischaemia and late arrival of coronary flow in the RCA territory.

P1349 Safety of adenosine stress cardiac MRI (SCMR) early after acute ST elevation myocardial infarction (STEMI) post primary angioplasty

D.T.L. Wong, R. Das, M.C. Leung, K. Williams, B.K. Dundon, P. Molaee, G.Y.H. Liew, K.S. Teo, M.I. Worthley, S.G. Worthley. *Royal Adelaide Hospital, Adelaide, Australia*

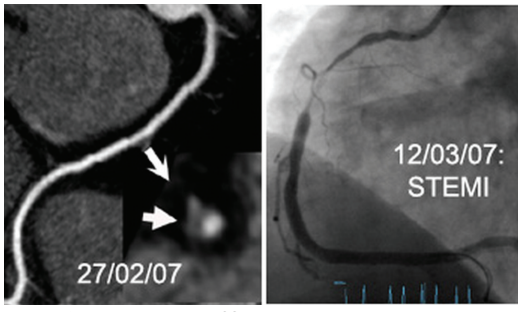
Purpose: Patients presenting with STEMI frequently have multivessel disease. After successful culprit lesion stenting, the functional significance of other lesion(s) has an impact on patient management. Adenosine stress cardiac MRI has high accuracy in detection of reversible ischaemia, although safety concerns using this technique in the immediate post-STEMI setting remain. We sought to determine the safety of adenosine SCMR early after acute STEMI post primary angioplasty.
Methods: 60 STEMI patients, age 63±9 (mean ± SD), who had successful primary angioplasty and stenting were prospectively recruited to undergo a CMR imaging protocol which included cardiac function assessment, rest and adenosine-stress perfusion, and early and delayed gadolinium enhancement at day 4±1 with 1.5 Tesla MRI scanner. Patient's rhythm, oxygen saturation and blood pressure (BP) were closely recorded. Further comprehensive safety subgroup analysis was performed comparing 25 STEMI patients (age 63±9) with 18 elective (age 63±9) adenosine SCMR patients (control) with chest pain for investigation. From this subgroup of patients, symptoms of nausea, chest tightness/pain, flushing, dyspnoea during and after scanning were recorded. Comparison of continuous variables was by unpaired t-test and categorical variables by Chi-square test.
Results: All patients completed adenosine stress protocol and it was well tolerated. STEMI group included 37% anterior, 38%-inferior, 2%-lateral and 23%-inferoposterior STEMI. No significant arrhythmia requiring intervention was detected during scanning in all 60 patients. Three patients had transient (<3 seconds) bradyarrhythmia during adenosine infusion requiring no treatment. In subgroup analysis, there was no difference in nausea, chest pain/tightness, flushing and dyspnoea compared to control. Nausea was experienced by 16% STEMI patients compared to 22% in control p=0.67, chest pain (20% vs 11%,p=0.39), flushing (60% vs 50%, p=0.24), dyspnoea (52% vs 22%,p=0.09), chest tightness (48% vs 38.9%,p=0.46), AV block (4% vs 0%,p=0.38), tachyarrhythmia (4% vs 0%,p=0.38).
Conclusion: Adenosine stress CMR is safe early after acute STEMI patients who had successful primary angioplasty.

CARDIAC COMPUTED TOMOGRAPHY: CORONARIES

P1350 Coronary CT angiography predicts outcome in intermediate pre-test probability individuals: a prospective study on 1157 patients

G.M. Feuchtner, I. Aglan, D. Jodocy, W. Dichtl, K. Feuchtner, O. Pachinger, G. Friedrich. *Innsbruck Medical University, Innsbruck, Austria*

Purpose: to assess the prognostic value of coronary computed tomography angiography (CCTA) in patients (pts) with intermediate probability of CAD.
Methods: 1157 consecutive pts (57y; 54% males) underwent with 64-slice CCTA. Pts were scored according to CCTA findings as (0) no plaques, (1) plaques/no stenosis, (2) plaque/<50% stenosis and as (3) >50% stenosis. Non-calcifying and mixed plaque were distinguished. A 1-2 year follow-up was performed. Primary endpoint (EP) was >50% stenosis by invasive angiography (IA), secondary EP cardiac events. On multivariate logistic regression (MVR) analysis, CCTA findings and conventional risk factors were tested.
Results: 944 pts completed F/U (mean 13.3 months). On CCTA, 36% pts had no plaques (0); 19% had plaques (1), 21% had <50% sten. (2); 24% had >50% sten. (3). 38% had a non-calcifying plaque component (incl. mixed). 5.4%pts had exclusively non-calcifying plaques (zero CCS). Primary EP (101pts+): On MVR analysis, >50% stenosis by CCTA was the strongest predictor (p<0.0001), non-calcifying plaques (incl. mixed) were less significant (p=0.04) but conventional risk factors were none. The sens., spec., PPV and NPV of CCTA for >50% stenosis were: 98%; 93%, 65% and 99.7% (0.93 AUC). Secondary EP (8 pts+): The cardiac event rate in pts with >50% stenosis by CCTA was with 2.6% (n=6) significantly higher than in others with 0.3% (n=2) (p=0.0004). Event rate was 0% in pts without plaque (0), and 0.5% in pts with plaque (1)+(2).



Non-calcifying plaque causing ACS

Conclusion: CCTA predicts >50% stenosis, and can accurately exclude. The outcome of patients without plaques is excellent (0% event rate) but significantly worse for pts with >50% stenosis by CCTA. Non-calcifying (+/- mixed) plaques may be a potential important risk factor with a higher impact than conventional ones.

P1351 Diagnostic accuracy of 320-slice multi-slice computed tomography in the non-invasive evaluation of significant coronary artery disease

F.R. De Graaf, J.D. Schuijf, J.E. Van Velzen, L.J. Kroft, A. De Roos, M.J. Schalij, F. Spano, J.W. Jukema, E.E. Van Der Wall, J.J. Bax. *Leiden University Medical Center, Leiden, Netherlands*

Background: Over the past decade multi-slice computed tomography (MSCT) has emerged as a robust imaging technique for the non-invasive evaluation coronary artery disease (CAD). Recently, 320-slice MSCT systems were introduced, with 16 cm cranio-caudal coverage, and increased gantry rotation time, allowing image acquisition of the entire heart within a single gantry rotation. The aim of the present study was to assess the diagnostic accuracy of 320-slice multi-slice computed tomography (MSCT) coronary angiography in patients with known or suspected CAD.
Methods: a total of 51 patients (30 male, mean age 63±14 years) underwent MSCT and conventional coronary angiography. All MSCT scans were evaluated for the presence of significant coronary stenosis (>50% luminal narrowing) by a

blinded expert, and results were compared to quantitative coronary angiography (QCA).
Results: Table 1 presents an overview of diagnostic accuracy and negative and positive predictive values on patient basis. In total, three MSCT scans were rendered non-diagnostic and were excluded from further analysis.

Table 1. Patient Analysis

Excluded	3/51, 6%
Sensitivity	27/27 (100%)
Specificity	19/21 (90%)
Positive Predictive Value	27/29 (93%)
Negative Predictive Value	19/19 (100%)
Diagnostic Accuracy	46/48 (96%)

Diagnostic accuracy of 320-slice MSCT.

Conclusions: The current study has shown that 320-slice MSCT allows accurate non-invasive assessment of significant CAD.

P1352 Computed tomography coronary angiography in patients with diabetes mellitus and suspected coronary artery disease: prognostic value and impact of presenting symptoms compared with nondiabetic patients

S. Seitun, E. Maffei, A.A. Palumbo, C. Martini, F. Cademartiri.
Azienda Ospedaliero Universitaria, Parma, Italy, Italy

Objectives: To assess the prognostic relevance of Multislice Computed Tomography Coronary Angiography (MSCT-CA) and symptoms in diabetics and non-diabetics referred for cardiac evaluation.
Methods and materials: We followed 210 patients with diabetes type-2 (DM) and 203 non-diabetic patients referred to MSCT-CA for ruling out CAD. All patients were without known history of CAD and were divided into four categories on the basis of symptoms at presentation (none, atypical angina, typical angina, and dyspnea). Clinical end-points were major cardiac events (MACE): cardiac related death, nonfatal myocardial infarction, unstable angina and cardiac revascularizations. Cox proportional-hazard models, with and without adjustment for risk factors, were developed to predict outcome.
Results: Diabetics showed a larger plaque burden. In both DM and non DM patients, the higher prevalence of obstructive CAD (luminal narrowing $>50\%$) was documented in patients with typical angina. At mean follow-up of 20.4 months, DM patients had worse cardiac event-free survival in comparison with non-DM (90% vs. 81%, p=0.02). In multivariate analysis, MSCT-CA evidence of obstructive CAD ($p<0.0001$) and the presence of typical angina ($p\leq0.02$) were independent predictors of MACE in both groups. In DM patients, adjunctive significant predictors of events were increasing age and the presence of dyspnea ($p\leq0.007$).
Conclusions: Diabetics had a worse outcome compared with nondiabetic patients. In both groups prognosis is strictly correlated with typical angina. Among DM patients, dyspnea carried a high event risk. MSCT-CA findings were strongly predictive of outcome and proved valuable for further risk stratification.

P1353 Epicardial adipose tissue predicts the presence and severity of coronary artery disease detected by multidetector computed tomography coronary angiography

E. Tulumen, B. Kaya, H. Yorgun, O. Ertugrul, O.S. Deveci, T. Hazirolan, K. Aytemir, S.L. Tokgozoglu, H. Ozkutlu, A. Oto.
Medicine Faculty of Hacettepe University, Ankara, Turkey

Purposes: Epicardial adipose tissue (EAT), is a component of visceral adiposity and might be associated with increased risk for coronary artery disease (CAD). The aim of the present study was to evaluate the relationship between epicardial fat thickness and presence and severity of CAD detected by multidetector computed tomography angiography (MDCTA).
Methods: A total of 140 patients (mean age 58±9) underwent MDCTA were enrolled in the study. EAT and pericoronary fat thickness were measured with MDCTA and presence and severity of coronary atherosclerosis was assessed by presence of any lesion and of any stenotic ($>50\%$) coronary vessel, respectively.

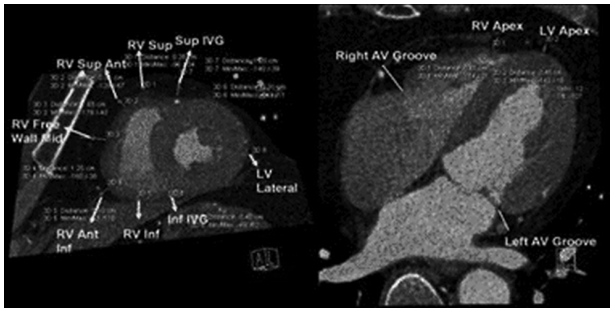


Figure 1. EAT thickness measurements

EAT thickness measurements were performed in 28 different loci perpendicular to myocardium from the base, mid and apical segments of the heart (figure 1).
Results: Patients with normal coronary arteries had EAT thickness lower than the patients with CAD in RV (right ventricular) free wall (FW) mid, RV superior (sup) anterior (ant) and RV sup wall, AVG (atrioventricular groove), superior and inferior IVG (interventricular groove) pericoronary fat regions (8.9±4.1 mm vs 11.4±5.6 mm; 8.3±3.7 mm vs 10.4±5.0 mm; 6.9±3.2 mm vs 8.7±4.0 mm; 19.2±3.2 mm vs 21.0±3.4 mm; 20.0±4.5 mm vs 22.1+4.4 mm; 14.1±3.8 mm vs 15.1±3.1 mm, respectively, $p<0.01$, for all). EAT thickness in RV FW mid, RV sup ant and RV sup wall was significantly high in patients with significant stenoses compared to patients without significant CAD (12.1±6.1 mm vs 9.3±3.9 mm; 11.0±5.5 mm vs 8.5±3.5 mm; 9.2±4.3 mm vs 7.2±3.2 mm; respectively, $p<0.01$, for all).
Conclusions: EAT thickness is associated with presence and severity of CAD indicating fat surrounding heart and coronary arteries may have a role in the coronary atherosclerotic process.

P1354 MSCT coronary angiography: just the coronaries

D. Tavella[1], R. Malago[2], F. Beltrame[1], F. Cademartiri[3], R. Pozzi Mucelli[2], P. Benussi[1]. *[1]Cardiology Unit Ospedale Policlinico, Verona, Italy; [2]Radiology Departiment University of Verona, Verona, Italy; [3]Azienda Ospedaliero Universitaria di Parma, Parma, Italy*

The improvements in multislice CT (MSCT) technology allow performing multi slice CT coronary angiography MSCT-CA. While scanning the heart and the coronary arteries, non-cardiac collateral findings may be revealed but are usually not assessed. The aim of the study is to describe the prevalence of non-cardiac collateral findings during MSCT-CA in a multicenter study. 2323 patients undergoing MSCT-CA with 16-slice (446/2323) and 64-slice (1877/2323) MSCT-CA acquired between January 2005 and August 2008 due to suspected coronary artery disease were retrospectively reviewed in a three center study. All datasets obtained with a large Field of view (FOV) were in blind analysed by 2 radiologists, using standard mediastinal and lung window settings. Collateral findings were divided according to clinical importance into: non significant, remarkable and compulsory to be investigated. Among significant diseased patients, medical records were reviewed to check the clinical follow-up, subsequent examinations, or surgical procedures of non-cardiac abnormalities in the 6 months after MSCT-CA. 86% of the patients revealed coronary artery disease. Only 478/2323 (20.6%) patients were without any additional finding. 1695 additional findings were recorded, divided into non significant findings: 1453 (85.7%), mild: 884 (52.1%), 161 (9.5%) compulsory to be studied. A total of 161 patients (6.93%) had significant non-cardiac pathology requiring clinical or radiological follow-up. Among these new discovered pathologies were revealed in 7 patients (2.5%). A significant number of non-cardiac findings might have been missed in MSCT-CA scans and the appropriate approach should be as a team trained in Cardiology and Radiology.

P1355 Atherosclerotic plaque burden and morphology: a comparison between intravascular ultrasound virtual histology and CT coronary angiography

M. Ciardetti, M. Bianchi, E. Lami, M. Shlueter, M. Coceani, A. Perinazzo, A. Mazzarisi, P. Marraccini. *CNR Istituto di Fisiologia Clinica, Pisa, Italy*

Purpose: Atherosclerotic plaque characteristics, beyond stenosis severity, condition clinical manifestations and prognosis of coronary artery disease. Several imaging techniques permit an evaluation of coronary artery morphology, but among these only CT coronary angiography (CTCA) is non invasive. The aim of the study was to compare the perfomance of CT coronary angiography, compared to a gold standard invasive technique such as intravascular ultrasound virtual histology (IVVH), in the evaluation of coronary plaque burden and morphology.
Methods: Twelve patients (mean age 65±8 years, 75% male) with at least one $>50\%$ stenosis in one principal artery at CTCA were enrolled in the study. The subjects subsequently underwent coronary angiography and IVVH of the stenotic lesions. With both techniques, we evaluated total plaque volume, as well as the volume of the individual components – calcium, fibrous and lipidic – of the lesions. Plaque characterization with CTCA was performed using a commercially available software based on a three-dimensional densitometric analysis. With regards to IVVH, images were obtained through a pullback at 1 mm/sec.
Results: CTCA and IVVH data are shown in Table 1. Volumes obtained with the two techniques were similar, with the exception of calium which was underestimated by CTCA.

Table 1. CTCA and IVVH data

	Total volume (mm^3)	Calcium (mm^3)	Fibrosus (mm^3)	Lipidic (mm^3)
CTCA	308±67	12±3.6	191±55	105±22
IVVH	444±92	72±21	208±41	160±34
P value	0.28	0.01	0.80	0.23

Data are expressed as means ± standard error.

Conclusions: The present study confirms the feasibility of non invasive examination of coronary atherosclerosis through CTCA. In particular, fibrous and lipidic components – the latter of which is a predictor of plaque instability - show a close correlation between CTCA and IVVH.

P1356 Diagnostic accuracy of low-dose coronary CT angiography: comparison between prospective and retrospective ECG gating

G. Pontone, D. Andreini, A.L. Bartorelli, S. Cortinovis, S. Mushtaq, E. Bertella, A. Annoni, A. Formenti, P.G. Agostoni, M. Pepi. *Centro Cardiologico Monzino, Milan, Italy*

Background: Multidetector computed tomography (MDCT) with retrospective ECG gating is a very promising technique for coronary artery evaluation. However radiation dose exposure is a major concern. Recently, a prospective ECG-gating has been introduced. With this technique, radiation is only applied at a predefined time point of the cardiac cycle as with retrospective ECG gating. The aim of the study is to compare the diagnostic performance of MDCT with prospective ECG-gating versus retrospective ECG-gating.
Methods: One hundred-eighty consecutive patients scheduled for invasive coronary angiography (ICA) were enrolled in this study. Twenty patients were excluded due to controindications to sustain MDCT. Of the 160 remaining patients, 80 were studied using MDCT with prospective ECG gating (Group1) and 80 using a retrospective ECG gating (Group2). Concerning artery evaluation and in-stent restenosis, feasibility (number of segments evaluable/total number of coronary segments) and accuracy were calculated versus ICA for segments classified as evaluable and in a second analysis for all segments rating as positive the non-diagnostic segments. The diagnostic performance between the two groups was compared using the pairwise McNemar's test. The individual effective radiation dose was calculated as the product of dose-length product multiplied by a conversion coefficient for the chest (K: 0.017 mSv/mGy cm) and the differences between the two groups were evaluated using Student t-test.
Results: In non-stented segments, the feasibility of Group1 and Group2 was 96% vs. 97% (p=0.05), the accuracy in segment-based model was 93% vs. 96% ($p<0.05$) including diagnostic segments and 91% vs. 94% ($p<0.01$) including all segments. In a patient-based model the accuracy was 98% in both groups. In stented segments the feasibility in Group1 and Group2 was 92% vs. 94%, respectively and the accuracy was 93% vs. 92% including diagnostic stented segments and 90% vs. 89% including all stented segments. Group1 presented lower radiation dose compared to Group2 (5.7 ± 1.5 mSv vs. 20.5 ± 4.3 mSv, $p<0.01$).
Conclusions: low-dose cardiac MDCT with prospective ECG gating can reduce the radiation exposure and the associated risk with a slight reduction of feasibility and accuracy of non-invasive imaging of coronary arteries and non differences of in-stent evaluation. Indeed, despite a slight reduction of accuracy in coronary vessels analysis in a segment-based model, this dose-reduction technique is associated with more favorable ratio of benefit to risk in patients with suspected or known coronary artery disease.

P1357 Feasibility and diagnostic accuracy of low dose multidetector computed tomography coronary angiography in the evaluation of coronary stent patency

D. Andreini, G. Pontone, S. Mushtaq, S. Cortinovis, A. Annoni, A. Formenti, D. Trabattoni, A. Bartorelli, P.G. Agostoni, M. Pepi. *Centro Cardiologico Monzino, Milan, Italy*

Introduction: An accurate evaluation of in-stent restenosis (ISR) by noninvasive imaging modalities can be clinically useful, however the substantial artifacts generated by the metallic stent struts have limited the role of 16-slice multidetector computed tomography (MDCT) in this clinical field. Previous studies about detection of ISR by 64-slice MDCT have shown a significant improvement in the diagnostic performance of MDCT but also a significant increase in the effective radiation dose, compared to the previous generation of scanners.
Aim of the study: to assess the diagnostic performance of a new scanning protocol employing axial acquisitions and prospective ECG-gating (MDCT-XT), recently proposed to reduce the radiation exposure.
Methods and materials: 63 patients (57 males; mean age 63 ± 9 years) with previous implanted coronary stents (135 stented lesions; mean diameter 3.15 ± 0.53 mm) underwent MDCT, followed by invasive coronary angiography (ICA). After MDCT, each stent was classified as "evaluable" or "unevaluable". Obstructive ISR (stenosis >50%) was visually and quantitatively determined in evaluable stents. MDCT data were acquired using a 64-slice CT (General Electric).
Results: The mean effective dose was 5.8 ± 2 mSv. The MDCT was able to evaluate the patency of all stents with the exception of 8 cases, classified as unevaluable. Overall, after the comparison with ICA, 22 of 24 (91.6%) ISR were correctly detected and localized by MDCT. ISR was correctly ruled out for all the remaining stented lesions (103 stents). In the segment based analysis, the feasibility of MDCT was 94% (127 out of 135 stents). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 91.6%, 100%, 100%, 98% and 98.4%, respectively. In the patient-based analysis, feasibility, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 93.6% (59 out of 63 patients), 91%, 95%, 90.9%, 95% and 93.5%, respectively.
Conclusions: Our results indicated that MDCT-XT has a diagnostic performance in non-invasive evaluation of coronary stent patency similar to that reported in the studies performed with retrospective ECG-gating and helical scan, whereas a significant reduction of radiation exposure was observed.

P1358 Accuracy of dual-source CT to identify coronary artery stenoses in patients with atrial fibrillation: comparison with invasive coronary angiography

M. Marwan, T. Schepis, A. Renz, T. Pflederer, D. Ropers, W.G. Daniel, S. Achenbach on behalf of University of Erlangen-Nuernberg. *University of Erlangen-Nuremberg, Erlangen, Germany*

Objectives: It has been previously reported that the sensitivity and specificity of multislice CT for detecting significant CAD (coronary artery disease) is high. Regular sinus rhythm has been considered a prerequisite for an adequate examination. Atrial fibrillation is common among patients with coronary heart disease and has been an obstacle for coronary assessment using CT angiography. We evaluated the sensitivity and specificity of Dual-Source CT to detect and rule out significant coronary stenoses in patients with atrial fibrillation and chest pain.
Patients and Methods: 96 consecutive patients with atrial fibrillation who had been admitted for a first diagnostic coronary angiogram were screened for participation in the study. 40 patients were excluded either due to renal insufficiency (creatinine > 1.5 mg/dl), or due to rapid atrial fibrillation. 56 remaining patients (mean age 71 ± 8 yrs.) were included and subjected to CT-angiography using Dual-Source CT (Definition, Siemens Medical Solutions, Germany) within 24 hours before invasive coronary angiography. A contrast-enhanced volume data set was acquired (100 kV, 360 mAs/rot, collimation $2 \times 64 \times 0.6$ mm, retrospective ECG gating). Data sets were evaluated concerning the presence or absence of significant coronary stenoses and validated against quantitative invasive coronary angiography. A significant stenosis was assumed if the diameter reduction was $\geq$ 50%.
Results: Mean heart rate during CT was was 69 ± 16 bpm (range 32-107 bpm). Optimal image quality was found in systole in 30% of patients and in very late diastole in 45% of patients. In 25% of patients reconstructions in both systole and diastole were required. On a per-patient basis, the sensitivity and specificity for Dual-Source CT to detect significant CAD in vessels > 1.5 mm diameter was 94% (16/17) and 89% (35/39), respectively, with a negative predictive value (NPV) of 97% and a positive predictive value (PPV) of 80%. On a per-artery basis, 221 vessels were evaluated (left main, left anterior descending, left circumflex and right coronary artery in 56 patients in addition to one bypass graft, with four non-assessable vessels) with a sensitivity of 94% (29/31) and specificity of 95% (180/190); NPV was 99% and PPV was 74%.
Conclusion: Our study demonstrates high sensitivity, specificity and negative predictive value of Dual-Source CT to detect significant CAD in patients with atrial fibrillation and a controlled heart rate. Dual-Source CT angiography may be useful to rule out coronary artery stenoses and avoid invasive angiograms in selected patients even when not in sinus rhythm.

P1359 Impact of diabetes mellitus on coronary atherosclerosis in patients with zero calcium score using 64-MDCT

K. Harada, H. Fujinaga, T. Okumura, N. Kageyama, A. Saitoh, T. Yamamoto. *Tokushima Prefectural Central Hospital, Tokushima, Japan*

Background: The coronary artery calcium score has emerged as a marker for predicting coronary artery disease (CAD) in patients with diabetes mellitus (DM). However, it is unknown the characteristics of coronary atherosclerosis in diabetic patients who have no coronary calcification.
Purpose: The purpose of this study was to clarify the impact of DM in patients with zero calcium score using 64-MDCT.
Methods: From November 2007 to December 2008, 64-MDCT was performed in 448 consecutive patients. All patients were underwent calcium score scan prior to noninvasive coronary angiography with 64-MDCT, and calcium was quantified using the Agatston method. Of these patients, 160 patients had zero calcium score. They were divided into two groups, patients with DM (n=57) and without DM (n=103). In this study, CAD was determined by the presence of either significant stenosis (>50% coronary artery diameter stenosis) or noncalcified plaque.
Results: There were no significant differences in clinical characteristics between the two groups. Patients with DM had more presence of CAD (65% vs. 32%, $p<0.01$), number of noncalcified plaques (1.5 vs. 0.5, $p<0.001$), presence of noncalcified plaques (65% vs. 32%, $p<0.001$) and presence of lipid rich plaques (<50HU) (35% vs. 9%, $p<0.01$) than without DM. There were no significant differences in the presence of coronary stenosis (11% vs. 3%, p =0.10) and positive remodeling (remodeling Index >1.1) (18% vs. %7, p=0.07). DM (OR=3.1, 95%CI=1.50-6.50; $p<0.01$) and age (OR=1.1, 95%CI=1.02-1.10; $p<0.01$) were independent predictors for the presence of CAD.
Conclusions: The present study shows that complication of DM relates to the presence and severity of CAD in despite of zero coronary artery calcium by 64-MDCT.

P1360 Influence of visceral fat accumulation and high-molecular-weight adiponectin levels to coronary plaque as detected by multidetector computed tomographic angiography

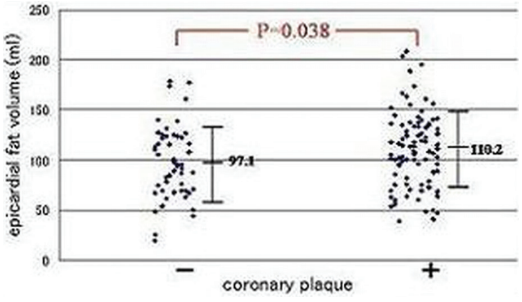
N. Ohashi, H. Yamamoto, T. Kitagawa, E. Kunita, Y. Kihara. *Hiroshima university, Hiroshima, Japan*

Objectives: We sought to evaluate that abdominal visceral fat is associated with coronary atherosclerotic lesions by multidetector computed tomographic angiography (MDCTA).
Methods and Results: We consecutively studied 363 patients (65±11 yrs, 223 males) suspected of coronary artery disease who underwent MDCTA and coronary calcium measurement (CC). The abdominal fat scan was simultaneously obtained. Visceral fat area (VFA) was positively correlated with CC scores in each gender. Each non-calcified plaque (NCP) was evaluated with the minimum CT density, positive remodeling (PR), and spotty type adjunct calcium deposits. Patients with PR also had larger VFA than those without in men (170±86cm^2 vs. 128±56cm^2, $p<0.001$) and women (127±34cm^2 vs. 92±47cm^2, $p<0.001$). The VFA remained as an independent predictor of existence of CC (odd ratio: 1.91), NCP (1.67), and PR lesion (1.92). From ROC analysis, the optimal cut-off values of VFA to predict CC were identified as 116cm^2 in men, and 82cm^2 in women, which corresponded to waist size of 87.7cm in men and 82.6cm women. In a subgroup analysis (N=97), plasma high-molecular-weight adiponectin (AD) levels were significantly lower in patients with PR than in those without (6.6±0.8 vs. 10.4±0.9 μg/mL, p=0.002).
Conclusion: The amount of visceral fat is associated with increase in CC and plaque vulnerability, decreasing plasma AD levels.

P1361 The association of epicardial fat volume with coronary plaque using cardiac 64-multislice computed tomography

K. Okada[1], K. Harada[1], H. Funahashi[1], K. Arai[1], A. Hirashiki[1], M. Hayashi[1], H. Ishii[1], X.W. Cheng[1], M. Yokota[2], T. Murohara[1]. *[1]Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Aichi Gakuin, Nagoya, Japan*

Purpose: Metabolic syndrome has been reported to be a coronary risk factor. The production of adipokines by visceral adipose tissue may provide a mechanistic link between obesity and the coronary artery disease (CAD).We hypothesized epicardial adipose tissue could locally modulate the coronary artery and could be a predictor of CAD. We investigated the relation between epicardial fat volume (EFV) and coronary atherosclerosis.
Methods: A protocol was devised to measure EFV using 64-multislice computed tomography (MSCT) in 157 patients with suspected CAD (age 38 to 85 years, mean 65 years). Cross sectional tomographic cardiac slices (3.0 mm thick) from base to apex were traced semi-automatically and EFV was measured by assigning Hounsfield units, ranging from -30 to -190, to each fat area. The actual EFV was then calculated by commercially available software. Coronary atherosclerosis was determined with MSCT. In MSCT analysis, plaque components were classified as non-calcified, mixed, or calcified.
Results: EFV ranged from 19.9 to 228.6 ml (mean 106.4±41.7ml), correlated with BMI, visceral fat area, adiponectin, HDL/LDL, TG/HDL. Patients with coronary plaques had increased EFV, compared with patients without coronary plaques (110.2ml vs 97.1ml, p=0.038). Patients with metabolic syndrome also had increased EFV, compared with patients without metabolic syndrome (114.1ml vs 99.6ml, $p<0.001$). Further, patients with non-calcified plaque had increased EFV compared with those with calcified plaque (122.4ml vs 99.7ml, p=0.020).



Correlation between EFV and plaque

Conclusions: These results suggest EFV is associated with the coronary soft plaque extent, which is associated with CAD. The measurement of EFV may provide additional information for assessing CAD risk and predicting the extent of coronary atherosclerosis.

P1362 The routine use of multi-detector coronary computed tomography in the fast track evaluation of patients with acute chest pain

R. Beigel, D. Oieru, O. Goitein, P. Chouraqui, E. Konen, S. Brosh, A. Shamiss, H. Hod, J. Or, S. Matetzky. *Sheba Medical Center, Tel Hashomer, Israel*

Background: The recently published AHA/ACC guidelines suggest that multidetected computed tomography (MDCT) may be appropriate for investigating acute chest pain (ACP). Only a few small studies have evaluated the use of MDCT in ACP, where it was not part of routine investigation.
Purpose: We sought to evaluate the routine use of MDCT in a large cohort of patients presenting with ACP, in a real-world setting.
Methods: We studied 785 consecutive patients with ACP who underwent evaluation by MDCT or myocardial perfusion scintography (MPS) in our chest pain unit after an observation period of ≥ 12 hours. Patients with findings suggestive of significant coronary artery disease (CAD) were referred to coronary angiography.
Results: Forty-two patients were hospitalized due to evidence of myocardial ischemia and 44 patients were discharged after the observation period without noninvasive imaging. Of the remaining 699 patients, 340 underwent MDCT and 359 MPS. In 22 (7%) patients MDCT showed significant CAD and in 32 (9%) patients MPS showed significant ischemia. Significant CAD was confirmed by coronary angiography in 65% and 60% respectively. MDCT was non-diagnostic in 31 patients (9%). Extracardiac findings which might be related to ACP and/or necessitated further investigation were demonstrated by MDCT in 71 (21%) patients. During a 3-month follow up, 1 (0.3%) patient with negative MDCT and 9 (3%) with negative MPS suffered an acute coronary syndrome or death. Re-hospitalization, due to recurrent chest pain, occurred in 9 (3.3%) and 21 patients (7.2%) respectively.
Conclusions: MDCT could be an appropriate alternative to the traditional noninvasive modalities for investigating ACP.

P1364 Usefulness of dual - source computed tomography for the detection of coronary artery disease in patients with arrhythmia - comparison to invasive angiography

J. Rixe, A. Rolf, D. Erkapic, A. Koch, H. Moellmann, H. Nef, C.W. Hamm, T. Dill. *Kerckhoff Klinik GmbH, Bad Nauheim, Germany*

Background: Cardiac CT is considered a reliable tool fornon – invasive detection of coronary artery stenoses. However, due to limited temporalresolution, its use has been so far limited to patients with sinus rhythm. We investigated the feasibility of Dual -source CT (DSCT) with a temporal resolution of 83 ms for the detection ofcoronary artery disease in patients with atrial fibrillation compared toconventional quantitative coronary angiography (QCA).
Methods: 30 consecutive patients (21 male, mean age 64.9±14 y) with suspected coronary artery diseaseand atrial fibrillation underwent DSCT (Siemens Somatom Definition, collimation64 x 0.6 mm). No heart rate control was performed prior to examination. Rawdata sets were reconstructed in 5% - intervals of the RR – cycle, and data setwith best image quality was evaluated by two expert observers in consensus forthe presence of stenoses of > 50% diameter reduction and for the occurrenceof artefacts. Unassessable coronary segments were regarded as havingsignificant stenosis, QCA served as standard of reference.
Results: Mean heart rate during scan was 73±16 bpm (range 53 - 115 bpm). 459 coronarysegments were included into the study, of which 427 could be visualized withoutartifacts (93% of all segments). Of 32 coronary segments classified unevaluable,22 were affected by motion (69%). Exclusion of coronary artery stenoses waspossible in 13 patients and 405 segments, 24 stenoses were correctly identifiedin 13 patients. No stenosis was missed by DSCT, but 4 patients were evaluatedfalse positive. Segment based analysis revealed a sensitivity of 100%,specificity and overall accuracy were 93%; in per - patient analysissensitivity was 100%, specificity 76.4% and accuracy was 87%. NPV and PPV were100% and 44% in segment based analysis, in patient based analysis they were 100%and 76%, respectively. The estimated mean radiation dose for DSCT was 13.5±4.2 mSv.
Conclusion: For patients with atrial fibrillation, DSCTallows non - invasive detection of coronary artery disease with good diagnosticaccuracy, and it correlates well with invasive coronary angiography. However, for these patients a substantial radiation dose exposure has to be considered.

P1365 Sleeping less than 5 hours daily is associated with increased prevalence of coronary calcification in an asymptomatic male Asian population

S.Y. Tan[1], M.N.D. Rico[1], F. Keng[1], F.K. Cheah[2], J. Huang[2], P.H. Tan[3], D.S. Swee[3], T. Chua[1]. *[1]National Heart Centre, Singapore, Singapore; [2]Singapore General Hospital, Singapore, Singapore; [3]Singapore Armed Forces Medical Corps, Singapore, Singapore*

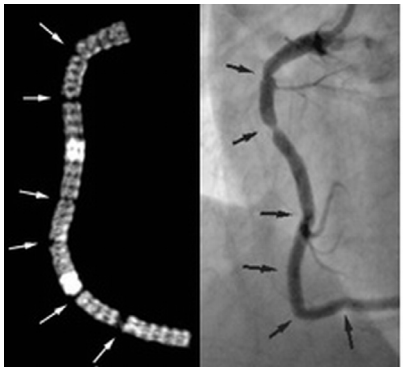
Introduction: Recent studies have shown an association between coronary calcium and sleep. We investigated this relationship in the Singapore Armed Forces Coronary Atherosclerosis Project (SAFCAP), which seeks to determine the prevalence of coronary calcium in asymptomatic Singaporean men and determine its relationship with risk factors and other parameters including sleep.

Methods: 417 asymptomatic men aged >40 years, of Asian ethnic origin underwent calcium scoring by Multi-slice Cardiac CT as part of the SAFCAP study. All had no history of diabetes or coronary atherosclerosis. A positive calcium score was any score more than 0.The amount of sleep an individual had was calculated from a patient filled PAQ (Physical Activity Questionnaire). The PAQ is based on a questionnaire that has been validated and use in studies done at Stanford University.
Results: Overall, patients slept a mean of 7.0 hrs (±1.06). The mean age of patients was 44.6 (± 3.8). 27% (103/376) of patients who slept more than 5 hours had coronary calcium whilst 49% (20/41) of those who slept less than 5 hours had coronary calcium (p=0.003). Logistic regression revealed a positive correlation with the presence of coronary calcium and sleep. This association persisted even after correction for the presence of hypertension and current smoking.
Patients who slept less than 5 hours had a HR of 1.6 CI (1.2 – 2.2) p=0.03) of having coronary calcium score > 0.
Conclusion: There is a significant correlation between the number of hours of sleep and coronary calcium score in asymptomatic Asian males, such that those sleeping less than 5 hours a day have a higher risk (x 1.6) of coronary calcification. The implications of this finding require further investigation.

P1366 Stent fracture detected by multislice computed tomography after in-stent restenosis caused by multiple overlapping drug-eluting stents

T. Ito, M. Kimura, M. Ehara, M. Terashima, K. Nasu, Y. Kinoshita, K. Asakura, Y. Asakura, E. Tsuchikane, T. Suzuki. *Toyohashi heart center, Toyohashi, Japan*

Background: Stented segment length and multiple overlapping stents are predictive factors for restenosis after drug-eluting stents (DES) implantation and coronary stent fracture has been noticed as a cause of in-stent restenosis (ISR). Nonetheless adequate modality is not available for clear visualization of in-vivo stent fracture. Therefore we investigated the general prevalence and the morphological characteristics of stent fracture site and evaluated the impact of stent fracture on ISR using computed tomography (MSCT) when long lesions were treated by multiple overlapping DESs.
Methods and results: Between January 2007 and December 2008, 55 consecutive patients and 60 lesions with multiple overlapping DES underwent follow-up MSCT. Lesions were divided into fracture or non-fracture. Of 60 stented lesions, 58 lesions were available for evaluation. An average stented length was 51.2±19.7mm. Among 58 lesions, stent fracture was detected in 8 lesions (14%) and observed more frequently in the longer stented lesion and right coronary artery (RCA). The ISR rate was significantly higher in the fracture group (63% vs 10%, p =0.0024).



Stent fracture and restenosis

Conclusion: Stent fracture detected by MSCT is a independent factor predisposing ISR for long lesion treated by multiple overlapping DESs.

P1367 The assessment of radial arteries used as an access at percutaneous coronary intervention by optical coherence tomography

T. Yonetsu, T. Kakuta, T. Iwamoto, T. Lee, K. Takayama, N. Kawaguchi, H. Fujiwara. *Tsuchiura Kyodo Hospital, Tsuchiura, Japan*

The benefits of transradial coronary intervention (TRI) have been well documented, although resulting acute injury and chronic effects including intimal hyperplasia could be a limitation, especially when considering a radial artery as a conduit for coronary artery bypass graft. We sought to assess the extent and nature of radial artery injuries after TRI using optical coherence tomography (OCT). We studied 30 radial arteries in 30 patients who underwent PCI by OCT guidance. OCT was performed after PCI completion, and 0.2mg nitroglycerin was given through a radial sheath before examination. OCT imaging was done by continuous manual injection of Ringer's solution at 2-3ml/s under compression of a brachial artery at the mean blood pressure. Presence of intimal and/or medial injuries was assessed, and intimal (IT) and medial thickness (MT) were also evaluated at 1mm intervals. Obtained findings were compared between first-TRI (n=13) and repeat-TRI patients (n=17) groups. Mean arterial length observed with sufficient image quality was 80±28mm. Two intimal flaps and 1 deep medial injury were observed in first-TRI group (23%), and 5 intimal flaps and 3 deep medial injuries in repeat-TRI group (47%)(p=0.2). All these injuries were located in the proximal segment corresponding to the distal to the tip of the sheath, probably caused by insertion or retrieval of the devices. Mean IT and MT were 75±67μm and 221±78μm in first-TRI group, and 102±89μm, 246±78μm in repeat-TRI group, respectively. In 14 cases of all 30 radial arteries (46%), minor irregularity of smooth luminal surface not classified as intimal flap, possibly caused by minute acute injuries including endotherial denudation, was observed. In none of these cases, thrombus formation was detected. There was a trend toward more thickened intima in patients who underwent multiple TRI procedures. Time dependent progression of intimal thickening as assessed by the presence of more intimal thickening in patients with longer interval between previous TRI and the current procedure was not confirmed in this study. Acute injury was located exclusively at the proximal segment of the sheath. OCT clearly visualized minute acute arterial injuries and chronic effects on radial artery after TRI.

P1368 Aortic annulus and ascending aorta: comparison of preoperative and perioperative measurement in patients with aortic stenosis

M. Smid, J. Ferda, J. Cech, J. Baxa, T. Hajek, R. Rokyta on behalf of Charles University Prague Research Projects nr. MSM 0021620817 granted by the Ministry of Education, Youth and Physical Education ofthe Czech Republic. *University Hospital Plzen, Plzen, Czech Republic*

Purpose: Our aim was to compare the precision of measurement of the aortic annulus and ascending aorta using magnetic resonance (MR), multidetector-row computed tomography (MDCT), transthoracic echocardiography (TTE), and transoesophageal echocardiography (TEE) in patients with degenerative aortic stenosis.
Methods: 15 patients with degenerative aortic stenosis before aortic valve replacement were enrolled into this prospective study. Preoperatively, TTE was performed in all patients, while TEE was performed in 10 patients, MDCT in 14 patients and MRI in 11 patients.The values obtained were compared with perioperative measurements performed by the main surgeon in all patients.
Results: A total of 15 patients underwent aortic valve replacement due to degenerative aortic stenosis. The average mean gradient on the aortic valve was 50±17.3 mmHg, while the average left ventricular ejection fraction was 62.6±10.6%. MR was found to be the most precise technique for the measurement of the aortic annulus, followed by MDCT, TTE, and TEE. For the measurement of ascending aorta, MR again was found to be the most precise technique, followed by MDCT, TEE, and TTE. Results of the correlation coefficient and regression equation for the measurement of the aortic annulus respective techniques are shown in summary table 1.

Table 1

Method (no. of measurements)	Correlation coef.	P	Regression equation y=a+bx	
			a	b
TTE (15)	0.651	0.009	0.963	0.593
TEE (10)	0.606	NS	1.152	0.530
CT (14)	0.770	0.001	0.602	0.717
MR (11)	0.825	0.002	0.575	0.722

TTE – transthoracic echocardiography, TEE – transoesophageal echocardiography, CT – computerized tomography, MR – magnetic resonance, P – statistical significance, regression equation – regression of the perioperative size to the size obtained by the respective techniques, a, b – regression coefficients, y – predicted value, x – actual value measured by the respective technique, NS – non-significant.

Conclusion: In our study, magnetic resonance was found to be the most precise technique for the measurement of aortic annulus and ascending aorta in patients with severe degenerative aortic stenosis. Ultrasound techniques in patients with degenerative aortic stenosis are more precise for the measurement of ascending aorta than aortic annulus.

P1369 Effect of N-acetylcysteine on serum creatinine and cystatin C levels after cardiovascular procedures

E. Alioglu[1], U. Turk[1], E. Ercan[2], G.S. Tamer[3], I. Tengiz[1], B. Kirilmaz[2], S. Saygi[4], N. Tuzun[1]. *[1]Central Hospital, Izmir, Turkey; [2]Canakkale Onsekiz Mart University, Canakkale, Turkey; [3]Kocaeli University, Kocaeli, Turkey; [4]Karsiyaka State Hospital, Izmir, Turkey*

Objectives: Prophylactic oral N-acetylcysteine (NAC) has been widely used for prevention of contrast-induced nephropathy (CIN).Previous studies with NAC have found conflicting results in the prevention of CIN. We investigated NAC for the prevention of CIN by monitoring serum creatinine and cystatin C levels.
Methods: We conducted a prospective, randomized trial on 75 patients with moderately impaired kidney function (33 patients in NAC group and 42 patients in control group) who were scheduled for cardiovascular procedures. Patients in NAC group receive acetylcysteine 600 mg twice a day, on the day before and on the

day of coronary angiography. All patients received peri-procedurally 1 ml/kg/h of 0.45% saline for 24 h. Serum cystatin C and creatinine levels were measured before and at 48 h after procedure.

Results: Between NAC group (n = 33) and control group (n = 42) there was no difference in baseline demographics, baseline laboratory characteristics and cardiac angiography procedure (Table 1). The overall incidence of cystatin C-based CIN among all study subjects was 17.3% (21.2% in NAC group and 14.9% in control group, p=ns) and that of serum creatinine-based CIN was 13.3% (15.1% in N-acetylcysteine group and 11.9% in control group, p=ns).

Table 1

	NAC group (n=33)	Control group (n=42)	p value
Age, years	63,42±11,12	63,60±9,15	ns
Men, %	63,6	81,0	ns
BMI, kg/m^2	29,0±6,618	27,03±3,17	ns
Volume of contrast agent, mL	90,06±42,24	86,02±41,62	ns
Mehran risk score	7,00±2,96	6,36±2,904	ns
GFR (MDRD),ml/min	53,64±15,45	56,98±12,44	ns
Baseline creatinine, mg/dL	1,35±0,28	1,33±0,22	ns
Creatinine at 48 h, mg/dL	1,43±0,62	1,43±0,57	ns
Baseline cystatin C, mg/L	3,49±1,95	3,90±2,04	ns
Cystatin C at 48 h, mg/L	3,67±1,96	3,72±1,85	ns
LVEF, %	51,79±8,51	51,33±10,21	ns

BMI: body mass index; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; MDRD: Modification of diet in renal disease.

Conclusion: In the current study, oral NAC had no effect on the prevention of CIN in patients with moderate renal insufficiency undergoing cardiovascular procedures.

P1370 Di-chromatic synchrotron angiography - quantitative perfusion measurements in the heart

K. Walenta[1], B. Scheller[1], H.W. Schenk[2], T.C. Nurdan[2], K. Nurdan[2], S. Fiedler[3], A.H. Walenta[2], M. Boehm[1]. *[1]Universitaetsklinikum der Saarlandes, Homburg, Germany; [2]Universität Siegen, Siegen, Germany; [3]ESRF, Grenoble, France*

Therapeutic value of selective coronary angiography is beyond discussion. However, more detailed information is required for evaluating wall movement, viability of the myocardium and extent of heart damage. Up to now, all implemented high precision methods suffer from at least one or more of inherent deficiencies such as spatial and time resolution, model dependent perfusion measurement or sensitivity. Studies with the method of K-edge subtraction radiography with synchrotron radiation sources (SYRI) assessed potential for non-invasive coronary angiography by intravenous injection of contrast medium applications as well as minimum invasive catheterization for dynamic precision measurements. SYRI was performed in domestic pigs using intravenous and intracoronary contrast agent. Myocardial ischemia was initiated in left coronary artery. High spatial resolution permitted detection down to vessels of 5th order, allowing quantification of active volumes as arteries, myocardium, veins, atria and ventricles as well as detection of pulmonary vessels and decrease of myocardial perfusion in ischemic areas. To exploit the very good and background free measurement of the amount of visible contrast medium a simulation program has been developed taking into account the time variation of flow and compartments with inhomogeneous microstructures. This allowed quantification of flow and comparison with myocardial perfusion in non-dependent areas. For the first time quantitative data on venous outflow could be measured such that quantitative data on diffusion into the interstitial volume could be obtained. Beyond this detection of other vessels such as aorta, renal arteries and pulmonary vessels was possible with a single-shot of contrast agent with warranty of high temporal and spatial resolution. A very low radiation dose of less than 100μSv was sufficient for myocardial perfusion measurements. A precision for this value of about 5% can be reached with a dosis far below 0.1mSv. Model based extrapolations even suggest lowering of the dosis down to 20μSv without severe degradation of the measured contrast. Di–chromatographic synchrotron angiography, a novel tool in diagnostic methods in cardiology, provides images with excellent contrast and sufficient spatial resolution. It permits next to detection of coronary vessels, myocardial and local perfusion parameters also quantification of left- and right-ventricular ejection fraction. Furthermore, the extreme low radiation dose will give rise to further broad clinical investigations. Further investigations have to be performed focusing on the non- invasive implementation.

P1371 Right ventricular remodelling in pulmonary hypertension: the importance of interventricular septum delayed contrast-enhancement on cardiac magnetic resonance

M. Perazzolo Marra[1], G.D. Aquaro[2], C. Bauleo[2], L. Cacciavillani[1], C. Basso[3], S. Iliceto[1], G. Thiene[3], C. Marini[2], M. Lombardi[2]. *[1]Department of Cardio, Thoracic and Vascular Sciences, Univerisity of Padua, Padua, Italy; [2]Fondazione G. Monasterio, Pisa, Italy; [3]Department of Medic-Diagnostic Sciences and Special Therapies, University of Padua Medical School, Padua, Italy*

Introduction: Pulmonary arterial hypertension (PAH) is a life-threatening malignant disease characterized by increased pulmonary vascular resistance leading to pressure overload on the right ventricle (RV). To normalize wall stress, RV remodelling with hypertrophy also occur. Cardiac magnetic resonace (CMR) provides not only the evaluation of traditional index of adaptative mechanism as increased mass and volumes, but also allows a tissue characterization such as detection of junction delayed contrast-enhancement (DE).

Aim: to assess the relationship between traditional RV remodelling parameters and DE with haemodinamic indexes, evaluating in particular the influence of the therapy in the respect of DE.

Methods: Twenty-three consecutive patients (age, 56±16 years, 17 females) with PAH underwent to complete diagnostic evaluation including the cardiac catheterization with vasoreactivity test and contrast-CMR. CMR was performed on a 1.5-T scanner to determine RV mass and volumes, ejection fraction, and finally extent of DE in grams of myocardial mass. A subgroup of patient during follow-up performed a second CMR and RV catheterization.

Results: Mean pulmonary artery pressure (mPAP) was 44±19 mmHg and cardiac output 3±0,5 L/min. On contrast-CMR 20 patients (87%) showed DE localized in all the cases into the RV insertion points of the interventricular septum: the mean weight of DE myocardial mass was 9±4,4 g. The RV mass correlated positively with mPAP (r2=0,26, p=0,025) and interestingly also DE mass was related to increase mPAP (r2=0,20, p<0,001); neither to cardiac index. Patients non-responders started specified pulmonary theraphy and six patients performed the second catheterization and CMR one year later. In this subgroup was confirmed the association between RV mass and mPAP, but the most important result was the strong relationship between mPAP reduction and corresponding DE mass (r2=0,963, p=0,001).

Conclusions: Our results confirm the relationship between RV mass and haemodinamic impairment in PAH. The major findings is the demonstration, in a subgroup of patients, that extent of DE in this setting is not an irreversible injury suggesting that some potential mechanisms as inflammation and edema could play an important role.

P1372 In vivo characterization by magnetic resonance imaging in patients with mild to moderate carotid atherosclerosis

D. Periat[1], R. Wyttenbach[2], I. Sudano[1], M. Oberson[3], M. Di Valentino[3], J.M. Segatto[3], N. Bianda[3], G. Noll[1], A. Gallino[3], R. Corti[1]. *[1]Cardiovascular Center Cardiology University Hospital, Zurich, Switzerland; [2]Radiology Hospital San Giovanni, Bellinzona, Switzerland; [3]Cardiology Hospital San Giovanni, Bellinzona, Switzerland*

Purpose: Magnetic resonance imaging (MRI) has been shown to be an accurate non-invasive method to detect mild atherosclerotic changes of the vessel wall. Using MRI we previously reported significant effects of brachytherapy, balloon angioplasty and lipid-lowering on the vessel wall structure. We report the initial results of a prospective study on the natural history of atherosclerosis in patients with carotid atherosclerosis.

Methods: Asymptomatic patients (n=33, mean age 68.4±7.6 years, 23 males, 10 post-menopausal women) with hemodynamic non-significant (<70%) internal carotid artery stenosis under current optimal medical care underwent high-resolution cross-sectional MRI (1.5 T) of the carotid arteries using fat saturated T1w, PD and T2w sequences with an acquired in-plane resolution of 0.6x0.6 mm and a slice thickness of 2 mm. MRI was performed at baseline and at 1 year. Patient risk profile and therapy are shown in table 1. Blinded image analysis was performed by manual tracing of the vessel borders using a dedicated software (GT-Volume, Gyrotools Ltd. Zurich). Twelve cross-sectional images per patient were traced and averaged for statistical analysis. Changes in total vessel area (TVA), lumen (LA) and vessel wall area (VWA) as surrogate of atherosclerotic burden were assessed.

Results: A total of 770 cross-sections were analyzed. After 12 months TVA increased significantly by 3.2% (from 73.6±13.9 mm^2 to 76.0±15.4 mm^2, p=0.012) and VWA by 4.4% (from 47.3±9.8 mm^2 to 49.5±10.0 mm^2, p=0.009). LA did not change (from 26.2±8.2 mm^2 at to 26.5±8.3 mm^2, p=0.553)

Table 1. Risk factors and therapy

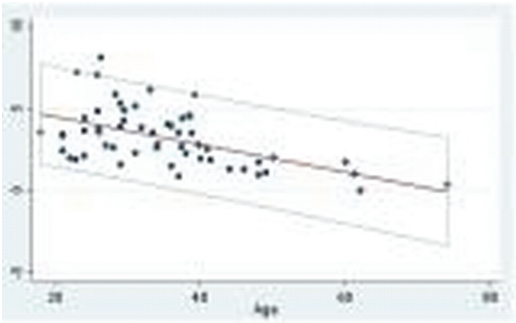
Risk Factors	Number (%)	Therapy	Number (%)
Diabetes	13 (39.4%)	Aspirin	24 (72.7%)
Renal failure (creatinine clearance < 60ml/min)	16 (48.5%)	Clopidogrel	17 (51.5%)
Combination of diabetes and renal failure	8 (24.2%)	ACE-inhibitors	14 (42.4%)
Dyslipidemia	32 (97.0%)	ARB	9 (27.4%)
Smoking	8 (24.2%)	Betablockers	27 (81.8%)
History of coronary artery disease	15 (45.5%)	Ca-antagonists	12 (36.4%)
Arterial hypertension	30 (90.9%)	Statins	27 (81.8%)

Conclusions: In our prospective study in a cohort of patients with moderate carotid atherosclerosis high-resolution MRI demonstrated progression of atherosclerosis in the carotid artery over one year despite current optimal therapy.

P1373 Normal values of aortic elasticity in 58 adults using Cine-MRI

C. Billard Philip[1], A. Lalande[1], O. Bouchot[1], J.L. Philip[1], A. Cochet[1], J.C. Eicher[1], R. Cartier[2], P.M. Walker[1], F. Brunotte[1], J.E. Wolf[1]. *[1]CHU de Dijon, Dijon, France; [2]Montreal Heart Institute, Montreal, Canada*

Currently, the recommendation for prophylactic intervention of aortic replacement is based on aortic diameters. Clinical trials have shown that this parameter is not always reliable. Aortic elasticity is a crucial parameter in the follow up of patients at risk. Compliance and distensibility measures can distinguish patients at risk for rupture or dissection from healthy adults, although no norm exists.
The purpose of this study was to determine normal values of compliance/distensibility of the thoracic aorta in healthy adults using cine-MRI. The influence of sex and tobacco was evaluated.
58 adults (mean age 34.8±11 years), with no history of cardiovascular disease were recruited. Cine-MRI was performed at the level of the pulmonary trunk. Aortic compliance is defined as the relative change in aortic cross-sectional area divided by the change in arterial pressure. Distensibility is calculated as compliance reported to minimal surface area. Automatic post-processing was used to analysis surface areas.



Distensibility of ascending aorta/b.a.

Results show that sex and tobacco have no influence on compliance and distensibility, confirming their small impact on thoracic aortic aneurisms and dissections. Compliance and distensibility values from the ascending aorta correlated negatively with age (r=0,68; $p<0.0001$ and r=0,77; $p<0.0001$). Age relative to body surface area is the main factor in aortic stiffness variations in healthy subjects. Prediction curves characterizing normal compliance and distensibility values for a given age are created with confidence interval of 95%.This study on a healthy subject population provides reference values for aortic stiffness. In the management of patients, compliance and distensibility parameters should support surgical indication for patients.

P1374 Myocardial oedema predicts myocardial injury and ventricular function after primary percutaneous intervention following ST elevation myocardial infarction as assessed by T-2 weighted cardiac MRI

R. Das, D.T.L. Wong, M.C. Leung, K. Williams, G. Liew, P. Molaee, B. Dundon, K.S. Teo, M.I. Worthley, S.G. Worthley. *Cardiovascular Research Centre, Royal Adelaide Hospital, Adelaide, Australia*

Topic
T-2 weighted cardiac MRI to assess myocardial oedema following primary percutaneous intervention for ST elevation myocardial infarction and its relation to myocardial function, infarct mass and microvasular obstruction.
Purpose: T2-weighted cardiac MRI sequences have been shown to successfully visualize infarct-related oedema, and recent results indicate its clinical applicability for differentiating acute from chronic infarctions. Despite successful opening of the infarct related artery by primary percutaneous intervention (PPCI) for ST elevation myocardial infarction (STEMI), intermittent coronary artery occlusion affects the entire perfusion bed and results with transient and permanent myocardial damage which is best assessed by cardiac magnetic resonance imaging. We sought to test the hypothesis whether extent of myocardial oedema correlates with myocardial function, infarct size and degree of microvascular obstruction (MVO) following PPCI for STEMI.
Method: Cine MRI, T-2 weighted oedema imaging and late gadolinium enhancement imaging was performed in 26 patients (mean age 60±10, M=25) at day 3 to 6 (median 4 days, IQR 3) after successful PPCI for STEMI. We evaluated myocardial function (ejection fraction, wall motion score, wall motion index), and CMR indices of myocardial injury (infarct mass, infarct area and microvascular obstruction area). A 17 segment model was used to semiquantitavely assign each segment of left ventricle a score of 0 (total absence of oedema) or 1 (presence of oedema). The segment score for the entire left ventricle was finally summated. Association between continuous variables was assessed by Pearson's correlation and independent samples T-test: Statistical significance was accepted at $p<0.05$.
Results: The T-2 weighted oedema score (Mean score 3 SD 3) was highly correlated with infarct mass (r=0.7), MVO size (r=0.8), infarct area (r=0.8), wall motion score (r=-0.8), ejection fraction (r=-0.6) and peak CK (r=0.7). There were significant differences in oedema scores ($p<0.05$) between anterior (N=10; mean score 6, SD 2) and non-anterior STEMI (N=16; mean score 1 SD 1). Anterior STEMIs had adverse CMR infarct characteristics with respect to infarct mass, degree of microvascular obstruction and myocardial function (lower EF% and wall motion scores) as compared with non-anterior STEMI.
Conclusion: Using T-2 weighted imaging, the presence of myocardial oedema following successful primary percutaneous intervention for STEMI correlates with myocardial function, infarct mass and extent of microvascular obstruction.

P1375 Assessment of myocardial area at risk in patients with a ST-elevation myocardial infarction; T2-weighted cardiac magnetic resonance imaging compared to angiographic and electrocardiographic methods

M. Versteylen, S.C.A.M. Bekkers, M.W. Smulders, C. Mihl, M.H.M. Winkens, H.J.G.M. Crijns, A.P.M. Gorgels. *University Hospital Maastricht, Maastricht, Netherlands*

Purpose and objectives: Estimation of initial myocardial area at risk is essential in evaluating the efficiency of therapeutic interventions in patients with ST-elevation myocardial infarction (STEMI). Experimental studies have shown that the hyperintense area seen on T2 weighted cardiovascular magnetic resonance imaging (T2W-CMR) is associated with area at risk. Our objective was to compare T2W-CMR area at risk to other clinical estimators of area at risk, angiographic and electrographic, in a group of STEMI patients.
Methods: We studied 102 patients with a first STEMI. Mean age was 61±11 years, 70% were male. The culprit lesion was the LAD, RCX or RCA in 30%, 13% and 57%, respectively. TIMI flow was graded 0 in 58%, 91% acquired TIMI flow 3 after PCI. CMR imaging was performed at average 5±2 days after admission in 87 patients. Breath-hold T2-weighted and late gadolinium enhancement CMR were used to determine area at risk and final infarct size. Angiographic (BARI, APPROACH, Duke) and ECG (Aldrich, ST-deviation) scores were used to determine area at risk, blinded from T2W-CMR results. Agreement between area at risk scores was performed using a linear regression model to calculate correlation coefficients, and using Bland-Altman analysis.
Results: CMR determined area at risk and final infarct size were 27±12% and 16±11% of LV mass, respectively. Mean BARI, APPROACH, Duke, Aldrich and ST-deviation score were 27±10%; 25±10%; 24±11%; 21±9% and 18±12%, respectively. Area at risk correlation between T2W-CMR and the angiographic BARI, APPROACH and Duke scores were r = 0.36; r = 0.42 and r = 0.43 respectively (p = 0.001). Correlation coefficients with the ECG Aldrich and ST-deviation scores were r = 0.13 and r = 0.20 (p = ns). In a subgroup of 16 patients with low reperfusion (TIMI flow < 2, Rentrop score < 2, door-to-balloon time > 180 minutes), correlations of T2W-CMR with BARI, APPROACH and Duke score improved (r = 0.58; r = 0.71 and r = 0.76, respectively, p = 0.02). In this subgroup, BARI, APPROACH and Duke scores correlated best with final infarct size (r = 0.70; r = 0.82 and r = 0.85; respectively, p = 0.002).
Conclusion: In general, T2W-CMR determined area at risk correlated only weakly with angiographically and electrocardiographically determined area at risk, but improved in a subgroup of patients with low reperfusion. Our results indicate that before using T2W-CMR as an accurate estimation of area at risk in the clinical setting, further validation is necessary.

P1376 Adenosine stress perfusion for detection of coronary artery stenosis at 3T is not inferior to 1.5T magnetic resonance imaging in comparison to invasive coronary x-ray angiography

P. Bernhardt, J. Spiess, R. Gradinger, V. Hombach. *Universitaetsklinikum Ulm, Ulm, Germany*

Background: Adenosine-stress magnetic resonance imaging (CMR) at 1.5T has established for diagnosis of inducible myocardial ischemia in patients with suspected coronary artery disease. However, little is known about feasibility and accuracy of stress-perfusion performed at higher magnetic field strength in clinical routine. Aim of our study was to compare 1.5T and 3T stress perfusion for diagnosis of inducible myocardial ischemia representative for coronary artery stenosis in patients with suspected coronary artery disease.
Methods: Patients with clinical indications for coronary x-ray angiography underwent previously adenosine-stress CMR at 1.5T (Intera, Philips Medical Systems) and 3T (Achieva, Philips Medical Systems) within 48 hours. Within 72 hours after the last CMR examination coronary angiography was performed in these patients. A SSFP-based sequence was used for perfusion imaging at 1.5T and a gradient-echo sequence at 3T. Three short axis distributed along the left ventricle were acquired, consequently after three minutes of adenosine infusion at a constant rate (140μg/kg/min) to visualize myocardial first-pass of 0.075 mmol/kg Gadolinium-based contrast agent (Dotarem, Guerbet). Ten minutes later the same perfusion sequences using a second contrast bolus were performed during rest. All CMR images were analyzed by two blinded and experienced readers in consensus for presence of hypoperfuion during stress perfusion. Perfusion sequences were evaluated using the 17-segment-model. A relevant coronary stenosis was defined by QCA as luminal reduction ≥70% in a vessel with ≥2mm diameter.

Results: 123 perfusion territories of LAD, LCX and RCA were analyzed. 11 territories were excluded due to poor image quality in one of the examination at either magnetic field strength. In 45 coronary arteries stenoses ≥70% were found by coronary x-ray angiography. 1.5T CMR stress perfusion yielded a sensitivity of 0.89, a specificity of 0.93 and an overall accuracy of 0.91. Sensitivity of 3T CMR stress perfusion was 0.91, sensitivity 0.90 and overall accuracy 0.90.
Conclusion: Adenosine-stress CMR perfusion using a gradient-echo sequence at 3T is feasible for diagnosis of coronary artery stenosis and is not inferior to the established 1.5T CMR stress perfusion. Further studies are warranted to evaluate whether 3T stress perfusion could also be used for quantitative perfusion analysis an may even be superior to 1.5T examintion.

P1377 P wave signal averaged electrocardiogram (P-HiRes) for atrial fibrillation risk evaluation in patients with acute myocardial infarction

D. Toader, R. Musetescu, D.-D. Ionescu. *Cardiology Center, Craiova, Romania*

Purpose: P wave high resolution electrocardiography (P-HiRes) is a method identical to ventricular SAECG, for atrial fibrillation risk evaluation; it also uses Frank leads X, Y, Z. This method reveals low amplitude potentials (μV) – late atrial potentials (LAP), which are present at the end of P wave representing late depolarization of atrial myocardium (areas with slow conduction) were reentrant arrhythmias can start. P-HiRes parameters are: signal averaged P wave duration – SAPWD, root mean square – RMS40, integral of P wave. An increased filling pressure during acute phase of myocardial infarction may lead to damage of left atrium and reentry arrhythmias. Aim of the study was evaluation of atrial fibrillation risk patients with acute myocardial infarction using P-HiRes and correlation with echocardiographic changes and cardiovascular risk factors.
Methods: A number of 40 patients (22 males and 18 females) aged 36-82 years, admitted with acute myocardial infarction were evaluated during the first week of hospitalization by: clinical examination, 12 lead standard ECG, echocardiographic measurements of LAVI: cutoff level for dilatation of left atrium (DLA) was 32ml/m^2, LVMI: cutoff levels for left ventricular hypertrophy (LVH): 131g/m^2 for males and 110 g/m^2, for females, presence of mitral regurgitation (MR). P-HiRes: criterias for late atrial potentials: SAPWD>140ms, RMS40>3,5μV, integral of Pwave>800μV, number of averaged beats: 250, filters: 25-40 MHz, noise level<0,1 μV (target); diabetes mellitus: fasting plasma glucose>126 mg/dL, dyslipidemia: LDLc>100 mg/dl; HDLc<40 mg/dl, triglycerides>150 mg/dl. All patients received thrombolytic therapy.
Results: 1.The presence of LAP in patients with AMI: LVH 6(+): 71,42%, p<0,01; DLA(+): 80%, p<0,004 and MR(+): 78,265, p<0,004. 2.The presence of LAP in diabetic patients with AMI: LVH(+): 86,36%, p<0,05, DLA (+): 85% p<0,004, and MR (+): 77,77% p<0,004. 3.LAP in dyslipidemic patients with AMI: LVH(+): 84,46% p<0,01, DLA (+): 87,5% p<0,004 and MR (+): 80,95% p<0,004.
Conclusions: 1.P wave signal averaged electrocardiography is a good method used for atrial fibrillation risk evaluation in patients with acute myocardial infarction. This revelead the link between an increased filling pressure and damage of left atrium during acute phase of myocardial infarction which may lead to reentry arrhythmias. 2.This was more obvious in patients with increased LAVI and LVMI, correlated with other risk factors like diabetes, dyslipidemia, probably due to an increased filling pressure.

P1378 Aortic calcification is a marker of severity of coronary artery disease

D. Alonso Rodriguez[1], J. Gaztanaga[2], J. Sanz[2], I. Iglesias Garriz[1], L. Fernandez[2], G. Pizarro[2], M.A. Rodriguez Garcia[1], M. Garcia[2]. [1]*Hospital de Leon, Leon, Spain;* [2]*Mount Sinai Hospital, New York, United States of America*

Purpose: Peripheral vascular and aortic valve calcifications are markers of atherosclerosis and have been related to coronary artery disease (CAD). The presence of these calcifications on multi-detector CT (MDCT) is potentially a marker of CAD, but its significance continues to be investigated.
Methods: We studied a cohort of 219 mostly symptomatic patients without known CAD (117 men, 102 women; age 30 to 87 years) referred for MDCT coronary calcium score and angiography. Aortic calcification was quantified using the Agatston and volume scoring methods. The aortic calcium measurements were done in the ascending and descending aorta and aortic valve. In addition, patients were classified into four groups, (1) no evident CAD (no plaques and calcium score=0) [n=103], (2) nonobstructive CAD (luminal narrowing <50% on MDCT angiography) [n=60], (3) single-vessel CAD (luminal narrowing ≥50% in a single vessel [n=29], or (4) multivessel CAD (luminal narrowing ≥50% in the left main coronary artery and/or multiple vessels) [n=27].
Results: Aortic calcium was present in 42% of the patients. The severity of aortic calcification increased in relation with the severity of CAD (table). There was a significant linear correlation between CAD severity and aortic Agatston and volume scores (Spearman's r=0.28 and 0.29, respectively, p<0.0001 for both). There was an excellent correlation between aortic Agatston and volumen scores (Spearman's r=0.998) Receiver operating characteristic analysis revealed that an Agatston score cutoff of 7 (c-statistic 0.77) detected the presence of significant CAD (Groups 3 and 4) with a sensitivity and specificity of 74 and 77%, respectively.

	Group 0 (n=103)	Group 1 (n=60)	Group 2 (n=29)	Group 3 (n=27)	Significance
% patients with aortic calcification	17.5	50.0	69.0	85.2	p<0.0001
Median aortic calcium score (IQ25-75)	0 (0-0)	1.3 (0-253.1)	103.3 (0-399.6)	340.0 (52.4-835.9)	p<0.0001

Conclusions: The presence of aortic calcification is a marker of CAD in symptomatic patients referred for coronary MDCT. There is a direct relationship between aortic calcification and severity of coronary CAD

P1379 Cardio-ankle vascular index as a predictive determinant for coronary artery calcification as assessed by multi-detector row computed tomography

R. Mitsutake, S. Miura, Y. Shiga, H. Sako, K. Saku. *Fukuoka University Hospital, Fukuoka, Japan*

Background: Recently, cardio-ankle vascular index (CAVI) has been developed as a predictor of atherosclerosis evaluated by invasive coronary angiography or carotid intima-media thickness. The coronary artery calcification (CAC) score determined by multi-detector row computed tomography (MDCT) predicts coronary artery disease (CAD). However, little is known about the association between CAVI and the CAC score.
Methods and results: Subjects included 513 consecutive patients (male 54%, age 64±11 years) who underwent coronary angiography using 64-MDCT. We assessed the presence of CAD, and quantified the CAC score on MDCT and measured visceral fat area, subcutaneous fat area, abdominal circumference, ankle-brachial index, pulse wave velocity and CAVI.
The mean CAC score and CAVI were 264±778 and 6.0±2.5, respectively. CAVI was significantly increased in proportion to the accumulation of the number of the components of the metabolic syndrome. Since we previously reported that a higher number of coronary stenosed vessels was associated with a higher CAC score, the CAC score were divided into three groups (lower group, CAC score 0-12; intermediate group, score 13-445; higher group, score>445). The CAC score group was significantly associated with age, sex, prevalence of hypertension and DM, systolic blood pressure, plasma levels of LDL-C and uric acid, ABI, PWV, and CAVI. In a multivariate logistic regression analysis, sex (p=0.0007), age (p=0.0055), hypertension (p=0.0039) and CAVI (p=0.0009) remained significant independent variables for the CAC score group.
Conclusion: CAVI was useful for predicting coronary artery calcification. Thus, measurement of CAVI should be performed before MDCT angiography, because the assessment of coronary artery lumen narrowing could not be diagnosed in patients with severe calcification. This study might help to decrease excessive radiation exposure and/or patient's financial burden.

P1380 Value of 64-slice multi-detector computed tomography for predicting revascularization in patients with coronary artery disease

H.S. Lim, S.J. Tahk, H.M. Yang, J.S. Park, M. Zheng, S.K. Kim, Y.S. Kwon, B.J. Choi, S.Y. Choi, M.H. Yoon. *Ajou University Medical Center, Suwon, Korea, Republic of*

Purpose: Despite its excellent diagnostic role in evaluating coronary artery disease (CAD), there have been few studies on the value of multi-detector computed tomography (MDCT) as a guidance for determining therapeutic strategies in CAD. We aimed to find out the informations that MDCT can provide for predicting revascularization before coronary angiography (CAG).
Methods: We studied 1121 major epicardial arteries (≥2mm) of 404 patients undergoing elective CAG for suspected CAD after 64-slice MDCT. All arteries were classified into 3 groups according to percent diameter stenosis (%DS) by MDCT (group1,<30%DS; group2,30%-50%DS; group3,≥50%DS). Treatments were decided by angiographic and/or intravascular ultrasound and/or fractional flow reserve guidance and categorized into medical treatment and revascularization that is consisted of percutaneous coronary intervention and/or bypass surgery.
Results: By artery-based comparison between MDCT and CAG, sensitivity, specificity, and positive and negative predictive value for the presence of significant CAD≥50% DS were 78%, 93%, 73% and 95%, respectively. Arteries for medical treatment were 650 (95%), 138 (79%) and 96 (36%) and revascularized arteries were 35 (5%), 37 (21%) and 169 (64%) in group 1, 2 and 3, respectively. Hypertension, clinical presentation of acute coronary syndrome (ACS), plaque character and %DS were univariate predictors for revascularization in group 2 which means moderately stenosed CAD by MDCT (p=0.079, p<0.001, p=0.041 and p=0.102, respectively). Among these predictors, clinical presentation of ACS [odds ratio (OR) = 7.637, 95% confidence interval (CI) 2.816-20.707] and %DS (OR=1.116, 95% CI 1.018-1.222) were independent predictors of revascularization in this group 2.
Conclusion: Although 64-slice MDCT has high negative predictive value for diagnosis of significant CAD, one fifth of coronary arteries with moderate, non-significant stenosis by MDCT imaging were treated with revascularization. In clinical application of 64-slice MDCT, we need more careful assessment in the pa-

tients with high probability of ACS and with higher %DS even in the moderately stenosed coronary lesions by MDCT.

P1381 Cardiac MR has superior reproducibility compared to cardiac CT for volumes and function analysis of the systemic right ventricle

M.M. Winter[1], S.A.H. Romeih[1], B.J. Bouma[1], M. Groenink[1], W.A. Helbing[2], A.M. Spijkerboer[1], B.J.M. Mulder[1]. *[1]Academic Medical Center, Amsterdam, Netherlands; [2]Erasmus Medical Center - Sophia Children's Hospital, Rotterdam, Netherlands*

Purpose: Cardiovascular Magnetic Resonance Imaging (CMR) is considered the gold standard for volumes and function measurements of the systemic right ventricle (RV). However, 20% of patients with a systemic RV are pacemaker dependent, and therefore unsuitable to undergo CMR. Multidetector Row Cardiac Computed Tomography (MDCT) could provide a reliable alternative for CMR in these patients. The aim of the study was to compare intra- and interobserver reproducibility of CMR with MDCT for volumes and function measurements.
Methods: Thirty-two patients with a systemic RV (12 congenitally corrected transposition of the great arteries and 20 atrially switched transposition of the great arteries) were included. Twenty patients underwent CMR (80% male, mean age 36±13 years), and 12 patients underwent MDCT (33% male, mean age 32±9 years) to assess systemic right ventricular volumes [end diastolic volume (EDV), end systolic volume ESV)] and function [ejection fraction (EF)]. Measurements were performed twice by a single observer, and once by another observer. Intra- and interobserver reproducibility were assessed for both modalities, and quoted as coefficient of variability (CV).
Results: Significant differences in intra- and interobserver reproducibility of measurements were found between CMR and MDCT. Intraobserver reproducibility of CMR was higher compared to MDCT, with lower CV for RV EDV (CV 6.1% vs 8.9%, $p<0.05$), ESV (6.7% vs 8.3%, $p<0.01$), and EF (5.8% vs 12.0%, $p<0.001$). Similar results were found for interobserver reproducibility, with lower CV for EDV (CV 10.0% vs 16.9%, $p<0.001$), ESV (12.7% vs 20.2%, $p<0.001$), and EF (7.5% vs 21.7%, $p<0.01$) for CMR compared to MDCT.
Conclusion: CMR remains the method of preference for volumes and function measurements of the systemic RV, as it has superior reproducibility over MDCT. Research on CMR compatibility of cardiac devices is warranted to provide these patient with adequate diagnostic tools.

P1382 Evaluation of left ventricular volumes and ejection fraction with 320-slice multi-slice computed tomography: a head-to-head comparison to 2D-echocardiography

F.R. De Graaf, J.D. Schuijf, J.E. Van Velzen, G. Nucifora, A. De Roos, J.W. Jukema, E.E. Van Der Wall, J.J. Bax. *Leiden University Medical Center, Leiden, Netherlands*

Background: Multi-slice computed tomography (MSCT) has been demonstrated as an accurate imaging modality for non-invasive evaluation of coronary artery disease (CAD) and left ventricular (LV) function. With the recent introduction of 320-slice systems, image acquisition of the entire heart within a single heartbeat has become feasible. The present study evaluated the accuracy of 320-slice MSCT for assessment of global LV function and volumes. Two-dimensional (2D) echocardiography served as the standard of reference.
Methods: A head-to-head comparison between 320-slice MSCT and 2D-echocardiography was performed in 102 patients (59 male; mean age 61±12 years) who were clinically referred for coronary computed tomography angiography (CTA). Intravenous contrast agent was administered and the entire heart was imaged in a single heartbeat, using prospective dose modulation (maximal tube current during 65-85% of R-R interval). Additional scan parameters were: gantry rotation time 350 ms, tube voltage 120 kV, tube current 500-580mA. LV end-diastolic volumes (LVEDV) and LV end-systolic volumes (LVESV) were derived and the LV ejection fraction (LVEF) was calculated.
Results: Mean LVEF was 62±7% (range 50 - 78%) on MSCT, compared with 61±7% (range 47 - 77%) as determined on 2D-echocardiography. Evaluation of LVEF by linear regression analysis showed a good correlation between MSCT 2D-echocardiography and MSCT ($r = 0.84$; $p < 0.001$). Good correlations between MSCT and 2D-echocardiography were demonstrated for the evaluation of LVEDV ($r = 0.93$; $p < 0.001$) and LVESV ($r = 0.92$; $p < 0.001$). Using Bland-Altman analysis, mean differences (± SD) of 7.6±12.6 ml ($p < 0.05$) and 1.7±7.5 ml ($p < 0.05$) were shown between MSCT and 2D-echocardiography for LVEDV and LVESV respectively. Consequently, LVEF was slightly overestimated with MSCT (1.0±3.7%; $p < 0.05$).
Conclusion: Accurate evaluation of LV volumes and ejection fraction is feasible with 320-slice MSCT in patients referred for MSCT coronary angiography.

SIGNALLING AND METABOLIC PATHWAYS INVOLVED IN MYOCARDIAL PROTECTION

P1383 Investigating the signal transduction pathways underlying remote ischaemic preconditioning and postconditioning

E.K. Iliodromitis[1], A. Papalois[1], G. Gritsopoulos[1], D.T. Kremastinos[1], D.M. Yellon[2], D.J. Hausenloy[2]. *[1]2nd University Department of Cardiology, University of Athens, Athens, Greece; [2]The Hatter Cardiovascular Institute, University College London & Medical School, London, United Kingdom*

Purpose: Applying brief ischaemia/reperfusion to a limb either prior to myocardial ischaemia (remote ischaemic preconditioning, RIPC) or after the onset of myocardial ischaemia (remote ischaemic postconditioning, RIPost) can reduce myocardial infarct size. We hypothesised that RIPC and RIPost limit infarct size by activating the adenosine receptor and the PI3K-Akt pathway at the onset of myocardial reperfusion.
Methods: Mini-swines (25-30kg) were subjected to in situ left anterior descending (LAD) coronary artery ischaemia (60min) followed by myocardial reperfusion (180min) at the end of which infarct size was determined using tetrazolium staining. Animals were randomised to the following: (1) Control- No additional intervention; (2) RIPC- Four-5 min cycles of lower limb ischaemia/reperfusion (femoral artery clamping/declamping) were administered prior to the onset of myocardial ischaemia; (3) RIPC+Wort or 8SPT: Wortmannin (20μg/kg, a PI3K inhibitor) or 8-SPT (10mg/kg, an adenosine receptor inhibitor) were given intravenously 30 seconds before myocardial reperfusion to RIPC-treated animals; (4) RIPost- Four-5 min cycles of lower limb ischaemia/reperfusion were administered at the end of myocardial ischaemia, one minute before the onset of myocardial reperfusion; (5) RIPost+Wort or 8-SPT: Wortmannin or 8-SPT were given 30 seconds before myocardial reperfusion to RIPost-treated animals
Results: Both RIPC and RIPost significantly reduced myocardial infarct size (13.3±2.2% with RIPC, 18.2±2.0% with RIPost versus 48.8±4.2% in control:$P<0.05$:$N>5$/group). Wortmannin, the PI3K-Akt inhibitor, partially abolished the infarct-limiting effects of RIPC (33.2±6.0% with RIPC+Wort versus 13.3±2.2% with RIPC:$P<0.05$:$N>5$/group) but not RIPost (18.0±3.4% with RIPost+Wort versus 18.2±2.0% with RIPost:$P>0.05$: $N>5$/group). 8-SPT, the adenosine receptor inhibitor, did not influence the infarct-limiting effects of either RIPC (10.4±2.0% with RIPC+8-SPT versus 13.3±2.2% with RIPC:$P>0.05$:$N>5$/group) or RIPost (17.6±40% with RIPost+8-SPT versus 18.2±2.0% with RIPost:$P>0.05$: $N>5$/group).
Conclusion: RIPC but not RIPost reduces myocardial infarct size by activating the PI3K-Akt pathway at reperfusion. Neither RIPC nor RIPost require activation of the adenosine receptor at the time of reperfusion for their infarct-limiting effects.

P1384 The cardioprotective effect of TRO40303 is related to binding to the mitochondrial translocator protein and inhibition of the mitochondrial permeability transition pore

S. Schaller[1], R. Assaly[2], S. Paradis[2], M.A. Ostuni[3], J.J. Lacapere[3], R. Zini[2], A. Berdeaux[2], R. Pruss[1], D. Morin[2]. *[1]Trophos S.A., Marseille, France; [2]INSERM U 955 Equipe 03, Creteil, France; [3]INSERM U 773/CRB3, Paris, France*

Purpose: Mitochondrial permeability transition pore (mPTP) opening is a key event leading to cell death during myocardial ischemia-reperfusion injury. As the Mitochondrial Translocator Protein (TSPO) (formerly known as Peripheral Benzodiazepine Receptor) is closely associated with mPTP at the level of the mitochondrial outer membrane, we investigated TRO40303 binding to the cholesterol site of TSPO and whether protection of rat myocardium against ischemia-reperfusion injury may be related to TSPO and mPTP inhibition using TRO40303.
Methods: Anesthetized male Wistar rats were submitted to 35min coronary artery occlusion followed by 24h reperfusion. Infarct size was evaluated by triphenyltetrazolium staining. TRO40303 (0.3 to 3 mg/kg, i.v.) was given 10 min before reperfusion. Direct mPTP opening was assessed in isolated adult rat cardiomyocytes subjected to 2h hypoxia followed by 2h reoxygenation by means of the calcein loading/CoCl2 quenching technique resulting in mitochondrial localization of calcein fluorescence. Binding studies were performed on proteoliposomes containing reconstituted wild-type recombinant TSPO using (3H) cholesterol as a ligand.
Results: Inhibition of (3H) cholesterol binding by TRO40303 indicated that TRO40303 bound with a high affinity to the cholesterol site of TSPO (Ki = 150 nM). TRO40303 did not exhibit any affinity for more than 85 other receptors, enzymes, transporters or ion channels labelled by specific radioligands indicating its high selectivity for TSPO.
TRO40303 reduced infarct size in a dose-dependent manner as compared with corresponding values obtained after vehicle administration (e.g.15±2% of the area at risk at 3 mg/kg vs 33±5% in controls; $p<0.01$). In isolated adult rat cardiomyocytes, TRO40303 (3 μM) delayed mPTP opening and this effect was similar to that observed with the direct mPTP inhibitor cyclosporine A (1 μM). This was accompanied by an increase in cell survival measured by nuclear staining with propidium iodide.
Conclusion: These data demonstrate that a new TSPO ligand, TRO40303, pro-

tects the myocardium against ischemia-reperfusion injury and that this protection is at least in part mediated by prevention of mPTP opening. Thus, TSPO ligands such as TRO40303 may represent novel and promising cardioprotective agents.

P1385 Double-edged role of the SDF-1/Cxcr4 axis in experimental myocardial infarction

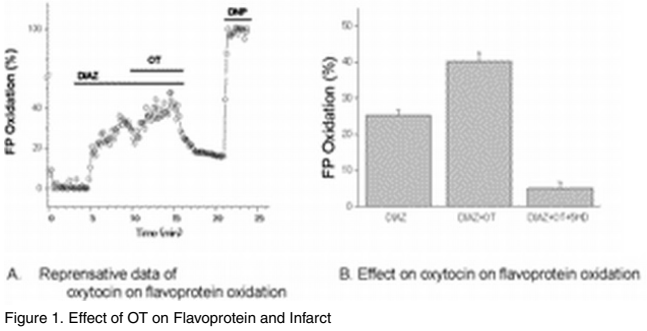
E. Liehn[1], N. Tuchscheerer[1], I. Kanzler[1], M. Drechsler[1], S. Zandler[2], A. Schuh[2], M. Merx[2], R. Koenen[1], A. Schober[1], C. Weber[1]. *[1]RWTH Aachen, Institute for Molecular Cardiovascular Research, Aachen, Germany; [2]RWTH Aachen, Department of Cardiology, Pulmonology and Vascular Medicine, Aachen, Germany*

Background: Myocardial necrosis triggers inflammatory changes and a complex cytokine cascade that are only incompletely understood. The chemokine receptor Cxcr4 promotes regeneration by mediating recruitment of progenitor cells into ischemic area in response to its ligand Cxcl12/SDF-1alpha. Here we assess the effect of Cxcr4 on remodeling after myocardial infarction (MI) using Cxcr4-heterozygote (Cxcr4+/-) mice.
Methods and Results: MI was induced in Cxcr4+/- or wild-type mice by permanent ligation of the proximal LAD. After four weeks infarct size was reduced by 42% in Cxcr4+/- mice compared with wild-type mice. Mobilization of neutrophils was blunted in Cxcr4+/- mice 1 day after infarction, whereas no differences were observed in peripheral monocytes. Accordingly, myocardial infiltration with neutrophils was decreased 2-fold in Cxcr4+/- mice. Although neutrophil content declined in both groups at 4 days after MI, myocardial neutrophil infiltration was 3.5-fold lower in Cxcr4+/- mice. In contrast, intramyocardial monocyte content was reduced at 4 days after MI but increased significantly thereafter resulting in a higher monocyte infiltration at 14 days in Cxcr4+/- mice as compared to wild-type mice. Notably, peripheral Gr-1high monocytes were reduced in Cxcr4+/- mice, whereas Gr-1low monocytes in the circulation were increased in Cxcr4+/- mice at 1d, 14 days, and 21 days after MI. However, despite a reduction in infarct size, left ventricular function as determined by echocardiography or in Langendorff-perfused hearts was not increased 4 weeks after MI in Cxcr4+/- mice. This might be due to reduced basal coronary flow and impaired recovery of coronary flow 4 weeks after MI in Cxcr4+/- compared with wild-type mice (coronary flow 1.2±0.3 vs 3.1±0.1 ml/min; $P<0.05$). Furthermore, incorporation of CD31+ endothelial cells into the infarct area was diminished in Cxcr4+/- mice indicating insufficient neoangiogenesis (969±265 versus 448±263 vessels/mm^2).
Conclusions: Although therapeutic application of Cxcl12/SDF-1alpha has been advocated after MI, CXCR4+/- mice were morphologically protected due to a reduced pro-inflammatory response. However, ventricular function was not preserved in Cxcr4+/- most likely owing to impaired vascularization. Therefore, our results indicate a more complex role of the Cxcl12/Cxcr4 axis after MI than hitherto appreciated.

P1386 Oxytocin confers cardioprotection through the opening of mitochondrial ATP-sensitive potassium channels

H. Nishida, T. Sato, N. Inamura, H. Nakaya. *Chiba University Graduate School of Medicine, Chiba, Japan*

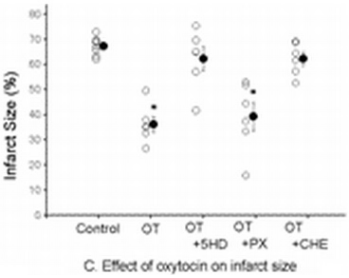
Purpose: Mitochondrial ATP-sensitive K$^+$ (mitoKATP) channels are activated by protein kinase C (PKC) and implicated in the mechanism of cardioprotection. Oxytocin (OT) is a small peptide hormone and binds to its membrane receptors on the endometrial cells to increase the activity of phospholipase C, yielding diacylglycerol which activates PKC. Accordingly, we assessed the hypothesis that OT confers cardioprotection by opening of mitoKATP channels.
Methods: Flavoprotein fluorescence in rabbit ventricular myocytes was measured to assay mitoKATP channel activity. Infarct size after ischemia (30 min)/reperfusion (120 min) in Langendorff-perfused rabbit hearts was measured by triphenyltetrazolium chloride staining.
Results: The mitoKATP channel opener diazoxide (100 μM) reversibly oxidized flavoprotein to 27±2% (n = 6) of the maximum value induced by 2,4-dinitrophenol (100 μM). OT (30 nM) significantly augmented the oxidative effects of diazoxide to 40±2% (n = 6, $P < 0.05$). The mitoKATP channel blocker sodium 5-hydroxydecanoate (500 μM) completely inhibited the oxidative effects of diazoxide and OT to 5±2% (n = 6). Treatment with OT (30 nM) for 5 min before ischemia significantly reduced infarct size from 67±1% (n = 8) in controls to 36±3% (n = 6, $P < 0.05$). The infarct size-limiting effect of OT was abolished by both 5-hydroxydecanoate (500 μM, 62±5%, n = 6) and the potent PKC inhibitor chelerythrine (1 μM, 62±3%, n = 6), but not by the mitochondrial Ca^{2+}-activated K$^+$ channel blocker paxilline (2 μM, 39±6%, n = 6).
Conclusions: These results indicate that OT potentiates the opening of mitoKATP channels in a PKC-dependent manner and the infarct size-limiting effect of OT is mediated by activation of mitoKATP channels.



A. Reprensative data of oxytocin on flavoprotein oxidation

B. Effect on oxytocin on flavoprotein oxidation

Figure 1. Effect of OT on Flavoprotein and Infarct



C. Effect of oxytocin on infarct size

Figure 1. Effect of OT on Flavoprotein and Infarct (continued)

P1387 Calpain inhibition at reperfusion limits infarct size in vivo

C.L. Sartorio, J. Inserte, V. Hernando, M. Poncelas, D. Garcia-Dorado. *Hospital Universitario Vall d'Hebron, Barcelona, Spain*

Calpains contribute to reperfusion induced myocardial cell death. However, it remains controversial whether its activation occurs during ischemia or at reperfusion. The aim of this study was to analyse the regulation and time-course of calpain activation secondary to transient ischemia, and to assess the efficacy of its inhibition as a potential strategy to limit infarct size.
Methods: Translocation of m-calpain to the sarcolemma and calpain activation, assessed by proteolysis of its substrate fodrin, and their regulation by Ca^{2+} and pHi were measured in isolated rat hearts subjected to different durations of ischemia, followed or not by reperfusion. The in vivo effect of calpain inhibition on infarct size was analysed in rats subjected to 30 min of left anterior descending coronary occlusion followed by 2 hours of reperfusion. The calpain inhibitor MDL-28170, or its vehicle, was infused i.v. during the first 30 min of reperfusion (3.3 mg/kg).
Results: Ischemia induced a time dependent translocation of calpain to the membrane. Translocation started at the onset of ischemic contracture but was not associated with fodrin degradation. Translocation of calpain during ischemia was dependent of Ca^{2+} entry through reverse mode of Na^+/Ca^{2+}-exchanger, as demonstrated the results obtained with the Na^+/Ca^{2+}-exchanger inhibitor KB-R7943, and was independent of acidosis or the presence of MDL-28170. Reperfusion decreased the amount of calpain in the membrane fraction and resulted in degradation of fodrin. There was a close linear correlation between the magnitude of the calpain translocation during ischemia, calpain activation and cell death during reperfusion. Degradation of fodrin during reperfusion was prevented by perfusing the hearts with buffer adjusted at pH 6.4 during the first 3 min of reperfusion. In rats subjected to in vivo myocardial ischemia/reperfusion, MDL-28170 administration during reperfusion resulted in a significant reduction of infarct size (43.9±3.9% vs. 60.2±4.7, p=0.046, n=18) and fodrin degradation.
Conclusions: These results support the hypothesis that during ischemia increased Ca^{2+} induces calpain translocation to the membrane but low pHi prevents its activation. Reperfusion results in calpain activation as consequence of pHi correction. Reduction of infarct size by postischemic administration of MDL-28170 demonstrates that calpain is a potential therapeutic target in reperfusion cardioprotection.

P1388 Role of GSK-3beta in negative regulation of mitochondrial permeability transition pore by the mitochondrial KATP channel

T. Miura, Y. Terashima, O. Maas, T. Miki, M. Tanno, S. Ishikawa, K. Shimamoto. *Sapporo Medical University, Sapporo, Japan*

Background: Activation of the mitochondrial KATP (mKATP) channel and inhibition of glycogen synthase kinase-3 beta (GSK-3beta) by its Ser9 phosphorylation are important steps in cardioprotection afforded by various interventions. Here, we examined the relationship between the mKATP channel and GSK-3beta in regulation of mitochondrial permeability transition pore (mPTP) opening, a trigger of cell death, in cardioprotection.
Methods: In isolated buffer-perfused rat hearts, infarction was induced by 20-min global or 35-min regional ischemia followed by 2-h reperfusion. Complex formation of adenine nucleotide translocator (ANT), a major subunit of mPTP, and cyclophilin-D (CypD), a trigger of mPTP opening, was determined by immuno-

precipitation and immunoblotting. Reactive oxygen species (ROS) generated in cultured cardiomyocytes were determined by 2',7'-dichlorofluorescein.
Results: Activation of the mKATP channel by diazoxide (100 microM) before ischemia reduced infarct size as % of area at risk (%IS/AR) after global ischemia from 62.5±3.5% to 32.2±8.8%, and a GSK-3β inhibitor (SB216763; 1 microM) also afforded cardioprotection (%IS/AR = 34.2±9.0%). The combination of diazoxide and SB216763 did not afford further protection (%IS/AR = 28.2±3.8%), indicating a common step in cardioprotection by the mKATP channel and that by GSK-3β inhibition. Although diazoxide infusion commenced 10 min before reperfusion following regional ischemia was not protective, infusion of a GSK-3beta inhibitor (3 mM LiCl) in the same schedule limited %IS/AR from 40.4±3.3% to 27.7±5.8%. Diazoxide infused before ischemia increased Ser9-phospho-GSK-3beta level by 47% and reduced ANT-CypD complex level upon reperfusion by 50%. In contrast, inhibition of GSK-3beta activity by LiCl did not change the ANT-CypD complex level. However, ROS production after hypoxia/reoxygenation was significantly suppressed by LiCl (77.5±1.9 vs. 63.3±3.2 in arbitrary units) in cardiomyocytes.
Conclusion: Suppression of ROS production by inhibitory phosphorylation of GSK-3beta and inhibition of ANT-CypD interaction are dual mechanisms by which the activated mKATP channel elevates the threshold for mPTP opening upon reperfusion, leading to prevention of myocyte necrosis.

P1389 Enhanced ANT-cyclophilin-D interaction underlies reduced anti-infarct tolerance and loss of protective response to erythropoietin in hypertensive hypertrophied hearts

T. Miki, T. Yano, T. Miura, M. Tanno, K. Shimamoto. *Sapporo Medical University, Sapporo, Japan*

Objective: The aim of the present study was to examine the hypothesis that enhanced susceptibility to infarction in hypertensive hypertrophied hearts is a result of dysregulation of mitochondrial permeability transition pore (mPTP) opening, a trigger of cell death, and/or impaired cytoprotective signaling upstream of mPTP.
Methods: Myocardial infarction was induced by 20-min coronary occlusion/2-hr reperfusion in stroke-prone spontaneously hypertensive rats (SHR-SP) and Wistar-Kyoto rats (WKY) with or without erythropoietin injection (EPO, 5000 IU/kg) before ischemia or ischemic preconditioning (IPC). IPC was performed by two cycles of 5-min ischemia/5-min reperfusion. Tissues were sampled after pretreatments or upon reperfusion for immunoblotting and immunoprecipitation.
Results: Infarct size as % of area at risk (%IS/AR) was significantly larger in SHR-SP than in WKY (69.6±4.5% vs. 54.8±3.7%). EPO limited %IS/AR in WKY (44.2±2.8%) but not in SHR-SP (65.0±5.2%), though IPC significantly reduced %IS/AR in SHR-SP as well (20.8±2.8%). There was no difference between phosphorylation levels of Akt, ERK1/2 or GSK-3beta after EPO infusion in SHR-SP and WKY, and protein levels of adenine nucleotide translocator (ANT), a major subunit of mPTP, and cyclophilin-D (CypD) were comparable under baseline conditions in the two groups. However, the level of CypD co-immunoprecipitated with ANT after reperfusion was two-fold higher in SHR-SP than in WKY, and this difference was almost eliminated by infusion of N-(2-mercaptopropionyl)-glycine (1 mM), a free radical scavenger. In contrast to EPO, IPC inhibited ANT-CypD complex formation upon reperfusion in both WKY and SHR-SP.
Conclusion: Reduced threshold for mPTP opening by enhanced ANT-CypD complex formation, but not lack of pro-survival signaling to mPTP, is a mechanism of reduced anti-infarct tolerance and resistance to EPO-induced protection in hypertrophied hearts of SHR-SP. Enhanced free radical generation, which is inhibitable by IPC, is likely to mediate the enhanced ANT-CypD interaction in the hypertrophied heart.

P1390 The loss of MKK7 is beneficial in a murine model of ischemia and reperfusion

J.G.J. Voelkl[1], G. Neely[2], B.J. Haubner[1], K. Enthofer[1], N. Malicki[1], O. Pachinger[1], J.M. Penninger[2], B. Metzler[1]. *[1]Innsbruck Medical University, Innsbruck, Austria; [2]IMBA, Vienna, Austria*

Background: The highly conserved mitogen-activated protein kinases have proven to be of great importance regarding myocardial development, hypertrophy, and survival. Mitogen-activated protein kinase kinase 7 (MKK7) – JNK pathways demonstrated dichotomous properties during myocardial survival and remodeling.
The in vivo role of MKK7, using a muscle-specific knock-out strategy, in the setting of cardiac ischemia and reperfusion remained unclear.
Methods: We therefore subjected muscle-specific MKK7 knock-out (KO) mice compared to MKK7 wild-type (WT) rodents to experimental myocardial ischemia and reperfusion. Cardiovascular magnetic resonance (CMR), echocardiography and histological methods were used to characterize the transgenic phenotype.
Results: The extent of ischemia/reperfusion injury was significantly reduced in MKK7 KO compared to WT mice. Following 30 minutes of ischemia and 3 hours of reperfusion, MKK7 mutagenic rodents presented significantly reduced levels of troponin T (WT: 2,97±0,39 vs. KO: 1,78±0,26 ng/ml; $p<0,05$; n=13 per group). This early decrement of troponin T in the transgenic cohort was followed by smaller areas of infarction after 1 week (WT: 3,58±0,50 vs. KO: 1,77±0,30mm^2; $p<0,05$; n=14 per group; sum of 3 sections per heart). Concordantly, functional analysis after 1 week of reperfusion showed a greater reduction of contractility in MKK7 WT mice compared to the transgenic strain.
Conclusion: Our data provide the first in vivo knock-out evidence for the critical role of MKK7 during myocardial ischemia/reperfusion injury. MKK7 deficient mice show a significantly better outcome concerning troponin T elevation, infarction area, and loss of contractility at all stages of reperfusion.

P1391 Bone marrow chimeric mice reveal the prosurvival potential of PI3Kgamma in the heart

B.J. Haubner[1], G. Neely[2], J.G.J. Voelkl[1], K. Kuba[2], Y. Imai[2], O. Pachinger[1], J.M. Penninger[2], B. Metzler[1]. *[1]Innsbruck Medical University, Innsbruck, Austria; [2]IMBA, Vienna, Austria*

Introduction: PI3Kγ functions within the immune compartment to promote inflammation in response to G-protein-coupled receptor agonists. PI3Kγ also acts within the heart itself as a negative regulator of cardiac contractility and as a pro-survival factor.
To directly test whether the in vivo effects of PI3Kγ during myocardial ischemia/reperfusion are due to its function in the immune system or in the myocardium, we generated bone marrow (BM) chimeras.
Methods: Freshly isolated total host bone marrow cells were injected into the lateral tail vein of syngenic recipient mice 24 hours after irradiation. PI3Kγ-/-(KO) rodents carrying PI3Kγ+/+(WT) bone marrow and vice versa were then tested using our reversible coronary artery ligation model.
Results: PI3Kγ mutant mice receiving PI3Kγ WT bone marrow exhibited severe infarction (WT-BM→KO: 1,02±0,19 vs. KO-BM→WT: 0,64±0,19 mm^2; $p<0,05$; n=7 per group) and markedly increased Troponin T release (WT-BM→KO: 3,27±1,9 vs. KO-BM→WT: 1,01±0,31 ng/ml; $p<0,05$; n=7 per group) following ischemia/reperfusion injury compared to WT rodents with KO bone marrow. This greater extent of myocardial damage in the KO cohort was further confirmed by a greater loss of fractional shortening after 1 week of reperfusion.
PI3Kγ+/+ (WT-BM→WT) and PI3Kγ-/- (KO-BM→KO) controls confirmed that PI3Kγ is beneficial during ischemia/reperfusion injury. Western blotting and immunohistochemical analysis revealed Akt/PKB and ERK as crucial cardiac downstream targets of PI3Kγ in our experiments.
Conclusion: We found that disrupting PI3Kγ function in the immune system using bone marrow chimeric mice had no protective effect on myocardial ischemia/reperfusion injury. PI3Kγ seems to be the key kinase that mediates activation of the pro-survival Akt/PKB and ERK pathway at the site of cardiac injury.

P1392 Mechanisms involved in the cardioprotective effects of ivabradine against ischemia-induced ventricular fibrillation

Q. Timour[1], F. Vaillant[1], A. Mazzadi[2], P. Dagorn[3], J. Descotes[4], A. Tabib[5], B. Bui-Xan[1], D. Belhani[1], P. Chevalier[6]. *[1]Laboratory of Medical Pharmacology, Inserm ERI 22, Lyon, France; [2]CERMEP, Lyon, France; [3]IRIS, Courbevoie, France; [4]Poison Center and Pharmacovigilance Department, Lyon University Hospitals, Lyon, France; [5]Institute of Forensic Medecine, Claude Bernard University, Lyon, France; [6]Hopital Louis Pradel, Lyon, France*

We showed previously that ivabradine (IVA), a selective If current inhibitor, achieved protection against ischemia-induced ventricular fibrillation (VF). This protective effect was characterized by a significant increase in the electrical threshold of VF (VFT) and was correlated to: 1) the reduction of heart rate (HRR) 2) the limitation of ischemic-induced reduction of monophasic action potential duration and 3) the reduced ischemic area. Here, we investigated the mechanism(s) involved in the cardioprotective effects of IVA.
Method: Myocardial ischemia was induced in pigs by total 1-min occlusion of the coronary artery following the iv administration of saline (n=6) or IVA (0.25 mg kg^{-1}, n=6). Electrophysiological and hemodynamic parameters, the ischemic area and the presence of mitochondrial anomalies (using electron microscopy) were evaluated. The regional myocardial blood flow (RMBF) was assessed using positon emission tomography following ischemia-reperfusion in pigs (n=6) receiving an iv bolus of IVA (0.25 mg kg^{-1}).
Results: At baseline, all measured parameters were identical between groups. Compared to saline, IVA induced a significant HRR (-13%), a significant increase in VFT (x2.1), a significant reduction of the ischemic area (18.66±4.20% vs. 29.7±2.06%) but no significant changes in left ventricular dP/dt max. The main ultrastructural changes are summarized in the table. The evaluation of RMBF, showed that under basal conditions, the ischemic area becomes hyperemic after lifting arterial ligation and following the HRR induced by IVA, the RMBF was markedly increased in the ischemic area (147% vs 97% at baseline, $p<0.05$).

	IVA	saline
Mitochondria (shifting, swelling, degranulation, crest breaks)	<20%	>80%
Nuclei (dispersal or irregular packing of chromatin)	<10%	>90%
Sarcolemma, junction breaks and necrotic foci	<5%	>95%
Capillary changes	<15%	>85%

Conclusion: The beneficial effects of IVA against ischemia-induced VF were associated with: 1) a reduction of the ischemic area; 2) lesser myocardial histological alterations, especially a conserved mitochondrial structure (maintained

myocardial energy supply); 3) increased RMBF. Overall, these effects provide explanation to the protective effects of IVA against ischemia-induced VF.

P1393 Combined protective effects of postischemic conditioning and remote perischemic conditioning in a rat ischemic/reperfusion injury model, a comparative study with ischemic preconditioning

P. Xin[1], W. Zhu[2], J. Li[2], M.Y. Liu[1], J.B. Li[1], A.N. Redington[2], M. Wei[1]. *[1]Shanghai Sixth Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, People's Republic of; [2]Hospital for Sick Children, University of Toronto School of Medicine, Toronto, Canada*

Background: Ischemic Postconditioning (PostC) is a practical alternative way for protecting the heart against ischemic/reperfusion injury (IRI). However, it is not always as efficient as ischemic preconditioning (PreC) due to a limited time window. Remote ischemic perconditioning (RPerC) delivered at index ischemic period provides another new therapeutic window. The present study aimed to assess whether combination of RPerC and local PostC could result in improved protective effects.
Methods: SD rats (weighing 250∼280g) were randomly assigned to the following five groups (36 rats for each group): 1), MI groups, IRI was created with 45 minutes LAD coronary ligation followed by 2 hours reperfusion; 2), PreC group, MI rats were given 4 cycles of 5 minutes LAD ligation followed by 5 minutes reperfusion before LAD ligation; 3), PostC group, MI rats were given PostC which was delivered at first 2 minutes of reperfusion with six cycles of 10 seconds reperfusion followed by 10 seconds LAD reocclusion; 4), RPerC group, RPerC was delivered during the 45 minutes index ischemic period by occluding hind limb blood flow with a cuff for 4 cycle of 5 minutes occlusion followed by 5 minutes release; 5) Combination (Com) group, MI rats received both PostC and RPerC therapy. At the end of reperfusion period, 6 rats from each group were sacrificed. Infarct size (IS) was quantified by TTC staining and expressed as percentage of risk area marked by Evans Blue staining. In situ superoxide generation was measured by DHE staining with heart tissue obtained at 1, 2,10 and 30 minutes, and 1 and 2 hours after reperfusion (6 rats for specified time points from each group).
Results: While PostC and RPerC resulted in similar decreases in IS (PostC, 31.33±4.13%; RPerC, 37.57±6.56%, respectively) compared with IS in MI group (54.98±6.91%; $p<0.05$, respectively). PreC provided even better cardiac protection, a further decrease in IS (23.7±4.08%; $p<0.05$, respectively). Interestingly, a similar protective effect was achieved in Com group (IS, 27.57±4.9%) compared with PreC group ($p>0.05$). Although PostC and Com group rats showed the lowest superoxide generation at 1 minute of reperfusion among the five groups, however, starting at 10 minuts and throughout the reperfusion period, the lowest superoxide was demonstrated in PreC and Com group rats. The patterns of cardiac protection were consistent with the percentage TUNEL positive cells and Bax/BCL2 protein expression ratio.
Conclusion: Cmbination of PostC and RPerC therapy may serve as a novel method for protecting the heart from IRI.

P1394 Cannabinoid receptor activation protects coronary endothelium against reperfusion induced intercellular gap formation in a cellular model of ischemia and reperfusion

S.A. Kasseckert, H.M. Piper, Y. Abdallah. *Justus Liebig University, Giessen, Germany*

Ischemia and reperfusion provokes barrier failure of the coronary microvasculature through activation of the endothelial contractile machinery and formation of intercellular gaps, leading to myocardial edema development that jeopardizes functional recovery of the heart. In vivo studies have shown that cannabinoid receptor (CBR) activation protects reperfused hearts against reperfusion injury.
The aim of the present study is to investigate whether CBR activation with the nonspecific CBR agonist R1-Methanandamide (R1M, 10μM) can protect coronary endothelium against reperfusion induced intercellular gap formation.
Cultured rat coronary endothelial monolayers were subjected to conditions of simulated ischemia (ANoxia 40min; pH6.4; no glucose) and reperfusion (NORMoxia 40min; pH7.4; with glucose). Stimulation of cannabinoid receptors during reperfusion significantly reduced reperfusion-induced intercellular gap formation (gaps[a.U.]:control:283±21; R1M:172±10*; n=12-16; *$p<0.05$ vs. control). CB1 receptor blocking with AM251 [250nM] during reperfusion and R1M application completely abolished the R1M mediated protection (gaps[a.U.]: R1M+AM251: 269±32#; n=10; #$p<0.05$ vs. R1M). Whereas the protective effect of R1M application during reperfusion could be further enhanced if AM630 [300nM], a CB2 receptor antagonist, was added to the reperfusion medium simultaneously to R1M application (gaps[a.U.]: R1M+AM630:132±23#; n=12; #$p<0.05$ vs. R1M). Inhibition of nitric oxide synthases (NOS) through application of L-NAME [200μM] during reperfusion significantly blunts the protection against reperfusion induced gap formation (gaps[a.U.]:control:305±29; R1M:221±21*; R1M+L-NAME:270±27#; n=6-8; *$p<0.05$ vs. control; #$p<0.05$ vs. R1M).
In conclusion, activation of endothelial cannabinoid receptors protects the coronary endothelium against reperfusion-induced gap formation. This protection is mediated through CB1 receptor mediated NOS activation, whereas simultaneous CB2 receptor activation diminishes this protective effect.

P1395 Ketamine dose-dependently interferes with diazoxide and anaesthetic pre- and postconditioning elicited cardioprotection

D. Muntean, G. Gheorghiu, V. Ordodi, N. Mirica, C. Hentia, A. Raducan, O. Duicu, O. Bedreag, M. Papurica, D. Sandesc. *University of Medicine and Pharmacy, Timisoara, Romania*

Pharmacological pre- and postconditioning confer potent cardioprotection against ischaemia-reperfusion injury. Ketamine is currently used in experimental settings, albeit it has been reported to block protection elicited by ischaemic preconditioning. The present study was designed to investigate the effects of high (80 mg/kg, H-Keta) vs. low (20 mg/kg, L-Keta) dose of ketamine on cardioprotection elicited by pre- and postconditioning with: (i) volatile anaesthetics, isoflurane (Iso) or sevoflurane (Sevo), 1 MAC each, and (ii) diazoxide (Dx, 10 mg/kg). To this aim ketamine (either H or L dose) and xylazine (5 mg/kg) anaesthetized rats (n = 6-8/group) subjected to 30 min of regional ischaemia and 120 min reperfusion were randomized to receive: (i) no additional intervention (Ctrl); (ii) Iso preconditioning (Iso Prec) achieved by 3 episodes of 5 min Iso interspersed with 10 min washout; (iii) Iso postconditioning (Iso Post) achieved by 5 min of volatile agent administration (3 min before and 2 min after reperfusion); (iv) Sevo preconditioning (Sevo Prec) achieved by 2 episodes of 5 min Sevo administration each followed by 10 min of washout; (v) Sevo postconditioning (Sevo Post) according to the same protocol as for Iso Post; (vi) diazoxide preconditioning (Dx Pre) and (vii) diazoxide postconditioning (Dx Post) with the drug given IV 10 min before the index ischaemia and at reperfusion, respectively. Myocardial infarct size (IS) was determined by tetrazolium staining and was expressed as percent of the area at risk. In the presence of H-Keta both Iso Pre and Sevo Pre protocols significantly reduced infarct size (25±7% and 28±5%; mean ± SE) albeit to a lesser degree than in animals anaesthetized with L-Keta (19±7% and 24±6%) vs. control (51±8%; $p < 0.05$). Protection was lost for the postconditioning protocols with both volatile agents (43±8% and 47±10%) in animals anaesthetized with H-Keta, but was restored when L-Keta was used (28±8% and 31±4%; $p < 0.05$ vs. Control) for Iso Post and Sevo Post, respectively. Similarly, H-Keta but not L-Keta anaesthetic regimen abolished Dx protection against necrosis (IS of 46±12% and 32±4%, respectively) in the preconditioning groups (Dx Pre). When given at reperfusion Dx was not associated with anti-infarct protection, regardless of the dose of ketamine used (IS of 46±10% for H-Keta and 42±12% for L-Keta, respectively). In the in vivo rat model of regional ischaemia-reperfusion injury, high- but not low-dose ketamine abolished cardioprotection associated with anaesthetic postconditioning and diazoxide preconditioning.

P1396 Depletion of extracellular rna reduces vascular permeability, edema formation and myocardial infarction size

P. Stieger[1], M. Grebe[1], S. Fischer[2], K.T. Preissner[2], H. Tillmanns[1], D. Sedding[3]. *[1]Dept. of Cardiology, Giessen University, Giessen, Germany; [2]Dept. of Biochemistry, Giessen University, Giessen, Germany; [3]Universitaetsklinikum Giessen und Marburg GmbH, Giessen, Germany*

Background: Cell injury due to myocardial infarction (MI) leads to the release of intracellular material and is associated with increased endothelial cell (EC)-permeability and edema formation in the vicinity of the damage, a process that contributes to tissue injury throughout the ventricle. We previously demonstrated that endogenous RNA, released during tissue injury, dramatically augments vascular endothelial growth factor (VEGF)-dependent EC-permeability. In the present study we evaluated the impact of extracellular RNA on edema formation and tissue injury in vivo after induction of MI in mice.
Methods and Results: The left coronary artery (LAD) of C57/Bl 6 was ligated and RNase (100 or 250μg) or control buffer was administered intravenously 30 min, 3 and 6 hours following LAD ligation. Wet and dry weight of heart slices were measured for analysis of myocardial edema, and evans blue dye and tetrazolium were used to delineate the area at risk and infarction size within the myocardium 24h after ligation. Cardiac function as measured by fractional shortening was assessed by echocardiography. Plasma RNA concentration was significantly increased following MI, however, administration of RNAse prevented the MI-induced increase of extracellular RNA levels. Importantly, RNAse had no effect on blood pressure, total plasma protein or albumin levels, peripheral blood cell counts or glucose levels. RNAse treatment dose-dependently and significantly prevented MI-induced edema formation as measured by wet/dry ratio (250μg: 3.73±0.08 vs. 4.58. ± 0.32; n=8; $P<0.01$). Despite similar risk zone sizes, the infarction size was significantly smaller in RNAse treated mice (49±9% vs. 68±17%; n=8; $P<0.05$). Moreover, Fractional shortening analysis determined by echocardiography revealed a significantly enhanced myocardial contractility in RNAse treated mice (25.3±2.6% vs. 13.8±2.6%; n=8; $P<0.05$). Furthermore, application of RNAse resulted in a significantly increased survival rate of mice 10 weeks following MI.
Conclusion: These results identify extracellular RNA as a novel endogenous permeability factor which augments ischemia-induced edema formation and thus myocardial infarction size. Moreover, depletion of extracellular RNA by RNase treatment may serve as a novel vessel-protective modality, preventing MI-induced edema formation and tissue injury.

P1397 Ivabradine reduces heart rate without affecting metabolic fluxes of normoxic working hearts

B. Lauzier[1], F. Vaillant[1], B. Bouchard[1], E. Thorin[1], P. Gluais[2], J. Roussel[2], J.C. Tardif[1], C. Desrosiers[1]. [1]*Montreal Heart Institute, Montreal, Canada;* [2]*International Research Institute Servier, Courbevoie, France*

Background: Heart rate reduction (HRR) is an important target in the management of patients with chronic stable angina. Many of the currently available drugs for HRR have additional effects, which include energy metabolic alterations that may eventually adversely affect cardiac function. Ivabradine (IVA) is the first clinically available agent from a new class of drugs called If inhibitors, which selectively inhibit the major pacemaker current in the sinoatrial node and lead to HRR. However, its impact on cardiac energy metabolism has not been assessed. This study aimed at testing whether HRR by IVA alters substrate fluxes through energy producing pathways.
Methods: Using our established ex vivo working heart model and 13C-methodology, we assessed the metabolic and functional phenotype of 12-week-old mouse (C57bl/6) hearts perfused under normoxia with physiological concentrations of carbohydrates (CHO) and fatty acid in the absence (ctrl; n=10) or in the presence of 3 μM IVA (n=10). Other hearts were perfused with 3 μM IVA and subjected to atrial pacing to match the HR of controls (n=10). Hemodynamic (HR, cardiac flows, developed left ventricular pressure) and biochemical (oxygen consumption, membrane integrity) parameters were monitored continuously and hearts were freeze-clamped for determination of metabolic flux parameters.
Results: Addition of IVA significantly reduced the HR of perfused working hearts by 35.6±4.8% and increased stroke volume by 18±7% ($p<0.05$); other measured functional parameters were not significantly affected, including cardiac flows, power (IVA: 6.6±0.8 vs. ctrl: 6.36±1.1 mWatts gww^{-1}) and efficiency (IVA: 1.3±0.1 vs. ctrl: 1.2±0.1 mWatts μmolO2-1 min^{-1}). Hearts perfused with IVA and paced displayed parameters that were similar to controls. At the metabolic level, hearts perfused with IVA with or without pacing displayed values that were similar to controls for flux parameters relevant to mitochondrial energy production via the Krebs cycle, which include substrate selection for energy production, as well CHO partitioning between oxidation (i.e. energy; 90±1%) vs. anaplerosis (i.e. re-fueling of catalytic carbons; 10±1%).
Conclusion: Acute administration of IVA to isolated normal working hearts selectively reduces HR without affecting substrate fluxes through energy producing pathways, a determinant factor of cardiac function and disease progression. These results emphasize the selective action of IVA and provide the impetus for testing the impact of HRR by IVA in models of cardiomyopathy that display energy metabolic alterations.

P1398 PPARgamma or PPARbeta/delta activation reduces insulin responsiveness in cultured cardiomyocytes

C.H. Montessuit, I. Papageorgiou, R. Lerch. *Division of Cardiology, Geneva, Switzerland*

Insulin resistance is the failure of insulin to stimulate the transport of glucose into its target cells. A highly regulatable supply of glucose is important for cardiomyocytes to cope with situations of metabolic stress. Metabolic stress stimulates glucose uptake in cardiomyocytes by a mechanism that shares final steps with insulin stimulation: phosphorylation of AS160 and translocation of the glucose transporter GLUT4. PPARα agonists are used to reduce the dyslipidemia leading to insulin resistance; PPARβ/δ agonists have similar therapeutic potential. The direct influence of PPARα or β/δ agonists on insulin- or metabolic stress-stimulated glucose transport in cardiomyocytes is unknown. We measured basal and stimulated glucose uptake in cardiomyocytes exposed for 7 days to the selective PPARα agonist GW7647, the selective PPARβ/δ agonist GW0742 or 9-cis retinoic acid (RA). 9-cisRA is an agonist of the nuclear receptor RXR, thus activating all PPAR/RXR complexes. No agonist significantly influenced basal glucose uptake. Insulin-stimulated glucose uptake was markedly increased in cardiomyocytes exposed to 9-cis RA. In contrast, in cardiomyocytes exposed to GW7647 or GW0742, insulin-stimulated glucose uptake was significantly reduced.
Unlike insulin-stimulated glucose uptake, glucose uptake stimulated by metabolic stress (oligomycin) was unaffected by PPARα or β/δ agonists, thus suggesting that PPARα or β/δ agonists impact on mechanisms specifically triggered by insulin. The phosphorylation in response to insulin of the insulin receptor β subunit and of the downstream signaling protein Akt was modestly reduced in cardiomyocytes exposedto PPARα or β/δ agonists. The phosphorylation of AS160 downstream of Akt was however unaffected.
PPARα or β/δ activation is known to stimulate fatty acid oxidation in cardiomyocytes, which could explain the reduction of insulin-stimulated glucose uptake. This interpretation is however unlikely because 1. 9-cis RA, which stimulates glucose uptake, increased fatty acid oxidation to the same extent as PPARα or β/δ agonists and 2. Inclusion of fatty acids (0.4 mM) in the culture medium, which also stimulates fatty acid oxidation, only minimally reduced insulin-stimulated glucose uptake, but markedly reduced oligomycin-stimulated glucose uptake.
In conclusion, direct PPARα or β/δ activation in cardiomyocytes results in compromised insulin responsiveness with preserved glucose uptake in response to metabolic stress. The reduced insulin-stimulated glucose uptake is seemingly unrelated to increased fatty acid oxidation.

P1399 Des-acyl ghrelin has similar anti-apoptotic and more beneficial metabolic effects than ghrelin in cardiomyocytes

P.V. Lear, M.J. Iglesias, D. Rodriguez-Penas, S. Feijoo-Bandin, J.R. Gonzalez-Juanatey, M.F. Lago. *Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, Spain*

Purpose: Des-acyl ghrelin (DAG) is an isoform of the peptide ghrelin which circulates at plasma levels up to 10-fold higher than ghrelin and has recently been shown to have several non-endocrine actions similar to ghrelin, including cardiovascular effects. The aims of our study were to investigate whether in cardiomyocytes DAG can regulate cell viability, and whether ghrelin and/or DAG may play a role in metabolite uptake.
Methods and Results: DAG, like ghrelin, was able to prevent apoptosis in HL-1 cardiomyocytes previously induced by treatment with cytosine arabinoside, and analysed using Hoechst vital dye staining (7.12±0.86% of cells after DAG pre-treatment, compared with 12.83±0.79% of cells without pre-treatment ($p<0.01$, n=3). Also similar to ghrelin, DAG did not affect HL-1 cardiomyocyte metabolic activity as indicated by MTT. DAG treatment did however significantly increase fatty acid uptake of +30±6% vs untreated cells ($p<0.05$, n=5; indicated by BODIPY-induced fluorescence intensity), while co-treatment with ghrelin prevented this stimulatory effect of DAG in HL-1 cardiomyocytes. Conversely, ghrelin inhibited the increase in glucose uptake normally induced by insulin (shown by the rate of incorporation of 2-[3H]deoxy-D-glucose), thus, glucose uptake levels only increased by 18±11% when cells were pre-treated with ghrelin prior to 100nM insulin administration, vs 47±12% for insulin-only controls ($p<0.01$; n=5). DAG lacked this effect and was also able to reverse the inhibitory effect of ghrelin on insulin-induced glucose uptake. Several studies in cardiomyocytes have shown that Akt, a serine-threonine kinase, is activated by insulin and inhibited by the phosphatase PTEN. Western blots showed that the antagonistic effects of ghrelin and DAG on glucose uptake were not mediated by PTEN or Akt. Real-time PCR indicated that expression levels of ghrelin O-acyltransferase (GOAT) RNA (the enzyme responsible for the acylation of DAG at serine position 3 to produce ghrelin) were comparable between HL-1 cells, human myocardial tissue, and stomach tissue (the main site of production) obtained from both humans and mice.
Conclusions: In HL-1 cardiomyocytes, DAG shares with ghrelin a protective effect against the apoptosis induced by the cardiotoxic drug AraC. With respect to metabolism, DAG counteracts the negative effect of ghrelin on insulin-induced glucose uptake, and stimulates long-chain fatty acid uptake. Our study re-emphasises the continuing necessity to elucidate many of the often subtle mechanisms by which ghrelin and DAG interact and regulate each other in cardiovascular function and dysfunction.

P1400 Diabetic and non-diabetic patients express similar adipose tissue adipokine levels

E. Teijeira Fernandez, S. Eiras, L. Grigorian Shamagian, A. Salgado Somoza, J.M. Martinez Comendador, J.R. Gonzalez-Juanatey. *Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, Spain*

Objective: Epicardial (EAT) and subcutaneous (SAT) adipose tissues produce a pathogenic profile of adipokines. Hypoadiponectinemia and hyperleptinemia are associated with an increased risk of diabetes (DM) and other related conditions.

Abstract P1400 – Table 1. Comparison between DM and non-DM patients

		Male						Female					
		Non-CAD			CAD			Non-CAD			CAD		
		N	Mean (SD)	P	N	Mean (SD)	P	N	Mean (SD)	P	N	Mean (SD)	P
EAT mRNA adiponectin (a.u.)	Non-DM	20	15.5 (3.1)	0.98	33	13.9 (3.9)	0.23	15	15.1 (3.3)	0.19	7	14.7 (2.2)	0.47
	DM	8	15.5 (3.1)		21	12.5 (3.9)		5	18.1 (6.6)		11	15.7 (3.1)	
SAT mRNA adiponectin (a.u.)	Non-DM	18	16.2 (4.0)	0.92	22	14.3 (4.1)	0.93	7	16.6 (1.9)	0.11	7	13.8 (3.8)	0.57
	DM	5	16.3 (1.8)		18	14.4 (4.9)		5	20.2 (5.3)		6	15.0 (3.7)	
			Mean rank			Mean rank			Mean rank			Mean rank	
EAT mRNA leptin (a.u.)	Non-DM	20	14.7	0.88	33	28.7	0.47	14	9.6	0.64	7	9.1	0.82
	DM	8	14.1		21	25.6		5	11.0		11	9.7	
SAT mRNA leptin (a.u.)	Non-DM	17	11.4	0.91	21	20.9	0.59	6	5.8	0.86	7	6.1	0.23
	DM	5	11.8		18	18.9		5	6.2		7	8.9	

However, EAT and SAT adiponectin and leptin levels in DM patients remain still unknown.
Material and methods: We collected samples of EAT from 120 patients and SAT from 88 of the same group of patients undergoing elective cardiac surgery, for coronary artery bypass grafting (n=69) or other surgical procedures (n=51). Adiponectin and leptin expression levels were analyzed by real time reverse transcription PCR.
Results: 45 DM and 75 non-DM subjects were included. Mean (SD) age was 70.1 (7.8) years. Adipokine expression levels were similar in both groups (EAT adiponectin 14.4 (4.3) vs. 14.6 (3.4) arbitrary units (a.u.) respectively, P=0.79; SAT adiponectin 15.6 (4.7) vs. 15.1 (3.9), P=0.54; EAT leptin 9.3 (interquartile range 2.5) vs. 9.5 (1.9) a.u., P=0.72; SAT leptin 9.9 (interquartile range 3.6) vs. 10.0 (2.5) a.u., P=0.96). These findings persisted after stratification for sex and coronary artery disease. Further comparisons based on treatment with statins or oral antidiabetic drugs did not show significant differences in adipokines expression.
Conclusions: DM and non-DM subjects express similar EAT and SAT adiponectin and leptin levels. Counter-regulatory mechanisms of adipokines expression in patients with established diabetes may account for these findings.

P1401 Feasibility of clinical 1,5T MRI scanners in murine cardiac examination

J.G.J. Voelkl, B.J. Haubner, C. Kremser, A. Mayr, K. Pedarnig, N. Malicki, K. Enthofer, O. Pachinger, B. Metzler. *Innsbruck Medical University, Innsbruck, Austria*

Background: Mouse models are widely used in research of cardiac pathologies. Still, the acquisition of in vivo functional cardiac parameters in small rodents requires specialized equipment not widely available. Therefore, we tested the feasibility of a standard clinical 1,5T MRI scanner on mice compared with echocardiography. Moreover, we determined quantification of infarct size evaluated by late gadolinium enhancement (LGE) in comparison with histological methods.
Methods: Mice subjected to ischemia/reperfusion procedure were randomized in groups of 0min (n=5), 30min (n=5) and 60min (n=5) of ischemia followed by Troponin T measurement. LGE using an adapted PSIR sequence (preoperative, 24h and 1week postoperative) facilitated the determination of in vivo infarct sizes. Acquired MRI infarction data were compared to TroponinT values and histological sizes of infarction. In addition, fractional shortening (FS) measured with echocardiography was matched to fractional area change (FAC) assessed with CINE MRI: preoperative, 24 hours postoperative, and 1week postoperative.
Results: In order to characterize interobserver variability, LGE determined infarctions were measured by three blinded investigators. Correlation analysis revealed a highly significant similarity among these observers (O) (O1:O2 r=0,98, O1:O3 r=0,97, O2:O3 r=0,95, all $p \leq 0{,}001$). Infarct size measured through adapted PSIR sequence markedly correlated with histological infarct sizes (O1: r=0,97 $p \leq 0{,}001$) and Troponin levels (O1: r=0,93 $p \leq 0{,}001$). In addition, CINE imaging (FAC) and echocardiography (FS) correlated at all examinations significantly (preoperative r=0,61 p=0,036, 24 hours r=0,61 p=0,02, and 1 week r=0,7 p=0,036). Impairment of left ventricular function measured by CINE MRI significantly associated with histological infarction size (1W r= -0,94 $p \leq 0{,}001$), Troponin T levels (1W r= -0,95 $P \leq 0{,}001$) and LGE measured infarct size (O1:1W r= -0,093 $p \leq 0{,}001$).
Conclusion: Here we demonstrate for the first time that routine clinical MRI scanners (1,5T) enables accurate quantification of in vivo infarction areas in mice and correlates very well with echocardiographic measurements. Furthermore, CINE imaging greatly improves the quality of cardiac functional assessment in our mouse model providing exact measurements and detailed anatomical information.

SIGNALLING PATHWAYS IN CARDIAC GROWTH AND DEATH

P1402 The impact of MKK7 on cardiac stress adaptation

B.J. Haubner[1], G. Neely[2], J.G.J. Voelkl[1], N. Malicki[1], K. Enthofer[1], O. Pachinger[1], J.M. Penninger[2], B. Metzler[1]. *[1]Innsbruck Medical University, Innsbruck, Austria; [2]IMBA, Vienna, Austria*

Background: Mitogen-activated protein kinase kinase 7 (MKK7) phosphorylates and thereby activates the crucial c-Jun N-terminal kinases (JNKs) in cardiomyocytes. This highly conserved pathway is suggested to be involved in a broad range of physiological functions, including cardiovascular homeostasis. The precise in vivo cardiac role of MKK7 using muscle-restricted MKK7 knock-out (KO) rodents remained unclear.
Methods: Therefore, mice carrying a conditional MKK7 gene were generated. Crossbreeding with Mck-Cre positive rodents assured a muscle-restricted MKK7 knock-out (KO) model. We used cardiovascular magnetic resonance, echocardiography and histological methods to characterize the transgenic phenotype. In addition, the transaortic constriction procedure facilitated the examination of mutagenic hearts upon cardiac stress.
Results: At the age of 8 weeks, MKK7 KO hearts presented a markedly decreased contractility compared to WT mice (fractional shortening: KO 30,8±2,1 vs. WT 44,3±3,0%; p=0,001; n=9 per group). This was further combined with a significant left ventricular dilatation, independent of the cardiac cycle.
Upon 7 days of transaortic constriction, MKK7 KO mice but not WT rodents developed heart failure with a marked increase of the left ventricular systolic and diastolic diameter (LVESD, KO 3,1±0,2 vs. WT 1,4±0,1 mm; p=0,001; LVEDD, KO 4,2±0,2 vs. WT 2,8±0,2 mm; p=0,001; n=7 per group). Whereas the WT cohort slightly gained contractility, the function of KO hearts further significantly deteriorated after constriction of the aorta.
Moreover, histological analysis revealed a dilated phenotype following 7 days of pressure overload.
Conclusion: Our in vivo data demonstrate for the first time, that the muscle-restricted loss of MKK7 leads to a significant reduction of cardiac functions and heart failure upon cardiac pressure overload, respectively. This implies a distinct role of MKK7 in cardiac stress adaptation.

P1403 KMUP-1 attenuates cardiac hypertrophy in rats with isoproterenol-induced cardiac hypertrophy

J.H. Hsu[1], J.L. Yeh[2], I.J. Chen[2], Z.K. Dai[1], J.R. Wu[3]. *[1]Dept. of Pediatrics and Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Dept. of Pharmacology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Dept. of Pediatrics, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan*

Purpose: To determine whether KMUP-1, a novel xanthine-based derivative, attenuates cardiac hypertrophy in rats with isoproterenol-induced cardiac hypertrophy, and if so, whether the antihypertrophic effect is mediated by the nitric oxide pathway.
Methods: Cardiac hypertrophy was induced by daily intraperitoneal injection of isoproterenol for 10 days in male Wistar rats. In the treatment group, KMUP-1 was administered one hour before each dose of isoproterenol. After 10 days, all rats were sacrificed and the effects of KMUP-1 on survival and cardiac hypertrophy were evaluated. In addition, the effects of KMUP-1 on the NO/cGMP/PKG pathway and hypertrophy signaling pathways (calcineurin A and ERK1/2) were also examined. To further investigate the role of nitric oxide synthase (NOS) in the effects of KMUP-1, a NOS inhibitor, N-omega-nitro-L-arginine (L-NNA) was administered along with KMUP-1.
Results: KMUP-1 attenuated the cardiac hypertrophy and fibrosis, improved the survival of rats with isoproterenol-induced hypertrophy. Plasma NOx (nitrite and nitrate) and cardiac eNOS, cGMP and PKG were all increased by KMUP-1. The activation of hypertrophic signalling by calcineurin A and ERK/1/2 in isoproterenol-treated rats were also attenuated by KMUP-1. All these effects of KMUP-1 were blunted by simultaneous administration of L-NNA.
Conclusions: KMUP-1 attenuates cardiac hypertrophy in rats with isoproterenol-induced cardiac hypertrophy. These effects are mediated, at least in part, by NOS activation. This novel agent targeting the NO/cGMP pathway has a potential role in the prevention of cardiac hypertrophy.

P1404 ANT1-overexpression compensates TGFbeta induced apoptosis via stabilization of the mitochondrial permeability transition pore

J. Heger[1], Y. Abdallah[1], T. Shahzad[1], G. Euler[1], H.M. Piper[1], A. Doerner[2]. *[1]Justus-Liebig University, Giessen, Germany; [2]Charite - Campus Benjamin Franklin, Berlin, Germany*

Adenine nucleotide translocator (ANT) is a protein complex in the inner membrane of mitochondria and part of the mitochondrial permeability transition pore (MPTP). It was shown that in renin-overexpressing rats ANT1 overexpression works against development of apoptosis. The question arises whether ANT1 overexpression also protects cardiomyocytes against other apoptosis inducing stimuli and whether MPTPs are involved.
To answer this question we performed studies on isolated ventricular cardiomyocytes of WT and ANT1 rats under apoptosis inducing conditions with TGFβ1 (1 ng/ml). Incubation of cardiomyocytes with TGFβ1 enhanced the number of apoptotic cells in WT from 8.8±1.9% to 13.3±2.9% (n=20, $p<0.01$) whereas cardiomyocytes of ANT1 rats did not show a significant increase in apoptosis (from 8.5±1.7% to 11.1±2.2%; n=20). BAX expression was already decreased under basal conditions in ANT1 rats (100.4±16.8% vs. 65.2±5.0%; n=8-12). Under stimulation with TGFβ1 bax expression increased in WT to 144.7±16.8%, whereas in ANT1 cardiomyocytes bax expression decreased to 52.0±7.7% ($p<0.01$; n=8-9). To analyze the involvement of MPTPs, mitochondrial calcein loss was measured by the use of calcein/cobalt method and membrane potential $\Delta\psi$ by JC-1. After treatment of WT cells with ionomycin (5 μM) a marked loss of calcein fluorescence about 40% occurred after five minutes indicating the opening of MPTP. In cardiomyocytes of ANT1 rats drop in calcein fluorescence due to ionomycin was significantly reduced. When cardiomyocytes were incubated with TGFβ1 membrane potential in WT cardiomyocytes declined by 18.0±3.7% after 60 minutes. The decline in membrane potential in ANT1 rats under TGFβ1 was only 7.2±2.8% ($p<0.05$; WT n=25, ANT1 n=18). This drop in JC-1 fluorescence could be blocked when WT cells were incubated prior to TGFβ1 stimulation with cyclosporine A (200 μM), an inhibitor of MPTPs (90.7±1.5%). This indicates that the decrease in JC-1 fluorescence after TGFβ1 stimulation is due to MPTP opening.

Conclusion: ANT1 overexpressing adult cardiomyocytes are protected against TGFβ1 triggered apoptosis because of reduced MPTP opening and decreased bax expression.

P1405 Myocyte stress 1 plays an important role in hypertrophy and cardioprotection via a MRTF/SRF signalling pathway

A.L. Koekemoer, N.W. Chong, A.H. Goodall, N.J. Samani. *University of Leicester, Leicester, United Kingdom*

Background: We have previously identified and characterised a novel gene, designated myocyte stress 1 (ms1), which is up-regulated within 1 hour in the left ventricle following aortic banding in the rat, suggesting a possible role for ms1 in the initial signalling of the hypertrophic response. ms1 is also expressed during cardiac development and is transiently up-regulated during ischaemia-reperfusion in vitro. This suggests that ms1 may play a more widespread role in cardiac physiology. This is further supported by findings showing that ms1 can stimulate serum response factor (SRF) dependent transcription by inducing the nuclear accumulation of myocardin-related transcription factors (MRTFs) A and B through a mechanism dependent on RhoA and actin polymerisation. The aim of this study was to directly determine whether ms1 induces cardiac cell hypertrophy and protects such cells against apoptosis.
Methods: ms1 was transiently over-expressed in a heart-derived rat cell line, H9c2, by plasmid transfection. Empty vector transfection was used as a control. We examined the effect of ms1 over-expression on cell size, proliferation and ability to protect against staurosporine-induced apoptotic cell death. In addition, to identify putative target genes and downstream pathways to ms1, altered gene expression following ms1 over-expression was examined.
Results: Transient over-expression of ms1 in H9c2 altered expression of known hypertrophic and cardioprotective target genes of the MRTF/SRF transcriptional pathway (cardiac α-actin, brain natriuretic peptide (BNP), interleukin-6 (IL-6), leukemia inhibitory factor (LIF), apoptosis repressor with caspase recruitment domain (ARC) and adrenomedullin). The size of cells over-expressing ms1 was significantly increased by an average of 47% when compared to empty vector control ($P < 0.01$) and over-expression of ms1 markedly inhibited staurosporine-induced apoptosis by approximately 89%, $P < 0.01$ (ms1 transfected cells, 3.5% ± 1.0% versus empty vector control, 32.4% ± 3.8%).
Conclusions: These findings suggest that ms1 induces a hypertrophic response and provides cardioprotection possibly via a MRTF-SRF signalling mechanism. The findings provide for the first time direct evidence of the involvement of ms1 in hypertrophy and cardioprotection.

P1406 The role of bone marrow derived stem cells in a mouse model of hypertrophy

S. Voss[1], H.M. Nef[1], C. Troidl[2], M. Rauch[1], S. Kostin[2], C. Hamm[1], A. Elsaesser[1], J. Rixe[1], A. Rolf[1], H. Moellmann[1]. *[1]Kerckhoff Klinik GmbH, Bad Nauheim, Germany; [2]Max-Planck-Institut fuer Herz und Lungenforschung, Bad Nauheim, Germany*

Background: Bone marrow derived stem cells (BMCs) contribute to cardiac remodelling after myocardial infarction and play a role in scar formation by means of transdifferentiation in different cell types. The involvement of BMCs in cardiac hypertrophy is yet only marginally investigated. Therefore, the aim of our study was to investigate the potential role of stem cells during remodelling and reverse remodelling processes in hypertrophied myocardium.
Methods: C57BL6/6J mice (n=45) were sublethally irradiated (11 Gy) followed by bone marrow transplantation using eGFP-transgenic donor mice. FACS-analysis served as control of the successful transplantation. Three months later, animals were randomized into 3 groups and pressure overload of the left ventricle (LV) was induced by transverse aortic constriction (TAC). After 8 weeks, hearts were excised (TAC group, n=14). Sham-operated mice served as controls (n=10). In the Debanding group (n=14), the ligature was removed after 8 weeks, and hearts were excised 2 weeks later. LV functional parameters were assessed by echocardiography and magnetic resonance imaging before TAC surgery, after 8 weeks and 2 weeks after Debanding, respectively. Morphological analysis was performed using immunohistochemistry.
Results: Successful bone marrow transplantation was confirmed by FACS-analysis of the peripheral blood. All animals with TAC developed a cardiac hypertrophy with significantly impaired LV function (EF: 59.9±3.4% vs. 77.3±1.5%, $p<0.001$) and an increased myocyte diameter (31.2±1.0μm vs. 20.7±0.7μm, $p<0.001$). Co-staining of eGFP+ cells with CD31 and vimentin revealed a transdifferentiation of BMCs in endothelial cells and fibroblasts. However, no differences could be detected between sham-operated animals and TAC-mice. 8 weeks after TAC, scattered eGFP+ cardiomyocytes and dedifferentiated α-smooth muscle actin-positive cardiomyocytes were found. The number of eGFP+ cells in the myocardium was unchanged after TAC, compared to controls (5.8±1.0/mm^2 vs. 5.0±1.2/mm^2, p=n.s.). After Debanding, myocyte diameter significantly decreased and functional parameters improved in terms of a reverse remodelling. During those reverse remodelling processes, no increase of eGFP+ cells was detected in the myocardium. A relevant differentiation of BMCs into cardiomyocytes, smooth muscle cells or myofibroblasts could be excluded in all groups.
Conclusion: The development of cardiac hypertrophy is not accompanied by an enhanced migration of BMCs into the myocardium. Furthermore, BMCs do not contribute significantly to reverse remodelling processes after LV pressure release.

P1407 Transcription factor farnesoid X receptor is expressed in rat cardiomyocytes and regulates cardiomyocytes apoptosis through a mitochondria-dependent pathway

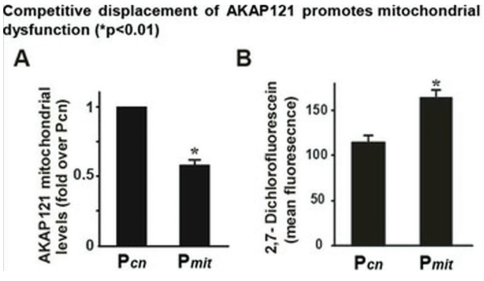
J. Pu, B. He, P. Shan, A. Yuan, L. Shen, L. Shen, L. Jiang. *Shanghai Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, People's Republic of*

Background: Farnesoid X receptor (FXR) is a recently discovered member of the nuclear hormone receptor superfamily. FXR is abundantly expressed in the liver and digestive tract, where they regulate the homeostasis of bile acids. FXR is also found in numerous other tissues not classically considered as being bile acid targets. Until now, the possible function of this receptor in cardiomyocytes has never been investigated.
Methods and Results: In this study, we showed for the first time that FXR was expressed in rat primary cultured cardiomyocytes as well as H9c2 rat ventricular cells. Treatment of rat cardiomyocytes with natural and synthetic agonists of FXR, chenodeoxycholic acid and GW4064 respectively, led to apoptosis, as evidenced by the morphological characteristics of nuclear condensation as well as in situ nick end-labeling (TUNEL). The induction of apoptosis by GW4064 could be antagonized by treatment with the FXR antagonist guggulsterone or through inhibition of FXR expression by short interfering RNA. Moreover, FXR activation by GW4064 induced a reduction in adenosine 5'-triphosphate content, a loss of mitochondrial membrane potential, cytochrome c release from the mitochondria into the cytosol, and caspase-3 activation in rat cardiomyocytes.
Conclusion: These results suggest that transcription factor FXR is functionally expressed in rat cardiomyocytes and that the receptor may serve as a novel molecular target for manipulating cardiomyocyte apoptosis.

P1408 AKAP121 controls mitochondrial function and survival of cardiomyocytes

G.G. Schiattarella, C. Perrino, G. Gargiulo, G. Pironti, A. Feliciello, M. Saviano, L. Zaccaro, R. Guerriero, G. Esposito, M. Chiariello. *Azienda Ospedaliera Universitaria Federico II, Naples, Italy*

cAMP signals are received and integrated by a family of scaffold proteins (A Kinase Anchor Proteins, AKAPs) that tether cAMP-dependent Protein Kinase A (PKA) to discrete cellular locations. AKAP121 transmits cAMP signals to the mitochondria. In cardiomyocytes, AKAP121 levels are regulated by cAMP levels. In response to pressure overload, cardiac AKAP121 levels were significantly reduced, and this was associated with impaired mitochondrial function, increased reactive oxygen species (ROS) and heightened rates of apoptosis. To precisely determine the effects of dampened mitochondrial cAMP signalling in cardiomyocytes, we synthesized soluble peptides containing AKAP121 mitochondrial anchoring domain but lacking the binding site for PKA (Pmit), in order to competitively displace AKAP121 from mitochondria (Figure, panel A). Control peptides (Pcn) having the same aminoacid sequence of Pmit, but in random sequence were also synthesized and assayed. The cell permeability of these peptides was tested by confocal microscopy studies using peptides Pmit and Pcn coniugated with fluorescein. In contrast to Pcn peptides, after 24 h incubation Pmit peptides induced mitochondrial damage (Figure, panel B), increased mitochondrial ROS and induced DNA damage and apoptosis in rat cardiomyocytes. Importantly, in vivo administration of Pmit peptides increased mitochondrial ROS in the absence of any other pathological stimuli.



These data suggest that AKAP121 is an important regulator of mitochondrial function and cell survival, and therefore reduced mitochondrial cAMP signaling in response to pressure overload might represent an early molecular event linked to heart failure.

P1409 Effects of simvastatin on cellular hypertrophy in adult cardiomyocytes in long-term culture

L. Guzun[1], V. Ivanov[2], I. Popovich[2], N. Ciobanu[2], M. Popovich[2], S. Kostin[3]. [1]*CFR Clinic, Brasov, Romania;* [2]*Institute of Cardiology, Chisinau, Moldova, Republic of;* [3]*Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany*

Background: Statins are widely used clinical drugs that beyond lipid-lowering have been shown to exert beneficial effects on cardiac hypertrophy and myocardial remodeling. Most of the in vitro studies which demonstrated anti-hypertrophic and cytoprotective effects of statins have used neonatal cardiomyocytes or freshly isolated adult cardiomyocytes. However, their characteristics differ from that of remodeling cardiomyocytes in long-term in culture. These cells in culture undergo de- and redifferentiation processes and show a phenotype similar to cardiomyocytes in failing hearts, i.e. loss of contactile material and a marked hypertrophic response. The aim of the present study, therefore, was to investigate the effects of statins on cell hypertrophy in adult rat cardiomyocytes (ARC) in long-term culture. We also studied the effects of statins on expression levels of p70 S6 kinase which acts downstream of the statins target – protein kinase Akt.
Methods: Enzymatically dissociated ARC were kept in culture for 10 days with 10% fetal calf serum (FCS). Thereafter, ARC were maintained with 2% FCS without (control cultures) or with simvastatin treatment (in the range of 100 nmol/L to 1 μmol/L) for 48 hours. Immunostaining for alpha-actinin, myomesin, F-actin and p70 S6 kinase was analysed by laser confocal microscopy. The cell surface area which is an indicator of hypertrophy was quantified by using Imaris 4.5 (Bitplane) image analysis software.
Results: ARC sizes significantly increased without simvastatin treatment. In contrast, 48 hours of exposure to simvastatin resulted in a marked, dose-dependent decrease in cell size by more than 40% (at 1 μmol/L) and a better organization of sarcomeric cross-striations as compared with control ARC. Quantitative immunoconfocal analysis revelead a progressive augmentation of the fluorescence intensity of p70 S6 kinase in control ARC which was abolished by simvastatin treatment reaching a statistical significance at the dose of 1 μmol/L ($p<0.01$). To specifically address whether the effects of simvastatin is associated with reduced mevalonate levels, ARC were exposed to mevalonate (5 μmol/L) and simvastatin (1 μmol/L). These experiments showed that mevalonate reduced the inhibitory effect of simvastatin on both ARC sizes and expression levels of p70 S6 kinase.
Conclusions: The present study demonstrates for the first time that statins can attenuate cellular hypertrophy in remodelled adult cardiomyocytes in long-term culture and this effect is mediated by a S6 kinase dependent pathway.

P1410 Reverse remodeling of the left ventricle during the early phase after relief of pressure overload in a mouse model

J.L. Bjornstad[1], I. Sjaastad[1], S. Nygard[2], A.V. Finsen[1], A. Hasic[1], H. Attramadal[1], M.S. Ahmed[1], G. Christensen[2], T. Tonnessen[1]. [1]*Oslo University Hospital, Oslo, Norway;* [2]*University of Oslo, Oslo, Norway*

Purpose: Chronic pressure overload due to aortic stenosis (AS) induces concentric myocardial remodeling with hypertrophy, fibrosis and reduced cardiac function. Patients with excessive remodeling carry a particular peri-operative risk when treated with aortic valve replacement (AVR). AVR leads to reverse remodeling, with regression of hypertrophy and fibrosis. The mechanisms regulating reverse remodeling remain unknown. The aim of this study was to study reverse remodeling after relief of pressure overload in a mouse model of aortic banding-debanding and if possible identify mediators regulating the reverse remodeling process.
Methods: A novel mouse model with banding-debanding of the ascending aorta and echocardiographic evaluation up till 14 days after debanding was established. To avoid confounding effects, mice with signs of heart failure were excluded from the study. Myocardial gene expression was examined using Affymetrix microarray 4 weeks following aortic banding and 3 days after debanding. Regulation of functional gene groups was assessed using the topGO software. The findings were verified by RT-PCR. Quantitative measurements of myocardial collagen were performed by HPLC of hydroxyproline and by Western blot analysis of collagen subtypes.
Results: Aortic banding increased left ventricular weight by 44%, with reduction to sham level by 14 days after debanding. The gene ontology group "extracellular matrix structural constituent" and in particular the collagen genes were most significantly regulated following debanding. These genes were up-regulated after aortic banding and reduced back to sham levels 3 days after debanding. Myocardial collagen content was 2.3-fold increased after banding, and remained increased by 1.6-fold and 1.7-fold at 3 days and 7 days following debanding. There was a shift in collagen subtypes from collagen type III following 4 weeks of banding to type I at 3 days and type VIII at 7 days after debanding. Active mediators regulating reverse remodeling were not identified. However, we found that following debanding the balance between pro- and anti-remodeling factors was shifted in favour of anti-remodeling factors.
Conclusions: Regression of extracellular matrix gene expression was the most significant alteration on the gene level during the early phase of reverse remodeling. After debanding, the collagen protein content remained increased, with an isoform shift which might affect the biomechanical properties of the myocardium. Reverse remodeling seems to be regulated by a balance shift favouring anti-remodeling factors.

P1411 Myocardial expression of the E3-ubiquitin ligases MuRF1 and MafBx in patients with recent myocardial infarction

V. Adams[1], V. Conraads[2], S. Moebius-Winkler[1], A. Linke[1], N. Mangner[1], S. Gielen[1], G. Schuler[1]. [1]*Herzzentrum der Universitaet Leipzig, Leipzig, Germany;* [2]*University of Antwerp, Antwerp, Belgium*

Background: Ventricular remodeling following nonfatal myocardial infarction (MI) includes hypertrophy of the surviving myocardium, a process that requires increased protein synthesis and sarcomer assembly. The inhibitory activity of MuRF1/MafBx, both muscle specific E3-ubiquitin-ligase involved in muscle atrophy, in the setting of cardiomyocytes hypertrophy has been demonstrated in cultured cells, but data concerning its expression in human myocardium after MI are not available. Therefore, the aim of the present study was to assess the expression of MuRF-1/MAFbx in patients (pts) early after myocardial infarction (MI) in comparison to a control group (CG).
Methods: Left ventricular myocardial biopsies were obtained in MI pts (retrograde aortic approach, non-infarcted area; n=10) and in CG (during CABG in pts with normal systolic function and left ventricular dimensions; n=5). The myocardial expression of Murf-1/MAFbx was assessed using RT-PCR and Western blot (WB). In addition the expression of troponin I and myosin, targets for MuRF1/MafBx mediated protein degradation, was quantified by WB.

Results

	Control	MI	p-value
MuRF-1 (RT-PCR)	4.87±0.54	2.56±0.38	0.003
MuRF1 (WB)	3.56±0.44	1.27±0.61	0.013
MafBx (RT-PCR)	7.72±0.68	4.77±0.89	0.048
MafBx (WB)	1.58±0.16	0.21±0.08	<0.0001
Troponin I (WB)	0.86±0.04	1.96±0.57	0.044
Myosin (WB)	3.66±0.26	3.17±1.38	0.68

The values are given as mean value ± SEM.

Conclusion: These results demonstrate for the first time, that in myocardial tissue of patients shortly after myocardial infarction the expression of MuRF1 and MafBx, both enzymes which are involved in atrophy, is downregulated. This downregulation might permit hypertrophy, which is supported by the upregulation of troponin I, a component of the contractile apparatus.
Conclusion: These results demonstrate for the first time, that in myocardial tissue of patients shortly after myocardial infarction the expression of MuRF1 and MafBx, both enzymes which are involved in atrophy, is downregulated. This downregulation might permit hypertrophy, which is supported by the upregulation of troponin I, a component of the contractile apparatus.

P1412 The arginine competition: eNOS deficiency and polyamine metabolism

R. Schreckenberg, S. Forst, K.D. Schlueter. *Universitaet Giessen Physiologisches Institut, Giessen, Germany*

Aims: There is upcoming evidence that the lack of an appropriate increase in eNOS activity by induction of eNOS expression induces disease stages under stress even though eNOS expression is sufficient under basal conditions. eNOS heterozygous mice (eNOS+/-) represent a suitable model to prove this finding. Recently it was shown that physical training is sufficient to induce a cardiac phenotype in eNOS+/- mice. As this requires an activation of the sympathetic nervous system that activates ornithine decarboxylase (ODC), the rate limiting enzyme of the polyamine metabolism, we now challenged the hypothesis that ODC activation induces heart disease in eNOS+/- mice due to the competition for arginine required for both pathways.
Methods: We investigated a total of 34 female eNOS+/- mice. Creatinin serum level, heart weight to body weight ratio (HW/BW), and left ventricular expression of fibrotic, apoptotic, hypertrophic markers and calcium handling proteins (quantitative real-time RT-PCR) were determined at the age of 6 months.
Results: 34 eNOS+/- mice were analyzed in this study and subdivided into quartiles in order of their left ventricular ODC expression. ODC mRNA expression of the four groups were 0.67, 1.09, 1.60, and 2.05 arbitrary units (each $p<0.05$). As ODC is known to be regulated exclusively on the mRNA expression level this represents an activation of the polyamine metabolism. We found a positive correlation between the severeness of illness (distress score ranking), and an inverse correlation to body weights. The group with the highest left ventricular ODC expression had the highest HW/BW ratio and the highest lung wet weight (both $p<0.02$ vs. the group with the lowest ODC expression). Positive correlation to ODC expression were also found for elastin, elastin-to-collagen-1 ratio, bax, ANF, and decorin. An inverse correlation was found for the bcl-2-to-bax ratio and NCX expression.
Conclusion: An activation of ODC competes with the NO pathway for arginine. An imbalance between these pathways favouring the polyamine metabolism induces the expression of pro-fibrotic, hypertrophic, and apoptotic pathways. In the absence of only one allele of eNOS this is sufficient to induce a moderate type of heart failure.

P1413 Erythropoietin receptor deficient mice have impaired cardiac adaptation during voluntary exercise

W.T. Ruifrok, A.H. Maass, I. Baudoin, B.D. Westenbrink, A.A. Voors, D.J. Van Veldhuisen, W.H. Van Gilst, R.A. De Boer. *University Medical Center, Groningen, Netherlands*

Objective: recently, we have demonstrated that erythropoietin (EPO) via its receptor (EPO-R) improves cardiac function in experimental heart failure mainly due to its angiogenic effects. Since it is believed that physiological hypertrophy of the heart is accompanied by compensatory angiogenesis, we hypothesised that cardiac EPO signalling influences exercise capacity.
Methods: we employed transgenic-rescued EPO-R-null mutant mice (EPO-R-/-rescued) that express EPO-R exclusively in the hematopoietic cells. These mice have normal development without clear cardiac phenotype. C57Bl/6 mice were used as controls. Both groups were subdued to exercise in a model of voluntary wheel running; mice had unlimited access to a running wheel for 28 days. Furthermore, sedentary mice of both groups were studied. In total 69 mice were analysed. We measured exercise performance: average distance, average daily speed, maximum speed and average running time. At sacrifice heart weight and haemodynamic parameters were measured. Prior to sacrifice we performed echocardiography.
Results: control mice ran 7.8±2.1 km/day, whereas EPO-R-/-rescued mice ran 5.1±2.6 km/day ($P<0.01$). This was due to a lesser average speed (1.59±0.26 km/hrs vs. 1.08±0.31 km/hrs, $P<0.001$) and a reduced average running time (4:42±0:44 hrs vs. 3:51±1:36 hrs, P=NS). In the control group, running increased the heart weight (heart weight-to-body weight ratio: 7.51±1.02 vs. 5.80±0.63 mg/g, $P<0.001$). However, in the EPO-R-/-rescued mice, running did not increase heart weight. Stroke volume as assessed with echocardiography was increased after exercise in the control running mice (74.00±11.98 vs. 62.48±12.93 μl, $P<0.05$), where exercise in the EPO-R-/-rescued mice did not increase stroke volume. Indices of contractility and relaxation were increased after exercise in both the control mice (dPdtmax: 10611±1369 vs. 8969±973 mmHg/s, $P<0.01$; dPdtmin: -10057±867 vs. -8318±1604 mmHg/s, $P<0.05$), as well in the EPO-R-/-rescued mice (dPdtmax: 11081±1491 vs. 8901±1432 mmHg/s, $P<0.05$; dPdtmin: -11122±1656 vs. -8278±1092 mmHg/s, $P<0.001$).
Conclusions: in EPO-R-/-rescued mice, voluntary wheel running lead to improved cardiac function, but it did not lead to hypertrophy and increased stroke volume. This maybe partly explained in difference in voluntary wheel running performance. However, we postulate that EPO signalling is crucial for myocardial adaptation during sustained exercise.

P1414 Overexpression of myocardial CCN2/CTGF prevents heart failure and improves survival after myocardial infartion

J. Gravning, H. Attramadal, V.N. Martinov, M.S. Ahmed. *Rikshospitalet University Hospital, Oslo, Norway*

Background: Myocardial CCN2/CTGF - connective tissue growth factor is robustly induced in experimental and human heart failure (HF). Yet, its role in the pathophysiologic mechanisms of HF remains unresolved.
Methods and Results: To elucidate the role of myocardial CTGF in HF, transgenic mice with cardiac-restricted overexpression of CTGF (Tg-CTGF) were employed and compared with nontransgenic controls (NLC). Myocardial infarction was induced by ligation of the left coronary artery in Tg-CTGF (n=22) and NLC mice (n=21). Sham-operated animals underwent the same procedure without ligation of the artery. All mice were followed for 4 weeks in order to investigate the development of HF. Area at risk was estimated in a separate group of animals, harvested immediately after ligation and perfused with Evans blue dye. Area at risk was similar among Tg-CTGF and NLC mice (42.7±1.6%, n=8 vs 40.4±2.1%, n=8, p=0.39). During follow-up, significant improvement of survival was found in Tg-CTGF mice (63.6% vs. 38.1%, $p<0.05$). In vivo pressure-volume analysis performed after 4 weeks displayed preserved cardiac performance in Tg-CTGF mice, as measured by dp/dt, end-diastolic pressure and cardiac output. End-point analysis revealed attenuation of cardiac hypertrophy in Tg-CTGF mice vs NLC mice (Heart weight/body weight ratio; 5.3±0.2mg/g, n=14 vs 8.0±0.9mg/g, n=9, $p<0.05$). Consistently, markers of myocardial remodelling, i.e. BNP and β-myosin heavy chain, measured by real-time qPCR, were significantly less up-regulated in Tg-CTGF than NLC hearts. Concentration-effect curves of isoproterenol-stimulated contractility in myocardial strips uncovered marked attenuation of inotropic responses in Tg-CTGF hearts (increase of maximal contractility; 123±14% vs. 427±27%, $p<0.01$). Selective upregulation of G-protein receptor kinase 5 (GRK5) in cardiac myocytes of Tg-CTGF hearts were found and confirmed as the mediator of this functional desensitization. Western blot analysis also revealed activation of salvage kinase pathways in Tg-CTGF hearts, evident as increased phosphorylation of AKT (Ser 473) and GSK-3β (Ser 9). Interestingly, induction of myocardial collagen contents four weeks after myocardial infarction, determined by quantitative HPLC of hydroxyproline, was lower in Tg-CTGF mice than in NLC mice.
Conclusion: This study uncovers novel, unexpected properties of CTGF as cardioprotective factor in ischemic HF. Myocardial CTGF prevents development of HF and improves survival after myocardial infarction, possibly due to activation of salvage kinase pathways and inhibited neurohumoral stimulation of the heart.

P1415 Impedes Mitogenic Signal Propagation (IMP) is responsive towards neurohumoral stimulation controlling MAPK mediated development and cardiac growth

T. Seidler, C. Grebe, P. Schott, B. Unsoeld, C. Boecker, A. Schmidt, K. Kurz, R. Knoell, K. Guan, G. Hasenfuss. *University of Göttingen, Göttingen, Germany*

Neurohumoral activation strongly stimulates mitogen activated protein kinase (MAPK) pathways in the heart, which signal to and activate downstream effector pathways highly relevant to hypertrophy and heart failure. IMP was recently identified as an important modulator of Ras dependent activation of MEK/ERK MAPK signaling in non-cardiac cells.
We examined IMP in both adult and neonatal rat cardiac myocytes, where adenoviral IMP overexpression profoundly suppressed MEK and ERK MAPK activation under baseline conditions and following Raf- stimulation. A mammalian two-hybrid construct confirmed a direct inhibitory effect on cRaf-MEK protein-protein interaction, suggesting an inhibitory effect of IMP on both adaptive hypertrophy and anti-apoptotic signaling. Using this system, we were also able to confirm an inverse relation of IMP activity on Raf-Mek association towards Ras activity, as Ras promoted auto-ubiquitination of IMP leading to inhibition of IMP, but not an ubiquitin ligase deficient IMP mutant. In addition, Ras activation by PMA rapidly decreases IMP protein suggesting IMP is readily susceptible towards neurohumoral stimulation in cardiac myocytes. Three independently created IMP-transgenic (TG) mouse lines in two different genetic backgrounds exhibited grossly enlarged hearts, compared to wildtype littermates (WT). Echocardiography confirmed dilation (left ventricular end-diastolic diameter 4.57±0.17 vs. 3,57±0.04 mm; $p<0.05$ IMP vs. WT; $p<0.05$; TG vs WT) and significant reduction of fractional shortening (14±3% vs. 40±0.4%; IMP TG vs. WT; $p<0.001$). Invasive hemodynamic measurements confirmed a phenotype consistent with a severe dilative cardiomyopathy. Kaplan-Maier analysis showed a significantly decreased survival with 50% of mice dying before the age of 24 weeks. Higher p38 MAPK activity, Bax/Bcl ratio and cytoplasmic cytochrome c release indicated mitochondrial dysfunction contributed to the phenotype. Gene-targeted IMP mice were not born in mendelian ratios, as homozygous IMP gene-targeted mice were observed to die at embryonic day 9.5-10.5 associated with developmental retardation, while heterozygous mice survived without phenotypic abnormalities until 12 months. These data indicate that IMP is subject to neurohumoral control and can control cardiac size and function via profoundly altered MAPK signalling and that IMP is essential to embryonic development.

P1416 Cardiac-specific overexpression of beta3-adrenoreceptors attenuates isoproterenol-induced hypertrophy and fibrosis

C. Belge[1], J.L. Hammond[1], A. Markl[1], A. Vanderper[2], B. Sekkali[1], A. Pouleur[1], D. Langin[3], P. Herijgers[2], C. Dessy[1], J.L. Balligand[1]. *[1]Université Catholique de Louvain, Brussels, Belgium; [2]Katholieke Universiteit Leuven, Leuven, Belgium; [3]INSERM U858, Toulouse, France*

Background: β1-2 adrenoceptors (AR) are key regulators of cardiac contractility and remodelling in response to catecholamines. We previously identified the expression of β3AR in human cardiac myocytes, where their acute activation mediates a negative inotropic effect. However, the effects of chronic activation of β3-AR on cardiac remodelling is unknown.
Methods and Results: The phenotype of mice with cardiac myocyte-specific (alpha-MHC-driven) expression of the human β3AR (β3TG) was analysed. Heterozygote males from a moderately overexpressing line were treated for 10 days with 50mg/kg/day isoproterenol (Iso) i.p. or saline. Left ventricular (LV) morphometry was analysed by echocardiography. Cell dimensions were measured on WGA-stained mid-ventricular heart sections, and cardiac fibrosis assessed by sirus red staining.
Cell dimensions were comparable between the 2 strains at baseline and after saline. As expected, Iso produced LV hypertrophy in WT mice (ΔLV mass/tibial length: +1.01±0.2 vs 0.16±0.1mg/mm (saline); P=0.002; n=9). However, it failed to produce a significant hypertrophy in β3TG mice (0.4±0.14 vs 0.10±0.07mg/mm (saline); P=0.078; n=9). Similarly, Iso produced an increase in transverse (139.6±5.8 vs 97.6±5.8 μm^2 $P<0.0001$; n=6) and longitudinal (46.2±1.3 vs 35.6±1.4μm; $P<0.0001$; n=5) dimensions of cardiac myocytes in WT hearts, but not in β3TG hearts (Transv: 84.2±3.5 vs 81.0±3.3μm^2; P=0.51; Long: 37.1±0.9 vs 35.4±1.1μm; P=0.24; n=6). WT mice, but not β3TG mice, developed prominent cardiac fibrosis following Iso ($P<0.05$; n=6-9 hearts)
βAR mRNA abundance was measured by qRT-PCR. At baseline, β1AR expression was lower in β3TG mice than WT; β2AR expression was comparable between the two strains. Chronic Iso did not affect β2AR expression in either strain but decreased the abundance of β1AR in the WT (50.0±7.8% of saline; P=0.023), but not the in β3TG mice, resulting in similar β1-AR mRNA levels under Iso in both strains. Despite lower β1AR mRNA expression in β3TG mice baseline, hemodynamic parameters were comparable between the two strains, as were their acute chronotropic and inotropic responses to Iso. Chronic Iso did not result in significant impairment of LV function in these mice.
Conclusion: Cardiac-specific moderate overexpression of β3AR does not affect cardiac morphology at baseline, but inhibits the hypertrophic and pro-fibrotic response to chronic β-adrenergic stimulation in vivo. Activation of the cardiac β3AR

pathway may provide future therapeutic avenues for the modulation of hypertrophic cardiomyopathy.

P1417 Adenovirus-mediated overexpression of p38 MAPK isoforms induce distinct functional and structural changes in the heart

H. Pennanen, H. Leskinen, R. Serpi, O. Tenhunen, J. Rysa, E. Mustonen, H. Ruskoaho. *Department of Pharmacology and Toxicology, Institute of Biomedicine, Oulu University, Oulu, Finland*

Purpose: The mitogen-activated protein kinase (MAPK) signaling pathways serve as pivotal transducers of diverse biological functions including cell growth, differentiation, proliferation, and apoptosis. The p38 branch of MAPK pathway cascade includes four separate isoforms, p38α, p38β, p38γ, and p38δ. The major isoform of p38 MAPK expressed in the heart is p38α, while the role of p38β-isoform is poorly understood. In the present study, we defined the functional and structural effects of α- and β-isoforms of p38 MAPK in the adult rat heart.
Methods: The α- and β-isoforms of p38 MAPK with their upstream regulator MKK3 were overexpressed by direct adenoviral-mediated gene transfer into the anterior wall of the left ventricle of rat heart in vivo. The effects were analysed by histological analysis and echocardiographic measurements one week after gene transfer, and the activation of underlying signaling pathways were investigated by Western blot.
Results: Western blot analysis revealed a significant increase in the levels of phospho-p38 by adenovirus-mediated overexpression of both p38α and p38β MAPK isoforms. The overexpression of the p38 MAPK β-isoform resulted in a significant thickening of the interventricular septum (3,0±0,31 mm vs. 2,0±0,08 mm, $P<0,05$) and reduction of systolic function (left ventricular ejection fraction: 59,5±4,8% vs. 74,1±4,9%, $P<0,05$) while p38 MAPK α-isoform overexpression did not cause any significant functional changes. In contrast, the number of Ki-67 positive cells (5,4±0,62 cells vs. 2,9±0,52 cells, $P<0,05$) and capillary density (α: 349±27 pcs vs. β: 261±32 pcs, $P<0,05$), as assessed by immunostaining of endothelial cells, were increased in the hearts overexpressed with p38 MAPK α-isoform, but not with p38 MAPK β-isoform. Histological sections showed an infiltration of inflammatory cells both in the p38α- and -β-treated hearts, while neither of the p38 MAPK isoforms influenced on fibrosis in Masson's trichrome stainings. The phosphorylation of the small heat shock protein 27 was increased by overexpressing both isoforms, but treatments had no effect on phosphorylation of MAPKAP-kinase-2.
Conclusions: The present results demonstrate that in the adult heart, the physiological consequence of p38 MAPK β-isoform overexpression is thickening of the left ventricular wall and decrease in cardiac function, while α-isoform induces cellular proliferation and angiogenesis without compromising left ventricular systolic function. These structural and functional effects may involve activation of the small heat shock protein 27 but not MAPKAP-kinase-2.

P1418 Protective effect of a quinasoline-type poly(ADP-ribose)polymerase inhibitor against the development of hypertensive cardiopathy

E. Bartha[1], I. Solti[2], L. Kereskai[3], E. Plozer[1], K. Magyar[1], T. Kalai[4], K. Hideg[4], B. Sumegi[2], K. Toth[1], R. Halmosi[1]. *[1]University of Pécs, School of Medicine, First Department of Medicine, Pécs, Hungary; [2]University of Pécs, School of Medicine, Department of Biochemistry and Medical Chemistry, Pécs, Hungary; [3]University of Pécs, School of Medicine, Department of Pathology, Pécs, Hungary; [4]University of Pécs, School of Medicine, Department of Organic and Medicinal Chemistry, Pécs, Hungary*

Purpose: The spontaneously hypertensive rat (SHR) is a suitable model for studies of hypertension and consequential left ventricular hypertrophy. It is known, that activation of poly(ADP-ribose)polymerase enzyme (PARP) plays an important role in the development of postinfarction myocardial remodeling. In this study we examined the protective effect of a quinazoline-type PARP inhibitor (L-2286) on the development of hypertensive cardiopathy in SHR.
Methods: 6-week-old SHR male rats were treated with L-2286 (5 mg/b.w. in kg/d, n=9, SHR-L) or placebo (n=8, SHR-C) orally for 24 weeks. 6-week-old male CFY Sprague-Dawley rats were used as aged-matched, normotensive control (n=7, CFY). Before the study and at the end of the 24 week period echocardiography was performed and at the end of the experiment blood pressure and plasma BNP activity were determined. To detect the extent of fibrotic areas, histologic samples were stained with Masson's trichrome. The phosphorylation state of Akt-1, GSK-3β, FKHR, MAPK, Hsp72, 90 and PKC cascades were monitored by Western blotting.
Results: Deposition of collagen and activity of plasma BNP were significantly ($p<0.05$) elevated in SHR-L and SHR-C groups compared to the CFY group. These parameters showed improving tendencies due to L-2286 treatment, but these changes were not statistically significant. The activation of ERK 1/2 was increased ($p<0.05$), while JNK, Hsp72 and p38-MAPK were not altered significantly by L-2286 treatment. The phosphorylation of Akt-1, GSK-3β, FKHR, Hsp90 and PKC ε were increased significantly ($p<0.01$), while the activation of PKC α/β, ζ were mitigated ($p<0.05$ vs. SHR-C) by L-2286 administration. The elevated blood pressure of both SHR groups ($p<0.05$ vs CFY) were not attenuated by L-2286. Echocardiographic study showed that ejection fraction and fractional shortening did not differ significantly among the three groups while left ventricular end-diastolic and end-systolic volumes increased significantly ($p<0.05$ SHR-L and SHR-C vs. CFY). The thickness of the left ventricular wall (posterior wall and septum) and the mass of left ventricles were significantly higher ($p<0.05$ SHR-L and SHR-C vs. CFY). These parameters were significantly decreased ($p<0.05$) by L-2286 treatment (SHR-L) compared to SHR-C group.
Conclusions: In conclusion, we could detect the signs of myocardial hypertrophy in SHR group. Our results suggest that PARP inhibition with L-2286 treatment has beneficial effect on the development of left ventricular hypertrophy in young SHRs, mainly due to the activation of the PKC ε, and the Akt-1/GSK-3β signaling pathways.

P1419 Autoregulation of human relaxin-2 critically involves relaxin and glucocorticoid receptor binding to glucocorticoid response half-sites in the relaxin-2 promoter

T. Dschietzig, C. Bartsch, G. Baumann, K. Stangl. *Charité, Campus Mitte, Department of Cardiology and Angiology, Berlin, Germany*

The relaxin peptide family exerts diverse biological effects - from regulating central nervous processes and reproduction to modulating cardiovascular and kidney function as well as connective tissue composition - through different G protein-coupled receptors (RXFP1 through 4). We reported earlier that relaxin-2 acts as compensatory mediator in human congestive heart failure and reported encouraging results in the first clinical pilot trial. Additionally, relaxin interacts with the human glucocorticoid receptor (GR) in an agonistic manner. Prompted by the discovery of GR-binding sites in the relaxin-2 promoter we investigated the possible auto-regulation of relaxin-2 via the GR pathway. We found that exogenous relaxin increased the secretion of human relaxin-like immunoreactivity in HeLa and THP-1 cells. Silencing of GR gene expression completely abolished this effect whereas transfection of wild-type GR into naturally GR-devoid HT-29 cells established relaxin sensitivity. Relaxin was shown to stimulate CAT expression driven by different deletion constructs of the 5'-flanking region of the relaxin-2 promoter. In chromatin immunoprecipitation assays, we detected both GR and relaxin binding to the relaxin-2 promoter. Gel shift assays indicated binding of relaxin-activated GR to half-glucocorticoid response elements (half-GREs) located between 160 and 200 bp upstream of transcription start but not to the complete GRE at -900 bp. Finally, we visualized, by immunofluorescence, nuclear co-localization of relaxin and GR in response to relaxin exposure. In conclusion, we have shown here that a positive self-regulatory loop of human relaxin-2 expression exists which involves GR and relaxin/GR binding to half-GREs in the relaxin-2 promoter. This finding deepens our understanding of the complex relaxin signaling and may also be relevant to the emerging clinical cardio-vascular use of the peptide.

P1420 Hepatocyte growth factor a new marker for prognosis in acute coronary syndrome

A. Konopka, J. Janas, J. Stepinska. *Institute of Cardiology, Warsaw, Poland*

The main aim of the study was a comparison of plasma concentration of hepatocyte growth factor (HGF) with markers of myocardial injury and estimation of its prognostic value in patients (pts) with acute coronary syndrome (ACS).
Material and methods: Between January 2006 and October 2008, we investigated 100 pts with the first episode of ACS in their lives. As soon as possible after admission to hospital and 24h after the first measurements, the following parameters were measured: concentration of HGF, cTnI, CK-MB, hsCRP and NT-proBNP. Patients were divided into 3 groups. Group A (major myocardial injury – 39 pts) comprised pts with anterior or antero-lateral MI with occlusion or significant LAD branch stenosis and/or multivessel disease. In Group B were included 28 pts with inferior and/or posterior MI and with singlevessel disease but not LAD (moderate myocardial injury). Group C consisted of 33 pts with NSTE-ACS and without a significant increase of myocardial injury markers (minor myocardial damage). All patients received heparins, aspirin and clopidogrel at admission. Most of them underwent primary PCI and additionally abciximab was administrated.
Results: In the first measurements, the same values of hsCRP, NT-proBNP, cTnI and CK-MB were noted in each group, while plasma HGF concentration in Groups A and B was much more elevated (4085 and 4194 pg/ml respectively) than in Group C (2314 pg/ml p=0.05). In the assessments performed 24h afterwards, the values of NT-proBNP, cTnI and CK-MB increased considerably while HGF concentration was already decreased to the same level in all the three groups. Three days after ACS symptoms appeared, EF determined by echocardiography was reduced to 51, 55 and 58% in Groups A, B and C, respectively (p=0.01). Composite end-point of the study was estimated at 3 month follow-up and included death, MI, exacerbation of angina, reintervention, stroke, symptoms of heart failure and rehospitalization due to cardiovascular causes. The study shows that the mean value of HGF observed in the first measurements in patients without any events (67 pts – 67%) was lower (2923 pg/ml) than in patients with any complication mentioned above (33 pts – 33% - 4765 pg/ml). This difference was significant (p=0,01).
Conclusion: HGF is a very early, good marker of myocardial ischemic injury and a sensitive, promising prognostic factor, which might be useful especially in difficult diagnostic situations mainly in NSTE-ACS, which could pinpoint patients with

major susceptible myocardial damage who, by early stratification to a risk group, should be qualified to aggressive invasive therapy.

P1421 Leptin induces interleukin-18 via endothelin-1-Rho/Rho-kinase-PPAR/NF-kB pathway in cardiomyocytes

T. Doi, T. Sakoda, T. Akagami, T. Naka, T. Tsujino, T. Masuyama, M. Ohyanagi. *Hyogo College of Medicine, Nishinomiya, Japan*

Purpose: Leptin is known to be an adipocyte-derived hormone and regulates weight control and energy metabolism. Recent studies indicate that leptin may contribute to heart failure. Interleukin-18 (IL-18), a member of the IL-1 family, is a proinflammatory cytokine with multiple biological functions. IL-18 induces myocardial hypertrophy, loss of contractility of cardiomyocytes and apoptosis leading myocardial dysfunction. Increased levels of circulating IL-18 are thought to be one of risk factors for heart failure. However, the effect and mechanism by which leptin induces heart failure with inflammatory cytokine were still unclear. Therefore, in the present study, we examined how leptin induces heart failure with increased IL-18.
Methods: We used cultured rat neonatal cardiomyocytes stimulated with leptin in order to measure IL-18 mRNA and protein expression, and Rho-kinase and NF-kB activity. We also investigated the effects of peroxisome proliferator-activated receptors (PPAR) agonists on these actions.
Results: Leptin increased IL-18 mRNA and protein expression with dose- and time-dependent manner. BQ123, an endothelin A receptor (ETAR) antagonist inhibited leptin-induced IL-18 expression. Moreover, leptin induced endothelin-1 (ET-1) production in cultured media and ET-1 increased IL-18 expression. These results indicate leptin induces IL-18 expression intermediates ET-1 via ETAR. Furthermore, C3 toxin, RhoA inhibitor, fasudil, Rho-kinase inhibitor, simvastatin, an HMG-CoA reductase inhibitor, and PPAR agonists, pioglitazone and bezafibrate led to a significant reduction in leptin-induced IL-18 expression. On the other hand, leptin up-regulated the activities of Rho-kinase and NF-kB. PPAR agonists attenuated the leptin-induced IL-18 expression and NF-kB activity but not the Rho-kinase activity. These results indicate that leptin induced the IL-18 expression through a mechanism that involves, at a minimum, ET-1 acting via the Rho/Rho-kinase and PPAR/NF-kB pathway and PPAR agonists attenuate the leptin-induced IL-18 expression at a point downstream from Rho/Rho-kinase.
Conclusions: The induction of IL-18 in cardiomyocytes by leptin and ET-1 might, therefore, cause a deterioration of the cardiac function in an autocrine and paracrine fashion. The inhibition of the IL-18 expression by PPAR agonists might be one of the mechanisms whereby the beneficial cardiovascular effects are exerted.

P1422 Left ventricular fibrosis secondary to pressure overload is prevented in mice by neutralizing transforming growth factor-beta

A.V. Villar[1], M. Cobo[2], M. Llano[2], M. Tramullas[2], V. Exposito[2], R. Martin-Duran[2], R. Merino[3], M.A. Hurle[1], J.F. Nistal[2]. *[1]University of Cantabria, Santander, Spain; [2]Hospital Universitario Marques de Valdecilla, Santander, Spain; [3]Instituto de Biomedicina y Biotecnologia de Cantabria, Santander, Spain*

Purpose: Patients with aortic stenosis (AS) develop left ventricular (LV) hypertrophy secondary to pressure overload. In this context, myocyte hypertrophy together with extracellular matrix structural changes progressively lead to diastolic and, eventually systolic, myocardial dysfunction. The para-autocrine action of transforming growth factor-βs (TGFβs) on myocardial cells has been suggested to play a role in LV remodeling. The aim of the study was to assess in mice how treatment with a neutralizing antibody anti-TGF-β (TGFβAb) modifies pressure overload-induced changes in echocardiographic parameters, as well as in myocardial expression of some remodeling-related proteins.
Methods: Pressure overload was generated by calibrated transverse aortic constriction (TAC). Animals were killed 2 weeks after TAC. Echocardiographic, histological (Masson trichrome) and immunofluorescence studies, as well as determination of myocardial collagens I and III gene expression (real time-PCR) were conducted in sham operated (n=5) and in TAC mice treated for 2 weeks with saline (n=7) or TGFβAb (1.5 mg i.p. every other day).
Results: Two weeks after TAC, both saline and TGFβAb treated mice showed similar transcoartation aortic gradients (saline: 68.5±6 mm Hg; TGFβAb: 60.4±9 mmHg). Myocardial expression levels of genes encoding collagens were significantly higher in saline-treated TAC mice compared with the sham group. On the other hand, TGFβAb-treated TAC mice did not display increased expression of fibrosis-related genes [collagen I (sham: 9.6±2.6; saline-TAC: 45.3±12.1; TGFβAb-TAC: 20.9±10.3); collagen III (sham: 2.0±0.3; saline-TAC: 14.3±2.9; TGFβAb-TAC: 5.9±3.4). Gene expression changes were confirmed at the protein level by histological staining, showing a lower presence of fibrosis in myocardial sections from TGFβAb-treated mice. TGFβAb treatment did not prevent heart mass gain, measured either by echocardiography [LV mass increase at 1st week (saline-TAC: 34.5±10.1%; TGFβAb-TAC: 37.0±10.4%); LV mass increase at 2nd week (saline-TAC: 70.1±11.5%; TGFβAb-TAC: 60.6±13.4%)] or by weight (mass index 2 wk after TAC, sham: 4.6±0.2 mg/g; saline-TAC: 6.3±0.2 mg/g; TGFβAb-TAC: 6.4±0.3 mg/g). At the functional level, the ejection fraction was unaltered by TGFβAb treatment (2 wk sham: 79.9±4.6%; 2 wk saline-TAC: 77.2±7.5%; 2 wk TGFβAb-TAC: 74.2±8.4%).
Conclusions: TGF-β neutralization with a specific antibody modifies the pattern of pressure overload-induced myocardial remodeling by blunting profibrotic processes, but it does not prevent the increase in LV mass. (Funded by FIS-PI 060240)

P1423 The sarcolemmal calcium pump modulates the cardiac beta-adrenergic response via interaction with spatially confined nNOS

T.M.A. Mohamed, D. Oceandy, N. Alatwi, F. Baudoin, E. Cartwright, L. Neyses. *The University of Manchester, Manchester, United Kingdom*

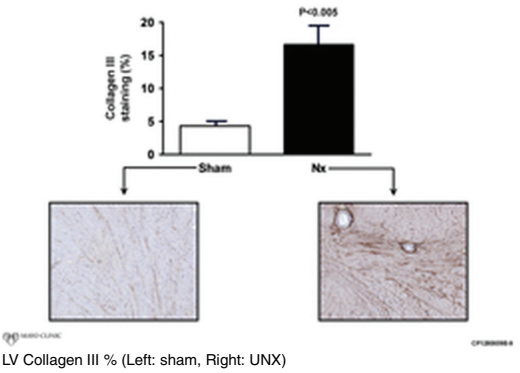
Modulations of the β-adrenergic (β-AR) response are key in heart failure progression. NO from neuronal NOS (nNOS) is necessary to sustain the β-response, but the regulators of nNOS are largely unknown. Recently, we have shown that isoform 4 of the plasma membrane calcium ATPase (PMCA) interacts with the PDZ-domain of nNOS and reduces NO production through calcium depletion in the vicinity of nNOS, which is also a calcium/calmodulin dependent enzyme. When active, PMCA4 ablates the β-adrenergic inotropic response in the heart. We here aimed to investigate the mechanisms of this novel and unexpected observation.
In transgenic mice overexpressing PMCA4 in the heart and in neonatal rat cardiomyocytes (NRCM) with adenoviral overexpression of PMCA4, a significant increase in phosphorylation of phospholamban (PLB) at serine-16, as well as troponin-I was observed prior to β-AR stimulation (n=5, $p<0.05$). However, the increase in PLB and troponin-I phosphorylation following isoprenaline treatment was severely attenuated explaining the blunted physiological response to β-adrenergic stimulation that we have observed in vivo. This effect was emulated in WT cardiomyocytes treated with the specific nNOS inhibitor S-methyl-L–thiocitrulline. In addition, the effect of PMCA4 overexpression on PLB and troponin-I phosphorylation was overridden by treatment with the cell permeable cGMP analogue, 8-bromo-cGMP (100μM). PMCA4 overexpression in both models reduced nNOS activity, as measured by the ability to convert tritium-labelled L-arginine to L-citrulline, and led to a reduction in the subsequent production of NO by 21.4±5.11% and cGMP by 24±5.09% (n=6, $p<0.05$). cAMP was significantly increased by 32±5.5% (n=8, $p<0.05$) leading to stimulation of protein kinase A activity and phospholamban phosphorylation. Regulation of cardiac phosphodiesterase (PDE) activities was found to determine the balance between cGMP and cAMP following PMCA4b overexpression.
In conclusion, these findings show that PMCA4 inhibits nNOS mediated nitric oxide and cGMP production. This reduction leads to inhibition of cGMP dependent PDEs, cAMP elevation and increased Serine16-PLB as well troponin-I phosphorylation in the basal state. The phosphorylation response to isoprenaline is blunted explaining the ablation of the β-response in PMCA4 overexpressing animals. Furthermore, these findings provide mechanistic insight into how the plasma membrane bound PMCA4 confers specificity of action to spatially confined molecules of nNOS.

INTEGRATED PATHOPHYSIOLOGY

P1424 Kidney removal alters myocardial genes and mediates cardiac fibrosis: a kidney-heart connection in cardiorenal regulation

F.L. Martin, B.K. Huntley, J. Korinek, G.E. Harders, J.C. Burnett. *Mayo Clinic, Rochester, United States of America*

The cardiac response to a reduction in total renal mass produced by the removal of a kidney is unknown. Such information is of clinical importance because removal of a kidney is performed not only to produce models of experimental chronic kidney disease but for renal malignancies, infections and organ transplantation. Further, it is also well established that impaired renal function in chronic renal disease leads to increases in cardiovascular morbidity and mortality.



LV Collagen III % (Left: sham, Right: UNX)

Methods and results: Cardiorenal function and structure were assessed in rats without (sham) and with unilateral nephrectomized (UNX) (n=10 per group) four weeks after UNX. At 4 weeks, glomerular hypertrophy was observed in UNX (Sham:1±0.04, UNX:1.6±0.1 μ3x106, p<0.001). GFR tended to decrease with a reduction in renal blood flow (sham:8±1, UNX:5±1 ml/min, p<0.005). Sodium and water excretions were not different between groups with no activation of PRA, aldosterone or BNP. Examination of the LV myocardium of UNX compared to Sham revealed greater fibrosis (sham:2.4±0.1, UNX:4.2±0.4%, p<0.001). LVEF and LV end-systolic and end-diastolic diameters were normal. Early diastolic strain rates (Csr-E) were lower in UNX group while Csr-A increased which resulted in decreased Csr-E/A ratio indicating myocardial diastolic dysfunction. However, blood pressure was not different between groups. Importantly, genome wide microarray analysis of the LV myocardium revealed that 278 genes significantly changed with UNX (1.5 fold, P<0.05) compared to Sham.
Conclusion: These studies support an important kidney - heart connection in the control of myocardial structure and function with implications for both kidney removal and chronic kidney disease in cardiorenal homeostasis.

P1425 Myocardial infarction mediates renal molecular and structural remodeling

F.L. Martin, B.K. Huntley, S.J. Sangaralingham, P.M. Mckie, G.E. Harders, S.M. Sandberg, H.H. Chen, J.C. Burnett. *Mayo Clinic, Rochester, United States of America*

Studies suggest that alterations in renal function may occur and contribute to poor outcomes even in the absence of heart failure (HF) after myocardial infarction (MI). Specifically, After MI a decline in renal function may be seen acutely by mechanisms which are unclear. To date, the more long term consequences of MI upon renal function and structure remain poorly defined. We hypothesized that even without preexisting renal disease, renal functional and structural changes even at the molecular level would be present following MI.
Methods: Cardiorenal function and structure were assessed in Wistar rats, Sham (S; n=10) and MI groups (n=9) 3 weeks after MI. GFR was determined by inulin clearance. Blood was obtained for PRA and aldosterone. Hearts and kidneys were harvested for histological analysis. Cardiac function was assessed by echo. Genome-wide microarray analysis was performed of both the kidney cortex (KC) and medulla (KM) (Affymetrix GeneChip Rat Genome 230 2.0).
Results: EF decreased after MI (S:62.8±2.3, MI:42.8±6.5%, p<0.01) and LVEDd increased (p<0.005) PRA and aldosterone activation were absent. Blood pressure (BP) was not different between groups. There was no HF as sodium and water excretion was maintained. GFR tended to decrease (S:2.9±0.3, MI:2.4±0.2 ml/min, NS). Picrosirius Red staining for collagen in the KC and KM after MI showed greater fibrosis especially in the RM (KC S:1.1±0.2, MI:3.5±0.6%, p<0.001 and KM S:1±0.2, MI:18.8±6%, p<0.005). Microarray analysis revealed that 303 genes significantly changed in KM and 407 genes in the KC after MI (1.5 fold, P<0.05). Gene dysregulation was related to cell proliferation, metabolic processes and cell communication (Z value>2).
Conclusion: We conclude that experimental MI results in renal structural remodeling characterized by renal cortical and medullary fibrosis with a mild reduction in GFR and extensive modulation of genetic pathways related to renal growth and metabolism. This investigation provides evidence for a heart-kidney connection after MI by mechanisms which still remain to be defined. We conclude as well that therapies for MI targeting the heart also should be evaluated for properties of renoprotection.

P1426 The role of interleukin-17 and RANTES in the development for prognostic factors in acute coronary syndromes

R. Shakur[1], R. Riemersma[2], K.A.A. Fox[2]. *[1]Nuffield Department of Medicine. The John Radcliffe Hospital. Firm A, Oxford, United Kingdom; [2]Royal Infirmary of Edinburgh, Edinburgh, United Kingdom*

Purpose: We investigated the role of serum Interleukin-17 (IL-17) and RANTES levels as predictors of future cardiac events in acute coronary syndrome (ACS) patients.
Methods: Patient selection: 60 Consecutive patient plasma samples were collated prospectively from patients who had consented to being part of the GRACE Study (Global Registry of Acute Coronary Events). Patient follow up was 6 months post recruitment.
Patients were matched to the event cohort for age ± 5yrs, sex and smoking status ± current smoker. The event cohort was split into 2 groups which focused on no events, but differed in their status for percutaneous coronary intervention (PCI).
Two plasma samples were taken from each patient, one taken as 'baseline' values upon 6-12h post admission to the A&E department with the symptoms of chest pain.
A second sample was taken approximately 24h after the first sample. Day 2 samples for the intervention group were taken 24h after their intervention.
Both IL-17 and RANTES levels were determined by ELISA (Enzyme- Linked Immunosorbent assay).
Results: There was no statistically significant difference between IL-17 or RANTES levels at either baseline or day 2 levels in patients who had events after 6 months follow up. There was a modest negative correlation between IL-17 (r=-0.4, p=0.002) at baseline and day 2. Similarly there was a positive correlation for RANTES levels (r=0.5, p=0.004) at baseline and day 2.

Table 1. Correlation between RANTES and IL-17 at baseline and day 2

Groups	Sqrt RANTES baseline	Sqrt RANTES day 2
Log IL-17 baseline	r=0.35, P=0.06	r=0.87, P=0.7
Log IL-17 day 2	r=-0.16, P=0.4	r=0.037, P=0.8

Conclusion: We are the first to report on IL-17 and RANTES levels together in regards to ACS patients in the GRACE cohort. We found no statistically significant difference in either IL-17 or RANTES levels in ACS patients who had events 6 months after their initial event. However, we envisage that larger sample numbers and more research in this area will enhance our understanding of the potential of these cytokines/chemokines as potential prognostic markers in ACS patients.

P1427 Sleep disordered breathing and high altitude hypoxia: gender related differences. The highcare project

C. Lombardi[1], P. Meriggi[2], M. Bartesaghi[3], G. Caldara[3], K. Styckiewicz[4], G. Bilo[1], G. Savia[3], M. Di Rienzo[2], G. Mancia[1], G. Parati[1] on behalf of HIGHCARE Team. *[1]Univ. Milano Bicocca; Istituto Auxologico Italiano IRCCS, Milan, Italy; [2]Biomedical Technology Department, Fond. Don Carlo Gnocchi Onlus, Milan, Italy; [3]Istituto Auxologico Italiano IRCCS, Milan, Italy; [4]Jagiellonian University, Krakow, Poland*

Purpose: Respiratory periodicity during night at high altitude is frequently reported and is due to alternance between respiratory center stimulation by hypoxia and its subsequent inhibition by hyperventilation-induced hypocapnia. This respiratory pattern may be influenced also by sex hormones. In fact estrogens and progesterone have been suggested to protect from sleep-related breathing disorders (SRBD) at sea level. Aim of our study was to explore whether a different ventilatory pattern during night sleep might characterize women and men during acute exposure at high and very high altitude hypoxia.
Methods: In 27 healthy subjects, 23 male (mean age 40 years) and 14 female (mean age 36 years) participating in the HIGH altitude Cardiovascular Research project (HIGHCARE), we performed nocturnal portable polysomnography with a new wearable system (MAGIC vest) and with a standard portable system in the following conditions: 1) at sea level (SL), 2) during the first or second night at Namche Bazaar (3500 m above SL) and 3) during first or second night at Mt Everest Base Camp (5400 mt slm). During the recording we monitored 1) air flow, 2) thoraco-abdominal movements; 3) finger pulse oximetry (SpO2), 4) body position, 5) ECG, 6) snoring. Mean and minimum SpO2 during night, number of central and obstructive apneas, oxygen desaturation index (ODI), apnea-hypopnea index (AHI) were measured.
Results: During night at Namche Bazar (3500 slm) AHI was 57,7±33,4 in male and 4,68±2.7 in female (p<0.05) the difference being due to a strikingly higher number of central sleep apneas and hypopneas in male than in female subjects (central AHI: 54.1±33 vs 4,68±2,7, p<0.01), leading to a corresponding difference in oxygen desaturation index (ODI, 49,14±25 vs 9,1±7 respectively, p<0.01). At Base Camp AHI was 92±41 in male and 53,6±45 in female. The difference was still referred to central sleep apneas. ODI values were 75,12±28 vs 49,1±25 respectively, p<0.05.
Conclusions: Under exposure to high and very high altitude hypoxia periodic breathing at night affects more frequently male than female subjects. Females started to present a significant number of central sleep apnea only at the highest hypobaric hypoxia level achieved. This data highlight the presence of a gender-related difference in respiratory center stimulation by hypoxia, which leads to trigger periodic breathing in males earlier and more frequently than in females. This data may also have important implications for pathogenesis and cardiovascular consequences of SRBD at sea level which are reported to be significantly more frequent in males than in females.

P1428 Increased Wnt-signaling in cardiac repair after myocardial infarction

M.I.F.J. Oerlemans[1], M.J. Goumans[2], H. Clevers[3], P.A. Doevendans[1], J.P.G. Sluijter[1]. *[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]Leiden University Medical Center, Leiden, Netherlands; [3]Hubrecht Laboratory, Institute for Developmental Biology, Utrecht, Netherlands*

Purpose: Following myocardial infarction (MI), injured myocardium is replaced by non-functional scar tissue leading to heart failure for which no therapeutic options are currently available. Although promising, endogenous regeneration in vivo remains a big challenge as many different pathways are likely to control activation and differentiation of resident cardiac progenitor cells. One of the factors suggested to be involved is Wnt signaling, a regulatory signal of stem cell biology and behavior. Although extensively studied in heart development, the exact role of Wnt signaling after MI still needs to be unraveled. Contradictory results were found upon inhibition and stimulation of Wnt or its downstream targets with respect to the adaptive response on different hypertrophic stimuli and permanent LAD ligation. These studies suggest that Wnt is involved in different phases of infarct healing. We set to evaluate the role of active Wnt signaling in the heart

during different phases following MI. For this, we used the Axin2-LacZ reporter mouse which will result in β-galactosidase expression in those cells that have active Wnt signaling.
Methods: After LAD ligation C57BL/6 Axin2-LacZ reporter mice were sacrificed at 0, 1, 3, 7, 14 and 21 days after MI. Hearts were snap-frozen for immunohistochemistry (IHC) or digested to obtain a single cell suspension for FACS analysis. Samples were stained to detect β-galactosidase activity and with antibodies against Sca, CD31, c-kit and CD45. For IHC, antibodies against β-galactosidase, tropomyosin, Sca and CD31 were used. Data (mean ± s.e.) were analyzed by Mann-Whitney U test, using a significance level of $P<0.05$.
Results: Total Wnt signaling after MI increased significantly in the myocardium, starting from 7 days up to 21 days post MI ($P<0.01$, n=5-8 in each group). Using Sca and CD31 to identify progenitor and endothelial cells, a significant increase in both Sca+/CD31- (and c-kit) and Sca-/CD31+ cells co-expressing Wnt was observed at day 7 and 14, respectively. CD45+ population, expressing Wnt, showed a peak at 3 and 7 days post MI, but returned to basal levels afterwards.
Conclusion: Wnt signaling increases significantly after MI, especially in Sca+/CD31- and Sca-/CD31+ cell populations, suggesting involvement of Wnt signaling in cardiac regeneration and neovascularization through activation of resident Sca+ progenitor cells as well as endothelial cells. Furthermore, all cell populations studied displayed active Wnt signaling, suggesting a broader role of Wnt in cardiac responses to injury than restricted to progenitor cell populations.

P1429 Prolonged cardiac unloading in young healthy subjects induces physiologic cardiac atrophy with preserved LV geometry and attenuated longitudinal myocardial function

M. Kozakova[1], E. Malshi[1], C. Morizzo[1], F. Santini[1], S. Pedri[2], M. Pagani[3], C. Palombo[1]. *[1]Department of Internal Medicine, University of Pisa, Pisa, Italy; [2]Esaote, S.p.A., Florence, Italy; [3]Centre for Neurovegetative Therapy, Internal Medicine, University of Milan, Milan, Italy*

Background: prolonged exposure to microgravity results in physiologic cardiac atrophy (CA) as the cardiac muscle responds to chronic circulatory unloading. Previous evidence suggests that CA is associated with changes in diastolic but not systolic left ventricular (LV) function. Furthermore, it is not known whether CA involves myocardiocytes, connective tissue, or both.
The aim of this study was to investigate the effect of a prolonged head-down-tilt bed rest (HDTBR), an established model of chronic circulatory unloading, on cardiac structure, systolic and diastolic myocardial performance and myocardial acoustic properties.
Methods: ten healthy male volunteers (age 23±2 years) were studied by Doppler-echocardiography one day before and within one day after a 35-day HDTBR. LV remodeling, stroke volume/work and LV filling were assessed by conventional ultrasound (B-mode, M-mode and PW-Doppler). Load-independent indices of myocardial performance (systolic and early diastolic longitudinal, radial and circumferential strain rate, SR) were obtained by tissue tracking (X-strain, Esaote, Italy). Myocardial acoustic properties were evaluated by ultrasonic densitometry (mean grey level and entropy) of LV posterior wall.
Results: at baseline, LV mass was directly related to BMI and stroke work (r=0.75 and 0.68, p at least <0.05). HDTBR induced a significant (p at least <0.05) decrease in LV mass (148±31 vs.166±34 g, delta -11.2±4.9%), mean wall thickness (7.7±0.8 vs.8.1±0.7 mm), end-diastolic diameter (49.8±3.4 vs. 51.2±3.4 mm), stroke work (91±15 vs. 116±21 g-m/beat) as well as in longitudinal SR, both systolic (-0.83±0.15 vs.-0.99±0.12 1/s) and diastolic (0.99±0.16 vs. 1.23±0.21 1/s), whereas isovolumic relaxation time increased (84±8 vs. 74±7 msec). In contrast, relative LV wall thickness, ejection fraction, E/A ratio, systolic and diastolic radial and circumferential SR as well as myocardial mean grey level and entropy did not change. Delta LV mass was directly related to delta stroke work (r=0.65, $p<0.05$) and delta longitudinal systolic and diastolic SR (r=0.71 and 0.78, p at least <0.05).
Conclusions: these data confirm that prolonged circulatory unloading leads to physiologic CA, which parallels the decrease in cardiac workload. A decrease in both LV inner diameter and wall thickness contribute to the development of physiologic CA, thus preserving LV geometry. CA is also associated with a significant reduction in LV longitudinal myocardial performance, systolic and diastolic, but not with changes in radial and circumferential performance or in the acoustic properties of myocardium.

P1430 Altered expression of PAP-3 (Pancreatitis Associated Protein 3) during left ventricular remodeling

H. Sakkinen, H. Tokola, J. Aro, H. Leskinen, H. Ruskoaho, J. Rysa on behalf of Heikki Ruskoaho. *University of Oulu, Oulu, Finland*

Objectives: Pancreatitis associated protein 3 (PAP-3) is a lectin-related secretory protein, associated with pancreatic stress and injury. Since changes in the composition of cardiac tissue develop in response to myocardial infarction and hypertensive left ventricular hypertrophy, and lead to structural remodeling of the myocardium, we characterized PAP-3 expression in experimental models of cardiac overload.
Methods: Experimental myocardial infarction was produced via ligation of left anterior descending coronary artery. Spontaneously hypertensive rats (SHR) and their normotensive controls Wistar-Kyoto rats (WKY) were used as a model of chronic pressure overload. Adenovirus-mediated intramyocardial gene transfer of mitogen-activated protein kinase kinase 3bE (MKK3bE) and p38α mitogen-activated kinase (MAPK) was performed into the anterior wall of the left ventricle (LV) in rats.
Results: After myocardial infarction left ventricular PAP-3 gene expression increased rapidly within one day (12.8-fold versus sham, $P<0.001$, n=6) returning to baseline at 2 weeks. In SHR, LV PAP-3 mRNA levels increased with aging being 3.3-fold ($P<0.01$, n=6-11) higher at the age of 20 months compared with 12 months old SHR. No change in LV PAP-3 mRNA expression with ageing was observed in WKY rats. Adenoviral overexpression of p38 MAPK resulted in cell proliferation, inflammation and fibrosis associated with 5.2-fold ($P<0.001$, n=10) increase in LV PAP-3 mRNA levels 3 days after MKK3bE+p38α gene transfer. Immunohistochemistry revealed that the increased expression of PAP-3 was localized in the cardiac fibroblasts and myofibroblasts in the proliferating connective tissue of p38 MAPK treated hearts.
Conclusions: These results show that PAP-3 mRNA levels are upregulated after myocardial infarction and pressure overload as well as by p38 MAPK overexpression. We hypothesize that PAP-3 may contribute to subsequent cardiac fibrosis during LV remodeling process.

P1431 Differential effects of telmisartan, ramipril and the combination in renal (pro)renin levels in diabetic rats

I. Toma, S.L. Vargas, J.J. Koo, J. Peti-Peterdi. *University of Southern California, Los Angeles, United States of America*

Background: Blockade of the renin-angiotensin system (RAS) by either angiotensin-converting enzyme inhibition (ACEI) or angiotensin receptor blockade (ARB) reduces cardiovascular mortality, renal risk and albuminuria. In the ONTARGET trial the combination of ACEI (ramipril) and ARB (telmisartan) was compared to each drug in monotherapy. Interestingly, the greater blood pressure reduction found in the combination arm did not lead to additional cardiovascular benefit. Furthermore, a worsening of major renal outcomes was found in the combination arm. The underlying mechanisms, however, remain elusive. Elevated plasma prorenin, a newly re-discovered element of RAS is a predictor and suspected cause of diabetic microvascular complications and the occurrence of microalbuminuria. We recently identified the renal collecting duct (CD) as the major source of prorenin in diabetes and showed that ARB effectively reduces renal and plasma levels of prorenin. In this study we evaluated the effects of the combination of an ACEI+ARB on CD prorenin synthesis.
Methods: (Pro)renin content in the intact kidney was visualized in control and streptozotocin (STZ) treated, diabetic Munich-Wistar-Fromter rats using in vivo multi-photon fluorescence microscopy. Rats were treated for 28 days after STZ-injection with telmisartan (3mg/kg/day), ramipril (1mg/kg/day), or both. Renal tissue and plasma renin activity were measured before (renin) and after (renin+prorenin) trypsinization. Direct effects of angiotensin II (ANGII) and bradykinin (10nM each) on CD prorenin synthesis were measured using in vitro cell cultures and renin immunocytochemistry.
Results: STZ-diabetes caused a 3-fold increase in CD (pro)renin content which was completely abolished by telmisartan, but not by ramipril or telmisartan + ramipril combined. Similarly, renal tissue and plasma prorenin levels increased 2-fold in STZ-diabetes which was prevented by telmisartan (0.8-fold of control), but not by ramipril (2.2-fold) or telmisartan + ramipril combined (1.8-fold). Similarly to ANGII, bradykinin increased immunoreactive (pro)renin content in cultured CD cells 35-fold which was prevented by the bradykinin B2 receptor blocker HOE-140.
Conclusion: Elevated CD prorenin content in high ANGII states is most effectively inhibited by telmisartan monotherapy. Combined ARB+ACEI is associated with high CD synthesis and plasma levels of prorenin most likely due to the direct stimulatory effect of bradykinin. These findings could be one potential molecular mechanism behind the apparent lack of benefit observed with the combination in the ONTARGET trial.

P1432 Insulin-like growth factor system activity is associated with the course of coronary artery disease

A. Ushakov, D. Mitrushkin, K. Selivanova, A. Gagarina. *Crimea State Medical University, Simferopol, Ukraine*

Purpose: Comparative study of insulin-like growth factor (IGF) system in patients with stable course of coronary artery disease (CAD) versus patients with the history of acute coronary syndrome (ACS) episodes.
Methods: The total of 90 CAD patients were included: group I - 50 patients with coronary atherosclerosis without history of ACS; group II - 40 patients with coronary atherosclerotic lesion and history of ACS episodes (unstable angina pectoris or non-Q-wave myocardial infarction) but stable for at least 6 months at the moment of examination. Groups were age, gender, duration of CAD (5.4±1.2 and 4.7±1.5 years) and cardiovascular risk factors matched. Patients having any concomitant diseases known to influence IGF system, history of Q-wave myocardial infarction, heart failure, diabetes mellitus were not enrolled in the study. Control group was age and gender matched with study groups and included 20 persons without angiographic signs of coronary atherosclerosis and without clinical manifestations of CAD.

Serum levels of IGF-I, IGF-I binding protein-3 (IGFBP-3) were measured by enzyme-linked immunosorbent assay. Expression of IGF-I type 1 receptors (IGF-1R) on CD14+ blood cells was assessed by flow cytometry.
Results: Serum level of IGF-I in patients with stable course of coronary atherosclerosis was higher, than in the controls (168.3±12.0 vs 140.9±6.1 ng/ml, $p<0.05$) while concentration of IGFBP-3 was lowered (2597.7±90.4 vs 3036.0±131.2 ng/ml, $p<0.05$). IGF-1R expression on CD14+ cells in group I was 19.9% lower ($p<0.05$) compared to controls, while the count of CD14+ cells was increased. In group II serum level of IGF-I was 18% lower compared to group I (138.2±9.1 vs 168.3±12.0 ng/ml, $p<0.05$). IGF-1R expression on CD14+ cells in group II in contrast was 71% higher than in group I (38.5±2.7 vs 22.5±1.9%, $p<0.05$). Serum levels of IGFBP-3 in group II did not differ from group I. Multifactor analysis has shown that IGF system and CAD course associations are independent from classic cardiovascular risk factors.
Conclusions: The data testify to the influence of IGF system on the development of coronary atherosclerosis. Increased activity of IGF system is associated with stable course of CAD. The lack of IGF system activation in patients with coronary atherosclerosis is associated with vulnerability of the lesion and predisposition to the development of coronary atherothrombosis and ACS.

P1433 Myocardial remodeling of the right atrium in patients with ventricular septal defect

E. Czarnowska, A. Turska-Kmiec, M. Brudek, W. Kawalec, J. Daszkowska-York, W. Lipinski, L. Ziolkowska, M. Pronicki. *Child's Health Center in Warsaw, Warsaw, Poland*

The presence of ventricular septal defect (VSD) provides the basis for serious clinical presentation in which cellular abnormalities are not known. Noninvasive Echo estimation of RV systolic pressure from systolic pressure gradient between left and right ventricle (Gr LV-RV) helps to treat pts with VSD properly. The aim of this study was to evaluate effects of haemodynamic abnormalities on myocardium of RA remodeling in pts with VSD.
Tissue samples of RA were obtained from 16pts (aged 4-22 month) undergoing transatrial surgical closure of VSD. Preoperative Echo revealed in 3pts subaortic, 13 pts –perimebranous defect, with left to right shunt, good systolic function of LV, increased diameter of: LV and LA, main pulmonary artery. Two groups of pts were defined according to Gr LV-R: (A) <64mmHg, 7pts and (B) >67mmHg, 9pts. Tissue samples were investigated using routine histopathological, histochemical (Trichrom Masson staining and PAS) and immunohistochemical methods to define inflammatory cell infiltration, apoptosis, desmin and PPARα expression, and ultrastructural sections. Cardiomyocytes were organized in a well-aligned and striated network, myocardial tissue infiltrated by similar number of LCA and CD68 positive cells and no CD4 and CD8 positive lymphocytes in both group. Tendency to decreased fibrosis and increased compensative expression of desmin in cardiomyocytes was in group A. Ultrastructural investigations revealed increase in number of mitochondria in cardiomyocytes in both groups. In group A swollen mitochondria with irregular matrix and disarrangement of cristae, and nuclei with abnormal distribution of heterochromatin and single apoptotis were characteristic feature. Interestingly only in single cardiomyocyte nuclei (in about 2%) expression of PPARα was found in this group. While in group B the PPARα was expressed in 13,71±3,71% nuclei and followed by increased accumulation of PAS(+) material. Ultrastructure of intercalated disk revealed short desmosomes and irregular fascia adherens in both group. Data obtained from RA tissue samples suggest an enhanced desmin expression as marker of early stage of haemodynamic dysfunction followed by unfavourable myocardial remodelling progress in which increased number of mitochondria is probably feature dedicated to compensate myocardial metabolic order. Decreasing of systolic pressure Gr LV-RV may indicate more advanced myocardial remodeling in pts with VSD.

P1434 Effects of physical training and aortic constriction on electrical and mechanical activity in rat papillary muscles

A. Scridon[1], D. Dobreanu[1], M. Perian[1], R.C. Serban[2]. *[1]University of Medicine and Pharmacy, Department of Physiology, Targu Mures, Romania; [2]Institute of Cardiovascular Diseases and Transplant, Targu Mures, Romania*

Background: The mechanism that differentiates physiological and pathological left ventricular hypertrophy (LVH) is far from clear.
Material and Methods: 60 Wistar rats were assigned to four groups: control (CONT), physiological LVH (PHYS), pathological LVH (PATH) and SHAM operated (SHAM). PHYS was submitted to swimming for 90 min/day, 5 days/wk, 6 weeks. For PATH, the aorta was isolated above the origin of renal arteries, a needle of 0.6g was placed longitudinally and the aorta was reduced to the dimensions of the needle. LV weight/body weight ratio, histological measurement of myocites were used in order to confirm LVH. Action potential duration to 90, 75, 50 and 25% of complete repolarization (APD) and the velocity of depolarization ($\Delta p/\Delta t$) were used as electrical parameters, and peak tension (PT), time to peak tension (TPT) and time to half relaxation (T1/2R) as mechanical parameters. The parameters were then compared: PHYS vs CONT, PATH vs SHAM.
Results: For both PHYS and PATH the criteria for LVH were fulfilled. The APD prolongation was based especially on the prolongation of depolarization for PHYS (APD25 increase 53.9%, $p<0.001$) and of repolarization for PATH (APD90 increase 81.6%, $p<0.001$). Both groups showed a significant increase in PT, TPT and T1/2R ($p<0.001$ for both PHYS vs CONT and PATH vs SHAM). There was a significant correlation between APD75, APD50 and all parameters of contraction for PHYS and only with TPT and T1/2R for PATH.

Electrical and mechanical parameters

Parameter	CONT	PHYS	PATH	SHAM
APD90 (msec)	75.44±1.03	89.11±0.43	136.98±0.44	75.22±0.49
APD75 (msec)	45.44±0.67	54.51±0.61	78.11±0.45	45.56±0.47
APD50 (msec)	21.12±0.61	29.91±0.51	26.06±0.59	21.29±0.26
APD25 (msec)	13.02±0.83	21.39±0.58	14.41±0.38	13.09±0.27
$\Delta p/\Delta t$ (V/sec)	15.49±0.62	6.69±0.19	13.61±0.23	15.21±0.25
PT (μN)	485.6±2.28	746.06±2.76	880.06±1.66	484.33±2.02
TPT (msec)	87.96±2.30	110.03±0.53	105.02±0.21	88.02±0.37
T1/2R (msec)	126.02±2.76	194.02±0.59	220.06±1.43	126.54±0.51

Conclusions: The repolarization prolongation in PATH could explain cardiac arrhythmia in patients with pathological LVH. The fact that PHYS showed a significant correlation between all parameters of contraction and APD suggests that this state doesn't develop alterations in electro-mechanical coupling, meanwhile PATH does.

P1435 Effects of high altitude exposure on 24 h ambulatory blood pressure - the HIGHCARE2008 project

G. Bilo[1], B. Bilo[2], M. Revera[1], G. Caldara[2], A. Giuliano[1], F. Gregorini[2], K. Styczkiewicz[3], A. Faini[1], G. Mancia[1], G. Parati[1] on behalf of HIGHCARE Team. *[1]Univ. Milano Bicocca; Istituto Auxologico Italiano IRCCS, Milan, Italy; [2]Istituto Auxologico Italiano IRCCS, Milan, Italy; [3]Jagiellonian University, Krakow, Poland*

Background: High altitude induces physiological changes that may simulate the effects of some chronic pathological conditions. An increase in blood pressure (BP) was previously reported on the basis of spot conventional measurements, but the effects on 24 h BP profile and its time course under prolonged permanence at high altitude are unknown. Aim: to assess changes in 24h ambulatory BP during acute and prolonged high altitude exposure.
Methods: In 21 healthy, normotensive volunteers (age 37.6±9.5, 14 M/7 F, BMI 21.7±2.4 kg/m^2) ambulatory BP monitoring (ABPM) was performed with validated Spacelabs devices: 1) at sea level (SLbas); 2) during acute (1-3 days) exposure to altitude of 3500 m a.s.l. (Ac); 3) 1-3 days after ascent to Everest Base Camp at 5400 m a.s.l. (BC1); 4) after 7-9 days' at Base Camp (BC2); 5) within 5 days after return to sea level (SLret).
Results: Average systolic (S) and diastolic (D) BP values and heart rate (HR) are shown in Table [p (ANOVA) always <0.001 between SL and altitude conditions].

Table 1

		SLbas	Ac	BC1	BC2	SLret
SBP(mmHg)	24 h	116.4±8.6	125±8.7	130.7±11.2	127.8±12.1	117.6±8.7
	Day	121.7±9.6	130±9.7	134.6±12	132.1±11.8	122.5±8.7
	Night	105.1±8.3	113.9±8.2	123.4±11.8	120±13.6	108.8±10
DBP (mmHg)	24 h	74±5.8	81.1±5.7	84.2±6.6	83.7±7.7	75±6.1
	Day	78.8±6.7	86.3±6.3	88.5±7.8	88±7.5	80.6±6.4
	Night	63.6±5.6	69.9±5.8	76.1±6.7	75.6±9.3	64.9±7.1
HR (bpm)	24 h	68.8±9.3	81.1±9.7	86.7±13.2	84.1±11.2	71.4±9
	Day	73.2±10.3	86.7±9.5	93.7±13	92.3±12.2	76.4±10.4
	Night	59.2±8.5	69±10.8	73.5±14.8	68.8±10.8	62.3±8.4

Conclusions: Ambulatory BP shows a sustained increase over 24 h at high altitude, proportional to the altitude reached, persisting under prolonged permanence at very high altitude. At very high altitude BP rise was particularly pronounced at night, with a pronounced nocturnal BP fall. BP values returned to baseline immediately after return to sea level. These data may have implications for the management of subjects exposed to high altitude hypoxia and may be relevant to understanding and management of BP changes in patients with chronic hypoxemia

P1436 Abnormal muscle vascular responses during exercise in patients with recent myocardial infarction

M.U.B. Rondon[1], D.G. Martinez[1], J.C. Nicolau[1], R.L. Lage[1], M.C. Laterza[1], I.C. Trombetta[1], L.D.J. Matos[1], C.E. Negrao[2]. *[1]Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil; [2]School of Physical Education and Sport USP, Sao Paulo, Brazil*

Purpose: It has been shown previously that myocardial infarction (MI) leads to an increased sympathetic nerve activity and a decreased peripheral blood flow. However, the neurovascular control during exercise in patients with recent MI remains poorly understood. We tested the hypothesis that muscle sympathetic activation would be exacerbated and muscle vasodilatation would be reduced during exercise in patients with recent MI.
Methods: We studied prospectively 23 patients between 30 and 40 days post MI (mean 39±2 days) (mean age 52±2 years; 74% males, ejection fraction= 56±1%) and 8 age-matched healthy controls (C) during handgrip exercise (3 minutes) at 30% of maximal voluntary contraction. Muscle sympathetic nerve ac-

tivity (MSNA) and forearm blood flow were measured by microneurography technique and venous occlusion plethysmography, respectively. Blood pressure was monitored noninvasively and intermittently from an automatic and oscillometric cuff.
Results: Baseline MSNA was higher (57±4 vs. 35±2 bursts/100HB, P=0.006) and forearm vascular conductance (FVC) lower (1.62±0.1 vs. 2.97±0.4 units, P<0.002) in MI patients when compared with C. Mean blood pressure was similar between groups (90±5 vs. 86±2 mmHg, P=0.61). MSNA increased significantly and similarly during exercise in both groups (58±4 to 65±4 bursts/100HB for MI, P<0.001, and 36±2 to 47±3 bursts/100HB for C, P<0.001). On the other hand, FVC increased significantly during exercise in C (2.60±0.3 to 4.13±0.6 units, P<0.001), but not in MI patients in whom FVC was unchanged (1.48±0.1 to 1.53±0.2 units, P=0.99).
Conclusion: MSNA responses during exercise are preserved in patients with recent MI. In contrast, FVC responses during exercise are reduced in patients with MI. These findings highlight abnormal muscle vascular responses, but not sympathetic nervous responses, during physiological maneuvers in patients with recent MI.

P1437 Decreased ventilatory response to exercise by dopamine-induced inhibition of peripheral chemosensitivity

C. Janssen, S. Beloka, P. Kayembe, G. Deboeck, D. Adamopoulos, R. Naeije, P. Van De Borne. *Erasme University Hospital, Brussels, Belgium*

Purpose: The contribution of the peripheral chemoreflex to the ventilatory response to exercise and aerobic exercise capacity remains incompletely understood. Low-dose dopamine has been reported to specifically inhibit the peripheral chemoreceptors.
Material and methods: We investigated the effects of intravenous dopamine (3 $\mu g\ kg^{-1}\ min^{-1}$) on muscle sympathetic nerve activity (MSNA), heart rate, blood pressure, pulse oximetry (SpO2) and ventilation (VE) during normoxia, isocapnic hypoxia, hyperoxic hypercapnia, a handgrip manoeuvre, and on cardiopulmonary exercise test (CPET) variables, in 13 healthy young male subjects. The study was prospective, placebo-controlled, randomised and followed a cross-over design with more than 24 hours between placebo and dopamine administrations.
Results: Dopamine increased MSNA, heart rate and blood pressure in normoxia but not in hypercapnia or during handgrip manoeuvre. Dopamine decreased SpO2 and VE in hypoxia, and approximately halved the ventilatory response to hypoxia measured as $\Delta VE/\Delta SpO2$ (0.19±0.09 vs. 0.09±0.09 L min^{-1}.%-1.m-2, placebo vs. dopamine, p=0.002). Dopamine decreased the VE/VCO2 output slope during the CPET (23.09±1.81 vs. 24.61±1.84, dopamine vs. placebo, p=0.025), without affecting maximum workload, VE and O2 uptake.
Conclusion: Specific inhibition of peripheral chemoreflex function with dopamine decreases the ventilatory response to dynamic exercise, with no interference with the metabolic reflex, and no change in aerobic exercise capacity.

P1438 Isoform-specific activation of NFAT signalling in ANGII and NA-stimulated neonatal cardiomyocytes of mice

I.G. Lunde, G. Christensen, C.R. Carlson. *Institute for Experimental Medical Research, Oslo University Hospital, Ullevaal, Oslo, Norway*

A fundamental mechanism involved in cardiac hypertrophy and subsequent heart failure is sympathetic adrenergic hyperactivity accompanied by activation of the renin-angiotensin system, in which noradrenaline (NA) and angiotensin II (ANGII) are primary effectors mediating hypertrophic, apoptotic and fibrotic events in the heart. As NA and ANGII have been shown to affect intracellular calcium in cardiomyocytes, we hypothesize that the calcium-sensitive calcineurin-Nuclear Factor of Activated T-cell (NFAT) signalling pathway is activated downstream of these factors. More specifically, our aim was to investigate isoform-specific activation of NFATs in ANGII and NA-mediated hypertrophy. The NFAT transcription factors have previously been shown to be important in the regulation of pathological hypertrophy in cardiomyocytes, and it is likely that each of the four isoforms, termed c1-c4, play specific roles in this regulation. However, little is known about the endogenous protein expression of the NFATs in cardiomyocytes, their differential regulation or their possible role in ANGII or NA signalling.
We have stimulated neonatal ventriculocytes from C57/B6 mice for 5, 10, 15 or 30 minutes or 24 hours with 1 μM ANGII or 100 μM NA. NFAT activity was quantified on Western blots using specific antibodies against the phosphorylated, inactive form of the isoforms.
Our results show that both ANGII and NA regulate the activity of NFATc4 and NFATc1, however neither of them regulate the activity of NFATc2 or NFATc3. More specifically, after 24 hours, the level of pNFATc4 was reduced by 31 and 19% by ANGII and NA stimulation, respectively. Similarly, pNFATc1 was reduced by 11 and 16% (n=4). ANGII reduced the level of pNFATc4 by 43% already after 10 minutes of stimulation and pNFATc1 by 41% after 30 minutes, while NA reduced pNFATc4 by 22% after 30 minutes of stimulation (n=3).
To our knowledge, we are the first to show isoform-specific activation of endogenous NFATs in isolated cardiomyocytes and we here demonstrate that the NFAT signalling system is controlled by both ANGII and NA. As today's main therapies for heart failure aim at antagonizing the adrenergic and renin-angiotensin systems, understanding their molecular mechanisms of action is of clinical importance, and our data indicate that ANGII and NA act partly through activation of the NFAT signalling system.

DIABETES

P1439 Increased cardiovascular mortality associated with glibenclamide and tolbutamide in diabetic patients with acute myocardial infarction that undergo early percutaneous coronary intervention

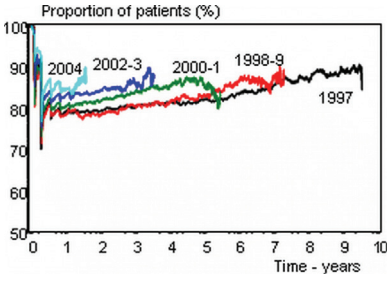
C.H. Joergensen[1], G.H. Gislason[2], D.M. Bretler[1], R. Soerensen[1], T.K. Scramm[2], S.Z. Abilstroem[3], C. Torp-Pedersen[1], P.R. Hansen[1]. *[1]Department of Cardiology, Gentofte Hospital, Hellerup, Denmark; [2]Rigshospitalet (The Heart Centre), Copenhagen, Denmark; [3]Glostrup University Hospital, Glostrup, Denmark*

Purpose: Sulfonylurea glucose-lowering agents (SU) have been linked to increased cardiovascular risk, e.g., by inhibition of myocardial preconditioning, and this effect may be increased in patients with acute myocardial infarction (AMI) undergoing early reperfusion. We therefore conducted a nation-wide study to examine the impact of SU on the prognosis of patients with AMI receiving early percutaneous coronary intervention (PCI).
Methods: We identified all Danish patients treated with glucose-lowering agents who were admitted with first-time AMI in the period 1997-2006 and underwent PCI within 48 hours of admission. Multivariable Cox proportional-hazard models with time-dependent covariates were used to analyze the risk of cardiovascular death and non-fatal and fatal AMI associated with SU compared to treatment with metformin.
Results: The study included 845 patients of whom 212 died during the observation period. The overall cumulative 1 year mortality rate was 17,5%. Adjusted Cox proportional-hazard analysis showed increased risk of cardiovascular death with glibenclamide (hazard ratio [HR] 2,56; 95% confidence interval [CI] 1,07-6,14; p=0.0355) and tolbutamide (HR 2,65; 95% CI 0,96-7,30; p=0.0600) monotherapies, compared to patients receiving metformin alone. Moreover, the risk of fatal or non-fatal AMI was increased in patients receiving glibenclamide (HR 2,34; 95% CI 1,02-2,57; p=0.0453) and tolbutamide (HR 2,64; 95% CI 1,00-6,97; p=0.0500). The risks of cardiovascular death and fatal or non-fatal AMI were not significantly increased in patients receiving the newer generation SU (glicazide, glipizide, and glimepiride) alone or in combination with insulin.
Conclusions: In diabetic patients with AMI undergoing early PCI, treatment with glibenclamide and tolbutamide is associated with increased risk of cardiovascular death and fatal and non-fatal AMI compared to patients receiving metformin. Such adverse outcomes were not observed with newer generation SU or combination glucose-lowering therapy.

P1440 Initiation and adherence to statin treatment in patients with diabetes receiving glucose-lowering medications 1996- 2007

H. Dominguez[1], T.K.S. Schramm[2], G.H.G. Gislason[3], S.Z.A. Abidstrom[4], L.K. Kober[2], C.J. Jorgensen[1], M.L.N. Nygaard[1], T.G. Guterbaum[5], H.E.P. Poulsen[2], C.T.P. Pedersen[1]. *[1]Copenhagen University Hospital, Gentofte, Copenhagen, Denmark; [2]Rigshospitalet (The Heart Centre), Copenhagen, Denmark; [3]Copenhagen University Hospital, Heart Center, Rigshospitalet, Copenhagen, Denmark; [4]National Institute of Public Health, Copenhagen, Denmark; [5]Panum Institute, Copenhagen, Denmark*

Objective: Since 2001 guidelines recommend statin treatment in patients with diabetes. We investigated secular changes in initiation and adherence to statin treatment during a 10-year period in a nationwide cohort of patients receiving glucose-lowering medication (GLM).
Methods: All Danish citizens 30 years and older who claimed prescriptions of GLM and statins between 1996 and 2004 were identified from nationwide registers of drug dispensing from pharmacies and hospitalization, and followed until end of 2006. By logistic regression we identified factors (age, sex, year of GLM initiation, previous myocardial infarction and income) related to initiation and persistence to statin treatment.



Results: A total of 174 537 diabetes patients were included. In 1997, less than 5% of the patients on GLM received statins within the first year since GLM prescription, increasing to 32.7% in 2004. Despite increasing statin prescriptions over the 10-year observation period, less than 60% were using statins at the end of follow up. The chance to ever receive statins was lowest if not initiated within 180-days following the first purchase of GLM (odds ratio (OR) 0.75, 95% CI 0.74-0.76). Previous myocardial infarction was associated with increased statin treatment (OR 6.87; 95% CI 6.47 -7.29), while low income was associated to lower use of statins (OR 0.67; 95%CI 0.63-0.71). Between 75-85% of the patients who initiated statins treatment were persistent to treatment by 2007.
Conclusions: Prescription of statins in patients has increased slowly over time but most patients remain untreated. Those who started were persistent to treatment. Focus is needed on early initiation of statin treatment in diabetic patients for long-term benefits.

P1441 Effects of pioglitazone on body weight in the PROactive study population: The obesity paradox in type 2 DM patents with high risk of cardiovascular events

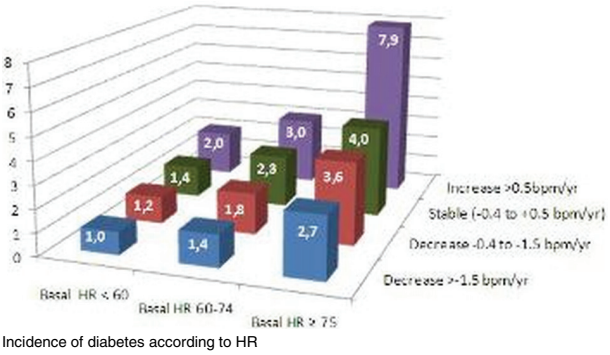
W. Doehner[1], E. Erdmann[2], R. Cairns[3], J.A. Dormandy[4], E. Ferrannini[5], S.D. Anker[1]. [1]*Charite - Campus Virchow-Klinikum, Berlin, Germany;* [2]*Universitaetsklinikum Koeln, Cologne, Germany;* [3]*Clinical Trials Center, Nottingham, United Kingdom;* [4]*St George's Healthcare NHS Trust, London, United Kingdom;* [5]*University of Pisa Medical School, Pisa, Italy*

Background: Weight gain due to glitazone treatment is regarded as an unwanted effect as weight gain is unanimously perceived to deteriorate of metabolic balance, cardiovascular (CV) risk and outcome. In contrast, an obesity paradox has been termed in CV patients to describe the survival advantage of overweight patients. The impact of weight gain and weight loss in diabetic patients with CV co-morbidity is not clear.
Methods: Body mas index (BMI) and weight change were assessed in association to all cause mortality in the PROactive study population. PROactive was a double-blind, placebo controlled outcome study including 5,238 patients with type 2 DM and evidence of pre-existing CV disease. Patients were randomized to pioglitazone (n= 2605) or placebo (n=2633) in addition to their concomitant glucose-lowering and CV medication. Mean Follow up was 34.5 months.
Results: Pioglitazone induced significant weight gain (mean 3.8±6.4 kg) compared to placebo (-0.6±5.6 kg, P<0.0001) and the degree and frequency of weight gain were not dependent of BMI at baseline. Weight gain in the pioglitazone group when adjusted for oedema was a significant predictor of improved survival in univariable Cox analysis (HR for 1% weight gain 0.96 [0.92-1.00] P=0.037). In multivariable analysis including all 14 cardiovascular risk factors of the primary prospective PROactive analysis weight gain remained an independent predictor of improved survival (HR 0.96 [0.92-1.00] P=0.035). No such effect was observed in the placebo group. Weight loss, in turn, was predictive of increased mortality in both groups in univariable and multivariable analysis (all p<0.0001).
Cox proportional hazard analysis of BMI at baseline showed the lowest risk for all cause mortality for patients with BMI 30-35 kg/m^2. In the placebo group, patients with BMI <22 kg/m^2 (HR 2.96 [1.27-6.86; P=0.012) and BMI 22-25 kg/m^2 (HR 1.88 [1.11-3.21]; P=0.019) had a significant increased risk of all-cause mortality. This paradox association of body weight and survival was abrogated in the pioglitazone group, where no significant differences in mortality between BMI subgroups has been observed.
Conclusion: Pioglitazone induced and oedema-free weight gain predicts improved survival independent of other prognostic markers in the PROative study population. In contrast, weight loss is associated with impaired survival in these diabetic patients. Increased mortality in "normal" BMI patients as compared to overweight patients suggests the presence of an obesity paradox in patients with type 2 DM and CV disease. Pioglitazone may in part reverse this obesity paradox.

P1442 Heart rate as an independent predictor of new onset diabetes in a presumably healthy population. The IPC cohort

N. Danchin[1], F. Thomas[2], K. Bean[2], E. Eschwege[2], O. Hanon[2], T. Simon[3], B. Jego[2], B. Panier[2]. [1]*European Hospital George Pompidou (AP-HP), Paris, France;* [2]*IPC centre, Paris, France;* [3]*AP-HP - Hopital St Antoine, Paris, France*

Aim: to determine factors related to occurrence of new onset diabetes (NOD) in a population screened at a preventive medicine centre.
Methods: We identified a population of 62,014 subjects having had 2 visits at the IPC centre, 6 years apart on average. Among those, we selected the subjects without antidiabetic medications and in whom fasting glycemia at first visit was <126 mg/dL. Occurrence of NOD was defined as either treatment with antidiabetic medication or fasting blood glucose ≥126 mg/dL at follow-up visit. Baseline HR was categorised in tertiles and annual change in HR in quartiles.
Results: 1462 patients (2.4%) developed NOD. In univariate analyses, both baseline HR and change in HR between the 2 visits were correlated with NOD: % of patients with NOD increased from 1% if baseline HR <60 bpm and HR decrease >-1.5 bpm/year to 7.9% if baseline HR >75 bpm and HR increase >0.5 bpm/year (Figure). In multivariate analyses, both baseline HR>75 bpm and annual change in HR were independent predictors of NOD: OR=1.52 (95%CI: 1.31-1.75) for baseline HR >75 bpm; OR =1.33 (95%CI:1.13-1.57) for annual increase >0.5 bpm, OR=0.86 (95%CI: 0.72-1.02) for annual decrease from -0.4 to -1.5 bpm, OR=0.72 (95%CI: 0.59-0.86) for annual decrease > -1.5 bpm, compared with patients with HR stable over time. Other independent correlates were older age, male gender, BMI, high waist/hip ratio, higher baseline SBP, family history of DM, lower education, higher baseline glycemia, lower potassium, higher triglyceride/cholesterol ratio, higher gamma GT, higher WBC count.



Incidence of diabetes according to HR

Conclusion: Elevated heart rate is a correlate of the occurrence of NOD in apparently healthy individuals. The fact that the risk of NOD diminishes when HR decreases (and conversely) may suggest a causal role for HR in the occurrence of diabetes.

P1443 New-onset diabetes mellitus and cardiovascular events: a 6 years prospective study in a cohort of 1446 Greek hypertensives

D. Tsiachris, C. Tsioufis, E. Vezali, C. Thomopoulos, D. Chatzis, G. Hararis, A. Portsi, E. Taxiarchou, A. Moulakakis, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: The impact of new-onset Diabetes mellitus (DM) on cardiovascular outcome in hypertensive patients remains controversial. The purpose of our study was to determine the incidence of new onset DM in treated non-diabetic hypertensives and to evaluate its effect on CAD and stroke.
Methods: We followed-up 1446 non-diabetic hypertensives (aged 54.2 years, body mass index 28.4 kg/m^2, office BP 146/93 mmHg,) for a mean period of 6 years and cases of new onset DM (fasting plasma glucose ≥126 mg/dl) were recorded. The incidence of CAD (presence of at least one of the following: myocardial infarction, PTCA, CABG, significant stenosis at angiography), and stroke (defined as rapid onset of a new neurological deficit persisting at least 24 hours unless death supervened) were examined. Odds ratios (OR) and confidence intervals (CI) were calculated for each group using multivariate logistic regression analyses.
Results: During follow-up period, the incidence of new-onset DM was11.5% while new or recurrent cases of CAD and stroke were 7.3% and 6.2%. The independent predictors for new-onset DM were family history of DM, age, body mass index, waist to hip ratio, serum glucose and triglyceride levels (p<0.001 for all cases), systolic blood pressure (p=0.018) and antihypertensive treatment (p=0.02). Hypertensive subjects with new onset DM compared to those who did not develop DM, exhibited higher incidence of stroke (10.2% vs 4.4%, p=0.001, OR 2.48, 95% CI: 1.41 to 4.38), especially of the ischemic type (7.2% vs 1.6%, p<0.001, OR 4.88, 95% CI: 2.34 to 10.17). However, groups did not differ regarding the incidence of CAD (6.6% vs 5.2%, p=0.458).
Conclusion: In our cohort the large proportion of hypertensives who developed DM (11.5%) supports and extends the pathophysiological link between hypertension and dysregulation of glucose metabolism. Moreover, new-onset DM exerts its adverse effect prominently on cerebral vasculature rather than on coronary circulation in the setting of hypertension.

P1444 Saxagliptin improves glycaemic control either as add-on therapy to metformin or as initial combination therapy with metformin in patients with type 2 diabetes

I. Gurieva[1], A. Pfuetzner[2], M. Antsiferov[3], E. Allen[4], S. Ravichandran[4], R. Chen[4]. [1]*Federal Bureau of Medicine and Social Expertise, Moscow, Russian Federation;* [2]*Institute for Clinical Research and Development, Mainz, Germany;* [3]*Endocrinology Dispensary, Moscow, Russian Federation;* [4]*Global Clinical Research, Bristol-Myers Squibb, Princeton, New Jersey, United States of America*

Purpose: Diabetes is a risk factor for cardiovascular disease, and optimal glycaemic control is important in reducing the risk of coronary events. Saxagliptin

(SAXA) is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme. The efficacy and safety of SAXA was assessed in two Phase III trials (CV181014/Study 1 and CV181039/Study 2), either as add-on therapy in patients with 2 diabetes mellitus (T2DM) inadequately controlled by metformin (MET) alone (HbA1c 7.0%–10.0%) or as initial combination therapy with MET in drug-naïve T2DM patients (HbA1c 8.0%–12.0%), respectively.

Methods: Following a placebo (PBO) run-in, patients (n=743) on MET in Study 1 were randomised to receive once-daily SAXA 2.5, 5 or 10 mg, or PBO, plus their stable MET dose, and drug-naïve patients (n=1306) in Study 2 were randomised to receive SAXA/MET 5/500 mg (S5/MET), 10/500 mg (S10/MET), SAXA 10 mg or MET 500 mg once-daily. In the MET treatment arms of Study 2, MET was up-titrated incrementally (Weeks 1–5) to a maximum of 2000 mg/day. HbA1c change from baseline at Week 24 was the primary endpoint for both studies.

Results: Treatment groups were well balanced at baseline for HbA1c (Study 1, 8.0%–8.1%; Study 2, 9.4%–9.6%). At Week 24, significant ($p<0.0001$) reductions in adjusted-mean HbA1c change from baseline were observed in Study 1 for SAXA 2.5, 5 and 10 mg (–0.59%, –0.69% and –0.58%, respectively), compared with PBO (0.13%), and in Study 2 for S5/MET (–2.53%) and S10/MET (–2.49%), compared with SAXA (–1.69%) or MET (–1.99%) alone. In each study, SAXA plus MET provided significant ($p<0.001$) reductions in fasting plasma glucose and postprandial glucose, increased proportions of patients with therapeutic glycaemic response (HbA1c <7%), and was well tolerated with no increased incidence of hypoglycaemia compared with matched controls.

Conclusions: SAXA add-on or initial combination therapy with MET provided significant and clinically meaningful reductions in key parameters of glycaemic control and was well tolerated in patients with T2DM.

P1445 Preoperative oral glucose tolerance testing in vascular surgery patients; long-term cardiovascular outcome

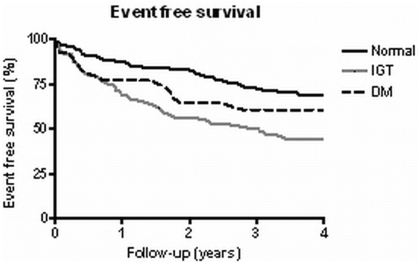
J.P. Van Kuijk[1], M. Dunkelgrun[1], F. Schreiner[1], W.J.P. Flu[1], W. Galal[1], R.T. Van Domburg[2], S.E. Hoeks[1], Y.R.B.M. Van Gestel[1], J.J. Bax[3], D. Poldermans[2]. *[1]Erasmus MC, Rotterdam, Netherlands; [2]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [3]Leiden University Medical Center, Leiden, Netherlands*

Background: Diabetes Mellitus (DM) is an important risk factor in vascular surgery patients, influencing late outcome. Screening for diabetes is recommended by fasting glucose measurement. Oral glucose tolerance testing (OGTT) could enhance the detection of patients with impaired glucose tolerance (IGT) and DM.

Aim: To asses the additional value of OGTT on top of fasting glucose levels in vascular surgery patients to predict late cardiovascular outcome.

Methods: 404 patients without signs or histories of IGT (plasma glucose 7.8-11.1mmol/l) or DM (glucose ≥11.1mmol/l) were prospectively included and subjected to OGTT. Cardiac risk factors were noted. Primary outcome was the occurrence of late cardiovascular events (composite of cardiovascular death, angina pectoris, myocardial infarction, PCI/CBAG or CVA/TIA), and secondary outcome included all-cause and cardiovascular mortality rates, in survivors of vascular surgery. Median follow-up was 3.0 [interquartile range 2.4 - 3.8] years.

Results: IGT (n=104) and DM (n=43) were detected by fasting glucose levels in 26 (25%) and 12 (28%) patients, and by OGTT in 78 (75%) and 31 (72%) patients, respectively. During follow-up, 131 patients experienced a cardiovascular event. Using multivariable analysis, patients with IGT showed a significant increased risk for cardiovascular events (HR 2.77, 95% C.I. 1.83-4.20) and mortality (HR 2.06 95% C.I. 1.03-4.12). Patients with DM showed a non-significant increased risk for cardiovascular events.



Conclusion: Vascular surgery patients with IGT or DM detected by pre-operative OGTT, have an increased risk of developing cardiovascular events and mortality during long-term follow-up. It is recommended that non-diabetic vascular surgery patients should be tested for glucose regulation disorders prior to surgery.

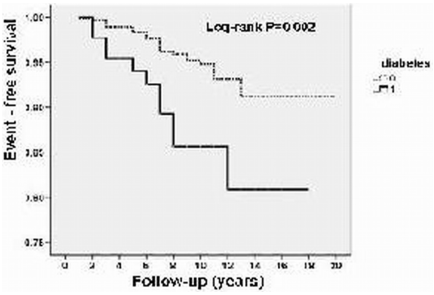
P1446 The impact of diabetes on major cardiovascular events in patients with familial combined hyperlipidemia

C. Masoura, I. Skoumas, C. Pitsavos, K. Aznaouridis, V. Metaxa, F. Platsouka, L. Papadimitriou, T. Tsokanis, N. Giotsas, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: To evaluate the impact of diabetes mellitus (DM) on cardiovascular risk in patients with familial combined hyperlipoproteinemia (FCH).

Methods: We studied prospectively 657 FCH patients (423 males) for 8.9±3.8 years. Demographic characteristics and biochemical parameters were measured at enrolment, before the initiation of treatment. Diagnosis of DM was made according to the ADA criteria. Hard cardiovascular end-points, like acute myocardial infarction (AMI) and cardiovascular death, were recorded.

Results: Compared to the non-diabetics, the 87 patients with DM were older (52.4±9.2 vs. 48.4±11.0 years, P=0.002) and had higher waist/hip ratio, triglycerides and glucose levels, but they had lower HDL-C levels (all $P<0.001$). The combined endpoint (AMI and/or deaths) occurred in 11 patients with DM and 27 patients without DM (12.6% vs. 4.7%, P=0.003 by chi-squared test). Kaplan-Meier analysis showed a difference in the event-free survival between patients with and without DM (log-rank P=0.002, figure). Cox regression analysis showed that DM at enrolment predicts AMI and/or death at follow-up independent of age and sex (adjusted odds ratio 2.53, 95% CI 1.24-5.14, P=0.01).



Conclusions: Diabetes represents an independent predictor of major cardiovascular events in FCH patients.

P1447 Cardiac hypertrophy in diabetic mice is prevented by ablation of the G-protein Galpha11

H. Reuter[1], D. Hoyer[1], S. Groenke[1], Y. Korkmaz[1], T. Wilkie[2], N. Wettschureck[3], S. Offermanns[3], K. Addicks[1], E. Erdmann[1]. *[1]Universitaetsklinikum Koeln, Cologne, Germany; [2]UT Southwestern Medical Center, Dallas, United States of America; [3]Universitaetsklinikum Heidelberg, Heidelberg, Germany*

Large clinical studies provided evidence of a lower incidence of cardiac hypertrophy and contractile dysfunction in diabetic patients treated with Angiotensin II Type 1- (AT1)- receptor blockers. The AT1 receptor is coupled to the Gq class of G-proteins, which stimulate proteinkinase C (PKC) via activation of phospholipase Cβ. To study the role of the Gq protein Gα11 and its signaling through PKC in diabetic heart disease, we induced type 1 diabetes in wild type and Gα11 knockout mice by i.p. injection of streptozotocin.

After eight weeks of stable hyperglycemia (> 300 mg/dl), cardiac morphology and function were assessed in vivo by echocardiography and myocardial expression and translocation of PKC isoforms were determined by immunohistochemistry and immunoblot after tissue fractionation.

Diabetic wild type mice (n=8) developed ventricular hyertrophy with preserved systolic function. In contrast, diabetic Gα11 knockout animals (n=8) showed no signs of cardiac hypertrophy and maintained normal contractility. PKC isoforms α, βII, δ, ε, ζ and θ were all detected in myocardium of wild type animals. Compared to normoglycemic control animals, PKC isoforms α and ζ showed increased expression levels in diabetic wild type mice (PKCα [rel. units], control: 16.1±3.3, diabetic: 29.1±1.6, p=0.005; PKCζ, control: 32.1±4.6, diabetic: 48.8±3.9, p=0.02). In addition, PKC ζ was phosphorylated at Thr410/403 and showed strong translocation to nuclear membranes in cardiomyocytes of diabetic but not of control animals. Hearts from normoglycemic Gα11-deficient mice showed lower expression levels of PKC isoforms α and δ compared to wild type control animals (PKCα [rel. units], wild type: 16.1±3.3; knockout: 6.9±1.1; p= 0.04; PKCδ [rel. units], wild type: 31.2±5.3; knockout: 17.0±1.2; p= 0.03). Upon induction of hyperglycemia in Gα11 knockouts, expression of PKC δ was slightly increased to the level found in non-diabetic wild types. Expression, phosphorylation and translocation of PKC α, βII, ε, ζ and θ, however, remained unaffected by the induction of diabetes in Gα11-deficient mice.

We conclude that Gα11 is central to the induction of myocardial hypertrophy in experimental type 1 diabetes. Activation of PKC α and ζ appear to be important pathways in hypertrophic sigaling via Gα11. The inhibition of this signaling pathway via Gα11 may in part explain the strong therapeutic benefit of AT1 receptor blockade in diabetic patients.

P1448 Acute mountain sickness and energy expenditure in type 1 diabetes during high altitude mountaineering

S.T. De Vries[1], P. De Mol[2], E.J.P. De Koning[3], A.W.J. Van 'T Hof[1], R.O.B. Gans[4], H.J.G. Bilo[1]. [1]*Isala Klinieken, Zwolle, Netherlands;* [2]*Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands;* [3]*Leiden University Medical Center, Leiden, Netherlands;* [4]*University Medical Center, Groningen, Netherlands*

Purpose: An increasing number of patients with Type 1 Diabetes Mellitus (T1DM) participate in extreme physical activities such as high altitude mountaineering which is known to require a considerable amount of energy. Higher altitudes and hypoxia are also associated with an increased risk of acute mountain sickness (AMS), reduced appetite and reduced exercise capacity. The objective of this study is to evaluate energy expenditure (EE) and AMS at high altitude and to determine whether subjects with T1DM are at a higher risk for developing AMS.
Methods: 16 subjects (8 T1DM and 8 Non-DM) climbed Mt Kilimanjaro during a 7-day expedition. A Sensewear Pro device was used, measuring EE in 8 subjects with T1DM, and in 7 controls. Seven subjects with T1DM and 8 non DM controls completed the Lake Louise AMS scoring list (5 items, score 0-3, max score 15).
Results: All 16 subjects (T1DM: 5 men and 3 women, 31.6±5.3 yrs, mean duration of DM 10.4±8.1 yrs, mean HbA1C 6.8±0.8%; non-DM: 4 men and 4 women, 43±10.2 yrs) reached the summit of Mt. Kilimanjaro (5895 m). AMS scores remained modest except for a significantly higher score on the summit day (day 7; $p<0.05$) and were not different between DM and non-DM subjects. EE was high, especially on the summit day, but no differences were observed between DM (baseline 3013±578 vs summit day 5044±937 Kcal/day; $p<0.01$) and non-DM subjects (baseline 2839±431 vs summit day 4843±735 Kcal/day; $p<0.01$). Weight loss during the climb amounted to 2,7 kg in DM and 1,9 kg in non-DM subjects (NS).
Conclusion: High altitude mountaineering is associated with similar degrees of AMS, EE and weight loss in T1DM patients compared to controls. Well-trained and prepared T1DM patients are able to participate in high altitude mountaineering with AMS symptoms and energy expenditure comparable to nondiabetic controls.

P1449 Renin-angiotensin system blockade improves the prognosis in diabetic patients. The Barbanza diabetes study

R.C. Vidal Perez, F. Otero-Ravina, J. Dopico-Pita, M.J. Eiris Cambre, A. Nores-Lorenzo, C. Caneda-Villar, J. Torres-Colomer, L. Grigorian, J.R. Gonzalez-Juanatey on behalf of Barbanza Diabetes Study. *Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, Spain*

Purpose: The renin-angiotensin system (RAS) blockade has shown to reduce the nephropathy risk and improve the prognosis of diabetics. However, we lack of "real world" data about the impact of this pharmacological intervention in diabetic patients not included in clinical trials. The objective is to known the influence of RAS blockade in an unselected population of diabetics in an outpatient setting
Methods: Multicenter prospective cohort study involved 1423 consecutive patients with diabetes mellitus who were recruited by 31 primary care physicians. The patients' characteristics were recorded and they were followed up for 45±10 months
Results: The mean age of the patients (50% male) was 66 years, 64% had hypertension, 70% had dyslipidemia, and 26% had had a previous cardiovascular event. The treatment profile of these patients shown RAS blockade in 55.1%, diuretics 20.9%, beta blockers 6.4%, calcium antagonists 18%, antiaggregants 20.9%, nitrates 6.8% and lipid lowering agents 44.9%. By the end of follow-up, 393 (30%) had been hospitalized, 179 (14%) of whom for cardiovascular disease, and 81 patients (6.2%) had died, 40 (3%) of whom due to cardiovascular causes. The multivariate analysis identified the following factors as independent predictors of mortality: age (hazard ratio [HR] =1.08; 95% confidence interval [CI], 1.05-1.11), previous cardiovascular disease (HR=2.15; 95% CI, 1.12-4.14) and diuretic treatment (HR=3.40; 95% CI, 1.76-6.56), while the prescription of an RAS blockade drug, angiotensin converting enzyme inhibitor or an angiotensin-receptor antagonist had a protective effect (HR=0.48; 95% CI, 0.25-0.93)
Conclusions: The RAS blockade diminish the mortality risk and major cardiovascular complications in an unselected population of diabetics in an outpatient setting

P1450 Adiponectin protects against type-2 diabetes in adult men

S. Sans[1], T. Padro[2], L. Badimon[2]. [1]*Institute of Health Studies, Department of Health, Barcelona, Spain;* [2]*Barcelona Cardiovascular Research Center, CSIC-ICCC, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Purpose: Adiponectin is secreted by adipose tissue and is crossectionally associated with a number of metabolic risk factors and hypertension. The purpose of this study is to investigate the longitudinal relationship of serum adiponectin levels with incidence of type-2 diabetes in a cohort of adult Mediterranean men.
Material and methods: A general population random sample cardiovascular survey was conducted during 1986-88 in men aged 35 to 68 years (n=1011, response rate 77%). This cohort was re-examined in 1996-97 (n=741, response rate 73%). Methods followed the WHO-MONICA protocol, plus the diabetes questionnaire of the Hispanic NHANES (national health and nutrition examination survey). Height and weight were measured with a roman balance. Body mass index (BMI) was calculated by Quetelet index. Blood pressure was measured with a random zero mercury sphygmomanometer. A 12-hour fasting venous blood sample was taken and analyzed within 24 hours for lipids and glucose with conventional enzymatic methods. HDL-cholesterol was measured by manual precipitation. Determination of adiponectin and insulin levels were carried out in serum kept frozen at -80°C by X-Map luminex technology. Type-2 diabetes was defined as 12-hour fasting glucose ≥7.0 mmol/l or self-report of diabetes diagnosed by a doctor. New onset diabetes was defined as absence of these criteria at baseline but presence at re-examination. Statistical analysis was carried out with SPPS-13, X2 test, ANOVA and logistic multiple regression. Prevalent diabetics were excluded for association analysis. Adiponectin and insulin variables were log transformed.
Results: Prevalence of type-2 diabetes was 8.9% (n=90) and incidence was 8/thousand.year (n=81), both increased with age. Mean adiponectin was 20.98 (sd 10.66) μgr/ml with no change with age. Incidence of new diabetes decreased significantly by quartiles of increasing adiponectin levels (X^2=21.34,df3, $p<0.0001$, ORQ4-Q1=0.15), while prevalent diabetes was not clearly associated with adiponectin level in crossectional analysis (X^2=5.46,df3,$p<0.142$). In multivariate logistic regression, log-adiponectin remained a significant predictor of new diabetes ten years later (OR=0.15, 95%CI 0.05-0.51), after adjusting for BMI, years of school, diastolic blood pression, HDL-cholesterol and HOMA index. Neither insulin levels nor HOMA index measured were significant predictors of onset of new diabetes.
Conclusion: Incidence of type-2 diabetes is high and serum adiponectin is a significant protector for diabetes-2, independently of BMI and lipid and glucose metabolism factors, in this Mediterranean male population.

P1451 Incremental value of global left ventricular systolic strain imaging for the prediction of coronary atherosclerosis in asymptomatic patients with type 2 diabetes mellitus

A.J.H.A. Scholte, G. Nucifora, R. Djaberi, V. Delgado, J.D. Schuijf, J.W. Jukema, E.E. Van Der Wall, J.J. Bax. *Leiden University Medical Center, Leiden, Netherlands*

Asymptomatic patients with type 2 diabetes mellitus may have left ventricular dysfunction possibly due to coronary atherosclerosis. Left ventricular dysfunction can be evaluated using global left ventricular systolic strain (GLS) imaging. We evaluated whether GLS can be used as an independent predictor for the presence of coronary atherosclerosis providing incremental information over baseline patient characteristics.
234 patients underwent measurement of coronary artery calcium (CAC) score and two-dimensional transthoracic echocardiography including, global left ventricular longitudinal strain. Univariate- and multivariate logistic regression analysis was performed to identify potential predictors for CAC. Furthermore, the incremental value of GLS over baseline clinical variables was assessed using the global chi-square model.
CAC was absent in 95 (41%) patients. In the remaining 139 (59%) patients, an average CAC score of 319±901 was observed. Left ventricular ejection fraction was similar among patients with (68%±11%) and without CAC (68±9) (p=0.91). In patients without CAC 11 (12%) patients had diastolic dysfunction compared to 22 (16%) patients with CAC (p=0.002). GLS was significantly different between patients without CAC (-18.0±2.8) compared to patients with CAC (-16.3±3.0) ($p<0.0001$). Age, male gender, hypertension, hypercholesterolemia and GLS were identified as significant predictors ($p<0.05$) of the presence of CAC. GLS had a significant incremental value over age, male gender, hypertension, and hypercholesterolemia to identify the presence of CAC (p=0.001).

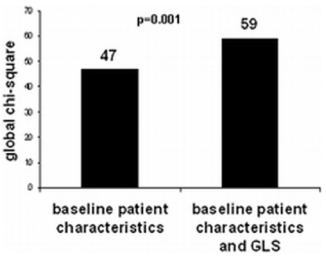


Figure 1

GLS has incremental value over baseline clinical characteristics for the prediction of CAC in asymptomatic patients with type 2 diabetes mellitus and may be useful in the selection of patients requiring further evaluation.

P1452 Effect of valsartan, an angiotensin II receptor blocker, on postchallenge hyperglycemia and hyperinsulinemia in patients with coronary artery disease

S. Koga[1], S. Ikeda[1], T. Yamasa[2], T. Yasunaga[1], T. Nakata[1], S. Kohno[3], K. Maemura[1]. *[1]Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [2]Department of Cardiology, Sasebo Municipal General Hospital, Sasebo, Japan; [3]Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan*

Objectives: Postchallenge hyperglycemia and hyperinsulinemia are involved in the morbidity and mortality associated with coronary artery disease (CAD). Although angiotensin II receptor blockers (ARB) improve insulin resistance and sensitivity, their effects on postchallenge glucose and the insulin response are unclear. The aim of our study was to investigate whether the ARB, valsartan, can ameliorate postchallenge hyperglycemia or hyperinsulinemia in patients with CAD.
Methods: Forty-five patients (mean age 62±11 years) without previously diagnosed diabetes and with CAD treated by percutaneous coronary intervention were randomly assigned to groups given valsartan (valsartan group; n = 21) or not (control group; n = 24). Both groups also underwent diet therapy. We measured plasma glucose and insulin concentrations at 0, 60 and 120 min after a 75 g oral glucose tolerance test (OGTT) at baseline and at 6 months after randomization.
Results: Age, body mass index, blood pressure, glucose and insulin level during OGTT did not significantly differ at baseline between the two groups. After 6 months, plasma glucose and insulin at 120 min significantly decreased in the valsartan group (169±41 to 145±49 mg/dL, p = 0.015 and 94±88 to 56±41 μIU/mL, p = 0.043, respectively), whereas no significant changes were evident in the control group. Plasma insulin values at 120 min were significantly lower after 6 months in the valsartan, compared with the control group (90±54 vs. 56±41 μIU/mL, p = 0.023). Plasma glucose levels at 120 min were also lower after 6 months in the valsartan, compared with the control group but the difference did not reach significance (165±52 vs. 145±49 mg/dL).
Conclusions: Valsartan improves postchallenge hyperglycemia and hyperinsulinemia in patients with CAD treated by percutaneous coronary intervention. This ameliorating effect of valsartan might lead to a better outcome in CAD patients with impaired glucose tolerance.

P1453 Differences in atherosclerotic plaque burden and morphology between type 1 and 2 diabetes mellitus as assessed by multi-slice computed tomography

R. Djaberi[1], J.D. Schuijf[1], E. Boersma[2], L.J.M. Kroft[1], J.W. Smit[1], A. De Roos[1], E.E. Van Der Wall[1], J.M. Van Werkhoven[1], J.W. Jukema[1], J.J. Bax[1]. *[1]Leiden University Medical Center, Leiden, Netherlands; [2]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Purpose: Based on previous studies in patients with type 2 diabetes mellitus (DM2), current guidelines on primary prevention recommend aggressive anti-atherosclerotic therapy in all asymptomatic diabetic patients. However, it is unclear whether coronary atherosclerotic plaque burden is similar in patients with type 1 - (DM1) and DM2. We compared the presence, degree and morphology of coronary artery disease (CAD) in asymptomatic patients with DM1 and DM2.
Methods: Prospectively, multi-slice CT (MSCT) coronary angiography was performed in 135 asymptomatic patients (65 patients with DM1 and 70 patients with DM2). Age and gender were comparable between patients with DM1 and DM2. All risk factors for CAD were registered.
Based on MSCT, coronary artery calcium (CAC) score and the presence of coronary plaques were assessed. Plaques were classified as non-obstructive or obstructive (≥50% luminal narrowing). Distribution of plaque phenotype (non-calcified, mixed and calcified) was analyzed in each group.
Univariate analysis of risk factors was performed to identify potential predictors of the presence of MSCT end points of coronary atherosclerosis. Independent predictors were identified using backward elimination in a multivariate model.
Results: No difference was observed in average CAC score (217±530 vs. 174±361) nor the prevalence of coronary atherosclerosis (65% vs. 71%) in asymptomatic patients with DM1 and DM2. In contrast, the prevalence of obstructive atherosclerosis was higher in DM2 patients (n=24, 34%) as compared to DM1 patients (n=11, 17%). Also, a higher mean number of atherosclerotic and obstructive plaques was observed in DM2. In addition, the percentage of non-calcified plaques was higher in DM2 (66%) versus DM1 (27%) (p<0.001), resulting in a higher plaque burden for each CAC score as compared to DM1 patients.
Importantly, after correction for other atherogenic risk factors, presence of DM2 (as compared to DM1) remained a significant predictor of the number of atherosclerotic plaques (p<0.001), obstructive plaques (p=0.012) and non-calcified plaques (p<0.001).
Conclusions: Although CAC scores and prevalence of coronary atherosclerosis were similar between DM1 and DM2, CAD was more extensive in the latter. Also, a relatively higher proportion of non-calcified plaques was observed in DM2. These observations may be valuable in the development of targeted management strategies adapted to diabetes type.

P1454 Endothelial dysfunction related to the glycemic control as a very early vascular abnormality in young subjects with type 1 diabetes without complications

R. Di Stefano[1], C. Palombo[2], L. Gnesi[2], C. Morizzo[2], F. Massart[3], F. Santini[4], M. Kozakova[2], P. Spontoni[1], A. Balbarini[1], G. Federico[3]. *[1]Cardiac, Thoracic and Vascular Department - University of Pisa, Pisa, Italy; [2]Department of Internal Medicine - University of Pisa, Pisa, Italy; [3]Department of Pediatrics - University of Pisa, Pisa, Italy; [4]Department of Integrated Activities of Endocrinology and Metabolic Diseases - University of Pisa, Pisa, Italy*

Purpose: in type 1 diabetes (DM1) clinical complications are rare in childhood and adolescence, but preclinical vascular abnormalities may develop a few years after the onset of the disease. Aim of this study was to evaluate preclinical cardiovascular involvement in adolescents and young adults with early onset DM1, and its relation with glycemic control.
Methods: 30 normotensive patients with DM1 free of macrovascular complications, microalbuminuria, retinopathy or neuropathy (mean age 19.3±3.1 years; BMI 22±3 kg/m^2; disease duration: 11±5 years; HbA1c - average over the past four years in each patient - 7.9±1.4) and 14 controls of comparable age (mean age 20.4±3.2 years) and BMI (21.6±2.1kg/m^2) were studied. Common carotid IMT was measured by B-mode ultrasound. The forearm peripheral reactive hyperemia index (RHI), a validated index of endothelial function, was assessed using EndoPAT system. Circulating EPC were analyzed for the expression of surface antigens anti-CD34 and anti-human kinase insert domain receptor (KDR). The frequency of peripheral blood cells positive for above reagents was determinated by flow cytometry. Validation of the assay was performed by the ISHAGE method. Left ventricular (LV) geometry and function were assessed by Doppler-echocardiography.
Results: Compared to controls, DM1 patients, although normotensive, had significantly higher diastolic BP (68±7 vs 62±5mmHg, p<0.05), interventricular septal thickness (IVS: 0.76±0.11 vs 0.65+0.10 mm, p<0.05) and LV relative wall thickness (0.31±0.04 vs 0.28±0.03, p<0.05). Carotid artery IMT did not differ in patients vs controls (0.49±0.05 vs. 0.49+0.05 mm; p= n.s.). The percent of CD34+KDR+ cells was significantly lower in DM1 against controls (50±42 vs.175±156 events/10^6 events, p< 0.005). The RHI was significantly reduced in DM1 patients with HbA1c > 7.5% than in DM1 patients with HbA1c ≤ 7.5% and controls (1.5±0.35; 2.1±0.69 and 2.1±0.53, p<0.05), and correlated inversely with DBP (r = -0.38, p<0.05). DBP correlated directly with stroke work (r = 0.3; p<0.05), and disease duration (r = 0.36; p=0.06) in DM1 patients. Stroke work and HbA1c was independent predictor of IVS thickness.
Conclusions: Adolescents and young adults with a long-standing and satisfactorily controlled type 1 diabetes, although free of clearcut macro- and microvascular complications, may have an endothelial dysfunction apparently related to the glycaemic levels over time, which could contribute to mildly elevated diastolic BP and initial LV remodeling.

P1455 Prevalence and control of hypertension and dyslipidaemia in the diabetic population

N. Cortez-Dias[1], S. Martins[1], A. Belo[2], M. Fiuza[1]. *[1]Hospital Santa Maria, Lisbon, Portugal; [2]Portuguese Society of Cardiology, Lisbon, Portugal*

Purpose: To determine the prevalence of cardiovascular risk factors (CV-RF) [hypertension (HT), obesity, abdominal obesity and metabolic syndrome (MS)] and to evaluate the effectiveness of HT and dyslipidaemia treatment in Primary Health Care (PHC) diabetic users in Portugal.
Methods: Cross-sectional study performed in PHC setting, involving 721 general practitioners (GP) representative of all regions of Portugal. The first two adult patients scheduled for an appointment on a given day were invited to participate, irrespective of the reason for consultation. A questionnaire on sociodemographic, clinical and laboratory data was completed by the GP, and two blood pressure (BP) measurements were obtained after a 5-minute seated rest. Diabetes was defined by fast glycaemia ≥126mg/dL or antidiabetic agents; HT by BP ≥130/80mmHg or anti-hypertensive treatment (aHT); MS by ATP III criteria and coronary artery disease (CAD) by angina pectoris or previous myocardial infarction.
Results: The study included 16,856 individuals (58.1±15.1 years; 62% women), being identified 3,215 diabetics. The prevalence of diabetes in PHC users was 14.9% (M: 16.8%; F: 13.2%). Among diabetics, 91% had HT, 40% were overweight, 45% were obese, 69% had abdominal obesity, 72% had MS, 12% presented CAD and 5% had past history of stroke. The prevalence of CV-RF among diabetics was higher in women. Among hypertensive diabetics, 78% were on aHT, being the proportion receiving 2-, 3- and >3 classes 37%, 17% and 5%, respectively. Antihypertensive drugs most frequently used were diuretics (50%), ACE inhibitors (46%), angiotensin receptor blockers (44%), calcium antagonists (30%) and beta-blockers (14%). Among hypertensive diabetics, only 9.3% had BP<130/80mmHg (M: 9.5%; F: 9.1%). Moreover, among diabetic patients with CAD 94% were taking anti-hypertensive medication, but only 9.8% had controlled BP (M: 13.7%; F: 6.1%). About 59% of the diabetic population was treated with statins, but only 6.7% had simultaneously total cholesterol <200mg/dL, triglycerides <150mg/dl and HDL-cholesterol >60mg/dL. About 77% of diabetic patients with CAD were treated with statins, but only 29% had total cholesterol <175mg/dL (M: 34%; F: 24%).

Conclusions: The prevalence of CV-RF in the diabetic Portuguese population is extremely high and rates of control are poor, with particular relevance for BP and lipids. These results highlight the difficulties in the management of diabetics and demand better treatment strategies for an effective CV risk reduction, particularly in women.

P1456 Ominous prognosis of insulin treated patients undergoing percutaneous coronary intervention

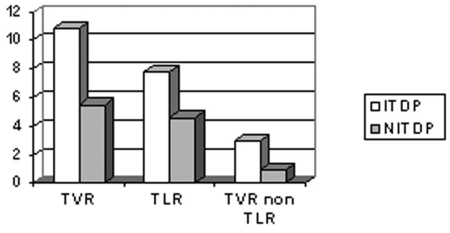
R. Castro, R. Teles, S. Lima, P. Carmo, L. Raposo, R. Cale, J. Brito, P. Goncalves, M. Almeida, J.A. Silva. *Hospital Sta Cruz, Lisbon, Portugal*

The reasons for increased cardiovascular risk in diabetic patients (DP) are complex and are not fully explained, but it is recognized the existence of significant deleterious effects of hyperglycaemia and insulin on vascular function and structure.

Aim: To compare the clinical outcomes after percutaneous coronary intervention (PCI) in DP insulin treated (IT) versus non-insulin treated (NIT).

Methods: Retrospective analysis of 1431 DP (mean age 65±10 years; 69% male), 204 ITDP and 1227 NITDP, undergoing PCI between January 2003 and December 2008. In this population 492 DP (34%) had history of PCI, 243 DP (17%) of coronary artery bypass grafting and 1239 DP (87%) had a normal left ventricular function. There were implanted 1131 (79%) DES and 225 (18%) BMS. ITDP were younger than NITDP (63.7±11 vs. 65.3±10 years; p = 0.028); and NITDP were predominantly male. We evaluated the clinical results during follow-up (FUP median 15, IQR 9; 25 months).

Results: At the end of FUP less NITDP had re-PCI (22.5% vs. 15.4%, p= 0.014; Odds Ratio (OR): 0.62, 95% CI: 0.43-0.89; 95%), either for instent restenosis (10.8% vs. 5.5%, p= 0.007; OR: 0.48, 95% CI: 0.29-0.89), or for new lesions (11.8% vs. 6%, p= 0.006; OR: 0.48: 95% CI: 0.29-0.78) (picture). There were no significant differences after correction for the type, number, length and diameter of stents implanted. The overall mortality was 8.2%, similar in both groups.



Conclusion: Among diabetics, insulin treated patients were associated with an higher rate of revascularization, either for instent restenosis or progression of disease, despite drug-eluting stent use and reflecting the greater severity of coronary disease in this group of patients.

P1457 N-terminal pro B type natriuretic peptide in overweight and obese patients with and without diabetes: An analysis based on the body mass index and LV geometry

K.I. Cho[1], B.H. Kim[2], D.W. Lee[1], H.G. Lee[1], T.I. Kim[1]. *[1]Maryknoll Medical Center, Pusan, Korea, Republic of; [2]Pusan National University Hospital, Pusan, Korea, Republic of*

Background: Recent studies have shown that obesity is an independent predictor of lower N-terminal pro-BNP (NT-proBNP) levels and raised concerns about the validity of this biomarker in obese subjects. BNP has been shown to be increased in patients with DM, even in the absence of structural heart disease, and obesity frequently coexists with diabetes, so it is important to consider the joint influences on natriuretic peptide levels. So we evaluated the influence of diabetes on the correlation BNP and BMI.

Method and Results: Simultaneous NT-proBNP and echocardiographic examinations were performed in 933 patients with dyspnea undergoing cardiac catheterization between Feb. 2006-Nov.2007 in Maryknoll cardiac center who had creatinine of <2.0, no evidence of systolic heart failure. Patients were divided into body mass index (BMI) >25kg/m^2 (obese), 23 to 25 (overweight), and <23 kg/m^2 (non obese). NT-proBNP levels, mitral early diastolic/tissue Doppler annular velocity (E/Ea), left ventricular (LV) geometry pattern using relative wall thickness and LV mass index and myocardial performance index (Tei index) were compared with groups. In 733 non-diabetic patients, mean plasma NT-proBNP levels were significantly lower in obese (n=287, 289.62±164.9 pg/ml) and overweight patients (n=216, 601.69±159.6 pg/ml) compared with nonobese (n=230, 856.39±237.3 pg/ml) patients (p<0001, respectively). However, in 200 diabetic patients, mean plasma NT-proBNP levels was 963.19±223.7 pg/ml, 1450.15±457.3 pg/ml, 658.05±147.1pg/ml, respectively. so there was no correlation between BMI and pro-BNP (r=-0.91,p=0.19). NT-proBNP did not correlate with mitral E/Ea in obese diabetic patients (r= 0.14, p= 0.56), whereas NT-proBNP significantly correlated with this variable in the non obese (r=0.24) and non diabetic (r=0.32) groups. However, LV mass index was significantly correlated with NT-pro-BNP all BMI groups (r=0.61,p<0.001), and patients with concentric hypertrophy showed the highest BNP levels.

Conclusion: The present study demonstrates that NT-proBNP is not suppressed in obese patients with diabetes and the correlation between plasma BNP and LV mass index was more robust than any other echocardiographic or hemodynamic parameter as well as any patient's characteristics.

P1458 Endothelial progenitor cells reduction in normoglycaemic patients with family history for type 2 diabetes and normal endothelial function

R. Di Stefano[1], M.C. Barsotti[1], C. Grigoratos[1], L. Pucci[2], D. Lucchesi[2], L. Ghiadoni[3], S. Taddei[3], G. Penno[2], S. Del Prato[2], A. Balbarini[1]. *[1]Cardiac, Thoracic and Vascular Department - University of Pisa, Pisa, Italy; [2]Department of Endocrinology & Metabolism - University of Pisa, Pisa, Italy; [3]Department of Internal Medicine - University of Pisa, Pisa, Italy*

Purpose: Circulating endothelial progenitor cells (EPCs) contribute to integrity of endothelial monolayers. The concept of repair of damaged dysfunctional endothelium by EPCs has recently emerged. EPC reduction has been associated with vascular dysfunction. Aim of our work was to assess if endothelial dysfunction is accompanied by EPC quantitative alterations in subjects with different cardiovascular risk. Methods: The study population was composed of 34 subjects with impaired glucose regulation (IGR), 18 newly diagnosed type 2 diabetics (naiveT2D) and 26 normoglycaemic (NGT) with (n. 13, NGT/Fam+) and without (n. 13, NGT/Fam-) first-degree family history for type 2 diabetes. Endothelial function (flow-mediated dilation, FMD) of brachial artery was assessed by ultrasound; circulating EPCs (CD34/KDR double positive cells) were determined by flow cytometry.

Results: IGR and naiveT2D were older than NGT (55±5 and 58±8 vs 45±10 yrs, p=0.001), had higher systolic BP (p=0.001) and HbA1c values (6.0±0.4 and 65±0.6 vs 5.5±0.4%, p<0.0001). Endothelium independent dilation (glycerol trinitrate, GTN) was not different, while FMD was lower in naiveT2D (Δ% 4.4±.3 M±SD) compared with IGR (Δ% 6.0±2.8) and in both naiveT2D and IGR compared to NGT (Δ% 7.9±3.6; Kruskal-Wallis p=0.0017). The same pattern was observed for the FMD/GTN ratio, an expression of the selective endothelial function impairment. Both patterns were confirmed between genders and in young (age <50 yrs, n. 27, p=0.07) and older (age >50 yrs, n. 51, p=0.04) subjects. EPCs were higher in NGT/Fam- (608±87 cells/ml, M±SE), similarly reduced in NGT/Fam+ (457±68 cells/ml) and in IGR (479±65 cells/ml), and even more reduced in naiveT2D (254±51 cells/ml, Kruskal-Wallis, p =0.01).

Conclusions: In conclusion, naiveT2D subjects showed EPC depletion as well as impaired FMD. In subjects with non-diabetic hyperglycemia, reduction in FMD was paralleled by an intermediate EPC depauperation. This impoverishment is already apparent in NGT/Fam+ suggesting that EPC reduction may precede impairment in endothelial function.

P1459 Increased left ventricular torsion in uncomplicated type 1 diabetes: the role of coronary microvascular function

G. Nallur Shivu, K. Abozguia, T.T. Phan, I. Ahmed, R. Weaver, A. Wagenmakers, P. Narendran, M. Stevens, M.P. Frenneaux. *University of Birmingham, Birmingham, United Kingdom*

Background: Diabetic cardiomyopathy is a common cause of morbidity and mortality in diabetes. The early manifestations of this cardiomyopathy are however not well established. Left ventricular (LV) torsion followed by untwisting during diastole is an important component that affects LV filling. We used speckle tracking echocardiography to study the early changes in the LV torsion in patients with uncomplicated type 1 diabetes (T1DM) and used stress magnetic resonance imaging to assess the role of coronary microvascular function on LV torsion.

Methods: 33 asymptomatic subjects with T1DM (mean + 1SD age 32.9±8.4 y, diabetes duration 13.9 y) and 32 age-matched healthy controls (HC) (age 30.8±8.0y) were recruited into the study. All subjects underwent clinical examination, echocardiogram and exercise testing to exclude heart failure and ischaemic heart disease. Stress magnetic resonance imaging (MRI) was done in 30 subjects (8 healthy volunteers) to compute mean perfusion reserve index (MPRI) a measure of coronary microvascular function. LV rotation measurements were made using a commercially available speckle tracking system from grey scale two-dimensional image. LV twist curves were obtained by subtracting basal rotation from apical rotation using graphical software Dplot. Twist rates were obtained from first derivative of the twist curve.

Results: Left ventricular ejection fraction was 60.7±5% in the T1DM subjects and 61.4±5%in the HC (p=0.29 vs T1DM). Peak LV torsion was significantly increased in the T1DM as compared to HC (1.9±0.6 0/cm vs 1.4±0.7 0/cm, P<0.01). Peak LV torsion rate (12.7±5.1 0/cm/sec vs 10.9±4.8 0/cm/sec, P=0.08) and peak untwisting rate (-11.9±4.6 0/cm/sec vs -11.3±4.7 0/cm/sec, P=0.29) were not significantly increased in T1DM. The mean MPRI in T1DM was 1.9±0.5 significantly lower than in HC (2.3±0.4, P<0.05). On multivariate regression analysis rotational deformation delay (r=-0.48,P<0.05) and MPRI (r=-0.44, P<0.05) were independent predictors of LV torsion.

Conclusion: We demonstrate for the first time using speckle tracking that despite normal ejection fraction, LV torsion is increased in young patients with uncompli-

cated T1DM. This may represent the compensation of the myocardium to maintain the ejection fraction during early stages of diabetic cardiomyopathy. MPRI was reduced and an independent predictor of LV torsion in diabetes patients suggesting a key role of microvascular disease in the development of increased torsion in these individuals.

P1460 Relationship between the severity of obstructive sleep apnea with results of oral glucose tolerance tests in Japanese patients with obstructive sleep apnea

A. Tamura[1], Y. Kawano[1], T. Watanabe[2], J. Kadota[1]. [1]*Oita University, Yufu, Japan;* [2]*Oita Nakamura Hospital, Oita, Japan*

The relationship between the severity of obstructive sleep apnea (OSA) and results of oral glucose tolerance tests (OGTTs) has not been fully clarified in patients with OSA. Accoringly, we sought to calrify this relationship. We examined 167 Japanese patients without use of hypoglycemic drugs who underwent overnight polysomnography and a OGTT and who were diagnosed as having OSA (apnea-hypopnea index [AHI] ≥5). The patients were divided into the following 3 groups: 77 with AHI ≥30 (group A); 41 with 15≤ AHI <30 (group B); 49 with 5≤ AHI <15 (group C). Polysomnography and an OGTT were again performed at 6 months after nasal continuous positive airway pressure (nCPAP) therapy in 13 patients with impaired glucose tolerance. Plasma glucose levels at 2 hours after the glucose load (G-2h) differed significantly among the 3 groups (group A, 152 [130.5 - 191.5] mg/dl; group B, 135.0 [111.0 – 156.0] mg/dl; group C, 126.0 [94.0 – 144.5] mg/dl; p <0.001), but fasting plasma glucose levels did not. A multiple regression analysis revealed that age (p = 0.048), body mass index (p = 0.02), and ln AHI (p = 0.029) were independently associated with ln G-2h. In 13 patients with impaired glucose tolerance, nCPAP decreased G-2h from 162.7±19.9 mg/dl to 136.5±28.3 mg/dl (p = 0.006), without significant changes in body weight. In conclusion, the severity of OSA was independently associated with G-2h in patients with OSA, and nCPAP therapy decreased G-2h in those patients with impaired glucose tolerance, suggesting an association between OSA and abnormal glucose response after the glucose load.

P1462 Impact of type 2 diabetes mellitus on diffuse inflammatory activation of de novo atheromatous lesions: implications of systemic inflammation

M. Drakopoulou[1], K. Toutouzas[2], A. Synetos[2], E. Tsiamis[2], J. Karabelas[2], D. Tousoulis[2], A. Karanasos[2], E. Stefanadi[2], C. Tsioufis[2], C. Stefanadis[2]. [1]*University of Athens, Athens, Greece;* [2]*Hippokration General Hospital of Athens, Athens, Greece*

Purpose: Local coronary and systemic inflammation is pronounced in patients with diabetes mellitus (DM). Intracoronary thermography detects local inflammation and C-reactive protein (CRP) is a marker of systemic inflammation. We investigated whether in patients with DM thermal heterogeneity of culprit lesions (CLs) correlates with that of non-culprit lesions (NCL) and with systemic inflammation.
Methods: We included patients with DM and two angiographically significant lesions undergoing percutaneous coronary intervention. We measured the temperature difference (ΔT) between the lesion and the proximal vessel wall temperature.
Results: We included 104 (n=208 lesions) patients; 32 patients had DM and 72 patients were non-DM (control group). Both groups had similar ΔT in CLs and NCLs (DM:CLs; 0.12±0.06°C, NCLs; 0.13±0.08°C, p=0.49, vs non-DM:CLs; 0.06±0.04°C, NCLs; 0.06±0.05°C, p=0.65). ΔT was increased in DM in both CLs and NCLs (CLs; DM: 0.12±0.06°C, no DM: 0.06±0.04°C, p<0.01, vs NCL; DM: 0.13±0.08°C vs no DM: 0.06±0.05°C, p<0.01). CRP was higher in DM compared to non-DM (1.71±0.86mg/L vs 0.44±0.39mg/L, p<0.01). A linear correlation was detected between heat production in all lesions and CRP (R=0.45, p<0.01). Patients with DM had a positive correlation between ΔT and CRP (R=0.32, p<0.01)(Figure - red spots). However, in non-DM no correlation between ΔT and CRP was detected (DM: R=0.04, p=0.59)(Figure - blue spots). In the total study population a linear correlation was detected between heat production in CLs and NCLs, and CRP (CLs: R=0.43, p<0.01, NCLs: R=0.47, p<0.01).

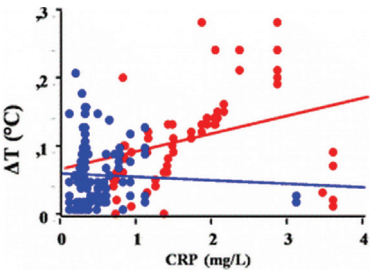


Figure 1

Conclusions: In patients with DM coronary inflammatory activation is diffuse and correlates with systemic inflammation supporting the concept of global coronary instability and widespread systemic inflammation.

P1463 Dysmetabolic profile in patients with established coronary heart disease

V. Bongard[1], J.B. Ruidavets[1], D. Taraszkiewicz[2], D. Carrie[2], M. Galinier[3], J. Ferrieres[4]. [1]*Department of Epidemiology - CHU de Toulouse - Université de Toulouse - INSERM U558, Toulouse, France;* [2]*Department of Cardiology B - CHU de Toulouse Rangueil, Toulouse, France;* [3]*Department of Cardiology A - CHU de Toulouse Rangueil, Toulouse, France;* [4]*Department of Cardiology B, CHU de Toulouse Rangueil - Université de Toulouse - INSERM U558, Toulouse, France*

Purpose: Current guidelines recommend lowering LDL-cholesterol below 2.6 mmol/L in patients with established cardiovascular disease. The potential benefit of an additional decrease in LDL-cholesterol has been suggested for coronary heart disease patients with diabetes or dysmetabolic profile (i.e. low HDL-cholesterol with high non HDL-cholesterol and elevated triglycerides), as these patients have a particularly high risk of recurrence. The aim of this analysis was to estimate the proportion of patients with poor metabolic profile among those with established coronary heart disease.
Methods: A sample of male patients with a history of acute coronary syndrome was recruited from 2001 to 2004, in the Department of Cardiology of the Toulouse University Hospital (South-Western France), as part of the GENES (Génétique et Environnement en Europe du Sud) Case-control Study. For the present analysis, only cases were taken into account. Patients with recent (in the past two months) acute coronary syndrome were excluded. A standardized clinical exam was performed for each participant and a blood sample was taken to assess glycaemia and lipid levels in a core laboratory.
Results: The sample comprised 824 men. Mean age was 60.3 years (standard deviation: 7.9), 22% of patients were still current smokers and 65% had high blood pressure (≥ 140/90 or 130/80 mmHg if diabetes). Diabetes was encountered in 32% of patients (20%, 36% and 38% from the 10-year age group 45-54 to 65-74 years, respectively, p<0.0001), low HDL-cholesterol (< 1 mmol/L) was observed in 42% (48%, 43%, 36%, p=0.021), high triglycerides (≥ 1.7 mmol/L) in 48% (58%, 49%, 38%, p<0.0001), and high non-HDL cholesterol (≥ 3.4 mmol/L) in 74% of patients (84%, 77%, 64%, p<0.0001). The combination of high non-HDL cholesterol and high triglycerides which reflects the atherogenic potential associated with remnant lipoproteins was encountered in 42% of patients (54%, 42%, 31%, p<0.0001) and 24% (32%, 24%, 17%, p<0.001) had a dysmetabolic profile (low HDL-cholesterol plus high non HDL-cholesterol and elevated triglycerides). Overall, 48% of patients (47%, 50%, 48%, p=0.706) presented either with diabetes or dysmetabolic profile, and thus should be considered at very high risk.
Conclusions: These data suggest that almost one half of patients with established coronary heart disease could be at very high risk, and may thus require a more intensive strategy to control lipids and to reduce global cardiovascular risk.

P1464 Type 2 diabetes significantly modulates the impact of TCF7L2 rs7903146 variant on the risk of coronary atherosclerosis

A. Muendlein[1], C.H. Saely[2], S. Rhomberg[2], G. Sonderegger[2], T. Winder[2], P. Rein[2], S. Beer[2], A. Vonbank[2], H. Drexel[2]. [1]*Private University in the Principality of Liechtenstein, Triesen, Liechtenstein;* [2]*VIVIT Institute, Feldkirch, Austria*

Objectives: Variations in the transcription factor 7-like 2 (TCF7L2) gene, particularly rs7903146, increase the risk of type 2 diabetes (T2DM). Coronary artery disease (CAD) is the most frequent cause of death in T2DM patients, and CAD shares common risk factors with T2DM. Potential associations between TCF7L2 variant rs7903146 and coronary atherosclerosis are unknown.
Methods: We addressed the association between rs7903146 and CAD in a large cohort of 1595 consecutive Caucasian patients undergoing coronary angiography for the evaluation of stable CAD. An additive model of inheritance was used; significant CAD was diagnosed in the presence of coronary stenoses ≥50%.
Results: The prevalence of T2DM significantly increased from homozygous carriers of the frequent allele over heterozygous subjects to those who were homozygous for the rare allele (20.3%, 24.9%, and 31.3%; ptrend=0.001). In the total study cohort, variant rs7903146 was significantly associated with the presence of significant CAD (adjusted odds ratio (OR) 1.27 [1.06-1.51]; p=0.008). Importantly, subgroup analyses with respect to the presence of T2DM showed a strong and significant association between variant rs7903146 and significant CAD in T2DM patients (n=373; OR=1.84 [1.27-2.68]; p=0.001), whereas in non-diabetic subjects (n = 1222), variant rs7903146 was not associated with significant CAD (OR=1.08 [0.88-1.32]; p=0.446). An interaction term T2DM x rs7903146 was significant (p=0.004), indicating that this variant had a significantly stronger impact on CAD in patients with T2DM than in non-diabetic individuals.
Conclusion: We conclude that T2DM significantly modulates the impact of TCF7L2 rs7903146 variant on angiographically characterized coronary atherosclerosis.

P1465 Abnormal glucose metabolism in non diabetics patients treated by percutaneous coronary intervention

S.B. Baptista, A.R. Ferreira, P. Magno, J.R. Loureiro, M. Nedio, C. Monteiro, P. Leal, R. Cabaco, P. Farto E Abreu, V.M. Gil. *Hospital Fernando Fonseca, Amadora, Portugal*

Background and Purpose: Glucose metabolism abnormalities are frequent in patients with coronary artery disease (CAD), and are associated with worst prognosis in this population. Current European guidelines recommend performing an oral glucose tolerance test (OGTT) in all non diabetic patients with CAD. However, this recommendation was not specifically evaluated in patients submitted to percutaneous coronary intervention (PCI) and was not widely adapted by interventional cardiologists, despite it could affect long term clinical results of PCI. The purpose of our study was to evaluate glucose metabolism abnormalities (GMA) in non diabetic patients submitted to PCI.
Methods: OGTT was performed according WHO recommendations in 132 non diabetic patients (mean age 61.6±11.4 years, 77.3% males) previously submitted to PCI. Glucose metabolism abnormalities were classified as impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM), based on OGTT results and according the 2003 ADA definition. Main epidemiological and clinical characteristics of patients were evaluated according the glucose metabolic status.
Results: OGTT was performed 165±65 days after the index PCI. It was considered normal in only 43.9% of patients. IFG was diagnosed in 22 (16.7%) patients, IGT in 28 (21.2%) and DM in 24 (18.2%). The incidence of GMA increased with BMI (51.5% in patient with normal weight, 54.0% in overweight patients and 69.2% in obese patients). Additionally, GMA were associated with lower HDL cholesterol levels (45.7±10,8 mg/d vs 50.8±14.3 mg/dl, p=0.024) and higher triglycerides levels (148,3±105.5 mg/dl vs. 112.9±47.3 mg/dl, p=0.023). The presence of 0, 1 or ≥2 of the risk factors hypertension, BMI>25 kg/m^2, low HDL cholesterol (<40 mg/dl in males and <50 mg/dl in females) and high triglycerides levels (>150 mg/dl), was associated with an incidence of GMA of 40.5%, 45.0% and 68,6%, respectively (p=0.008).
Conclusions: The incidence of glucose metabolism abnormalities is very high in non diabetic patients submitted to PCI. Considering the worst prognosis associated with these metabolic abnormalities, an OGTT should be performed in all these patients, particularly in the presence of other risk factors associated with pre-diabetic states.

P1466 Levels of circulating cytokines in type 2 diabetic patients with cardiac autonomic neuropathy

I. Bondar, A. Demin, O. Shabelnikova. *Novosbirsk State Medical University, Novosibirsk, Russian Federation*

Background and Aims: Cardiac autonomic neuropathy is important cardiovascular risk factor. To assess the relationship between cardiac autonomic dysfunction and markers of inflammation in patients with type 2 diabetic.
Materials and Methods: 92 type 2 diabetic patients (32M/60F, age 53.7±5.2 (SD) years) were examined, including 69 patients (22M/47F, age 54.0±5.3 years) with the cardiovascular autonomic neuropathy (group 1) and 23 patients (10M/13F, age 52.6±4.7 years) without autonomic neuropathy (group 2). Serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β) were determined in the immunoenzymatic method in all patients. A five standard cardiovascular reflex test battery, as proposed by Ewing, was performed in both groups.
Results: Levels of IL-6 (17.4 (11.0; 62.8) pg/ml and IL-1β 82.5 (22.8; 132.0) pg/ml in patients with cardiac autonomic neuropathy was significantly (P=0.017 vs. P=0.048) higher than in group without autonomic neuropathy (4.9 (2.0; 39.7) pg/ml vs. 53.4 (19.1; 89.0) pg/ml). TNF-α concentrations (21.9 (13.1; 61.8) pg/ml vs. 12.3 (9.3; 51.8) pg/ml) did not differ between both groups (P=0.083). A significant positive correlation was found between IL-6 and hyperglycemia (r=0.502, p=0.01), IL-6 and BMI (r=0.522, P=0.002), TNF-α and BMI (r=0.708, P=0.001) in group without autonomic neuropathy. A significant correlation was recorded between the parameters of cardiovascular reflex respiratory test and IL-6 (r=-0.230, P=0.028), the parameters of cardiovascular reflex test Valsalva and IL-1β (r=-0.214, P=0.038) in patients with cardiac autonomic neuropathy.
Conclusion: The results of the study indicate that cardiovascular autonomic neuropathy in patients with type 2 diabetes is associated with higher level IL-6 and IL-1β. These data suggest the role of inflammation on development of cardiovascular autonomic neuropathy inflammation.

P1467 The effect of drug-eluting stents on clinical and angiographic outcomes in diabetic patients: multicenter registry

S. Nakamura[1], H. Ogawa[2], J.H. Bae[3], Y.H. Cahyadi[4], W. Udayachalerm[5], D. Tresukosol[6], S. Tansuphaswadikul[7]. *[1]New Tokyo Hospital, Chiba, Japan; [2]Kumamoto University Hospital, Kumamoto, Japan; [3]Konyang University Hospital, Daejeon, Korea, Republic of; [4]Husada Hospital, Jakarta, Indonesia; [5]King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [6]Her Majesty's Cardiac Center, Siriraj Hospital, Bangkok, Thailand; [7]Chest Disease Institute, Bangkok, Thailand*

Aim: The aim of this study is to compare the safety and efficacy of Sirolimus (SES), Paclitaxel (PES), Zotarolimus (ZES) and Everolimus-eluting stent (EES) on the outcome of percutaneous coronary intervention in patients with diabetes mellitus (DM).
Methods: A prospective analysis of 1253 patients with DM (508 SES, 420 PES, 204 ZES, 121 EES) in five high volume Asian centers after successful stenting was performed. The study endpoints were major adverse cardiac events (MACE) at 30 days, 9 months and restenosis rate and target lesion revascularization (TLR) at 9 months.
Results: See table for clinical results.

	SES	PES	ZES	EES
Number of patients	508	420	204	121
Multivessel disease (%)	78.5	72.6	76.5	81.8
MACE at 30 days (%)	0.8	1.2	1.0	0
Lesion length (mean, mm)	25.8	23.9	28.3	24.8
Lesion type: % of B_2, C (%)	45.3	47.4	52.0	45.5
Reference diameter (mean, mm)	2.75	2.69	2.73	2.69
Minimum lumen diameter post procedure (mean, mm)	2.72	2.66	2.70	2.60
Minimum lumen diameter at 9 months (mean, mm)	2.54	2.38	2.08	2.52
Restenosis rate at 9 months (%)	7.9*	12.6	16.2	6.7*
TLR at 9 months (%)	6.5*	10.7	13.7	4.1*

*p<0.05 vs PES, ZES.

Conclusion: The use of drug-eluting stents in patient with DM was safe with low acute complication. Patients treated with SES and EES showed lesser rate of restenosis compared with other drug-eluting stents.

P1468 CRP and MCP-1 - independent predictors of previously unknown abnormal glucose regulation in patients with acute STEMI

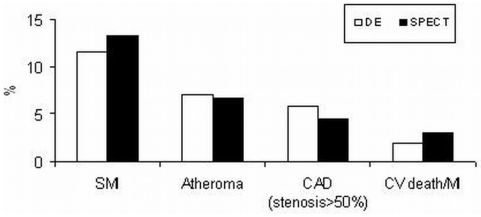
E.C. Knudsen[1], I. Seljeflot[1], M. Abdelnoor[2], J. Eritsland[3], A. Mangschau[3], H. Arnesen[1], G.Ø. Andersen[1]. *[1]Center for Clinical Heart Research, Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway; [2]Center of Clinical Research Unit of Epidemiology and Biostatistics, Oslo University Hospital Ullevål, Oslo, Norway; [3]Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway*

Purpose: Inflammation plays an important role in both cardiovascular disease and diabetes. Previous studies have shown that poor glycemic control is associated with high circulating levels of the chemokine monocyte chemoattractant protein-1 (MCP-1). Furthermore, MCP-1 seems to be related to coronary heart disease and future cardiovascular events. C-reactive protein (CRP) increases during the first days after a revascularised ST-elevation myocardial infarction (STEMI) and is also associated with hyperglycaemia, insulin resistance and type 2-diabetes. The aims of the study were to assess the ability of circulating levels of CRP and MCP-1 measured in-hospital to predict abnormal glucose regulation (AGR) in patients with acute STEMI without previously known diabetes. AGR was defined by an oral glucose tolerance test (OGTT) 3 months after the acute STEMI.
Methods: CRP and MCP-1 were measured in fasting blood samples from 201 patients within 24 hours after a primary percutaneous coronary intervention (PCI) treated STEMI. Three months later the patients performed a standardised 75 g OGTT. The patients were categorized according to the World Health Organisation criteria as normal glucose regulation, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2-diabetes. AGR was defined as the sum of IFG, IGT, and type 2-diabetes. The analyses were performed in an explanatory strategy. Continuous variables were categorised into quartiles. A linear trend analyses across the groups selected the cut off point of the 25th and 75th percentile, respectively. The Mantel-Haenzel method was used to quantify confounders and highlight effect modifiers. Adjustment for multiconfounders was done using a logistic model.
Results: Median (25th, 75th percentiles) of CRP and MCP-1 levels were 12.0 (6.4, 33.1) mg/L and 222 (190, 272) pg/mL, respectively. After adjustment for established cardiovascular risk factors, age and serum-cTroponinT, CRP levels > the 75th percentile was independently predicting AGR at 3 months with an adjusted OR of 3.24, p=0.002. Triglycerides was an effect modifier on the association between high levels of MCP-1 and AGR and the adjusted OR for high MCP-1 levels was 8.06, p=0.007 when patients with high triglycerides (≥1.8 mmol/l, highest quartile) were excluded.
Conclusions: High levels of circulating CRP and MCP-1 measured in patients the first morning after a PCI treated acute STEMI were independently of each other, associated with abnormal glucose regulation defined by an OGTT performed 3 months later.

P1469 Long term outcome after detection of silent myocardial ischemia in diabetic patients: a randomized study comparing isotopic and echocardiographic stress tests

O. Barthelemy[1], S. Jacqueminet[1], F. Rouzet[2], R. Isnard[1], A. Bouzamondo[1], D. Le Guludec[2], A. Grimaldi[1], J.P. Metzger[1], C. Le Feuvre[1]. *[1]Pitie-Salpetriere Hospital (AP-HP), Paris, France; [2]Bichat-Claude Bernard Hospital (AP-HP), Paris, France*

Aims: Compare stress myocardial scintigraphy (SPECT) versus dobutamine echocardiography (DE) for the screening of silent myocardial ischemia (SMI) and coronary artery disease (CAD) in asymptomatic type 2 diabetic patients with high cardiovascular (CV) risk ($\geq$ 2 others associated risk factors).
Assess long term clinical outcome according to SMI screening.
Methods: 199 asymptomatic type 2 diabetic patients at high CV risk were prospectively randomized between two SMI screening strategy: SPECT vs DE. A coronary angiogram was proposed in case of SMI, with revascularization for suitable lesions. Long term intensive treatment of CV risk factors was performed in all patients. Death and myocardial infarction (MI) were recorded during a 3 year follow up.
Results: Hundred patients underwent SPECT and 99 DE. Clinical characteristics were comparable in the two groups: mean age was 65±6 years, mean duration of diabetes was 15±10 years, and mean associated risk factors were 2.9±0.9. The prevalence of SMI and significant CAD were 13.3% and 4.4% in the SPECT versus 11.6% and 5.8% in the DE group, respectively (p=0.7 for both) (figure). Predictive positive values for the detection of significant CAD were 33% for SPECT vs 50% for DE (p=0,7). During a 2,8±1,3 years of follow up, 8 patients had coronary revascularization (7 PCI, 1 CABG). The rate of CV death & MI was 2.5% and similar in the 2 groups.



SMI, CAD & events according to stress test

Conclusions: The rates of SMI and significant CAD in asymptomatic high-risk type 2 diabetic patients are low The positive predictive values for the detection of significant CAD are quite similar whatever the screening test used: SPECT or DE.
Coronary revascularization and intensive CV risk factors therapy are associated with a very low rate of adverse CV events at 3 years, independently of the stress test used.

P1470 The heath economic value of aspirin in the primary prevention of cardiovascular disease in diabetic patients

K. Moeremans[1], M. Lamotte[1], K. Wittrup-Jensen[2], M. Pignone[3]. *[1]IMS Health, Brussels, Belgium; [2]Bayer Schering Pharma, Berlin, Germany; [3]The University of North Carolina at Chapel Hill, Chapel Hill, United States of America*

Low-dose aspirin for primary prevention of CVD is controversial, although meta-analyses support its use in persons at increased CVD risk (e.g. diabetes). This study assesses the cost-effectiveness of low-dose aspirin in diabetic patients in the US, based on a 10-year markov model. Coronary heart disease (CHD) risk reduction with aspirin was estimated to be 0.72, based on two meta-analyses. The model was applied to hypothetical patients at a different 10 year CVD risk levels based on Framingham risk equations. We first modelled hypothetical patients without diabetes at 4%, 7.5%, 15% and 20%. We then assumed that the same hypothetical patient groups had diabetes, raising their risk to 5.9%, 10.9%, 19.4% and 25,0%. Outcomes are expressed as difference in 10-year total costs and gains in quality-adjusted life years (QALY). Direct costs came from 2005 US national data, utility data from published sources. Future costs and effects were discounted 3%. In the base case, administering aspirin is cost saving and leads to QALY gains in both diabetic and non diabetic patients across the studied risk levels. Savings are more pronounced in patients with diabetes. Probabilistic sensitivity analysis revealed that in diabetic patients already at the lowest risk level aspirin is more effective and less costly in more than 85% of cases. The results are sensitive to the assumed reduction in CHD risk with aspirin. A 20% at very low risk to 16% at high risk CHD risk reduction with aspirin is needed to remain more effective. Administering low-dose aspirin to patients with or without diabetes is cost-saving for patients at 4% CVD risk or higher.

P1471 Factors relating to inadequate control of blood pressure in diabetic hypertensive outpatients

T. Livieratos, A.R. Tziovas, N. Fountas, P.A.N. Koustas, G.E. Kordosis. *General Hospital of Agrinio, Agrinio, Greece*

Hypertension is one of the greatest risk factors for cardiovascular morbidity and mortality. It is not well controlled in the majority of hypertensive patients with diabetes mellitus.
Purpose: To identify factors contributing to inadequate control of blood pressure (BP) in diabetic hypertensive patients in order to improve management in such patients.
Methods: The study included 315 (137 males and 178 females) hypertensive patients with diabetes mellitus (DM) from outpatient clinic of a regional Greek hospital from January to December 2008. We studied hypertensive medication use, co-morbidity and blood pressure in two different measurements. We also conducted patients' interviews covering demographic factors, knowledge of hypertension and medication side effects. The BP goal was defined as <130/80mmHg.
Results: Mean age of the patients was 66±11.The recommended target BP was achieved in 29.2% (92/315). 46.7% (147/315) of patients had stage 1 hypertension (SBP >130 to 159mmHg or DBP >80 to 99mmHg) and 24.1% (76/315) had stage 2 hypertension (SBP >160mmHg or DBP >100mmHg). Multivariate analysis indicated that inadequate BP control was associated with female gender, age >65 years, the use < 2 antihypertensive medications, obesity (BMI $\geq$30 kg/m^2), lack of knowledge of appropriate target of systolic blood pressure. Patients with coronary heart disease receiving oral nitrates had a higher likelihood of adequate blood pressure control.
Conclusions: The majority diabetic hypertensive patients remain uncontrolled despite regular medication. Female gender, obesity, older age (>65 years), the use less than two antihypertensive medications and lack of knowledge of appropriate systolic blood pressure were found to be factors associated with poor BP control. Identification of these factors can lead to improve management in diabetic hypertensive patients.

P1472 Relationships between carotid intima-media thickness with plaque and brachial-ankle pulse wave velocity in patients with type 2 diabetes

B.H. Kim, J.S. Jang, C.W. Lee. *Busan St.Mary's Medical Center, Busan, Korea, Republic of*

Background: Carotid intima-media thickness (IMT) and pulse wave velocity (PWV) have been shown to be good surrogate markers of clinical atherosclerosis. Recently, brachial-ankle PWV (baPWV) has been developed as a more noninvasive and convenient methods for assessment of arterial stiffness. Several studies have demonstrated a significant correlation between aortic PWV and carotid IMT. However, the interrelation between carotid IMT and baPWV in type 2 diabetes patients has not yet been fully clarified. We determined the relationships between carotid IMT with plaque and baPWV in patients with type 2 diabetes mellitus (DM).
Methods: One hundred twenty two patients (56 men, 66 women, mean age 60.8±10.5 years, mean DM duration 7.0±7.3 years) were included. Subjects with type 1 diabetes, peripheral artery obstructive disease were excluded. Carotid IMT and plaque formation was assessed using B-mode ultrasonography at both common carotid artery (CCA) [10mm distal to the bifurcation], bifurcation and internal carotid artery (ICA) [10mm proximal to the bifurcation]. baPWV was measured using an automated device.
Results: Maximal baPWV was 1648±363.2 cm/sec, mean IMT of Rt. carotid artery was 0.73±0.20mm, mean IMT of Lt. carotid artery was 0.79±0.26mm, maximal IMT of carotid artery was 1.19±0.41mm, and plaque was found in 11% of subjects. In bivariate correlation analysis, maximal baPWV was significantly correlated with IMT of Rt. CCA (r=0.322, p<0.01), mean IMT of Rt. carotid artery (r=0.235, p<0.01), IMT of Lt. CCA (r=0.221, p=0.02), mean IMT of Lt. carotid artery (r=0.412, p<0.01), maximal IMT of carotid artery (r=0.409, p<0.01) and plaque (r=0.369, p<0.01). Maximal IMT of carotid artery was significantly associated with age (r=0.314, p<0.01), systolic blood pressure (SBP)(r=0.369, p<0.01) and DM duration (r=0.200, p<0.03). The existence of plaque was significantly associated with age (r=0.265, p<0.01), SBP (r=0.271, p<0.01) and DM duration (r=0.224, p=0.02). Multiple regression analysis was performed with maximal IMT of carotid artery and plaque as a dependent variable respectively. Maximal IMT of carotid artery was significantly correlated with SBP (β =0.269, p<0.01). The existence of plaque was significantly correlated with maximal baPWV (β =0.280, p=0.02).
Conclusions: baPWV was significantly correlated with carotid IMT and plaque in patients with type 2 diabetes.

NUTRITION

P1473 Serum selenium concentrations and blood pressure in US adults

M. Laclaustra[1], A. Navas-Acien[2], S. Stranges[3], J.M. Ordovas[4], E. Guallar[1]. [1]*National Center for Cardiovascular Research (CNIC), Madrid, Spain;* [2]*Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America;* [3]*The Clinical Sciences Research Institute, Warwick Medical School, Coventry, United Kingdom;* [4]*JM-USDA Human Nutrition Research Center on Aging at Tufts University, Boston, United States of America*

Objectives: Selenium has potential interest for cardiovascular disease prevention because of its antioxidant properties. Studies of the association between selenium and hypertension available so far are scarce and inconsistent. We explored the relationship of serum selenium concentrations with blood pressure and hypertension in a representative sample of the US population.
Methods: Cross-sectional analysis of 2,638 adults ≥40 year old who participated in the National Health and Nutrition Examination Survey (NHANES) 2003-2004. Serum selenium was measured by inductively coupled plasma-dynamic reaction cell-mass spectrometry. Hypertension was defined as blood pressure ≥140/90 mmHg or current use of antihypertensive medication.
Results: Mean serum selenium was 137.1 μg/L. The multivariable adjusted differences (95% confidence interval) in blood pressure levels comparing the highest (≥150 μg/L) to the lowest (<122 μg/L) quintile of serum selenium were 4.3 (1.3, 7.4), 1.6 (-0.5, 3.7) and 2.8 (0.8, 4.7) mmHg for systolic, diastolic, and pulse pressure, respectively. The corresponding odds ratio (95% CI) for hypertension was 1.73 (1.18, 2.53). In spline regression models, blood pressure levels and the prevalence of hypertension increased with increasing selenium concentrations up to 160 μg/L.
Conclusions: High serum selenium concentrations were associated with higher prevalence of hypertension. Given the current interest in selenium supplementation for prevention, it would be advisable to further evaluate the risks and benefits associated with high selenium status before recommending supplementation to the general population.

P1474 Coenzyme Q10 and selenium in statin-associated myopathy treatment. Results of randomized double-blind clinical study

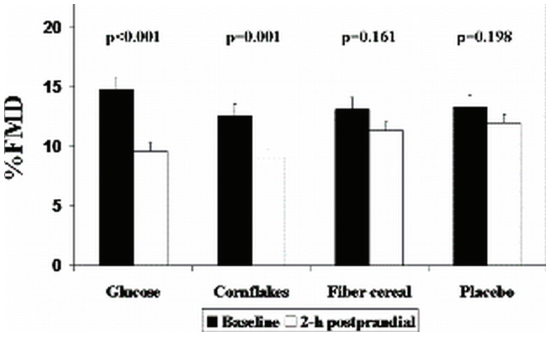
J. Fedacko, D. Pella, R. Rybar, P. Fedackova, D. Dudova. *Kosice University Medical School, Kosice, Slovak Republic*

Inhibition of HMG-CoA reductase by statins leads not only to decreased synthesis of cholesterol but also to decreased coenzyme Q10 (CoQ10) and several selenoproteins.
Aim of our double-blind randomized, single centre 3-month study using 2x2 factorial design (CoQ10 200mg/day vs. selenium 200ug/day vs. their combination vs. placebo administered to statin treated patients with statin-associated myopathy not leading to treatment withdrawal) was to evaluate possible benefits of coenzyme Q10 and selenium supplementation.
Methods: We screened 1, 142 patients treated with statins and found 60 eligible patients to be enrolled to the study. All patients underwent physical, laboratory (including plasma level of CoQ10 and selenium) examinations at the beginning, after one month of the study treatment and at the end of the study.
Results: Muscle pain was present in 40 of studied patients, muscle weakness in 21 of them, 22 patients described tiredness since statin use and cramps were present in 18 patients. All these symptoms of statin-associated myopathy significantly improved in the CoQ10 active group of patients treated by CoQ10 active form (p=0.0001). Plasma level of CoQ10 in the active group increased from baseline 0.81±0.39 μmol/L to 3.31±1.72 μmol/L at month 3 visit compared to placebo group at month 3 visit (p=0.001). Selenium supplementation (active or placebo) was not associated with a decrease of statin-associated myopathy, but with a significant increase of selenium plasma levels only in the selenium active group of patients. Our study confirmed that blood concentration of selenium in patients with statin-associated myopathy is suboptimal and increase of coenzyme Q10 plasma level is higher when supplemented along with selenium in comparison with isolated coenzyme Q10 supplementation, even though it does not reach statistical significance (p=0.1059).
Conclusion: Supplementation of statin treated patients with coenzyme Q10 resulted in a decrease of symptoms of statin-associated myopathy which could be associated not only with improvement of quality of life, but compliance to statin therapy as well. Selenium supplementation was associated with statistically significant increase of its plasma level but did not lead to significant improvement of statin side effects.

P1475 The acute effect of various glycemic index dietary carbohydrates on endothelial function in non-diabetic overweight and obese subjects

M. Shechter, A. Karasik, N. Koren-Morag, H. Kanety, M.S. Feinberg, T. Lavi. *Chaim Sheba Medical Center, Tel Hashomer, Israel*

Background: Postprandial hyperglycemia has been recognized as a cardiovascular risk factor in both the diabetic and general population. Endothelial dysfunction has been shown to occur in diabetic and hyperglycemic patients.
Objectives: To explore the effect of glycemic-index dietary carbohydrates on endothelium-dependent flow-mediated dilation (FMD) in overweight and obese non-diabetic volunteers.
Methods: We prospectively assessed brachial artery FMD in 56 healthy overweight and obese, non-diabetic volunteers [38 (67.9%) men, mean age 48±6 years] on 4 separate mornings, 1-2 weeks apart. Following overnight fasting percent FMD (%FMD) improvement and endothelium-independent nitroglycerin-mediated dilation (%NTG) were assessed, after which subjects were randomized to one of 4 groups: placebo (water) or a carbohydrate meal comprising either glucose, cornflakes or high-fiber cereal.
Results: Fasting and 2-hour postprandial serum glucose levels were similar in all 3 meals, while at 30-90 min, serum glucose levels were significantly higher following glucose and cornflakes (high-glycemic) compared to fiber (low-glycemic). Baseline %FMD, not significantly different in the 3 carbohydrate-based meals, was reduced 2 hours postprandial in all groups, showing statistical significance in only the high-glycemic index meals: glucose (15±9% vs. 10±8%, p<0.01); cornflakes (13±7% vs. 9±7%, p<0.01) (Figure). No correlation was observed between the reduction rate of %FMD and glucose levels throughout the study period.



Carbohydrates and Flow-Mediated Dilation

Conclusions: High-, compared to low-glycemic carbohydrate consumption significantly suppresses FMD in non-diabetic, overweight and obese volunteers, suggesting a mechanism whereby high-glycemic meals may enhance cardiovascular risk.

P1476 Serum selenium and prognosis in cardiovascular disease results from the atherogene study

C.R. Sinning, E. Lubos, R. Schnabel, P.S. Wild, T. Zeller, K.J. Lackner, D. Peetz, C. Bickel, T. Muenzel, S. Blankenberg on behalf of AtheroGene. *Johannes Gutenberg Universitaet, Mainz, Germany*

Introduction: In vitro and animal model data suggest a protective role of the essential trace element selenium against cardiovascular disease (CVD), whereas epidemiological data remains controversial. We aimed to investigate the impact of serum selenium concentration in patients presenting with stable angina pectoris (SAP) or acute coronary syndrome (ACS) on long term prognosis.
Methods: Baseline selenium concentration was measured in 1731 individuals (852 with SAP, and 879 with ACS). During a median follow-up of 6.1 years, 190 individuals died from cardiovascular causes.
Results: In those ACS patients who subsequently died of cardiac causes, selenium levels were lower compared to survivors (61.0 versus 71.5 μg/L; P<0.0001). In a fully adjusted model, patients in the highest tertile of selenium concentration had a hazard ratio of 0.38 (95% CI: 0.16 – 0.91; P=0.03) as compared with those in the lowest. In a backward Cox regression analysis, an increment of one standard deviation was protective against future cardiovascular death (HR 0.76, 95% CI: 0.62 – 0.94; P=0.013) in ACS patients. No association between selenium levels and cardiovascular outcome was observed in SAP.
Conclusion: Low selenium concentration was independently associated with future cardiovascular death in patients with ACS.

P1477 Role of serum zinc (Zn) levels and urinary Zn excretion in coronary artery disease (CAD)

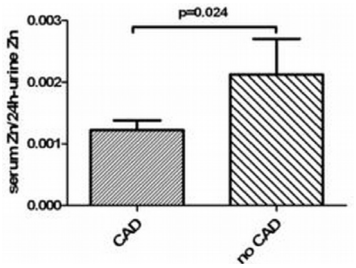
D.M. Konstantinou, L. Kovatsi, Y.S. Chatzizisis, G.D. Giannoglou. *Aristotle University of Thessaloniki, Thessaloniki, Greece*

Purpose: In vitro studies attribute anti atherogenic and insulin like properties to Zn. However, there are conflicting clinical data on the relationship between Zn and CAD, as well as glycemic indices. We investigated whether Zn associates with CAD and parameters of glucose homeostasis.
Methods: We studied 156 consecutive patients without prior history of myocardial infarction or revascularization who underwent coronary angiography for the evaluation of chest pain. The severity of CAD was estimated with three angio-

graphic scores. Zn in serum and 24 hours urine, as well as the ratio of serum Zn/24h urine Zn were determined.
Results: Serum Zn was not associated with CAD prevalence and severity. However, urinary Zn was significantly higher in CAD patients showing also a positive association with CAD severity. The ratio of serum Zn/24h urine Zn, used as surrogate marker of Zn deficiency, was inversely associated with CAD (fig), as well as with diabetes mellitus prevalence, fasting glucose and glycated haemoglobin levels (table).

Zn, CAD severity and glycemic indices

	Gensini score		Extent score		Arbitrary index		Fasting glucose		HbA1c	
	r	p	r	p	r	p	r	p	r	p
Serum Zn	0.119	0.142	0.109	0.179	0.118	0.145	0.065	0.413	-0.039	0.631
24h urine Zn	0.262	0.027	0.303	0.010	0.308	0.009	0.303	0.009	0.391	0.001
Serum Zn/24h urine Zn	-0.238	0.046	-0.302	0.010	-0.298	0.012	-0.318	0.006	-0.437	<0.001



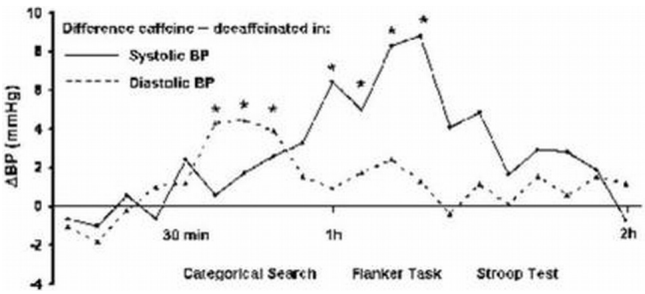
Serum Zn/24h urine Zn in relation to CAD

Conclusions: We show for the first time that Zn deficiency, as it is indicated by a low serum Zn/24 urine Zn ratio, is associated with atherosclerosis and impaired glucose homeostasis.

P1478 Blood pressure modifications after caffeine intake during cognitive tasks

G. Renda, M. Zimarino, A. Tatasciore, G. Committeri, M. Zurro, F. Santarelli, G. Galati, R. De Caterina. *Universita G. D'Annunzio, Chieti, Italy*

Background: The effects of caffeine assumed with coffee drinking on the cardiovascular apparatus are complex and incompletely characterized. Moreover, cardiovascular responses to caffeine during demanding cognitive tasks are still debated.
Aim of the study: To evaluate acute cardiovascular effects of caffeine during different cognitive tasks.
Methods: We recruited 127 male healthy volunteers (median age 26, range 18-40), who avoided coffee and other caffeine-containing drinks and foods for the 24 h preceding the study.
Each subject underwent 24-hour ambulatory blood pressure (BP) and heart rate monitoring at 6 min intervals. After the baseline evaluations, each participant was administered in double-blind a 40 mL volume of either a decaffeinated coffee preparation to which 3 mg/kg caffeine (about two cups of espresso coffee) had been added, or the corresponding vehicle. After 30 min from coffee administration, participants were submitted to a low intensity task of focused attention and choice reaction times (Categorical Search Task), to a classic interference task (Stroop Test) and to more demanding interference tasks (Flanker Task). The same protocol was repeated 24 h later administering the alternative coffee preparation.
Results: SBP increased 1 h after caffeine drinking (*P<0.05 vs decaffeinated preparation), coincident with the demanding Flanker interference test (see Figure). DBP increased after about 30 min from coffee consumption (*P<0.05). Both SBP and DBP showed no modifications during the study after decaffeinated consumption. Heart rate was similar in the two settings throughout the duration of the study.



ΔBP= Difference in BP after caffeine – decaffeinated

Conclusions: Coffee consumption causes an early increase in diastolic and a later increase in SBP during cognitive tasks.

P1479 Do calcium supplements lead to an increase in coronary calcification?

N. Van Pelt[1], P. Ruygrok[1], M.J. Bolland[1], G.D. Gamble[2], B. Mason[2], R. Ames[2], I.R. Reid[2]. *[1]Auckland City Hospital, Auckland, New Zealand; [2]The University of Auckland, Auckland, New Zealand*

Purpose: To investigate the effect of calcium supplements (Ca) on the coronary calcium score (CAC) in healthy men who had previously taken Ca or placebo in a randomized controlled trial.
Methods: Ca are commonly used to increase bone density and reduce fracture risk. However their use has been recently been linked with increased cardiovascular events. A potential mechanism for this is an acceleration of coronary calcification, which is a predictor of major cardiovascular events (MACE) independent of traditional risk factors.
We performed a calcium score scan, using a 64 slice CT scanner, on 163 healthy men 1.7 years (SD 0.41) after taking either 1200 mg of supplemental calcium or placebo for a period of 2 years, as part of a randomized clinical trial to investigate the effect on bone density.
Results: The mean age was 57 years (±10 yrs). There was no significant difference in the mean CAC between men who had taken Ca (223 Agatston Units) and those taking placebo (238, p= 0.88). The number of men taking Ca compared with those taking placebo who had a zero calcium score was not significantly different (20 vs. 24, p=0.54) although there was an increase in those on Ca with minimal calcium (CAC <10, 17 vs. 7, p=0.04). However, there was no difference in the number of men with mild calcium (CAC - 10-100), moderate calcium (CAC - 101-300) or extensive calcification (CAC >300) between the two groups.
In this study cohort, 2 men (2.4%) taking Ca suffered a MACE (myocardial infarction (MI) and coronary artery bypass surgery) compared to 1 man in the placebo group (percutaneous coronary intervention) (1.3%). The median CAC in the men who had a MACE was 1094 (1094, 2658) compared to 39 for the 160 men taking CS or placebo with no MACE (p=0.0063). In men taking Ca, those who had a MACE had a higher median CAC than those without a MACE (1667 (677, 2658) vs. 24 (1, 81) p=0.031. The CAC was strongly correlated with risk of having a MACE (area under the curve 0.96, p=0.0068).
Conclusion: Calcium supplementation was not associated with an increase in coronary calcification in healthy men. An increased calcium score was strongly associated with myocardial infarction in this study cohort.

P1480 Increase mortality and morbidity in acute coronary syndromes with low levels of natural anti-phosphorylcholine IgM antibodies

K. Caidahl[1], U. De'faire[1], K. Petersson[2], J. Herlitz[3], M. Hartford[4], J. Frostegard[1]. *[1]Karolinska Institutet, Stockholm, Sweden; [2]Athera, Stockholm, Sweden; [3]Sahlgrenska Academy, Göteborg, Sweden; [4]Sahlgrenska Academy and AstraZeneca, Göteborg, Sweden*

Objective: Natural antibodies against phosporylcholine (anti-PC) are atheroprotective and low titers are associated to an increased risk for CVD. We investigated if these antibodies can predict short and medium term outcome in patients with acute coronary syndromes (ACS).
Methods: We measured, by ELISA (CVDefineTM), anti-PC IgM in serum sampled within 24h of admission to hospital for ACS (n = 1185, mean age 65 years, 70% men). The relations between the initial antibody titers and mortality as well as a composite clinical endpoint (CV death or hospitalisation due to AMI, stroke, CHF or acute PCI or CABG) at 6, 12 and 18 months were investigated. Patients were divided into quartiles based on antibody titers, and the hazard ratios (HR) were determined.
Results: At all time points, patients in the lowest quartile of anti-PC IgM had significantly elevated risk for total mortality, and for the composite endpoint, compared to quartiles 3 and 4. The 2nd quartile was intermediate. Significances remained after adjustment for confounders (clinical disease severity, CRP and BNP). For mortality, HR (95% CI) were 2.48 (1.26, 4.85); 2.50 (1.34, 4.66) and 2.46 (1.37, 4.41) at 6, 12 and 18 months.
Conclusions: Low anti-PC IgM levels are associated with an increased risk for death and CV morbidity at 6, 12 and 18 months. Measurement of these antibodies will thus provide prognostic information beyond that obtained by clinical variables and other risk markers.

P1481 Calcium intake is independently associated with increased arterial stiffness: results from a cross-sectional follow-up study of two rheumatoid arthritis cohorts

S. Provan[1], K. Angel[2], A.G. Semb[1], D. Atar[2], T.K. Kvien[1]. *[1]Diakonhjemmet hospital, Oslo, Norway; [2]Aker University Hospital, Oslo, Norway*

Background: A recent placebo controlled randomized trial found that intake of oral calcium in healthy older women was associated with an increased risk of cardiovascular events over a 5 -year observation period. Furthermore, bone resorption has been suggested to be an independent predictor of arterial wall thickening in patients with RA.
Objective: To investigate the association between bone loss, calcium intake and

levels of the augmentation index (AIx) and pulse wave velocity (PWV), two arterial stiffness measurements and surrogate markers of cardiovascular disease.
Materials and Method: Arterial stiffness measurements were performed on 144 patients with RA. A study-nurse performed clinical examinations, BMD measurements and asked the patient to fill out a questionnaire. Linear regression models were constructed with AIx and PWV as the dependent variables. The univariate models were adjusted for age, sex, mean arterial pressure, heart- rate, body mass index and use of anti-hypertensive drugs. Predictors that were significant at the $p \leq 0.01$ level were entered into at multivariate model with possible confounders.
Results: Calcium supplementation was associated with significantly higher levels of AIx (p=0.02) and near-significant increased PWV (p=0.06) in both univariate and multivariate models (Table). Vitamin D and menopausal status were associated with higher levels of AIx in the basic analysis, but not in the multivariate model.

Table 1. Predictors of arterial stiffness

Dependent variable	PWV m/s β (CI)		AIx β (CI)	
Predicting variable	Univariate models	Multivariate model	Univariate models	Multivariate model
HRT	0.16 (-0.39-0.70)		1.08 (-1.69-3.85)	
Bisphoshonates	0.61 (-0.16-1.39)		3.04 (-0.44-6.52)	
D vitamins ever/never	0.26 (-0.25-0.77)		3.30 (0.76-5.85)*	
Calcium ever/never	0.43 (-0.05-0.90)	0.44 (-0.03-0.90)	3.75 (1.35-6.14)*	3.75 (1.35-6.14)*
Total hip BMD	-1.06 (-3.20-1.08)		-6.97 (-18.25-4.31)	
Lumbar BMD	-052 (-2.34-1.31)		-5.30 (-14.49-3.90)	
Fractures	0.17 (-0.35-0.70)		0.55 (-2.08-3.17)	
Male:				
Pre-menopausal:	0-0.11 (-0.87-0.32)		03.39 (-0.31-7.09)	
Post-menopausal:	-0.28 (-0.87-0.32)		3.63 (0.06-7.19)*	

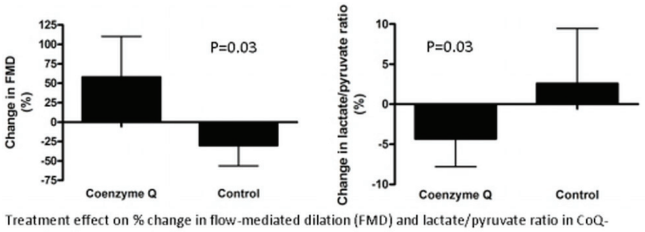
*$p<0.05$.

Conclusion: Calcium supplementation was associated with increased arterial stiffness in this cohort of patients with RA. Residual confounding cannot be ruled-out.

P1482 Reversal of mitochondrial dysfunction by Coenzyme Q10 supplement improves endothelial function in patients with ischemic heart failure

Y.L.E. Dai, T.H. Luk, C.W. Siu, K.H. Yiu, H.T. Chan, S. Lee, S.W. Li, S. Tam, C.P. Lau, H.F. Tse. *University of Hong Kong, Hong Kong, Hong Kong SAR, People's Republic of China*

Background: Heart failure (HF) is associated with endothelial dysfunction and mitochondrial dysfunction. It remains unclear whether mitochondrial dysfunction contributes to endothelial dysfunction in HF. To test this hypothesis, we determined the effect of Coenzyme Q10 (CoQ) supplement on reversing mitochondrial dysfunction to improve endothelial function in patients (pts) with ischemic HF.
Methods & results: We performed a randomized, double-blind, placebo-controlled trial to determine the effects of CoQ supplement (100mg tid, n=28) vs. placebo (Controls, n=28) for 8 weeks on brachial flow-mediated dilation (FMD) in pts with ischemic HF (left ventricular ejection fraction<45%). Mitochondrial function was determined by plasma lactate/pyruvate ratio (LP ratio). After 8 weeks, CoQ-treated pts had significant increases in plasma CoQ concentration (treatment effect 2.20μg/mL, P<0.001) and FMD (treatment effect 1.51%, P=0.03); and decrease in LP ratio (treatment effect -2.46, P=0.03) compared with Controls (Figure). However, CoQ treatment did not alter nitroglycerin-mediated dilation, blood pressure, blood levels of fasting glucose, hemoglobin A1c, lipid profile, high-sensitivity C-reactive protein and oxidative stress as determined by serum superoxide dismutase and 8-isoprostane (all P>0.05). Furthermore, the reduction in LP ratio significantly correlated with improvement in FMD (r=-0.29, P=0.047).



Treatment effect on % change in flow-mediated dilation (FMD) and lactate/pyruvate ratio in CoQ-treated patients vs. controls

Conclusion: In pts with ischemic HF, 8 weeks supplement of CoQ improved mitochondrial function and FMD; and the improvement of FMD correlated with the change in mitochondrial function. These findings suggest that mitochondrial dysfunction contributes to endothelial dysfunction in pts with ischemic HF.

P1483 Adherence to the Mediterranean diet and albuminuria levels in adolescents: Emerging data from the Lyceum Leontio Albuminuria (3L) study

A. Mazaraki, C. Tsioufis, K. Dimitriadis, D. Syrseloudis, C. Thomopoulos, P. Tolis, M. Selima, E. Stefanadi, I. Kallikazaros, C. Stefanadis. *First Cardiology Clinic, University of Athens,Hippokration Hospital, Athens, Greece*

Purpose: Mounting evidence supports that Mediterranean diet has favorable effects on the cardiovascular system, while albuminuria is associated with atherosclerosis progression and increased risk. The aim of the study was to investigate the relationship of dietary habits with urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR), in a cohort of adolescents.
Methods: A total of 365 adolescents 12-17 years of age [212 males, aged 13.9 years, office blood pressure (BP)=115/67 mmHg] that were included in the Lyceum Leontio Albuminuria (3L) study were considered for analysis. In all participants ACR values were determined in a morning spot urine and for each adolescent a questionnaire was completed in order to retrieve information on dietary habits (through a semi-quantitative Food Frequency Questionnaire), lifestyle and socio-economic characteristics. Moreover, the Mediterranean Diet Quality Index for children and adolescents (KIDMED) was estimated and accordingly subjects were divided into those with optimal (≥7), average (4-7) and low (<4) score.
Results: Only 6.8% of the participants had optimal KIDMED score, whereas 51.2% had an average and 42% had a low score. Participants with at least average KIDMED score (n=187) compared to those with low KIDMED score (n=153) were more frequently males (64.5 vs 53.4%, p=0.029), had higher body mass index (22.2 vs 21.4 kg/m^2, p=0.043) and waist circumference (77.6 vs 75.4 cm, p=0.044), spent more frequently time for sports activities outside school (75.2% vs 58%, p=0.001), reported less consumption of foods outside home (3% vs 14%, p<0.001), less hours of watching television (1.75 vs 2.05 hours, p=0.013) and more hours of leisure time (5.4 vs 4.4 hours, p=0.026). Moreover, those with at least average compared to those with low KIDMED score exhibited higher systolic BP (117 vs 114 mmHg, p=0.039) and pulse pressure (49 vs 47 mmHg, p=0.01), whereas had lower heart rate (84 vs 87 bpm, p=0.014) and ACR levels (12.6 vs 20.5 mg/g, p=0.015). In the total population, ACR was associated with age (r=-0.11, p=0.044), male sex (r=0.160, p=0.003), body mass index (r=-0.131, p=0.016), systolic BP (r=-0.144, p=0.008), heart rate (r=0.141, p=0.011) and KIDMED score (r=-0.111, p=0.041).
Conclusions: In adolescents there is an inverse relation of KIDMED score with albuminuria and those who adhere to the Mediterranean diet exhibit lower levels of ACR. However, the paradoxical associations of both ACR and KIDMED score with obesity markers and BP levels suggest distinct mechanisms of albuminuria development in adolescents.

P1484 Antiatheromatic and hypolipidemic activity of chios mastic gum in anesthetized rabbits

I. Andreadou[1], E.K. Iliodromitis[1], S. Paraschos[1], A. Zoga[1], S. Mitakou[1], L. Kaklamanis[2], A.L. Skaltsounis[1], D.T.H. Kremastinos[1]. [1]*University of Athens, Athens, Greece;* [2]*Onassis Cardiac Surgery Center, Athens, Greece*

Introduction: Chios Mastic gum, the resin of the trunk and brunches of Pistacia lentiscus var. Chia, has been used since antiquity and its healing properties are mentioned by most medical writers of the classic era. The main compounds of mastic are triterpenes, both acidic and neutral. Tirucallol and butyrospermol, the main neutral components, possess phytosterolic structure. This led to the hypothesis that mastic and particularly its neutral phytosterolic fraction possess antiatheromatic activities, because of the known effect of plant sterols on the atheromatic disease. In the present study was to evaluate the potential antiatheromatic activity of Chios Mastic gum in vivo.
Methods: Mastic Total Extract without Polymer (MTEWP) and the neutral mastic phytosterolic fraction (NMPF), were administered orally for 6weeks to rabbits. All the animals were divided into 6 groups and were subjected to 30 min regional ischemia of the heart, followed by 3 hrs reperfusion: Normal fed animals: Control with no additional intervention, Group A treated with 46.3mg/kg/d of MTEWP and Group B treated with 45.8mg/kg/d of NMPF. Animals fed with cholesterol-enriched diet for 6 weeks: CHOL group no additional intervention, Group C treated with 46.3mg/kg/d of MTEWP and Group D with 45.8mg/kg/d of NMPF. The infarct size was determined; small segments from the aorta and the heart were also taken for histologic examination. Blood samples were collected at different time points for malondialdehyde (MDA) assessment, as an index of lipid peroxidation and for total cholesterol determination.
Results: In the normally fed animals the phytosterolic fraction NMPF reduced the infarct size to 18.3±3.4%, vs 47.0±1.9% in Control, P <0.05, while the administration of mastic total extract MTEWP did not reduce it significantly (30.3±4.7%, P=NS). In the hypercholesterolemic rabbits both treatments were ineffective. Atherosclerosis was detected in all the animals fed cholesterol enriched diet in the form of subintimal accumulation of lipids and foamy macrophages. There was no detection of atherosclerosis in MTEWP and NMPF treated C and D groups. Treatment with MTEWP and NMPF reduced the total cholesterol levels by 47 and 88% respectively (P< 0.01) whilst had not effect on MDA levels.
Conclusions: The phytosterolic fraction NMPF reduces the infarct size in normal animals. Long –term treatment for 6 weeks of MTEWP and especially of NMPF

possesses significant antiatheromatic and hypolipidemic activities in rabbits fed cholesterol enriched diet but with no effect on infarct size and oxidative stress.

P1485 Twenty year analysis of nutrition, metabolic risk factors and cardiovascular mortality in Siberian population (1985-2005)

G.I. Simonova, O.M. Bragina, S.V. Shishkin, Y.U.P. Nikitin. *Institute of Internal Medicine SB RAMS, Novosibirsk, Russian Federation*

Purpose: To study twenty years dynamics of actual nutrition in Siberian population, to estimate its association with risk factors and cardiovascular mortality (cohort analysis 1985-2005 years).
Methods and materials: Representative samples of men and women 25-64 year old were studied. We used data of Novosibirsk center of WHO MONICA project and HAPEE study. Screenings were carried out in 1985, 1989, 1995, 2003-2005 years. Total number of subjects was 11670. Endpoints and cardiovascular mortality indexes for the period were taken from total mortality register and stroke register databases.
Results: The actual nutrition structure in urban Siberian population includes large part of total fat, small part of polyunsaturated fatty acids (~1%); large portion of sugar (up to 70-75 g daily) alongside with low consumption of compound carbohydrates, cellulose, fruits and vegetables.
In 2000s years there was a tendency to increase in convectional metabolic cardiovascular risk factors. Prevalence of obesity in men 45-64 years old by 2005 year was 21%, in women – 45%; prevalence of hypertension – 61% and 64%, levels of total cholesterol – 6,0 and 6,4 mmol/l, metabolic syndrome frequency – 18% and 33% respectively. Stroke and cardiovascular mortality remain at high level.
Cohort univariant analysis shows that high quartiles of saturated fat and protein consumption and 24 hours' energy in daily ration have the highest all-cause and CVD death ratio. High consumption of polyunsaturated fatty acids and common carbohydrates associated with small death ratio.
Conclusion: Thus, during the period 1985-2005 trends of cardiovascular mortality in Siberian population have increase periods (1990-1995, 1999-2004), and decrease periods (1996-1998, 2005-2007). Possibly it is associated with disbalanced nutrition and dynamics of CVD risk factors.

P1486 The association between adherence to the Mediterranean diet and fasting indices of glucose homoeostasis; the ATTICA Study

D. Panagiotakos[1], C. Chrysohoou[2], C. Pitsavos[2], J. Skoumas[2], J. Lentzas[2], A. Zeibekis[2], C. Paliou[2], C. Masoura[2], A. Katinioti[2], C. Stefanadis[2]. *[1]Harokopio University, Athens, Greece; [2]University of Athens, Athens, Greece*

Aims: We investigated the association between adherence to Mediterranean diet and fasting indices of glucose homoeostasis, in a Greek adult population.
Methods: During 2001 – 2002 we randomly enrolled 1514 men and 1528 women (18-89 years old) without history of CVD, from the Attica area. Diabetes mellitus (type 2) and impaired fasting glucose (IFG) were defined according to the established ADA criteria. Insulin resistance was evaluated by HOMA-IR. Dietary habits were assessed through a validated food frequency questionnaire and a diet score (range 0-55) was developed (higher values means greater adherence to the Mediterranean diet).
Results: The overall prevalence of diabetes type 2 was 7.9% in men and 6.0% in women (P = 0.05). Mean diet score was 26.3±6.8 in normoglycemic, 25.7±6.4 in IFG and 22.2±5.8 in diabetic subjects ($p < 0.001$). In normoglycemic subjects who were in the upper tertile of the diet score we observed 7% lower glucose ($p<0.05$), 5% lower insulin ($p<0.05$) and 15% lower HOMA-IR ($p<0.01$) levels compared to subjects in the lower tertile of the diet score. Additionally, in diabetic/IFG participants who where in the upper tertile of the diet score we observed 15% lower glucose ($p<0.05$), 15% lower insulin ($p<0.05$) and 27% lower HOMA-IR ($p<0.01$) levels compared to those in the lower tertile. However, multiple regression analysis, adjusted for age, sex, BMI, waist-to-hip ratio, physical activity, smoking status, and presence of hypertension and hypercholesterolemia, confirmed the previous associations in normoglycemic, but not in diabetic/IFG people.
Conclusion: An inverse association was observed between adherence to Mediterranean diet and indices of glucose homeostasis, only in normoglycemic people.

P1487 The effect of a Mediterranean diet combined with dietician supervision on soluble cellular adhesion molecules levels in subjects with abdominal obesity

L. Rallidis[1], G. Vamvakou[1], A. Kolomvotsou[2], A. Zampelas[3], S. Efstathiou[4], E. Voltyrakis[1], G. Georgoula[1], J. Lekakis[1], D. Kremastinos[1]. *[1]Athens University Hospital Attikon, Athens, Greece; [2]Harokopio University, Athens, Greece; [3]Agricultural University, Athens, Greece; [4]Hygeias Melathron, Athens, Greece*

Purpose: Abdominal obesity (AO) is associated with increased risk for cardiovascular disease and diabetes mellitus. We examined whether a close adherence to a Mediterranean-style diet affects soluble cellular adhesion molecules (sCAMs) levels in subjects with AO.
Methods: We recruited 90 subjects with AO (waist circumference >102 cm for men and >88 cm for women) without cardiovascular disease or diabetes mellitus. Participants were randomly allocated in the intervention and control group. Both groups were instructed to follow a Mediterranean–style diet for two months. Subjects in the intervention group had additionally to follow a specific relevant daily and weekly food plan and included close supervision by a dietician and provision of simple foods. Soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, soluble E-selectin (sE-selectin) and soluble P-selectin (sP-selectin) were measured by quantitative sandwich enzyme immunoassay before and after the intervention. Between-groups comparisons were performed by repeated measures analysis of variance.
Results: After two months subjects in the intervention group increased the intake of total fat due to higher consumption of monounsaturated fatty acids (26.4±3.6 vs. 19.6±4.2%, $p<0.001$) as well as the intake of dietary fibre, vitamin C, and alcohol compared to the control group (all $p<0.05$). Within group analysis revealed a decrease in levels of sE-selectin by 8.9% (p=0.01) and sP-selectin by 17% ($p<0.001$) only in the intervention group. However, between-groups analysis showed that Mediterranean diet had no significant effect on sCAMs levels compared to control group.
Conclusion: Mediterranean-style diet for two months combined with close supervision by a dietician had no effect on sCAMs levels in subjects with AO. This may be due to the shot period of intervention or to the relatively small number of participants.

P1488 Nuts and blood lipids in type 2 diabetes

C.W. Kendall, J.M. Wong, J.L. Sievenpiper, T.L. Parker, S. Mitchell, M.S. Banach, S. Nishi, C.P. Meneses, J.A. Jenkins. *University of Toronto, Toronto, Canada*

Background: Nut consumption has been associated with a reduced risk of coronary heart disease and with improved blood lipids in normal and hyperlipidemic subjects. Their effects in diabetes are less clear.
Objective: To assess the effect of a supplement of mixed tree nuts (including peanuts) on serum lipids in subjects with type 2 diabetes.
Subjects: 119 men and postmenopausal women with type 2 diabetes treated with oral antihyperglycemic medications and the majority taking cholesterol lowering medications.
Methods: In a parallel design, subjects were randomized to take supplements of mixed nuts, whole-grain muffins (muffins) or both nuts and muffins. Fasting blood samples, body weight and diet records were obtained at -1 week and 0 time and weeks 2, 4, 8, 10 and 12.
Results: LDL-C values prior to nuts, half and muffins were 2.53, 2.24 and 2.29 mmol/L. In the intent-to-treat analysis, with baseline value carried forward for non-completers, the respective changes over 12 weeks were nuts -0.20mmol/L, half -0.04mmol/L and muffins +0.08mmol/L. The difference for the change from baseline for nuts versus muffins was significant (P=0.018). A similar trend was seen for the TC:HDL-C ratio (P=0.058). No other lipid changes between treatments were significant.
Conclusions: Nuts lowered LDL-C in subjects with type 2 diabetes treated with statins who already had low LDL-C concentrations.

P1489 Inclusion of dietary evaluation in cardiovascular disease risk prediction models increases accuracy and reduces bias of the estimations

D. Panagiotakos[1], C. Pitsavos[2], C. Chrysohoou[2], J. Skoumas[2], C. Stefanadis[2]. *[1]Harokopio University, Athens, Greece; [2]University of Athens, Athens, Greece*

Objective: In past years the prediction of CVD risk has received special attention; however, some investigators assert that risk models have so far not been very successful. Thus, we examined whether the inclusion of dietary evaluation in a risk prediction model that already contained the classical CVD risk factors, increases the accuracy and reduces the bias in estimating future CVD events.
Methods: The database of the ATTICA study (that included information from 1514 men and 1528 women) was used. At baseline, the HellenicSCORE values (based on age, gender, smoking, systolic blood pressure and total cholesterol) were calculated; while overall assessment of dietary habits was based on the Mediterranean Diet Score (MDS) that evaluates adherence to this traditional diet. In 2006, the 5-year follow-up was performed in 2101 participants and development of CVD (coronary heart disease, acute coronary syndromes, stroke, or other CVD) was defined according to WHO-ICD-10 criteria.
Results: The MDS and the HellenicSCORE were significant predictors of CVD events, even after adjusting for various potential confounders ($p<0.05$). However, estimating bias (i.e., misclassification of cases) of the model that included HellenicSCORE and other potential confounders was 8.7%. The MDS was associated with the estimating bias of the outcome ($p<0.001$), and explained 5.5% of this bias. Other baseline factors associated with bias were increased body mass index, low education status and increased energy intake/BMR ratio.
Conclusion: The inclusion of dietary evaluation, as well as other lifestyle charac-

teristics increases the accuracy and reduces estimating bias of CVD risk prediction models.

P1490 Right atrial enlargement, P-wave extension, PR and QTc intervals prolongation after acute red wine assumption

A. Garzia[1], M. Cameli[1], P. Ballo[2], E. Palmerini[1], M. Lisi[1], A. Palazzuoli[1], T. Spinelli[1], S. Mondillo[1]. [1]*Department of Cardiovascular Diseases, University of Siena, Siena, Italy;* [2]*Cardiology Operative Unit, S. Andrea Hospital, La Spezia, Italy*

Purpose: Acute excessive alcohol consumption and new onset atrial fibrillation or other supraventricular and ventricular tachyarrhytmias have been often associated. The aim of the study was to establish which alterations, assessed after ethanol ingestion by echocardiography (atrial sizes) and electrocardiography (P-wave duration, time intervals), can explain this association.
Methods: Forty healthy young volunteers drank a light-to-moderate quantity of red wine (5ml/kg). As control, after few days the same population drank an analcoholic juice. Echocardiographic assessment of left and right atrial areas and ECG measurement of P wave duration, PR interval, QRS duration, QT interval, and corrected QT interval were performed at baseline and after 60 minutes from challenge.
Results: Blood ethanol concentration after red wine assumption was 0.48±0.06 g/l. Compared to baseline and to the assumption of the analcoholic drink, there was an extension of right atrial area from 13.2±2.9 to 15.4±3.7 cm^2 (p=0.0004), whereas no significant changes of left atrial area were found (p=0.17). Regarding ECG measurements there was a prolongation of P wave duration (from 100±11 to 108±14 ms, $p<0.0001$), PR interval (from 153±15 to 167±17 ms, $p<0.0001$), QT interval (from 346±27 to 361±24 ms, $p<0.0001$), and corrected QT (from 388±24 to 401±30 ms, p=0.0025). QRS duration did not vary (79±11 to 79±11 ms, p=0.89).
Conclusions: Acute ingestion of red wine is associated with an increase of right atrial area and most electrocardiographic time intervals in normal subjects. The potential arrhythmogenic impact of these effects is worthy of further exploration.

POLITICAL AND FINANCIAL ISSUES

P1491 Economical benefit of the prevention of contrast-induced nephropathy in patients with chronic kidney disease

H. Takano, E. Yamamoto, M. Takano, G. Takagi, K. Asai, M. Yasutake, K. Mizuno. *Nippon Medical School, Tokyo, Japan*

Background: As the prevalence of the recognition of chronic kidney disease (CKD) as significant risk of cardiovascular disease, an increasing number of CKD patients have received percutaneous coronary intervention (PCI). Likewise, they are at risk of further damage against renal function by exposure of contrast medium during PCI. Since maintenance hemodialysis costs ≈$60,000/year for 1 patient in Japan, an increase of patients developing end stage renal disease (ESRD) is a critical issue jeopardizing Japanese medical budget. In order to clarlify the economical significance of contrast-induced nephropathy (CIN), we investigated the influence of CIN on their long-term renal function in patients with CKD undergoing PCI.
Methods: Between Jan. 2002 and June 2005, 60 CKD patients (estimated GFR < 50 ml/min, serum creatinine: 1.89±0.68 mg/dl, age: 71±9) underwent elective PCI under the conventional prophylaxis. After June 2005, we completed all elective PCI using contrast dose ≤20 mL with a newly developed PCI technique utelizing selective angiography in 50 consecutive CKD patients (serum creatinine: 1.93±0.67 mg/dl, age: 72±8). We analyzed time-course of renal function after CIN and economical benefit of the prevention of CIN by minimizing contrast dose.
Results: Of the total of 110 CKD patients, 13 patients developed reversible CIN (RCIN) and 7 developed irreversible CIN (IRCIN). The median annual increase in serum creatinine level was 150.8% after IRCIN, 35.7% after RCIN, and 4.6% in patients with no CIN (each comparison, $p<0.05$). During the 3 year follow-up period, dialysis was introduced in 6 of 7 patients after IRCIN, 4 of 13 patients after RCIN and 3 of 79 patients having no CIN (no CIN vs. others, $p<0.05$). Our contrast saving PCI not only reduced the incidence of CIN (2% vs. 31.7%, $p<0.001$) but also suppressed the development of ESRD (5.2% vs. 18.3% $p<0.05$). The expense for dialysis saved by this prophylaxis was estimated ≈$15,000/PCI.
Conclusions: Not only IRCIN but also RCIN significantly affects the long-term outcome of renal function and contributes to the future development of ESRD. The prevention of CIN by minimizing the contrast dose confers significant economical benefit by postponing the start of dialysis.

P1492 SES is cost effective in treatment of diabetic patients with multiple vessel disease, but leads to a relatively high stent thrombosis rate: the EVASTENT study

C. Combescure[1], J. Machecourt[2], A. Foote[2], C. Castelli[1], N. Danchin[3], G. Vanzetto[2], J.P. Daures[1] on behalf of EVASTENT investigators. [1]*University hospital, Nimes, France;* [2]*Centre Hospitalier Universitaire de Grenoble, Grenoble, France;* [3]*European Hospital George Pompidou (AP-HP), Paris, France*

Background: EVASTENT, a nation wide matched-cohort registry allowing a direct comparison of diabetic (db+) and non-diabetic patients, according to the number of vessel disease (Single (SVD) or multiple (MVD)), has shown, after SES implantation, safety concerns in MVD db+ (higher 3-years stent thrombosis rate (5.9%) than in SVD db + (3.5%), MVD db-(3.5%) and SVD db-(1.8%). The main objective was to determine the cost efficacy (incremental cost/avoided revascularization) and the cost-utility (cost/QUALY) of SES vs BMS in these 4 subsets of patients.
Methods: 1731 patients (488 db+ SVD, 356 db+ MVD, 513 db- SVD, 374 db-MVD) were treated with SES. Direct hospital costs for hospitalization, PCI, BMS, SES, CABG, and treatment (including clopidogrel) were measured for the SES arm. Trajectories for costs and clinical outcomes were derived from a Markov model and Monte Carlo simulations, over a 3-year time horizon. The parameters in the SES arm were derived from EVASTENT data, whereas transition probabilities in the BMS arm were derived from the SES arm, considering a RR of new target lesion revascularisation (TLR) = 0.30 with SES/BMS during the first year, then RR=1 after one year. Sensitivity analyses have been performed. SES was considered cost effective if <10 000 Euros/TLR avoided.
Results: in the SES group at 3 years follow-up 299 (17.2%) patients, experienced a new revascularisation, including 45 (2.6%) CABG: 125 TLR patients (7.2%), and for 192 patients (11%) a non-TLR revascularization. table 1 gives the 3-year results. SES was cost effective in MVD db+ patients. Sensitivity analyses demonstrated dominance of SES in such patients if the price premium between SES and BMS is 400 Euros.

3-years Cost efficacy and cost utility

	SVD db+	MVD db+	SVD db-	MVD db–
Total costs SES	11,059 €	13,814 €	10,184 €	12,270 €
[95% CI]	[6702-19118]	[7425-22529]	[6619-15969]	[7331-19608]
Total costs BMS	9578 €	12,149 €	8684 €	9914€
[95% CI]	[4925-20328]	[5242-26440]	[4925-16179]	[5184-18767]
TLR SES arm (%)	5.7%	11.2%	4.3%	9%
Avoided TLR with SES	980 (n/10,000 pts)	2243	927	1512
Cost/avoided TLR	15,130 €	7422 €	16,187 €	15,583 €
Cost/QALY	141,652 €	63,669 €	118,590 €	422,938 €

Conclusion: in EVASTENT, SES are cost effective when compared to BMS in MVD diabetic patients, but these patients demonstrate a relatively high stent thrombosis rate.

P1493 Benefits of an intensified telemedical care program for patients with heart failure - outcomes of a naturalistic study

F. Zucca[1], K. Fidorra[2], K. Pethig[3], B. Neukirch[1]. [1]*Hochschule Niederrhein, University of Applied Sciences, Krefeld, Germany;* [2]*St. Vincenz Hospital, Limburg, Germany;* [3]*Clinic for Cardiology, EVK Hamm, Hamm, Germany*

Purpose: Previous clinical observations of home care telemonitoring for patients with heart failure proved the reduction of morbidity. We investigated in an observational design whether an intensive telemedical heart failure program provides timely intervention, reduces hospital readmissions and days in hospital, and saves hospital costs accordingly.
Methods: A total of 2.182 patients with at least one hospitalization due to heart failure within the last twelve month were evaluated. 425 patients were enrolled prospectively in a staged telemedical service program. They received in addition to usual care telemonitoring equipment and were asked to transmit body weight, blood pressure and pulse rate daily to a telemedical service center. Those patients could also transmit a 12-lead ECG on demand. 1.757 controls were matched 4:1 to each telemedicine patient (comparable age, gender and heart failure etiology).
Results: After an observation period of 12 months, 155 telemedicine patients (37%) were admitted to the hospital 258 times for various indications. The mean days in hospital were 4±8 per patient. Within the control group, 1.187 patients (68%) were hospitalized 2,892 for various indications. These patients had mean days in hospital of 14±21. The hospital admissions and the hospital days per year and patients were significantly lower in the intervention group ($p<0001$). Hospital costs for one year were significantly lower by 75% in the intervention group compared with the control group (2,997 € ± 6,314 € vs. 11,982 € ± 17,009 €; $p<0001$).
Conclusion: Initial findings of this analysis suggest that telemedical care and telemonitoring may improve patients' morbidity while saving hospital costs in patients with heart failure.

P1494 Cost effectiveness and clinical performance of dobutamine stress echocardiography in coronary artery disease evaluation in a district hospital setting

C.A. Miller, S. Srivastava, J. Tollitt, R. Brown, R.M. Egdell, A.A. Cubukcu. *East Cheshire NHS Trust, Macclesfield, United Kingdom*

Purpose: A recent UK Health Technology Assessment found that in the evaluation of patients with suspected coronary artery disease (CAD), dobutamine stress echocardiography (DSE) had a significant diagnostic failure rate, a high complication rate and questionable cost-effectiveness. We investigated the clinical performance and cost effectiveness of DSE in CAD evaluation in a district hospital setting.
Methods: All patients who underwent DSE between 1 April 2006-31 March 2008 were identified using an electronic appointment system. Information was gathered on every patient using case-notes, an electronic patient record and a DSE database. Additional follow-up information was acquired through a General Practitioner telephone questionnaire.
Results: 78 patients underwent DSE for the evaluation of suspected CAD. Patients were evenly split for gender, with a mean age of 63 (standard deviation 11) and a mean of 2.1 (1.3) CAD risk factors. DSE rather than exercise electrocardiography testing (ETT) was performed due to mobility in 57% and a precluding electrocardiogram in 15%. The remaining patients proceeded to DSE following ETT. DSE was performed using a protocol of 'ramped' dobutamine up to 40mcg/kg/min. Atropine was added to achieve target heart rate in 24% and transpulmonary contrast was used to aid image quality in 18%. DSE was considered diagnostic in 76 (97%) patients. There were no significant complications. 58 (74%) patients had a negative DSE, allowing 63% to be discharged from regular cardiology review. During a mean follow-up period of 16 months, no patient with a negative DSE died or suffered an acute coronary event. Of the 18 patients with a positive DSE, 5 had only a limited area of inducible ischaemia in right coronary artery territory and so subsequent coronary angiography (CA) was not performed. None of these patients suffered an adverse cardiac event during follow-up. In total therefore, 15 patients were offered CA (2 with inconclusive DSE and 13 with positive DSE). Local cost of DSE is 220Euros (272Euros with contrast) and for CA is 1546Euros. By using an initial strategy of DSE for CAD evaluation rather than proceeding directly to CA, a cost saving of 1019Euros was achieved per patient (total saving of 39755Euros/year).
Conclusions: DSE is a clinically effective, cost effective and safe method for the functional evaluation of patients with suspected CAD in a district hospital setting.

P1495 Using risk adjustment methodology to improve quality and safety in percutaneous coronary intervention

P. Sousa[1], F.J.P. Pinto[2], A. Sousa-Uva[1] on behalf of the investigators of PCI Registry of Portuguese Society of Cardiology. *[1]National School of Public Health, Lisbon, Portugal; [2]Hospital Santa Maria, Lisbon, Portugal*

Background: The use of risk adjustment methodology to quantify the differences among patients, groups and populations, regarding outcomes, has been used more often in the era of modern interventional cardiology, showing a trustworthy and balanced comparison of performance and supporting quality and safety improvement strategies in this clinical area.
Purpose: The aim of this study was to develop and test a risk adjustment model for major adverse cardiac and cerebrovascular events (MACCE), following PCI procedures, using data from a national, multi-centre registry and to highlight the use of the risk adjustment methodology when we evaluate the quality and safety of care in interventional cardiology.
Methods: Retrospective analysis of 10.399 consecutives PCI procedures performed between June 30, 2003 and June 30, 2006 was performed. Bivariate and multivariate logistic regression models were used to identify independent risk factors for MACCE. Performance and calibration of the model was done, the area under the receiver operating characteristics (ROC) curve, and the Hosmer-Lemeshow goodness of fit statistic, were calculated. After that the model was tested in the population who has undergone PCI between July 2006 and June 2007. The ROC curve and the Hosmer-Lemeshow test were calculated. After that, the model was tested in the population who has undergone PCI between July 2006 and June 2007. The ROC curve and Hosmer-Lemeshow test were also calculated
Results: Factors associated with MACCE included, among others: age >80 (adjusted odds ratio (AOR) = 3.910); female gender (AOR = 1.720); AMI (AOR = 2.682); cardiogenic shock (AOR = 6.048); renal failure (AOR = 2.981); ejection fraction severely reduced (AOR = 3.940); three or more vessels treated (AOR = 2.175); and PCI urgent/emergent (AOR = 2.105). The ROC curve and the Hosmer-Lemeshow goodness of fit statistic, for the multivariate prediction model, were 0.84 and 0.18, respectively, which indicate that this model has discrimination adequate for genuine clinical utility.
Conclusions: A risk adjustment model for in-hospital MACCE after PCI, was successfully developed using a large national, multicenter registry, with timely data analysis. The model was tested in a "real world" population, showing that it has discriminative power adequate for genuine clinical utility. These findings will likely represent an important contribution to improve quality and safety of care and should help driving new research and innovative approaches to different sub groups of patients who have higher chances of having an adverse event or poorer outcomes following PCI.

P1496 Impact of hospital case load on management and early mortality of patients admitted for acute myocardial infarction (AMI). A nationwide French survey of administrative data

A. Neuman[1], P. Tuppin[1], N. Danchin[2], A. Weill[1], P. Ricordeau[1], C. De Peretti[3], H. Allemand[1]. *[1]CNAMTS, Paris, France; [2]European Hospital George Pompidou (AP-HP), Paris, France; [3]INVS, Paris, France*

Aim: To assess the management (use of coronarography and PCI) and early mortality of patients admitted for AMI according to the annual number of AMIs taken care of at each institution (annual case load). In addition, the rate of recommended quadruple therapy at 6 months was assessed in survivors.
Population and methods: We used the national payment database of hospital stays (PMSI) during the first 6 month of 2006 for patients covered by the general health insurance scheme. Data were cross-linked with the outpatients medications reimbursement database (SNIIRAM). Overall, there were 14,788 hospital stays (for 14,007 patients). The annual case load was determined for each institution. Adjustments were made on age, sex, major concomitant diseases (diabetes, cancer, Alzheimer, ...), previous cardiological hospitalisations.
Results: There was a direct and significant inverse correlation between hospital case load and in-hospital mortality; beyond 300 cases per year, however, there was no further significant reduction in early mortality. In addition, there was a significant positive correlation between hospital case load and the early use of coronarography, PCI with stent, and reimbursed recommended medications at 6 months.

Institution	Coronary angiography (%)			PCI with stent (%)			Hospital mortality (%)			Quadruple therapy at 6 months (%)		
	Crude	Adjusted		Crude	Adjusted		Crude	Adjusted		Crude	Adjusted	
Annual number of AMIs:												
≤49	47.9	57.2	***	32.7	40.1	***	17.9	12.5	***	45.7	55.4	*
50-99	63.1	67.4	***	46.3	50.0	***	13.1	11.1	ns	52.6	56.6	**
100-299	80.8	79.0	*	63.4	61.9	***	9.1	9.7	ns	62.7	61.3	ns
≥300	85.0	80.8	***	65.4	61.7	**	7.6	8.9	ns	69.3	66.1	***
300-399	84.2	79.9	*	64.8	61.1	ns	7.7	9.0	ns	67.1	64.3	ns
≥400	85.8	81.5	***	66.0	62.2	**	7.6	8.9	ns	71.1	67.7	***
Total	76.0			58.2			10.1			62.1		

*p<0.05, **p<0.01, ***p<0.001. For each column, the adjusted subgroup rate was compared to the total rate.

Conclusion: The profile of patients with AMI is highly correlated with the type of institution they are admitted to (e.g. older patients admitted to smaller hospitals). Even after multivariate adjustment, however, mortality was higher in hospitals caring for fewer AMI patients and long term secondary prevention was less appropriate. Beyond 300 AMI cases/year, there was no further improvement in hospital outcome.

P1497 Time of admission, quality of PCI care, and outcome of patients with ST-elevation myocardial infarction

H. Theres[1], S. Behrens[2], C. Graf-Bothe[3], H. Kuckuck[4], J.-U. Roehnisch[5], R. Schoeller[3], H. Schuehlen[6], B. Maier[7] on behalf of Berliner Herzinfarktregister. *[1]Charite - Campus Mitte, Humboldt-Universitaet, Berlin, Germany; [2]Vivantes Humboldt Klinikum Berlin, Berlin, Germany; [3]DRK Kliniken I Westend Berlin, Berlin, Germany; [4]Vivantes Wenckebach Klinikum Berlin, Berlin, Germany; [5]Vivantes Klinikum Hellersdorf, Berlin, Germany; [6]Vivantes Auguste-Viktoria-Klinikum Berlin, Berlin, Germany; [7]Zig der Technischen Universitaet, Berlin, Germany*

Objective: Our study aimed to determine whether differences in hospital mortality between patients admitted in- and off-normal working hours with ST-elevation myocardial infarction (STEMI) could be reduced within the special logistical setting of Berlin.
Background: There is a debate whether patients with acute myocardial infarction admitted to hospital outside normal working hours experience higher mortality rates than those admitted within normal working hours.
Methods: This study analyzes data from the Berlin Myocardial Infarction Registry and comprises 2131 patients with STEMI treated with percutaneous coronary intervention (PCI) in 2004-2007. The results for patients admitted during in- and off-normal working hours were compared.
Results: There was significant difference in door-to-balloon time (median in-hours: 79 min.; median off-hours: 90 min., $p < 0.001$) and in hospital mortality (in-hours: 4.3%; off-hours: 6.8%, $p = 0.020$) between STEMI patients admitted in- and off-hours for treatment with PCI. After adjustment, admission off-hours remained an independent predictor for in-hospital death for patients (OR = 2.50; 95% CI: 1.38-4.56). In patients with primary care from physician-escorted Emergency Medical Services (EMS), door-to-balloon time was reduced by 10 minutes for in-hours as well as off-hours patients. The difference in hospital mortality between off-hour and in-hour admission was reduced to a non-significant OR = 1.61 (95% CI: 0.79-3.27).

Conclusions: Patients admitted off-hours experienced longer door-to-balloon times and greater hospital mortality than did those admitted in-hours. The differences observed between patients admitted in-hours and off-hours were reduced through physician-escorted EMS that prepared patients' treatment paths.

P1498 Euro heart survey on AF: costs of Atrial Fibrillation (AF) for ATHENA-like patients in Greece, Italy, Poland, Spain and the Netherlands

E. Holstenson[1], E. Morais[2], J. Berg[1], R. Nieuwlaat[3], A. Ringborg[1], H. Crijns[3]. [1]*i3Innovus, Stockholm, Sweden;* [2]*sanofi-aventis, Paris, France;* [3]*University Hospital Maastricht, Maastricht, Netherlands*

Purpose: ATHENA, a placebo-controlled, double-blind trial that studied the effect of dronedarone treatment in patients with atrial fibrillation (AF) or atrial flutter (AFL) demonstrated a 24% reduced risk of cardiovascular hospitalization or death ($p<0.001$). The aim of this analysis was to estimate the annual costs of ATHENA-like patients in Greece, Italy, Poland, Spain and the Netherlands based on data collected through the Euro Heart Survey on AF (EHS-AF). These were the countries participating in the EHS-AF that enrolled more than 200 patients.
Methods: Patients recruited to the EHS-AF with a risk factor profile similar to that of patients in the ATHENA trial (paroxysmal or persistent AF at inclusion; age $\geq$ 75 years or 70-75 years with at least one of the following risk factors: diabetes mellitus; hypertension; prior stroke; prior TIA; prior systemic embolism; left atrium enlarged; left ventricular ejection fraction <40%) were identified. Annual costs were estimated by multiplying quantities of resource use as recorded in the EHS-AF by country-specific unit costs obtained from public sources in 2007 €. Diagnostic and interventional procedures, drugs, inpatient care and consultations were included in the estimations.
Results: The ATHENA-like patients recruited in the EHS-AF included 46 from Greece, 181 from Italy, 38 from Poland, 97 from Spain and 168 from the Netherlands. The mean total costs were €504, €3015, €1218, €2498 and €2614 respectively (see table for 95% CIs). Inpatient care and interventional procedures were identified as the main drivers of costs.

Table 1

Nation	ATHENA-like patients		All EHS-AF patients	
	N	Total costs	N	Total costs
Greece	46	504 (352; 715)	251	1540 (1026; 2415)
Italy	181	3015 (2253; 3926)	645	3294 (2848; 3796)
Poland	38	1218 (698; 1850)	203	1032 (828; 1287)
Spain	97	2498 (1681; 3537)	720	2365 (2017; 2758)
The Netherlands	168	2614 (1740; 3740)	686	2377 (1925; 2921)

Mean (95% CI) annual costs.

Conclusion: This analysis provides real-life cost of illness data of ATHENA-like patients in five European countries. Novel therapies like dronedarone should reduce cardiovascular hospitalizations in similar patients and therefore reduce associated health care costs.

STENT THROMBOSIS AND NEO INTIMAL COVERAGE

P1499 Is there a different early and late benefit - risk balance of DES vs BMS? The role of very late stent thrombosis

X. Flores Rios, A. Garcia Campos, A. Rodriguez Vilela, G. Aldama Lopez, P. Pinon Esteban, J. Salgado Fernandez, R. Calvino Santos, J.M. Vazquez Rodriguez, N. Vazquez Gonzalez, A. Castro Beiras. *Hospital Juan Canalejo, A Coruna, Spain*

Introduction: Drug-eluting stents (DES) seem to have a slightly higher risk of stent thrombosis (ST) in comparison with bare metal stents (BMS), particularly of very late ST. We sought to compare the risk of ST between DES and BMS in a real-world population and assess its clinical consequences after long-term follow-up.
Methods: We selected all consecutive patients who had received $\geq$ 1 paclitaxel-eluting stent (PES) and $\geq$ 1 BMS from January, 2003 to December, 2004 at our Interventional Cardiology Unit. Study end-points were probable or definite ST (according to ARC definitions), clinically-driven in-stent restenosis (ISR), target-lesion revascularization (TLR), myocardial infarction (MI), and cardiovascular death. We employed Cox regression analysis to examine the association between the use of DES vs BMS and each endpoint, accounting for the differences in clinical and angiographic characteristics of these cohorts.
Results: 1698 patients (1268 patients with BMS; 430 patients with PES) were followed for a median time of 45 months (IQR 12 months). Overall, PES reduced the risk of ISR in comparison with BMS, but they were associated with a higher risk of ST. There were no statiscally significant differences for the risk of cardiovascular death, MI and TLR. In the 1st year after stent placement, PES had a lower risk of TLR and ISR. After this limit, PES increased the risk of MI and TLR, as they led to a higher risk of ST (Table).
Conclusions: Our finding support the notion of a different benefit–risk relation early and late after PES implantation. Very-late ST of DES may limit long-term clinical benefits of PES vs BMS. Further studies are required, as it remains uncertain how this excess of risk of ST for PES will translate into an even longer-term outcome balance.

Adjusted risk for clinical events

	Overall		1st year		After 1st year	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Cardiovascular death	0.9 (0.6–1.4)	0.406	1.1 (0.7–2.4)	0.836	0.7 (0.5–1.4)	0.323
MI	1.1 (0.7–1.9)	0.642	0.6 (0.1–6.2)	0.649	2.0 (1.0–4.2)	0.056
ST	3.2 (1.3–7.7)	0.009	0.7 (0.2–3.1)	0.638	13.6 (3.0–60.4)	0.001
ISR	0.3 (0.2–0.6)	0.001	0.2 (0.1–0.6)	0.001	0.4 (0.1–1.3)	0.160
TLR	0.7 (0.4–1.1)	0.111	0.2 (0.1–0.5)	0.001	2.5 (1.1–3.7)	0.027

This table summarizes the adjusted risk for clinical endpoints for PES vs BMS (overall, in the first year and after the first year).

P1500 Do drug-eluting stents really have a higher risk of stent thrombosis than bare-metal stents?

X. Flores Rios, E. Barge Caballero, R. Campo Perez, P. Pinon Esteban, G. Aldama Lopez, J. Salgado Fernandez, R. Calvino Santos, J.M. Vazquez Rodriguez, N. Vazquez Gonzalez, A. Castro Beiras. *Hospital Juan Canalejo, A Coruna, Spain*

Background: There is great controversy about stent thrombosis (ST), especially whether drug-eluting stents (DES) carry a higher risk of ST than bare-metal stents (BMS). We sought to perform an exhaustive comparison of both types of devices in a real-world population regarding ST.
Methods: All consecutive patients who received $\geq$1 paclitaxel-eluting stent (PES)and $\geq$ 1 BMS from January, 2003 to December, 2004 at our Interventional Cardiology Unit were enrolled. PES were the only DES available at our hospital during that time period. Patients with a combination of both types of devices were excluded. The incidence of ST (including probable and definite ST) in these two groups was compared using survival analysis (log-rank test). Adjusted risk for thrombotic events was estimated using Cox regression analysis, accounting for the overt differences in clinical and angiographic characteristics of these cohorts.
Results: The study population was composed by 1698 patients (1268 patients treated with BMS; 430 patients who received PES). After long-term follow-up (median time of 45 months), cumulative incidence of ST was higher in the PES group (3.5% for PES vs 1.3% for BMS, p= 0.003). There were no differences in the subacute ST rates (0.5% vs 0.8%, p= 0.574) but late and very late ST was much more common in the PES cohort (3.0% vs 0.5%, $p<0.001$). After statistical adjustment, PES had a higher risk of ST (hazard ratio HR 3.2, 95% CI 1.3 to 7.7). There were no differences in the adjusted risk of subacute ST, but PES were associated with a 9-fold risk of late and very late ST when compared with BMS.

	BMS		PES		Log-rank test	Adjusted HR
	N	%	N	%		
Subacute definite and probable ST	10	0.79%	2	0.47%	0.574	0.45 (0.1-2.7)
Late and very late definite and probable ST	7	0.55%	13	3.02%	< 0.001	8.9 (2.9-27.1)
Total ST	17	1.34%	15	3.49%	0.003	3.2 (1.3-7.7)

N = No. events.

Conclusions: In a common clinical practice setting, PES are associate with a higher risk of ST than BMS, mainly due to a significant increase in the risk of late and very late ST.

P1501 The principle of glycocalix biomimicry: a new coating stent design for patients with unstable coronary lesions. Early results of the Camouflage registry

J. Mieres, M. Rodriguez-Granillo, C. Carlos Fernandez-Pereira, G. Gustavo Risau, A. Rubilar, G. Perez, C. Llaurado, A. Incarbone, I. Di Pasquo, A. Rodriguez. *Sanatorio Otamendi, Buenos Aires, Argentina*

Background: In preclinical studies, the semisynthetic dense coating of the bare metal Camouflage stenting (Eucatech AG, Rheinfelden, Germany) mimics luminal endothelial cell glycocalix preventing the activation of the coagulation system, giving to the stent design, in theory, a potential advantage in high risk thrombotic lesions or in patients unable to receive for long term antiplatelet therapy.
Purpose: To determine in a clinical phase registry the acute and long term clinical and angiographic outcome of this antithrombotic coated stent design in patients with acute coronary syndromes (ACS) or unable for long term clopidogrel therapy.
Methods: Since March 2007 to December 2008, 150 patients undergoing coronary stent implantation in three centers in Buenos Aires Argentina were included in our registry. Patients with ACS, including non ST and ST elevation MI in or unable for long term dual antiplatelet therapy were considered for inclusion. Primary end point was major adverse cardiovascular events (MACE) defined as incidence of cardiac death, MI and target lesion revascularization (TLR). Incidence of acute and late stent thrombosis (SET) was also analyzed. Angiographic late loss and presence of late stent malapposition (LSM) was recorded at 9 months of follow up. Clopidogrel was prescribed for one months.
Results: 54.7% patients have acute MI, 31% ST segment elevation MI and 20.7% of patients were unable for long term clopidogrel therapy for previous planned non vascular or general surgery within 30 days after PCI. During 12.4 months

of clinical follow up, 2% suffered cardiac death, 4% MI, TLR of 8.9% and overall cumulative MACE of 13%. No patient developed acute or late SET. Patients undergoing surgery had zero in hospital complication rate. IVUS study do not detected presence of LSM.

Conclusion: In this high risk thrombotic patient population, Camouflage coated stent design, demonstrated a very good safety profile as reflected by the low incidence of hard adverse cardiac events included SET acutely and at late follow up.

P1502 Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy

M. Basalus[1], K.G. Van Houwelingen[1], M.J.K. Ankone[2], P.W. Serruys[3], C. Von Birgelen[1]. *[1]Thoraxcentrum Twente, Department of Cardiology, Enschede, Netherlands; [2]Institute for Biomedical Technology (BMTI), University of Twente, Enschede, Netherlands; [3]Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands*

Objective: The success of drug-eluting stents (DES) with durable-polymer coatings is overshadowed by unsettled discussions on late stent thrombosis and reduction of mortality, while few data are available on the post-expansion DES morphology.

Methods: To classify coating irregularities, Taxus Liberté, Endeavor Sprint, Endeavor Resolute, and Xience V DES (3 samples of each) were explored by light microscopy and scanning electron microscopy (SEM) following stent expansion at 14atm in water. Incidence and size of irregularities were then measured during thorough quantitative examinations of a total of 360 SEM images.

Results: Fourteen types of irregularities were classified into four categories according to amount and homogeneity of coating (see table). The total incidence of irregularities (6.6±4.2/image at 60-fold magnification) differed among DES types ($p<0.0001$). All types showed areas with bare metal-aspect, but incidence, shape, and size differed largely; Endeavor Sprint showed the largest areas. Cracks were found in Endeavor Sprint and Resolute only, while wrinkles were exclusively seen in Taxus Liberté and Xience V ($p<0.0001$). The coating of each DES type showed some inhomogeneity of distribution, but the incidence differed ($p<0.0001$) and was least in Taxus Liberté, which on the other hand was the only DES that showed webbing associated with large bare-metal exposure. Different DES types showed certain irregularities at constant locations, resulting in typical patterns.

Cracks and bare metal areas on DES

Conclusion: The incidence and size of various coating irregularities on different types of DES varied widely. These data may be considered in ongoing discussions on between-DES differences and may serve as reference to compare novel DES.

P1503 Greater late lumen loss after paclitaxel-eluting stent implantation is not associated with homogeneous neointimal coverage

K. Fukushima, Y. Kobayashi, H. Kitahara, Y. Iwata, N. Ishio, T. Asano, N. Kuroda, I. Komuro. *Chiba University Graduate School of Medicine, Chiba, Japan*

Background: Paclitaxel-eluting stents (PES) have greater late lumen loss compared to sirolimus-eluting stents (SES). However, it does not translate into less stent thrombosis. This intravascular ultrasound (IVUS) study evaluated neointimal coverage within PES and SES.

Methods: Follow-up IVUS was performed in 40 lesions that had undergone PES implantation. A control group for comparison was composed of 40 matched lesions undergoing follow-up IVUS after SES implantation. Stent and lumen diameters and areas were manually traced at 1-mm intervals. Late lumen loss was defined as minimum stent diameter minus minimum lumen diameter. Neointima area was calculated as stent area minus lumen area. In each measured cross-section, neointimal coverage was semi-quantified into 4 categories according to the degree of neointima-covered area within stent: 1) ≤90°, 2) 91-180°, 3) 181-270°, and 4) >270°.

Results: There was no significant difference in the incidence of diabetic patients between the SES and PES groups (60% vs. 63%, NS). Table shows IVUS measurements. Greater neointima was observed within PES compared to SES. However, more than half of cross-sections in PES were neointima-free, which may serve as nidus of stent thrombosis.

Table 1. Results

	SES	PES	p Value
Mean stent area (mm^2)	7.2±1.6	7.6±2.1	0.28
Mean lumen area (mm^2)	7.0±1.6	7.0±2.4	0.86
Late lumen loss (mm)	0.06±0.10	0.36±0.38	<0.001
Mean neointima area (mm^2)	0.14±0.15	0.68±0.71	<0.001
Neointima-free segment (%)	80.8±16.5	56.8±27.4	<0.001
Neointima-coverd area (%)			
≤25%	87.6±15.0	65.7±27.1	<0.001
26-50%	9.5±11.5	14.9±13.3	0.05
51-75%	2.1±3.6	5.4±6.6	<0.001
>75%	0.8±2.2	14.0±22.2	<0.001

Conclusions: PES have greater neointimal hyperplasia compared to SES. It results in greater late lumen loss. However, neointimal coverage within PES is not homogeneous, while SES inhibit intimal hyperplasia homogeneously. These may explain that greater late lumen loss is not associated with less stent thrombosis.

P1504 Endothelial progenitors cells, circulating endothelial cells and cd14+ monocytes in coronary artery disease: effect of stenting with bare-metal, drug-eluting and the genous cd34 antibody coated stents

A. Siddique[1], E. Shantsila[1], R.A.S. Ahmad[2], A.D. Blann[1], D.L. Connolly[2], C. Varma[3], G.Y.H. Lip[1]. *[1]University department of medicine, city hospital, birmingham, Birmingham, United Kingdom; [2]Sandwell General Hospital, Birmingham, United Kingdom; [3]City Hospital, Birmingham, Birmingham, United Kingdom*

Purpose: Arterial injury due to stenting and the associated inflammatory response involving white blood cells (WBCs), specifically CD14+ monocytes, is associated with in-stent restenosis. The inflammatory response triggers release of endothelial progenitor cells (EPCs) from the bone marrow. Coronary artery stenting leads to increased levels of circulating endothelial (CECs) in the blood. We studied the responses of CD14+ monocytes, EPCs and CECs to bare-metal stent (BMS,n = 10), drug eluting stent (DES,n = 39) and the Genous CD34 antibody coated stent (n = 16) in patients undergoing elective stenting.

Methods: We quantified WBCs, CD14+monocytes, EPCs and CECs in the peripheral blood in 65 patients undergoing percutaneous coronary intervention (PCI). Levels were measured at baseline and 48 hours afterwards, by fluorescence activated cell sorting.

Results: In patients with DES, the WBC count significantly increased (p=0.028), but no changes in CD14+monocytes, EPCs or CECs were seen [Table]. No significant changes in WBCs, CD14+ monocytes, EPCs or CECs were seen patients with BMS or those with CD34 antibody coated stents.

	Bare-metal stents	Drug eluting stents	CD34 antibody coated stent
WBC pre-PCI (cells/ml)	6.9 (2.0)	7.1 (1.7)	7.0 (1.9)
WBC post-PCI (cells/ml)	7.3 (2.0)	7.6* (2.5)	7.0 (2.7)
CD14+monocytes pre-PCI (cells/ml)	128 (100-253)	255 (111-324)	113 (48-377)
CD14+ moncytes post-PCI (cells/ml)	349 (122-586)	264 (130-417)	156 (62-347)
EPCs pre-PCI (cells/ml)	22 (8-37)	24 (14-56)	16 (11-34)
EPCs post-PCI (cells/ml)	18 (12-25)	28 (14-54)	18 (11-33)
CECs pre- PCI (cells/ml)	2 (1.7-4.4)	2.9 (0.7-5.9)	1.7 (0.7-4)
CECs post-PCI (cells/ml)	1.8 (1-4.3)	1.9 (0-4)	2.2 (0.4-4.8)

*p=0.028. All other p values for changes were non-significant.

Conclusion: Apart from a small increase in WBCs after DES implantation, no statistically significant changes with monocytes, EPCs or CECs were seen with 3 different stents, suggesting that peripheral quantification of these parameters may not reflect the pathophysiological associations with these different stent types.

P1505 Optical coherence tomography analysis of vascular responses following paclitaxel-eluting stent implantation in the lesion with acute coronary syndrome

M. Habara, M. Terashima, K. Nasu, M. Kimura, Y. Kinoshita, M. Ehara, E. Tsuchikane, Y. Asakura, O. Katoh, T. Suzuki. *Toyohashi Heart Center, Toyohashi, Japan*

Background: Safety and feasibility of drug-eluting stent in the lesion with acute coronary syndrome (ACS) is still controversial. Optical coherence tomography (OCT) is a high-resolution intravascular imaging modality, which is expected to visualize microscopic vascular response to coronary intervention. The purpose of this study is to evaluate the difference of vascular responses following stent implantation in the ACS lesions between paclitaxel-eluting stent (PES) and bare-metal stent (BMS) using OCT.

Method: Fifty-three ACS patients who were treated with either PES or BMS (30 PESs and 23 BMSs) underwent OCT at 3 months follow-up, and 28 of them (16 PESs and 12 BMSs) also had 9 months follow-up OCT. Every observed stent struts were analyzed at intervals of 1mm. Neointimal coverage of struts, stent apposition, neointimal thickness (NIT), and the presence of thrombus were evaluated.

Result: (In total, 7148 struts in PESs and 5477 struts in BMSs were analyzed at 3-month, and also 3252 struts In PESs and 1894 struts in BMSs at 9-month.) At 3 months, frequencies of exposed-struts/stent and of incompletely-apposed-struts/stent were 7.89±9.53% and 2.3±4.45% in PESs, 3.07±5.26% and 0.7±1.40% in BMSs (p=0.053, p=0.117, respectively). Mean thickness of neointima was 0.14±0.08 mm in PESs and 0.34±0.15mm in BMSs (p<0.001). Thrombus was detected in 6 PESs (20.0%) and in 3 BMSs (13.0%; p=0.715). At 9 months, frequencies of exposed-struts/stent and of incompletely-apposed-struts/stent were 3.70±3.57% and 0.59±0.98% in PESs, 0.95±1.36% and 0.04±0.11% in BMSs (p=0.050, p=0.132, respectively). Mean thickness of neointima was 0.23±0.11mm in PESs and 0.48±0.19mm in BMSs (p<0.001). Thrombus was detected in 2 PESs (12.5%) and in 1BMS (8.3%) (p=1.0).
Conclusion: A nonsignificant trend for more frequent exposed strut was observed in PESs than in BMSs; however, frequencies of incomplete stent apposition and incidence of intracoronary thrombus were not different between PESs and BMSs at both 3 and 9 months follow up. Neointimal growth was suppressed more strongly by PESs than by BMSs. These data would suggest safety and feasibility of PES for the ACS lesions.

P1506 Very late stent thrombosis in sirolimus-eluting stents after ST-elevation myocardial infarction: three-year clinical outcome of the mission intervention study

J.Z. Atary, B.L. Van Der Hoeven, S.S. Liem, J.W. Jukema, H. Putter, D.E. Atsma, M. Bootsma, K. Zeppenfeld, E.E. Van Der Wall, M.J. Schalij. *Leiden University Medical Center, Leiden, Netherlands*

Purpose: To evaluate the long-term incidence of stent thrombosis comparing sirolimus-eluting stents (SES) to bare-metal stents (BMS) for acute ST-segment myocardial infarction (STEMI).
Method: All 310 patients (age 59±11years, 78% male) from the single-blind, single-center, randomized MISSION-intervention study were followed for a median of 38 months. Clinical end points were definite, probable and possible stent thrombosis further subdivided into acute (≤1day), subacute (>1day - ≤1month), late (>1month - ≤1year) and very late (>1year), according to the Academic Research Consortium definition. All patients were treated with aspirin for life and clopidogrel for 1year after stent implantation.
Result: There were no significant differences in baseline and angiographic characteristics between the treatment groups (158 SES, 152 BMS). The cumulative rate of definite stent thrombosis at 3.5years follow up was 4.0% for SES treated patients and 0.7% for BMS treated patients (p=0.11). No acute and late definite stent thrombosis was observed. The cumulative rate for subacute definite stent thrombosis was the same for SES and BMS groups (0.6% vs. 0.7%; p=0.99). There was however a higher incidence of very late definite stent thrombosis at 3.5 years in the SES group compared to the BMS group (3.3% vs. 0%; p=0.05). Cumulative rates for probable and possible stent thrombosis were similar between the treatment groups.
Conclusion: After 3.5 years a higher cumulative incidence of very late stent thrombosis was observed in SES treated STEMI patients compared to BMS treated STEMI patients.

P1507 Correlations between intracoronary cytokines levels and native coronary artery plaque composition as assessed by intracoronary ultrasound virtual histology

S. Fuchs[1], I. Lavi[2], O. Tzang[2], S. Fuchs[2], D. Brosh[1], T. Bental[1], S. Einav[2], R. Kornowski[1]. *[1]Rabin Medical Center, Petah Tikva, Israel; [2]Dept. of Biomedical Engineering, Tel Aviv University, Tel Aviv, Israel*

Background: Various cytokines and chemokines (C&C) are associated with development and progression of coronary artery disease along with increased rate of adverse cardiac events. The latter may also be due to plaque destabilization and development of acute coronary events. Accordingly, we investigated the association between intracoronary levels of six C&C with high-risk features of plaque composition as assessed by intravascular ultrasound (IVUS) virtual histology (VH), in ischemic patients with coronary artery disease.
Methods: Using ELISA, we measured CD40L, CRP, MCP1, MMP-9, P-selectin and VEGF levels proximal and distal to the culprit lesion in 40 patients who underwent detailed IVUS and IVUS-VH analysis. Correlation between C&C levels and VH-defined necrotic core (NC), calcium (Ca), fibrous (F) and fibrofatty (FF) components was performed after logarithmic transformation of C&C levels.
Results: C&C levels proximal and distal to the culprit lesions were similar with very high correlation for the two site-measurements (P<0.001). CRP had the strongest correlation to baseline clinical characteristics, mainly total cholesterol/HDL (r=-0.47, p=0.005), while P-selectin (r=-0.42, p=0.009) levels inversely correlated with age and higher VEGF levels were noted in younger patients (p=0.0029). MCP1 was the major C&C, which significantly correlated with plaque components. Strong correlation was noted with NC area (r=0.46, p=0.003) and Ca area (r=0.43, p=0.006). Similar correlations were observed with plaque composition at maximal NC site and with total segmental plaque components. Intraplaque NC and Ca distribution analysis revealed correlation between MCP1 level and grouping of NC areas (r=0.37, p=0.019) and Ca (r-0.33, p=0.043) within the plaque.
Conclusions: While several C&C levels are correlated with higher-risk patient characteristics, MCP1 levels are correlated with the amount and specific patterns of NC and Ca depositions. As increased NC component is a characteristic of higher-risk plaque morphology, the impact of reduction in specific C&C such as MCP1 on modulation of plaque composition should be further investigated.

P1508 The incidence of incomplete stent strut apposition. Insights from the randomized, multicenter OCT Resolute III substudy

E. Regar[1], C. Dimario[2], C. Macaya[3], Y. Termijn[4], P. Gobbens[4], K. Commissaris[4], N. Gonzalo[1], P.W. Serruys[1]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]Royal Brompton Hospital, London, United Kingdom; [3]Hospital Clinico San Carlos, Madrid, Spain; [4]Cardialysis B.V., Rotterdam, Netherlands*

Background: Incomplete stent strut apposition despite an optimal angiographic result has been observed incidentally by intracoronary optical coherence tomography (OCT), a high resolution imaging technology with an in-vivo resolution in the range of 15 micron. Little is known, however, on the incidence of incomplete strut apposition and its clinical consequences.
Aim: To assess the incidence of incomplete stent strut apposition (ISA) in a consecutive, real world patient population undergoing state of the art coronary stent procedures.
Methods: The Resolute III study is a prospective, multicenter, randomized trial to compare the outcome after zotarolimus-eluting vs. everolimus-eluting stent implantation in an all-comer population. The OCT was performed in 3 centers, patients with ostial or left main lesions, renal impairment and hemodynamic instability were excluded. OCT was performed with a 1300nm light source and an 0.019 inch imaging wire (Lightlab Imaging, Westford, MA). OCT data analysis was performed by a central corelab blinded to the randomization.
Results: OCT analysis of the first 25 patients was performed in n=32 stented segments (n=34 stents, n=9131 struts). The minimal stent area was 5.73±1.67 mm^2, stent expansion was 108±45% of the mean reference area. ISA was observed in 25 (73%) stents and affected 167 out of 9131 struts (1.8%). The distance of the struts to the vessel wall ranged from 0.02mm to 0.57mm, the ISA area was 0.44±0.32 mm^2.
Conclusion: In a prospective, multicenter series of patients, incomplete apposition of individual stent struts within a stented segment is not uncommon, as revealed by OCT. Analysis of the causes and the clinical significance of these findings might help to further improve the procedural outcome in the future.

P1509 Optical coherence tomography assessment of the acute effects of stent implantation on the vessel wall

N. Gonzalo Lopez, P.W. Serruys, T. Okamura, S. Zujun, Y. Onuma, H.M. Garcia-Garcia, G. Sarno, C. Schultz, J. Ligthart, E. Regar. *Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Purpose: To evaluate the frequency and types of vessel wall injury caused by stent implantation visible by optical coherence tomography (OCT) and to compare them in stable vs unstable patients.
Methods: All consecutive patients in whom OCT was performed after stent implantation were included in the study. Qualitative and quantitative assessment of edge dissection, intrastent dissection and tissue prolapse were performed.
Results: Seventy-three patients (80 vessels) were analyzed. Tissue prolapse was visible in 78/80 vessels (97.5%). The median number of tissue prolapse sites was 8 [Interquartile (IQ) range 4-19]. The tissue prolapse area was 1.04±0.9 mm^2. Intrastent dissection flaps were visible in 69/80 vessels (86.2%) with a median number of flaps of 3 (IQ range1.25-6) and a maximum flap length of 450±220 μm. Fifty-five out of 80 vessels showed dissection cavities with a median number of 2 (IQ range 0-4.75) visible per vessel and a maximum depth of 340±170 μm. The table shows the comparison of the acute effects of stent implantation as assessed by OCT in stable and unstable patients.

	Stable (n=45)	Unstable (n=35)	p
Tissue prolapse visible (%)	43/45 (95.6)	35/35 (100)	0.5
Number sites tissue prolapse	11 (5-22)	7 (13-16)	0.06
Tissue prolapse area (mm^2)	1.21±1.0	0.80±0.6	0.028
Tissue prolapse maximum length (μm)	260±65	247±85	0.5
Intrastent dissection flap visible (%)	39/45 (86.7)	30/35 (85.7)	0.9
Number intrastent dissection flaps	3 (2-7)	3 (1-4)	0.3
Intrastent dissection flap maximum length (μm)	488±238	419±197	0.1
Intrastent dissection cavity visible (%)	32/45 (71.1)	23/35 (65.7)	0.6
Number intrastent cavities	2 (0-4.5)	1 (0-5)	0.6
Maximum depth cavity (μm)	336±183	357±150	0.6
Edge dissection visible (%)	9/41 (22)	11/34 (32.4)	0.3

Conclusions: 1) A very high proportion of patients showed tissue prolapse or intrastent dissections visible by OCT after stent implantation. 2)There were no significant differences in the frequency or quantitative measurements of intrastent or edge dissections and frequency of tissue prolapse between patients with stable and unstable clinical presentation but the tissue prolapse area was higher in stable patients.

P1510 Rapid evaluation of vessel healing after angioplasty (REVEAL) study: an optical coherence tomography comparative study with a polyzene-f stent versus bare and drug eluting stents at 7 and 30 days

A.G. La Manna[1], M.E. Di Salvo[1], D. Capodanno[1], A. Sanfilippo[1], G. Barrano[1], F. Prati[2], C. Tamburino[2]. *[1]Ferrarotto Hospital - University of Catania, Catania, Italy; [2]San Giovanni Hospital, Rome, Italy*

Purpose: Aim of the present randomized study is to address vessel healing at 7 and 30 days after stenting with a proprietary formulated polyphosphazene cobalt chromium stent by applying optical coherence tomography (OCT), and perform a comparison with two distinct groups of drug eluting stents (DES: sirolimus eluting stent [SES], paclitaxel eluting stent [PES]) and bare metal stents (BMS).
Methods: Twenty-two consecutive patients with two significant short lesions ($\leq$ 20 mm) located in remote vessels will be treated with two distinct stents (length $\leq$ 20 mm). One of the two stents will be a polyphosphazene stent, while the second one will be a BMS or a DES, according to the randomization protocol. OCT will be performed to address stent coverage and percentage of neointima at 30 days in all stents. Another arm of the study will consider 12 patients with the same features undergoing polyphosphazene and DES or BMS implantation in remote vessels with OCT follow up at 7 days.
Presence of sub-optimal stent visualization in more than 10% of stent struts will be a reason for stent exclusion from analysis.
For any stent the percentage of healed stent struts, defined as coverage with a linear rim of tissue and without thrombosis, will be defined. Presence of stent malapposition, overlapping or fracture will be recorded.
Major study end-point will be to compare the percentage of healed stent struts in group 1 (polyphosphazene stent) and group 2 (DES). Based on our statistical assumptions, to get a 99% chance of detecting a difference of absolute 20% rate in stent struts coverage at 30 days between group 1 (polyphosphazene stent with estimated stent struts coverage in 80% of struts) and group 2 (DES with estimated stent struts coverage in 60% of struts) with a significant level of 0.01, 494 stent struts had to be analyzed at OCT follow-up.
Preliminary results
Sixteen stents (8 polyphosphazene stent, 4 BMS [cobalt-chromium] and 4 DES [SES or PES]) were studied at 30 days with a total of 13,704 stent struts analyzed; 7,084, 3,273 and 3,347 struts analyzed, respectively.
The mean percentages of uncovered struts were 4.6% in the polyphosphazene stent group, 10.9% in the BMS and 18.9% in the DES groups (p = 0.019 versus proprietary polyphosphazene). Final results with both qualitative and quantitative analysis of vessel healing at 7 and 30 days will be provided.
Conclusions: Preliminary results of the present study show that the polyphosphazene stent placement lead to improved early vessel healing in comparison with either BMS or DES. The polyphosphazene stent coverage promises to reduce both acute and subacute in-stent thrombosis.

P1511 Evaluation in 3 moNths Duration of nEointimAl coVerage after zOtaRolimus-eluting stent implantation by Optical Coherence Tomography (ENDEAVOR OCT)

J.-S. Kim, C. Fan, T.H. Kim, J.S. Kim, S.M. Park, Y.G. Ko, D. Choi, Y. Jang, W.H. Shim, S.Y. Cho. *Yonsei University, Seoul, Korea, Republic of*

Background: Zotarolimus-eluting stents (ZES) has different characteristics with biocompatible polymer and rapid drug elution compared to the 1st generation drug eluting stents. However, no data is available for vascular response in early period after ZES implantation.
Methods and results: The ENDEAVOR OCT trial (Evaluation in 3 moNths Duration of nEointimAl coVerage after zOtaRolimus-eluting stent implantation by Optical Coherence Tomography) is prospective, single center study evaluating the vascular healing pattern using OCT at 3-month after stent implantation.
A total of 31 ZESs in 30 patients were undertaken serial IVUS and OCT at initial and 3 months. Cross-sectional OCT images were analyzed at 0.5-mm intervals, and malapposition and neointimal coverage were evaluate at each stent strut in the serial OCT images. Malappostion rates at baseline and 3 months were 5.8% and 0.2%, respectively. But, late acquired malapposition was not detected at 3 months. The mean percentage of stent strut coverage was 99.9±0.4% and there was also similar rate of stent strut coverage between patients with acute coronary syndrome and stable angina (99.9±0.3% vs. 99.9±0.4%, p= 0.926). Intracoronary thrombus was detected in 1 stent (3.4%).
Conclusion: Neointimal coverage of stent struts was nearly complete and late acquired malapposition was not found at 3-month after ZES implantation. Therefore, current study demonstrated the ZES might be related to a favorable vascular response in vivo even at 3-month after stent implantation.

PRE-CLINICAL STUDIES IN PERCUTANEOUS ANGIOPLASTY

P1512 Vascular healing in comparator drug-eluting stents: differential response of limus-eluting stents?

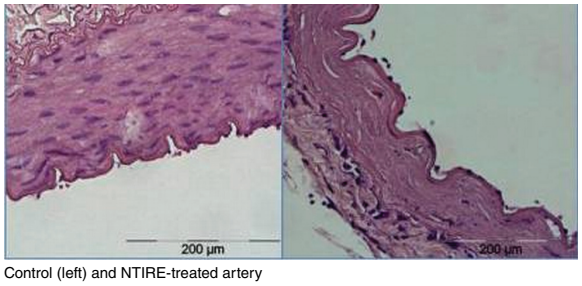
K. Steigerwald[1], M. Joner[1], S. Chin Quee[2], S. Schoenhofer-Merl[1], M. Vorpahl[3], A. Kastrati[1], A. Schoemig[1], R. Virmani[3]. *[1]Deutsches Herzzentrum Muenchen, Munich, Germany; [2]Abbott Vascular, Santa Clara, United States of America; [3]CVPath, Inc., Gaithersburg, United States of America*

Objective: Sirolimus and its derivatives everolimus and zotarolimus are preferentially used as anti-proliferative substances on drug-eluting stents (DES). From clinical practice it is unclear whether these therapeutics have differential effects on vascular healing. The aim of the current study was to assess the sole impact of different rapamycin analogues on arterial healing in a rabbit model of iliac artery stent implantation.
Methods: Bare metal stent (BMS) backbones were coated with a non-degradable fluorinated copolymer containing sirolimus, everolimus or zotarolimus (drug load 100μg/cm^2) to manufacture DES with identical stent backbone and release kinetics. DES were randomly implanted into the external iliac arteries of New Zealand white rabbits. BMS without coating served as control. Animals were sacrificed at 14 days after stent deployment for semi-quantitative scanning electron microscopy (SEM) analysis (n=6 for each stent), and at 28 days for complete histomorphometric examination (n=6 for each stent).
Results: SEM analysis revealed, that less than a third of the stent struts were endothelialized within the treatment groups (everolimus: 19.2%±13.7%, sirolimus: 30.3%±18.2%, zotarolimus: 28.9%±10.5%, p=NS), while the control stent showed almost complete endothelialization (88.9%±12.4%). Percent stenosis was significantly reduced in the treatment groups (everolimus: 11.21%±3.08%, sirolimus: 10.94%±3.61%, zotarolimus: 10.27%±3.69%) compared to control stents (18.69%±4.13%, p=0.02). Fibrin score was significantly greater in the treatment groups (everolimus: 0.99±0.15; sirolimus: 0.52±0.64; zotarolimus: 0.87±0.24) compared to control stents (0.17±0.19, p=0.02).
Conclusions: Sirolimus and its derivatives are potent anti-proliferative drugs affecting endothelial re-growth, neointimal thickening and vascular healing. The different DES tested showed similar rates of endothelialization and fibrin deposition suggesting that stent-performance regarding vascular healing is strongly determined by release kinetics of the drug, polymer choice and stent design

P1513 Endovascular non-thermal irreversible electroporation, a novel electric ablation method, efficiently ablates vascular smooth muscle cells in rabbit iliac arteries evaluated at 7 and 35 days

E. Maor[1], A. Ivorra[1], J. Mitchell[2], B. Rubinsky[3]. *[1]University of California at Berkeley, Berkeley, United States of America; [2]Angiodynamics, Queensbury, New-York, United States of America; [3]The Hebrew University of Jerusalem, Jerusalem, Israel*

Purpose: Non-thermal irreversible electroporation (NTIRE) is a biophysical phenomenon in which a series of electrical field pulses damage only the lipid bilayer of the cell membranes, with no damage to extra-cellular structures. This is the first study to evaluate the use of endovascular NTIRE for vascular smooth muscle cell (VSMC) ablation.
Methods: Custom made endovascular devices with four longitudinal electrodes on top of 2.5-mm diameter inflatable balloon were used to apply electroporation pulses to arterial walls. Finite element simulations were used to characterize NTIRE protocols that will not induce thermal damage to treated tissues. Right iliac arteries of eight rabbits were treated with 90 NTIRE pulses (length - 100 μs, frequency - 4 Hz). Angiograms were preformed before and immediately after the procedures. Left iliac arteries were used as controls. Arterial specimens were harvested at 7 (n=4) and 35 (n=4) days, and sent to an independent pathology lab. Evaluation included Hematoxylin & Eosin, elastic Van Gieson and Masson trichrome stains.
Results: Animals survived the procedure with no complications. At 7 days all NTIRE-treated arterial segments displayed complete transmural ablation (Figure). In nearly all sections the damage was circumferential with minor perivascular inflammatory reaction. At 35 days, VSMC loss persisted, elastic lamina remained



Control (left) and NTIRE-treated artery

intact. Occasional mural inflammation was noted. In few segments small focus of metaplastic cartilage was noted.
Conclusions: NTIRE can be applied in an endovascular approach. It efficiently ablates vessel wall within seconds and with no damage to extra-cellular structures. This innovative endovascular method has immediate applications in many fields of clinical cardiology, including arterial restenosis and cardiac arrhythmias.

P1514 Intravenous nicorandil immediately before percutaneous coronary intervention can prevent slow coronary flow phenomenon and result in a better outcome

Y. Kawai[1], K. Hisamatsu[2], H. Matsubara[2], K. Dan[2], S. Akagi[2], K. Miyaji[2], M. Munemasa[2], Y. Fujimoto[2], K.F. Kusano[3], T. Ohe[4]. *[1]Fukuyama City Hospital, Fukuyama, Japan; [2]National Hospital Organization Okayama Medical Center, Okayama, Japan; [3]Okayama University Graduate School of Medicine, Okayama, Japan; [4]The Sakakibara Heart Institute of Okayama, Okayama, Japan*

Purpose: It has been reported that slow coronary flow (SCF) phenomenon is a poor prognostic factor in percutaneous coronary intervention (PCI). Recently, several studies have demonstrated that nicorandil can reduce the incidence of SCF phenomenon in patients with acute coronary syndrome (ACS). However, a standard procedure for preventing SCF phenomenon in PCI has not been established yet. We assessed the effect of intravenous bolus administration of nicorandil on SCF phenomenon not only in patients with ACS but also in patients with non-ACS.
Methods: Our preliminary study in 12 patients indicated that intravenous bolus administration of 6 mg of nicorandil significantly increased coronary flow compared with 1 mg or 3 mg of nicorandil, without lowering systemic blood pressure. Thus, 408 patients scheduled to undergo emergent (n=108) or elective (n=300) PCI were randomly assigned to receive intravenous administration of 6 mg nicorandil immediately before PCI. The nicorandil group consisted of 206 patients, including 47 patients with ACS and 159 patients with non-ACS, and the control group consisted of 202 patients, including 61 patients with ACS and 141 patients with non-ACS. The incidence of SCF phenomenon, serum maximum CK and CK-MB levels in patients with acute myocardial infarction (AMI), rate of target vessel revascularization (TVR) and MACE for 12 months after PCI were compared in the two groups.
Results: The incidence of postprocedural SCF phenomenon was significantly lower in the nicorandil group than in the control group (4.4% vs. 17.8%). The incidence of postprocedural SCF phenomenon was significantly lower in both ACS and non-ACS patients in the nicorandil group than in those in the control group (4.3% vs. 26.2% and 4.4% vs. 14.2%, respectively). The serum maximum CK and CK-MB levels in patients with AMI were significantly lower in the nicorandil group than in the control group (1767±1272 vs. 2974±2484 IU/ml and 166±122 vs. 260±180 IU/ml, respectively). The rate of TVR was significantly lower in ACS patients in the nicorandil group than in ACS patients in the control group (10.3% vs. 30.4%). There was no significant difference in the rate of MACE for 12 months after PCI.
Conclusions: Intravenous administration of 6 mg of nicorandil immediately before PCI is a safe and simple procedure for preventing SCF phenomenon not only in patients undergoing emergent PCI for ACS but also in patients undergoing elective PCI for non-ACS. The rate of TVR is significantly lower in ACS patients in the nicorandil group than in ACS patients in the control group.

P1515 Ischemia-induced delayed regional relaxation is resolved after 24 hours from percutaneous intervention

M.S. Shin[1], B.R. Kim[2], O.R. Kim[1], W.J. Chung[1], S.H. Han[1], C.I. Moon[1], T.H. Ahn[1], I.S. Choi[1], E.K. Shin[1]. *[1]Gachon University Gil Medical Center, Incheon, Korea, Republic of; [2]Seoul Medical Center, Seoul, Korea, Republic of*

Background: Diastolic left ventricular (LV) abnormalities are sensitive early signs of myocardial ischemia. Ischemia-induced delay in the onset of regional relaxation has been demonstrated in the perfusion territory of the involved coronary artery in animal and clinical models. This study was designed to determine whether delayed regional relaxation is resolved after percutaneous intervention (PCI) in patients with stable angina.
Methods: Thirty patients with stable angina going to PCI were involved. Parasternal short axis views of the LV at the level of papillary muscle were obtained. Two-dimensional speckle tracking echocardiographies were performed before and after PCI to evaluate regional myocardial tissue velocity and strain. We analyzed strain and tissue velocity of myocardium according to the territory of coronary arteries.
Results: Sixteen patients were taken one vessel PCI and 14 patients were taken PCI at two vessels. Myocardial regions supplied by coronary artery with significant stenosis showed delayed onset of regional relaxation in strain (974±436 ms vs. 725±326 ms, $p < 0.05$) and tissue velocity (512±352 ms vs. 386±298 ms, $p < 0.05$) compared with normal myocardial regions. Post-PCI images showed significant shortness in the onset of regional relaxation after 24 hours from PCI (mean change 231±195 ms, $p < 0.05$), but did not show the improvement in delayed relaxation immediately after PCI within 30 minutes.
Conclusion: Delayed regional relaxation due to ischemia was not resolved within 30 minutes after PCI but resolved after 24 hours. Therefore the evaluation of diastolic function of ischemic myocardium to detect PCI effect should be performed after 24 hours from PCI due to diastolic stunning.

P1516 Efficacy of low-pressure drug delivery with a paclitaxel-coated balloon in restenosis inhibition

B. Cremers[1], N. Hattangadi[2], M. Biedermann[3], U. Speck[3], D. Mahnkopf[4], M. Boehm[1], B. Scheller[1]. *[1]Universitaetsklinikum der Saarlandes, Homburg, Germany; [2]ev3 Inc., Plymouth, United States of America; [3]Charite - Campus Mitte, Humboldt-Universitaet, Berlin, Germany; [4]IMTM GmbH, Immune Technologies & Medicine, Rottmersleben, Germany*

Background: Paclitaxel-coated balloon catheters allow for non-stent-based local drug delivery, markedly reducing neointimal proliferation. In the treatment of non-stenotic vessel lesions or after previous bare metal stent implantation, atherectomy or laser treatment, additional injury of the vessel wall by high inflation pressures should be avoided, and low inflation pressures may be sufficient for drug transfer to the vessel wall. The aim of the present study was to compare the influence of high- and low-pressure application of paclitaxel-coated balloons in the porcine coronary overstretch model.
Methods: Forty-eight stainless steel stents (diameters, 3.0 and 3.5 mm; length, 18 mm) were implanted in LAD and Cx of 24 domestic pigs with a balloon inflation pressure of 10 atm. The animals were randomized to post-dilatation of the stented vessel areas with paclitaxel-coated (3 $\mu g/mm^2$ balloon surface) balloons and inflation pressures of either 2 ("low-pressure"=LP) or 12 ("high-pressure"=HP) atm. In the low pressure group contact to the vessel wall was ensured by using slightly oversized balloon diameters. Uncoated balloons served as control. After four weeks, quantitative angiography and histomorphometry of the stented arteries were performed.
Results: Paclitaxel balloon coating markedly reduced neointimal proliferation, independently of the inflation pressure applied. Quantitative coronary angiography revealed a highly significant reduction of late lumen loss for both HP and LP treatment. Despite the marked reduction of neointimal proliferation, endothelialization of stent struts was present in both treatment groups. There were no thrombotic complications and no other significant adverse events in the treatment groups during or after coronary interventions.
Conclusion: Paclitaxel-coated balloon catheters were found to effectively reduce neointimal proliferation regardless of inflation pressure in the porcine coronary overstretch model. This might be of clinical relevance in cases where high-pressure angioplasty is not desired and potentially harmful.

P1517 Factors that influence measurements and accurate evaluation of stent apposition by optical coherence tomography; Assessment using a phantom model

T. Sawada, J. Shite, T. Shinke, D. Ogasawara, H. Kawamori, H. Kato, N. Miyoshi, N. Yoshino, A. Kozuki, K. Hirata. *Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate Schoo, Kobe, Japan*

Background: Optical coherence tomography (OCT) is expected to be a useful modality for PCI with its high resolution image, however, factors influencing measurements and accurate evaluation of stent apposition by OCT are not established.
Methods: Phantom models of known luminal sizes were evaluated by OCT under various conditions (frame-rates; 8.2 F/s or 15.6 F/s, pullback speeds; 1.0 or 2.0mm/s, image wire position; in-center or off-center, >0.5mm or <0.5mm from phantom wall) and their measurements were compared with actual values. For longitudinal measurements, a known length of both a straight and an angulated model was examined. Stents (2 drug eluting stent, 5 bare metal stent) implanted into models were also examined by OCT to validate the measurement point on the strut surface for accurate evaluation of stent apposition. Strut thickness was measured at three points (midpoint, inner and outer surfaces of the stent shadow). These measurements were compared to the manufacture's specified strut thickness.
Results: The precision of OCT measurements of lumen diameter and area was satisfactory when the image wire was positioned in-center, but the error and deviation were unsatisfactory when the image wire was positioned eccentrically using a low frame-rate. Longitudinal OCT measurements were close to actual values under all conditions. Pullback speed did not affect OCT measurements. Measurements from the midpoint of the stent shadow to the adjacent vessel wall surface coincided with actual stent thickness.

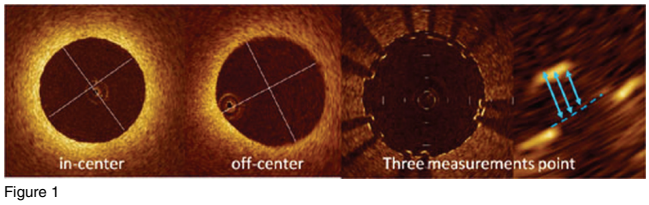


Figure 1

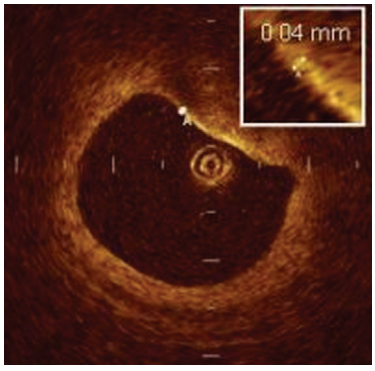
Conclusion: Significant measurement error can occur if the image wire is positioned eccentrically using a low frame-rate. To accurately evaluate stent apposition, the stent surface should be measured from the center of the stent reflection. OCT could be a useful tool for PCI at high frame-rate.

INTRAVASCULAR IMAGING OF ATHEROSCLEROSIS

P1518 Combined use of intravascular ultrasound, virtual histology and optical coherence tomography for detecting vulnerable and complicated atherosclerotic plaques

G. Sanchez-Elvira, I. Coma-Canella, M. Artaiz, J.A. Paramo, J. Barba, J. Calabuig. *Clinica Universitaria de Navarra, Pamplona, Spain*

Purpose: To detect vulnerable and complicated coronary lesions with 3 imaging techniques: intravascular ultrasound (IVUS), virtual histology (VH) and optical coherence tomography (OCT).
Methods: Twenty two patients (17 stable) scheduled for coronary angiography were included. General analyses, including high sensitivity C reactive protein (hs-CRP), were performed. After angiography, 44 lesions (29 angiographically significant) were studied with IVUS, VH and OCT. Endovascular treatment was performed in 21 patients. The statistical analysis was performed using an available software. Student t test and Anova were used with continuous variables and Chi2 for categorical variables. Spearman Rho was used to assess correlations between continuous variables.
Results: IVUS detected positive remodelling in 18 lesions and VH detected significant necrotic core in 15. OCT detected thin cap fibroatheroma (TCFA) in 10, calcium nodule with thin fibrous cap in 8, erosion in 4, dissection in 2 and thrombus in 5. Six TCFA lesions had positive remodelling, 3 no remodelling and only one presented negative remodelling. No complications regarding the procedure were recorded. The amount of necrotic core was significantly correlated with the amount of calcium ($p<0.001$). Patients with vulnerable lesions had higher levels of hs-CRP (p=0.019).



Thin cap fibroatheroma (TCFA) with OCT

Conclusions: The combination of IVUS-VH and OCT in coronary patients undergoing angiography and endovascular treatment is feasible and safe. The novel information provided by them is complementary. They enable the detection not only of TCFA but also of erosions, calcified nodules, thrombi and dissections.

P1520 Plaque vulnerability and its distribution of the eccentric plaque in gray scale intravascular ultrasound: a study of virtual histology intravascular ultrasound

H. Amano[1], K. Wagatsuma[1], J. Yamazaki[2]. *[1]Division of interventional Cardiology, Cardiovascular Center, Toho University Omori Medical Center, Tokyo, Japan; [2]Division of Cardiovascular Medicine, Department of Internal Medicine, Omori Medical Center, Toho Uni, Tokyo, Japan*

Background: It has been reported that a large presence of eccentric plaque in culprit coronary lesions is identified by gray scale gray scale intravascular ultrasound (IVUS) in acute coronary syndrome (ACS) lesions. However, plaque properties cannot be discriminated by gray scale IVUS, the vulnerability of the eccentric plaque are unclear. Since Virtual Histology-IVUS (VH) enables classification of plaque properties, VH was used to study the vulnerability of eccentric plaque and the distribution of necrotic core.
Subject: Subjects were 80 patients with 85 lesions undergoing stent implantation for coronary stenosis, with 797 slices observed by VH-IVUS prior to percutaneous coronary intervention.
Method: Eccentric plaque was defined as plaque with maximum plaque thickness double that of minimum plaque thickness. Measurements were taken at 1 mm intervals throughout the culprit lesions, eccentric plaque was identified and necrotic core (NC)/dense calcium (DC) ratio that can be considered to be vulnerable, was calculated using VH.
Lesions revealing eccentric plaque were classified the Eccentric group (n=523), and those without eccentric plaque, the non-Eccentric group (n=274).
Of the Eccentric group, lesions with necrotic core present primarily in the superficial portion of the plaque, less than half the thickness of the plaque, formed the Eccentric superficial: Es group (n=187) and those with necrotic core primarily in the portion deeper than half the thickness of the plaque formed the Eccentric deep: Ed group (n=334).
Results: In ACS (n=493 slices) eccentric plaque was seen in 68.8% (339/493), and in Stable angina pectoris (SAP) (n=232 slices) this was seen in 58.2% (135/232), with significantly more eccentric plaque in ACS ($p<0.01$).
The Eccentric group had a significantly higher NC/DC ratio with Eccentric group 2.01±1.44 and non-Eccentric group 1.76±1.48 ($p<0.05$).
For distribution of necrotic core in eccentric plaque, there was a greater percentage of deep necrotic core in eccentric plaque with 64.1% (334/521) compared to the 35.9% (187/521) of superficial necrotic core
The Ed group made up 66.2% (223/337) of ACS (n=337 slices) and 53.3% (72/135) of SAP (n=135 slices), with a significantly larger percentage of Ed in ACS ($p<0.05$).
NC/DC was significantly higher in the Ed group with Ed group 2.16±1.52 and Es group 1.76±1.26 ($p<0.01$).
Conclusions: The high vulnerability of the eccentric plaque in gray scale IVUS was shown from the high NC/DC ratio by Virtual Histology intravascular ultrasound. Eccentric plaque with deep distribution of necrotic core had especially high vulnerability.

P1521 Coronary plaque patterns in men and women in relation to age: assessment with multi-slice computed tomography, gray-scale and virtual histology intravascular ultrasound

G. Pundziute, J.D. Schuijf, G. Nucifora, J.E. Van Velzen, J.W. Jukema, J.M. Van Werkhoven, A. De Roos, M.J. Schalij, E.E. Van Der Wall, J.J. Bax. *Leiden University Medical Center, Leiden, Netherlands*

Purpose: We evaluated coronary plaque patterns in men and women in relation to age using multi-slice computed tomography (MSCT). The findings were compared with observations on gray-scale and virtual histology (VH) intravascular ultrasound (IVUS).
Methods: 93 patients (59 men, 34 women) underwent 64-slice MSCT followed by conventional coronary angiography with IVUS. Plaque extent and composition were assessed on MSCT, gray-scale and VH IVUS. Coronary plaque patterns were compared between men and women in 2 age groups (<65 and ≥ 65 years old).
Results: More plaques were observed on MSCT in younger men (6±4 versus 2±2 in younger women, $P<0.001$). A larger plaque burden was observed on gray-scale IVUS (45.7±11.4% versus 36.3±11.6% in women, $P<0.001$). Similarly, more mixed plaques (a combination of non-calcified and calcified tissues) were observed in younger men (3±3 versus 1±1 in younger women, P=0.003), whereas a larger arc of calcium was detected on gray-scale IVUS (91.7±93.5 versus 25.7±51.0 degrees in women, $P<0.001$). On VH IVUS, the prevalence of thin cap fibroatheroma was higher in younger men (31% versus 0% in younger women). No differences in plaque patterns were observed in older patients.
Conclusions: Particular plaque patterns were observed on MSCT, gray-scale IVUS and VH IVUS in men and women. More extensive atherosclerosis and more calcified lesions were observed in younger men as compared with younger women. These differences were lost in older patients.

P1522 Culprit lesions located in the proximal segments of the coronary arteries are characterized by more complex morphological characteristics. An optical coherence tomography study

K. Toutouzas, A. Synetos, A. Karanasos, E. Tsiamis, C. Tsioufis, D. Tousoulis, M. Riga, M. Drakopoulou, E. Stefanadi, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: The location of the culprit lesions (CL) in patients (pts) with acute coronary syndromes (ACS) has not been extensively investigated. Recent evidence suggests that the majority of the CL are found in the proximal segments of the coronary arteries. We therefore investigated whether CL of pts with ACS have distinct morphological characteristics according to their location.
Methods: The study population was comprised of pts with ACS undergoing cardiac catheterization within 24 hours from symptom onset. Twenty-six men and 4 women (mean ages 59.6±5.7 years) were recruited. Culprit lesions were classified as proximal or distal depending on their distance from the ostium of the culprit artery. Fibrous cap thickness (FCT) measured in the thinnest part of the plaque of all CL was measured by optical coherence tomography. Plaques were categorized as having thick fibrous cap (FCT$>$65 μm) or thin fibrous cap (FCT$\leq$65 μm).
Results: We examined 30 CL of 30 patients, 16 located in the distal part of the coronary arteries and 14 proximally. Mean FCT of all lesions was 69±12 μm. Twenty-one of the patients (70%) had thin fibrous cap. Mean FCT of the proximal

CL group was 44±17 μm versus 69±36 μm in the group of distal CL ($p<0.05$). In the group of the distal CL, 56.25% (n=9) had thin cap, while in the group of proximal CL 85.71% (n=12) presented such morphology (p=0.08). A rupture was found in 78.57% of the proximal lesions and in 50% of the distal lesions (p=0.10).
Conclusions: Culprit lesions located in the proximal part of the coronary arteries have thinner fibrous cap compared to the lesions located in the distal part of the coronary arteries, as assessed by optical coherence tomography. Our findings implicate that the higher incidence of thrombosis in plaques located more proximally may be due to morphologic discrepancies of the proximal lesions.

P1523 In vivo analysis of ruptured plaques in patients with ST-segment elevation myocardial infarction using IVUS-VH

M. Jaster, W. Knie, H.P. Schultheiss, B. Witzenbichler. *Charite - Campus Benjamin Franklin, Berlin, Germany*

Objectives: We investigated culprit lesions in patients with STEMI by IVUS-VH. The aim was to assess plaque composition in vivo.
Background: Lesions, which have the propensity to rupture and develop atherothrombosis, are often non-flow limiting. Conventional greyscale IVUS indicates positive remodelling to be related to plaque rupture and instability, but is in contrast to IVUS-VH not suitable to analyze plaque composition in vivo.
Methods: A total of 74 patients with STEMI underwent IVUS-VH prior to any balloon dilatation. Morphological and compositional data were obtained at rupture site and the site of maximal vessel area (EEMmax.-site).
Results: Forty four (59%) of the rupture sites (RS) showed a positive remodelling. Negative remodelling at RS was significantly more often seen in patients with diabetes mellitus compared to non diabetic patients (10 of 21 diabetic vs. 12 of 53 non diabetic patients, $p < 0.05$). Amount of necrotic core (NC) area was significantly higher at the rupture site compared to the EEMmax.-site (36.1±8.1% vs. 18.9±10.4% $p < 0.0001$). The best cut-off value of NC area for prediction of plaque rupture was 25%, with a sensitivity of 96% and a specificity of 81%. Necrotic core area > 25% strongly predicted plaque rupture (OR 11.3, CI 4.3 – 29,3, $p < 0.001$).
Conclusions: The plaque rupture site in culprit lesions of STEMI patients can be identified by greyscale IVUS. A typical pattern at the rupture site was found using virtual histology. Analysis of plaque composition by IVUS-VH revealed that the rupture site was at the area of most necrotic core within the plaque formation.

PHYSIOLOGY, HAEMODYNAMICS AND MICROCIRCULATION

P1524 Prognostic impact of non-HLA antibodies targeting vascular receptors for the development of microvasculopathy in biopsy after heart transplantation

C. Renner[1], N.E. Hiemann[1], R. Meyer[1], E. Wellnhofer[1], C. Schoenemann[2], H. Heidecke[3], R. Hetzer[1], D. Dragun[2]. *[1]Deutsches Herzzentrum Berlin, Berlin, Germany; [2]Charite - Campus Virchow-Klinikum, Berlin, Germany; [3]CellTrend GmbH, Luckenwalde, Germany*

Purpose: Non-HLA antibodies (Abs) are an increasingly recognized component of the immune response to organ transplants. In renal allografts non-HLA Abs targeting and activating angiotensin II type 1 receptor (AT1Rabs) induce severe vascular lesions. We tested the impact of non-HLA Abs targeting vascular receptors on rejection and microvasculopathy (MVP) in heart transplant (HTx) recipients.
Methods: We studied prospectively 30 consecutive HTx pts (22 men, mean age 48 yrs) at 24 hrs, 2 weeks, 1 month, 6 months and 1 yr post HTx for presence of IgG directed against endothelin-1 type A (ETAR-Abs) and angiotensin II type 1 (AT1R-Abs) receptors (elevated level cut-off >10 U/L) by means of cell-ELISA. Endomyocardial biopsies were obtained at 1 month (Bx1=20) and 1 yr (Bx2=20). Conventional histology (H&E) served for diagnosis of acute cellular rejection [ISHLT] and MVP. Immunohistochemical reactions for alpha-actin were performed to identify smooth muscle cells (clone 1A4, Dako) in order to detect microvascular remodeling (medial disease) associated with MVP.
Results: At 1 month and 1 yr post HTx, acute cellular rejection was found in 40% and 13% of biopsies, and stenotic MVP was present in 37% and 40% of biopsies, respectively.
During the first year post HTx, 50% of pts presented elevated levels (>10 U/L) of ETAR-Abs and 53% high levels of AT1R-Abs. Pts with high AT1R-Abs presented more often with acute cellular rejection than pts without (77% vs. 33%, p=0.06). Increased density of muscularized microvessels were found at 1 month post HTx in pts with high ETAR-Abs (88% vs. 44%, p=0.06) and at 1 yr post HTx in pts with high AT1R-Abs (80% vs. 27%, p=0.05). CRP pre-HTx was higher in pts with elevated ETAR-Abs (3.9±0.9 vs. 0.9±0.3 mg/dL, p=0.01) or AT1R-Abs (3.8±0.7 vs. 0.8±0.3 mg/dL, p=0.01), implicating putative permissive role of inflammation.
Conclusions: HTx recipients frequently develop non-HLA antibodies targeting ETAR and AT1R after transplantation. Elevated levels of ETAR-Abs and AT1R-Abs are associated with stronger alloimmune response and earlier onset or faster progression of microvascular remodeling post HTx. Mechanistic and therapeutic studies using ETAR and AT1R antagonists in affected patients are planned.

P1525 Microvasculopathy in biopsy following heart transplantation: 3-year results from a prospective clinical study

N.E. Hiemann, E. Wellnhofer, C. Knosalla, H.B. Lehmkuhl, R. Hetzer, R. Meyer. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Purpose: Microvasculopathy (MVP) in biopsies harvested during the first year post heart transplantation (HTx) has been shown to be a media disease and to be strongly correlated to evidence of endothelial disease in biopsy. However, the further course of MVP during intermediate follow-up remains uncertain.
Methods: The population consisted of 78 consecutive cardiac transplant recipients (67 males, mean age 50 yrs), who underwent prospective analyses at 4 wks (FU1=78), 1 yr (FU2=64) and 3 yrs (FU3=33) after HTx. In biopsies, acute cellular rejection was classified according to the ISHLT. Additionally, microvascular endothelial cells and non-stenotic and stenotic media alterations (=stenotic MVP) were studied using routine histologic staining (H&E, x200).
Results: Endothelial alterations were exclusively non-stenotic and affected almost half of the patients at each FU (FU1=50%, FU2=44%, FU3=46%).
The prevalence of non-stenotic medial alterations decreased from FU1 (37%) to FU2 (32%) and remained stable at FU3 (33%), while stenotic MVP increased continuously from FU1 (40%) to FU2 (57%) and FU3 (67%).
A regression of stenotic MVP at FU2 was given in 29% of biopsies, while progressive alterations were found in 73% of samples without medial alterations and 50% of samples with non-stenotic medial alterations.
From 4-wk (FU1) to 3-yr (FU3) follow-up but also from 1-yr (FU2) to 3-yr (FU3) follow-up regression of stenotic MVP was given in 1/3 of biopsies, while 2/3 of patients with non-stenotic media disease or without media disease showed a progression towards stenotic MVP.
Endothelial disease at FU1 (55% vs. 24%, p=0.005) and at FU2 (70% vs. 46%, p=0.045) but not at FU3 (67% vs. 67%, p=0.643) was significantly associated with evidence of stenotic MVP. We found no association between non-stenotic and stenotic medial alterations.
Acute cellular rejection episodes according to the ISHLT (FU1=16%, FU2=5%, FU3=none) were not correlated to evidence of endothelial disease or stenotic MVP in biopsy.
Conclusions: We demonstrated prospectively that during the first post-transplant year endothelial disease is strongly correlated to the development of stenotic MVP in biopsy. Beyond the first year post HTx this correlation seems to disappear. During the first 3 yrs post HTx, endothelial cells seem not to be involved in the process of microvascular stenosis itself.

P1526 Correlation between microvascular obstruction and intracoronary physiologic parameter indexes for assessment of microvascular injury in patients with acute myocardial infarction

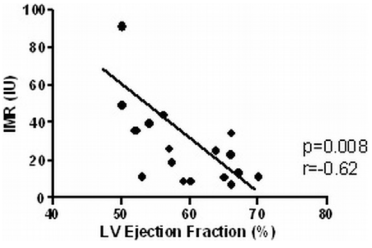
J.H. Koh[1], Y.H. Jo[2], D.K. Jo[1]. *[1]Myongji Hosipital, Kwandong University, Goyang, Korea, Republic of; [2]Myongji Hospital, Kwandong University, Goyang, Korea, Republic of*

Objectives: Coronary flow measurements might be useful to a mounts of microvascular obstruction (MO) and it is important in the evaluation of the severity and extent of myocardial damage. Therefore, we studied a concordance between abnormal intracoronary physiologic parameters, characteristics assessed in the cardiac catheterization laboratory and microvascular obstruction detected noninvasively by Cadiac magnetic resonance imagine (MRI) in acute myocardial infarction.
Methods: We enrolled 34 consecutive patients who underwent primary percutaneous coronary intervention (PCI) for acute myocardial infarction patients. After successful PCI, using a pressure- temperature sensor-tipped coronary wire, the thermodilution-derived CFR (CFR-thermo) and coronary wedge pressure (Pcw) were measured and mean aortic pressure (Pcw/Pa) was calculated, along with a index of microcirculatory resistance (IMR). MO and infarct size were assessed with cardiac magnetic resonance imagine (MRI).
Results: We were divided into two groups according to the present of MO on the MRI: no-MO group (MRI with homogeneous enhancement of myocardium;n=16), and MO group (MRI with hypoenhanced region; n=18). The extent of MO correlated with IMR (r=0.67; p=0.02), Pcw (r=0.41; p=0.001), and Pcw/Pa of the infarct-related artery (r=0.46; p=0.02). An inverse relation was observed between the extent of MO and CFR-thermo (r= -0.39 p=0.06). Multivariate regression analyses showed that the extent of MO was the only independent factor related to both Pcw/Pa and IMR. The results were found regarding the size of MO, the relationship between MO size and IMR was as strong as its extent.
Conclusions: The extent of MO as assessed by cardiac MRI correlated well with intracoronary physiologic parameter indexes parameters (CFRthermo, IMR, coronary wedge pressure). Furthermore, after adjusting for MO, IMR was able to predict myocardial injury with high accuracy during the acute phase of myocardial infarction.

P1527 Microvascular resistance of culprit and non-culprit territories in the chronic phase of myocardial infarction and LV function

A. Ntalianis[1], C. Trana[1], C. Baliauw[2], O. Muller[1], J. Bartunek[1], E. Barbato[1], E. Wyffels[1], W. Wijns[1], P. Vanhoenacker[2], B. De Bruyne[1]. *[1]Cardiovascular Center OLV Hospital, Aalst, Belgium; [2]OLV Hospital, Department of Radiology and Imaging, Aalst, Belgium*

Objectives: We aimed at assessing invasively the microvascular resistance of previously infarcted myocardium and detect possible relations with left ventricular function.
Methods: Fifty three patients, 56±12 years old, with an anterior (94%) or large inferior myocardial infarction in the past, referred for coronary angiography, were prospectively included. After coronary angiography and left ventriculography, the Index of Microcirculatory Resistance (IMR), Coronary Flow Reserve (CFR), Mean Transit Time (Tm) and Fractional Flow Reserve (FFR) of both: a) the previously infarcted (I) and b) the normal myocardium (N), were assessed. A Cardiac Magnetic Resonance Imaging was performed shortly after the catheterization and LV Ejection Fraction (EF), End diastolic (ED) and Systolic (ES) Volumes, Mass (M) and Stroke Volume (SV) were calculated off-line.
Results: A significant lower CFR (2.6±1.3 vs 3.5±1.7, p=0.003), FFR (0.78±0.01 vs 0.92±0.01, p<0.0001) and higher Tm (0.46±0.4 vs 0.32±0.3, p=0.005) of the vessel subtending the I was observed. A trend towards a higher IMR of the I was also noticed (29±23 vs 24±22, p=0.1). There was no correlation between IMR, CFR and Tm and LVED, LVES volumes, SV or LVEF. There was an inverse correlation between IMR of the I and LVEF (p=0.0008, r=-0.62) in patients with LVEF ≥50%. (Figure)



Conclusions: CFR is lower and IMR tends to be higher in previously infarcted myocardium. There is no significant interrelation among LV function/LV remodeling and invasive indexes of microvascular resistance and flow in the chronic phase of myocardial infarction.

P1528 Independent association of pulse pressure and coronary flow velocity at rest in subjects without coronary artery disease

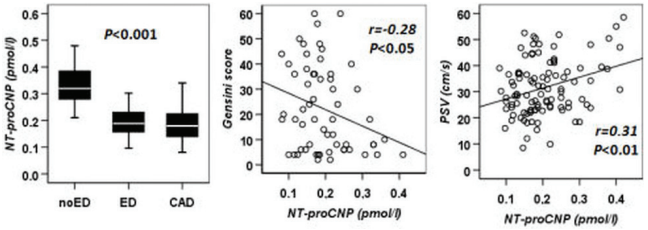
M. Galderisi[1], F. Rigo[2], S. Gherardi[3], L. Cortigiani[4], R. Sicari[5], A. D'Errico[1], E. Picano[5]. *[1]Azienda Ospedaliera Universitaria Federico II, Naples, Italy; [2]AO dell'Angelo ASL 12, Mestre, Italy; [3]AO Bufalini, Cesena, Italy; [4]AO di Lucca, Lucca, Italy; [5]CNR Istituto di Fisiologia Clinica, Pisa, Italy*

Purpose: To evaluate the relationships between pulse pressure (PP), raw index of arterial stiffness, and non invasively determined coronary flow reserve (CFR) in subjects without angiographic evidence of coronary artery disease.
Methods: The study population included 342 subjects (151 women, mean age = 61 years, arterial hypertension prevalence = 83.8%) with angiographically normal epicardial coronary arteries. Subjects underwent high-dose dipyridamole (0.84 mg/kg over 6') stress echocardiography with Doppler derived CFR evaluation of left anterior descending artery. CFR was calculated as the ratio between dipyridamole and resting coronary diastolic peak velocities. According to PP values (= systolic blood pressure – diastolic blood pressure) subjects were divided in 2 groups: 72 with normal PP (< 50 mmHg) and 270 with pathologic PP (≥ 50 mmHg).
Results: The two groups were comparable for body mass index, heart rate and diastolic blood pressure. Subjects with PP ≥ 50 mmHg had higher systolic blood pressure (p<0.0001) and also showed higher values of coronary diastolic peak velocities at rest (29.2±7.8 cm/s) in comparison with subjects with PP < 50 mmHg (27.3±5.4 cm/s) (p<0.01), while high-dose dipyridamole coronary velocities and CFR (2.6±0.6 versus 2.7±0.8) did not differ between the two groups. In the pooled population PP was significantly related to CFR (r = -0.14, p<0.01) and to coronary velocities at rest (r = 0.20, p<0.0001) but not to high-dose dipyridamole coronary velocities (r = 0.03, NS). After adjusting for sex, age, body mass index and heart rate by separate multiple linear regression analyses, PP was independently associated with coronary diastolic peak velocities (standardized β coefficient = 0.181, p<0.0001) but not with CFR (standardized β coefficient = -0.071, NS).
Conclusions: In subjects with angiographically normal coronary arteries pulse pressure is positively and independently associated with coronary flow velocity at rest. The greater wall stress exerted by the increased arterial stiffness on the coronary flow may be an explanation of these findings.

P1529 N-terminal pro C-type natriuretic peptide levels and erectile function in men with or without coronary artery disease

N. Ioakeimidis, C. Vlachopoulos, D. Terentes-Printzios, I. Dima, K. Aznaouridis, N. Alexopoulos, A. Bratsas, G. Sakellariou, C. Fassoulakis, C. Stefanadis. *Hippokration General Hospital of Athens, Athens, Greece*

Purpose: Endothelial dysfunction is a common abnormality in erectile dysfunction (ED) and coronary artery disease (CAD). C-type natriuretic peptide (CNP) is a potent endothelial derived relaxant factor which plays an essential role in the regulation of cardiovascular homeostasis. Aim of this study is to identify potential links between CNP, ED and CAD.
Methods: Levels of N-terminal fragment CNP (NT-proCNP) were measured in three groups with similar risk factor profile: 56 men with angiographically documented CAD, 76 ED patients without evidence for CAD, and 31 non ED volunteers without CAD. ED patients were evaluated with penile Doppler ultrasound. Lower Doppler velocities indicate impaired arterial function and vice versa. The extent of coronary narrowing was estimated by calculation of the Gensini score.
Results: NT-proCNP levels were comparable among men with documented CAD and men with ED and significantly lower than those in volunteers with normal erectile function (left figure). Interestingly, a greater coronary and penile artery narrowing were associated with a lower circulating NT-proCNP level (middle and right figure). In a multivariate linear regression model, Gensini score was significantly (p<0.05) associated with NT-proCNP level, after controlling for age, blood pressure, metabolic profile and levels of C-reactive protein, fibrinogen, interleukin-6 and interleukin-18 (adjusted R2 of model=0.34).



NT-proCNP levels, ED and CAD

Conclusions: ED patients exhibited lower CNP levels compared to men without ED. Furthermore, decreased CNP concentrations are associated with an unfavorable effect on erectile function and coronary atherosclerosis. These findings provide further insights into the potential role of CNP in penile and coronary atherosclerotic disease.

P1530 Adenosine induced maximal coronary hyperemia for myocardial fractional flow reserve measurements - comparison of administration by femoral venous versus antecubital venous access

M. Lindstaedt[1], A. Yazar[1], W. Bojara[1], T. Holland-Letz[2], L. Mueller[1], A. Muegge[1], A. Germing[1]. *[1]University Hospital Bergmannsheil - Medical Clinic II, Bochum, Germany; [2]Department of Medical Informatics, Biometry, and Epidemiology, Ruhr-University, Bochum, Germany*

Purpose: Maximal hyperemia is a critical prerequisite for correct fractional flow reserve (FFR) measurements. Continuous administration of adenosine by femoral venous access is considered the gold-standard. However, antecubital venous access is used as an alternative route of administration. Because of a potentially larger cross sectional venous area in the arm – theoretically associated with slower flow velocities – and the extremely short half-life of adenosine, there are concerns whether this route of administration is truly equivalent to the femoral route.
Methods: Fifty randomly selected patients with coronary artery disease were included. FFR was measured with a pressure monitoring wire and the recording was digitally stored. Hyperemia was successively induced by adenosine via the antecubital vein at a dose of 140 μg/kg/min (A140), via the antecubital vein at a dose of 170 μg/kg/min (A170), and via the femoral vein at a dose of 140 μg/kg/min (F140).
Results: Induction of hyperemia by A140 yielded significantly lower hyperemic responses than compared with A170 (p=0.038) and F140 (p=0.005). No significant difference was seen between adenosine administration by A170 versus F140

Table 1. Mean differences in FFR-values

Tested pairs for differences of mean FFR	t-test of paired differences				
	mean value of difference	STD of difference	95% CI of difference (lower)	(upper)	p-value
A140 - F140	0.0126	0.0277	0.0037	0.0195	0.005
A140 - A170	0.0064	0.0213	0.0004	0.0124	0.038
A170 - F140	0.0052	0.0029	-0.0007	0.0111	ns

CI = confidence interval; FFR = fractional flow reserve; ns = not significant; STD = standard deviation; A140, A170, F140 = routes and doses of adenosine administration.

(Table 1; global p<0.0001, Friedman Test). Hyperemic stimulation by A140 underestimated lesion severity near the ischemic threshold of FFR more frequently than the other modalities.
Conclusions: The intravenous application of adenosine via antecubital venous access is feasible but slightly less effective than the femoral approach. In this setting, an antecubital dosage of 170 μg/kg/min is comparable to the standard dosage of 140 μg/kg/min in the femoral vein. In some patients this regimen might prevent an underestimation of lesion severity.

P1531 Inhibition of ATP degradation reduces macromolecule permeability in rat mesentery arterioles and oedema formation in rat hearts in vivo

D. Guenduez[1], U. Krieger[1], L. Becker[1], M. Aslam[2], I. Hussain[1], F.V. Haertel[2], R. Voss[1], M. Grebe[1], T. Noll[2], H. Tillmanns[2].
[1]*Universitaetsklinikum Giessen und Marburg GmbH, Giessen, Germany;* [2]*Universitaet Giessen Physiologisches Institut, Giessen, Germany*

Background: Failure of endothelial barrier function induced by inflammatory mediators, causes severe oedema that impedes functional recovery of the organ. We have previously shown that extracellular ATP can reduce endothelial hyperpermeability during reperfusion and induced by inflammatory mediators. It is well known that cardiovascular cells release ATP and adenosine under different (patho-)physiological conditions, which play important role in the development of vascular complications. Here we analyzed the effects of ATP and adenosine on endothelial barrier function in an in vitro and in vivo model.
Methods: In vitro vascular permeability was measured by flux of labelled albumin through monolayers of rat heart microvascular endothelial cells cultured on filter membranes. In vivo rat mesenteric artery vascular permeability was measured by intravital microscopy and the cardiac oedema was measured by measuring the water contents of rat heart.
Results: We found that extracellular ATP (50 μM) had a biphasic effect on microvascular permeability both in vitro and in vivo. First, it reduced permeability and after 30 minutes it increased the vascular permeability. Addition of ARL 67156 (100 μM, an ectonuleotidase inhibitor) prevented the increase in permeability during the second phase. Contrariwise, addition of apyrase (1 IU/ml, a soluble ectonucleotidase) abolished the ATP-mediated reduction in permeability during the first phase, rather it increased the permeability. The increase in permeability during the second phase could be reduced by a panspecific adenosine receptor inhibitor (8-phenyltheophylline, 10μM). Similar effects were observed on myocardial water contents.
Conclusion: The results of the present study show that ATP released by vascular cells could be protective to vasculature; however, it is rapidly hydrolyzed to adenosine which has opposite effects. If the rate of ATP degradation is slowed, its protective effects are evident and could be a beneficial strategy during pathological conditions.

P1532 The inflammatory response post percutaneous coronary intervention is associated with increased microvascular resistance in patients with stable angina

B. Patel[1], L. Smith[1], A. Alahmar[2], P. Browning[2], G. Hart[1], M. Fisher[1]. [1]*Royal Liverpool University Hospital, Liverpool, United Kingdom;* [2]*Cardiothoracic Centre Liverspool NHS Trust, Liverpool, United Kingdom*

Purpose: Microvascular dysfunction has increasingly been implicated in the poor outcome to revascularisation in certain patients. The underlying mechanisms however are still disputed and the effect of inflammation on microvascular function has received little attention. The aim of this study was to investigate the relationship between inflammation and microvascular function in patients undergoing percutaneous coronary intervention (PCI).
Methods: We measured the index of microvascular resistance (IMR) in the target vessel and a reference vessel (either left anterior descending or circumflex artery) using the thermodilution technique and a pressure wire in patients with stable angina and single vessel disease. IMR was calculated at maximal hyperaemia during intravenous infusion of adenosine at 140μg/kg/min, in both vessels, before and after PCI. We measured CRP and IL-6 levels before and 24 hours post PCI. Data is presented as mean ± SEM. Statistical analysis was performed using paired t-test and linear regression. The effect of PCI on IMR and inflammatory markers is presented as a ratio of post/pre PCI levels.
Results: 21 patients were included in the study. Mean age 60.6 years. CRP increased 24 hours post PCI (2.71±0.34 vs 3.09±0.31 mg/l p=0.02). IL-6 levels also increased 24 hours post PCI (6.91±0.79 vs 13.01±1.41 pg/ml p<0.001).There was no correlation between baseline CRP and IL-6 levels with modification of IMR, in either the target or reference vessel. There is a strong correlation between peri-procedural effect on CRP and IMR of the target vessel (r=0.89 p<0.01) and a correlation between peri-procedural effect on IL-6 and IMR of the target vessel (r=0.69 p<0.01). There was no correlation in the reference vessel.
Conclusion: The degree of change of CRP and IL-6 correlates with degree of change in IMR. There is no relationship between baseline inflammatory markers and the effect of PCI on IMR suggesting that it is the inflammatory response to PCI rather than baseline inflammation which are associated with an increase in microvascular resistance. This relationship is only seen in the target vessel suggesting a local mechanism is responsible for microvascular dysfunction. Whether this is a direct effect of the inflammatory response or not remains to be studied.

P1533 Right ventricular and pulmonary artery pressures correlate with endomyocardial remodelling after heart transplantation

N.E. Hiemann, E. Wellnhofer, J. Zoschke, R. Hetzer, R. Meyer.
Deutsches Herzzentrum Berlin, Berlin, Germany

Purpose: Elevated right ventricular and pulmonary artery pressures are associated with right ventricular hypertrophy in non-transplanted hearts. However, the correlation between right ventricular hemodynamics and endomyocardial remodelling following heart transplantation (HTx) has not been tested yet.
Methods: The population consisted of 27 consecutive cardiac transplant recipients (23 men, mean age 44 yrs). Cardiac grafts underwent baseline biopsy pre-HTx (n=27) and prospective analyses with biopsy and right ventricular hemodynamic testing at 4 wks (FU1=24), 1 yr (FU2=24) and 3 yrs (FU3=16) after HTx. The size of cardiomyocytes was assessed using EasyMeasure (H&E, x400), and >200 cells per biopsy were evaluated. Hemodynamic testing was done according to standard clinical practice.
Results: Mean diameter of cardiomyocytes pre-HTx and at FU1, FU2 and FU3 was 13.6±0.4, 13.8±0.5, 14.0±0.4 and 14.7±0.6 μm, respectively. Mean pulmonary artery pressure at FU1, FU2 and FU3 was 17±1, 17±1 and 19±1 mmHg. Only three (14%), one (7%) and two patients (14%) had evidence of pulmonary hypertension at FU1, FU2 and FU3, respectively. Corresponding right ventricular systolic and end-diastolic pressures were 27±2 and 6±1, 27±2 and 7±1, and 33±2 and 6±1 mmHg. No correlation was found between right ventricular hemodynamic data and size of cardiomyocytes at 4 wks or 1 yr post-transplant. Maximum size of cardiomyocytes in biopsies pre-HTx correlated inversely with right heart systolic (r=-539, p=0.038), end-diastolic (r=-0.683, p=0.005) and right atrial pressures (r=-0.676, p=0.008) in the late follow-up (3 years after HTx=FU3). Maximum size of cardiomyocytes in biopsies at 4 wks post-HTx correlated significantly with pulmonary systolic (r=0.715, p=0.006), diastolic (r=0.630, p=0.021) and mean pressures (r=0.736, p=0.004) in FU3. At 3 years after HTx, mean size of cardiomyocytes correlated significantly with pulmonary systolic (r=0.657, p=0.015) and mean pressures (r=0.566, p=0.044) and right ventricular systolic pressure (r=0.610, p=0.021).
Conclusions: Elevated right heart and pulmonary artery pressures are associated with endomyocardial remodelling in the late follow-up after HTx. However, a higher baseline size of cardiomyocytes pre-HTx might be beneficial with regard to increasing pulmonary pressures post-HTx.

P1534 Effects of different vasodilators on no-reflow phenomenon during percutaneous coronary intervention in patients with acute myocardial infarction

D. Huang, J. Ma, F. Zhang, X. Wang, L. Ge, J. Qian, J. Ge.
Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China, People's Republic of

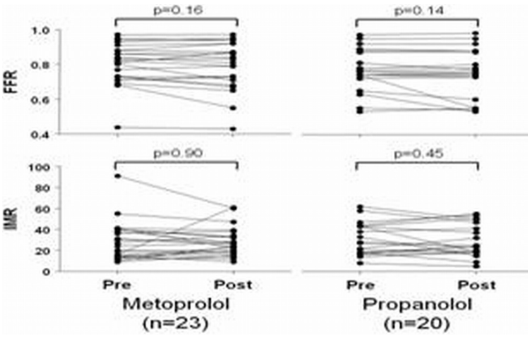
Purpose: The present pharmacological management of no-reflow phenomenon during primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) involves the use of different vasodilators including nitrates, verapamil, adenosine and nicorandil. The prospective randomized study was designed to compare angiographic and clinical outcomes in AMI patients undergoing primary PCI with no-reflow/slow-flow phenomenon using three different vasodilators diltiazem, verapamil and nitroglycerin.
Methods: In a consecutive series of 433 primary PCI for AMI, no-reflow/slow-flow phenomenon (TIMI flow grade<3) was observed in 63 patients (14.5%). All lesions in the infarction-related-coronary (IRC) were treated by stents. The 63 patients were randomised to one of three investigational vasodilators groups: intracoronary infusion of diltiazem (n=21), verapamil (n=21) and nitroglycerin (n=21). All the drugs were given via an infusion microcatheter distal to the angioplasty site. Pre-PCI, post-PCI and after drugs were given, IRC flow was assessed using TIMI flow grade (TFG) and corrected TIMI frame count (cTFC) by blinded angiographic readers. Left ventricular ejection fraction (LVEF) through echocardiography and NT-proBNP levels were measured at days 1 and 30 post-PCI.
Results: There were no statistically significant differences in demographic data of patients, procedural characteristics and the baseline IRC flow post-stenting in the three groups. The average intracoronary infusion drug dose was diltiazem 1.2mg, verapamil 0.6mg and nitroglycerin 0.6mg. All the three drugs could improve the IRC flow measured by TFG and cTFC significantly (p<0.05). Compared with nitroglycerin, diltiazem and verapamil could improve the IRC flow more significantly (p<0.05). The improvements in TFG and cTFC did not differ significantly between the diltiazem and verapamil groups (p>0.05). Eight patients in the verapamil group and two in the diltiazem group developed transient atrioventricular block or severe sinus bradycardia (p<0.01). During 30 days follow-up, the LVEF improved insignificantly in the three groups. At days 1 and 30 post-PCI, the NT-proBNP levels in the diltiazem and verapamil groups were lower than nitroglyc-

erin group ($p<0.05$). There is no significant difference in the NT-proBNP levels between the diltiazem and verapamil groups.
Conclusions: The intracoronary infusion of diltiazem or verapamil can reverse no-reflow/slow flow phenomenon more effectively than infusion of nitroglycerin during primary PCI for AMI. The efficacy of diltiazem and verapamil is similar but diltiazem seems safer.

P1535 Fractional Flow Reserve (FFR) and Index of Microvascular Resistance (IMR) measurement are not influenced by beta-blockers

G. Sarno, C. Trana Berza, B. De Bruyne, J. Bartunek, E. Wyffels, A. Ntalianis, F. Mangiacapra, O. Muller, W. Wijns, E. Barbato.
Cardiovascular Center OLV Hospital, Aalst, Belgium

Beta-blockers have been reported to increase microvascular resistance and reduce coronary flow reserve. Full microvascular dilation is a prerequisite for optimal assessment of Fractional Flow Reserve (FFR), a surrogate index of myocardial ischemia, and of the Index of Microvascular resistance (IMR), used to detect microvascular dysfunction.
Purpose: To investigate whether the selective β1-blocker, metoprolol, and the non-selective β-blocker, propanolol, might exert an influence on FFR and IMR.
Methods: Forty-three patients (pts) with normal left ventricle and intermediate coronary stenosis (diameter stenosis: 44±16%) at angiography, underwent FFR and IMR measurement during IV adenosine (140 μg/kg/min) before and after IC bolus of metoprolol (40 μg/kg, 23 pts) and propanolol (30 μg/kg, 20 pts). Reference diameter (RD), minimal lumen diameter (MLD) and diameter stenosis (%DS) were assessed on angiography acquired at the baseline and at the end of the protocol. Blood pressure and heart rate were continuously monitored during the study.
Results: Metoprolol and propanolol significantly decrease rate pressure product (Metoprolol: pre, 6319±1485 vs. post, 5718±1097, p=0.013; Propanolol: pre, 7077±1723 vs. post, 6321±1068, p=0.031), with no changes in vessel dimensions. FFR and IMR were not significantly affected by both β-blockers (figure).



Conclusion: Metoprolol and propanolol do not influence FFR and IMR measurement.

P1536 Uric acid level is a predictor of coronary collateral development in patients with non st segment elevation acute coronary syndrome

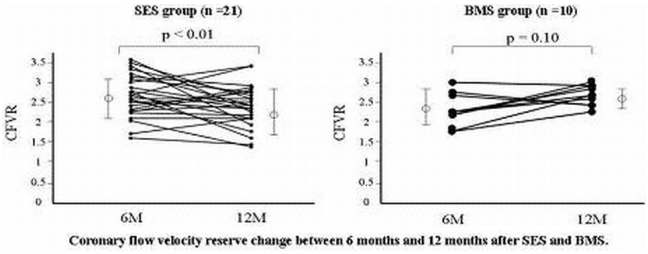
M.G. Kaya, A. Kasapkara, R. Topsakal, B. Sarli, A. Oguzhan, M.T. Inanc, A. Dogan, M. Duran. *Erciyes University School of Medicine, Department of Cardiology, Kayseri, Turkey*

Background: It is known that uric acid is associated with oxidative stress, endothelial dysfunction and endothelium dependent nitric oxide activation. In many studies, consistent relation between high levels of uric acid and cardiovascular diseases were shown. High level of uric acid is related with poor prognosis and increased cardiovascular mortality. The underlying mechanism of uric acid effects on atherosclerosis and mortality is not well understood. We aimed to determine uric acid levels and its association with coronary collateral vessel development in non ST segment elevation acute coronary syndrome patients.
Method: The study population included 175 patients with non ST segment elevation acute coronary syndrome patients. At the first day of their entry to hospital, complete blood counting, kidney function test, lipid profile, fasting glucose and uric acid levels were analyzed for all patients at blood samples. CK, CK-MB and troponin T levels were measured by three times with 6 hours intervals and patients were diagnosed by results. Coronary angiography was performed to all patients within 24-72 hours. Patients with 75% or more lumen occlusion in at least one of coronary arteries were included to study and Rentrop collateral classification was performed. It is accepted that rentrop class 0-I is poor-developed collateral, rentrop II-III is well-developed collateral. Patient with normal and elevated uric acid levels were compared according to collateral development degree.
Results: According to uric acid levels, patients were divided into two groups; group 1 consisted of 102 patients with normal uric acid levels (90 male, 12 female) and group 2 consisted of 73 patients with elevated uric acid levels (59 male, 14 female). Basal characteristics, diagnoses and presentation of cardiovascular risk factors were similar between groups. In group 1, poor-developed collateral was determined in 54 patients (%54) and well-developed collateral was determined in 46 patients (%46). In group 2, poor-developed collateral was determined in 54 patients (%76.1) and well-developed collateral was determined in 17patients (%23.9). In comparison of two groups, uric acid levels were significantly and negatively correlated with degree of coronary collateral development (p=0,004).
Conclusion: Coronary collateral development is poor in patients with high levels of uric acid. Uric acid level is an indicator of coronary collateral development.

P1537 Coronary flow velocity reserve deteriorate late (12 months) after sirolimus-eluting stent implantation

Y. Miyamoto, T. Maehama, K. Saito, K. Imai, N. Okahashi, K. Obase, A. Hayashida, Y. Neishi, T. Kawamoto, K. Yoshida. *Kawasaki Medical School, Kurashiki, Japan*

Aims: The purpose of this study was to evaluate coronary microvascular endothelial function late (6 and 12 months) after Sirolimus-eluting stent (SES) implantation by using transthoracic Doppler echocardiography.
Methods and Results: A total of 21 lesions from 21 patients with significant (>75%) left anterior descending artery stenosis who underwent percutaneous coronary intervention (PCI) with SES were enrolled and studied. As a control group, 10 patients who were treated with bare metal stent (BMS) were also studied. CFVR was measured at 6 and 12 months after PCI. Coronary angiography was also performed at 6 and 12 months (SES only) after stenting. Between 6 and 12 months after SES implantation, there was no significant difference in angiographical diameter stenosis (15.6±7.5% vs 14.2±6.3%, p=0.5). On the other hand, CFVR significantly decreased between 6 and 12 months in SES group (2.5±0.5 vs 2.2±0.5, $p<0.01$), but not in BMS group (2.3±0.4 vs 2.5±0.3, p=0.1) (figure).



Coronary flow velocity reserve change between 6 months and 12 months after SES and BMS.

Conclusions: Coronary microvascular endothelial function may deteriorate between 6 and 12 months after SES implantation. Long-term impact of the late microvascular impairment after SES implantation on clinical outcome needs to be investigated.

P1538 Transthoracic Doppler MCE identification and analysis of perforating intra-myocardial coronary arteries - A new and early signal of LAD patency post STEMI thrombolysis

J. Coucello[1], L. Soares[2], J. Azevedo[1], L.C. Bronze Carvalho[1], A. Aleixo[1]. [1]*Unicard-Hospital Francisco Xavier, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal;* [2]*Hospital Barlavento, Portimão, Portugal*

Non reperfusion and early re-occlusion after coronary artery therapeutic interventions are important prognostic factors during AMI. The sensitivity and specificity of the different clinical, laboratorial and ECG reperfusion indices remains low. The purpose of our study was to assess the relationship between blood flow within the perforating intra-myocardial (PIM) coronary arteries by myocardial contrast echocardiography (MCE) and the patency of the LAD after intravenous thrombolysis (T) by quantitative coronary angiography. In a group of 44 pts, mean age 56±11 yrs, 60% male, with <6 hours anterior STEMI and significant LAD stenosis submitted to T, transthoracic MCE was performed to increase the Doppler signal intensity in the PIM coronary vessels of the septal, anterior and apical LV wall segments. Immediately after T, the PIM vessels were interrogated within the LAD territory after MCE agent (SonoVue, Bracco, Italy) 8 mmol/ml intravenous infusion. The presence (PIM+, n=33 pts) or absence (PIM-, n=11 pts) of MCE blood flow signal of the PIM coronary arteries was correlated with LAD successful patency (n=30 pts) or sustained occlusion (n=14 pts) after T, assessed by coronary angiography. The time interval between MCE and coronary angiography was less then 4 hours. MCE study and identification of the PIM blood flow revealed sensitivity and specificity values of 100% and 79%, and positive and negative predictive values of 91% and 100%, respectively, for the identification of successful LAD patency after T.
Conclusion: In our study, the evaluation of blood flow within the PIM coronary vessels by MCE was useful in the early assessment of LAD patency after thrombolysis. This new method has high sensitivity and specificity values, revealing clear advantages as a non invasive tool for the clinical decision making process, therapeutic and interventional strategies during AMI.

P1539 Impact of anemia and serum erythropoietin levels on collateral vessel development in patients with coronary artery disease

B. Candemir, C. Ozdol, S. Gulec, A.O. Ozdemir, C. Erol. *Ankara University School of Medicine, Ankara, Turkey*

Objectives: To determine impact of anemia and serum erythropoietin (EPO) levels on collateral formation.
Methods: Serum hemoglobin (Hb) and erythropoietin levels were assessed in 256 patients who had collaterals in coronary angiography and were divided into 2 groups according to degree of collateral formation as; poor (n=108) or good (n=148). Anemia was defined by WHO criteria.
Results: Mean age was 63±11 and 197 were male (77%). 140 patients were admitted with stable angina pectoris and the rest with acute coronary syndrome. Anemia was present in 72 patients (28%) and was found to be significantly more common in good collateral group (21% vs 33%; p=0.038) whereas EPO level was not (p: 0.397). (Table-1) Mean EPO level was 10.0±10.3 mU/ml. Only stable angina and anemia were predictors for good collaterals in multivariate logistic regression analysis (p: 0.033 and 0.014, respectively). There were no correlation between collateral grade and other variables.

	Poor Collateral (n=108)	Good Collateral (n=148)	p Value
Age	63±11	62±11	0.765
Male Gender	86 (80)	111 (75)	0.385
Hypertension	73 (68)	110 (74)	0.239
Diabetes	37 (34)	50 (34)	0.937
Smoking	38 (35)	52 (35)	0.993
Previous MI	52 (48)	73 (49)	0.853
Stable angina pectoris	51 (47)	89 (60)	0.040
Anemia	23 (21)	49 (33)	0.038
Erythropoietin (mU/ml)	9.7±11.3	10.1±9.4	0.397
Body mass index	28±4.6	28±4.6	0.697
Hemoglobin	13.8±1.7	13.5±1.9	0.136
LDL	104±38	107±40	0.509
Creatinine	1.04±0.2	1.05±0.3	0.774
Ejection Fraction	45±12	47±14	0.409
Beta Blocker	80 (74)	101 (68)	0.311
ACE/ARB	78 (72)	116 (78)	0.256
Statin	76 (70)	104 (74)	0.554

Conclusion: This study demonstrated that anemia but not EPO level is associated with good coronary collaterals.

P1540 Wall shear stress as a determinante for atherosclerotic remodeling in human coronary arteries

H. Hetterich[1], M. Gehring[1], A. Ibrahim[1], T. Potzger[1], T. Redel[2], K. Nikolaou[1], C. Schmidt-Tannwald[1], V. Klauss[1], J. Rieber[1]. *[1]Klinikum der Universitaet Muenchen, Munich, Germany; [2]Siemens AG, Health Care Sector, Forchheim, Germany*

Introduction: Wall shear stress (WSS) is regarded as a key local factor for the initiation and progression of atherosclerosis. Computational fluid dynamics (CFD) is a validated tool for the calculation of parameters of fluid tissue interaction. Lately a correlation between WSS as calculated by CFD and plaque burden as determined by intravascular ultrasound (IVUS) could be demonstrated. Atherosclerotic lesions may show either positive or negative remodeling. Positive remodeling is often associated with instable lipid rich plaques, whereas negative remodeling is often observed in stable fibrous or calcified lesions. The aim of this study was to correlate different patterns of WSS with the type of arterial remodeling.
Methods and Results: We prospectively included 10 patients with suspected coronary artery disease who received CTA (Dual source 64 slice CT) and invasive conventional coronary angiography. Intravascular ultrasound was attempted in all three epicardial vessels. The data of the axial CTA images was transferred to a dedicated software package for segmentation, mesh building and CFD calculation. The surface of each vessel was divided into quartiles based on the levels of WSS. The remodeling-index (RI) was calculated as the area surrounded by external elastic lamina at the site of the lesion with the lowest lumen area or highest plaque burden divided by the average vessel area of the reference segments. Flow pattern calculations and calculation of WSS were performed in 21/30 vessels. IVUS analysis was successfully performed in 15/30 coronary arteries resulting in a total number of. 45 atherosclerotic lesions. The average degree of stenosis was 29±14% and the RI 0,99±0,12. The RI was significantly depending on the level of WSS with a predominantly positive remodeling (RI=1,08±0,05) in areas of low WSS (lowest quartile) and a predominantly negative remodeling (RI=0,94±0,13) in areas of high WSS (highest quartile) ($p<0,05$). Areas with lumen obstruction (>30%) as proven by IVUS were also associated with increased WSS.
Conclusion: These data indicate that WSS plays an important role in remodeling processes within the coronary arteries during the development and progression of atherosclerosis. Prospective serial assessments are necessary to further elucidate these initial results.

P1541 A new angiographic method to assess coronary flow reserve

H. Rittger[1], A. Kuper[2], O. Breithardt[1], A. Sinha[1], M. Schmidt[1], A. Jakob[1], B. Bluem[1], J. Brachmann[1]. *[1]Klinikum Coburg, Coburg, Germany; [2]Paieon Medical, Rosh Hayin, Israel*

Background: Coronary Flow Reserve (CFR) is defined as the ratio between coronary artery flow during maximal hyperemia and rest. It is considered as a marker for the integrity of the epicardial coronary circulation and the microcirculation. CFR measurement typically requires the introduction of a guide wire into a diseased coronary artery, which carries the potential for serious complications like coronary spasm and dissection. We tested a new algorithm, which allows to estimate CFR by analysis of coronary angiogramms without the need for direct intracoronary measurements.
Methods: 27 patients (10 female, mean age 64±11 years) underwent diagnostic cardiac catheterization for the evaluation of chest pain. A Dopplerwire was introduced into the diseased coronary artery and CFRdoppler was calculated by the flow velocity ratio between rest and maximal hyperemia, induced by intravenous administration of 140μg/kg adenosine. This was compared to the angiographically determined CFR (CFRangio) under the same conditions (rest and induced maximal hyperemia) by densitometry. CFRangio was based on the creation of 2 time density curves representing the disappearance of contrast over time. CFRangio was the resulting ratio between the density values during hyperemia and rest.
Results: An excellent correlation was found between CFRdoppler and CFRangio: CFRangio = 1x CFRdoppler ($r=0.87$; $p<0.0001$). The average absolute difference between both indeces was 0.36±0.31.
Conclusion: Measurement of CFRangio by densitometry is feasible and provides results which are comparable to Doppler derived intracoronary flow velocity measurements, without the potential hazards associated with intracoronary insertion of a Dopplerwire.

P1542 Different haemodynamic determinants of aortic pulse wave velocity and central pulse pressure augmentation index: an invasive study

E. Franchi, G. De Luca, L. Giuliani, L. Venegoni, E. Rondano, G. Dell'era, S. Iorio, P. Marino. *Clinical Cardiology, Eastern Piedmont University, Novara, Italy*

Aortic Pulse Wave Velocity (PWV) is an accepted measure of aortic stiffness. The Augmentation Index (AI) is the proportion of central pulse pressure attributed to reflected wave overlap in systole. The relationship between these two parameters has been investigated mainly noninvasively, and it is still controversial.
Purpose: The aim of the study is to investigate the relationship between PWV and AI, both invasively measured in the aorta, and whether these two parameters are related to other central haemodynamic features.
Methods: We examined prospectively 474 patients who consecutively underwent left cardiac catheterization in our institution, between 08/05/2008 and 30/01/2009. 125 patients were excluded from the analysis because of atrial fibrillation, bundle branch block, pacemaker, radial approach. Data from 349 patients (69% males, mean age 67.6±10.8 yrs) were analyzed. Aortic pressure waves, with synchronized electrocardiogram, were invasively measured during cardiac catheterization using a fluid-filled pressure transducer at two sites: one in the ascending aorta and the other at the renal arteries level. Aortic PWV was calculated as the pressure wave transit time divided by the distance between the two measuring sites. Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), heart rate (HR), left ventricular ejection time (LVET), and aortic AI were measured from the recordings in ascending aorta. Left ventricular ejection fraction (LVEF) was quantified echocardiographically.
Results: At univariate analysis PWV significantly correlates with age ($r= 0.31$, $p <0.001$), SBP ($r= 0.25$, $p <0.001$), DBP ($r= 0.13$, $p <0.05$), PP ($r= 0.22$, $p <0.001$), whereas it does not correlate with height, LVET, HR, LVEF. AI correlates with age (r -0.14, $p <0.05$), height ($r= 0.18$, $p <0.001$), SBP ($r= -0.18$, $p <0.001$), PP ($r= -0.26$, $p <0.001$), LVET ($r= -0.21$, $p <0.001$), HR ($r= -0.15$, $p <0.05$), whereas its correlation with DBP and LVEF is not significant. At regression analysis PWV is negatively and significantly related with AI ($r=-0.15$, $p=0.008$). At multivariate analysis including only the univariate significant variables, the predictors of PWV result to be age, SBP and PP, whereas for AI the predictors are PP, LVET, and height.
Conclusions: According to our data the main determinants of AI are partly different from those affecting PWV. Decreasing AI with increasing aortic stiffness may be attributable to impedance matching and reduced wave reflection at the interface between the aorta and the muscular arteries. Our study suggests that central AI may not be a surrogate for aortic stiffness estimate.

P1543 Diastolic dysfunction alterations in diabetic patients assessed with Doppler echocardiography: relationship between atheromatosis and coronary microcirculatory disturbances

H.J. Colmenarez, J. Escaned, M.C. Ferrer, P. Jimenez-Quevedo, F. Alfonso, C. Banuelos, L. Perez De La Isla, J.L. Zamorano, C. Macaya, R. Hernandez. *Hospital Clinico San Carlos, Madrid, Spain*

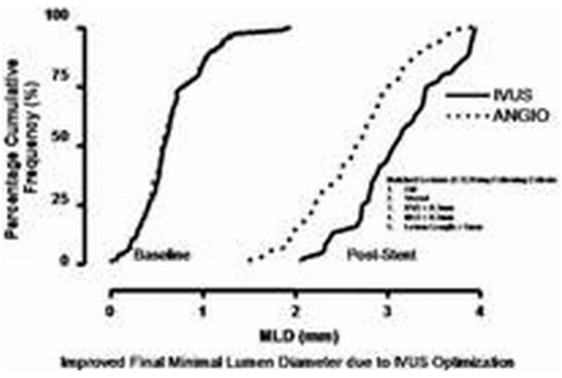
Diabetes mellitus (DM) is associated with both left ventricular diastolic dysfunction and coronary macro- and microcirculatory pathology. The aim of this study was to assess the relationship between these manifestations of diabetic heart disease.
Methods: In 14 patients with DM and ischemic heart disease the atherosclerotic load in the left anterior descending branch (LAD) was quantified by means of intravascular ultrasound (IVUS) with volumetric analysis (TOMTEC). Pressure measurements and intracoronary blood flow velocity (Doppler) were digitally recorder for further analysis. Coronary flow velocity reserve (CFVR), coronary conductance and zero-flow pressure (bothon the basis of the relation between flow velocity and pressure in diastole during maximum hyperemia) and coronary resistance index (pressure/coronary flow velocity ratio) were measured. The relationship between 2 Doppler indices of left ventricular diastolic function (LVDF) (E/A and E/e' ratios) and intracoronary measurements was investigated.
Results: Left ventricular ejection fraction (LVEF) was 65.71± 7,50%. Estimated diastolic function indices were E/A=0.9±0.37 and E/e'=10.47±3.50. A strong and directly proportional relation (r=0.63, p=0.05) between E/e' and coronary resistance index (2.02±0.72 mmHg cm^{-1} s) and a significant and inversely proportional relation (r= -0.74 p=0.02) betweenE/e' and coronary conductance (2.02±0.72 cm s^{-1} $mmHg^{-1}$) was found. There was no significant relation between LVDF indices and CFVR (2.43±0.56) nor Pf0 (40.41±10.66 mmHg). Volume of atheroma in the 20 proximal mm of the LAD branch was of 184.70±48.95 mm^3 (average plaque area 8.57±1.55 mm^2) was not related to LVDF indices.
Conclusions: These results suggests that in DM the development of diastolic dysfunction: 1. bears relation to coronarymicrocirculatory pathology; and 2. it does not seem to be influenced by the atherosclerotic load in epicardic vessels. Besides, they support the superiority of the E/e' index in detecting early changes in diastolic function associated to microcirculatory impairment.

LONG TERM OUTCOME AFTER PERCUTANEOUS CORONARY SYNDROME

P1544 Improving DES revascularization rates using new intravascular ultrasound optimization criteria

R.T. Gerber[1], A.S.P. Sharp[1], A. Latib[2], A. Ielasi[2], C. Godino[1], A. Chieffo[2], M. Carlino[2], I. Michev[1], M. Montorfano[2], A. Colombo[1]. *[1]Columbus Hospital and San Raffaele Hospital, Milan, Italy; [2]San Raffaele Hospital, Milan, Italy*

Introduction: A new criteria for IVUS optimization of drug-eluting stents (DES), based on vessel size (media-to media) has been proposed for implantation. We report the one year outcomes using these new criteria.
Methods: The criteria require that all patients initially undergo conventional angiographic guided stenting, followed by post-dilatation with a non-compliant balloon. The size of this balloon is decided by measuring the average vessel diameter within the stented segment on IVUS (e.g. media-to-media size of 3.3 by 3.7mm within proximal stent would require a 3.5mm post-dilation balloon). The final acceptable minimal cross sectional area (CSA) within the stent must then be $\geq$ 70% of the CSA of the non-compliant balloon used, otherwise further post-dilatation is indicated.
Using these criteria, IVUS optimized complex lesions from one institution were 1:1 matched with lesions from another institution (where stents were implanted using conventional angiographic guidance) in order to establish safety and revascularization rates at one year.
Results: 113 consecutive, complex lesions underwent IVUS-guided stenting. The cumulative frequency plot (Figure 1) demonstrates a significant increase in final MLD in this group when compared to standard angiographic optimization (3.09±0.50 v 2.67±0.54 mm; p<0.0001). There were no cases of vessel rupture. Clinical follow-up was completed in 100% of patients at 12 months. In the IVUS cohort, there was 1 TLR and 2 TVR (revascularization rate 2.7%). In the IVUS group. In the matched cohort, the revascularization rate was 8.8% (TLR 8% and TVR 9%).
Conclusions: We have demonstrated improvements in the final MLD by using IVUS optimization and that this is associated with lower revascularization rates at 12 months.



Improved Final Minimal Lumen Diameter due to IVUS Optimization

P1545 The mechanosensitive calcium-channel TRPV4 is involved in neointimal hyperplasia after coronary stent implantation

H.M. Nef[1], H. Moellmann[1], C. Troidl[2], S. Voss[3], G. Markus[3], S. Kostin[2], K. Troidl[2], M. Weber[1], C.W. Hamm[1], A. Elsaesser[4]. *[1]Kerckhoff Klinik GmbH, Bad Nauheim, Germany; [2]Max-Planck-Institut fuer Herz und Lungenforschung, Bad Nauheim, Germany; [3]Franz-Groedel-Institut der Kerckhoff-Klinik GmbH, Bad Nauheim, Germany; [4]Klinikum Oldenburg, Oldenburg, Germany*

Purpose: In-stent restenosis remains still a severe complication of coronary interventions after stent implantation. However, the underlying molecular mechanisms are still not fully elucidated. It is known that implantation of stents lead to altered flow profile. Thus, in cell culture and in a porcine coronary stent model we investigated the mechanosensitive transient receptor potential cation channel, subfamily V, member 4 (TRPV4) and its downstream targets which are known to be involved in shear stress dependent remodelling of the vascular wall.
Methods: Porcine aortic endothelial cells (PAEC) were cultured under standard conditions (20% O2, 5% CO2 at 37°C) but exposed to not-laminar flow by brandishing the culture dish for 60 min (NLF). Cells were harvested from RNA isolation or protein analysis after 1, 5, 18 and 48 h. Controls wereplated under equal conditions and time period but kept under static conditions (STAT). By using quantitative real time PCR mRNA abundance of TRPV4, myocyte enhancer factor 2c (MEF2c), nuclear factor of activated T-cells (NFAT) and its co-activator calcineurin were investigated. In a porcine overstretch coronary stent model (n=9, 26±1 kg) bare metal stents (3.5/18 mm) were implanted. The pigs were euthanized after 1, 3 and 7 days. The stented arteries were explanted for qRT-PCR and immunohistochemistry.
Results: Under not-laminar flow culture experiments showed asignificant increase of TRPV4 mRNA abundance after 18 h (STAT: 0.62±0.13 vs.NLF: 1.59±0.28; p<0.05), which decreased to control levels after 48h. MEF2c (STAT: 2.15±0.28 vs. NLF: 4.1±0.26; p<0.05) and calcineurin (STAT: 1.26±0.2vs. NLF 3.41±0.27; p<0.05) showed a similar pattern of mRNA abundance. Theincreased level TRPV4 mRNA was also demonstrated in coronary arteries 3 daysafter stent implantation in pigs compared to untreated controls (4.87±1.30 vs.2.31±0.29; p<0.05). This was confirmed on protein level by immunohistochemistry. Furthermore, increased level of expression was found forNFAT (1.76±0.15 vs. 0.71±0.07; p<0.001) and calcineurin (0.56±0.07 vs. 0.27±0.02;p<0.05) 7 days after treatment.
Conclusion: In flow culture experiments using PAEC we could demonstrate a flow-dependent increase of TRPV4 and calcium-dependent transcription factors. This could also be documented in the overstretch-model in pig showing increased levels of TRPV4, NFAT and calcineurin within the neointima. Thus, these results provide evidence that the mechanosensitive Ca^{2+}-channel TRPV4 is involved in the shear stress dependent neointima formation after stent implantation.

P1546 Polymorphisms of the interleukin 8 gene and restenosis after percutaneous coronary intervention

K. Vogiatzi[1], S. Apostolakis[1], V. Voudris[2], S. Thomopoulou[2], G.E. Kochiadakis[3], D.A. Arfanakis[3], D.A. Spandidos[1], P.E. Vardas[3]. *[1]Laboratory of Clinical Virology, Faculty of Medicine, University of Crete, Heraklion, Greece; [2]Onassis Cardiac Surgery Center, Athens, Greece; [3]Cardiology Dept. Heraklion University Hospital, Heraklion, Greece*

Purpose: Interleukin-8 is a strong mediator of inflammation and has been implicated in the biochemical pathways involved in a wide range of inflammatory diseases including atherosclerosis. We investigated the potential influence of two common functional polymorphisms of the interleukin (IL)-8 gene: −251A/T (rs4073) and 781C/T (rs2227306) on susceptibility to in-stent restenosis (ISR) following percutaneous coronary intervention (PCI).
Patients and Methods: The hypothesis was tested by screening for the prevalence of the above polymorphisms in 201 coronary artery disease (CAD) patients subjected to PCI and presenting with symptoms or signs of recurrent ischemia. Patients were angiographically re-evaluated and formed the ISR group (n=73) and the non-ISR group (n=128) based on the presence or absence of ISR. 147 patients without angiographic evidence of CAD formed a reference control group (non-CAD group).
Results: A borderline statistically significant higher frequency of the rare TT251TT781 combined genotype was observed in patients with ISR on re-evaluation compared with patients with normal follow-up angiography (odds ratio (OR)=1.2; 95% Confidence intervals (CI): 1-1.9, p=0.049). The predominance of TT251TT781 was independent of conventional risk factors for cardiovascular dis-

ease. Consequently, T251T781 haplotype was significantly more common in the ISR group compared to the non-ISR group (haplotype frequency: 0.058 vs. 0.004 respectively; OR=15.7; 95% CI: 1.9-126; p=0.001).
Conclusions: The above observations indicate that the genetic diversity of the IL-8 gene influences patient susceptibility to ISR and suggests the implication of IL-8-mediated pathways in the process of ISR. However, the rarity of T251T781 haplotype (less than 2% of the total population gene pool) makes any clinical application of the above observations unfeasible

P1547 Systemic inflammatory response after stent implantation: a randomized comparative study of sirolimus-eluting (SES) and bare metal stents (BMS)

D.A. Arfanakis, G.E. Kochiadakis, M.E. Marketou, E.I. Skalidis, N.E. Igoumenidis, M.I. Hamilos, P.E. Vardas. *Cardiology Dept. Heraklion University Hospital, Heraklion, Greece*

Purpose: Stent implantation causes significant injury to the vascular wall, resulting in inflammatory activation. Although SES seem to have anti-inflammatory properties, their effect on periprocedural systemic inflammatory response has not been sufficiently investigated.
Methods: 75 consecutive patients, who underwent successful PCIs were randomly allocated to SES (n=37) or BMS (n=38). Blood samples were taken 24 h before, at 24 h, 48 h and 1 month after angioplasty; levels of high sensitive C-reactive protein (hsCRP) were determined on each occasion. Follow-up coronary angiography was performed 6-8 months later and in stent late luminal loss (LL) was calculated.
Results: hsCRP after BMS implantation increased rapidly over 24 hours ($p<0.001$) and then remained steady throughout the study period. In contrast, patients with SES exhibited a reduction to below baseline values by the end of the first month. A significant correlation was found between hsCRP and LL at 6 months in both groups.

Plasma levels of hsCRP before and after PCI and stenting (values are expressed as mean values and 95% CI)

	hsCRP (mg/dL)			
	Before	24 hours	48 hours	1 month
BMS	1.089 (0.758 -1.420)	2.265* (1.805 - 2.724)	2.417* (1.835 - 2.998)	1.912* (1.498 - 2.326)
SES	1.070 (0.700 - 1.440)	1.146 (0.632 -1.659)	1.346 (0.696 - 1.996)	0.653* (0.191 - 1.116)

*Significant change from baseline, BMS: bare metal stents, SES: sirolimus-eluting stents, CI: confidence interval, hsCRP: high sensitive C-reactive protein, PCI: percutaneous coronary intervention.

Conclusion: Patients with SES exhibited attenuation of the post-procedural systemic inflammatory activation during a one-month follow-up period after stent implantation. Considering that inflammatory stress is related to LL at 6-month follow-up, this could contribute to the difference in restenosis rate between these 2 types of stents and suggests that the mechanism of restenosis might not be the same in these two stents.

P1548 Evaluation of homeostasis model assessment of insulin resistance (HOMA-IR) index as a predictor of restenosis after percutaneous coronary intervention

T. Komatsu, I. Yaguchi, K. Tanaka, K. Takizawa, Y. Sakai, K. Takayanagi. *Department of Cardiology, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan*

Introduction & Hypothesis: Percutaneous coronary intervention (PCI) has been widely adopted as an effective treatment strategy for patients with ischemic heart disease; however, the rate of restenosis is high. Diabetes mellitus has been reported as an independent factor of restenosis. The aim of this study was to clarify the factors associated with coronary restenosis after PCI and evaluate the homeostasis model assessment of insulin resistance (HOMA-IR) index as a predictor of restenosis. We reviewed the clinical records of 189 patients who had been subjected to elective PCI between August 2004 and December 2007. We distributed these patients by the value of HOMA-IR into a Group P (n=124; HOMA-IR $\geq$2.5, positive) and a Group N (n=65; HOMA-IR $<$2.5, negative). Then, we measured the minimal lumen diameter (MLD) and late lumen loss by quantitative coronary angiography (QCA).
Results: The rate of restenosis was significantly higher in group P (16.9%) than in group N (3.1%, $p<0.05$). In non-diabetic patients whose hemoglobin A1c was less than 6.5%, patients with a positive HOMA-IR index accounted for 13.9 vs 3.8%, $p<0.05$). In group P the MLD was significantly smaller (2.21 ± 0.91 vs 2.59 ± 0.57mm, $p<0.05$), and the late lumen loss and % stenosis were significantly larger (0.82 ± 0.86 vs 0.42 ± 0.47mm, and 24.5 ± 26.9% vs 12.0 ± 9.1%, respectively, $p<0.05$). The logistic analysis showed that the only independent predictor of restenosis was insulin resistance (OR 6.42; 95% CI 1.46-28.33, $p <$ 0.014).
Conclusion: HOMA-IR index is easy to calculate and a useful predictor of restenosis; furthermore, improvement of insulin resistance may contribute to prevent coronary restenosis after PCI.

P1549 Impact of left ventricular ejection fraction on outcomes of percutaneous drug-eluting stenting for unprotected left main disease: insights from a multicenter registry of 975 patients

M. Bollati[1], G. Biondi-Zoccai[1], T. Palmerini[2], C. Tamburino[3], M. Margheri[4], G. Vecchi[5], G. Sangiorni[6], S. De Servi[7], I. Sheiban[1]. *[1]University of Turin, Turin, Italy; [2]Azienda Ospedaliera S. Orsola Malpighi, Bologna, Italy; [3]University of Catania, Catania, Italy; [4]Università di Firenze, Firenze, Italy; [5]Ospedale S. Maria delle Croci, Ravenna, Italy; [6]Centro Emocolumbus, Milan, Italy; [7]Ospedale Civile, Legnano, Italy*

Background: Despite the well-known prognostic impact of systolic dysfunction in unselected patients undergoing percutaneous coronary intervention (PCI), limited data are available on its current predictive role in after PCI for unprotected left main disease (ULM). We thus appraised the prognostic role of left ventricular ejection fraction (LVEF) in patients undergoing PCI for ULM with drug-eluting stents (DES).
Methods: Consecutive eligible subjects were retrospectively enrolled in a national registry. Patients were pre hoc divided in 3 groups: LVEF$<$30%, LVEF 30-45%, and LVEF$>$45%. Relevant baseline and outcome data were compared with bivariate and multivariable tests.
Results: 975 subjects were included (LVEF$<$30% group: 46, LVEF 30-45%: 208, LVEF$>$45% group: 721). Patients with LVEF$<$30% had several other unfavorable clinical features, including older age and higher EuroSCORE. Adverse event rates were different already at 7 days (p=0.012 for all-cause death and p=0.015 for MACE), with even more significant trends up to 30 days, and at long-term ($p<0.001$ for death, and $p<0.001$ for MACE). After a median of 18 months, risks of death totaled 39% vs 13% vs 8% ($p<0.001$) and risk of MACE 44% vs 24% vs 22% (p=0.003). Multivariable analyses showed however that reduced LVEF was not a significant independent predictors of adverse events at any time-point. Conversely, the only independent predictor of all-cause death was EuroSCORE (OR=1.38, $p<0.001$), the only predictors of cardiac death were EuroSCORE (OR=1.24, p=0.012) and MI as admission diagnosis (OR=1.73, p=0.018), the only predictor of MI was renal failure (OR=3.41, p=0.010), and the only predictor of MACE was EuroSCORE (OR=1.13, p=0.031).
Conclusions: Reduced LVEF is a significant predictor of adverse events after PCI with DES for ULM. However, its strong apparent prognostic impact is only due to clustering of other adverse features. Thus, reduced LVEF should not be perceived per se as a contraindication to PCI for ULM.

P1550 Long term results of drug eluting stenting in saphenous venous grafts

A.E.L.R. Assali, H.V.A. Hana Vaknin-Assa, E.L. Eli Lev, I.T. Igal Teplitsky, T.B. Tamir Bental, D.B. David Brosh, D.D. Danny Dvir, S.F. Shmuel Fuchs, A.B. Alexander Battler, R.K. Ran Kornowski. *Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel*

Background: Percutaneous coronary intervention (PCI) of saphenous vein graft (SVG) lesions is associated with worse outcomes and high incidence of in-stent restenosis compared with PCI of native coronary arteries.
Objectives: The purpose of the present report was to evaluate the long-term clinical and angiographic outcomes of DES implantation in SVG lesions.
Methods: Data from consecutive patients who underwent PCI of SVG were imputed into a clinical Database. We evaluated the clinical outcomes up to three years after DES stenting. Included 90 patients [97-grafts] [89% male]. Major adverse cardiac events (MACE) including death, myocardial infarction, target lesion revascularization (TLR), and target vessel revascularization (TVR) were recorded.
Results: The patients mean age was 69 ± 9yrs and the mean age of SVG was 10.6 ± 5.2yrs. The presenting diagnosis was ACS in 71% of patients. And 59% had DM and 14% of lesions were 'in-stent' restenotic. Distal protection device was used in 39% of cases and procedural success was achieved in all patients.
TABLE

	Six months [n=90]	One year [n=90]	Two years [n=83]	Three years [n=51]
Death	1-1.1%	1-1.1%	6-7.2%	6-11.7%
MI	2-2.2%	4-4.4%	5-6%	6-11.3%
Definite Stent thrombosis	0-0%	2-2.2%	3-3.6%	3-5.9%
TVR/graft	7-7.2%	11-11.3%	22-24%	26-4.2%
TLR/graft	6-6.2%	9-9.3%	19-21%	23-38%
CABG	1-1.1%	3-3.3%	5-6%	5-9.8%
MACE	9-10%	15-16.6%	25-30%	28-47%

Conclusions: DES implantation in SVG lesions appears safe with favorable and improved short-term outcomes. Nonetheless, long-term results are limited by disease progression in degenerated SVGs and high rate of target lesions/vessel revascularization procedures.

P1551 Prevalence, predictors, and long-term prognosis of discontinuation of oral antiplatelet therapy after DES implantation

R. Rossini[1], G. Musumeci[1], C. Lettieri[2], T. Nijaradze[1], G. Biondi Zoccai[3], M. Romano[2], N. Lortkipanidze[1], N. Cicorella[2], A. Gavazzi[1], D.J. Angiolillo[4]. *[1]Ospedali Riuniti di Bergamo, Bergamo, Italy; [2]Ospedale Carlo Poma, Mantova, Italy; [3]Division of Cardiology, University of Turin, Torino, Italy; [4]University of Florida-Shands Jacksonville, Jacksonville, United States of America*

Purpose: Discontinuation of antiplatelet therapy is associated with an increased risk of adverse cardiac events, including stent thrombosis particularly after drug-eluting stents (DES) implantation. The aim of this study was to determine the prevalence and predictors of discontinuation of oral antiplatelet therapy after DES implantation and to evaluate its effects on long term prognosis.
Methods: A prospective observational cohort study was conducted on 629 consecutive patients successfully treated with DES and discharged on dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day). Clopidogrel was maintained for at least 12 months. Patients were followed-up for 32.4±11.3 months. Prevalence and predictors of aspirin and/or clopidogrel discontinuation were assessed. Major adverse cardiac events (MACE), defined as cardiovascular death, acute coronary syndrome leading to hospitalization, and non-fatal stroke, were recorded. All cause death and definite stent thrombosis were also recorded.
Results: A total of 10.8% of patients discontinued one or both antiplatelet agents within the first 12 months (early discontinuation) and 5% withdrew aspirin after 1 year (late discontinuation). Patients who discontinued antiplatelet therapy had a higher incidence of all-cause death (11.0% vs 3.0%, p=0.001), MACE (22.0% vs 9.2%, p<0.001) and definite stent thrombosis (4.4% vs 1.3%, p=0.064). Discontinuation of antiplatelet therapy was predicted by a history of prior stroke (OR=4.46, p=0.018) and occurrence of major bleeding (OR=6.71, p=0.001). The independent predictors of early discontinuation were history of prior stroke (OR=3.05, p=0.045), occurrence of major bleeding (OR=14.1, p<0.001) and occurrence of minor bleeding (OR=3.96, p=0.001), whereas a history of prior stroke was the only predictor of late discontinuation (OR=7.47, p<0.001).
Conclusions: Discontinuation of antiplatelet therapy is strongly associated with increased overall mortality, MACE, and definite stent thrombosis. Strategies to improve compliance to antiplatelet therapy in patients with greater likelihood to interrupt treatment are warranted.

P1552 Antiplatelet treatment after coronary stent implantation. A "over-compliance" situation

T.H. Bampali, A. Konstantinidis, B. Salma, T.H. Pappas, K. Kalantzi, A. Papathanasiou, C.H. Katsouras, J. Goudevenos. *University of Ioannina Medical School, Ioannina, Greece*

Purpose: The current recommendations state that the patients with previously implanted coronary stent should be treated with dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75mg) for one month after Bare-Metal-Stent and one year after Drug-Eluting-Stent implantation, followed by aspirin for lifetime. Our purpose was to evaluate the compliance of patients/doctors in NW Greece with the above.
Methods: In this cross-sectional study, we enrolled every patient who proceeded for hospitalization in our department and had undergone coronary stent implantation.
Results: From November 2007 until January 2009, 341 patients (86% men) were identified with history of prior coronary stenting. 67% of them (230 patients) had been treated with BMS, 27% (91 patients) with DES and 6% with both types. There was no statistically significant difference among the sub-groups, relatively to major cardiovascular risk factors. The median time from the angioplasty to the interview was 6.4 years (IQR 1-15 years). 239 patients had received long-time dual antiplatelet therapy for a median time of 2.9 years and only 27 patients had been treated according to the recommendations. No premature discontinuation was reported. In the sub-group of the BMS-treated patients only 17 (7.4%) had received dual antiplatelet therapy for 1 month, whereas the rest for longer period (median 2.8 years). Respectively, in the DES-treated sub-group only 9 patients had received dual therapy for 1 year, whereas the majority (90%) for a median time of 3 years. In this category of the "over-complianced" patients 34 bleedings occurred (25 in the BMS sub-group). The severity of the bleedings was major (2), intermediate (1), low (31), according to the GUSTO Stratification). We reported 67 cases of acute coronary syndrome (ACS) (47 in the BMS sub-group). Respectively in the category of the "complianced" patients 2 bleedings (1 intermediate, 1 low risk) and 8 ACSs occurred.
Conclusions: Despite of the recommendations for the optimum duration of the dual antiplatelet treatment after angioplasty, 70% of the patients in our study continued to receive them, and this was correlated with a 2-fold increase of the bleeding risk (14.2% vs 7.4%, p <0.05). No significant difference in the occurrence of the ACSs (28% vs 29.6%, p>0.7) was shown.

P1553 Long-term clinical outcome of conservative versus aggressive intervention strategy in patients with multivessel coronary artery disease undergoing drug-eluting stent implantation

B.J. Choi, S.J. Tahk, J.S. Park, H.S. Lim, S.Y. Choi, M.H. Yoon, H.M. Yang, M.Z. Zheng, J.W. Hwang, U.J. Choi. *Ajou University School of Medicine, Suwon, Korea, Republic of*

Backgrounds: We compared the long-term clinical outcome of patients with multivessel coronary artery disease who underwent drug-eluting stent implantation with either conservative or aggressive percutaneous coronary intervention (PCI) strategy to determine the impact of PCI strategies on the long-term clinical outcome.
Methods: Conservative PCI strategy was defined as brief PCI of only the culprit stenosis causing ischemia. Aggressive PCI strategy was defined as PCI of all visible angiographic lesions including both culprit stenosis and concomitant intermediate lesions in vessels >2.5 mm. The primary endpoint was a major adverse cardiac event (cardiac death, Q-wave myocardial infarction [MI] and target vessel revascularization [TVR]) at 24 months.
Results: A total of 437 patients were included in the study, of whom 164 met the criteria for conservative PCI strategy and of whom 273 met those for aggressive PCI strategy. The conservative PCI group was treated with a smaller number (1.6±0.6 vs 3.0±0.7, p=0.014) of stents and a shorter length (32.9±11.9 vs 79.9±18.2 mm, p=0.004) of stent implantation. Stent overlapping was less frequent in the conservative PCI group (16% vs 73%, p=0.002). At 24 months, there was no significant difference in MACE (17.7% vs 14.2%, p=0.41). Cardiac death (1.9% vs 1.1%, p=0.68), Q-wave MI (3.1% vs 2.6%, p=0.77) and TVR (13.1% vs 11.6%, p=0.65) were similar between the groups. However, the rate of target lesion revascularization was significantly lower in the conservative group (4.4% vs 10.5%, p=0.03).
Conclusions: In conclusion, conservative PCI strategy is comparable to aggressive PCI strategy and may be useful as a treatment option for multivessel coronary artery disease.

P1554 Comparison of drug eluting stents and bare metal stents in saphenous vein graft PCI; a single centre experience

S. Balakrishnan Nair[1], S. Chacko[1], B. Clarke[1], M. El-Omar[1], F. Ordoubadi[1], D. Fraser[1], V. Mahadevan[1], R.S. Khattar[1], L. Neyses[2], M. Mamas[2]. *[1]Manchester Royal Infirmary, Manchester, United Kingdom; [2]The University of Manchester, Manchester, United Kingdom*

Objective: Both large multi centre trials and registry studies have demonstrated that PCI with drug eluting stents (DES) is associated with reduced restenosis and MACE rates compared to bare metal stents (BMS) in native coronary vessels. Optimal PCI treatment of saphenous vein graft (SVG) lesions remains unclear despite SVG procedures representing up to 15% of PCI cases. In the recent randomized DELAYED RRISC trial DES were associated with a greater mortality than BMS for SVG disease. We therefore studied mortality and MACE outcomes in BMS and DES in SVG PCI cases.
Methods: We retrospectively studied 388 consecutive patients admitted to our centre for PCI to SVG lesions from 2001 to 2008. Primary endpoint was defined as total mortality and secondary endpoint was major adverse cardiac event (MACE) defined as composite endpoint of Death, Stroke, MI, Stent Thrombosis and Target Lesion/Vessel Re-vascularisation.
Results: Of the 388 patients studied, 219 patients had BMS and 169 had DES. Mean follow up period was 41.9±23.5 months (median 41.5 months). 86.3% were men in BMS vs 76.3% in DES group (P<0.05). Mean age was 70±8.6 in BMS and 68±8.3 in DES (P= NS), 52 patients (23.7%) were diabetic in BMS and 67 (39.6%) in DES (P<0.01). Other demographic parameters were similar in both groups. Number of stents used were similar in both groups (1.9±0.1) as was mean stent length (mm) 42.1±4.3 in BMS and 42.1±3.6 in DES (P=NS) although mean stent diameter (mm) was larger in the BMS group (4.0±0.1 vs 3.6±0.1; P<0.01). There were no significant differences in mean graft age (years) (11.9±4.4 BMS vs 12.0±5.3 DES; P=NS). Over the period studied there were a total of 13/169 deaths in the DES group (7.7%) and 30/219 in the BMS group (14.7%) P<0.05, although 1-year mortality rates were 4.0% and 6.0% in the DES and BMS groups respectively (P=NS). MACE was observed in 50/169 (29.5%) in the DES group and 80/219 (36.5%) in the BMS group (P=NS). 1 year MACE rates were 12.3% and 11.6% in the DES and BMS groups respectively (P=NS).
Conclusion: In the largest registry series with the longest mean follow up period to date to our knowledge, we have demonstrated a greater mortality in patients receiving BMS compared to DES during SVG PCI, despite a greater adverse risk profile in the DES group. These observations are in contrast to the findings of the recent randomized DELAYED RRISC trial (75 patients) in which an adverse outcome was associated with DES use in SVG cases. DES in SVG PCI is safe and is not associated with an excess mortality or MACE rates compared to BMS.

P1556 Field triage of STEMI patients to primary angioplasty significantly reduces treatment delay and improves long-term prognosis

S. Pedersen, P.R. Hansen, S. Galatius, U. Davidsen, R. Mogelvang, A. Iversen, U. Abildgaard, A. Galloe, J.K. Madsen, J.S. Jensen.
Gentofte Hospital, Hellerup, Denmark

Purpose: Reduction of treatment delay is vital for patients with ST-segment Elevation Myocardial Infarction (STEMI). This study evaluates the independent impact of field triage on treatment delay and long-term outcome, in a large contemporary consecutive population of STEMI-patients treated with routine primary angioplasty.
Methods: From January 2005 to July 2008 1437 STEMI-patients were treated with primary angioplasty in a single invasive center. Complete data on triage, treatment-delay and relevant baseline-variables were collected. Median follow-up time was 1 $\frac{3}{4}$ years. Endpoints were death and the composite of death, re-MI or stroke. Endpoints were collected through national registers and validated via source data.
Results: A total of 585 patients were admitted via field triage and 852 via emergency departments (85% from referral hospital and 15% from the hospital holding the invasive center). Only minor differences were found in baseline- and angiographic variables between the two populations. However, patients admitted via field triage had significantly shorter median symptom-to-balloon time compared to non-field triage (148 minutes; IQR: 110-234 vs. 200 minutes; IQR: 150-305; P<0.001), as well as shorter door-to-balloon time (34 minutes; IQR: 25-58 vs. 101 minutes; 80-135; P<0.01). At the end of follow-up, 7.5% in the field triage group had died compared to 10.9% in the non-field triage group (P=0.03). A total of 11.1% in the field triage group versus 16.5% in the non-field triage group reached the combined end-point of death, re-infarction or stroke (P<0.01). After adjustment for all relevant baseline variables, patients admitted via field triage had reduced risk of reaching the combined end-point: death, re-MI or stroke (HR: 0.73; 95% CI: 0.54-0.98; P=0.038). When all-cause mortality was analyzed separately in the multivariate analysis, we found a trend towards an improved outcome in the field triage group (HR: 0.78; 95% CI: 0.53-1.12; P=0.18).
Conclusions: This study shows that field triage of STEMI-patients to primary angioplasty, significantly reduces treatment delay and improves outcome. This suggests that field triage - if possible - should be implemented in areas where pPCI is the treatment of choice for STEMI-patients.

P1558 Local persistent hypercoagulability after drug-eluting stent implantation: sirolimus-eluting stent vs. paclitaxel-eluting stent

K. Yamaguchi, T. Wakatsuki, T. Niki, K. Kusunose, K. Koshiba, T. Iwase, H. Yamada, T. Soeki, M. Akaike, M. Sata. *Department of Cardiovascular Medicine, Tokushima University Hospital, Tokushima, Japan*

Purpose: We have previously reported more apparent peristrut fibrin deposition in paclitaxel-eluting stent (PES) than sirolimus-eluting stent (SES) and bare metal stent (BMS) in one-human histopathological specimen and also demonstrated increased local coagulative response after SES implantation by measuring plasma prothrombin fragment F1+2 (frF1+2) levels. We compared local hypercoagulability following the implantation of BMS, SES and PES in the chronic phase.
Methods: Thirty-eight patients treated six months earlier with a coronary stenting, with no evidence of restenosis, were studied. Twelve patients had been stented with BMS, 26 had been with drug-eluting stent (DES) [16 SES and 10 PES]. We measured plasma levels of frF1+2 sampled in coronary sinus (CS) and sinus of Valsalva (V). The transcardiac frF1+2 gradients (Δ) were defined as CS level minus V level.
Results: The ΔfrF1+2 was larger in the DES group than in the BMS group (23.4±21.1 vs. 4.7±13.4pmol/l, p=0.03). The ΔfrF1+2 was larger in the PES group than in the SES and BMS group (32.3±24.2 vs. 18.3±19.2, 4.7±13.4pmol/l, p=0.06, p=0.008, respectively). The ΔfrF1+2 significantly correlated with the total stent length in the DES group (r= 0.53, p=0.03).
Conclusions: An increased local coagulative response were observed long term after PES implantation as compared to SES and BMS. These findings might be associated with hypersensitivity reaction to the drug or polymer in the PES group.

CARDIOMYOPATHIES FROM BENCH TO CLINICAL OUTCOMES

P1559 Brain natriuretic peptide and cardiac imaging allow for early detection of heart involvement in Chagas disease

A. Garcia-Alvarez[1], M. Sitges[1], M.J. Pinazo[1], E. Posada[1], S. Poyatos[1], M. Heras[1], M. Azqueta[1], J. Gascon[1], G. Sanz[2].
[1]Hospital Clinico Universidad de Barcelona, Barcelona, Spain; [2]Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain

Purpose: Chagas' disease is becoming a relevant public health problem in Europe as the result of the migratory movements. Our aim was to analyse the potential role of brain natriuretic peptide (BNP) serum levels and cardiac imaging to detect early myocardial damage in patients with Chagas' disease.
Methods: A total of 50 patients were included, 7 patients with incipient cardiac involvement - ECG changes but normal left ventricular (LV) ejection fraction-, 23 patients in the undetermined phase -positive serology but no signs of cardiac involvement- and 20 control individuals. A comprehensive 2D-echocardiography was performed in all cases with diastolic function analysis and image acquisition with color-coded Doppler tissue imaging (DTI) scans for later off-line analysis. DTI peak systolic myocardial velocities (Vel) were obtained from color-coded scans of the LV at the 4 and 2-chamber apical views. Radial 2D-strain data were obtained from the short-axis plane at the level of the papillary muscles.
Results: BNP serum levels, left atrial area, early diastolic mitral annular velocity (Em), mitral deceleration time (DT), Vel of the LV infero-basal segment and myocardial strain at the postero-basal and infero-basal LV segments were statistically different among groups (table). Analysis for trend was statistically significant for Em, DT and infero-basal Vel. Moreover DT was significantly longer in patients in the undetermined phase as compared to control individuals.

BNP and cardiac imaging among groups

	Incipient Chagas heart disease (N=7)	Undetermined Chagas (N=23)	Controls (N=20)	P between groups	P for trend
BNP (pg/ml)	62±96	22±22	11±7	0.01	0.3
LA area (cm^2)	17±1	15±4	13±4	0.04	0.08
Em (cm/sec)	11±3	14±4	16±3	<0.01	0.03
TD (msec)	285±34	220±59	205±43	<0.01	<0.01
Infero-basal Vel (cm/sec)	5.6±2.1	6.2±1	7.2±1.9	0.04	0.05
Infero-basal strain (%)	34±22	73±24	73±21	<0.01	0.9
Postero-basal strain (%)	40±17	71±22	79±20	<0.01	0.4

Conclusion: Early cardiac involvement in Chagas' disease induces a progressive increase in BNP serum levels, diastolic dysfunction and segmental motion abnormalities affecting the basal inferior and posterior LV segments. TD lengthening might be the earliest sign of cardiac involvement in these patients.

P1560 End-tidal carbon dioxide concentration can determine the appropriate recommendation to wean off extracorporeal membrane oxygenation in cardiogenic shock

T. Naruke[1], T. Inomata[1], H. Imai[2], H. Shinagawa[1], T. Koitabashi[1], M. Nishii[1], I. Takeuchi[1], H. Takehana[1], N. Aoyama[1], T. Izumi[1].
[1]Kitasato University, School of Medicine, Department of Cardio-Angiology, Sagamihara, Japan; [2]Kitasato University, School of Medicine, Department of Emergency and Critical Care Medicine, Sagamihara, Japan

Background: Although extracorporeal membrane oxygenation (ECMO) has been widely used for circulatory collapse as a bridge to recovery or to convert to a ventricular assist device, there have been few reports of clinical variables to predict the adequate timing of weaning off ECMO, especially continuously-measurable parameters.
Method & results: We retrospectively investigated consecutive 28 patients supported by ECMO for hemodynamic collapse due to acute coronary syndrome or fulminant myocarditis. The patients were divided into 2 groups based on their clinical outcome regarding whether ECMO could be weaned off leading to recovery (W group; n=20) or not (NW group, n=8). ECMO was weaned according to the criteria of the National Survey of Fulminant Myocarditis. Concerning the W group, univariate analysis showed that only the cardiac index calculated by thermodilution method (CIT, 0.7±0.6 vs. 2.0±0.6 L/min/m^2, P<0.01) and end-tidal carbon dioxide (ETCO2, 11±3 vs. 28±5 mmHg, P<0.01) had significant difference to compare clinical variables between on the time-points of ECMO introduction and of ECMO weaning to the level less than 60% of the maximal flow. The incessant ascending limb in conjunction with ECMO weaning could be observed concerning CIT and ETCO2 in W, but not in NW, shown in representative case in the Figure. Concrete time-points predicting sebsequent recovery could defined only in ETCO2 (R-point), not in CIT, as it increasing more than 5% per 12h and to be maintained at least for the following 24h, prior to the beginning of ECMO weaning.

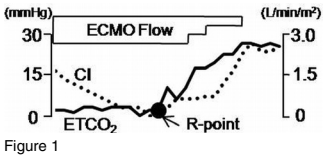


Figure 1

Conclusions: ETCO2 is a useful parameter to estimate hemodynamics continuously and to determine the timing of weaning ECMO at the bedside, presumably indicating proper cardiac function through pulmonary arterial flow independent from the bypassed circuit.

P1561 Cardiac energetic impairment in non-obstructive hypertrophic cardiomyopathy: relation to exercise capacity and dynamic diastolic dysfunction

K. Abozguia[1], T.T. Phan[1], I. Ahmed[1], G. Nallur Shivu[1], A.R. Maher[1], R. Kalra[1], W. Mckenna[2], H. Watkins[3], P.M. Elliott[2], M.P. Frenneaux[1]. *[1]University of Birmingham, Birmingham, United Kingdom; [2]University College London, London, United Kingdom; [3]University of Oxford, Oxford, United Kingdom*

Introduction: Hypertrophic cardiomyopathy (HCM) patients typically exhibit abnormalities of diastolic function thought to be important in the genesis of breathlessness. Previous studies had shown that HCM patients manifest impaired cardiac energetics. Accordingly, we hypothesized that impaired cardiac energetics may lead to diastolic dysfunction in symptomatic HCM patients.
Methods: 51 symptomatic non-obstructive HCM patients (39 male and mean age of 54 years) and 35 age matched controls were enrolled. All participants had an ECG, echocardiogram and cardiopulmonary exercise test. We measured radionuclide indices of left ventricular diastolic filling (Time To Peak Filling [TTPF] and normalised for heart rate Time To Peak Filling Rate [nTTPF]) at rest and during submaximal exercise (50% of heart rate reserve). Myocardial energetic status (PCr/γ ATP ratio) was measured by 31P magnetic resonance spectroscopy (MRS) using a Philips 3 Tesla scanner.
Results: HCM patients exhibited marked exercise limitation vs healthy controls (peak VO2 24±6 vs 38±8 ml kg^{-1} min^{-1}, p<0.0001), and reduced PCr/γATP ratio (1.41±0.48 vs 2.26±0.59, p<0.0001). Resting nTTPF was similar in patients and controls. nTTPF fell during submaximal exercise in controls (0.18±0.08 to 0.16±0.08 sec), but increased in patients (0.17±0.07 to 0.32±0.09 sec), (p<0.0001). PCr/γATP ratio inversely correlated with nTTPF during exercise (r= -0.38, p=0.01). These correlations remained significant after excluding patients on beta blockers.
Conclusion: We show here symptomatic HCM patients have impaired myocardial energetic which correlates significantly with diastolic dysfunction during submaximal exercise. Augmenting myocardial metabolism may have a potential role in the management of these symptomatic patients.

P1562 Cardiomyopathy in the course of nucleopathies, echocardiographic and clinical features

M. Marchel[1], A. Madej[2], J. Kochanowski[1], R. Steckiewicz[1], K.J. Filipiak[1], I. Hausmanowa-Petrusewicz[2], G. Opolski[1]. *[1]Warsaw Medical University, Warsaw, Poland; [2]Polish Academy of Science, Warsaw, Poland*

Purpose: Emery-Dreifuss muscular dystrophy (EDMD) is characterized by musculoskeletal abnormalities, accompanied by cardiac defects. Sudden cardiac death is the most common mechanism of death in this group. The genetic background of EDMD is a mutation in nuclear proteins: lamin A/C and emerin. The aim of the study was to analyse the clinical picture and to characterize the left ventricular (LV) function in EDMD pts.
Methods: The study comprised 25 pts with genetically confirmed EDMD (17 with an X-linked inheritance [defect in the STA gene, emerinopathy] and 8 with an autosomal dominant form [defect in LMNA, laminopathy]) as well as 25 healthy volunteers. All pts were subjected to echocardiography with the assessment of myocardial velocities, strain and strain rate. We determined plasma levels of: troponin I, CK-MB, myoglobin, BNP, NT-proBNP, and NT-proANP.
Results: The mean age was 29,3±11,5. (5/25, 20%) pts presented HF symptoms. (8/25, 32%) pts had ventricular arrhythmias, (10/25, 40%) atrial fibrillation/flutter. (17/25, 68%) had a pacemaker implanted because of advanced AV conduction defects. The mean LV ejection fraction (LVEF) was 51,3±9,1% and 65,5±2,6 for EDMD pts and for controls respectively (p<0,0001). Significantly higher E/E' (9,4±5,5 vs. 6,0±0,8; p=0,01) in comparison to the controls were documented. Moreover, systolic septal myocardial velocities of the mitral ring longitudinal motion were lower (7,4±1,8 vs. 8,9±0,9; p=0,001) and perfectly correlated with the EF (R=0,88, p<0,0001). NT-proBNP and NT-proANP levels were significantly higher in EDMD in comparison to the controls (161±232 vs. 41,1±31,5; p=0,002 for NT-proBNP) and (1,42±0,96 vs. 0,75±0,15; p=0,0002 for NT-proANP). The same concerned the plasma concentrations of troponin I (0,01±0,01 vs. 0,00±0,00; p=0,05), CK-MB (18,5±15,0 vs. 1,00±0,08; p=0,0001) and myoglobin (273±146 vs. 37,2±21,0; p=0,0001). The cut-off values for the prediction of systolic dysfunction in EDMD pts were determined by ROC analysis. (Swave≤7,65 cm/s; ε≤5,94%; SR≤0,7 1/s and troponin I>0,0 ng/ml; NT-proBNP>54,0 ng/ml; NT-proANP>1,59 ng/ml). BNP levels higher that 13,8ng/ml proved to be the best predictors of significant diastolic dysfunction (E/E'>10, 100% sensitivity, 86% specificity; p<0,0001).
Conclusions: Atrioventricular conduction defects (68%), subclinical LV systolic dysfunction (28%) as well as diastolic dysfunction (24%) are common in EDMD pts. Natriuretic peptide and troponin I measurements and TDI technique may be useful tools for the early assessment of systolic dysfunction.

P1563 Electrocardiographic changes in "apical ballooning" versus anterior myocardial infarction

B. Schneider, K. Peters, J. Stein. *Klinik fuer Kardiologie, Sana Kliniken, Luebeck, Germany*

Background: Left ventricular apical ballooning (AB) is characterized by electrocardiographic (ECG) changes and apical akinesia mimicking anterior myocardial infarction (AMI) in the absence of coronary stenoses.
This study aimed to assess if the ECG could reliably differentiate between these two syndromes with a similar clinical presentation.
Methods: Among 2086 patients with an acute coronary syndrome undergoing coronary angiography, 33 patients (1.6%) with AB were identified (29 f, 4 m, median age 77 years). These AB patients were compared to 28 consecutive age and sex matched AMI patients undergoing successful PCI of the LAD with similar findings on LV angiography.
Results: AB patients were admitted to the hospital later after symptom onset (21 [12–44] vs 5 [3–12] hours; p <0.001). On the admission ECG, the number of leads with ST-segment elevation (4 [3–6] vs 5 [5–7] leads; p=0.005) and the sum of the level of ST-segment elevation (0.7 [0.5–0.9] vs 0.9 [0.7–1.5] mV; p=0.002) were significantly greater in AMI. Reciprocal ST-segment depression was similar (27% vs 54%; p=ns). During the following days, AB patients displayed significantly more leads with T-wave inversion (8 [8–9] vs 6 [5–8] leads; p<0.001), and the sum of the level of T-wave inversion (2.9 [2.2–4.6] vs 1.4 [0.9–2.3] mV; p<0.001) was larger. T-wave inversion was similar in I, avL and the precordial leads (V2-V5). AB patients, however, displayed T-wave inversion also in lead II (74% vs 22%; p<0001), III (34% vs 4%; p=0.004) and aVF (51% vs 11%; p=0.001), respectively. The QTc interval was significantly longer in AB, being maximal in AB on day 2 and in AMI on day 3 (515 [482–543] vs 458 [435–484] ms; p<0.001). An abnormal Q wave at presentation was more frequent in AMI (21% vs 79%; p<0.001) and persisted in half of AMI patients but was not longer present in AB at discharge (0% vs 61%; p<0.001). Ventricular tachycardia was not significantly different (2% vs 14%; p=ns). Atrial fibrillation was identified only in AB (21% vs 0%; p=0.013). The ECG completely normalized in AB but only in 1 AMI patient (p<0.001). A formula considering ST-segment elevation on admission and T-wave inversion as well as Q waves during follow-up allowed discrimination between AB and AMI with a sensitivity of 93% and a specificity of 86%.
Conclusion: ECG findings in AB are significantly different from those in AMI. At initial presentation, the extent of ST-segment elevation and the number of abnormal Q waves are greater in AMI. During follow-up, no Q wave, a longer QTc interval and a greater extent of T-wave inversion are typical findings in AB.

P1564 A longitudinal clinical follow-up of tako-tsubo cardiomyopathy

R. Proietti[1], P. Silva[2], A. Compare[3], E. Grossi[4]. *[1]Sant'Andrea Hospital, Vercelli, Italy; [2]Niguarda Hospital, Milano, Italy; [3]University of Bergamo, Bergamo, Italy; [4]CDI, Milano, Italy*

Notwithstanding the fact that tako-tsubo cardiomyopaty (TTC) or apical ballooning syndrome (ABS) can be characterised by acute heart failure, the short term prognosis of this syndrome is almost always favourable. Currently, few reports are available in literature regarding the long term prognosis of this syndrome and of those available most of them have been retrospectively carried out. Our research consisted in a longitudinal clinical follow-up of a cohort of TTC patients.
We enrolled 37 patients who had been diagnosed with a TTC which satisfied the Mayo Clinic criteria for ABS. Follow-up was periodically performed including ambulatory visits. Median follow-up was 54±42 months.
The male to female ratio was 1:9; mean patient age was 68 (59-75) years. Cardiovascular risk factors were distributed as following: 6% had diabetes, 36% hyperlipidemia, 31% a family history, 14% smoking and 75% hypertension. After hospital discharge patient therapy included: ASA 72%, β-blockers 56%, statins 28% and ACE-inhibitors were 50%. In the considered period four patients belonging to our casistica died, though none of cardiovascular pathologies. 7 patients required hospital admissions for other diseases (3 for oncologic pathology, 1 for cerebral ictus, 2 for abdominal surgery, 1 for thyroid disease). We observed no cases of recurrent apical ballooning syndrome.
In our cohort 24 patients reported recurrence of chest pain (group A) of variable intensity after discharge, while 13 patients did not refer chest pain or other symptoms (group B). The frequency and degree of chest pain was highly variable and difficult to classify. All patients referred that their chest pain was associated more with stressful events than with physical exercise. Most patients referring recurrence of chest pain reported other associated symptoms such as tiredness, palpitation and dyspnea. In 14 cases chest pain was so intense that it lead to at least one emergency department admission, and 2 cases resulted in hospital admissions (no angiogram was performed). We found no significant differences in home therapy and the distribution of cardiovascular risk factors between groups A and B of our casistica.
We report in our cohort of patients with tako-tsubo syndrome a high mortality (~11% at eight years) and morbidity. Specifically, our survey shows that most tako-tsubo patients (64%) continue to refer chest pain recurrence after the main event; furthermore, home therapy seems not able to provide a useful prevention against chest pain recurrence. Thus, these results suggest that a great effort should spent on the long-term management of ABS.

P1565 Tako-tsubo cardiomyopathy and chronobiology

R. Citro[1], M. Previtali[2], O. Vriz[3], M.M. Patella[4], C. Astarita[5], C. Armentano[6], G. Provenza[1], G. Gregorio[1], E. Bossone[7], R. Manfredini[8] on behalf of Tako-Tsubo Italian Network. *[1]San Luca Hospital, Vallo Della Lucania (Sa), Italy; [2]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3]Division of Cardiology ASS4, San Daniele Del Friuli (Pn), Italy; [4]Santa Maria Hospital, Terni, Italy; [5]Santa Maria Hospital, Sorrento (Na), Italy; [6]Ospedale 'Guglielmo Da Saliceto', Piacenza, Italy; [7]CNR-Istituto di Fisiologica Clinica, Lecce, Italy; [8]Dept Clin Exp Med University of Ferrara, Ferrara, Italy*

Background: Aim of the study was to evaluate the occurrence of seasonal, circadian and circaseptan (weekly) variation in the onset of tako-tsubo cardiomyopathy (TTC).
Methods: 112 consecutive patients (pts; 105 females, mean age 63.58±10.55 yy), from January 2002 to December 2008, that fulfilled Mayo Clinic diagnostic criteria for TTC were enrolled. The day of symptom onset was categorized both into 12 one-month intervals and 4 three-month intervals for seasonal analysis, into four six-hour intervals (night: 00:00-05:59 AM, morning: 06:00-11:59 AM, afternoon: 12:00-17:59 PM, evening: 18:00-23:59 PM) for circadian analysis and into six one-day intervals (according to day-of-week) for circaseptan analysis. The distribution of symptom onset within the 4 three-month periods, within the four six-hour periods and by day of week was tested for uniformity in the overall population by the chi-square test for goodness of fit. The chronobiological analysis was performed by applying a partial Fourier analysis to the time series data. Significance levels were set at $p<0.05$.
Results:-The final group included 112 pts for seasonal and weekly analysis, and 102 (10 cases were excluded due to the lack of data) for circadian analysis, respectively. TTC was most frequent in summer (n= 65, 58.0%) and least so in autumn (n= 15, 13.4%) (chi-square= 65,29, $p < 0.001$) As for monthly distribution, the peak number of TTC occurred in July (n= 22, 19.6%) and the trough in March (n= 2, 1.8%), being the difference statistically significant ($p< 0.001$). Inferential chronobiological analysis identified a significant annual rhythmic pattern in TTC, with the peak in late July, and 95% Confidence Limits in July-August both for total cases (PR 67.5%; MESOR 9.37±1.28; Amplitude 7.83±1.82, p = 0.006). TTC was most frequent in morning (n= 42, 41.2%) and least so in night (n= 11, 10.8%) (χ^2= 18,24, $p < 0.001$) TTC was most frequent on Monday (n= 21, 18.8%) and least so on Saturday (n= 11, 9.8%), with a trend not statistically significant between maximum and minimum value (chi-square = 3,15, p= 0.078). Inferential chronobiological analysis identified a significant weekly rhythmic pattern for females, with the peak on Monday (PR 81.0%; MESOR 14.86±0.66; Amplitude 3.88±0.94, p = 0.036).
Discussion: Our data indicate a seasonal, circadian, and weekly variation in the onset of TTC in Caucasian pts. characterized by a summer, morning and Monday preference respectively. Whereas the morning and Monday pattern resemble that of acute myocardial infarction, the circannual rhythm is opposite.

P1566 Fibrosis in left ventricular hypertrophy: cardiac magnetic resonance accurately distinguishes myocardial infarction from myopathic fibrosis

S.P. Page, L.A. Mcgill, T.R. Burchell, A. Mathur, C. Davies, M.A. Westwood, P.G. Mills, S.A. Mohiddin. *The London Chest Hospital, London, United Kingdom*

Background: Tissue characterisation by cardiac magnetic resonance (CMR) using delayed gadolinium enhancement (DGE) identifies areas of focal myocardial fibrosis. Myocardial infarction (MI) due to coronary artery disease (CAD) results in sub-endocardial or transmural DGE. Different patterns of DGE (mid-myocardial or patchy) are often found in left ventricular (LV) hypertrophy, particularly in hypertrophic cardiomyopathy (HCM). We sought to determine whether DGE distribution reliably distinguishes between patients with LV hypertrophy and prior MI and those with LV hypertrophy alone.
Methods and Results: We studied 72 consecutive patients (58 male, mean age 62±13 years) with left ventricular (LV) hypertrophy (maximal LV wall ≥ 13mm, mean 19 mm ±5, range 13-34) in whom CAD status was defined. DGE imaging was performed using standard CMR techniques and any abnormalities defined as MI type (sub-endocardial or transmural) or non-MI type (mid-myocardial or patchy). An asymmetrical pattern of hypertrophy was found in 62, 7 were concentric and 3 apical. At angiography, 26 (36%) had obstructive CAD. DGE was detected in 45 patients (63%); MI type only in 12, non-MI in 29 and both types in 4. Although more frequent in CAD patients, the presence of DGE did not reliably distinguish between CAD and non-CAD LVH (χ^2 = 3.3, p=0.07; specificity 47%, sensitivity 74%, NPV 67%, PPV 56%). However, the MI type pattern of DGE was highly specific for obstructive CAD (χ^2 23, $p< 0.0001$; specificity 100%, sensitivity 47%, NPV 68%, PPV 100%,). All 4 patients with both MI and non-MI DGE had HCM and CAD.
Conclusions: Both MI and non-MI DGE patterns are frequently detected in LVH patients. In such patients, including those with HCM, DGE patterns accurately distinguish between LV fibrosis following MI from that resulting from a cardiomyopathic process.

P1567 The non-pharmacological relief of left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy

R. Maczynska-Mazuruk, L.S. Chojnowska, K. Kukula, M. Klopotowski, M. Dabrowski, B. Kusmierczyk, M. Polanska, M. Demkow, A. Witkowski, W. Ruzyllo. *Institute of Cardiology, Warsaw, Poland*

Purpose: Approximately 25% of patients with hypertrophic cardiomyopathy (HCM) have dynamic left ventricular outflow tract obstruction (LVOTO) at rest with a gradient 30 mmHg or more. Among drug-refractory, symptomatic patients with HCM and significant haemodynamic outflow tract obstruction non-pharmacological treatment can be executed. There are three methods to relief LVOTO: surgical myectomy (SM) – "gold standard", alcohol septal ablation (ASA) and dual-chamber pacing with short A-V delay (AV). We analyzed the prognostic implications of non-pharmacological (NPH) treatment of LVOTO in HCM population.
Methods: Among 736 consecutive HCM patients (54% male, age at diagnosis: 33,6±18,3 years) LVOTO with a gradient ≥30 mmHg occurred in 263 HCM patients. In population of 141 patients with HCM and LVOTO a NPH gradient reduction to <30 mmHg was achieved. All patients were followed for 11,8±7,2 years (1 to 32 years), subgroup with NPH treatment were followed for 7,55±5,1 years (1 to 22 years). Factors predisposing to SCD or SCD equivalents [cardiac arrest (CA)/appropriate intervention of cardioverter-defibrillator (aICD)] were analyzed. Logistic regression was used to assess independent risk factors of SCD development. Long-rank test was used to evaluate survival in LVOTO and non-LVOTO group. ORs and 95% CIs were calculated using of Cox proportional-hazard regression.
Results: Long-term NPH gradient reduction obtained a 100 HCM patients (SM-23%, ASA-51%, AV- 26%). In logistic regression NPH gradient reduction <30 mmHg was an independent negative risk factor for SCD (OR 0,0999, 95%CI 0,022-0,44, p=0,0024).
Subgroup with long-term NPH gradient reduction had rare SCD when compared with group with LVOTO gradient ≥30 mmHg. (log rank p=0,021). Also subgroup with long-term NPH gradient reduction had rare SCD/CA/aICD when compared with group with LVOTO gradient ≥30 mmHg. (log rank p=0,0442).
During follow up subgroup with long-term NPH gradient reduction and subgroup without significant LVOTO did not significantly differ in risk of SCD (log rank p= 0,2) as well as in risk of SCD/CA/aICD (log rank p=0,36).
Conclusions: Non-farmacological gradient reduction is associated with a marked reduction risk of SCD as well as risk of SCD/CA/aICD. In group with long term gradient reduction <30 mmHg the risk of SCD and SCD/CA/aICD is similar to the risk in group without significant LVOTO.

P1568 Impairment of Von Willebrand factor after exercise echocardiography: an acute effect of latent obstruction in patients with hypertrophic cardiomyopathy

T. Le Tourneau, A. Millaire, N. Lamblin, S. Susen, M. Richardson, A.S. Polge, E. Van Belle, C. Bauters, B. Jude, G. Deklunder. *Hopital Cardiologique CHRU de Lille, Lille, France*

Background: Von Willebrand factor (VWF) is sensitive to high shear stress conditions. Baseline obstruction impairs VWF in hypertrophic cardiomyopathy (HCM). We sought to assess the acute effect of exercise-induced obstruction on VWF, and the determinants of obstruction and VWF impairment.
Methods: Outflow obstruction was evaluated through rest and exercise echocardiography in patients with HCM. Sixteen patients (44±16 years, 14 males) with latent obstruction (baseline peak gradient < 30 mmHg and exercise peak gradient ≥ 30 mmHg) were compared with 16 patients without obstruction. Blood was sampled before and after exercise to assess VWF.
Results: Baseline median [25-75th percentiles] peak gradient was 8[6-11] mmHg but rose up to 32[17-104] mmHg with exercise. At rest, VWF function was slightly impaired in patients with latent obstruction. VWF-collagen binding activity to antigen ratio (VWF:CB/Ag) and the percentage of high molecular weight multimers of VWF (%HMWM) did not change after exercise in the non obstructive group but were lowered in patients with latent obstruction (both p=0.003). In multivariate analysis incomplete SAM at rest was the strongest independent predictor of latent obstruction (β=0.76, $p<0.0001$) and of %HMWM drop (β=-0.70, $p<0.0001$). %HMWM after exercise tightly correlated with exercise peak gradient (r=-0.78, $p<0.0001$) and the persistence of obstruction during the recovery period (r=-0.67, p=0.005).
Conclusion: Outflow peak gradient rise during exercise induces a rapid cleavage of VWF multimers in patients with HCM and latent obstruction. Multimers proteolysis is related to both the magnitude of peak gradient or shear stress during exercise and the persistence of obstruction during recovery. The greater effect of persistent obstruction after exercise on VWF suggests a graded biological effect of latent obstruction related not only to the maximum peak gradient but also to the duration of obstruction after exercise. This result deserves further consideration not only in the setting of the physiology of VWF, but also for the evaluation and management of patients with an obstructive form of HCM.

P1569 Immunotherapy of beta1-receptor antibody-induced cardiomyopathy with epitope-mimicking cyclopeptides: specific targeting of the B cell compartment

M. Merkl[1], V. Kocoski[1], N. Beyersdorf[1], M. Mueller[2], V. Boivin[2], T. Kerkau[1], T. Huenig[1], M.J. Lohse[2], R. Jahns[3]. *[1]Institute of Virology and Immunobiology, Wuerzburg, Germany; [2]Institute of Pharmacology and Toxicology, Wuerzburg, Germany; [3]Department of Internal Medicine I, Cardiology, Wuerzburg, Germany*

Stimulating antibodies (Abs) directed against the 2nd extracellular loop of the beta1-adrenoceptor (beta1-ECII; 100% homology human/rat) cause dilated immune-cardiomyopathy (DiCM) in rats. In this model we analyzed the immunologic effects of a recently developed antibody-neutralizing ECII-homologous 25 amino-acid (AA) cyclopeptide (ECII-25CP) and a novel 18AA ECII-cysteine/serine CP-mutant (ECII-18CPm), and compared the CP-effects on the immune-system with those of their corresponding linear counterparts (ECII-25LIN and ECII-18LINm).

N=40 Lewis rats were monthly immunized with beta1-ECII/GST fusion-proteins. Nine months after induction of stimulating beta1-ECII-Ab (determined by FRET-assay) and DiCM, the rats were monthly injected with 1.0 mg/kg of (a) ECII-25CP (n=10), (b) ECII-25LIN (n=5), (c) ECII-18CPm (n=10), (d) ECII-18LINm (n=5), or (e) received no specific treatment (pos. control, n=10). N=10 neg. control rats were injected with 0.9%NaCl. Beta1-ECII-Ab titers were checked by ELISA. At study-end cardiac function was assessed by LV-catheterization (month 21); then, the heart and inner organs were excized. To analyze the effects of the peptide-variants on the immune-system we determined size & function of the CD4+ T-cell compartment by in vitro antigenic recall assay, and frequency of ECII-specific memory B-cells by ELISPOT & FACS analysis. B- and T-cells in 2μm-sections of heart- and spleen were counterstained by anti-CD45RA and anti-CD3.

Treatment with either ECII-25CP or -18CPm significantly reduced beta1-ECII–Ab titers and reversed the DiCM-phenotype. The in vitro recall response of CD4+ T-cells to the fusion-protein used as immunogen was not reduced after treatment with linear or cyclic peptides. In contrast, the frequency of ECII-Ab specific memory B cells was significantly reduced in Ab-pos. rats treated with ECII-25CP or -18CPm, but not in those receiving linear ECII-peptides (ECII-Ab specific B-cells/1000 IgG-producing cells; untreated vs. ECII-25CP/-18CPm: 1.84$\pm$0.5 vs. 0.69$\pm$0.3/0.47$\pm$0.2; $p<0.01/p<0.003$). By immunohistochemistry we did not reveal any relevant B- or T-cell infiltration, neither in hearts from Ab-pos. untreated rats, nor in Ab-pos. animals treated with cyclic or linear ECII-peptides.

We conclude that ECII-homologous 25AA- or mutant 18AA-CP besides scavenging beta1-ECII-Abs directly from the circulation also target autoreactive memory B cells, resulting in a stable reduction of stimulating beta1-ECII-Ab and reversal of Ab-induced DiCM in vivo. Therefore, our novel approach might be also useful to combat anti-beta-ECII-Abs in human DCM.

P1570 National keshan disease surveillance 2006

T. Wang, Q. Li, C. Jiang, H. Wei, J. Hou, B. Xu, H. Feng, L. Zhang. *Institute of Keshan Disease, Harbin Medical University, Harbin, China, People's Republic of*

Keshan disease (KD) is an unknown cause cardiomyopathy mainly occurring in mainland China. National KD surveillance program started in 1990. Purpose The aim is to get information on KD prevalence and incidence of the disease areas with high historical KD incidence, and the factors associated with KD occurrence in order to provide evidence for the Ministry of Health to make the national policy on KD control. Methods The methodology of KD surveillance is an annual cross-sectional survey of the residents of the sentinels (villages) with high historical incidence in the disease provinces by cluster sampling. KD cases are diagnosed by specialists in accordance with the Standard of Diagnosis of Keshan Disease. Hair and food selenium levels were also measured. Results 27 surveillance sites in 12 provinces reported their surveillance data. 4 provinces did not. The total number of people surveyed was 13,090. 378 KD case were found, 6 subacute KD cases in Sichuan province, 78 chronic KD cases, and 295 latent KD cases. Of the 6 subacute KD cases, 1 was new, the other five were old ones, and 4 were found in Mianning county, where the subacute KD detection rate of the surveillance site was 0.66% (4/606). The national KD prevalence was 2.85%, and the 95% confidence interval (95% CI) was 2.56%, and 3.14%. The national prevalence rates of chronic and latent KD were 0.6% (95% CI: 0.47%, 0.73%) and 2.25% (95% CI: 2.00%, 2.50%) respectively. Based on the population of 7,500,000 people at risk in KD areas, the estimated number of KD patients in China in 2006 was 2,137,500 (95% CI: 1,923,708, 2,351,292). Of them, 450,500 (95% CI: 350,776, 549,224) were chronic KD patients, and 1,687,500 (95% CI: 1,496,955, 1,878,045) were latent KD patients. Inner Mongolia province had the highest chronic KD prevalence (2.39%), followed by Jilin (2.3%), and Sichuan (1.82%). These provinces had been the most sever disease areas. The chronic KD prevalence of Yunnan province, one of the former sever disease area in the southwest was only 0.14%, much lower than the national average level. Lichuan county of Hubei province and Xicang county of Sichuan province did not detect any chronic KD case. The average level of hair selenium of the people sampled was 0.3282 mg/kg (mean). The average selenium level of the foods sampled was 0.0148 mg/kg (mean). Conclusions KD is still a serious public health issue in KD areas. Priorities of KD control should be on prevention by selenium supplementation in Sichuan, and providing financial and medical aid to chronic KD patients, the most socio-economically disadvantaged population.

CHRONIC PULMONARY INTERVENTION

P1571 Epidemiology of pulmonary arterial hypertension: comparison between clinical trials and registries

A. Manes, L. Negro, M. Palazzini, A. Marinelli, E. Leci, S. Gambetti, E. Conficoni, M.L. Bacchi-Reggiani, A. Branzi, N. Galie. *Institute of Cardiology- University of Bologna, Bologna, Italy*

Purpose: The efficacy of pulmonary arterial hypertension (PAH) approved drugs has been currently assessed in 23 randomized controlled trials (RCTs) published up to October 2008. It is not clear if the characteristics of the patients included in the RCTs are comparable with those of the patients assessed in the common clinical practice. We compared the demographic, clinical, functional and hemodynamic baseline characteristics of the patients enrolled in RCTs with those included in multicenter registries (REGs).

Methods: RCTs were searched in the Medline database from January 1990 to October 2008. The data of three recent multicenter REGs were retrieved either from the published manuscripts (French and Scottish REGs) or from the abstract presentation (REVEAL-USA REG). Weighed means were utilized to combine multiple studies data.

Results: Patients included in the RCTs and in the REGs were 3199 and 2548 respectively. Average age and female gender prevalence were 47.5 years and 77% in RCTs as compared to 51.0 years and 74% in REGs, respectively. Idiopathic PAH and PAH associated with connective tissue diseases were the most frequent etiologies: 63% and22% in RCTs, 53% and 23% in REGs, respectively. WHO functional class III and IV patients were 72% in RCTs and 60% in REGs. Mean pulmonary arterial pressure, and cardiac index were 55 mmHg and 2.5 l/min/m^2 in RCTs and 53 mmHg and 2.5 l/min/m^2 in REG, respectively. Six-minute walk distance was 345 m in RCTs and 357 in REGs.

Conclusions: Patients included in RCTs appear to be younger, more frequently with idiopathic PAH and in WHO functional class III and IV and with a reduced six-minute walk distance as compared to subjects included in REGs. In contrast, baseline hemodynamics are remarkably similar.

P1572 Epidemiology of pulmonary hypertension in Spain: preliminary analisys of the Spanish pulmonary hypertension registry (REHAP)

M.C. Jimenez Lopez Guarch[1], P. Escribano[1], A. Roman[2], J.A. Barbera[3], M. Lopez-Meseguer[2], I. Blanco[3], F. Garcia-Hernandez[4], P. Morales[5], T. Subirana[6], J. Segovia[7] on behalf of Spanish Pulmonary Arterial Hypertension Registry. *[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [3]Hospital Clinico Universidad de Barcelona, Barcelona, Spain; [4]Hospital Virgen del Rocio, Seville, Spain; [5]Hospital La Fe, Valencia, Spain; [6]Hospital de Sant Pau, Barcelona, Spain; [7]Hospital Universitario Puerta de Hierro, Madrid, Spain*

There is a lack of data regarding the epidemiology and clinical management of pulmonary hypertension (PH) in Spain. A prospective PH registry was designed to analyze the prevalence, incidence and clinical management issues of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), and to compare baseline data between both entities.

Methods: Voluntary reporting of consecutive adult patients (>14 y) diagnosed of PAH or CTEPH was conducted between July 1st, 2007 to June 30, 2008. PH was defined as a mean pulmonary artery pressure (PAP) >25 mm Hg, pulmonary vascular resistance (PVR) >3 Wood Units (WU) and pulmonary capillary wedge pressure <15 mm Hg. Physicians from 31 centers reported cases, although 75% of the data were collected from the 5 largest PH centers.

Results: A total of 723 patients have been registered (567 prevalent and 156 incident cases). 598 patients had PAH (idiopathic, 41%; connective tissue disease, 18%; congenital heart disease, 19%; HIV infection, 9%; portal hypertension, 6%; and toxic oil syndrome, 3%). 125 patients had CTEPH. Characteristics of both PH groups are shown in the Table.

Comparison between PAH and CTPH

	Age (yrs)/ % female	NYHA III-IV	6MWD (m)	mPAP (mmHg)	CI lpm/m^2	Prevalence (PMP)	Incidence (PMP/yr)
PAH (N=598)	46$\pm$17*/73%*	68%	378$\pm$116*	51$\pm$15*	2.7$\pm$0.8*	15.3	3.15
CTPH (N=125)	62$\pm$15/57%	71%	328$\pm$112	45$\pm$11	2.4$\pm$0.6	3.2	0.89

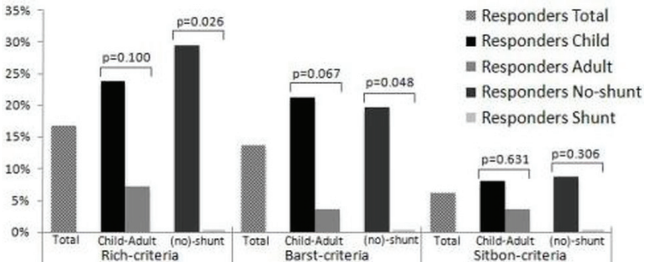
*$p<0.05$. 6MWD: six-min walk distance; PMP: per million adult population.

Conclusion: 1) Epidemiological data reported in the Spanish REHAP registry on PAH are consistent with other national registries. 2) Patients with PAH are still diagnosed in advanced functional class. 3) The REHAP registry is the first to report data on CTEPH epidemiology, showing that CTEPH patients are older and diagnosed at an even more advanced clinical stage

P1573 Prevalence and prognostic value of acute pulmonary vasodilator response in children and adults with pulmonary arterial hypertension

J.M. Douwes, R.L.E. Van Loon, E.S. Hoendermis, M. Talsma, R.M.F. Berger. *University Medical Center, Groningen, Netherlands*

Purpose: Investigate the prevalence and prognostic value of acute pulmonary vasodilator response in children and adults with pulmonary arterial hypertension (PAH).
Methods: Sixty-six PAH patients (38 children,28 adults; 20 with and 46 without post-tricuspid shunt) underwent acute pulmonary vasodilator challenge. Responders were identified according to three currently used criteria: 1) Rich-criteria,1992: decrease in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) of ≥20%; 2) Barst-criteria,1986: decrease in mPAP of ≥20%, unchanged or increased cardiac index and decreased or unchanged pulmonary to systemic vascular resistance ratio (PVR/SVR); 3) Sitbon-criteria,2005: decrease in mPAP of ≥10mmHg reaching a mPAP ≤40mmHg and an increased or unchanged cardiac output. We evaluated the prevalence of acute response in all patients, separately in children versus adults and separately in patients with versus without post-tricuspid shunt. Next, we analyzed whether responders had better survival.
Results: The prevalence of acute pulmonary vasodilator response in all groups depended on the criteria used (Figure). "Sitbon-responders" tended to have better survival than non-responders (5-year survival 100% vs 77.4% respectively, p=0.29), whereas "Rich- and Barst-responders" showed no difference in survival compared to non-responders. Lower PVR/SVR and mPAP/mSAP ratio both at baseline and after vasodilator challenge predicted improved survival.



Acute pulmonary vasodilator response

Conclusions: The prevalence of acute pulmonary vasodilator response is highly dependent on the criteria used, appears to be higher in children, but absent in patients with a post-tricuspid shunt. Only responders according to the strict Sitbon-criteria showed improved survival. PVR/SVR and mPAP/mSAP ratio appear good predictors of survival in PAH.

P1574 French pulmonary arterial hypertension registry in children: 2-year follow-up data

A. Fraisse[1], X. Jais[2], J.M. Schleich[3], S. Di Filippo[4], P. Maragnes[5], M. Beghetti[6], D. Tardy[7], C. Dauphin[8], F. Godart[9], D. Bonnet[10]. *[1]AP-HM - Hopital de la Timone, Marseille, France; [2]AP-HP - Hopital Antoine-Beclere, Clamart, France; [3]Hôpital Pontchaillou, Rennes, France; [4]Hopital Louis Pradel, Lyon, France; [5]Hôpital Côte de Nacre, Caen, France; [6]Hopitaux Universitaires de Geneve, Geneva, Switzerland; [7]Actelion Pharmaceuticals France, Paris, France; [8]Gabriel Montpied Hospital, Clermont Ferrand, France; [9]Hopital Cardiologique CHRU de Lille, Lille, France; [10]AP-HP - Hopital Necker, Paris, France*

Purpose: Pulmonary arterial hypertension (PAH) is a devastating disease with poor survival but there are limited data describing its impact in the paediatric population. The objectives of this national prospective registry were to collect clinical and epidemiological data and to investigate the outcome of children with PAH.
Methods: All consecutive patients <18 years with PAH seen in 16 referral PAH centres in France were included and evaluated after 1 and 2 years of follow-up for WHO functional class (FC), 6-minute walk distance (6MWD) and quality of life (QoL; CHQ-PF50 questionnaire). Persistent pulmonary hypertension of the newborn and PAH due to congenital heart disease (CHD) were excluded.
Results: Fifty patients were included between May 2005 and June 2006. Mean age at diagnosis was 8.7±5.4 years and male/female ratio was 1/1. The prevalence of pediatric PAH was 4.2 cases/million. A history of prematurity, cancer and major surgery was noticed in respectively 19%, 6% and 4% of patients. At inclusion, 28% of patients were in WHO FC III or IV. Aetiology of PAH was idiopathic in 60%; familial in 10%, associated with but not due to CHD in 24%, related to connective tissue disease in 4% and to portal hypertension in 2%. Nine patients (18%) died during the 2-year follow up. Survival estimates at 1 and 2 years were 86% and 82%. Seventy three percents of patients improved or did not change WHO FC (n = 44). Patients remained stable regarding 6MWD (n = 25), hemodynamics (n = 11), and QoL (n = 19). During the 2-year follow-up, combination of PAH-specific therapies was increasingly prescribed (44% patients vs. 22% at inclusion).
Conclusions: This first national paediatric registry showed (1) the presence of multiple PAH aetiologies in children, that could be different from those seen in adults, (2) the association with other co-morbidities, and (3) the stabilization or even improvement in patient's condition with the therapeutic management recommended in the current era.

P1575 Changing survival in connective tissue disease associated pulmonary arterial hypertension

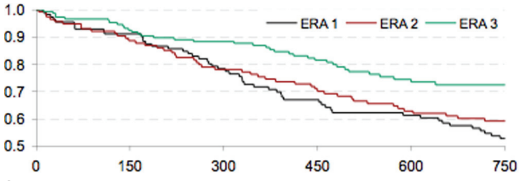
C.J. Valerio, C. Handler, C. Das, A. Gallimore, C.E. Denton, J.G. Coghlan. *Royal Free Hospital, London, United Kingdom*

Purpose: To establish the improvements in survival seen in connective tissue disease associated pulmonary arterial hypertension (CTD-PAH) & look for possible causes.
Methods: Patients with confirmed pulmonary arterial hypertension on right heart catheterisation (at rest only) in association with connective tissue disease were identified from the royal free hospital database. Patients were grouped by treatment era at time of diagnosis: era 1, IV prostanoid therapy, includes diagnoses made before the end of 2001, era 2, early oral therapy 2002-2004 inclusive, and era 3, modern regimens using combination oral therapy, from 2005-2007. Censor point for survival analysis by the log rank test was 750 days.
Results: See graph & table.

Summary data by treatment era

	N	mPAP (mmHg)	PVR (dynes/s/cm^5)	6MWD* (m)	WHO FC II/III/IV	SSc %	FVC* %	DLco* %	1-year survival	2-year survival
Era 1	112	41.4	720	–	23/60/29	95	77.1	41.3	72%	54%
Era 2	114	40.7	699	216	18/59/37	82	74.4	38.9	75%	59%
Era 3	148	40.4	629	265	18/99/31	71§	83.5	43.2	87%†	72%†

†p<0.05 (log rank) compared with Era 1 & Era 2. §p<0.05 (chi-squared) compared with Era 1 & Era 2 combined. *Incomplete data set.



Survival plots by treatment era

Conclusions: Survival in CTD-PAH has improved compared with previous treatment eras. Reasons for this may include: the use of newer alternative therapies alone or in combination, better functional status at diagnosis, increasing recognition of CTD-PAH in diseases other than scleroderma with a better prognosis and differing burden of lung disease. We have not established a causal relation for this improvement.

P1576 Survival of patients with pulmonary hypertension and sickle cell disease in the UK

I.Z. Cabrita[1], M. Abubakar[1], D.M. Layton[1], A. Gilmore[2], G. Cho[2], J. Howard[2], P. Nihoyannopoulos[1], J.S.R. Gibbs[1]. *[1]Imperial College London, London, United Kingdom; [2]Central Middlesex Hospital, London, United Kingdom*

Background: Pulmonary hypertension has been reported to be a predictor of adverse prognosis in sickle cell disease (SCD). Studies in the USA have demonstrated that pulmonary arterial hypertension (PAH) as defined by a tricuspid regurgitant jet velocity (TRV) ≥2.5 m/sec occurs in 30–40% of patients with SCD and is associated with a high mortality rate. In this study we evaluated the mortality of pulmonary hypertension in the UK sickle cell disease population.
Methods: A total of 156 patients with SCD (95 SS, 36 SC, 19 Sb-thalassemia, 6 SOther), who had previously undergone echocardiographic screening for pulmonary hypertension at steady state were followed up for survival. PAH on echocardiography was defined as a TRV ≥ 2.5 m/sec. The PASP was calculated from the modified Bernoulli-equation and addition of the right atrial pressure estimated from IVC diameter and response to inspiration. Data was collected until the time of death or loss to follow-up.
Results: The mean age of the population was 40.8±13.1 years, the range was 18to 83 years and 66% female. The median follow-up interval was 32 months. Pulmonary hypertension was present in 29% of patients (n=45), of whom 15% had TRV ≥ 2.5 – 2.69 m/s, 9% had TRV 2.7 – 2.99 m/s and 5% had TRV ≥ 3.0 m/s. PAH was more common in SS (31.5%) than SC (22.9%) or Sb-thalassaemia (21%). Five patients (3%) had echocardiographic evidence for left ventricle diastolic dysfunction. There were 5 deaths, 4 of these patients had PAH giving a mortality rate in this group of 11%. Five patients were lost to follow up. Due to the small number of deaths in the study population it was not possible to estimate a risk ratio for mortality associated with PAH.
Conclusions: In a UK SCD population the prevalence of PAH was 29%. After 32 months follow up the mortality rate was 11.1%. This mortality rate is strikingly lower than in previously reported studies in USA. This may reflect the free access

to specialist health care in UK. Further studies are needed to identify the reasons for differences in outcome among patients with PAH and SCD from different health systems.

P1577 Hemodynamic efficacy and safety of the oral soluble guanylate cyclase stimulator BAY 60-4552 in patients with biventricular heart failure

V. Mitrovic[1], H.A. Ghofrani[2], B. Swidnicki[1], W. Mueck[3], N. Kirschbaum[4], J. Mittendorf[5], J.P. Stasch[6], G. Wensing[3], R. Frey[3], S. Lentini[3]. *[1]Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany; [2]Department of Internal Medicine, University Hospital Giessen and Marburg GmbH, Giessen, [3]Clinical Pharmacology, Bayer Schering Pharma AG, Wuppertal, [4]Global Biostatistics, Bayer Schering Pharma AG, Wuppertal, [5]Medicinal Chemistry, Bayer Schering Pharma AG, Wuppertal, [6]Cardiovascular Research, Bayer Schering Pharma AG, Wuppertal, Germany*

Purpose: Elevated pulmonary artery mean pressure (mPAP) in patients with biventricular heart failure (bivHF) is associated with poor prognosis. BAY 60-4552 is an oral direct soluble guanylate cyclase (sGC) stimulator acting independently of nitric oxide. In preclinical studies, BAY 60-4552 exhibited potent vasorelaxing properties and end-organ protective effects. We assumed that BAY 60-4552 would improve cardiopulmonary hemodynamics and be well tolerated in patients with bivHF.

Methods: Safety, tolerability and invasive hemodynamics of BAY 60-4552 were studied in patients with bivHF (LVEF≤45%, mPAP≥25 mmHg, pulmonary capillary wedge pressure [PCWP]≥18 mmHg). After single dose escalation with 1, 2.5, 5, 7.5 and 10 mg (part A), hemodynamics were evaluated using 7.5 and 10 mg BAY 60-4552 (part B).

Results: 31 male and 11 female patients (65±11 years; BMI: 27.4±4.4 kg/m^2) were included. Hemodynamic parameters (mean±SD) at baseline were PCWP: 23.9±4.5 mmHg; right atrial pressure (RAP): 10.6±4.3 mmHg; mPAP: 35.7±8 mmHg mmHg; systolic blood pressure (SBP): 119±17 mmHg; systemic vascular resistance (SVR): 1721±534 dyn s cm^{-5}; heart rate (HR): 70.6±11.2 bpm; and cardiac index (CI): 1.99±0.48 L/min/m^2. Table 1 summarizes changes in invasive hemodynamics after single doses of 7.5 and 10 mg. No relevant HR increase was observed. BAY 60-4552 was safe and well tolerated with mild adverse events (asymptomatic hypotension, n=1; facial flushing, n=5; mild headache, n=4). Pharmacokinetics were linear with $t_{1/2}$ of 14 - 20h.

Table 1. Change from baseline (absolute and [relative] mean±SD, p<0.5) of invasive hemodynamics after oral administration of 7.5 and 10 mg BAY 60-4552

	7.5 mg (n=12)	10 mg (n=12)
PCWP [mmHg]	-8.4±3.1 [-36±13%]	-9.3±2.5 [-43±11%]
mPAP [mmHg]	-8.0±3.3 [-24±9%]	-7.3±3.3 [-23±8%]
RAP [mmHg]	-4.3±1.9 [-40±15%]	-4.0±2.3 [-39±15%]
SVR [dyn s cm^{-5}]	-523±293 [-33±15%]	-546±267 [-31±12%]
CI [L/min/m^2]	+0.57±0.38 [+31±22%]	+0.67±0.53 [+33±25%]

Conclusion: In patients with bivHF, oral administration of BAY 60-4552 was well tolerated and induced a potent vasodilation, which resulted in significant reductions in cardiac pre- and afterload and an increase in cardiac index. These first clinical results with an oral sGC stimulator in patients with bivHF demonstrate the potential of this new therapeutic principle.

P1578 REVEAL registry: two year outcome of patients with congenital heart disease-associated pulmonary arterial hypertension (CHD-APAH)

R.J. Barst[1], A.J. Foreman[2], D.D. Ivy[3], M.D. Mcgoon[4]. *[1]Columbia University College of Physicians and Surgeons, New York, United States of America; [2]ICON Clinical Research, San Francisco, United States of America; [3]University of Colorado Denver School of Medicine, The Children's Hospital, Aurora, United States of America; [4]Mayo Clinic, Rochester, United States of America*

Purpose: The Registry to EValuate Early And Long-term PAH Disease Management (REVEAL) is a 54 center, observational, US study evaluating 3500 PAH patients (pts). Pts are followed ≥5yrs from baseline (BL) enrollment. REVEAL objectives include outcomes in CHD-APAH pts.

Methods: Outcomes (survival and all-cause hospitalization) for CHD-APAH pts were compared to idiopathic PAH (IPAH) pts.

Results: Of 2967 pts entered (4/06–9/07), 342 had CHD-APAH at BL: 78 complete repair, 184 unrepaired/38 partial repair (combined as unrepaired, n=222), and 42 unclassified. Demographics, treatments and outcomes are in the Table. FC and hemodynamics were worse in unrepaired than repaired pts. Interestingly, both 2yr survival from BL and 5yr survival from diagnosis (dx) are similar for repaired vs unrepaired; differences of these two subgroups are being investigated.

Conclusions: Historically, there was a significantly better outcome for CHD-APAH vs IPAH. However, 2 yr outcomes from BL and 5 yr survival from dx are similar with current treatment. Longer follow-up is needed to discern whether these outcome similarities will continue. Furthermore, although the unrepaired CHD pts are worse by FC and hemodynamics at BL, outcomes are similar at 2 yrs from BL and 5 yr survival from dx. Longer follow-up is important to determine if repairing is appropriate for all APAH-CHD pts.

P1579 Sitaxentan (Thelin) therapy for patients with World Health Organization functional class II pulmonary arterial hypertension

N. Galie[1], R. Benza[2], G. Burgess[3], M. Dilleen[3], A. Torbicki[4]. *[1]University of Bologna, Bologna, Italy; [2]Gerald McGinnis Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, United States of America; [3]Pfizer Global Research and Development, Sandwich, United Kingdom; [4]Institute of Tuberculosis and Lung Diseases, Warsaw, Poland*

Purpose: To assess response to sitaxentan in patients with World Health Organization functional class (FC) II pulmonary arterial hypertension (PAH) from the Sitaxentan To Relieve Impaired Exercise (STRIDE) clinical trials.

Methods: Data from the double-blind, placebo-controlled STRIDE-1 and -2 trials and subsequent extension studies were evaluated to compare outcomes in FCII and FCIII patients treated with sitaxentan 100 mg once daily.

Results: Data from 38 and 49 FCII patients and 75 and 70 FCIII patients from STRIDE-1 and -2, respectively, were analysed. Compared with placebo, median 6-minute walk distance at week 12 (last observation carried forward) improved 20 and 6 m (P=not significant) in FCII and 41 and 37 m (P<0.01) in FCIII patients in STRIDE-1 and -2, respectively. Estimated median differences from placebo in change from baseline at week 12 were significant (P<0.05) for pulmonary vascular resistance (–124 and –241 dyne s/cm^5), pulmonary vascular resistance index (PVRI, –202 and –448 dyne s/cm^5/m^2) and cardiac index (0.5 and 0.3 L/min/m^2) for FCII and FCIII, respectively, in STRIDE-1 (not assessed in STRIDE-2). Change in PVRI in STRIDE-1 was significantly correlated with change in FC (r=0.28, P<0.001). Long-term survival was assessed in 59 FCII and 80 FCIII patients who were either randomised to sitaxentan 100 mg in STRIDE-2 or switched per protocol to this dose (ex-placebo or ex-sitaxentan 50-mg patients) in the extension study. Day 1 of sitaxentan dosing was day 1 for the survival analysis. Long-term survival was associated with FC at baseline (hazard ratio, 2.12; P=0.02) and was higher for FCII vs FCIII (table).

Survival Analysis for Sitaxentan 100 mg by World Health Organization Functional Class

	Year 1 Cutoff		Year 2 Cutoff		Year 3 Cutoff	
	FCII	FCIII	FCII	FCIII	FCII	FCIII
Patients died, n	0	5	3	16	9	19
Patients censored, n (%)	0	0	7 (12)	7 (9)	7 (12)	8 (10)
Patients at risk, n	59	75	49	57	43	53
Kaplan-Meier rate, % (95% CI)	100 (100–100)	94 (88–99)	94 (88–100)	79 (70-88)	83 (73-93)	75 (65–85)

Conclusion: Haemodynamic improvement found also in FCII patients and its correlation with FC changes suggest that earlier treatment might prevent/delay deterioration.

Abstract P1578 – Table 1

	CHD (n=342)	CHD - Complete repair (n=78)	CHD - Unrepaired (n=222)	IPAH (n=1386)	P-value CHD vs IPAH	P-value CHD Complete vs Unrepaired	P-value CHD Complete vs IPAH	P-value CHD Unrepaired vs IPAH
Age at baseline, mean (SD), yrs	39 (18)	35 (20)	40 (17)	51 (18)	<0.001	0.044	<0.001	<0.001
Time from dx to BL, mean (SD), mos	61 (72)	57 (71)	60 (72)	40 (43)	<0.001	0.80	0.001	<0.001
≤18y at dx, %	21	31	18	7	<0.001	0.023	<0.001	<0.001
Female, %	74	72	76	78	0.078	0.50	0.19	0.41
Newly Dx, %	7	8	7	15	<0.001	0.78	0.080	0.001
NYHA FC I/II	50	62	46	46	0.32	0.024	0.012	0.95
ETRAs at BL	55	43	59	47	0.009	0.019	0.57	<0.001
Prostacyclins at BL, %	33	23	36	47	<0.001	0.034	<0.001	0.004
PVRi at BL, units x m^2, mean (SD)	20 (12)	17 (10)	22 (13)	19 (11)	0.18	0.017	0.20	0.006
mPAP at BL, mmHg mean (SD)	58 (19)	52 (17)	61 (19)	50 (14)	<0.001	<0.001	0.42	<0.001
2-year survival from BL, %	88	92	86	87	0.49	0.34	0.30	0.87
2-year freedom from hospitalization from BL, %	65	69	64	60	0.18	0.33	0.18	0.56
5-year survival from dx, %	72	65	73	67	0.65	0.73	0.49	0.72

P1580 Impact of anemia in patients with pulmonary hypertension

S.A. Hart[1], R.A. Krasuski[1], B. Smith[2], A. Wang[3], J.K. Harrison[3], T.M. Bashore[3]. [1]*Cleveland Clinic, Cleveland, United States of America;* [2]*Altarum Institute, San Antonio, United States of America;* [3]*Duke University Medical Center, Durham, United States of America*

Background: Anemia is a marker of worsened clinical outcome in patients with heart failure from left ventricular dysfunction. Pulmonary hypertension often results in right ventricular failure and shares a similar inflammatory milieu. We sought to examine the prognostic role of hemoglobin levels in patients with pulmonary hypertension.
Methods: Baseline demographic information and fasting blood work was obtained in a cohort of 169 patients with pulmonary hypertension referred for pulmonary vasodilator testing.
Results: Baseline characteristics of the cohort included age (mean ± SD) 55.8±14.6 years, 75% women, 50% with idiopathic pulmonary hypertension, mean pulmonary artery pressure 46.1±14.2mm Hg and arterial O2 saturation 91±6%. Hemoglobin levels ranged from 8.4 to 18.2 mg/dl and 38 patients (26.2%) were anemic. The most commonly utilized pulmonary hypertension-specific therapeutic agents were epoprostenol (27%), sildenafil (21%), bosentan (17%), and treprostinil (6%). Over a median follow-up of 2.1 years, there were 39 deaths (26.9%). Anemic patients had significantly increased all-cause mortality. After adjustment for baseline differences and known predictors of death in pulmonary hypertension, anemic patients were more than three times as likely to die than non-anemic patients (HR 3.4; 95% CI [1.6 – 7.0]).

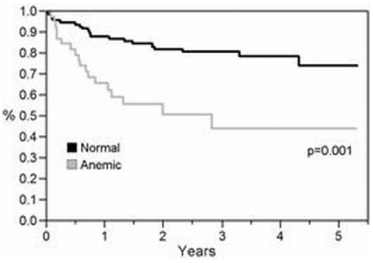


Figure 1

Conclusions: Hemoglobin levels closely parallel survival in pulmonary hypertension. Modification of even mild anemia in this disorder could significantly impact clinical outcome.

P1581 Detection of agonistic autoantibodies against alpha-1 adrenergic and endothelin-1 receptors in sera of patients with pulmonary arterial hypertension

M. Dandel[1], G. Wallukat[2], A. Englert[1], H.B. Lehmkuhl[1], R. Hetzer[1]. [1]*Deutsches Herzzentrum Berlin, Berlin, Germany;* [2]*Max Delbrück Centrum für Molekulare Medizin, Berlin, Germany*

Purpose: Pulmonary arterial alpha-1-adrenergic receptors (alpha-1-AR) show particularly high sensitivity for noradrenaline (NA) and NA plasma levels are elevated in patients with pulmonary arterial hypertension (PAH). Experimental data also suggest that vasodilative and antiproliferative effects of calcium-channel blockers, prostacyclin and adenosin are mainly based on their ability to antagonize intracellular signals caused by alpha-1-AR stimulation.
In PAH patients production of endothelin-1 (ET-1) is increased and elevated ET-1 plasma levels correlate with PAH severity.
After repeated detection of agonistic antibodies against the ET-1 A receptor (ETA) and the alpha-1-AR in PAH patients' sera we assessed their prevalence and properties.
Methods: Using spontaneously beating rat neonatal cardiomyocytes as bioassay we analyzed sera of PAH patients for the presence of functional autoantibodies (AABs) aganst G-protein coupled receptors. AABs were purified by affinity chromatography.
Results: Of 54 tested patients with advanced PAH, 51 (94%) tested positive for AABs against alpha-1-AR and/or ETA. Only 3 patients (6%) showed no evidence of these AABs. Among the 51 AAB positive patients, 38 (75%) showed AABs against both alpha-1-AR and ETA and 13 (25%) had AABs only against alpha-1-ARs. AABs against alpha-1-ARs exerted agonistic dose-dependent positive chronotropic effects on neonatal cardiomyocytes which were blocked by the alpha-1-AR blockers. AABs against ETA exerted agonistic negative chronotropic effects on neonatal cardiomyocytes, which were blocked by the ETA antagonist BQ610. Both AAB types induced permanent stimulation without desensitization of the receptor mediated signal cascade.
First attempts to eliminate by immunoadsorption these AABs against alpha-1-AR and ETA (which appeared to belong to the IgG3 and IgG2 subclass, respectively) in 4 PAH patients showed encouraging results. After AAB removal, at the first control performed 3 weeks later, these patients showed reduction in right ventricular diameters, lower pulmonary anterial pressure, higher cardiac index and improved exercise tolerance (increase in VO2max).
Conclusions: The vast majority of patients with advanced PAH tested positive for functional serum AABs against ETA and alpha-1-AR. These AABs activate the receptors, like the corresponding agonists, but prevent the desensitization of the receptor-mediated signal cascade normally seen with ongoing receptor stimulation.
Our results suggest that these AABs could be involved in PAH pathogenesis. AAB removal by immunoadsorption might be a possible new therapeutic approach.

P1582 Alteration of endothelial cells in patients with pulmonary arterial hypertension estimated by endothelial cell-derived microparticles

H. Maruyama, S. Sakai, T. Sumida, D. Goto, S. Kawano, T. Ishizu, S. Watanabe, K. Aonuma. *University of Tsukuba, Tsukuba, Japan*

Purpose: It is well known that the deteriorated properties of endothelial cells are the initial trigger for pulmonary arterial hypertension (PAH), in which pulmonary arterioles are negatively remodeled and finally obstructed. Since we diagnose PAH based on the increase of pulmonary arterial pressure, >70% of capillary beds are necessarily devastated at this stage. PAH, especially associated with connective tissue diseases, confers grave prognosis. Better prognosis will be obtained by diagnosing the preclinical stage. We assessed the hypothesis that altered characteristics of endothelial cells of PAH can be estimated by endothelial cell-derived microparticles (EMPs). EMPs, which are released during cell activation or apoptosis, are also detectable from stationary state. EMP carries membrane-bounded antigens from the derived cells.
Methods: We measured circulating plasma EMPs by flow-cytometry in control subjects (CTR, n=12) and patients with connective tissue diseases accompanied with PAH (PAH, n=8) defined as mean PAP >20 mmHg, and free from PAH (NPAH, n=12), who were diagnosed in our institute.
Results: In PAH, PECAM-1-positive EMPs significantly increased compared to CTR (533±156[mean±SD]/μl vs 385±88/μl, $p<0.05$); percentage of co-expression of ICAM-1 in PECAM-1-positive EMPs significantly decreased (6.0±2.1% vs 9.1±3.1%, $p<0.05$); however, we did not observe differences between NPAH and CTR. Percentage of β1-integrin-, PDGF-receptor β-, or KDR-co-expression did not show significant differences. Intracellular domain of Notch-1 significantly decreased in both PAH and NPAH than CTR (34.3±9.5%, 39.0±8.4% vs 54.5±6.0%, $p<0.001$ respectively), suggesting activated signal transduction of Notch pathway in endothelial cells.
Conclusions: ICAM-1 and PECAM-1 on EMPs may become molecular markers for early stage of PAH, being independent on physiologic sign. Notch signal pathway might be the key of vascular complication of connective tissue diseases, including PAH. It will be informative to profile molecules on EMPs for elucidating the mechanism of PAH.

P1583 Influence of different eNOS- polymorphism on pulmonary artery hypertension in chronic heart failure patients

M. Knappe, V. Adams, G. Schuler, S. Moebius-Winkler. *Herzzentrum der Universitaet Leipzig, Leipzig, Germany*

Backround: Dyspnoe is a major symptom in patients with chronic heart failure (CHF). The incidence of pulmonary hypertension in those patients is common, but not all patient with CHF develop pulmonary hypertension. Endothelial dysfunction was described in CHF patients and is possibly responisble for the development of pulmonary hypertension in those patients. Endothelial nitric oxide synthase (eNOS) is a key enzym for regulating vascular tone. There are some eNOS polymorphism which are responisble for eNOS malfunction. We therefore examined the influence of two polymorphism of the eNOS gene on mean pulmonary artery pressure (PAPm) in patient with CHF.
Methods: Overall we recruited 131 patients. In all patients, mean pulmonary artery pressure (PAPm) was measured by right heart catheterization. Furthermore we conducted genetic analyses of the promotor region and the (Glu298Asp) exon 7 region of eNOS gene to identify the wild type (WT), heterocygous type (HT) and the homocygous type (MT).
We divided the study population in three groups: Group A consisted of 78 patients with HF [mean left ventricular ejection fraction (LVEF) 23±7%] and pulmonary hypertension (PAPm 39±8mmHg); Group B was comprised of 30 patients with CHF (LVEF 25±8%) and normal PAPm (17±5mmHg); finally, patients with preserved LVEF (61±10%) and an elevated PAPm (36±8mmHg) were defined as group C.
Results: No significant differences between the three groups were found concerning both the incidence of the polymorphisms in the promoter region of eNOS gene and the exon 7 region polymorphisms (promoter region: Group A: WT 39%, HT 48% MT 13%; Group B: WT 37%, HT 50%, MT 13%; Group C: WT 45%, HT 43%, 12%, $p>0.05$; Exon 7 region polymorphism: Group A: WT 52%, HT 37% MT 11%; Group B: WT 55%, HT 31%, MT 14%; Group C: WT 54%, HT 36%, 9%, $p>0.05$).
Conclusion: Polymorphisms of the promotor region and the (Glu298Asp) exon 7 region of eNOS are not associated with an increased PAPm in patient with CHF. Also patients with pumonary hypertension due to other underlying diseases with normal ejection fraction, where not more concerned by polymorphism of eNOS. Therefore polymorphism of the eNOS may not play a role in the development of pulmonary hypertension within those patients.

P1584 In vitro assesment of platelet activity in patients with pulmonary arterial hypertension

M.M. Can, I.H. Tanboga, A. Ozkan, F. Koca, N. Keles, H.C. Tokgoz, B. Yaymaci, K. Sonmez, M. Saglam, C. Kaymaz. *Kartal Kosuyolu Heart Education and Research Hospital, Istanbul, Turkey*

Pulmonary arteriel hypertension (PAH) is a devastating disease that is characterized by an imbalance between vasoconstrictive and vasodilatative factors leads to proliferative pulmonary vasculopathy. In situ thrombosis has been implicated in the pathogenesis of PAH. Increased platelet activity was not studied previously whether it has play role in the pathogenesis of in situ thrombosis in patients with PAH.

Our objectives were to determine the platelet aggregation in healthy controls and patients with PAH subgroups before the PAH specific therapy and to evaluate the difference of agonist-induced aggregation capacity and blood rheologic parameters between patients with PAH and healthy controls.

Methods: The study group comprised 34 patients with PAH and 34 healthy controls. Patients with different etiologies were as follows; idiopathic PAH (IPAH) in 16 pts, Eisenmenger (Eis) in 18 pts. Peripheral venous blood samples were obtained before the therapy, and fibrinojen, d-dimer, platelet count, mean platelet volume levels were measured as blood coagulation markers. Platelet aggregation was induced by the agonist agents adenosine diphosphate (ADP), collagen (COL) was determined in whole blood by multiplate electrical impedance aggregometry.

Results: Plasma concentrations of fibrinojen (357±98 vs 188±31, p=0,0001), d-dimer (0,42±0,31 vs 0,19±0,09, p=0,001), mean platelet volume (9,1±1 vs 8,2±0,8, p=0,001), platelet aggregation induced by ADP (1018±263 vs 669±204, p=0,0001) and COL (1053±212 vs 679±238, p=0,001) were significantly higher in patients with PAH compared with healthy controls. Platelet number was comparable between patients with PAH and controls (238±87 vs 237±65, p=NS).

Conclusion: PAH patients had significiantly higher platelet activity as compared to healthy controls.In vitro assesment of hyperaggregation may be indicative of in vivo activated platelets in circulation related to in situ thrombosis

P1585 Patients with pulmonary arterial hypertension related to HIV: Effects of antiretroviral and disease-specific PAH therapy

T. Neumann[1], P. Krings[1], N. Reinsch[1], H. Kaelsch[1], T. Konorza[1], S. Esser[1], R. Wachter[2], A. Goehler[3], R. Erbel[1] on behalf of on behalf of the Competence Network of Heart Failure. *[1]Universitaetsklinik Duisburg-Essen, Essen, Germany; [2]Universitaetsklinik Goettingen, Goettingen, Germany; [3]Harvard University, Boston, United States of America*

Objective: Treatment with disease-specific drugs reduces mortality in idiopathic pulmonary hypertension (PAH). Nevertheless, it is unclear, if these treatment options or antiretroviral therapy (ART) should be recommended for patients with HIV-related PAH (HIV-PAH). The present manuscript analyses treatment and survival of HIV-infected patients in a systematic review of accessible literature reporting individual patient data.

Methods: From a systematic literature search 192 case reports and 7 clinical studies, including three prospective controlled trials, were identified. Kaplan-Meier statistic was used to estimate overall survival.

Results: The median survival of patients with HIV-PAH was 360 days (95%-CI: 231 – 488 days) with 1-, 3- and 5-years survival rates of 50%, 20% and 15%, respectively. Median survival in the group of patients with disease-specific treatment for PAH was 540 days (95% CI 335-744 days) compared with 240 days (95% CI 165-314 days) in patients without such therapy. The median survival of patients receiving ART was 540 days (95% CI 410-659 days) compared with a median survival of 270 days (95% CI 191-348 days) of patients without ART. Survival analysis revealed significant advantage for vasodilator treatment (p<0,001) and ART (p<0,007) compared with no treatment.

Conclusion: The overall survival of patients with HIV-PAH is poor. Disease-specific treatment for PAH and antiretroviral therapy go along with an improved survival in HIV-PAH. Although there may be drug interactions and high costs, HIV-patients with PAH should be considered for specific pulmonary vasodilator treatment and combination antiretroviral therapy.

P1586 Osteopontin - A new prognostic biomarker in patients with pulmonary hypertension

M. Rosenberg[1], F.J. Meyer[2], E. Gruenig[3], M. Lutz[2], D. Lossnitzer[2], R. Wipplinger[2], H.A. Katus[2], N. Frey[1]. *[1]Universitätsklinik Schleswig-Holstein, Campus Kiel, Germany; [2]Universitaetsklinikum Heidelberg, Heidelberg, Germany; [3]Thoraxklinic Heidelberg gGmbH, Heidelberg, Germany*

Background: The extracellular matrix protein Osteopontin (OPN) was found upregulated in several models of cardiac failure and appears to play an important role in myocardial remodeling. Moreover, our group recently showed that OPN plasma level are not only elevated in patients with left sided heart failure, but also correlated with an adverse prognosis. Since right ventricular dysfunction is an important predictor of morbidity and mortality in patients with pulmonary hypertension (PH), we now tested the diagnostic and prognostic power of OPN in this patient cohort.

Methods: We included 101 patients with PH of different etiology in this study, while 40 healthy individuals of similar age and sex distribution served as controls. OPN plasma levels were determined by ELISA and assessed for correlation with clinical severity, echocardiographic parameters of right ventricular dysfunction, right ventricular remodeling and prognosis.

Results: Median OPN was significantly elevated in patients with PH compared to healthy controls (776 ng/ml vs. 382 ng/ml; p<0.0001). Furthermore, OPN levels were higher in patients with moderate to severe right heart failure compared to patients with no or mild symptoms (WHO Fc III/IV 903 ng/ml vs. WHO Fc I/II 650 ng/ml; p<0.001). OPN plasma levels also showed a positive correlation with the right ventricular enddiastolic diameter (r=0.46; p<0.0001). In a multivariate analysis including demographical, clinical and biochemical parameters such as NT-proBNP, OPN emerged as an independent predictor of right ventricular dysfunction (OR 3.9; 95%-CI 1.2-12.9; p=0.02). Finally, patients with PH and OPN plasma levels above the Median display a significant higher 1 year mortality of 24% vs. 0% in patients with lower OPN values (HR 0.12; 95%-CI 0.03-0.49; p=0.003).

Conclusion: In summary, our data show for the first time that OPN plasma levels are not only elevated in patients with PH, but also correlate with clinical status and right ventricular remodelling. Preliminary data also suggest that OPN is predictive for right ventricular dysfunction and an adverse prognosis in PH. We therefore believe that OPN might improve the non invasive monitoring of patients with PH.

P1587 Prognostic role of right ventricular function in pulmonary hypertension: a tissue Doppler and strain imaging study

L. Ernande[1], P.Y. Leroux[2], S. Huez[3], R. Naieje[3], A. Mulliez[4], B. Aublet Cuvelier[4], C. Khouatra[5], M. Ovize[1], J.F. Cordier[5], G.A. Derumeaux[1]. *[1]Inserm U 886, Claude Bernard Lyon 1 University, Lyon, France; [2]Echocardiography Laboratory, Louis Pradel Hospital, Lyon, France; [3]Erasme Hospital, Bruxelles, Belgium; [4]Gabriel Montpied Hospital, Clermont Ferrand, France; [5]Department of pneumology, Louis Pradel Hospital, Lyon, France*

Background: Right ventricular (RV) function is one of the determinants of prognosis in patients (pts) with pulmonary hypertension (PH) but is difficult to evaluate in this population because of increased afterload.

Aim: To evaluate the prognostic value of conventional echocardiographic and tissue Doppler imaging (TDI) indices of RV function.

Methods: 159 pts (60±16 years) with severe PH (sPAP: 78±21 mmHg, idiopathic PH: 42%, connective tissue diseases: 35%) underwent a clinical evaluation and a standard echocardiography associated with TDI. The following RV function parameters were measured in apical 4-chamber view: tricuspid annular plane systolic excursion (TAPSE) using M-mode; peak velocity during isovolumic (IVCt) and ejection (St) phase and time of isovolumic relaxation (IVRT) using pulsed TDI at the tricuspid annulus; systolic longitudinal strain of the RV free wall (ε_L: mean value of strain at the basal, mid and apical segments) using color TDI.

Results: During a mean follow-up of 12.2±9.6 months, 33 pts died. Baseline data are shown in table. Parameters significantly associated with death by univariate analysis were: 6'walk test, diastolic eccentricity index, right atrial area indexed by height, TAPSE, IVCt, St, IVRT and ε_L (p<0.05 for all). At multivariate analysis, the only independent predictors of death were 6'walk test ≤ 310 m (p=0.03) and IVCt ≤ 9cm/s (p=0.005).

6' walk test (m)	372±136
NYHA I-II / NYHA III-IV	93 (58%) / 66 (42%)
LV ejection fraction (%)	66±10
RA area/height (cm^2/m)	15.1±5.6
Diastolic eccentricity index	1.47±0.45
Pericardial effusion	27 (17%)
TAPSE (mm)	17.9±5.1
IVCt (cm/s)	9.4±3.9
St (cm/s)	11.5±3.3
IVRT (ms)	68.8±41
ε_L (%)	-18.0±7.1

Conclusion: This study demonstrates the key role of RV contractility as assessed by IVCt in predicting mortality in PH and confirms also the role of 6'walk test evaluation.

P1588 Early pulmonary vasculopathy reflected by exercise gas exchange abnormalities in patients with scleroderma

D. Dumitrescu[1], R.J. Oudiz[1], G. Karpouzas[1], A. Hovanesyan[1], A. Jayasinghe[1], S. Rosenkranz[2], K. Wasserman[1]. *[1]Los Angeles Biomedical Research Institute, Torrance, United States of America; [2]Universitaetsklinikum Koeln, Cologne, Germany*

Purpose: Pulmonary arterial hypertension (PAH) is a major cause of death in patients (pts) with scleroderma (SSc). A significant amount of pulmonary vascular bed has to be compromised by pulmonary vasculopathy (PV), the histologic background of PAH, before symptoms occur at rest, so that first manifestations of the disease become evident only during exercise. We hypothesized that cardiopulmonary exercise testing (CPET) would be a non-invasive and specific way

to indicate an early mismatch of pulmonary perfusion to ventilation, suggestive of PV.

Methods: We prospectively recruited 30 consecutive SSc pts from our local Rheumatology clinic, who had not been previously diagnosed with PAH and were not suspected to have the disease. Each patient performed CPET. Pts with abnormal gas exchange were categorized by the etiology of their exercise intolerance. High VE/VCO2 ratios combined with a low PETCO2, both at the anaerobic threshold (AT), or a decrease in PETCO2 during exercise were considered to be suggestive of PV.

Results: Exercise tolerance was reduced in 18 of the 30 pts. 9 pts showed signs of PV, and 9 showed rather symptoms of left ventricular dysfunction. Table 1 shows the different etiologies of exercise intolerance which we found in this cohort, and the key parameters which we analyzed in these groups.

Table 1. Pathophysiology and type in the scleroderma population, revealed by CPET

	Normal exercise exercise capacity (n=12)	Pulmonary vasculopathy (n=9)	Left-sided heart disease (n=9)
Limited/diffuse SScl	9/3	8/1	6/3
FVC % predicted	94.9±13.8	81.2±15.3	81.0±22.9
DLCO % predicted	89.8±22.6	57.9±15.7	64.4±19. 5
6-MWD (m)	444±78	339±68	367±116
Peak VO2 (% predicted)	73.5±13.1	49.3±13.3	48.1±11.8
AT (% predicted)	102.0±17.8	72.8±20.9	64.8±10.3
$VE/VECO_2$ @AT	29.8±2.9	38.6±9.0	32.6±5.7
$PETCO_2$ @AT (mmHg)	37.9±4.5	30.6±2.5*, (p=0.001)	37.0±3.6
Difference $PETCO_2$ (AT-Start Ex., mmHg)	3.2±2.3	-2.1±2.1*, (p< 0.001)	2.9±1.6

*p<0.05, Pulmonary vasculopathy vs. left-sided heart disease.

Conclusions: CPET detected PV in 9 of 30 pts, and differentiated the pathophysiology of exercise intolerance in SSc pts. Serial measurements are being performed to assess the rate of progression of early PV, eventually leading to overt PAH in this patient cohort.

P1589 3-year survival of patients treated with sitaxentan sodium (Thelin) for pulmonary arterial hypertension

N. Galie[1], R. Naeije[2], G. Burgess[3], M. Dilleen[3]. *[1]University of Bologna, Bologna, Italy; [2]Erasme University Hospital, Brussels, Belgium; [3]Pfizer Global Research and Development, Sandwich, United Kingdom*

Purpose: To assess survival of patients from the 18-week, randomised, Sitaxentan To Relieve Impaired Exercise (STRIDE)–2 trial who entered the continuation trial for a total duration of 3 y.

Methods: The analysis included 145 patients who were either randomised to sitaxenan 100 mg once daily (approved dose) in STRIDE–2 (n=61) or switched per protocol to this dose from placebo (n=31) or sitaxsentan 50 mg (n=53). For the analysis of survival, day 1 of sitaxentan dosing was day 1 of the first administration of the active drug, regardless of the dose. Survival was computed as the number of days elapsed from day 1 to day of death. For patients who did not die, survival was censored on the last day on which the patient was known to be alive. Survival at 1, 2, and 3 y was calculated using Kaplan-Meier estimation (95% CI).

Results: The 145 patients had moderate to severe (NYHA/WHO functional class II [n=59], III [n=80], or IV [n=6]) pulmonary arterial hypertension, that was either idiopathic (61%) or associated with connective tissue disease (29%) or congenital heart disease (10%). 112 (77%) patients were women, age ranged from 14–78 y, and the mean (SD) age was 56 (14) y. Mean (SD) baseline pulmonary arterial pressure was 46 (13) mmHg, pulmonary capillary wedge pressure was 9 (4) mmHg, and pulmonary vascular resistance was 10 (6) mmHg/L/min. Survival is shown in the table.

Survival Analysis for Sitaxentan 100 mg

	Year 1 Cutoff	Year 2 Cutoff	Year 3 Cutoff
Patients died, n	6	21	30
Patients censored before cutoff,* n (%)	0	17 (11.7)	18 (12.4)
Number of patients at risk, n	139	107	97
Kaplan-Meier rate, % (95% CI)	95.9 (92.6-99.1)	84.7 (78.6-90.7)	77.5 (70.4-84.6)

*Censored because of loss to follow up.

Conclusion: After 3 y of treatment, 77.5% of patients treated with sitaxsentan 100 mg survived.

P1590 Right heart catheterisation significantly outperforms echocardiography in the diagnosis of pulmonary hypertension

N. Dwyer, D. Kilpatrick. *University of Tasmania, Hobart, Australia*

We retrospectively compared the performance of right heart catheterisation (RHC) and echocardiography (echo) in patients with pulmonary hypertension (PH) at our institution.

All 142 patients with treated pulmonary arterial hypertension (PAH) were studied. In 48 of 71 patients (67%) with mild PAH (PAPm ≥ 25-34 mm Hg), initial echo underestimated the pressure (<38 mm Hg on tricuspid regurgitant (TR) jet) or could not detect the TR jet (15 patients). In 11 of 29 patients (38%) with moderate PAH (≥ 35-44 mm Hg) echo missed the diagnosis (TR jet undetectable in 2). In 8 of 42 patients (19%) with severe PAH (≥ 45 mm Hg) the diagnosis was missed (TR jet undetectable in 1).

RHC established the diagnosis of PAH in 67 of 142 patients (47%) that would have been missed by echo estimation alone. This has implications for the utility of echo screening for PAH, particularly in mild disease where other echo evidence of right ventricular pressure overload is absent, yet patients are severely limited functionally and improve with treatment.

In addition, RHC importantly excludes left heart dysfunction. Whilst the ratio of mitral inflow velocity to early diastolic velocity of the medial mitral annulus (E:E') is thought to be the best echo estimate of left ventricular end diastolic pressure (LVEDP), where E:E' <8 predicts normal and > 15 predicts elevated LVEDP, very often an indeterminate value of 8-15 is seen (associated with a wide range in LVEDP).

182 RHC in 169 patients were performed over a recent three year period. 92 patients had PH (PAPm ≥ 25 mm Hg) of which 34 (37%) had an elevated pulmonary capillary wedge pressure (PCWP) > 18 mm Hg, and 80 patients (87%) had complete RHC and echo data performed within 30 days of each other. Of the 27 patients with PCWP > 18 mm Hg at RHC and complete data; 8 (30%) had E:E' > 15; 5 (19%) had E:E' < 8; and 14 (52%) had E:E' 8-15. Thus in 19 of 27 patients (70%) with high PCWP, echo could not confidently determine that raised atrial pressures were present. Of the 53 patients with PCWP ≤ 18 mm Hg; 18 (34%) had E:E' < 8; 9 (17%) had E:E' > 15; and 26 (49%) had E:E' 8-15. Thus in 35 of 53 patients (66%) with normal PCWP, echo could not confidently determine that normal atrial pressures were present. Overall, echo could not make a conclusive determination of left atrial pressure in 54 of 80 patients (68%).

It is evident that echo may miss PH or is unable to accurately determine LVEDP in a significant number of patients at our institution. This suggests RHC is required for the diagnosis of PH in high risk populations and that echo screening lacks sufficient sensitivity.

P1591 Importance of hydration and exercise in the diagnosis of pulmonary arterial hypertension secondary to scleroderma

A.T. Burns, A. La Gerche, W. Stevens, A. Macisaac, D. Prior. *St. Vincent's Health, Melbourne, Australia*

Purpose: Pulmonary arterial hypertension (PAH) occurs in a significant proportion of patients with scleroderma and is associated with marked limitation of physical activity and premature death, both of which can be ameliorated with pulmonary vasodilator therapy. The diagnosis of PAH requires the measurement of mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) via right heart catheterisation (RHC). The effect of fluid loading and exercise on these parameters in patients with scleroderma is poorly characterised.

Methods: Patients with limited or diffuse scleroderma with suspected PAH without significant interstitial lung disease, who required RHC were studied in the fasting state, after a 500mL intravenous bolus and after supine bicycle ergometry. Diagnostic criteria for PAH were resting mPAP>25mmHg or exercise mPAP>30mmHg in the presence of PCWP<18mmHg. One-way repeated-measures ANOVA and Bonferroni post-test comparison were used to compare changes between conditions.

Results: Eighteen consecutive patients (9 limited and 9 diffuse scleroderma, 17 female, mean age 58.1±9.2 yrs, mean DLCO of 57.5±14.5% of predicted) were included in the study of which 14 completed the exercise protocol (peak workload: 71.4±16.6Watts). Fluid loading resulted in significant increases in mPAP (table), pulmonary artery systolic pressure (PASP) and PCWP but did not affect cardiac output (CO) or pulmonary vascular resistance (PVR). Exercise resulted in significant increases in mPAP, PASP and CO but did not affect PCWP or PVR. PAH was diagnosed in 12 patients, 50% in the fasting state, 33% after the administration of fluid and a further 17% after exercise.

Effect of fluid loading and exercise

	Fasting	Fluid	Exercise
PASP (mmHg)	36.7±16.0	42.7±13.9†	60.1±17.2‡
mPAP (mmHg)	22.4±10.0	28.3±8.4†	40.1±12.2‡
PCWP (mmHg)	9.7±5.0	13.9±5.1‡	12.2±4.6
CO (L/min)	5.3±1.3	5.6±1.4	9.9±1.9‡
PVR (Woods units)	2.4±1.5	2.7±1.4	2.9±1.3

*p<0.05, †p<0.01, ‡p<0.001.

Conclusions: In patients with scleroderma who are fasted for RHC, the diagnosis of PAH, which has important implications for therapy and prognosis, may be missed if fluid loading and exercise are not included in the diagnostic protocol.

P1592 Transthoracic echocardiography in patients with a first episode of Pulmonary Embolism (PE) for the detection of Chronic Thromboembolic Pulmonary Hypertension (CTPH)

D. Poli[1], E. Antonucci[2], E. Grifoni[2], G. Ciuti[2], M. Miniati[2], C. Arcangeli[1], G.F. Gensini[2], R. Abbate[2], D. Prisco[2]. *[1]Department of Heart and Vessels, Thrombosis Centre, Azienda Ospedaliera Universitaria Careggi, Florence, Italy; [2]Department of Medical and Surgical Critical Care, University of Florence, Florence, Italy*

Purpose and Methods: CTPH is a rare complication of PE. Patients with CTPH show elevated pulmonary pressure at echocardiography, but the diagnosis should be confirmed by invasive procedures. We prospectively followed consecutive patients who survived to a first episode of objectively documented PE, with or without deep vein thrombosis, to evaluate the incidence of symptomatic and asymptomatic CTPH and venous thromboembolic (VTE) recurrences.
Results: After 3-6 months of oral anticoagulation (OA) patients underwent transthoracic echocardiography to evaluate transtricuspid (rV-rA) gradient. When rV-rA gradient was >35 mmHg further evaluations were performed to rule in or out CTPH. During follow-up patients who developed persistent dyspnea were re-evaluated. CTPH was considered to be present if the systolic and mean pulmonary artery pressures exceeded 40 and 25 mmHg, respectively and the pulmonary-capillary wedge pressure was normal. Overall, 240 patients (males 118), median age 59 (16-89) yrs, were followed up for a median time of 36 (9-192) months. A rV-rA gradient >35 mmHg was detected in 2 young women and CTPH was confirmed. Among patients with normal rV-rA gradient, one developed persistent dyspnea 44 months after the first event and CPTH was confirmed. Among 206 patients who stopped OA, 23 (11.2%) had VTE recurrence, 11 PE (48%). Elevated Ddimer (DD) after stopping OA was associated with recurrence (p=0.006). None of the patients with recurrent VTE had elevated rV-rA gradient.
Conclusion: In conclusion, in our series the incidence of CTPH after a first episode of PE was 1.3%. All cases were detected firstly by transthoracic echocardiography and then confirmed. VTE recurrence and elevated DD seemed not to be related to the development of CTPH.

P1593 A high-calorie diet improves survival and myocardial function, preventing cardiac cachexia and apoptosis in monocrotaline-induced pulmonary hypertension and heart failure

F. Vasques-Novoa, A. Lourenco, R. Roncon-Albuquerque Jr, A.F. Leite-Moreira. *Faculdade Medicina do Porto, Porto, Portugal*

Background: One third of patients with advanced heart failure (HF) are cachectic. Cardiac cachexia (CC) independently predicts a worse prognosis by a factor of 2.6. Although a western-type diet is an established risk factor for the development of cardiovascular disease, hypercaloric diet regimens could have entirely distinct effects in advanced HF with CC. Our goal was to study the effects a high-calorie western-type diet in monocrotaline-induced pulmonary hypertension (PH), HF and CC.
Methods: Male Wistar rats (180-200g; n=132) randomly underwent (i) subcutaneous injection of 60mg/kg monocrotaline (MCT) or vehicle (Ctrl) and (ii) feeding with either a 5.4 Kcal/g, 35% simple carbohydrate and 35% animal fat (high-calorie diet, HCD), or a 2.9 Kcal/g, 60% complex carbohydrate and 3% vegetable fat (normal diet, ND). Food intake, weight and mortality were recorded. Right (RV) and left ventricular (LV) haemodynamics, morphometry, myocardial apoptosis rate (TUNEL) and histology (Masson's trichrome and H&E), RV and LV myocardial expression of endothelin-1 (ET-1) and tumor necrosis factor-α (TNF-α), and TNF-α plasma levels were evaluated 5 weeks later. Groups were compared with Kaplan-Meier survival analysis and simple or repeated measures two-way ANOVA. Quantitative variables: mean$\pm$SEM. $P<0.05$ considered significant.
Results: Although MCT groups presented increased RV maximal pressure, and similar degrees of RV hypertrophy, compared with their respective Ctrl groups. MCT HCD showed a significant reduction in RV maximal pressure and no medial hypertrophy of lung arterioles compared with MCT ND. These changes were accompanied by improved survival (46% vs 18%), improved LV myocardial systolic and diastolic function indexes. HCD also increased caloric intake, attenuated total weight loss, and LV mass wasting in MCT, without LV cardiomyocyte dimension changes. MCT fed ND also showed increased fibrosis and apoptosis rates, increased myocardial expression of ET-1, increased TNF-α LV mRNA and plasma levels, compared with ND fed Ctrl, whereas MCT fed HCD presented attenuation of fibrosis and gene expression of ET-1, and apoptosis rates and TNF-α LV mRNA and plasma levels similar to their respective controls. Except for increased body weight and fat mass, Ctrl HCD showed no differences from Ctrl ND.
Conclusions: Contrarily to their effects on the healthy heart's function, western-type diets may have beneficial actions in advanced or end-stage HF and CC, attenuating weight loss, myocardial apoptosis and neuroendocrine activation while improving myocardial function.

P1594 Relevance of non-invasive diagnostic procedures in the diagnosis of scleroderma-associated pulmonary hypertension

D. Dumitrescu, P. Moinzadeh, F. Dodos, K. Kremer, N. Hunzelmann, S. Rosenkranz. *Universitaetsklinikum Koeln, Cologne, Germany*

Purpose: Pulmonary arterial hypertension (PAH) is a major cause of death in patients (pts) with scleroderma (SSc). The gold standard for diagnosing PAH remains right heart catheterization (RHC). However, lung function testing, echocardiography, cardiopulmonary exercise testing (CPET), biomarkers, and 6-minute walking distance (6MWD) are routinely performed as non-invasive tests for screening purposes, and for initial workup when suspecting PAH. Here, we analyzed the correlation of these non-invasive tests with the presence of PAH which was confirmed or ruled out by RHC.
Methods: We prospectively recruited 31 consecutive pts with SSc, who had not been previously diagnosed with PAH, from our Dermatology clinic. They underwent lung function testing, echocardiography, CPET as well as measurements of the 6MWD and NTproBNP serum levels. Whenever there was suspicion of PAH, a RHC was performed. In the subgroup of pts who underwent RHC, all measured non-invasive parameters were analyzed with respect to their ability of confirming the disease.
Results: 17 of the 31 pts underwent RHC due to abnormalities in the non-invasive diagnostic workup. In this subgroup, 10 pts were found to have PAH, and in 7 pts the disease was ruled out. The correlation of the non-invasively obtained key measurements with the definite diagnosis of PAH in these 17 pts are shown in table 1.

Table 1. Correlation of non-invasively obtained parameters with the presence of PAH, confirmed or ruled out by RHC in 17 SSc patients

	PAH (n=10)	Non-PAH (n=7)	p-value (non-PAH vs PAH group)	Abnormality threshold	Se (%)	Sp (%)
Tricuspid pressure gradient (mmHg)	43.2±17.1	27.3±6.6	0.029	>30 mmHg	80	71.4
TAPSE (mm)	22.3±4.1	21.6±3.1	0.681	<18 mm	20	85.7
RVEDD (mm)	31.4±6.3	25.4±4.0	0.029	>28 mm	60	85.7
NT-proBNP (ng/l)	1436±1890	137±74	0.06	> calculated ULN	70	85.7
6-MWD (m)	354±92	517±65	< 0.01	<450 m	90	85.7
Peak VO2 (% predicted)	52.8±14.2	68.1±19.0	0.100	<75% pred.	90	14.3
VE/VCO2@AT	39.2±4.6	32.0±6.2	0.024	>34	100	71.4
PETCO2@AT (mmHg)	28.7±3.0	36.1±6.3	0.020	<32 mmHg	90	85.7
DLCO (% predicted)	53.9±14.0	61.2±8.6	0.206	<60%	80	71.4

Se, Sensitivity; Sp, Specificity.

Conclusions: Non-invasive diagnostic tests, although differing in their relevance, still remain important for the initial workup of SSc pts suspected to have PAH as well as for PAH screening procedures.

P1595 Role of heme oxygenase-1 and endothelial progenitor cells in the beneficial effects of erythropoietin on flow-associated pulmonary arterial hypertension

R.L.E. Van Loon[1], B. Bartelds[1], F.A.D.T.G. Wagener[2], M.E. Van Albada[1], N. Affara[1], S. Mohaupt[1], H. Wijnberg[1], R.M.F. Berger[1]. *[1]University Medical Center, Groningen, Netherlands; [2]Department of Pharmacology and Toxicology, Nijmegen Center for Molecular Life Sciences, University N, Nijmegen, Netherlands*

Purpose: We previously reported that erythropoietin (EPO) improves pulmonary vascular remodeling in rats with flow-associated pulmonary arterial hypertension (PAH). To test the hypothesis that EPO improves this remodeling through activation of heme oxygenase-1 (HO-1) and mobilization of endothelial progenitor cells (EPCs), we treated these rats with EPO with and without a HO-activity blocker (SnMP).
Methods: Flow-associated PAH was created in rats by injection of monocrotaline followed by an abdominal aorto-caval shunt. Rats were randomized to EPO (PAH+EPO,n=14), EPO+SnMP (PAH+EPO+SnMP,n=13), SnMP (PAH+SnMP,n=11) or no treatment (PAH,n=14). Three weeks later, hemodynamics, pulmonary vascular remodeling, number of EPCs in peripheral blood and pulmonary HO-activity were evaluated.

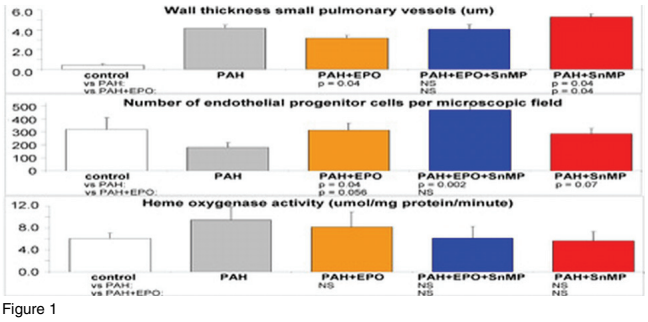


Figure 1

Results: Compared to PAH, wall thickness of small pulmonary vessels decreased after EPO, increased after EPO+SnMP and increased even more after SnMP treatment (Figure).
Number of EPCs increased after EPO and SnMP and increased even further after EPO+SnMP treatment. Pulmonary HO-activity remained stable after EPO and decreased after SnMP and EPO+SnMP. Pulmonary arterial pressure and right ventricular contractility remained unchanged.
Conclusion: In this rat model of flow-associated PAH, EPO improved pulmonary vascular remodeling, increased the number of EPCs in peripheral blood, but did not increase pulmonary HO-activity. HO-activity blockade alone worsened pulmonary vascular remodeling, while increasing the number of EPCs. This indicates that both EPO and HO have beneficial effects on PAH, however, mediated via different mechanisms. The beneficial effects of EPO do not seem mediated by increased HO-activity. Our data suggest, however, that HO may facilitate homing of EPCs to the diseased pulmonary vascular bed

P1596 Connective tissue disease-related pulmonary hypertension: a service model of outreach care with preliminary survival data

S. Reddecliffe, C. Das, C. Valerio, G. Coghlan. *Royal Free Hospital, London, United Kingdom*

Optimal management of connective tissue disease (CTD)-related pulmonary hypertension (PH) involves a multidisciplinary approach, and specialist expertise tends to be concentrated in a small number of centres of excellence.
To expand patient access to expert care, the Royal Free Hospital (RFH; London, UK) has established several outreach clinics. In this shared care model, patients are seen by their own consultant in their local hospital, together with the RFH consultant and nurse specialist. In line with UK guidelines, patients with New York Heart Association Class III PH are initiated on an endothelin receptor antagonist (ERA; guidelines recommend first-line bosentan). Under the RFH protocol, sildenafil is added if pulmonary arterial pressure remains >40 mmHg or if there is no fall in brain natriuretic peptide. Patients with Class IV PH are initiated on ERA plus sildenafil. All patients are re-catheterised during their disease process, which may not mirror national practice.
The RFH team act as a resource for clinical assessment, patient management and educational material, and carry out right heart catheterisation when necessary. They also manage funding arrangements, data collection and audit, and follow-up. When patients are prescribed inhaled or parenteral medications requiring a high level of nursing support, training is provided by the RFH, incorporating local services where possible. Monitoring data, including laboratory tests for patients receiving ERAs, and clinical outcome and attendance data, are submitted by the local centre to the RFH and are included in the UK PH database.
Annual audits, including a patient satisfaction questionnaire, are carried out by the RFH. Questionnaire responses have increased steadily from 64 in 2005 (40% of questionnaires sent) to 126 in 2008 (42%), and satisfaction has remained consistently high. For example, percentage of patients satisfied or very satisfied with availability of doctors and specialist nurses has ranged from 91 to 97% and 92 to 98%, respectively. Overall, 88–95% report being (very) satisfied with quality of outpatient follow-up care. As of January 2009, preliminary survival data are available for 173 patients treated at the RFH and 42 patients treated as part of the outreach programme. After 743 days of follow-up, survival was 71% in the RFH group and 83% in the outreach group.
In conclusion, the RFH outreach care model combines expert care from PH specialists with the convenience of patient consultations in their local hospital. Preliminary data suggest that participation in outreach care does not adversely affect survival.

P1597 Combined magnetic resonance and positron emission tomography imaging of the right ventricle to assess disease severity in arterial pulmonary hypertension

C. Bauleo[1], B. Formichi[2], L. Bruselli[1], R. Pancani[2], E. Rizza[2], G.D. Aquaro[1], M. Lombardi[1], D. Neglia[1], C. Marini[1]. [1]*Fondazione Toscana Gabriele Monasterio, Pisa, Italy;* [2]*Institute of Clinical Physiology CNR, Pisa, Italy*

Background: Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary arterial pressure (mPAP) higher than 25 mmHg at rest in the presence of a normal wedge pressure at right heart catheterization. Absolute levels of mPAP and pulmonary vascular resistance (PVR) are commonly used to measure hemodynamic impairment and define short term prognosis in these patients. Mixed venous oxygen saturation (SvO2) commonly expresses disease severity. Aim of the study was to assess whether the extent of the pulmonary hemodynamic impairment and disease severity in PAH can be predicted by right ventricular mass index (RVMI) and myocardial blood flow (MBF) as non-invasive indicators of RV overload from magnetic resonance imaging (MRI) and positron emission tomography (PET).
Methods: Twenty-four patients with moderate-severe PAH (19 females, age 54±15 yrs, mPAP 42±10 mmHg, wedge pressure 6±3 mmHg) were evaluated by right heart catheterization, MRI and PET within 6 days. PAH was idiopathic (N=8), postembolic (N=9) or associated with scleroderma (N=7). At time of catheterization, mPAP, PVR and arterial blood gases were measured. RV mass index (MI) and ejection fraction (EF) were obtained from MRI study. RV myocardial blood flow (MBF) was measured at rest by PET and 13N-Ammonia as a flow tracer.
Results: In PAH patients, RVMI was directly related with mPAP (r 0.48, P<0.05) or PVR (r 0.58, P<0.01) and inversely related with SvO2 (r -0.52, P<0.05). RV MBF was not related with mPAP and PVR and was inversely related with RVMI (r -0.57, P<0.01) and directly related with SvO2 (r 0.54, P<0.01). RV hypertrophy was associated with reduced RV systolic function as demonstrated by inverse relationship between RVMI and RVEF (r -0.47, P<0.001).
Conclusions: In patients with PAH of different origin, pulmonary hemodynamic impairment can be predicted by MRI indexes of RV overload. RV hypertrophy is associated with depressed myocardial perfusion and systolic function. The present results suggest the use of combination of MRI and PET as a new non-invasive approach for definition of disease severity in PAH.

P1598 Sildenafil therapy for patients with porto-pulmonary hypertension and pulmonary arterial hypertension associated with HIV infection

L. Negro, M. Palazzini, A. Manes, E. Leci, E. Conficoni, A. Marinelli, C. Bachetti, E. Beciani, A. Branzi, N. Galie'. *Institute of Cardiology, University of Bologna, Bologna, Italy*

Purpose: sildenafil, an orally active phosphodiesterase type-5 inhibitor, is effective in patients with idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue diseases. We assessed the effects of sildenafil in patients with PAH associated with portal hypertension (Po-PAH) and with human immunodeficiency virus infection (HIV-PAH).
Methods: between May 2004 and October 2008, 25 patients with Po-PAH and 22 patients with HIV-PAH received sildenafil [mean age 47±9 years; WHO functional class I (13%), II (36%), III (49%) and IV (2%)]. At baseline and after a mean treatment period of 3.6±1.2 months, patients underwent 6-minute walk distance (6MWD) assessment and right-heart catheterization.
Results: sildenafil dose was 10 mg tid in 7 HIV-PAH patients (due to concomitant highly active antiretroviral therapy); 20 mg tid in 38 patients and 40 mg tid in 2 patients. An increase in 6MWD was observed: from 447±115 m at baseline to 496±106 m after sildenafil treatment (p<0.001). Mean hemodynamic parameters are presented in the table. No significant adverse events have been reported.

Hemodynamic parameters

	RAP (mmHg)	mPAP (mmHg)	mSAP (mmHg)	CI (L/min/m^2)	PVR (Wood U)	MVO2 (%)
Baseline	9±6	50±11	91±14	2.8±0.9	9.1±6.0	62±11
Sildenafil	7±4	43±10	81±16	3.5±0.9	6.0±3.2	70±9
p	0.01	<0.001	0.050	<0.001	<0.001	<0.001

Right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), mean systemic arterial pressure (mSAP), cardiac index (CI), pulmonary vascular resistance (PVR), mixed venous oxygen saturation (MVO2).

Conclusions: sildenafil treatment of patients with Po-PAH and HIV-PAH is associated with improvements in exercise capacity and hemodynamic parameters. The effects of sildenafil in these subsets are similar to those observed in patients with other forms of PAH; no important drug related adverse events have been detected.

P1599 Cardiac troponin I in chronic obstructive pulmonary disease

C. Martins[1], J.P. Nunes[2]. [1]*Hospital S Joao, Porto, Portugal;* [2]*Faculdade Medicina do Porto, Porto, Portugal*

Introduction: Pulmonary disease, chiefly chronic obstructive pulmonary disease (COPD), has a strong cardiovascular impact, above all because of right ventricle loading, due to the development of pulmonary hypertension. Increased levels of cardiac troponin I (TpI) have frequently been shown to exist in left ventricular heart failure, among other cardiac disorders, but the possible role of TpI measurement in patients with COPD is not clear.
Purpose: We aimed to evaluate a possible association between TpI levels and adverse events in hospitalized patients with acute exacerbation of COPD.
Methods and design: Cross-sectional study, in which we analysed admissions to Internal Medicine department for acute exacerbation of COPD, from July through December 2007. Entry criteria included a TpI obtained in the first 24 to 48h of admission. A positive TpI test was defined as 0,012 ng/ml or higher. Correlation of TpI with length of stay, vital status and complications, was made by linear and logistic regression, respectively. Exploration of significant relationships between variables, among TpI quartiles was carried out and the significance level was established at 0.05, two sided.
Results: We observed 150 patients, with a mean age of 73.7 years, and male preponderance (66.1%). Chronic bronchitis (69.6%) and emphysema (13.9%) were the most frequent disorders in terms of COPD. Median hospital stay was 10 days, varying between 2 and 55 days. Near 51% of patients had an intercurrence, predominantly respiratory failure with need for non invasive ventilatory support (74.2%). Among cardiovascular complications, atrial flutter (6.1%) and fibrillation (6.1%) prevailed. One patient had non ST elevation myocardial infarc-

tion. The hospital death rate was 11%. Mean plasma TpI was 0.264 ng/ml and mean BNP was 557.9 pg/ml. Regression studies showed no correlation between TpI levels and hospital stay length. A non significant trend in mortality was seen when the fourth quartile of TpI was compared to first quartile (p=0.12). TpI levels correlated significantly with the need for non invasive ventilatory support (p = 0.05).
Conclusions: Cardiac troponin I did not predict hospital stay length nor mortality, among this sample. Nevertheless, TpI correlated significantly with certain complications, namely the need for non invasive ventilatory support.

P1600 Is neutrophil gelatinase-associated lipocalin a marker of renotubular dysfunction in pulmonary arteriel hypertension characterised by low arteriovenous perfusion gradients?

F. Koca, M.M. Can, I.H. Tanboga, A. Ozkan, H.C. Tokgoz, N. Keles, T. Bezgin, T. Akgun, E. Turkyilmaz, C. Kaymaz. *Kartal Kosuyolu Heart Education and Research Hospital, Istanbul, Turkey*

Neutrophil gelatinase-associated lipocalin (NGAL) is a novel marker in early detection of acute renal damage and renal tubular function. Despite the limited data concerning the NGAL in heart failure (HF), effects of right-sided pressure or volume overload secondary to pulmonary arterial hypertension (PAH) on renotubular function as assessed by NGAL has not been studied. We aimed to evaluate whether right-sided HF in PAH lead to renotubular dysfunction and abnormalities in serum and urinary NGAL.
The study group comprised 28 pts with PAH (F: 14, M: 14, age: 37±14,8) and 27 healthy controls (F: 13, M: 14, 34±12,86). None had a serum creatinine >1,5 mg/dl. In PAH group systemic arterial and pulmonar arterial systolic pressures (SAP, PAPs) were 104±17,9 and 96±17 mmHg respectively. Serum and urinary NGAL were measured with ELISA method. Estimated glomerular filtration rate (eGFR) was measured with two formulas; Cockcroft –Gault (CG) and Modification of Diet in Renal Disease study (MDRD). Plasma brain natriuretic peptide (BNP) levels were also assessed. Echo measures of right ventricular (RV) function were as follows; tricuspid annular plane systolic excursion (TAPSE), tissue Doppler velocity of lateral annulus (St), myocardial performance index (MPI) of RV, pulmonary artery systolic pressue estimated from tricuspid regurgitation (PAPs), cardiac index (CI), respiratory variation in vena cava inferior diameter (VCIrv). Moreover, CI measured by transthoracic impedance cardiography (ICG). Plasma BNP levels were 446±568 and 18±8 pg/ml in PAH pts and controls, respectively (p<0.0001). Patients with PAH had a lower eGFR with CG formula (99,45±29,4 vs 122,4±25,9 ml/min, p=0.04) as compared to controls. However, both serum NGAL (171±68 vs 151±78 ng/ml) and urinary NGAL levels (18±11 vs 14±7 ng/ml) were comparable between groups (p=NS). Serum and urinary NGAL levels were not correlated with BNP, eGFR calculated by CG and MDRD formulas, CI, TAPSE, St, MPI-RV,PAPs and VCIrv.
Conclusions: Estimated GFR seem to be impaired in PAH characterised by low arteriovenous perfusion gradients due to high venous pressures and normal SAP.However, neither serum,nor urinay NGAL levels seemed to be associated with plasma BNP, flow state, measures of RV volume and/or pressure overload and renotubular dysfunction in PAH.

P1601 Sildenafil attenuates endothilial cell injury in children with acquired pulmonary arterial hypertension

A.A. Kotby, O.A. Elmasry, N.M. Habib, S.R. Youssef, H.A. Aziz Eldin. *Ain Shams University, Cairo, Egypt*

Purpose: P-selectin levels, reflecting endothelial cell injury and platelet activation, are elevated in patients with pulmonary arterial hypertension (PAH) and are reported to improve with prostacyclin treatment. Sildenafil was found to improve exercise capacity, decrease pulmonary artery pressure (PAP) and improve symptoms in children and adults with PAH. We aimed to study Sildenafil effect on the clinical and echocardiographic parameters of PAH in children with congenital cardiac left to right shunt and acquired PAH (APAH) at initial presentation, as well as its effect on P-selectin.
Patients and Methods: 29 children with APAH (17 males, 12 females; age: 3.78±4.63 years) and 10 healthy children (4 males, 6 females; age 3.22±4.21 years) were studied. Following informed parental consent, all children underwent a full clinical examination, measurement of oxygen saturation (SaO2), 6 minute walk test (6MWT), full blood count, liver and kidney function tests, measurement of P-selectin via an ELISA assay, and 2D, M-mode, and Doppler echocardiographic evaluation. Thirteen patients were started on sildenafil therapy, in addition to conventional treatment, and 9 of them were available for follow up after 6 weeks of therapy.
Results: Patients had significantly lower 6MWT (mean 325.8±118.31m; median: 340m; IQR: 212.5-382.5m) and significantly higher P-selectin levels (mean 742.7±264.2ng/ml; median: 600ng/ml; IQR 550-800ng/ml) than controls (mean 637.5±77.59 m; median 637.5m; IQR: 573.75-701.25m [p=0.003]; mean 190±45.95ng/ml; median: 200ng/ml; IQR: 175-225ng/ml [p<0.0001] respectively). No correlation was found between P-selectin level and either 6MWT (p>0.05) or PAP (p>0.05). Following 6 weeks of sildenafil therapy, patients demonstrated an improvement in NYHA class by at least one NYHA class. The 6MWT increased from 371.8±144.64m (median: 403.75m; IQR: 276.25-467.5m) to 601.25±102.8m (median: 637.5m; IQR: 543.75-658.75m) but this was not statistically significant (p=0.07). PAP decreased from 87.6±17.43 mmHg to 84.69mmHg (p=0.003), and P-selectin levels dropped from 747.7±276.89ng/ml (median 750ng/ml; IQR: 575-1150ng/ml) to 470±173.49ng/ml (median 500ng/ml; IQR: 350-700ng/ml) (p=0.007). No adverse events were reported during the 6-week study period.
Conclusion: sildenafil improves the clinical and haemodynamic indices of PAH and significantly decreases P-selectin levels, reflecting a beneficial effect of sildenafil therapy on endothelial cell injury in children with APAH.

P1602 Screening of patients with sickle cell disease for pulmonary hypertension and for participation in interventional trial of sildenafil therapy (walk-PHaSST)

R.J. Barst[1], M.T. Gladwin[2], R.F. Machado[3], N.A. Yovetich[4], K.L. Hassell[5] on behalf of walk-PHaSST Steering Committee.
[1]Columbia University Medical Center, New York, United States of America; [2]University of Pittsburgh, Pittsburgh, United States of America; [3]The University of Chicago Medical Center, Chicago, United States of America; [4]Rho, Inc, Chapel Hill, United States of America; [5]University of Colorado Health Sciences Center, Denver, United States of America

Background: Pulmonary hypertension (PH) is associated with increased mortality in sickle cell disease (SCD). NT pro-BNP is also associated with increased mortality in SCD. Sildenafil (sild) is approved for PAH and has been shown to improve exercise capacity in a phase I/II trial of SCD-PH patients (pts).
Methods: We initiated a multi-center screening study to characterize the phenotype of ~800-1000 SCD pts and to identify pts with PH for a sild trial. All screened pts have NT pro-BNP levels assessed at screening. The Main Interventional Trial (MIT) of walk-PHaSST is a 16 week, multi-center, double-blind, randomized, placebo-controlled trial evaluating the safety and efficacy of sild in SCD-PH pts defined as TRV ≥ 2.7 m/sec. The MIT will randomize 132 pts, stratifying 1:1 by TRV (2.7-2.9 vs. ≥ 3.0 m/sec). The 1° endpoint is change in exercise capacity [via 6 minute walk distance (6MWD)]. Additionally, pts in the upper TRV stratum undergo a baseline (BL) and end-of-study (EOS) RHC to evaluate: 1) acute hemodynamic effects at BL (of iNO and of sild) and at EOS (iNO and study drug), and 2) hemodynamic changes after 16 weeks (2° endpoint). Pts who complete the MIT are eligible for a 1year open-label safety study.
Results: To date, 445 pts have been registered into screening. Qualification rates are consistent with protocol projections based on previous research. Thus far, of screened pts: 1) 34% qualified based on TRV (predicted: 10% - 32%), 2) 16% enrolled into the MIT (predicted: 15% - 20%), and 3) 10% have been randomized (predicted: 13%). A total of 23% of pts have both TRV ≥ 2.7 m/sec and compromised 6MWD (MIT enrollment criteria: 150-500 m). Three strata of screening TRV are used to group pts: < 2.7, 2.7-2.9 and ≥3.0 m/sec. For pts who completed the screening TRV, the 6MWD is 457±95 m/sec (n=221), 437±101 m/sec (n=87), and 411±85 m (n=43), respectively, for the three TRV groups [analysis of variance F (2,348)=4.91, p=0.008]. The median NT pro-BNP levels for the 205 pts analyzed to date are: 47 (IQR 27-90; n= 115), 84.5 (IQR=22-164; n=60) and 301.5 (IQR=156-790; n= 30) pg/ml, respectively, for the three TRV groups (Kruskal-Wallis, chi-square=35.3; p<0.0001).
Conclusions: The ongoing Walk-PHaSST study has screened ~50%, and randomized ~25% of the targeted pts in year one, Preliminary data suggest that in SCD, decreased exercise capacity and increased NT pro-BNP levels are associated with PH (estimated by TRV). These data raise the possibility that screening NT pro-BNP levels may guide referrals for evaluation of PH.

P1603 Extension of the 6MWT in children with pulmonary arterial hypertension: value of additional variables such as oxygen saturation, heart rate and Borg score in estimating disease severity and prognosis

M.B. Van Der Horst, R.L.E. Van Loon, M.T.R. Roofthooft, R.M.F. Berger. *University Medical Center, Groningen, Netherlands*

Purpose: To study the value of an "extended 6-minute-walk-test" (extended-6MWT) for monitoring disease severity and prognosis in children with pulmonary arterial hypertension (PAH), we measured –in addition to six-minute-walking-distance (6MWD)– the oxygen saturation (tcSO2), heart rate and Borg scores (both for dyspnoea and muscle weakness) before, directly after and 5 minutes after the test.
Methods: Thirty-seven children with PAH, either idiopathic (n=22) or associated with systemic-to-pulmonary shunt (n=15), performed an extended-6MWT at baseline and during follow-up at a national referral centre for paediatric PAH. Extended-6MWT-variables were correlated with WHO functional class, biological serum markers and hemodynamic variables in order to analyse the value of these additional variables in assessing disease severity. In addition, Cox proportional hazards survival analyses were performed to assess the predictive value of these variables for survival.
Results: Regarding disease severity, tcSO2, Borg dyspnoea and muscle weakness scores correlated with other currently used parameters. TcSO2, measured before (p=0.04), directly after (p=0.048) and 5 minutes after the 6MWT (p=0.006), correlated with WHO functional class. Borg dyspnoea and muscle weakness scores correlated significantly with serum markers (NT-pro Brain Natriuretic Pep-

tide, creatinine, uric acid) and hemodynamic variables (mean pulmonary arterial pressure and pulmonary vascular resistance). Regarding prognosis, the following variables were associated with decreased survival: lower saturation (p=0.02), and higher heart rate (p=0.05), both measured directly after the 6MWT, and less recovery of tcSO2 five minutes after the 6MWT (p=0.037). These correlations were independent from the type of PAH.

Conclusion: TcSO2, heart rate and Borg dyspnoea and muscle weakness scores, measured during 6MWT and after five minutes of recovery, appeared to correlate with parameters for PAH disease severity and to predict survival. Therefore, this "extended-6MWT" may be of additional value in monitoring disease severity and prognosis in children with PAH.

P1604 Thrombospondin-1 as a new biomarker for shearstress in pulmonary hypertension

R. Kaiser, C. Frantz, H. Wilkens. *Universitaetsklinikum der Saarlandes, Homburg, Germany*

Objective: One of the main treatment principles of pulmonary hypertension (PH) is vasorelaxation of pulmonary resistance vessels by accumulation of cGMP in the vascular smooth muscle cells. This common pathway of NO of the endothelium and applicated drugs can be counteracted by binding of thrombospondin-1 (TSP) to its receptors CD36 and CD47. TSP is released by activated thrombocytes and can be synthesized from both smooth muscle cells and endothelial cells under conditions of hypoxia or pathologically increased shearstress. All are relevant pathomechanisms in PH. We examined the clinical relevance of TSP in patients with PH as a new pathophysiological concept and biomarker.

Methods: After informed consent, 15 patients underwent right heart catheterization to confirm PH and examine vasoreactivity to ilomedin. Blood was drawn using CTAD to stabilize thrombocytes, processed and levels of TSP, PDGF-BB and big-endothelin were measured by ELISA according to vendor instructions. Ten healthy donors served as control.

Results: Patients with PH showed a significant elevation of both TSP (141.49±19.84ng/ml vs. 65.58±14.74ng/ml, p=0,01) and big-Endothelin (2.476±0.811pg/ml vs. 0.593±0.811pg/ml, p=0,04). Although thecontrol group was slightly younger, there was no correlation of age andTSP-level. Circulating PDGF-BB was significantly lower in PH opposed to healthy subjects (123.45 4.8pg/ml vs. 160.65 14.85pg/ml, p=0.036). Furthermore, a trend of decreased circulating TSP was observed after ilomedin testing.

Discussion: This data supports for the first time a role of TSP in the pathomechanisms of disease progress in PH. In vitro data has shown an increase of TSP under pathological shearstress and hypoxia. Increased levels of TSP lead to apoptosis in endothelial cells by interfering with cGMP, which is also the common pathway of NO and VEGF. Inhibition of phosphodiesterase-5 might therefore be rendered useless by binding of TSP to its receptors.

PDGF-BB is a strong inductor of TSP in vitro. The lower levels of PDGF in PH could resemble a feedback mechanism of chronic elevation of TSP. On the other hand, treatment of PH comprises anticoagulation and dysfunction of thrombocytes for example by sildenafil, which are a main source of PDGF in vivo. While previous biomarkers focus on endothelial function or myocardial strain, we examined for the first time TSP-1 as a biomarker of shearstress. Its predictive value remains to be elucidated.

P1605 Characterization of platelet activity in patients with pulmonary arteriel hypertension subgroups

M.M. Can[1], I.H. Tanboga[1], E. Turkyilmaz[2], T. Akgun[3], F. Koca[1], H.C. Tokgoz[1], A. Ozkan[1], T. Bezgin[1], O. Ozveren[4], C. Kaymaz[1]. *[1]Kartal Kosuyolu Heart Education and Research Hospital, Istanbul, Turkey; [2]Mus State Hospital, Mus, Turkey; [3]Batman State Hospital, Batman, Turkey; [4]Dumlupinar University, Kütahya, Turkey*

Pulmonary arteriel hypertension (PAH) is a devastating disease that is characterized by an imbalance between vasoconstrictive and vasodilative factors leads to proliferative pulmonary vasculopathy. In situ thrombosis has been implicated in the pathogenesis of PAH. Increased platelet actvity was not studied previously whether it has play role in the pathogenesis of in situ thrombosis in patients with PAH.

Our objectives were to determine the platelet aggregation in healthy controls and patients with PAH before the PAH specific therapy and to evaluate the differency of agonist-induced aggregation capacity and blood rheologic parameters between patients with PAH and healthy controls.

Methods: The study group comprised 34 patients with PAH and 34 healthy controls. Patients with different etiologies were as follows; idiopathic PAH (IPAH) in 16 pts, Eisenmenger (Eis) in 18 pts. Peripheral venous blood samples were obtained before the therapy, and fibrinojen, d-dimer, platelet count, mean platelet volume levels were measured as blood coagulation markers. Platelet aggregation was induced by the agonist agents adenosine diphosphate (ADP), collagen (COL) was determined in whole blood by multiplate electrical impedance aggregometry.

Results: Plasma concentrations of fibrinojen (357±98 vs 188±31, p=0,0001), d-dimer (0,42±0,31 vs 0,19±0,09, p=0,001), mean platelet volume (9,1±1 vs 8,2±0,8, p=0,001), ADP (1018±263 vs 669±204, p=0,0001) and COL (1053±212 vs 679±238, p=0,001) induced platelet aggregation were significantly higher in patients with PAH compared with healthy controls. Platelet number was comparable between patients with PAH and controls (238±87 vs 237±65, p=NS).As compared the PAH subgropus;IPAH patients had significianly higher ADP (1123±101 vs 916±332, p=0,009) and COL (1174±117 vs 957±242, p=0,002) induced aggregation than pts wih Eis. Plasma concentrations of fibrinojen, d-dimer,platelet number were comparable between subgroups.

Conclusion: PAH patients had significiantly higher platelet activity as compared to healthy controls.Morover pts with IPAH had signficiantly higher in vitro platelet activation than pts with Eis.Higher platelet overactivity in IPAH compared to Eis may be indicative of worse prognosis of IPAH than Eis pts as previously knowm data.

P1606 Evaluation of right ventricular volumes and function with three-dimensional echocardiography in patients with pulmonary hypertension

E. Talini, C. Giannini, M.G. Delle Donne, R. De Lucia, R. Martino, C. Palagi, C. Nardi, C. Cuono, V. Di Bello, M. Mariani. *Azienda Ospedaliero - Universitaria Pisana, Pisa, Italy*

Purpose: Right ventricular (RV) function and dimensions are important clinical markers in several cardiac conditions, but two-dimensional (2D) echocardiography has some limitations in the study of RV for its irregular and complex shape. Three-dimensional (3D) echocardiography provides volumetric measurements without geometric assumptions and has been validated by several comparative studies with the gold standard represented by MNR. Aim of this study is to evaluate dimensions and systo-diastolic function of RV in patients (pts) with pulmonary hypertension (PH) using classic 2D and M-mode echocardiography and Doppler parameters, Pulsed-Wave Tissue Doppler (PW-TDI) and 3D echocardiography.

Methods: 23 pts with PH of different aetiology (mean age: 43±6 yrs) and 16 healthy subjects matched for age and sex as control group (C) were investigated with 2D and 3D echocardiography and PW-TDI. 3D images were acquired on a Philips Ie33 system (Philips Medical Systems) with a matrix array-transducer and off-line post-processing was performed using a dedicated software (Tomtec).

Results: We found in PH a significantly higher RV diastolic diameters and volumes (PH: 138±52 vs C: 83±18; $p<0.0001$), an higher RV wall thickness and a lower RV ejection fraction (RVEF) (PH: 31±8 vs C: 52±4, $p<0.0001$), a lower tricuspid annular plane systolic excursion (TAPSE) (PH: 15±3 vs C: 21±2, $p<0.0001$) and in PH a significantly lower fractional shortening area. PH group was characterized by a significant alteration of diastolic PW-TDI parameters and of Tei index (PH: 0.54±0.1 vs 0.29±0.03, $p<0.0001$) an by a lower tricuspid E/Ea ratio. Significant correlations were found between pulmonary arterial systolic pressure (PAPS) and RVEF (r=-0.78; $p<0.0001$), between PAPS and TAPSE (r=-0.71, p=0.001) and between PAPS and Tei index (r=0.56, p=0.016).

Conclusions: 3D echocardiography and PW-TDI allow a good detection of RV dysfunction in pts with PH. Conventional M-mode, 2D and Doppler echocardiography data showed a good correlation with 3D echo parameters; their integrated information applied in clinical practice, might surely improve the knowledge of the complex morphological and functional analysis of RV.

P1607 Does tricuspid ring motion describe right ventricular function always reliably?

S. Giusca, V. Dambrauskaite, C. Scheurwegs, J. D'Hooge, P. Claus, L. Herbots, M. Magro, F. Rademakers, M. Delcroix, J.U. Voigt. *Catholic University of Leuven (KULeuven), Leuven, Belgium*

Patients (PT) with chronic thromboembolic pulmonary hypertension (CTEPH) benefit from pulmonary endarterectomy (PEA). We quantified the recovery of right ventricular (RV) function in PTs with CTEPH after PEA to compare the validity of echocardiographic (ECHO) parameters in assessing RV improvement.

Methods: 16 PT with CTEPH (60±15 years) had ECHO examinations before (baseline), at 1 week (1w) and at 1 (1m), 3 (3m) and 6 months (6m) after PEA. Tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RVFAC) as well as apical and basal peak strain (S) and peak ejection strain rate (SR) of the RV free wall were measured. Left ventricular (LV) apical lateral wall motion was regarded indicating changes in overall heart rocking motion (RM). We compared ECHO with hemodynamic data from right heart catheterization at baseline, 1w and 6m.

Results: After PEA, pulmonary pressure and resistance dropped significantly and remained low at 6m. S and SR improved during follow up in both RV segments (all $p<0.001$). RVFAC had returned to normal at 1w. In contrast, TAPSE decreased after operation ($p<0.001$) and never reached preoperative values again. Changes in LV apical motion explain this finding: At baseline, TAPSE was enhanced by

	before PEA	1w after PEA	1m after PEA	3m after PEA	6m after PEA
basal RV S (%)	-12.2±5	-12.5±4	-14.6±5	-21±7*	-21±5*
apical RV S (%)	-8.8±5	-9.4±4	-13±4*	-14.4±4*	-14.4±7*
basal RV SR (1/s)	-0.8±0.3	-1.2±0.4*	-1.1±0.4*	-1.5±0.6*	-1.5±0.5*
apical RV SR (1/s)	-0.8±0.3	-0.9±0.4	-1±0.4*	-1.±0.4*	-1.1±0.4*
RVFAC (%)	29±6	36.5±7*	42.5±5*	44±9*	43±7*
TAPSE (mm)	14.5±4	8.5±3*	10±2.5*	12±3*	11±2*
LV apical displacement (mm)	-1.1±3	4±2*	5±3*	5±2*	5±2*

*$p<0.01$ vs. baseline.

an RM of the heart due to the failing RV. Unloading RV by PEA terminated RM and TAPSE decreased. With recovering RV function, TAPSE increased again. TAPSE correlated with other function parameters only when corrected for RM (R_uncorrected=0.2 vs. R_corrected=0.7, $p<0.001$).
Conclusion: RV function of CTEPH PTs improves steadily after PEA. Unlike S, SR and RVFAC, this is not reflected by TAPSE due to postoperative changes in overall heart motion. Motion independent deformation parameters (S, SR) appear superior in the accurate description of regional RV function.

P1608 Interventricular septal curve: a new criterion of evaluation and prognosis in pulmonary arterial hypertension

N. Souletie, G. Brierre, B. Degano, L. Tetu, V. Bongard, D. Carrie.
CHU de Toulouse - Hopital de Rangueil, Toulouse, France

Purpose: Pulmonary arterial hypertension (PAH) is a rare and serious disease, characterized by increased pulmonary resistance leading to right heart failure and death. Transthoracic echocardiography has its place in screening and surveillance of PAH. The normal interventricular septal curve (SC) is convex towards the right ventricle in systole and in diastole. It is considered abnormal if it is flattened or convex towards the left ventricle in parasternal short-axis views through the base of the heart, in two-dimensional mode.
We aimed to study the relation between an abnormal SC and pulmonary pressure measurements, in the absence of systemic arterial hypertension.
Methods: Seventy-nine patients with PAH were prospectively included between June 2005 and February 2008. All patients underwent transthoracic echocardiography with direct measurement of systolic and diastolic pulmonary artery pressure, indirect measurement by calculation of mean pulmonary artery pressure and visual assessment of the interventricular septal curve (normal or abnormal).
Results: During the median follow-up of 12 months (interquartile interval: 5-21 months), 16 patients died of their pulmonary disease (mortality rate 18 for 100 person-years).
An abnormal end-diastolic septal curve was significantly associated with higher mortality (relative risk of death 5.33 [95% CI 1.21-23.5; p = 0.027]).

SC according to pulmonary pressures

	Normal systolic and diastolic SC N=14	Abnormal systolic or diastolic SC N=20	Abnormal systolic and diastolic SC N=45	P-value*
Age	63.7 [1]65.9 [54.4-76.1] [(2)]	52.546.8 [41.1-67.2]	60.663.4 [48.8-74.9]	0.050
SAP	138135 [122-150]	122126 [117-130]	124124 [110-140]	0.096
DAP	7881 [71-85]	7680 [68-80]	7880 [68-87]	0.716
sPAP	65 (1)64 [54-70][2]	7973 [67-84]	9186 [77-102]	<0.0001
dPAP	1718 [15-19]	2622 [20-28]	2928 [24-33]	<0.0001
mPAP	3333 [29-35]	4441 [35-50]	4948 [42-52]	<0.0001

SC: septal curve; [1]mean, [2]median [interquartile interval]; *Wilcoxon non-parametric test; SAP/DAP: systolic/diastolic arterial pressure; m/d/sPAP: mean/diastolic/systolic pulmonary artery pressure, measured by echocardiography.

Conclusions: The appearance of the interventricular SC, normal or abnormal, and its time period (systolic, diastolic, or systolic and diastolic) provides semi-quantitative information on the presence and severity of PAH. Abnormal end-diastolic SC is a factor of poor prognosis of the disease.

P1609 Right ventricular myocardial isovolumic relaxation time as novel method for evaluation of pulmonary hypertension: correlation with endothelin-1 levels

M.F. Elnoamany, A. Dawood. *Menoufyia Faculty of Medicine, Shebeen Elkom, Menoufyia, Egypt*

Background: Non-invasive assessment of pulmonary artery systolic pressure (PASP) has several limitations. Right ventricular (RV) isovolumic relaxation time (IVRT) is sensitive to changes in PASP. Blood pool-derived (RV-IVRT) correlates well with PASP. However, because of complex parameter derivation, the method is rarely used. Endothelin-1 (ET-1) levels are elevated in congestive heart failure (CHF) in relation with the severity of pulmonary hypertension (PH).
Objectives: To validate the measurement of Pulsed - wave Doppler tissue imaging (PWDTI)-derived myocardial RV IVRT as a predictor of PASP against invasively measured PASP and correlate this with ET-1 levels.
Patients & Methods: The current study enrolled 53 patients with PH & 20 age & sex matched healthy subjects as a control group. Transthoracic echocardiography with DTI and assessment of plasma level of ET-1 were performed just before right heart catheterization. PWDTI & M-mode echocardiography (MME) were used of assessment of tricuspid annular systolic motion. Ejection Fraction (EF) of RV was estimated by Simpson's rule. Blood pool-derived IVRT & PWDTI-derived IVRT were estimated and each was corrected for heart rate (IVRTc).
Results: Echo derived PASP, myocardial PWDTI-derived IVRTc, blood pool - derived IVRTc & ET-1 levels were significantly higher in patients than control subjects (68.66±21.88 mm Hg vs. 18.78±7.47 mm Hg, 121.75±49.11 ms vs. 28.33±25.1 ms, 77.21±42.66 ms vs. 26.79±19.85 ms & 7.04±2.45 pg/ml vs. 1.35±1.12 pg/ml,. respectively, $p<0.001$ for all). A strong positive correlation was found between invasively measured PASP and each of PWDTI-derived IVRTc (r=0.86), blood pool-derived IVRTc (r=0.75), ET-1 level (r=0.94) also between PWDTI-derived IVRTc & ET-1 levels (r=0.82); whereas strong negative correlation was detected between ET-1 levels and each of RV EF (r= -0.73) & RV Tei index (r= -0.73), <0.001 for all correlations.
Conclusion: Tricuspid annular PWDTI-derived IVRTc correlates very strongly with both invasively measured PASP & ET-1 levels therefore, can be used to predict PASP. It can even be considered as an alternative to tricuspid regurgitation (TR)-derived PASP when TR is nonrecordable.

P1610 Human fatty acid protein-the prognostic role of the biomarker in patients with chronic Pulmonary Hypertension (PH)

H. Schroetter[1], A. Schmeisser[2], D. Stolte[1], R.H. Strasser[1].
[1]Herzzentrum Dresden Universitaetsklinik, Dresden, Germany; [2]Universitaetklinikum Magdeburg, Magdeburg, Germany

Human fatty acid binding protein (H-FABP) is known as an early detection marker for patients (pat.) suffering from acute coronary syndromes as well as a prognostic tool in acute right heart failure due to pulmonary embolism (PE). In PE at least moderately elevated enzyme level are associated with a poor prognosis. The role and prognostic power of H-FABP in chronic pulmonary hypertension is still unknown.
Methods: In a prospective single centre study among pat. with mean pulmonary pressure >30mmHg, transpulmonary gradient of at least 18mmHg, pulmonary vascular resistance (PVR)>200 dyn*sec*cm-5 we evaluated physiologic data of 6-MWT, cardiopulmonary exercise test (CPET), H-FABP level and right heart catheter derived data. We observed them for 3 years to estimate the prognostic power of H-FABP on survival.
Results: 41 pat. (24 idiopathic PH, 8 chronic thrombembolic PH), mean age 62years, 56%female were included. Mean 6-MWT distance amounted for 282±30m. In CPET we assessed means in VO2AT 10,2±0,6, VO2peak 11,7±0,6; VE/VCO2Slope 55±3. The mean maximum of workload was 57Watts (55% of predicted level). Only 10pat. exhibited an elevated H-FABP level, whereas in 31pat. it was normal. 17 Pat. with a prior therapy of ETAB receptor blocker or PDE5 blocker tended to have lower H-FABP level than without medication (p=0,14). Neither invasively determined hemodynamic parameters nor 6MWT distance showed a correlation to H-FABP, whereas in CPET VO2AT, VO2peak and the maximum of workload were weakly negatively correlated to the biomarker. In the 36 month follow up period 9 pat. died or underwent heart-lung-transplantation. The mean survival time was 909 days. Neither H-FABP levels (p=0,1) nor 6MWT distances (p=0,78) were predictive for the prognosis of these pat. In a multivariate analysis for CPET parameters adjusted to age, gender and previous specific medication as well as therapy escalation, VE/VCO2 slope>60 and heart rate recovery within the first minute<8 beats, but also a Hb saturation <90% are independent parameters for a fatal outcome in PH pat.
Conclusion: H-FABP is an unsuitable marker to estimate the midterm prognosis of pat. suffering from PH.

P1611 Does heart rate variability predict the prognose in patients with pulmonary arteriel hypertension?

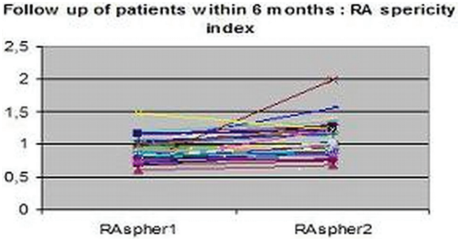
M.M. Can[1], I.H. Tanboga[1], H.C. Tokgoz[1], N. Keles[1], F. Koca[1], A. Ozkan[1], E. Turkyilmaz[2], O. Ozveren[3], K. Sonmez[1], C. Kaymaz[1].
[1]Kartal Kosuyolu Heart Education and Research Hospital, Istanbul, Turkey; [2]Mus State Hospital, Mus, Turkey; [3]Dumlupinar University, Kütahya, Turkey

The aim of this study was to investigate the effects of pulmonary arteriel hypertension (PAH) specific therapy on heart rate variability (HRV) in patients with PAH.
Methods: In this prospective study 38 PAH patients underwent electrocardiographic Holter monitorization. Both time domain (TD) and frequency domain (FD) means of HRV analysis were measured before and after 1 year of PAH specific therapy.For the TD, SDNN, SDANN, SDNN index, RMSSD, pNN50 were measured. For FD, high frequency (HF) and low frequency (LF) were detected. To compare HRV parameters before and after PAH specific therapy; paired sample t test was used for normally distributed variables and Wilcoxon signed rank test was used for the variables that were not normally distributed.Spearman correlation test was used to analyze the correlation between HRV and functional status (NHYA) and six minute minute walk distance (6MWD) echocardiographic measures including tricuspid anular plane excursion (TAPSE), tissue Doppler parameters of tricuspid valve (St), pericardial effusion (PE), pulmonary arteriel systolic pressure (PABs) and cardiac output (CO) estimated by impedance cardiography (ICG), plasma brain natriuretic peptide (BNP).
Results: All of the HRV indices were comparable before and after the therapy (p=NS). PAH patients had lower, NHYA (II vs III), PE (5 vs 0 pts, p<0,05) and higher 6 MWD (338±147 vs 216±143, p=0,004), higher CO (4,5±0,8 vs 3,8±1,1, p=0,001), whereas BNP (288±470 vs 295±304) and St (10,82±2,9 vs 11,6±2,9), TAPSE (17,5±5,3 vs 16±0,8), PABs (98±21 vs 100±21) were not statistically different before and after the PAH specific therapy (p=NS).
Conclusions: PAH specific therapy improves the functional and clinical satus but it may not improve or change echocardiographic measures which of them indices of right ventricular function and heart rate variability indices in PAH patients

P1612 Right atrial sphericity index in pulmonary hypertension: which is the direction of right atrial dilatation?

J. Grapsa, H. Pavlopoulos, D. Dawson, P. Nihoyannopoulos. *Hammersmith Hospital, London, United Kingdom*

Purpose: Pulmonary hypertension has been associated with right ventricular (RV) and right atrial (RA) dilatation. It is known that RA pressures determine survival. The aim of the study was to examine the RA dilatation over time, towards the long and the short axis.
Methods: Sixty – two patients were examined with two dimensional (2DE) and real time three dimensional echocardiographic study (3DE), at a baseline visit (1) and a follow up study 6 months later (2). The dimensions of the RA long and short axis (short axis defined as the axis parallel to the tricuspid annulus) were measured as well as the ratio of the short to the long axis (RA sphericity index). RV volumes and ejection fraction were measured with 3DE. Pulmonary arterial pressures (PASP) were determined by Bernoulli equation. Analysis was conducted in SPSS 13.0
Results: At the baseline visit, RA sphericity index was 0.85±0.15 while within 6 months it increased to 0.97±0.22. Short axis increased in length but not the long axis (short1: 5.3±1.1 mm vs short 2: 6.7±1.3 mm, long1: 6.1±0.86 mm vs long2: 6.2±0.92 mm). Pulmonary arterial pressures remained stable (RVSP1: 85±25 mmHg vs RVSP2: 85±24.6 mmHg) while there was mild decrease of RV ejection fraction (RVEF1: 38±12% vs RVEF2: 32±9.8%).



Right atrial (RA) sphericity index

Conclusions: Right atrium dilates towards the short axis and RA sphericity index might be a useful echocardiographic index for the follow up of RA dilatation and RA pressures.

P1613 A simple non-invasive diagnostic algorithm for pulmonary hypertension

A. Martischnig, P. Wexberg, H. Heinzl, R. Sadushi, C. Adlbrecht, N. Skoro-Sajer, I.M. Lang, D. Bonderman. *Medical University of Vienna, Vienna, Austria*

Background: Current guidelines for the diagnosis of precapillary pulmonary hypertension (PH) recommend right heart catheterization (RHC) in symptomatic patients or patients at risk with echocardiographic systolic pulmonary pressures (sPAP) ≥36mmHg. The growing awareness for PH, a high prevalence of postcapillary PH and the inability to discern between pre- and postcapillary PH by transthoracic echocardiography (TTE), have led to unnecessary RHCs. The aim of the present study was to test the ability of standard non-invasive diagnostic procedures to discriminate between pre- and postcapillary PH in a selected patient population with clinical and echocardiographic suspicion of PH.
Methods: In a first step, data from 251 patients with sPAP ≥36mmHg by echocardiography were retrospectively analyzed in a tertiary referral center for PH. The diagnostic value of clinical parameters, blood gas analyses, serum N-terminal brain natriuretic peptide (NT-proBNP) and ECG was assessed. Parameters with independent discriminative abilities derived from logistic regression were used to construct a diagnostic decision tree. In a second step, overoptimistic estimations of the decision tree were corrected by internal and temporal validation. For the latter, data from 121 prospectively recruited consecutive patients were used.
Results: NT-proBNP (OR[95%CI] 2.01[1.21-3.33], p=0.007) and electrocardiographic right ventricular strain (RVS) (OR[95%CI] 52.931[17.27-162.18], p<0.001) were predictors of precapillary PH. A diagnostic decision tree was derived that stratified patients into a group with and a group without RVS. The latter were further stratified by serum NT-proBNP levels below and above 80pg/ml. In the diagnostic pathway of precapillary PH, integration of the decision tree subsequent to TTE may increase specificity from 0% to internally validated 17.3% or prospectively temporally validated 26.3%. The validated sensitivity remains high at 97.9% or 100%, respectively.
Conclusion: The incorporation of ECG and NT-proBNP into the work-up of PH provides incremental diagnostic value and may reduce the number of invasive hemodynamic assessments.

P1614 Serum biomarkers of cardio pulmonary tissue remodeling in pulmonary arterial hypertension

F.M. Kramer[1], P.M. Lepper[2], H. Frank[3], T. Wibmer[3], K.M. Stoiber[3], L. Kruska[4], T. Krahn[1], C. Schumann[3]. *[1]Institute for Target Discovery/Biomarker, Bayer Schering Pharma AG, Wuppertal, Germany; [2]Dept. of Pneumology and of Intensive Care Medicine, University of Bern, Bern, Switzerland; [3]Clinic of Internal Medicine II, University of Ulm, Ulm, Germany; [4]Gemeinschaftspraxis für Laboratoriumsmedizin, Mikrobiologie und Humangenetik Dr. Stein & Kollegen, Moenchengladbach, Germany*

Background: Besides persisting high pulmonary arterial pressure (PAP) and increased pulmonary vascular resistance (PVR), remodeling of pulmonary tissues and subsequently the right heart are the key pathomechanisms of pulmonary arterial hypertension (PAH). Extracellular matrix (ECM) maintenance in this context plays a central role and is controlled particularly by matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs).
Methods: Serum concentrations of MMP2, TIMP4, tenascin C (TNC) and N-terminal b-type natriuretic peptide (NTproBNP) of 44 PAH patients (pts) were compared with those of 44 age and sex-matched healthy volunteers. Additionally, lung function, six-minute walk distance (6MWD) and right heart function were assessed.
Results: In PAH pts, significantly elevated serum levels of MMP2, TIMP4, TNC and NTproBNP were detected (see table). Mean serum TIMP4 levels were significantly different between pts with higher NYHA classification (NYHA I-II versus NYHA III, p<0.05), with higher carbon dioxide arterial tension (pCO2<35 vs pCO2>35 mmHg, p<0.01) and in pts displaying more severe right ventricular (RV) hypertrophy (no and mild hypertrophy vs moderate and severe hypertrophy, p<0.001). Mean serum MMP2 levels were found to be significantly different between pts assigned to NYHA class I-II and individuals displaying NYHA III status. Mean serum TNC levels did not differ significantly between pts displaying severe PAH as compared to individuals suffering from milder forms of the disease. ROC analysis revealed that PAH pts display more increased serum TIMP4, TNC, MMP2 and NTproBNP concentrations than healthy controls (AUC:TIMP4=0.84, TNC=0.87, MMP2=0.75, NTproBNP=0.99, all p<0.0001).

Biomarker	healthy	PAH
TIMP-4 [ng/mL], mean±SEM	1.35±0.66	2.32±0.15
MMP-2 [ng/mL], mean±SEM	199.2±6.7	258.7±11.3
TNC [ng/mL], mean±SEM	43.8±2.2	110.8±11.0
NT-proBNP [pg/mL], mean±SEM	65.8±9.0	1692.1±339.3

Conclusion: Monitoring of serum TIMP4 and to a lesser extent of MMP2 and TNC levels in PAH pts might help to assess beneficial effects of pharmacotherapy on tissue remodeling and therefore complement the information which can be gained by detection of the pressure overload biomarker NTproBNP.

ATRIAL FIBRILLATION CATHETER ABLATION

P1615 Long-term results after ganglionated plexi ablation for atrial fibrillation: anatomical approach versus selective approach

E. Pokushalov[1], A. Romanov[1], P. Shugaev[1], S. Artemenko[1], N. Shirokova[1], D. Katritsis[2]. *[1]State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation; [2]Euroclinic of Athens, Athens, Greece*

Purpose: Numerous reports have demonstrated an association between autonomic tone and atrial fibrillation (AF). Selective GP ablation and anatomical GP ablation both may eliminate paroxysmal atrial fibrillation (PAF). The purpose of this study was to assess the efficacy of these 2 techniques.
Methods: Eighty patients with symptomatic PAF (age, 53±9 years) were randomized to undergo GP ablation. Selective GP ablation (SGPA; n=40) - Atrial ablation target sites were identified as the places where vagal reflexes evoked by transcatheter high-frequency stimulation (HFS) were obtained. Anatomical GP ablation (AGPA; n=40) - In this variant of catheter ablation no selective search of GPs was performed, target sites for catheter ablation were defined using the data of their anatomical location.
Results: SGPA group, a mean of 4.2±1.8 RF applications were delivered over each targeted positive vagal site. Evoked vagal reflexes were observed during RF applications in 6 patients (15%). In 14 patients (35.0%) AF terminated during ablation, in 13 (92.8%) out of 14 patients AF was not reinducible postablation during rapid atrial pacing. AGPA group, in 31 patients (77.5%), AF was terminated during ablation. In 18 patients (45%) we observed one to several short-term sinus rhythm restoration episodes and then AF recurrence was taking place ("stop and restart" effect). Also in 5 patients (12.5%) short runs of AF initiation during ablation were observed, after the restoration of sinus rhythm. Among all these patients AF was not reinducible postablation during rapid atrial pacing. At 12.2 months, 42.5% of patients who underwent SGPA and 82.5% of patients who underwent AGPA were free of symptomatic PAF when not taking antiarrhythmic drug therapy (P=0.01, log-rank test). Immediately post-ablation, SDNN, rMSSD, and HF decreased, while HRmin, HRmean, and LF/HF increased. Parasympathetic

denervation was more prominent in patients free of AF compared to these with AF recurrence.
Conclusion: In comparison of two existing methods of GP ablation the method using the anatomical approach was proven to be more effective in a long-term period.

P1616 Small balloon, single freeze, cryo isolation of the pulmonary veins is highly effective in treating paroxysmal atrial fibrillation

B. Keweloh[1], M. Winterhalter[2], S. Siaplaouras[1], G. Calmez[1], F. Kleber[1]. *[1]Unfallkrankenhaus Berlin, ukb, Berlin, Germany; [2]SRH Waldkrankenhaus, Gera, Germany*

Introduction: Cryo-balloon based pulmonary vein isolation has emerged as a very safe and potentially curative therapy for paroxysmal atrial fibrillation (PAF). So far two different balloon sizes, one or two transseptal punctures and several long freezing applications per vein have been used.
Hypothesis: We tested the hypothesis that the small 23mm balloon efficiently occludes all pulmonary veins in patients with normal atrial sizes and that after a complete occlusion a single freezing interval efficiently isolates the pulmonary vein and is sufficient for therapeutic success.
Methods: We performed pulmonary vein isolation in 25 consecutive patients with symptomatic PAF in spite of treatment with β-blockers and with normal atrial sizes. Except in one patient we used exclusively the small 23mm balloon. In 85 from 104 treated veins without an early bifurcation a single cryo application per vein was used. Isolation of the veins was proven by use of a Lasso catheter testing exit- and entrance block. Follow up was done by 72h ECG at 3 and 6 month and will be done at 12 and 18 months in the ongoing trial, respectively.
Results: In 25 patients 107 pulmonary veins were treated. 95% could be angiographically totally occluded and 98% were electrically isolated. 11 from 25 patients had few symptomatic reoccurances of atrial fibrillation during the first weeks after PVI. The rate of freedom from atrial fibrillation after 3 and 6 months was 86% and 78%. We saw no cases of pulmonary vein stenosis, no fistula to the esophagus, one case of pericardial effusion and one left atrial flutter. During ablation of the right superior pulmonary vein 7 of 25 patients developed acute right phrenicus paresis. After immediately stopping of the cryo application the paresis was regredient in all cases. Despite a short freezing application time all of these veins proofed to be isolated as well.
Conclusion: Small balloon, single freeze cryo balloon ablation is highly efficient in treating paroxysmal atrial fibrillation in the short term follow up. After angiographic complete pulmonary vein occlusion a single freezing interval is sufficient to isolate the vein. The high isolation rate is specific for the very good occlusions by use of the small (23mm) balloon and cannot be reached with a single application of the big (28mm) balloon. Isolated right superior veins despite early stopped cryo applications in case of phrenicus paresis indicate that much shorter cryo application times than commonly used might be sufficient to isolate the veins.

P1617 Circumferential pulmonary vein ablation: does the use of a circular mapping catheter improve results? Prospective randomized study

L. Mont[1], D. Tamborero[1], A. Berruezo[1], E. Guasch[1], M. Nadal[1], M. Matiello[1], D. Andreu[1], M. Sitges[2], J. Brugada[1]. *[1]Hospital Clinic, University of Barcelona - Thorax Institute; Cardiology Dep. - Arrythmia Section, Barcelona, Spain; [2]Hospital Clinic, University of Barcelona - Thorax Institute; Cardiology Dep. - Echocardiographic Lab, Barcelona, Spain*

Introduction: To evaluate whether the use of a circular mapping (CM) catheter improved the outcome of circumferential pulmonary vein ablation (CPVA).
We hypothesized that assessment of pulmonary vein (PV) antrum isolation using a CM catheter could improve the outcome of the procedure as compared to use of a single catheter in the left atria (LA) both to ablate and map the electrical signal.
Methods: A series of 146 consecutive patients (83% males, 53±10 years, 53% paroxysmal AF) were randomized to two ablation strategies. In both, ipsilateral PV encirclement until disappearance or dissociation of the local electrogram within the surrounded area was performed by an irrigated tip catheter. In the first group, only the radiofrequency catheter was used, both to map and ablate (CPVA group, n=73). In the other group, a CM catheter was added to assess the electrical activity of the PV antrum (CPVA-CM group, n=73). In addition, ablation line along the LA roof was created in all patients. Procedure and fluoroscopic times were longer in the CPVA-CM group ($p<0.05$).
Results: Severe procedure-related complications occurred in 1 (1.4%) and 3 (4.1%) patients in the CPVA and CPVA-CM groups, respectively (p=0.317). Procedural efficacy was lower in the CPVA group as compared to the CPVA-CM: after a mean follow-up of 9±3 months, 31 (42.5%) and 47 (64.4%) patients, respectively, were arrhythmia-free without antiarrhythmic medication (p=0.008).
Conclusions: The use of a CM catheter to ensure the isolation of PV antrum improved the success of the CPVA although it increased some procedural requirements.

P1618 Catheter ablation of atrial fibrillation: three-dimensional transesophageal echocardiography replaces other imaging techniques for pulmonary vein visualization prior to an ablation procedure

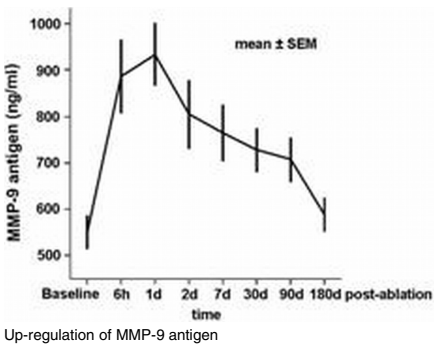
K. Kettering, S. Von Bardeleben, H. Mollnau, F. Gramley, C. Weiss. *Klinikum der Universitaet Mainz, Mainz, Germany*

Catheter ablation has become the first line of therapy in patients with symptomatic, recurrent, drug-refractory atrial fibrillation (AF). However, it is still challenging because of the high degree of variability of the pulmonary vein (PV) anatomy. Therefore, 3-D imaging systems (CT and MRI) are frequently used prior to an ablation procedure. Alternatively, 3-D transesophageal echocardiography (TEE) provides an excellent overview over the individual left atrial morphology without some of the limitations associated with other imaging techniques.
Methods: In 24 patients, 3-D TEE was performed immediately prior to an ablation procedure (paroxsmal AF: 12 patients, persistent AF: 12 patients). The images were available throughout the ablation procedure. Two different ablation strategies were used. In patients with paroxysmal AF, the cryoablation technique was used (Arctic Front Balloon, CryoCath Technologies). In the other patients, a circumferential pulmonary vein ablation was performed using the CARTO system (Biosense Webster). The PV isolation was verified using a circular mapping catheter in all cases.
Results: A 3-D TEE could be performed successfully in all patients and all PV ostia could be evaluated. The image quality was excellent and several variations of the PV anatomy could be visualized precisely (e.g. common PV ostia, accessory PVs, varying diameter of the left atrial appendage and its distance to the left superior PV). The image quality was good even if AF with rapid ventricular response was present during the examination. The TEE findings correlated well with the PV angiographies performed during the ablation procedures. All ablation procedures could be performed successfully (mean number of completely isolated PVs: 3.8±0.2 (cryo group), 3.6±0.4 (Carto group)). At 6-month follow-up, 71% of all patients were free from an arrhythmia recurrence (cryo group: 8/12 patients (67%), Carto group: 9/12 patients (75%)). There were no major complications.
Conclusions: Three-dimensional TEE overcomes most of the limitations of other imaging techniques (CT/MRI) currently used for evaluation of the PV anatomy (such as radiation exposure and inappropriate image quality in the presence of AF). A TEE should be performed prior to an AF ablation procedure to rule out the presence of a left atrial thrombus in all patients anyway. Thus, a 3-D TEE does not result in additional patient discomfort or cost and is less time-consuming than other techniques. Therefore, AF ablation procedures can be performed safely and effectively based on prior 3-D TEE imaging.

P1619 Biochemical markers reflecting cardiac repair predict left atrial structural changes and clinical outcome after ablation of atrial fibrillation

B. Richter, M. Gwechenberger, A. Socas, G. Zorn, J. Bergler-Klein, M. Marx, C. Bieglmayer, T. Binder, J. Wojta, H.D. Goessinger. *Medical University of Vienna, Vienna, Austria*

Purpose: Radiofrequency (RF) ablation of atrial fibrillation (AF) creates left atrial (LA) tissue damage initiating a cardiac repair process. We sought to prospectively monitor this repair process by biochemical markers and to evaluate its clinical relevance.
Methods: 30 consecutive patients (57.2±9yrs, 63% males) with paroxysmal AF underwent AF ablation comprising CARTO-guided LA antrum ablation, Lasso-guided segmental pulmonary vein isolation and ablation of complex fractionated potentials. Matrix metalloproteinase 9 antigen (MMP-9), transforming growth factor-β 1 (TGF-β1), both key regulators of tissue repair, and the aminoterminal propeptide of type III procollagen (PIIINP), representing collagen III turnover, were determined in venous blood samples before and 6 hours, 1, 2, 7, 30, 90 and 180 days after ablation.
Results: At 6 months of follow-up including 7-day-Holter-monitoring, 60% of patients were AF-free after a single procedure. All markers showed a significant ablation-induced up-regulation (maximum vs. baseline: MMP-9: 2.2±0.1-fold (mean ± SEM), TGF-β1: 3.3±0.4-fold; PIIINP: 1.4±0.1-fold). The markers remained significantly elevated until day 90 (MMP-9), day 7 (PIIINP) and day 2



Up-regulation of MMP-9 antigen

(TGF-β1) after ablation. The area under the curve (AUC) of MMP-9 and TGF-β1 significantly correlated with the ablation-induced reduction of LA volume measured by echocardiography before and 6 months after ablation (MMP-9: R=-0.56, $p<0.05$; TGF-β1: R=-0.57, $p<0.05$). The AUC of PIIINP predicted an adverse ablation outcome ($p<0.05$).
Conclusions: Markers of tissue healing show a significant up-regulation after AF ablation detectable for up to 3 months. A more pronounced up-regulation of TGF-β1 or MMP-9 levels is associated with a stronger reduction of LA size. High PIIINP predicts a poor ablation outcome.

P1620 Left atrial appendage isolation: evidence of discrete connections between the left atrial appendage and the main chamber

L. Di Biase[1], J.D. Burkhardt[2], R. Horton[2], J. Sanchez[2], G. Gallinghouse[2], D. Patel[2], S. Beheiry[3], D. Lakkireddy[4], R.A. Schweikert[5], A. Natale[2]. *[1]Texas Cardiac Arrhythmia Institute at St David Medical Center, Un. of Texas and University of Foggia, Austin, United States of America; [2]Texas Cardiac Arrhythmia Institute at St David Medical Center, Austin, United States of America; [3]Sutter Pacific Hospital, San Francisco, United States of America; [4]University of Kansas, Kansas City, United States of America; [5]Akron General Hospital, Akron, United States of America*

Introduction: The left atrial appendage has been recognized as a potential site of initiation of atrial fibrillation. Electrical isolation of the left atrial appendage (LAA) is sometimes required. We evaluated the extent of lesions required to isolate the LAA.
Methods: 987 consecutive patients (76% chronic and 24% paroxysmal) undergoing catheter ablation for symptomatic and drug resistant atrial fibrillation have been enrolled in this study. Patients requiring isolation of the left atrial appendage (LAA) were identified. In each case the extent of ablation required to isolate the LAA was recorded.
Results: 86 patients (52 female) out of 987 [(8.7%), (81 patients with chronic and 5 patients with paroxysmal AF), required isolation of the left atrial appendage after triggers initiating atrial fibrillation from this location were documented. The prevalence of this finding was 10.9% (81/741 pts) in chronic patients and 2% (5/246 pts) in the paroxysmal patients.
In 82% (71) of these patients, isolation of the LAA was achieved with segmental ablation. The remaining patients required nearly circumferential ablation.
Conclusions: Isolation of the LAA may be necessary during catheter ablation of atrial fibrillation. Similarly to the pulmonary veins, most LAAs can be isolated with segmental ablation.

P1621 Duty-cycled, unipolar-bipolar RF ablation via multi-electrode catheter in patients with paroxysmal atrial fibrillation

S. Yuan, O. Kongstad. *Lund University Hospital, Lund, Sweden*

Introduction: Techniques for catheter ablation of atrial fibrillation (AF) continue to improve, but often require complex equipment, high level of operator skill, and a long learning curve.
Methods: To simplify AF ablation, we investigated a system featuring a multi-channel radiofrequency (RF) generator that simultaneously delivers duty-cycled, bipolar-unipolar energy to operator selectable electrodes of a decapolar circular catheter (PVAC, Ablation Frontiers) for achieving pulmonary vein (PV) isolation via antrum ablation. RF was delivered in a temperature-controlled manner to achieve a target of 55-60 C° with power limited to 10W per electrode. PV angiography was performed to facilitate identification of the PV ostium. End-points are disappearance of all PV potentials and electrical isolation of the PVs as verified by use of a circular mapping catheter.
Results: Since Sept. 2007 we have treated 45 patients with paroxysmal AF, aged 60±9 years, using this technique. Average number of RF applications per PV was 7±3. Procedure time was 92±16 min and fluoroscopy time was 19±9 min. CT/MRI performed pre-procedure and at 2-4 months follow up ruled out asymptotic PV stenosis. No other complications were observed. 29 of the patients have had ≥ 5 months follow up. Holter monitoring demonstrated freedom of AF in 17/29 (59%) patients and significant reduction of AF burden (>90% reduction) in 9/29 (31%) patients. Thus, total effective rate after a single procedure was 90% (26/29 patients), though 17 of them (58%) are still on antiarrhythmic drugs.
Conclusion: This single-catheter method is safe, efficient, and feasible for AF ablation and has early results comparable to those of widely reported techniques. In addition, simplified catheter manipulation, shorter learning curve, shorter procedure time and independence from 3D-mapping system may make the method available to a larger number of centers.

P1622 Acute and long-term outcome of remote magnetic navigation for ablation of atrial fibrillation using a magnetic irrigated ablation catheter

X. Chen, J.H. Svendsen, S. Pehrson. *Rigshospitalet (The Heart Centre), Copenhagen, Denmark*

Purpose: Unavailability of magnetic irrigated (MI) catheter had limited the widespread use of the remote magnetic navigation (RMN) system in radiofrequency (RF) ablation of atrial fibrillation (AF). The purpose of current study was to evaluate the feasibility of the newly introduced MI catheter in ablation of atrial fibrillation (AF).
Methods: Ninety-eight patients (age 58±13, 75 male, 42 (42%) with persistent/permanent AF) underwent RF ablation using a MI catheter and RMN system. In the first series of 37 patients (group I), a prototype MI catheter was used. In the recent series of 61 patients (group II), the procedures were performed using a re-introduced modified MI catheter, which is now commercially available. The irrigation rate was set to 10-20 ml/min, with a target temperature of 48 C° and the power limit of 40 watts. For paroxysmal AF, pulmonary vein (PV) circumferential isolation and roof linear ablation were performed. For persistent/permanent AF, fractionated potentials in left atrium were targeted in group I, and in both left and right atrium in group II. After encirculation of PVs, careful mapping within the PV antrum was performed. If the AF was not terminated by RF ablation, patients were DC cardioverted and mapping within the PV antrum was re-performed during SR.
Results: Complete PV isolation was achieved in 94 of 98 (96%) patients. In 13 of 42 (31%) patients with persistent/permanent AF, AF was terminated by RF ablation. Stable SR was achieved in all patients after the procedure. The mean total procedure time was 141±35 min and RF application time was 39±22 min. The total fluoroscopy time was 7±5 min. Charring on catheter tip was found in two (2/37, 5%) group I procedures, but none in the last 61 group II procedures using the modified MI catheter. No major complications were observed during or after the procedures. During a mean of 12±2 (11-14) months follow up, 27 of the first 37 patients (73%) were free of AF.
Conclusions: RMN for ablation of AF using magnetic irrigated catheter is safe, with a short procedure- and fluoroscopic- time, and a promising long-term efficacy.

P1623 The effect of ganglionated plexi ablation on atrial fibrillation triggers: long-term results

E. Pokushalov, A. Romanov, S. Artemenko, P. Shugaev, A. Turov, N. Shirokova. *State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation*

Purpose: Elimination of the triggers is an important factor for the efficacy of the catheter ablations in patients with atrial fibrillation (AF). Existing data confirms that focal firing from the pulmonary veins (PV) is determined by autonomic nervous system (ANS) hyperactivity, that is by the presence of compromised ganglionated plexi (GP) that produce excess amounts of neurotransmitters. The purpose of this study was to assess the impact of GP ablation on atrial fibrillation triggers.
Methods: Spontaneous triggers and those provoked with isoproterenol (up to 20 microg/min) and/or cardioversion in 73 patients with AF were identified using multipolar catheter recordings. Radiofrequency ablation of the main clusters of GPs in the left atrium was performed in all patients with symptomatic, drug-refractory, paroxysmal (n = 56) and persistent (n = 17) AF.
Results: 118 reproducible triggers were noted in 73 patients with 91 from PV and 27 (22.8%) from non-PV sites ($p < 0.05$). The most PV triggers (41.7%) originated from "carina zone" segments ($p < 0.05$) from both right (47 triggers) and left (44 triggers) PVs. Ablation of the main clusters of GPs in the left atrium (without any changes of the PV conduction properties evaluated by multipolar catheter) abolished focal firing from the PVs in 69 (94.5%) patients and decreased the ability to induce sustained AF (>3 min) in all patients. GP ablation lead to the elimination of the triggers which were located at some distance from catheter ablation zones. During 14±8 months of followup after a single ablation procedure, 58.9% of patients were in sinus rhythm without antiarrhythmic drugs, 16.4% had AF, 10.9% had both AF and atrial flutter, 1.4% had persistent left atrial flutter, and 12.4% had sinus rhythm on antiarrhythmic drugs. The second ablation procedure was performed in 27.3% of patients. The 3-D maps from the first and repeated procedures were compared to find presence of any gaps. All the patients that underwent repeated procedure had gaps in the areas of catheter ablation. 18 out of 20 patients had triggers different from the initial localization ($p < 0.05$), 95% of which were adjacent to the gaps.
Conclusion: GP ablation lead to the elimination of most of the triggers, including the ones that were located at a significant distance from the ablation areas thus confirming their close connection with ANS. This fact can play a very important role in increasing the efficacy of the existing methods of AF ablation.

P1624 Antral vs. ostial circumferential isolation of pulmonary veins in patients with atrial fibrillation; when is antral isolation needed?

M. Kuniss, T. Neumann, S. Zaltsberg, A. Berkowitsch, D. Erkapic, D. Pajitnev, C. Hamm, H.F. Pitschner. *Kerckhoff Klinik GmbH, Bad Nauheim, Germany*

Introduction: Previous studies have shown that antral isolation of pulmonary veins (PVI) is a competing therapy strategy in comparison to conventional ostial circumferential PVI in patients with drug resistant atrial fibrillation. However no stratification regarding type of AF and stage of left atrial remodelling was performed in these studies. Our aim was to investigate efficiency of antral and ostial circumferential PVI depending on patients characteristics.
Methods: A total of 255 pts (183 male, age=58 IQR (49-63) years, n=136 parox-

ysmal AF, history of AF 6 IQR (3-8) years, LVEF 60% IQR (57-62), left atrial size 39 (35-42) x 55 (50-59) mm, n=23 with CAD, n=152 with hypertension) were enrolled in the study. In 105 pts the ostial circumferential PVI (additional linear lesions n=38 (36%)) was performed with LASSO mapping. In remaining 150 pts multipolar HD catheter (MESH, Bard inc.) was used for mapping and antral PVI was done (additional linear lesions n=65 (43%)). The pts were stratified according to type of AF (paroxysmal - 0; persistent - 1), and according to echo measurments of left atrial size (LAS), (LAS $<$ 42x60 mm - 0; LAS $>$ 42x60 mm - 1). The score was calculated as summation. The endpoint of study was first documented AF recurrence $>$ 30 sec. The first three months after index procedure were considered as blanking period. During the follow up period every 3 months 7-day Holter ECGs or event recordings for 3 weeks were performed.
Results: Out of 255 enrolled pts 143 (56.1%) were on sinus rhythm (SR) within follow up of 18 IQR (7-24) months. Generally the pts with lower score had better outcome independently of the kind of ablation. However, in pts with persistent AF and enlarged left atrium (score 2) the antral PVI (53.7% in SR) was revealed to be more efficient than the ostial one (22.2% in SR; p=0.021). In pts with score $<$2 no significant differences in outcome after antral and circumferential ostial PVI could be revealed (Score 0: 77.6% vs 61.1% (p$>$0.05); Score 1: 51% vs 39.4% (p$>$0.05)).
Conclusions: The advantage of antral PVI was revealed only in pts with persistent atrial fibrillation and enlarged left atrium.

P1625 The impact of radiofrequency catheter ablation combined with percutaneous transvenous mitral commissurotomy: a less invasive hybrid therapy for atrial fibrillation associated with mitral stenosis

T. Machino, H. Tada, K. Kuroki, H. Yamasaki, M. Igarashi, T. Arimoto, Y. Sekigchi, Y. Seo, K. Kuga, K. Aonuma. *University of Tsukuba, Tsukuba, Japan*

Background: The rhythm control of atrial fibrillation (AF) associated with mitral stenosis (MS) is often difficult by using antiarrhythmic drugs (AADs), even after a percutaneous transvenous mitral commissurotomy (PTMC). A maze procedure combined with mitral valve surgery has been well established for the treatment of AF and MS. Few studies, however, have examined the efficacy and safety of radiofrequency catheter ablation (RFCA) combined with a PTMC. Thus, this historical prospective study was designed to clarify this point.
Methods: Twenty consecutive patients with drug-resistant AF and rheumatic MS underwent RFCA combined with a PTMC (n=10; persistent AF-8, chronic AF-2; RFCA group) or DC following a PTMC (n=10; persistent AF-7, chronic AF-3; DC group). In all the patients, the mitral valve area (MVA) was less than 1.5 cm^2; the mitral valve morphology was amenable to a PTMC; and more than two AADs had been ineffective to maintain sinus rhythm (SR). In RFCA group, the segmental pulmonary vein isolation (PVI) was performed in the initial 5 patients, and the extensive PVI was performed in the remaining 5 patients. In DC group, transthoracic DC was performed with step-up protocol until SR was achieved or the highest energy was reached.
Results: No significant difference was found in the baseline parameters, including age, duration of AF history, and left atrial size between the 2 groups. Although the MVA and pulmonary artery wedge pressure were significantly improved in both groups after the PTMC, no significant difference was found in those parameters between the 2 groups before and after the PTMC. In RFCA group, elimination of all PV potentials and complete entrance block into all PVs were achieved, and noninducibility of AF was also confirmed in all the 10 patients. In DC group, although SR was achieved in 8 patients (80%), the DC failed to restore SR despite twice shocks with maximum energy in the remaining 2 patients (20%). During a mean follow-up period of 4.0$\pm$2.7 years, 8 patients (80%) in RFCA group were maintained in SR, as compared with 1 patient (10%) in DC group (hazard ratio, 0.16; 95% confidence interval, 0.03 to 0.75; P=0.008 by the log-rank test). The prevalence of the concomitant use of Class III AADs was comparable between the 2 groups (p=0.50). No complications occurred during the procedure and follow-up period in either group.
Conclusion: The hybrid therapy of RFCA and PTMC was safe and feasible as a less invasive strategy for AF and MS. Furthermore, it significantly improved the AF free survival rate compared to DC following a PTMC in patients with AF and MS.

P1626 Ganglionated plexi ablation for chronic atrial fibrillation: acute effects and long-term outcome

E. Pokushalov, A. Romanov, S. Artemenko, P. Shugaev, A. Turov, N. Shirokova. *State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation*

Purpose: Ganglionated plexi (GP) ablation is a new approach for the treatment of atrial fibrillation (AF). The purpose of this study was to prospectively assess acute and long-term successes of GP ablation for chronic AF.
Methods: Radiofrequency ablation of the main clusters of GPs in the left atrium was performed in 89 patients with symptomatic, drug-refractory, chronic AF (71 men, 56$\pm$7 years of age). They had been in chronic AF for 3.4$\pm$3.2 years, 3.2$\pm$2.8 cardioversion procedures and 2.1$\pm$0.9 class I/III antiarrhythmic drugs had failed.
Results: At the end of the ablation procedure AF had terminated in 21 of 89 patients (23.6%) by conversion to sinus rhythm (9 of 21 patients, 42.8%) or transformation to atrial tachycardia (12 of 21 patients, 57.2%). During RF applications, before SR was stabilized, 7 patients (33.3%) had one to several short-term SR restoration episodes and then AF recurrence was taking place ("stop and restart" effect). During 13$\pm$7 months of follow-up after a single ablation procedure, 58.4% of patients were in sinus rhythm without antiarrhythmic drugs, 16.8% had AF, 13.5% had both AF and atrial flutter, 2.2% had persistent atrial flutter, and 9.1% had paroxysmal AF on antiarrhythmic drugs. The second ablation procedure was performed in 32.5% of patients. Rapid activity between PV-LA junctions and adjoining GP was prevailing. There were multiple macroreentrant circuits in the majority of patients with atrial flutter. At 16$\pm$9 months after the last ablation procedure, 71.9% of patients were in sinus rhythm without antiarrhythmic drugs, 19.1% had persistent AF, 7.9% had paroxysmal AF, and 1.1% had atrial flutter. Independent predictors of later arrhythmia recurrences were longer AF duration (OR 1.06), left atrial volume (OR 1.21), history of hypertension (OR 1.58).
Conclusion: GP ablation in chronic AF leads to acute AF termination in 23.6% and long-term maintenance of sinus rhythm in 71.9% of cases. Rapid activity in the pulmonary veins and multiple macroreentrant circuits are common mechanisms of recurrent atrial arrhythmias.

P1627 Mechanistic insights, results of catheter ablation, and risk factors for atrial tachycardia after ablation of AF: ostial PV ablation, circumferential PV ablation and GP-ablation

A. Romanov, E. Pokushalov, P. Shugaev, S. Artemenko, A. Turov, N. Shirokova. *State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation*

Purpose: Patients who undergo catheter ablation of atrial fibrillation (AF) may develop atrial tachycardia (AT) during follow-up. The aim of this study was to determine the mechanism of AT that occurs after ablation of AF.
Methods: One hundred and forty five patients underwent an ablation procedure for AT after ostial PV ablation (n=21), circumferential PV ablation (n=86) and ganglionated plexi (GP) ablation (n=38) for AF. The 3-D maps from the AF and AT procedures were compared to determine the factors causing AT.
Results: A total of 197 ATs were mapped. Re-entry mechanism was found in 14 (58.3%) after ostial PV ablation, 117 (91.4%) after circumferential PV ablation and 14 (31.1%) after GP ablation. Focal mechanism was found in 10 (41.7%) after ostial PV ablation, 11 (8.6%) after circumferential PV ablation and 31 (68.9%) after GP ablation. 181 of those were gap-related ATs (145 re-entry and 36 focal ATs). Re-entry AT had more gaps in the left atrial istmus than did focal AT (89.8% vs 0%, P $<$ 0.01). Focal AT had a higher incidence of gap in the PV-LA junctions compared with re-entry AT (91.3% vs 11.6%, P $<$ 0.01). Re-entry mechanism prevailed in patients with performed ablation lines (ostial and circumferential), ATs were mostly terminated during the ablation creating the mitral and roof lines with crossing of the gaps. Focal mechanism was prevailing in patients after GP ablation, with the main sources of focal activity situated between PV-LA junctions and adjoining GP. Catheter ablation was successful in 72 of the 103 patients (69.9%) with re-entry mechanism of AT and in 39 of the 42 patients (92.8%) with a focal mechanism of AT. After a mean follow-up of 12$\pm$11 months, 102 of the 145 patients (70.4%) were free of AT/AF without antiarrhythmic medications.
Conclusion: These discoveries allow us to assume that the location of the AT gap may be related with the complex anatomy of the LA and most cases of AT can be prevented by linear lesions limitation, linear block evidence, and thorough ablation in PV-LA area during the initial AF procedure.

P1628 Is cryo-balloon isolation of the pulmonary veins safe for the oesophagus?

J.-S. Hermida, M. Kubala, V. Mouquet, A. Fournier, A. Jeu, S. Traulle. *Universiy Hospital, Amiens, France*

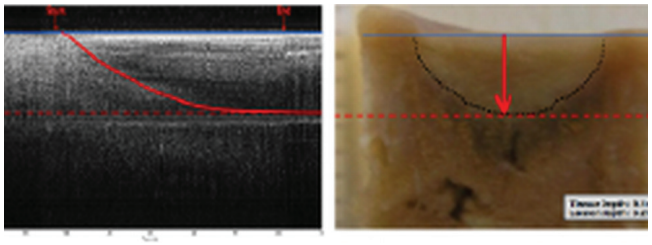
Preservation of the oesophagus integrity during RF catheter ablation of atrial fibrillation (AF) is a permanent and major concern. Preliminary reports have suggested that cryo-ablation avoid the risk of injury to the oesophagus. The aim of the study was to monitor oesophageal temperature during cryo-balloon isolation of PVs.
Methods: Balloon cryo-isolation procedures were performed in the left superior (LS), left inferior (LI), right superior (RS) and right inferior (RI) pulmonary veins (PV) in 105 patients (55$\pm$11 y.o; M=82) with paroxysmal (n=75) or persistent (n=30) AF. Cryo ablations were completed during 5 minutes periods. Electrograms of the targeted PVs were recorded before and after the cryo-ablation. Temperatures of the PVs and of the oesophagus were measured during cryo-ablation. The closest position between the balloon and the thermal probe in the oesophagus was checked by using fluoroscopy.
Results: A significant decrease of the temperature in the oesophagus was observed in all the cryo-ablations. The lowest temperatures were observed in the LSPV vs. RSPV (32.9$\pm$4.2 vs. 34.7$\pm$1.5°C; p=0.02) and in the LIPV vs. RIPV (32.5$\pm$2,2 vs. 34.2$\pm$2.2°C; p=0.02). Oesophageal temperature decreased less than 30°C in 25% of the pts (26/105) and less than 20°C in 5% of the pts (5/105). Oesophageal endoscopy was performed in the 2 pts in whom the temperature dropped to less than 15°C. A superficial parietal lesion associated to a clot was visualized in 1 case which recovered under PPI treatment. In the other case, a

12 h delayed tamponnade needing percutaneaous drainage occurred. The reduction of the oesophageal temperature under 20°C occurred in 5/5 cases with the 28 mm diameter balloon.
Conclusion: We observed, mainly in the left PVs, a weak but significant cooling of the oesophagus during cryo-balloon isolation of pulmonary veins. A temperature drop in the oesophagus less than 20°C occurred in 5% of the pts and should be avoided.

P1629 Real time lesion assessment using a combined radiofrequency and ultrasound ablation catheter

M. Wright[1], E. Harks[2], F. Suijver[2], Y. Shi[2], S. Deladi[2], M. Barley[2], F. Sacher[1], M. Hocini[1], M. Haissaguerre[1], P. Jais[1]. *[1]Hopital Cardiologique du Haut Lévêque, CHU Bordeaux, Pessac, France., Bordeaux, France; [2]Philips Research, Eindhoven, Netherlands*

Introduction: Although pulmonary vein isolation is an effective treatment for paroxysmal AF, the recurrence rate due to pulmonary vein reconnection is unacceptably high. This may be due to tissue oedema and ineffective lesions. We used a combined ultrasound probe and radiofrequency (RF) ablation catheter to determine whether lesion development could be assessed in real time.
Methods: In an in vivo open chest model, RF lesions were delivered to the atria and ventricles in 3 adult sheep using a custom-made irrigated ablation catheter (12Fr) with integrated ultrasound monitoring. During ablation changes in tissue contrast were monitored in real-time at the site of RF delivery using high frequency ultrasound (27MHz). The real-time ultrasound data were stored for off-line analysis. After the experiments the sheep were sacrificed and the heart immediately excised. The ultrasound data were blindly assessed by 3 observers and compared to the lesion depth.
Results: Ten RF lesions were delivered epicardially to the right ventricle (60sec, 5W, irrigation 10ml/min). Mean impedance before ablation was 179±18Ω and decreased by 39±15Ω during ablation. Mean tissue depth in the right ventricle, measured post mortem was 7.3±1.7mm. The mean lesion depth measured post mortem was 4.1±0.3mm (zone of haemorrhage) and 3.0±0.3mm (inner necrotic zone). This compared to the lesion depth as measured by ultrasound of 2.9±0.5mm (R=0.96), indicating that the changes in ultrasound contrast correlated with the formation of necrotic tissue.



Real Time Ultrasound of RF Lesions

Conclusion: Real time image assessment is accurately measured using a combined RF and ultrasound catheter and may allow power delivery to be accurately titrated during ablation resulting in improved clinical outcomes.

P1630 Catheter ablation of atrial fibrillation: radiofrequency catheter ablation for redo procedures after pulmonary vein isolation with the cryoballoon technique

K. Kettering, H. Mollnau, F. Gramley, C. Weiss. *Klinikum der Universitaet Mainz, Mainz, Germany*

Catheter ablation has become the first line of therapy in patients with symptomatic, recurrent, drug-refractory atrial fibrillation. Cryoablation has been shown to be a safe and effective technique for pulmonary vein isolation. However, the arrhythmia recurrence rate is high after cryoablation procedures and there are no established strategies for redo procedures in these patients. Therefore, we have summarized our initial eperience with two different strategies for redo procedures using radiofrequency catheter ablation.
Methods: Seventeen patients (paroxsmal AF: 12 patients, persistent AF: 5 patients) had to undergo a redo procedure after initially successful circumferential PV isolation with the cryoballoon technique (Arctic Front Balloon, CryoCath Technologies). The redo ablation procedures were performed using a segmental approach or a circumferential ablation strategy (CARTO; Biosense Webster) depending on the intra-procedural findings.
Results: During the redo procedure, a mean number of 2.2±0.5 re-conducting PVs were detected (using a circular mapping catheter). In 13 patients, a segmental approach was sufficient to eliminate the residual PV conduction because there were only a few recovered PV fibers. In the remaining 4 patients, a circumferential ablation strategy was used because of a complete recovery of the PV-LA conduction.
All recovered PVs could be isolated sucessfully again. At 3-month follow up, 82% of all patients were free from an arrhythmia recurrence (14/17 patients). There were no major complications.
Conclusions: In patients with an initial circumferential PVI using the cryoballoon technique, a repeat ablation procedure can be performed safely and effectively using radiofrequency catheter ablation. In most cases only a few re-conducting PV fibers were found and therefore, a segmental re-ablation approach seems to be sufficient in the majority of patients.

P1631 Impact of ablation in slow pathway area on vagal modulation to atria

Y. Xiaomeng, S. Zhang, L. Gao, Y. Xia, D. Yang, Y. Dong, D. Chang, Z. Lin, Y. Yang. *Department of Cardiology, First affiliated hospital of Dalian Medical University, Dalian, China, People's Republic of*

Purpose: This study aimed to investigate the impact of ablation in slow pathway area on vagal modulation to the sinus rhythm cycle length (SCL),the atrial effective refractory period (ERP) and vulnerability window (VW) of atrial fibrillation (AF).
Methods: 11 mongrel dogs were involved in this study. Bilateral cervical sympathovagal trunks were decentralized for vagal stimulation (VS). Metoprolol was given to block sympathetic effects. Linear lesion was performed from the middle area of Koch triangle to the coronary sinus ostium. ERP, VW and SCL were measured at high right atrium (HRA), lower right atrium (LRA), distal (CSd) and proximal coronary sinus (CSp) with and without VS.The underlying tissue were excised and stained with hematoxylin and eosin for microscopic examination.
Results: (1) SCL shortening during vagal stimulation remained unchanged before and after ablation (107±19 vs 108±8 bpm,$P>0.05$). (2) After ablation,the ERP shortening during vagal stimulation remained unchanged at HRA (55±34 vs 69±37ms, $P>0.05$), decreased slightly at CSd (42±32 vs 55±30ms, $P=0.08$), decreased significantly at LRA (19±21 vs 66±24ms, $P<0.001$) and CSp (7±18 vs 46±24ms, $P<0.001$). (3) After ablation,the VW of AF atrial fibrillation to vagal stimulation significantly decreased at LRA (1±3 vs 49±36ms, $P<0.005$) and CSp (10±12 vs 45±34ms, $P<0.05$), decreased slightly at CSd (35±37 vs 57±28ms, $P=0.07$), but remained unchanged at HRA (63±31 vs 63±25ms, $P>0.05$). (4) The architecture of ganglia at slow pathway area was significantly damaged by ablation.
Conclusions: The ablation in the slow pathway area result in remarkable vagal dennervation and attenuating the susceptibility to vagal mediated AF at the CSp and LRA,partly dennervation to the CSd,but could not modify the vagal innervation to the HRA.

P1632 Early and late recurrences after ganglionated plexi ablation for atrial fibrillation: prognostic value and the effect of reablation

A. Romanov, E. Pokushalov, S. Artemenko, P. Shugaev, A. Turov, N. Shirokova. *State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation*

Purpose: Several studies have reported early (EAT) and late (LAT) atrial tachyarrhythmias following atrial fibrillation (AF) ablation, but there is no information regarding recurrences of atrial arrhythmia after ganglionated plexi (GP) ablation. The purpose of this study was to investigate the predictors and the relationship between EAT and LAT after GP ablation.
Methods: A total of 892 patients with paroxysmal (56%), persistent (23%), and permanent (21%) AF underwent GP ablation. EAT and LAT were defined as an episode of AF or atrial flutter/tachycardia lasting longer than 1 minute that occurred within the first 3 months of ablation and after 3 months postablation, respectively.
Results: After a single ablation procedure, EAT developed in 527 (59%) patients and LAT in 205 (23%) patients. Independent predictors of EAT were longer: AF duration (OR 1.12), left atrial volume (OR 1.37), history of hypertension (OR 1.43). Patients with (n=68) and without (n=137) early reablation had similar baseline characteristics including echocardiographic parameters and the type of AF. During a mean follow-up of 18±9 months, 12 patients (17.6%) without early reablation experienced late clinical recurrences. Patients with early reablation had lower rate of clinical recurrences (14.2% vs 17.6%, $P < 0.05$) and fewer additional procedures (9.1% vs 6.8%, $P < 0.05$). However, the total number of procedures over the entire follow-up was greater in those patients with early reablation (2.8±0.4 vs 2.2±0.6, $P < 0.05$). Independent predictors of LAT were longer AF duration (OR 1.09), left atrial volume (OR 1.28), history of hypertension (OR 1.49). There was also a tendency for patients who underwent repeated ablations in combination of different procedures (ostial or circumferential) to have a higher AF-free survival when compared with patients subjected to the same procedure (P-value for log-rank test = 0.043).
Conclusion: The presence of EAT can not be considered as predictor of LAT and is not a reason for performing a repeated procedure. Longer AF duration, left atrial volume, history of hypertension are independent predictors of EAT and LAT.

P1633 Safety and indication of substrate-based catheter ablation of left ventricular tachycardias in patients with icd shock deliveries. a single centre experience

J. Schreieck, H.J. Weig, F. Girrbach, R. Laszlo, N. Rueb, S. Weretka, C. Freising, M. Gawaz. *Department of Cardiology, Medical University Tuebingen, Tuebingen, Germany*

Purpose: Catheter ablation of left ventricular tachycardias (VT) in patients with ICD shock deliveries are restrictedly used due to serious risks and uncertain outcome. We report our single centre experience about efficacy and safety of substrate-based VT ablation in patients with structural heart disease in order to discuss the indication for catheter ablation.
Methods: Over a period of 7 years 151 left ventricular substrate-based ablations were performed in 103 patients with ICD shock deliveries due to unstable VTs. Arrhythmogenic areas were identified by pace mapping for documented (12-leade holters) or inducible VTs after endocardial voltage and fractionation mapping during sinus or paced rhythm. Along delineable low voltage areas of less than 1.5 mV bipolar electrograms amplitude linear ablation lines were performed through best pace mapping points otherwise most delayed and fractionated local electrograms were targeted using cooled-tip radiofrequency applications (30-40 Watts, flow: 18 ml/min) with the endpoint of non-induciblity of all clinical VTs. ACT was kept above 250s by intravenous heparin throughout the procedure and anticoagulation with heparin was continued for at least 48 hours after the procedure. Thereafter, anticoagulation was continued in most patients with coumadin for three months depending on left ventricular function and extent of ablation.
Results: Success rate for ICD shock-free survival after one year follow up accounted for 77% in post infarction patients (n=74), however, was only 52% in patients with non-ischemic cardiomyopathy (n=29). Five procedure-related serious complications occured in 151 catheter interventions accounting for a 3.3% risk per procedure, in detail two pericardial tamponade, one of them was lethal (0.7%) during a bail-out ablation of an electrical storm, two major cerebrovascular events (1.3%) and one pulmonary embolism. All post infarction patients (n=74, with 103 ablation procedures) remained free of new compromising symptoms, since the two patients with cerebrovascular embolic events survived without compromising neurological symptoms due to immediate systemic thrombolytic therapy.
Conclusions: Substrate-based catheter ablation even of unstable VTs in post infarction patients was demonstrated to have a favorable outcome, however, efficacy to risk relation was less favorable in patients with non-ischemic cadiomyopathy. Our results are in favor of an extended indication for catheter ablation of VTs in post infarction patients in case of ICD shock deliveries.

P1634 Patient characteristics and ablation procedures in electrophysiologic centers: first results from the German ablation registry

A.M. Sinha[1], J. Senges[2], K.H. Kuck[3], D. Andresen[4], E. Hoffmann[5], J. Brachmann[1] on behalf of German Ablation Registry. *[1]Klinikum Coburg, Coburg, Germany; [2]Institut fuer Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; [3]Asklepios Klinik. St. Georg, Hamburg, Germany; [4]Vivantes Klinikum Am Urban, Berlin, Germany; [5]Staedtisches Klinikum Muenchen, Bogenhausen, Munich, Germany*

Background: The German Ablation Registry is designed as a multi-centric prospective registry for electrophysiologic ablation procedures. Patient (pt) characteristics and ablation procedures are documented by >55 German electrophysiologic centers. This is the first report about preliminary data from the German Ablation Registry.
Methods and Results: From 03/07 to 02/09, 7.356 pts (4509/61.3% male, median age 58y (30-73) were included in the registry. 2808 pts (38.2%) suffered from cardiac diseases, i.e. coronary artery disease in 1433 (51.0%), hypertension in 942 (33.5%), valvular heart disease in 555 (19.8%), and cardiomyopathy in 311 pts (11.1%). LV function was normal in 5593 pts (76.0%). 7044 pts (95.8%) had recurrent palpitations, and 5747 pts (78.1%) >1 episode/month. 5060 pts (68.9%) were refractory to antiarrhythmic medication. Patients were divided into 5 groups according to their tachycardia: 1. AV nodal reentry tachycardia (AVNRT), 2. AV reenty tachycardia (AVRT)/WPW syndrome, 3. atrial flutter (AFlut), atrial macroreentry tachycardia (ART), 4. focal atrial tachycardia (FAT), 5. atrial fibrillation (AF). The Table shows the results of the ablation procedures.

Data from the German Ablation Registry

	AVNRT	AVRT/WPW	AFlut/ART	FAT	AF
Number of patients	1659 (22.6%)	454 (6.2%)	2267 (30.8%)	257 (3.5%)	2719 (37.0%)
First ablation	1571 (93.8%)	397 (86.7%)	2056 (88.8%)	209 (77.7%)	2077 (75.6%)
3D mapping	90 (5.4%)	18 (3.9%)	237 (10.2%)	121 (45.0%)	1679 (61.1%)
3D imaging (CT, MRI, ICE)	1 (0.1%)	0 (0%)	8 (0.3%)	2 (0.7%)	78 (2.8%)
Successful ablation	1636 (98.7%)	429 (94.7%)	2171 (95.9%)	212 (82.5%)	2595 (95.5%)
Recurrence before discharge	10 (0.6%)	7 (1.6%)	26 (1.2%)	13 (5.1%)	205 (7.6%)
Minor complications	14 (0.9%)	8 (1.9%)	21 (1.0%)	5 (2.1%)	74 (3.6%)
Moderate complications	16 (1.0%)	3 (0.7%)	29 (1.4%)	6 (2.5%)	66 (3.2%)

Minor complications = AV block °1 or 2, or LBBB or RBBB etc. Moderate complications = TIA, reanimation, bleeding, high degree av block, sepsis, surgical interventions, etc.

Conclusion: Patients with SVT often presented with normal LV function without structural heart diseases. In case of structural heart diseases, coronary artery disease was most frequent. Ablation for AF has become the most frequent procedure with highest use of 3D mapping and imaging systems. However, this group also showed the highest rate of recurrent procedures and complications.

P1635 Validation of PV isolation of multi-electrode duty cycled radiofrequency ablation in patients with paroxysmal and persistent atrial fibrillation

A. Elvan, W.P. Beukema, J.J.J. Smit, P.P.H.M. Delnoy, A.R. Ramdat Misier. *Isala Klinieken, Zwolle, Netherlands*

Purpose: A novel multi-electrode catheter (PVAC) combining circular mapping and duty cycled multi-electrode radiofrequency energy delivery has been developed to map and isolate the pulmonary veins (PVs). The aim of this study was to validate the isolation of the PVs using a standard circular mapping catheter.
Methods: 102 consecutive patients, age 57.9±9.6 years, with paroxysmal or persistent drug refractory AF were referred for ablation. All pts had documented AF episodes with an AF duration of 9.3±7.5 years (range 1.5-25).
Results: The total procedure time was 117±55 min (65 to 204). In 5 pts additional ablation using conventional RF catheter ablation was necessary. The mean RF ablation time required to achieve complete PV isolation was 31±8 min (range 16-51). Isolation of the PVs was confirmed using a standard circular mapping catheter. In 8 pts with persistent AF additional ablations were performed to defragmentate septal and posterior part of the left atrium. At the latest follow up 73% of the patients were in sinus rhythm.
Conclusions: 1] This novel technique can be used safely for PV isolation and LA ablation, 2] The success rate for PV isolation was 100% using the PVAC alone and confirming isolation with a standard circular mapping catheter and 3] the PVAC is more effective in smaller PVs compared to pulmonary veins with a diameter >25 mm and 4] Larger studies are required to evaluate the whether the PVAC is associated with a different complication rate compared with standard PV isolation.

P1636 Which of the methods to choose for catheter ablation of chronic atrial fibrillation: ostial PV ablation, circumferential PV ablation or GP ablation?

E. Pokushalov, A. Romanov, S. Artemenko, P. Shugaev, A. Turov, N. Shirokova. *State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation*

Purpose: Each of the main approaches to catheter ablation of atrial fibrillation (AF) is associated with limited efficacy in patients with chronic AF. The objective is to report outcomes of ostial PV ablation, circumferential PV ablation and ganglionated plexi (GP) ablation in patients with chronic AF.
Methods: The patient population was composed of 94 patients (age 57±9 years) with chronic AF who underwent catheter ablation. 28 (29.8%) of those patients underwent ostial PV ablation, 32 patients (34%) - circumferential PV ablation and 34 patients (36.2%) - GP - ablation.
Results: After a follow-up of 13±7 months, the single-procedure success rate was 17.9% (n = 5) with an additional 10.7% (n = 4) showing improvement after ostial PV ablation. The procedure was repeated in 57.2% of the cases, the success rate was 39.2% (n = 11) with an additional 17.9% (n = 6) showing improvement. All patients who underwent repeated ablations recovered PV conduction. After circumferential PV ablation the success rate was 59.3% (n = 19) with an additional 12,5% (n = 4) showing improvement. The procedure was repeated in 28.1% of the cases, the success rate was 78,2% (n = 25) with an additional 15.6% (n = 5) showing improvement. After GP – ablation success rate was equal to 67.6% (n = 23) with an additional 8.8% (n = 3) showing improvement. We repeated the procedure for 26.5% of the cases with a success rate of 73.5% (n = 25) with an additional 11.8% (n = 4) showing improvement. There was also a tendency for patients who underwent repeated ablations in combination of different procedures (ostial, circumferential, and/or GP) to have a higher AF-free survival when compared with patients subjected to the same procedure (P-value for log-rank test = 0.032). Independent predictors of later arrhythmia recurrences were longer AF duration (OR 1.1), left atrial volume (OR 1.18), history of hypertension (OR 1.58).
Conclusion: After comparing long-term results, GP ablation demonstrated better results in the maintenance of sinus rhythm in the majority of patients with chronic AF for at least 13-month period.

P1637 Cryoballoon pulmonary vein isolation

P. Insulander, F. Tabrizi, G. Kenneback, J. Schwieler, H. Bastani, F. Braunschweig, B. Sadigh, N. Drca, M. Jensen-Urstad. *Dept of Cardiology, Karolinska University Hospital, Stockholm, Sweden*

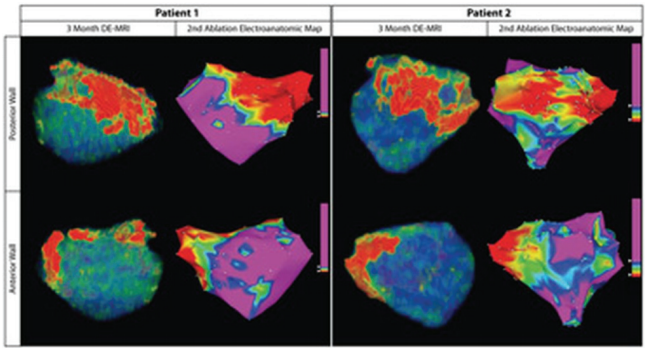
Purpose: Linear pulmonary vein isolation (PVI) with radiofrequency energy is widely used for catheter ablation in symptomatic patients with pharmacologic refractory paroxysmal atrial fibrillation (AF). A novel technology is cryothermal energy applied via a double lumen balloon catheter (ArcticFront).
Methods: We tested this technique in 75 consecutive patients with paroxysmal AF (median age 57; range 31-75; 21 women) who had failed anti-arrhythmic therapy. We used a 23 or 28 mm balloon depending on pulmonary vein diameter.

The end-point was pulmonary disconnection. PV conduction was verified before and after ablation by means of circular mapping-catheter in accordance with established criteria. If necessary touch-up ablation was performed using an 8 mm Freezor Max catheter. The movement of the diaphragm was verified very frequently using fluoroscopy when ablating the right-sided PVs.
Results: 273/304 (90%) of targeted veins were successfully isolated solely with the balloon. In 28 veins, the isolation was completed using the Freezor Max catheter. In 3 veins isolation failed. Procedure and fluoroscopy time were 204±59 and 46±19 minutes. Mean freeze time per vein was 15±8 minutes. Reversible phrenic nerve palsy was seen in 10 patients (one moderately symptomatic during two months). Four patients underwent 2 cryoballoon procedures. A substantial number of veins not isolated with the balloon were due to phrenic nerve palsy. After a median follow-up of 13 months (range 4-28), 68% were free of symptomatic AF and an additional 17% were significantly improved. 40% were still on AA at the time of evaluation.
Conclusion: Cryoballoon isolation of the pulmonary veins is feasible. In the majority of patients PVI can be achieved with a limited single balloon approach. Reversible nerve palsy was a limiting factor in 13% of treated patients. In this series touch-up was necessary in 22% of patients. Long-term outcome remains to be evaluated.

P1638 Correlation of delayed enhancement mri following atrial fibrillation ablation with repeat electroanatomical mapping

Y. Adjei-Poku, T.J. Badger, N.S. Burgon, N. Akoum, P. Anderson, E.V.R. Dibella, R.S. Macleod, N.F. Marrouche. *University of Utah, Salt Lake City, United States of America*

Purpose: Delayed-enhancement MRI (DE-MRI) has recently been introduced as a means to visualize post-AF ablation scar. However, this method has yet to be validated with electroanatomical mapping (EAM). We report the correlation between scar lesions on DE-MRI with low voltage regions on EAM obtained during repeat ablation.
Methods: Twelve patients received a DE-MRI scan three months following AF ablation. Three-dimensional models of the left atrium (LA) were then generated. Application of a color-look-up-table was then applied in order to better illuminate enhanced or scar tissue. The scar patterns on these models were then qualitatively compared with low-voltage regions (<0.1mV) on repeat EAM. The relationship was rated on a 0 to 4 scale where 0 was coded as "No Relationship", 1 was coded as "Poor", 2 was graded as "Mediocre", 3 as "Good", and 4 as "Excellent" by two independent and blinded reviewers on both the posterior and anterior views.
Results: All twelve patients had DE-MRI scar patterns consistent in size and location with low voltage regions (<0.1 mV) on repeat EAM. The average relationship between EA maps and MRI models was 3.65±0.55 (range 3 to 4). The figure below shows two patient examples of scar (red) on DE-MRI (left column) which corresponds to low voltage regions (red) on EAM (right column).



Repeat Ablation

Conclusion: We report the correlation between scar lesions detected on post-ablation DE-MRI with low voltage regions seen on repeat EAM. This comparison validates the accuracy of DE-MRI in detecting scar lesions post-AF ablation.

P1639 Long-term outcome of ablative therapy of post-operative supraventricular tachycardias in patients with univentricular hearts: an European multicenter study

N.M.S. De Groot[1], P. Lukac[2], N.A. Blom[1], A.K. Pedersen[3], P.S. Hansen[3], E. Delacretaz[4], M.J. Schalij[1]. *[1]Leiden University Medical Center, Leiden, Netherlands; [2]Aarhus University Hospital at Skejby, Aarhus, Denmark; [3]Varde Heart Center, Varde, Denmark; [4]Swiss Cardiovascular Center Bern, Bern, Switzerland*

Background: Catheter ablation has evolved as a possible curative treatment modality for supraventricular tachycardias (SVT) in patients with univentricular hearts (UVH). However, the long-term outcome of ablation procedures is unknown. In this multicenter study, we retrospectively evaluated the mechanisms of SVT, the procedural outcome of ablative therapy of late, post-operative SVT in UVH patients and studied arrhythmia recurrences after ablative therapy during long-term follow-up.
Methods: Patients with UVH (N=19, 11 male, 29±9 yrs) referred for ablation of SVT were studied. Ablation was guided by 3-dimensional electroanatomical mapping in all but 2 procedures. Based on activation maps, three different types of SVT were distinguished:
1) typical atrial flutter (AFL): a single (counter)-clockwise, cavo-tricuspid isthmus dependent macro-reentrant circuit, 2) intra-atrial re-entrant tachycardia (IART): a macro-reentrant tachycardia involving scar tissue, suture lines or prosthetic materials, 3) focal atrial tachycardia (FAT): electrical activation originating from a small, circumscribed region with spread of activation away in all directions from the site. In addition, atrial fibrillation (AF) was diagnosed according to usual electrophysiological characteristics. After the ablation procedure, patients were seen every 3 to 6 months at the out-patient clinic for clinical follow-up.
Results: SVT appeared 18±9 years after the first surgical intervention. Ablative therapy was applied 6±5 (0-19) years after first documented SVT episode. A total of 41 SVT were diagnosed as IART (N=30, CL 310±68 ms,), AFL (N=4, 288±42 ms), FAT (N=6, CL 400±60 * ms, P=0.01) and AF (N=1). Ablation was successful in 73% of the IART, 75% of the AFL and all FAT and focal AF. During the follow-up period of 53±34 months, 2 patients were lost to follow-up, 3 died due to heart failure, 2 underwent heart transplantation, 1 underwent conduit replacement. Of the remaining group, 8 had SR and 3 a SVT; anti-arrhythmic drugs were used by only 2 of them.
Conclusion: Focal and reentrant mechanisms underlie post-operative SVT in patients with UVH.
Successive SVT developing over time may be caused by different mechanisms. Ablative therapy is potentially curative with a procedural success rate of 78%. In patients who had multiple ablation procedures, the SVT originated from different atrial sites suggesting that these new SVT were caused by progressive atrial disease. Despite recurrent SVT, sinus rhythm at the end of the follow-up period was achieved in 72% of the patients (8/11).

P1640 Safety and efficacy of remote-controlled magnetic navigation compared to conventional navigation for atrial fibrillation ablation

P. Carmo[1], D. Cavaco[2], P. Adragao[2], L. Parreira[3], K. Santos[2], F. Morgado[1], S. Marcelino[3], A. Silva[1]. *[1]Hospital de Santa Cruz, Carnaxide, Portugal; [2]Hospital de Santa Cruz; Hospital da Luz, Lisbon, Portugal; [3]Hospital da Luz, Lisbon, Portugal*

Introduction: Radiofrequency ablation of atrial fibrillation (AF) requires precise catheter manipulation and stability that can be optimized by the use of remote magnetic navigation (RMN). The aim of this study was to compare the conventional and the RMN strategies with respect to safety and efficacy of AF ablation.
Methods: We studied 132 consecutive patients (pts) (mean age 54±11 years, 23% female) submitted to AF ablation performed by the same operator during 12 months. All pts underwent wide area bilateral pulmonary veins isolation (PVI) LASSO guided. Additional lesions (cavotricuspid and mitral isthmus, roof line, posterior wall line, and CAFE) were created in persistent and long persistent AF pts in a step wise approach. A conventional manually-manipulated catheter with an irrigated 3.5-mm-tip (NAVISTAR THERMOCOOL) was used in 57 pts, and a RMN-guided catheter (NAVISTAR RMT 8 mm; NIOBE II) with CARTO electroanatomic mapping was used in the remaining 75 pts. We recorded procedural complications and determined the frequency of complete isolation of all PV, and the incidence of AF recurrence accessed by clinical and Holter monitoring during a mean follow-up of 254±142 days.
Results: Both groups of pts were similar regarding demographic features and type of AF. 30% of pts had persistent AF. Left atrial volume was determined by computed tomography and found to be smaller in the RMN group (on average, 102±35mL vs 124±36mL in the conventional group). Complete PVI was achieved in 93% of all pts, and this proportion was similar for both groups. Cavotricuspid isthmus ablation was performed less frequently in the RMN group (4% vs 87%; P<0.001). All other additional ablation lines were performed with similar frequency in both groups. There were no cardiac or neurological complications related to the procedure. One pt in each group had a femoral vascular access complication. AF recurrence during follow-up was similar in both groups (overall, 32% in the RMN group and 41% in the conventional group; P=0.44), regardless of the type of AF before ablation.
Conclusion: AF ablation using a non-irrigated 8-mm-tip catheter, guided by remote magnetic navigation, was not inferior to ablation using a conventional irrigated 3.5-mm-tip catheter, with respect to safety, isolation efficacy, and clinical outcomes.

P1641 Morphology of the triangle of Koch and atrioventricular node in perinatal hearts with Ebstein malformation

B. Picazo-Angelin[1], V. Climent[2], M. Murillo[2], D. Sanchez-Quintana[2], J.A. Cabrera[3]. *[1]Hospital Costa del Soil, Marbella, Spain; [2]Department of Anatomy and Cell Biology. University of Extremadura, Badajoz, Spain; [3]Hospital Quiron-Madrid. Universidad Europea de Madrid, Madrid, Spain*

Introduction: Advances in catheter ablation procedures (cryoablation) have created the need for a better understanding of the morphology of the triangle of Koch and AV conduction system, particularly as how they relate in congenital heart disease. We have studied such relation in Ebstein malformation (EM).
Methods: A total of seventeen perinatal heart specimens, eleven with Ebstein malformation (7 male and 4 female; mean age 10±3 days after birth), and six controls with structurally normal hearts (4 male, 2 female; range 35 weeks of fetal life to 2 days after birth) were studied. The triangle of Koch and AV septal junctional area were removed in block and serially sectioned at 10-μm thickness at right angles to the AV annulus. We measured the lengths of the sides delineating the triangle of Koch, and the length of the compact AV node. The rightward and leftward inferior extensions were also calculated.
Results: With the displacement of the insertion of the septal leaflet in EM, the AV junction on the endocardial surface was marked by a small fibro-muscular ridge in 7 specimens (64%). In the thickness of this ridge the AV nodal artery was located in 3 specimens (27%). The diameter of the orifice of the coronary sinus showed a larger size in specimens with EM than in control hearts (3.5±1.2 mm vs 2.3±0.7mm). The area of the triangle of Koch in hearts with EM was significantly smaller than that of normal hearts (18.5±4.5mm^2 vs 25.5±6.5mm^2, $p<0.05$). However, the AV node and its inferior extensions have a similar length in the Ebstein than in control hearts (1.7±0.5mm vs 1.5±0.5mm). This leads to a smaller space within the triangle of Koch in EM specimens so that the body of the AV node and inferior extensions are displaced and located at the coronary sinus orifice, at the base of the triangle of Koch.
Conclusions: In patients with EM the nodal artery and/or the AV conduction tissues can be at risk of damage when ablative procedures are carried out at the base of the triangle of Koch.

P1642 Estimation of left atrial volume: comparison of multi-slice computed tomography with CARTO mapping by either remote-control magnetic navigation or manual navigation

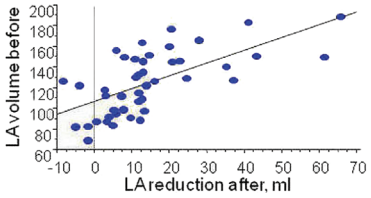
P. Carmo[1], P. Adragao[2], D. Cavaco[2], L. Parreira[3], K. Santos[2], F. Morgado[1], S. Marcelino[3], R. Bernardo[1], A. Silva[1]. *[1]Hospital de Santa Cruz, Carnaxide, Portugal; [2]Hospital de Santa Cruz; Hospital da Luz, Lisbon, Portugal; [3]Hospital da Luz, Lisbon, Portugal*

Introduction: Integration of electroanatomical mapping with multi-slice computed tomography (CT) may facilitate catheter ablation of atrial fibrillation. We compared the left atrial volumes estimated by CT and CARTO, using conventional manual navigation (CMN) and remote-controlled magnetic navigation (NIOBE II, Stereotaxis, Inc) (RMN).
Methods: We studied 225 patients (pts) (mean age 54±11 years, 19% female) submitted to AF ablation. Atrial anatomy and volume were assessed with CT in all. A conventional manually-manipulated catheter (NAVISTAR THERMOCOOL 3.5-mm) was used to construct the CARTO map in 153 pts (CMN group), and an RMN-guided catheter (NAVISTAR RMT 8-mm) was used for the same purpose in 72 pts (RMN group). We compared the difference between CT and CARTO volumes in both populations.
Results: Baseline clinical characteristics were similar in both groups. Left atrial volumes determined by CT were lower in the RMN group (101±35mL vs 127±41mL in the CMN group). The mean CARTO volume was lower than mean CT volume (114±40mL vs 100±36mL; p=0.001) and this difference remained significant regardless of the navigation method (CMN: 101±35mL vs 92±32mL; RMN: 127±41mL vs 113±35mL; p=0.001 for both comparisons). The mean ratio CT/CARTO volume was 1.18±0.32. CARTO and CT volumes were slightly more similar in the RMN group than in the CMN group (CT/CARTO ratio 1.13±0.29 in the RMN group vs 1.26±0.34 in the CMN group; p=0.05).
Conclusion: CARTO mapping generates slightly lower atrial volumes than the volumes determined by CT scan, regardless of the navigation method. RMN-guided catheters seemed slightly better than the conventional methods to determine left atrial volume.

P1643 Comparison of left atrial volumes measured from 3-dimensional CT/MR images before and after catheter ablation in patients with atrial fibrillation

L. Ren, O. Kongstad, S. Yuan. *Lund University Hospital, Lund, Sweden*

Introduction: Left atrial volume (LAV) in pts with AF is recommended as a marker of therapeutic result. However, available data on LAV are merely from 2-d echocardiography which has limitations in accurate LAV quantification. However, 3-d CT/MR images provide accurate LAV measurement.
Methods: 44 pts with paroxysmal AF underwent cardiac CT/MR scans 1-3 days before and 3 months after AF ablation. 3-d LA images were reconstructed using retrospective ECG gating and LAV calculated using commercial software (EnSite Verismo). AF ablation was performed using CARTO Merge and wide pulmonary vein (PV) encircling plus roof line and lines between the upper and lower PVs.
Results: 3 months after ablation, 28/44 (64%) pts were in sinus rhythm (SR group) and 16/44 (36%) still in paroxysmal AF (AF group). A significant reduction in LAV was observed in the SR group, from 118±31 to 101±22 ml, $p<0.001$, and the reduction was positively correlated with the LA size ($r=0.649$, $p<0.0001$, see Fig.). These findings are in line with the earlier reports, suggesting reverse LA remodeling as a result of SR resumption. Differing from the previously reported data, however, our AF group showed also a clear LA reduction, from 122±31 to 112±25 ml, $p<0.02$, though the reduction was less than that in the SR group (mean reduction 10 vs. 17 ml, $p<0.05$). This may suggest the involvement of extensive RF lesions and consequent scar formation in the LA reduction.



Conclusions: Significant LA reduction after AF ablation may be a combined effect of reverse remodeling and extensive RF lesions.

P1644 Remote robotic navigation for ablation of atrial fibrillation: catheter stability and impact on procedural outcome

R. Tilz, K.R.J. Chun, A. Fuernkranz, K. Neven, B. Koektuerk, E. Wissner, A. Metzner, D. Nuyens, F. Ouyang, B. Schmidt. *Asklepios Klinik. St. Georg, Hamburg, Germany*

Objectives: To describe the catheter stability and procedural outcome using a novel remote robotic navigation system (RNS) for circumferential pulmonary vein isolation (CPVI).
Methods: In 65 patients (pts) with paroxysmal AF (n=43) or persistent AF (n=22) complete CPVI was performed using the RNS in conjunction with different electroanatomical mapping systems. The ablation catheter used for left left atrial (LA) mapping and ablation and a transseptal sheath for a spiral mapping catheter were advanced into LA. PV ostia were determined by selective angiography. Ablation consisted of wide area CPVI until electrical isolation of all PVs. Ablation catheter stability was assessed at each quadrant of the ipsilateral PVs and classified as good (no catheter dislodgement during RF delivery), moderate or poor (1 or >1 interrupted RF application, respectively).
Results: Complete PVI, exclusively using the RNS, was achieved in 62/65 pts (95%) using the CARTO (n=42) or the NavX system (n=23). In 2 pts isolation of the left PVs had to be finalized manually, in 1 pt access to the LA could not be achieved due to a technical malfunction of the RNS.
In most cases catheter was stable at the superior aspect (right PVs: good in 97%, poor in 0%, left PVs good in 98%, poor in 0%) and at the inferior aspect (right PVs: good in 95%, poor in 2%, left PVs: good in 92%, poor in 5%). In contrast, catheter stability was more challenging at the posterior wall (right PVs: good in 74%, poor in 4%, left PVs good in 71%, poor in 6%) and anterior wall (right PVs: good in 81%, poor in 2%, left PVs: good in 54%, poor in 12%). Procedure time was 195±40 min. Fluoroscopy time was 17±7 min including 6±4 min using the RNS without exposure to the operator.
Three complications occurred: Transient ST segment elevation (n=1), cardiac tamponade following right atrial perforation by the RNS (n=1), and an oesophageal ulcer demonstrated by endoscopy that resolved within two weeks (n=1). After a single procedure 47/65 pts (73%) remained in SR during a median FU period of 239 (184-314) days.
Conclusions: CPVI using the novel RNS is feasible and effective in conjunction with different 3D mapping systems. Achieving catheter stability at the anterior left PV ostium remains a challenge. Using RNS, 1/3 of fluoroscopy time is used during remote navigation.

P1645 Incidence and causes of complete atrioventricular block during ablation of atrial flutter

B. Brembilla-Perrot, M. Lemdersi-Filali, P.Y. Zinzius, L. Groben, D. Beurrier, J. Cedano, P. Louis, A. Abdelaal, A. Terrier De La Chaise, O. Selton. *CHU de Nancy - Hopital de Brabois, Vandoeuvre les Nancy, France*

The purpose of the study was to evaluate the incidence and the causes of iatrogenic complete atrioventricular block (AVB) during radiofrequency (RF) ablation of typical atrial flutter. The technique is largely used to restore and maintain a sinus rhythm and is considered as safe and effective. Little is known on the risk of AVB. Population: Ablation of flutter was indicated in 748 patients (pts), 596 males

and 152 females aged from 18 to 90 years (mean 64±12) with recurrent or bad–tolerated typical atrial flutter; 324 pts had associated significant heart disease (valvular 66, congenital 23, ischemic heart disease 70, dilated cardiomyopathy 42, miscellaneous 79) or chronic pulmonary disease (44).
Methods: RF catheter ablation of the flutter was performed by conventional method with setting a HALO catheter in coronary sinus and using an 8-F quadripolar with an 8 mm-tip electrode catheter; a maximum power of 70 w and a maximum target temperature of 70° for 60 sec was used. Among pts with permanent atrial flutter, sinus rhythm was obtained by applying RF current at the level of right isthmus and then complete isthmus block was obtained in these pts and in those in sinus rhythm at the beginning of procedure.
Results: Failure of procedure was noted in 106 pts generally after the development of a permanent atrial fibrillation. Complete AVB (1%) occurred, when sinus rhythm was restored, in 8 pts aged from 59 to 89 years (mean 73±9) significantly older than other pts (63.5±12) ($p < 0.02$): 2 AVB's were accidental and related displacement of catheter on His bundle; they remained permanent; 2 AVB's were regressive and related to a traumatic block in pts with left bundle branch block; one AVB occurred in a 79 year old woman treated with class I antiarrhythmic drug and AVB disappeared after interruption of drugs; 3 AVB's were related to an ischemic complete AVB in pts with known coronary heart disease; in 2 of them ST segment elevation and AVB resolved with antithrombotic therapy; in another 59 year old man, AVB was related to an acute occlusion of the segment 3 of the right coronary artery. His recanalization by initial balloon angioplasty of right coronary artery and stent implantation was associated with the immediate restoration of a normal AV conduction.
Conclusion: Complete AVB was a rare complication of RF ablation of typical atrial flutter (1%), which concern generally old pts; the most frequent cause was the development of an ischemic AVB which was regressive after treatment of acute coronary syndrome. It occurred in 3 of 70 pts with known coronary heart disease.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR'S SPECIAL ISSUES

P1646 Impact of bacterial colonization on device infection in asymptomatic ICD patients undergoing generator replacement or lead revision

T. Kleemann, T. Becker, M. Strauss, U. Weisse, W. Saggau, U. Burkhardt, K. Seidl. *Cardiac Arrhythmia Institute at the Heart Center of Ludwigshafen, Ludwigshafen Am Rhein, Germany*

Aim of the study was to evaluate the prevalence of bacterial colonization of generator pockets in asymptomatic ICD patients and to analyse the impact of bacterial colonization on the incidence of device infection during follow-up.
Methods: In 122 asymptomatic ICD patients undergoing generator replacement or surgical lead revision between January 2006 and July 2008, microbiological cultures of generator pockets and extracted leads were consecutively obtained. Patients with clinical evidence of a device infection were excluded. Results: Positive cultures from the generator pocket and leads were found in 40 (33%) patients. The most common bacteria isolated were coagulase negative staphylococci (68%). Gram-positive organisms predominated (95%), with Gram-negative bacteria representing 2%. Polymicrobial cultures were present in 2 patients During a median follow-up time of 203 days after the revision surgery device infection occurred in 3 (7.5%) patients with a positive culture versus 2 (2.4%) patients with a negative culture ($p = 0.19$). In all three patients of the positive culture group the organism responsible for the device infection was identical to the one obtained previously during the revision surgery.

Table 1

	Positive culture (n=40)	Negative culture (n=82)	p-value p-value
Age (years)	67 (59 - 71)	67 (58 - 74)	0.92
Number of prior interventions	1	1	0.47
Time from last intervention (months)	40 (12 - 57)	38 (10 - 60)	0.68
Type of present intervention:			
Generator replacement only	38%	30%	0.44
Lead revision only	37%	42%	0.68
Generator replacement and lead revision	25%	28%	0.72

Conclusions: A third of ICD patients undergoing generator replacement or lead revision surgery have an asymptomatic bacterial colonization of the generator pocket. After the revision surgery, 7.5% of these patients develop a device infection with the same species of microorganism. This observation underlines the hypothesis that primarily asymptomatic bacterial colonization can cause device infection after revision surgery and may explain the increased infection rates after revision surgery compared to that after de novo implantation.

P1647 Novel intravascular defibrillator (InnerPulse PICD): defibrillation thresholds of PICD compared to Medtronic ICD in a canine model

W.E. Sanders[1], M. Richey[2], S.C. Masson[2], T. Ransbury[2], M. Urtz[3], R.E. Ideker[4], R.A. Malkin[5]. *[1]InnerPulse/University of North Carolina-Chapel Hill, Chapel Hill N C, United States of America; [2]InnerPulse Inc., Research Triangle Park N C, United States of America; [3]Synecor LLC, Research Triangle Park N C, United States of America; [4]University of Alabama, Birmingham, United States of America; [5]Duke University, Durham N C, United States of America*

Purpose: A totally intravascular, percutaneously placed implantable defibrillator has recently been developed. This device is rapidly introduced via the femoral vein and defibrillates utilizing a right ventricular (RV) single coil lead (first phase anode) and titanium electrodes in the superior vena cava (SVC) and the inferior vena cava (IVC) (cathodes). The purpose of this study was to directly compare defibrillation thresholds (DFTs) of the InnerPulse PICD to those of the Medtronic (Model #D165AWG) ICD in a canine model.
Methods: Eight Bluetick hounds (wt=30-40 kg) were anesthetized and randomized to initial placement of either an InnerPulse PICD or the Medtronic ICD. For each PICD DFT, an InnerPulse RV lead system (single coil defibrillator lead) was positioned in the RV apex and the device placed in the vasculature such that a titanium electrode was located in the SVC and a second titanium electrode in the IVC at the level of the diaphragm. With the Medtronic ICD, a Medtronic RV lead (Model # 6935) was placed in the RV apex and a Medtronic SVC coil (Model #6937A) was positioned in the SVC. A subcutaneous pocket was formed in the left anterior chest wall of the dog and the Medtronic ICD active can (AC) was positioned in the pocket appropriately and connected to the lead system. The wound was closed with suture. During threshold testing, waveforms were recorded by an oscilloscope and outputs and impedances measured. Each system was completely removed prior to DFT testing with the other. DFT was determined by a three-reversal, step up-down method. Two configurations were tested for the Medtronic ICD (Configuration #1- RV to SVC+AC, Configuration #2-RV to AC). A single configuration (RV to SVC+IVC) was used for the InnerPulse ICD.
Results: The InnerPulse PICD had a DFT of 14.8 J (stderr ±1.53). Medtronic configuration#1 demonstrated a DFT of 20.2 J (stderr ±2.45) and configuration #2 of 27.5 J (stderr ±1.95). The InnerPulse had a significantly lower DFT than the best Medtronic configuration (#1) (5.4±2.1 J, $p < 0.05$, paired t-test N=8).
Conclusions: The new InnerPulse intravascular defibrillator PICD had a significantly lower DFT than the Medtronic ICD in this canine model.

P1648 Are there any clinical or electrical parameters that predict the effectiveness of defibrillation testing with a 10 joule safety margin?

J.J. Blanc[1], A. Lazarus[2], P. Defaye[3], O. Paziaud[4], P. Chenevez[5], F. Halimi[6], J. Horvilleur[7], E. Mouton[8], A. Durand[8], N. Sadoul[9] on behalf of Leader study investigators. *[1]University Hospital, Brest, France; [2]Clinic Bizet, Paris, France; [3]University Hospital, Grenoble, France; [4]CCN, St Denis, France; [5]Clinic St Gatien, Tours, France; [6]CMC Parly II, Le Chesnay, France; [7]Institut Hospitalier Jacques Cartier, Massy, France; [8]Boston Scientific, Montigny Le Bretonneux, France; [9]University Hospital, Nancy, France*

Purpose: Defibrillation testing (DT) is routinely performed during implantation of cardioverter-defibrillators (ICDs) to assess efficacy of defibrillation (def) shock and accuracy of the detection of the ventricular fibrillation. However, this testing may increase the risk and the complexity of the procedure. The purpose of this study was to assess clinical or electrical parameters (prs) that could predict the effectiveness of the def threshold (DFT) at 21 joules (safety margin of 10 J).
Methods and results: Based on data collected at implant of an ongoing observational multicenter registry (LEADER), a multivariate stepwise analysis (MSA) was performed. The study included 776 patients implanted with ICD or CRT-D (57%). According to the results of DFT at the first tested lead position, 2 groups were compared: DFT < 21 J vs. DFT > 21 J. Only prs that reached p value ≤ 0.1 in groups' comparison were entered into the MSA. Finally, a p value < 0.05 was considered significant. Among 36 prs analysed, 12 were included in the MSA. Only age, apical lead position and R-wave sensing were independent predictors of DFT < 21 J. Right pectoral ICD location and CRT-D were independent predictors of failure.

Results of the MSA analysis

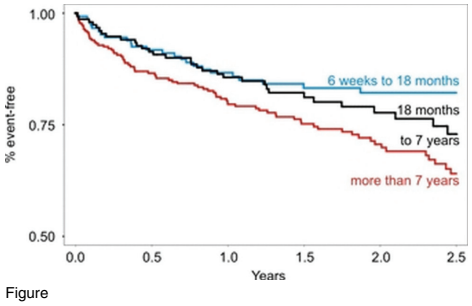
Patient parameters	DFT>21J (n=119)	DFT≤21J (n=657)	Odds Ratio	p value
Age (years)	58±13	62±13	1.044 [1.026; 1.063]	<0.0001
LVEF (%)	29±12	33±14	NA	NS
QRS width (ms)	136±40	123±37	NA	NS
NYHA Class	2.3±1.0	2.0±1.0	NA	NS
Ischemic cardiomyopathy (%)	53	63	NA	NS
Dilated cardiomyopathy (%)	39	24	NA	NS
Apical lead position (%)	48	69	2.083 [1.256; 3.453]	<0.001
Right pectoral ICD location (%)	13.7	6.3	0.347 [0.165; 0.727]	<0.01
R wave sensing (mV)	9.6±4.9	11.5±6.9	1.055 [1.005; 1.108]	<0.05
RV pacing threshold (V)	1.3±2.3	0.9±1.0	NA	NS
Amiodarone (%)	34	25		<0.05
CRT-D (%)	61	40	0.360 [0.214; 0.604]	<0.001

Conclusion: Some clinical and electrical parameters associated with ability to obtain 10 J safety margin have been identified and further study would be helpful to determine the best way to prospectively apply these findings.

P1649 Influence of time from last myocardial infarction on occurrence of therapies in patients with prophylactic ICD implantations: data from the SEARCH MI registry

G. Boriani[1], G.L. Botto[2], B. Schmidt[3], M. Lunati[4], A. Proclemer[5], A. Erdogan[6], W. Rauhe[7], M. Biffi[1], M. Messier[8], M. Santini[9] on behalf of SEARCH MI Investigators. *[1]Institute of Cardiology, Univ. of Bologna, Bologna, Italy; [2]Cardiology, Como, Italy; [3]Cardiology, Freiburg Im Breisgau, Germany; [4]Cardiology Hosp. Niguarda, Milano, Italy; [5]Cardiology, Udine, Italy; [6]Cardiology, Giessen, Germany; [7]Cardiology, Bolzano, Italy; [8]Medtronic, Maastricht, Netherlands; [9]Cardiology S Filippo Neri Hosp., Roma, Italy*

Background: The relationship between the time elapsed from last myocardial infarction (MI) and ICD activation in high-risk pts is the object of this exploration.
Methods: A population of 757 pts (age 66±10) with left ventricular dysfunction (LVEF<0.36) and NYHA class 1-3 was prospectively enrolled in a multicenter international registry and followed for 1.8±1.2 yrs. Data on ICD therapy were analyzed independently by at least 2 experts. The population was divided into 3 groups according to the time elapsed from last MI: Grp_1 (6 weeks to 18 months), Grp_2 (18 months to 7 years), Grp_3 (more than 7 years after MI).
Results: In high-risk post-MI pts implanted with a prophylactic ICD (+/-CRT), the time from MI is strongly related to the detection of the first ventricular tachyarrhythmia and to the need for appropriate ventricular therapy. The pts closest to the index MI had an event rate of 8.3% at the 2 year time point, while pts implanted more than 7 years after the MI presented with an even higher event rate of 11.4% at 2 years. The curve representing older MI separate immediately at study onset. Full cohort comparison yield a log rank p= 0.0099 across these 3 strata. Cox regression analysis of time from MI yields a hazard ratio as a function of time of 1.023 per year, p= 0.02), which translates as an average increased risk of 2,3% per annum from the time of MI. This benefit is also confirmed in a selected subanalysis of pts with biventricular-ICD (CRT-D), even though these have a two-fold lower event rate than VR/DR patients.



Figure

Conclusion: Pts implanted with an ICD a long time from MI continue to benefit from ICD therapy, even in the sub-group of CRT-D pts who present a lower occurrence of device interventions for ventricular tachyarrhythmias.

P1651 Deaths and serious injuries associated with ICD and pacemaker lead extraction

R.G. Hauser, W.T. Katsiyiannis, L.M. Kallinen. *Minneapolis Heart Institute Foundation, Minneapolis, United States of America*

Purpose: ICD and pacemaker lead extraction is a complex procedure that may be complicated by death or serious injury. An estimated 20,000-24,000 device-assisted lead extractions were performed in the United States during 2007 and 2008. The aim of this study was to assess the deaths and serious injuries reported to the U.S. Food and Drug Administration (FDA) by the manufacturers of lead extraction devices during these 2 years.
Methods: The FDA Manufacturers and User Defined Experience (MAUDE) database was queried for the years 2007 and 2008 using the search term "Lead extraction and death or injury". Data obtained from each report included type of lead extracted, extraction tool manufacturer and model, clinical circumstance, procedure, complications, and outcome.
Results: A total of 32 serious adverse events were identified by the MAUDE search during the extraction of 17 ICD leads, 7 pacemaker leads, and 8 unspecified leads. The indications for lead extraction were infection in half the patients and lead malfunction or elective replacement in the other cases. Overall, 19 patients died and 13 patients sustained serious injuries during lead extraction. Of the 19 reported deaths, 15 (79%) involved Spectranetics laser sheath extraction devices and 4 (21%) were associated with Cook Vascular extraction tools; 13 of these 19 patients underwent prompt thoracotomy to no avail. Twelve of the 19 deaths (63%) were caused by laceration of the superior vena (SVC), 5 (26%) were due to perforation of the right atrium or right ventricle, and 2 deaths (11%) were the result of procedural hemodynamic collapse without known cause. The 13 injuries were associated with Spectranetics laser sheath extractions (n=11;85%) and Cook Vascular sheaths (n=2;15%), and these resulted in SVC or innominate vein tears (n=10;77%) and 2 right atrial and 1 right ventricular perforation; all of these patients underwent prompt surgical repair. At least half of all deaths and serious injuries involved 16 French Spectranetics laser sheaths and most of these were used to extract leads that had been implanted>5years.
Conclusions: Device-assisted lead extraction may be complicated by death and serious injury; the incidence appears to be 1.5-3 per 1000 cases but may be higher due to underreporting. In this study, prompt thoracotomy was lifesaving in only half the cases. The need for larger laser sheaths to remove older leads appeared to increase risk, particularly when manipulating the sheath in the region of the superior vena cava. The results of this study imply that better approaches for extracting leads are needed.

P1652 Implications of beta-blockers therapy dose on Antitachycardia Pacing effectiveness and shocks incidence among Monomorphic Ventricular Tachycardias occurred in ICD patients

J. Jimenez-Candil, J. Morinigo, A. Martin, C. Ledesma, M. Ruiz, C. Martin-Luengo. *Hospital Universitario de Salamanca, Salamanca, Spain*

Since shocks (SH) increase mortality in ICD patients (ICD-P) with left ventricular dysfunction (LVF), avoiding them has become a relevant goal. Previous small and retrospective studies have reported that beta-blocker therapy (BBt), defined as a categorical variable (present vs. absent), increases the Antitachycardia Pacing (ATP) efficiency. However, there is not information regarding the relationship between the dose of BBt and the effectiveness and clinical consequences of ATP in terminating Monomorphic Ventricular Tachycardias (MVT) spontaneously occurred in ICD-P.
Our objective is to determine the relationship between the indexed dose equivalents (IDE) of BB (IDE-BB), and: 1- ATP efficiency; 2- incidences of SH and syncope due to MVT treated by ATP.
Methods: We prospectively studied 216 ICD-P with LVD (LVEF: 31±11; pacing site: right ventricular apex). ATP programming was standardized: Fast-VT zone (Cycle Length [CL]: 250-320 ms; 1 burst of 5 pulses at 84% of CL); slow-VT zone (CL: 321-390 ms; 3 bursts of 15 pulses at 91%). Failed ATP therapies were followed by SH. We determined the IDE-BB at each MVT presentation. Dose equivalents (DE) were defined with atenolol used as reference. IDE were calculated by dividing DE by body surface area (mg·m^2/day).
Results: During a follow-up of 21±12 months, 551 MVT (CL: 329±35 ms; 41% fast-VT; 21% no concomitant BB treatment) were recorded in 67 patients. ATP success rate was: 87% and 11% MVT required at least one SH to be terminated. Median of IDE-BB was 26 mg·m^2/day. IDE-BB was higher in the cases of efficient ATP (E-ATP): 23±17 vs. 15±16 (95% CI of the difference: 6; 16; p<0.001). Classifying the events into three groups according to the IDE: no BBt, low IDE (IDE <median) and high IDE (IDE ≥median) the frequency of E-ATP increased with the IDE-BB: 77% vs. 84% vs. 94% (all MVTs, p<001) and 47% vs. 84% vs. 97% (fast-MVTs, p<0.001). The incidences of SH and syncope due to MVT were closely related to the IDE-BB: 19% vs. 12% vs. 5.6% (SH, p=0.001), and 7.6% vs. 2.3% vs. 1.4% (syncope, p=0.018). By logistic regression which included LVEF, aetiology, indication, functional class and CL of MVT, IDE-BB remained as a significant predictor of E-ATP (OR: 1.05; p<0.001), SH (OR: 0.97;p=0.001) and syncope (OR: 0.94; p=0.005).
Conclusions: Among ICD patients, BBt increases the efficiency of ATP (especially in fast MVTs). This relationship is dose-dependent: the higher the IDE-BB, the more effective the ATP. As consequence, higher IDE-BB are independently associated with lower rates of SH and syncope due to MVT.

P1653 Mortality risk score in primary prevention implantable cardioverter defibrillator recipients with ischemic heart disease

C.J.W. Borleffs, G.H. Van Welsenes, L. Van Erven, R.J. Van Bommel, E.T. Van Der Velde, E.E. Van Der Wall, J.G. Van Der Bom, F.R. Rosendaal, J.J. Bax, M.J. Schalij. *Leiden University Medical Center, Leiden, Netherlands*

Introduction: Large trials have shown a beneficial effect of an implantable cardioverter defibrillator (ICD) in the primary prevention of sudden death. The aim of the current study was to create an easy-to-use risk score for the baseline estimation of the risk for all-cause mortality in primary prevention ICD patients with ischemic heart disease.
Methods: All patients with ischemic heart disease, receiving an ICD for primary prevention were included in the study and evaluated at baseline and during periodical three-six months follow-up. Using multivariate logistic regression analysis, a predictive model was constructed for mortality and subsequently converted into a usable risk-score.
Results: A total of 704 patients (615 male, 64±11 years) were evaluated. During a follow-up of 28±23 months, 94 (13%) patients died. Analysis showed that risk points corresponded to the following baseline characteristics: four risk points for renal clearance ≤ 60 ml/min; three risk points for a history of smoking; two risk points for diabetes, left ventricular ejection fraction ≤ 25%, or age ≥ 70 years; and one risk point for renal clearance 60-90 ml/min or QRS duration ≥ 130 ms.

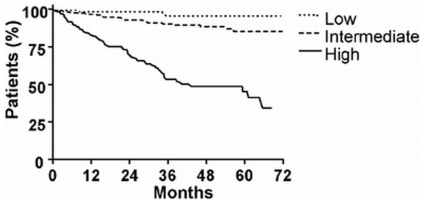


Figure 1

As is shown in Figure 1, survival after six years was 96% (95% CI 90-100%) when 0-2 risk points present (low risk), 85% (95% CI 79-91%) if 3-7 risk points were present (intermediate risk), and 34% (95% CI 18-51%) if eight or more risk points were present (high risk).
Conclusions: Implementation of an easy-to-use baseline risk score can stratify ischemic primary prevention ICD patients for the risk of mortality during follow-up.

P1654 Prediction of antitachycardia pacing effectiveness for monomorphic ventricular tachycardias based on the analysis of far-field electrograms morphology

J. Jimenez-Candil, J. Hernandez, A. Martin, M. Ruiz Olgado, J. Morinigo, C. Ledesma, C. Martin Luengo. *Hospital Universitario de Salamanca, Salamanca, Spain*

Modern implantable cardioverter-defibrillators (ICD) apply antitachycardia pacing (ATP) therapies -which are usually empirically programmed- for tachyarrhythmias classified as ventricular tachycardias (VT). Although ATP is very effective, in 5-25% of VT, depending on their cycle length (CL), shocks are needed to terminate the arrhythmia. Unsuccessful ATP therapies have negative clinical implications, because delaying the definitive therapy prolongs the episode duration. In addition, SH increase mortality in ICD patients with left ventricular dysfunction (LVD). To date, in VT occurred in ICD patients, no information is available regarding the ability of the far-field electrograms morphology (Ff-M) in predicting the result of the subsequent ATP. We hypothesized that the Ff-M, as pseudo-unipolar signal and thus, as an indicator of the direction of propagation front, could be related to the effectiveness of the first ATP attempt (f-ATP).
Methods: We prospectively studied 551 MVT (CL: 329±35 ms) occurred in 67 ICD patients (LVEF: 31±11; pacing site: right ventricular apex; Medtronic devices: 70%; Boston Scientific devices: 30%). First ATP programming was standardized. Configuration of Ff-M was ICD can vs. right ventricular coil.
Results: f-ATP effectiveness was 81%. VTs with a negative initial deflection (QS or QR pattern [Q-VT]) had a lower CL (326±31 vs. 334±41; p=0.01) and were associated with a higher left ventricular ejection fraction (LVEF) (36±7 vs. 32±7; p<0.001). The frequency of successful f-ATP was significantly higher in Q-VT: 87% vs. 71% (OR. 2.7; 95% Confidence Interval: 1.7-4.2; p<0.001). Table. By logistic regression analysis, which included LVEF, CL, etiology, functional class, beta-blocker therapy, device manufacturer and indication, a Q-VT pattern was found as an independent predictor of effective f-ATP: OR: 2.9 (95% CI: 1.7-5); p<0.001. As a result, VTs with a Q-VT in the Ff-M had a significantly lower duration (s): 11±7 vs. 18±9 (p<0.001).

f-ATP attempt effectiveness according to the Ff-M

QS (n=110)	QR (n=255)	R (n=113)	RS (n=73)
92%	85%	72%	70%

p<0.001, Chi-squared test for trend.

Conclusions: VTs in which the Ff-M had a negative initial deflection are more suitable for termination by the subsequent ATP therapy. This effect is associated with a significant reduction in their duration.

P1655 Increasing risk of sprint fidelis implantable defibrillator lead failure

R.G. Hauser[1], D.L. Hayes[2], L.M. Kallinen[1], M. Rott[2]. *[1]Minneapolis Heart Institute Foundation, Minneapolis, United States of America; [2]Mayo Clinic, Rochester, United States of America*

Purpose: The Medtronic Sprint Fidelis defibrillator lead is prone to fracture and was recalled in 2007 after 665 failures and 5 reported deaths. Approximately 150,000 patients at risk for sudden death have Sprint Fidelis leads. The rate of Sprint Fidelis lead failure may be increasing, and physicians are confronted with the decision to replace it prophylactically. The aim of this study was to determine if the risk of Sprint Fidelis lead failure is changing and compare its performance to other contemporary ICD leads.
Methods: All 3,120 transvenous implantable cardioverter-defibrillator leads implanted and followed at our two tertiary care referral centers between January 2004 and December 2008 were included. Lead failure data were entered prospectively by both centers via the Multicenter Registry. Clinical data were collected prospectively by each center and merged for the purpose of this study.
Results: During 5,703 years of follow-up (average: 1.8±1.3 years), 94 of 3,120 defibrillator leads failed (1.65%/year), including 72 of 853 (8.4%) Sprint Fidelis leads. The cumulative hazard of Sprint Fidelis failure was significantly greater compared to 2,267 other defibrillator leads (p<0.0001), and the hazard of Sprint Fidelis failure accelerated after the first year and continued to increase during the study. In contrast to other defibrillator leads, the Sprint Fidelis failure rate was significantly higher (3.74%/year vs 0.58%/year) and the 3-year estimated survival significantly lower (87.9%, 95% CI 84.9,91.0 vs 98.6%, 95% CI 97.8, 99.3) (p<0.0001). The chance that a Sprint Fidelis lead would survive another year decreased progressively during the study. Most Sprint Fidelis failures were caused by pace-sense conductor fracture (n=63; 87.5%), which caused inappropriate shocks in 36 of 72 patients.
Conclusion: The risk of Sprint Fidelis lead failure is increasing, while the failure rates of other defibrillator leads are low and stable. Physicians should consider these data when managing patients who have Sprint Fidelis leads.

P1656 Efficacy of calendar based ICD checks: conventional follow up compared to remote monitoring in the TRUST trial

N. Varma[1], A. Epstein[2], A. Irimpen[3], L. Gibson[4], C. Love[5]. *[1]Cleveland Clinic, Cleveland, United States of America; [2]University of Alabama Medical Center, Birmingham, United States of America; [3]Tulane University Medical Center, New Orleans, United States of America; [4]BIOTRONIK, Inc., Lake Oswego, United States of America; [5]Davis Heart & Lung Research Institute, Columbus, United States of America*

Background: Extension of follow-up from the recommended 3 months to longer is not evidence-based. Adherence to and problem detection rate with any follow-up schedule is unknown, and the effect of replacement of in clinic visits (CV) with remote monitoring technology (RMT), which differ operationally, is unclear. TRUST, a multicenter prospective trial, tested these points with RMT performing daily checks.
Methods: 1,312 patients were randomized post ICD implant 2:1 to remote monitoring (RM) or to conventional (C) groups. 3 month follow up was scheduled (S) in all patients: CV in C and remotely in RM. Between these time points in RM, ICDs triggered event notifications (EN) for arrhythmias and system integrity issues. CVs resulting from EN, and actionability (reprogramming, change in anti-arrhythmic therapy, or system revision) of S and CV checks were tracked.
Results: RM and conventional patients were similar (age 63±12 vs 64±12 yrs, 72 vs 73% male, NYHA II class 56 vs 61%, LVEF 29±11 vs 29±9%, CAD 64 vs 72%, amiodarone 80 vs 76%, primary prevention indication 72 vs 74%, and DDD implants 58 vs 57%).
Overall causes of actionability were reprogramming changes (75%), medication changes (27%), and lead system revision (4%). In RM, 54% of EN driven CV (n=102) occurring between 3 monthly S were actionable. Median time to event evaluation was <3 days compared to >30 days in C (p<0.001).

	3 month Scheduled		6 month Scheduled		9 month Scheduled		12 month Scheduled	
	Adherence	Action-ability	Adherence	Action-ability	Adherence	Action-ability	Adherence	Action-ability
RM	88%	13.0%	90%	16.7%	88%	12.0%	84%	8.5%
C	91%	12.1%	78%	9.2%	73%	11.0%	65%	10.0%

Conclusions: Adherence to scheduled clinic checks deteriorates rapidly in C but RMT based evaluation remains consistently high. However, actionability is similarly low in both indicating that simple replacement with RMT does not affect detection. In contrast, EN driven evaluations are prompt and highly actionable. The data question the efficacy of calendar based ICD monitoring and support RMTs providing automatic daily surveillance with rapid event notifications of important (including asymptomatic) events.

P1657 Comparison of single-lead ICD system capable of atrial sensing (A+ ICD) and a DDD-ICD system in patients without antibradycardia pacing indications

C. Sticherling[1], M. Niehaus[2], M. Zabel[3]. *[1]University Hospital Basel, Basel, Switzerland; [2]Medizinische Hochschule Hannover, Hannover, Germany; [3]University of Göttingen, Göttingen, Germany*

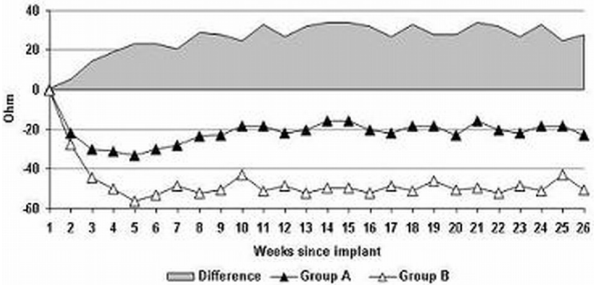
Purpose: Supraventricular tachyarrhythmia (SVT) is the main cause of inappropriate ICD therapy. Even in the absence of an antibradycardia pacing indication, many patients (pts) receive DDD-ICD systems to improve arrhythmia detection with the aid of atrial electrogram (AEGM). An "A+ ICD" system, capable of sensing AEGM by rings (floating bipole) mounted 15-18 cm from the tip of a single-coil ICD lead, may obviate the need to implant a separate atrial lead. We compared the overall performance and system related complications of A+ ICD and conventional DDD-ICD.
Methods: 253 pts without antibradycardia pacing indication (62±11 yrs, 87% male, 38% history of VT/VF, 18% history of SVT) were randomized to receive an A+ ICD (n=127; Biotronik Belos/Lexos A+) or DDD-ICD (n=126; Belos/Lexos/Lumos DR). The ICD leads in the A+ ICD group comprised Kainox (n=59) and Kentrox (68), and in the DDD-ICD group: Kainox (7), Kentrox (67), Linox (39), other (13). The pacing rate was programmed to VVI 40 bpm, a VT1 monitor zone to 130 bpm, and other detection zones were adjusted to the patient's individual demands. Implantation details, need for ICD system revision, and all arrhythmia episodes during follow-up were recorded.

Results: The implantation time was significantly shorter in the A+ ICD group (69±33 vs. 80±31 min; P=0.008), yet the fluoroscopy time was similar (A+: 7±6 vs. 6±6 min). Mean P-wave amplitude was 3.2±0.6 mV (DDD) and 3.5±0.8 mV (A+, owing to automatic atrial signal amplification). Mean R-wave was 11±3 mV (A+) and 12+3 mv (DDD). Ventricular pacing threshold was higher in A+ ICD (1.2±1.0 V vs. 0.8±0.6 V; P< 0.001) due to more frequent use of older-generation Kainox leads in the A+ arm (59 vs. 7). Pacing threshold for the newer-generation Kentrox leads did not differ between A+ (0.7±0.5 V, n=66) and DDD arms (0.8±0.4 V, n=68; P=0.25). Surgical revisions were necessary in 12 pts in the DDD (5 atrial and 4 ventricular lead revisions, 1 failure to defibrillate, 1 ventricular lead perforation, 1 pneumothorax) and 10 pts in the A+ arm (8 ventricular lead revisions, 1 failure to defibrillate, 1 pneumothorax). A total of 217 pts (85%) completed the 12 month follow-up, and 13 pts died (5.1%). Appropriate VT or VF detection was noted in 52 pts (325 episodes) in the A+ and 57 pts (263 episodes) in the DDD-arm. A total of 1566 SVT episodes were recorded in 67 pts in the A+ and 1051 episodes in 60 pts in the DDD-arm.
Conclusion: Implantation of the A+ ICD systems is faster and not inferior to DDD-ICD in VT/VF detection. It provides a safe alternative to obtain AEGMs without implanting an atrial lead.

P1658 Changes in impedance are associated with changes in ventricular volume in patients receiving defibrillators for resynchronization therapy

M. Landolina[1], M. Maines[2], M. Lunati[3], G. Zanotto[4], A. Proclemer[5], M. Santini[6], M. Vimercati[7], A. Varbaro[7] on behalf of OptiVol CRT CS Group. *[1]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Ospedale Santa Maria Del Carmine, Rovereto, Italy; [3]Ospedale Niguarda Ca' Granda, Milan, Italy; [4]Presidio Ospedale Civile Maggiore, Verona, Italy; [5]S. Maria della Misericordia Hospital, Udine, Italy; [6]Ospedale San Filippo Neri, Rome, Italy; [7]Medtronic Italia, Milan, Italy*

Purpose: Some defibrillators (ICD) are able to monitor intrathoracic impedance to detect pulmonary fluid overload. This is achieved by measuring impedance between the ICD case and the right ventricular (RV) lead. We hypothesized that the measured impedance would rise with improvement in left ventricular (LV) volumes during resynchronization (CRT), and that such impedance changes would be more apparent when measured with an alternative pacing vector.
Methods: We analyzed echocardiographic and impedance data from 170 heart failure patients (NYHA class 2.8±0.6, ejection fraction 27±6%, QRS duration 145±29ms) implanted with a CRT-ICD capable of intrathoracic impedance measurement for fluid accumulation diagnosis, and LV pacing impedance recording for lead integrity monitoring.
Results: At 6 months, the LV end-systolic volume (LVESV) decreased in the overall population, with 127 patients showing a reduction of LVESV (LVESV at 6 month – LVESV at baseline <0: Group A). For the remaining 43 patients (Group B) the change was ≥0. Despite comparable values at baseline (p=0.262), the impedances of groups A and B gradually diverged soon after the implant, and the values at the 6-month visit resulted different (p=0.001). The changes in LV dimensions produced larger differences between groups in the impedance measured between the LV and the RV leads (Figure). The regression analysis demonstrated an inverse correlation between paired changes of volume and intrathoracic impedance. Higher correlation coefficient was obtained using the LV-to-RV measurement vector (r=-0.635, p<0.001).



Conclusions: The changes in ICD-measured impedance seem associated with the LV volume changes induced by CRT. Specifically, the LV-to-RV impedance estimations seem to better correlate with paired changes of ventricular volumes.

P1659 Beta-2 Gln27Glu adrenergic receptor gene polymorphism and appropriate ICD shocks among the patients with heart failure

N. Pezzali[1], M. Metra[1], L. Covolo[2], A. Curnis[1], U. Gelatti[2], F. Donato[2], L. Dei Cas[1]. *[1]Sec. of Cardiovasc. Diseases, Department of Experimental and Applied Med., University and Hospital, Brescia, Italy; [2]Sec. of Hygiene, Department of Experimental and Applied Med., University, Brescia, Italy*

Purpose: to evaluate the possible influence of beta-2 adrenergic receptor gene polymorphism, associated with different beta-2 AR receptor densities and different sensitivity to adrenergic drive, on the risk of receiving appropriate ICD shocks for fast VT or VF and on the magnitude of arrhythmic storms in a population of patients (pts) with HF carrying an ICD. The impact of appropriate ICD shocks on survival was also assessed.
Methods: 107 pts with HF due to idiopathic (27%) or ischemic (73%) dilated cardiomyopathy carrying an ICD for SCD primary prevention according to guidelines indications were followed up for 25.1±18.5 months. Cardiovascular events occurring during the follow-up (including death or hospitalization for acute coronary syndromes, worsening heart failure, arrhythmias, sudden cardiac death) were recorded. The number of fast VT, VF and appropriate ICD shocks was analysed from ICD stored data. Genotyping was performed for beta-2 Gln27Glu adrenergic receptor gene polymorphism.
Results: Patients homozygotes for the beta-2 Gln27 adrenergic receptor gene polymorphism had a 2.26 higher relative risk of receiving appropriate ICD shocks compared to Glu27 carriers (95% CI 1,03 to 4,95, p=0.04) and an odds ratio of receiving appropriate ICD shocks equal to 2.83 compared to Glu27 carriers (95% CI 1,07 to 7,5, p=0.0361). Receiving appropriate ICD shocks had no impact on outcomes assessed by the combined endpoint of death for cardiovascular disease or cardiovascular hospitalization.
Conclusion: Beta-2 Gln27Glu adrenergic receptor gene polymorphism influences the risk of receiving appropriate ICD shocks for fast VT or VF, surrogate of SCD risk, thus helping identifying pts at higher risk of major arrhythmic events. Appropriate ICD shocks did not increase mortality and morbidity for cardiovascular events among pts with heart failure.

P1660 Antiarrhythmic effects of n-3 PUFA in patients with heart failure and an implantable cardioverter defibrillator in the GISSI-HF trial

A. Finzi[1], S. Barlera[2], D.M. Serra[2], M.G. Rossi[3], A. Ruggeri[4], A. Mezzani[5], M.G. Franzosi[2], R. Marchioli[6], F. Bianchini[7], L. Tavazzi[8] on behalf of GISSI-HF Investigators. *[1]Ospedale Maggiore Policlinico, Milan, Italy; [2]Istituto Mario Negri, Milano, Italy; [3]Fondazione Cardiocentro Ticino, Lugano, Switzerland; [4]Ospedale Policlinico, Reggio Calabria, Italy; [5]Istituto Scientifico - Fondazione Salvatore Maugeri IRCCS, Veruno, Italy; [6]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [7]Centro Studi ANMCO, Firenze, Italy; [8]Villa Maria Cecilia Ospedale, Cotignola, Italy*

Background: The antiarrhythmic effects of n-3 polyunsaturated fatty acids (n-3 PUFA) have been demonstrated in the setting of subacute ischemic heart disease. However, trials in patients treated with an implantable cardioverter defibrillator (ICD) have yielded conflicting results. Time to first occurrence of ICD discharge for ventricular fibrillation (VF) or tachycardia (VT) was the outcome measure to assess the antiarrhythmic effect of n-3 PUFA in patients with heart failure (HF) who received an ICD for secondary or primary prevention of VF/VT.
Methods: GISSI-HF was a double blind, placebo-controlled trial testing n-3 PUFA 1g daily. 578 out of 6975 patients, had an ICD implanted either before (42%) or after (58%) enrollment in the trial. Reasons for implant were syncope (15.7%), primary (56.4%) or secondary prevention (27.9%) of VT/VF. Clinical data and arrhythmia recordings were extracted from the device memory. Multivariate Cox models adjusted for clinical parameters significantly associated to the outcome were fitted.
Results: In this subset of patients, 566 pts had at least 1 follow-up visit: 278 received n-3 PUFA and 288 placebo. During a mean follow-up of 918 (SD=476) days, a total of 1,363 VT and 316 VF episodes were terminated by ICD pacing or shock. The endpoint was experienced in 174 patients (30.7%), 27.3% in n-3 PUFA and 34.0% in placebo group with an adjusted relative risk in favor of n-3 PUFA (HR= 0.80 [95% CI 0.59-1.09] p=0.15). Patients who received 1, 2-3, or >3 ICD discharges were 8.9%,7.1%,11.1% respectively in the PUFA group, as compared with 11.1%10.7%,12.1% in placebo. (n.s.). As to patients whose main indication was primary prevention, the adjusted relative risk was not different from that of the overall population (HR= 0.68 [95% CI 0.36 -1.26] p= 0.22). Total hospitalizations after ICD implant, occurred in 69.4% of patients treated with n-3 PUFA and 75.7% in placebo (log rank p=0.38). The latter figure is higher than that observed in the general population of GISSI-HF (57%).
Conclusion: As shown by device-stored events, treatment with PUFA was associated with a non significant, but consistent antiarrhythmic effect in HF patients with ICD. Indication for ICD implant does not seem to influence the effect of n-3 PUFA on outcomes.

P1661 Bleeding complications after device implantation in patients receiving dual antiplatelet therapy- the results of the prospective, two-centre registry

W. Kwasniewski[1], A. Przybylski[2], D. Urbanczyk-Swic[1], P. Derejko[2], A. Filipecki[1], J. Zakrzewska[2], W. Orszulak[1], M. Orczykowski[2], M. Trusz-Gluza[1], F. Walczak[2]. *[1]Slaski Uniwersytet Medyczny w Katowicach, Katowice, Poland; [2]Institute of Cardiology, Warsaw, Poland*

Introduction: There is a substantial number of patients treated with aggressive antiplatelet regimens, usually after percutaneous coronary interventions and requiring implantation of pacemakers or cardioverter-defibrillators (ICD). The aim of the study was to assess prevalence of bleeding events in patients treated with

dual antiplatelet therapy (DAT) in comparison to patients receiving acetylsalicylic acid (ASP).
Methods: From 626 first implantations of pacemakers, ICDs and cardiac resynchronization devices in two centers 194 patients receiving acetylsalicylic acid (ASP) and 53 patients receiving dual antiplatelet therapy (DAT) were enrolled throughout 12 months.
Results: There were no differences in clinical, demographic and procedure (e.g. venous access, implanter volume) variables between thge groups, except of the recent PCI rate (100% in DAT group). Bleeding complications were detected in 27 (16.2%) patients in the ASP group and in 13 (24.5%) in the DAT group (p=0.0637). The incidence of major complications (requiring blood transfusion or surgical intervention or prolonging hospital stay) was low (overall 3.6%), and similar in both groups (3.6 and 3.8% respectively, ns). The rate of minor complications (subcutaneous hematomas) was significantly higher in the DAT group (p=0.015).
Conclusions: The treatment with DAT does not increase the risk of major bleeding complications as a result of device implantation, however minor complications are significantly more frequent. Our results suggest that DAT could be continued in patients undergoing device implantation with a moderate risk of bleeding complications.

P1662 Biventricular pacing prevents progression to heart failure in patients with ICD indication and left bundle branch block

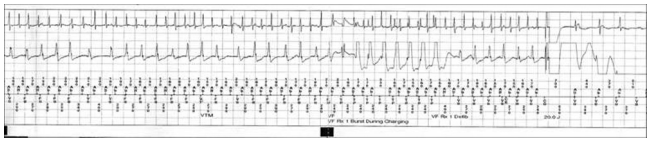
J. Brugada[1], I. Fernandez-Lozano[2], R. Ruiz[3], A. Berruezo[1], J.M. Porres[4], J. Alzueta[5], J. Zamora[6], J.G. Martinez[7], L. Mont[1].
[1]Hospital Clinic, University of Barcelona - Thorax Institute; Cardiology Dep. - Arrythmia Section, Barcelona, Spain; [2]Cardiology Department, Clinica Puerta de Hierro, Madrid, Spain; [3]Cardiology Department, Hospital Clinico, Valencia, Spain; [4]Intensive Care Unit, Donostia Hospital, Donostia, Spain; [5]Cardiology Department, Hospital Clinico, Malaga, Spain; [6]Statistics Department, Complutense University, Madrid, Spain; [7]Cardiology Department, General Hospital, Alicante, Spain

Background: The incidence of ventricular arrhythmias, and the progression towards heart failure in patients with an indication for an Implantable Cardioverter Defibrillator (ICD), a decreased ejection fraction (EF) and a left bundle branch block (LBBB) might be modified by implanting a biventricular device.
Objective: To demonstrate that biventricular pacing decreases the incidence of sustained ventricular arrhythmias (primary end-point) and prevents progression towards heart failure (secondary end-point) in patients with an ICD indication, EF<40% and a LBBB.
Methods: Seventy-one patients with an indication for ICD, no overt heart failure (NYHA class I or II), with an EF <40%, sinus rhythm, a LBBB with a QRS complex duration >140 msec were randomized to receive either a monocameral ICD (n=34) programmed in VVI pacing mode at 40 bpm, or a biventricular device (n=37) programmed to permanently resynchronize the ventricles.
Results: After a mean follow-up of 48+12 months, no statistically significant differences were observed in the occurrence of sustained ventricular arrhythmias between both groups (50% in monocameral ICD vs 35% in biventricular ICD, p=0.23). However, progression to heart failure defined as the combination of death from cardiac causes (12% vs 3%, p=0.18), need for heart transplant (3% vs 3%, p=0.49) or hospitalization due to heart failure (41% vs 11%, p=0.006) was significantly different between both groups (47% in monocameral ICD vs 17% in biventricular ICD, p=0.021).
Conclusions: Implanting a biventricular ICD in patients with an indication for ICD, low EF and complete LBBB does not modify the number of arrhythmic events during follow-up, however, it diminishes long-term progression towards heart failure.

P1663 Fast atrial fibrillation as dominant cause of inappropriate discharges in adult ICD recipients

E. Simeonidou[1], A. Papandreou[2], G. Tsigas[2], C. Michalakeas[1], C. Tsitlakidis[1], D. Alexopoulos[2], J. Lekakis[1], D. Kremastinos[1].
[1]Attikon University Hospital, Athens, Greece; [2]Patras University Hospital, Patras, Greece

Purpose: Implantable cardioverter defibrillator (ICD) is the most efficient treatment in patients (pts) with life threatening ventricular arrhythmias (VT/VF). In ICD pts inappropriate detection and therapy are the commonest side effects with serious impact in their quality of life and morbidity. Aim of the study was the assessment of incidence and causes of inappropriate discharges in ICD pts, who were followed up in our hospitals.
Methods: The study population: 350 consecutive pts, 43 women and 307 men, mean age 59±14 years, who received a single, dual chamber or biventricular ICD. The underlying disease: CAD (60%), DCM (36%), IVF (3%) and mean EF was 48±10%. In all pts electrical parameters and ICD performance during implantation were excellent. VT therapies were programmed according to the cardiac data of each pt before discharge. Pts were followed up in a regular basis and in case of reported ICD firing and detailed analysis of the saved data was undertaken.
Results: In 350 consecutive ICD pts, 890 VT/VF therapies with 90 inappropriate ones (10%) in 22 pts (6%), were detected. No pt experienced failure of appropriate recognition of real VT/VF. Inappropriate therapies were triggered by paroxysmal fast AF (PAF) (60%), by undesirable sensing of external sources of electromagnetic sources (30%) and by double counting TW because of oversensing-defective lead (10%). Successful management of the problem was achieved in all either by AA drugs or activation of available SVT discrimination algorithms and avoidance of interference. Only 3 pts demanded a new lead because of a defect.



Conclusions: In 6% of the ICD pts inappropriate therapy was detected because of VT/VF misdiagnosis. Fast PAF was found to be the main cause of inappropriate ICD therapy followed by electromagnetic interference.

P1664 ICD therapy in Brugada syndrome - a single center experience

C. Veltmann, R. Schimpf, J. Kuschyk, F. Streitner, N. Schoene, A. Krey, B. Staller, M. Borggrefe, C. Wolpert. *Universitaetklinikum Mannheim, Mannheim, Germany*

Introduction: Implantable cardioverter-defibrillators (ICD) are implanted for primary and secondary prevention in patients with Brugada syndrome who are at high risk for sudden cardiac death. This therapy is complicated by high incidences of inappropriate therapies and lead revisions in contrast to a very low incidence of appropriate therapies. Aim of the present study is the analysis of ICD therapy in patients with Brugada syndrome with respect to appropriate and inappropriate therapies, lead revisions and complications during long-term follow-up.
Methods: Between 2000 and 2008, 65 patients with Brugada syndrome (44 males; mean age 38±13 years) received an ICD for primary (n=58) or secondary (n=7) prevention. 64 devices (98%) were single chamber ICDs (n=34 St. Jude Medical, n=23 Medtronic Inc., n=7 Boston Scientific, n=1 Biotronik). All ICDs were programmed with a single detection zone and a cut-off rate of 222 bpm. A maximum of 6 shocks with the maximal output of the individual device was programmed. ICD interrogations were performed every 3 months.
Results: The patients were followed over a median follow-up of 48.7 months. All patients survived. Seven patients (11%) developed 12 episodes of ventricular fibrillation and received appropriate ICD shocks. No patient had unexplained syncope during follow-up. Five patients (8%) received an inappropriate ICD shocks due to T-wave oversensing and lead dislocation. One patient (1.5%) received inappropriate ICD shock due to very fast conducted atrial fibrillation, despite a VF cut-off rate of 222 bpm. 7 patients (11%) underwent revision (n=1 infection, n=5 lead dislocation, n=1 lead perforation).
Conclusions: 1) 11% of the patients received appropriate ICD therapy. 2) 5 patients (8%) received inappropriate ICD therapy due to lead dislocation and T wave oversensing. 3) The rate of inappropriate therapy due to supraventricular tachycardia is very low (1.5%) 4) The rate of appropriate ICD therapy is higher than the rate of inappropriate therapy. This is caused by the low incidence of inappropriate therapies due to supraventricular tachycardia using a single detection zone with a high cut-off rate.

P1665 Lead extraction versus additional lead implantation: impact of different strategies for the treatment of first ICD lead defect on the perioperative complication rates of the following lead revision

T. Kleemann, T. Becker, M. Strauss, U. Weisse, W. Saggau, K. Seidl.
Cardiac Arrhythmia Institute at the Heart Center of Ludwigshafen, Ludwigshafen Am Rhein, Germany

Background: Implantation of an additional implantable cardioverter defibrillator (ICD) lead versus extraction of the defective ICD lead and implantation of a new one is one therapeutic approach in cases of a defective ICD lead. Aim of the study was to assess the lead defect rate of the replaced ICD lead and to evaluate the impact of the different approaches on the perioperative complication rates of the second lead revision.
Methods: Between 1992 and May 2008, 166 patients with an ICD lead defect

Table 1

	Group 1 "additional lead" (n=23)	Group 2 "extracted lead" (n=15)	p-value
Second lead revision performed	21/23	15/15	n.s.
Lead extraction and lead reimplantation	15/21	10/15	n.s.
Perioperative complications	8/21	1/15	0.05
Pneumothorax	2/21	0/15	n.s.
Pocket hematoma needing revision	0/21	1/15	n.s.
Infection	2/21	0/15	n.s.
Hematothorax	1/21	0/15	n.s.
Incomplete extraction	1/21	0/15	n.s.
Massive hemorraghe	1/21	0/15	n.s.
Intraoperative resuscitation	1/21	0/15	n.s.

Perioperative complications in second lead revision: group "additional lead" versus group "extracted lead".

received either an additional transvenous ICD lead (n = 93, group 1) or the ICD lead was replaced (n = 73, group 2). The median follow-up time of the replaced ICD leads was 3 years.
Results: During the median follow-up time of 3 years the lead failure rate of the replaced ICD leads was 21% in group 1 versus 25% in group 2 (p = 0.5). Eight per cent of patients experienced nonfatal perioperative complications during the first lead revision (group 1: 5%; group 2: 12%, p = 0.11) and 25% of patients during the second lead revision (group 1: 38%; group 2: 7%; p = 0.05).
Conclusions: Patients with an additional ICD lead have a fivefold increased perioperative complication rate during the second lead revision compared to those patients where the ICD lead is primarily extracted. The lead failure rate of an additional ICD lead compared to a replaced ICD lead is not different between both groups.

P1666 Changes in intrathoracic impedance predicting heart failure decompesation episodes

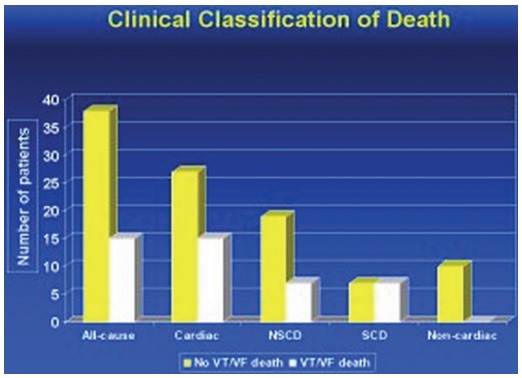
V. Castro, V.M.P. Monivas, E.P.P. Perez, V.M.M. Mariona, J.T.R. Toquero, E.S.S. Sufrate, L.N.F. Nombela, J.E.V. Escudier, C.G.L. Gutierrez, I.F.L. Fernandez Lozano. *Hospital Puerta de Hierro, Madrid, Spain*

Introduction: Patients with advanced chronic heart failure (CHF) have an elevated hospital admissions rate. The fluid status monitoring system (FSMS) is a method that evaluates changes in the intrathoracic impedance and, by this approach, can detect fluid overload before symptoms appear.
Purpose: Determine the efficacy of the FSMS identifying patients with CHF decompesation.
Methods: Between October of 2004 and May of 2008, we have implanted 65 cardioverter defibrillator devices (ICD) with the FSMS system, wich includes 35% of devices with cardiac resynchronization therapy (CRT). The follow up schedule has programmed with clinical evaluations every 6 months or, in the first 24 hours after an Optivol alert. If it was considered necessary in the clinical evaluation, the diuretic dose was adjusted.
Results: mean age was 58.8 years, 84% were male. Diagnosis by frequency order were: nonischemic dilated cardiomyopathy (DCM 37%), coronary artery disease (CAD 32%), rheumatic heart disease (10%) and hypertrophic cardiomyopathy (10%). Fifty three percent of patients were in NYHA class III. Basal echocardiographic parameters were: EDLVD 59±11 mm, ESLVD 48±14 mm, EF 33±16%.
After 36 months of follow up, there were 50 alerts (in 33 patients), wich were classified according to clinical evaluation in: 1) true positive alerts 20 (40%), with clinical correlation between alert and patient's symptoms or a clear cause of CHF decompensation; 2) probably positive alerts 7 (14%), patients with a cause of CHF decompensation and/or elevated NT-proBNP levels but asymptomatic; 3) false positive alerts 23 (46%), patients with no cause of decompensation and asymptomatic; and 4) false negative 3 (6%) patients, who were hospitalized because of CHF decompensation with any alerts detected in their devices.
The detected causes of CHF decompensation were: worsening of cardiac systolic function 54%, lowering in the diuretic dose 15%, atrial fibrillation 15%, fluid intake overload 12%, disfunction of CRT device (loss of capture of LV electrode) 2%. There were 8 hospital admissions because of decompensated CHF in 5 patients (including the 3 false negative cases). In the hospitalized patients, 4 received cardiac transplantation and 1 underwent septal myectomy.
Conclusions: the fluid status monitoring system effectiveness in the early detection of CHF decompensation episodes in our population was 40%. There is a lower sensibility than the observed in previous trials, probably in relation to the current implantation of devices with the FSMS to patients with higher NYHA class

P1667 Interrogation of ICD at time of death in MADIT II patients; Risk factors for arrhythmic vs non-arrhytmic death

C. Jons, A.J. Moss, W. Zareba, I. Goldenberg. *University of Rochester Medical Center, Rochester, United States of America*

Background: Implanted cardioverter defibrillator (ICD) therapy was associated with a significant 54% reduction in the risk of sudden cardiac death (SCD) in the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II). However, the risk arrhythmic mortality in ICD-treated patients not been assessed.
Methods: Interrogation data were assessed for 53 (65%) of 82 patients who died with an active ICD in MADIT-II. Sudden- and non-sudden cardiac deaths were further categorized by the presence of ventricular tachycardia or fibrillation (VT/VF) during the terminal event. Multivariate proportional hazards regression modeling was used to identify risk factors for VT/VF death in patient with an ICD.
Results: Fifteen patients (28%) experienced a least one episode of appropriate ICD shocks for VT/VF death during the terminal event. Ventricular tachyarrhymias were recorded in only 50% of the 15 patients who experienced sudden cardiac death and in 27% of the 26 patients who experienced non-sudden cardiac death. Clinical factors identified as independently associated with increased risk for VT/VF death included age <65 years (HR=5.60; p=0.005), creatinine >1.4 mg/dL (HR=3.11; p=0.008), the development of post-enrollment heart failure (HR=8.52; p<0.001); and a history of hypertension (HR=3.10, p=0.08).
Conclusions: Our data suggest that: a relatively large proportion of patients who



Clinical death classification and VT/VF

die with an ICD experience at least one episode of ventricular tachyarrhythmia during the terminal event; and that clinical assessment of the mode of death does not identify arrhythmic mortality in a considerable proportion of patients. Arrhythmic mortality in patients with an ICD is associated with specific clinical and laboratory risk factors.

P1668 Electrical Storm (ES) in patients with Implantable Cardioverter Defibrillator (ICD) - Long term follow-up

K. Gepner, A. Maciag, P. Syska, D. Zajac, M. Lewandowski, M. Sterlinski, H. Szwed. *Institute of Cardiology, Warsaw, Poland*

Purpose: Implanted ICD prolongs life when used for primary or secondary prevention of sudden cardiac death (SCD). The aim of our study was to determine the predictors of electrical storm (ES) in patient with ICD during long term follow-up.
Methods: Records of 600 consecutive ICD patients implanted between 1995-2008 were analyzed retrospectively. We looked for the patients who were hospitalized due to ES (3 or more VT/VF episodes within 24 h requiring device intervention). Clinical data such as reason for implantation, underlying disease, farmacological treatment, cause of ES, its management and patient mortality were analyzed.
Results: We identified 42 patients (36 male) aged 59,8±16,8 years who experienced at least one ES incident. 27 of them (64%) had coronary artery disease (CAD) and 15 patients (36%) had non-ischemic cardiomyopathy (non-CAD). ICDs were implanted for primary prevention of SCD in 4 patients (9,5%) and for secondary prevention of SCD in 38 patients (90,5%). During follow-up 5,9±3,1 years, 34 pts had one episode ES, 6 pts two and 2 pts three episodes ES. Mean time from implant to ES was 27 months. During the 30 days period after ES 7 persons died: 5 deaths (71,4%) in group with CAD (one in primary prevention of SCD) and 2 deaths (28,6%) in group with non-CAD (DCM, both in secondary prevention of SCD). As the reason of all deaths worsening of congestive heart failure was reported. Identifiable cause for ES was found in 14 pts. They were: worsened congestive heart failure (8pts), stenosis of coronary artery (2 pts), hypokaliemia (2pts), infection (1pt) and prolongation of QT after clarythromycine (1 pt). ES was treated by catheter ablation (9 pts), addition of amiodaron (9 pts), sotalol (7pts), mexiletine (3pts) or isoptin (2pts), change carvedilol to bisoprolol (3pts), optimalization of farmacological treatment of CHF (3 pts), revascularisation of coronary artery (2pts), implantation of epicardial electrode in patients with BiV-D (2 pts) due to left ventricular (LV) electrode dyslocation, infusion potassium (2 pts). In two pts the first ES resulted in death.
Conclusions: The study shows that ES is most common in patients with congestive heart failure of ischemic ethiology with ICD implanted for secondary prevention of SCD. This patients are the most exposed to the risk of death during ES and need to be closely monitored after implantation of ICD. The most often treatement of ES is antiarrhythmic drugs. In patients with monomorphic VT catheter ablation seems to be very promising for the future.

P1669 Clinical characteristics and ventricular tachyarrhythmia events in patients with an implantable cardioverter defibrillator and atrial fibrillation

S. Ammar, F. Streitner, N. Schoene, C. Veltmann, R. Schimpf, C. Wolpert, M. Borggrefe, J. Kuschyk. *1st Department of Medicine, University Hospital Mannheim, Medical Faculty Mannheim, Heidelberg Uni., Mannheim, Germany*

Objectives: We sought to investigate the clinical characteristics of patients with atrial fibrillation (AF) and an implantable cardioverter–defibrillator (ICD) and to assess the relationship between AF and ventricular arrhythmia events.
Methods: Out of 955 patients who received an ICD in our centre between 1998 and 2008, 302 (31,6%) patients had paroxysmal, persistent or permanent AF. We compared the clinical characteristics and arrhythmia events between two groups, with and without AF during a mean follow-up of 34±22 months.

Results: The ICD was implanted for primary prophylaxis in 82,8% in patients suffering from AF vs. 79,9% without AF (p=NS). Patients with AF were older (70±9 vs. 65±14 years, p<0,01) with a majority of men (81% vs. 76,4%, p=0,06). The incidence of diabetes was higher in patients with AF (22,2 vs. 12,4%, p<0,01). They had a lower left ventricular ejection fraction (LVEF) (31,6±12 vs. 37,5±16%, p<0,01), a worse functional status (NYHA III-IV: 39,6 vs. 31,3%, p<0,01) and a larger QRS duration (136,5±43 vs.130,7±40, p=0,06). With an empiric programming of the ICD therapy (VT: 160-220/min 5x ATP followed by ICD shocks, VF>220/min shocks), the incidence of adequate ICD therapy during follow-up was higher in case of AF (35,9 vs. 26,8, p<0,01) with a higher rate of ventricular tachycardia (VT: 29,6 vs. 23,3%, p=0.02) and ventricular fibrillation (VF: 18,8 vs 10,6, p=0,001). The incidence of inappropriate shocks was significantly higher in the AF group (26,5 vs. 13,7%, p<0,01).
Conclusions: 1) Patients with atrial fibrillation and ICD have worse clinical characteristics.
2) AF is associated with increased risk for ventricular tachyarrhythmias (VF/VT).
3) Avoiding inappropriate shocks due to atrial fibrillation by an optimal programming of the ICD remains a challenge.

P1670 Incidence of mortality and appropriate shocks in patients with ischemic and non-ischemic cardiomyopathy after receiving implantable cardioverter defibrillators

K. Gandhi, W. Aronow, H. Desai, H. Amin, H. Lai, W. Frishman, M. Cohen, C. Sorbera. *Westchester Medical Center/New York Medical College, Valhalla, United States of America*

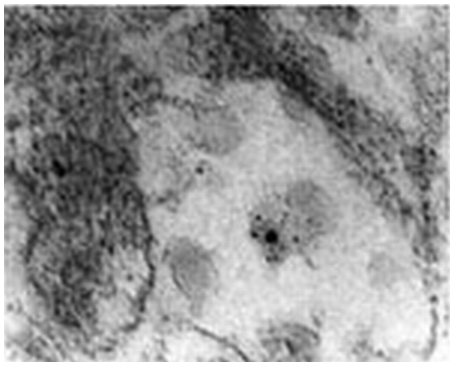
Introduction: While multiple randomized clinical trials have demonstrated the benefit of implantable cardioverter defibrillator (ICDs) in patients with ischemic cardiomyopathy, there are conflicting data on the role of ICD therapy in patients with non-ischemic cardiomyopathy. The purpose of this study was to compare the clinical outcomes in terms of mortality and appropriate shocks in patients with ischemic and non-ischemic cardiomyopathy after receiving ICDs.
Methods: In an academic cardiology practice, 894 patients received an ICD according to the American College of Cardiology/American Heart Association guidelines. The 894 patients included 735 men and 159 women, mean age 71±13 years. At follow-up every 3 months, the ICD was interrogated to see if any shocks occurred. The shocks were further evaluated by an electrophysiologist viewing the intracardiac electrocardiograms to see if they were appropriate. Of the 894 patients, 599 patients (67%) had ischemic cardiomyopathy and 295 patients (33%) had non-ischemic cardiomyopathy. All-cause mortality data were obtained from the Social Security Death Index.
Results: Of the 894 patients who had ICDs, 259 patients (29%) had appropriate ICD shocks during the 31-month follow-up. Appropriate shocks occurred in 181 of 599 patients (30%) with ischemic cardiomyopathy and in 78 of 295 patients (26%) with non-ischemic cardiomyopathy (p not significant). Death occurred in 221 of 894 patients (25%). Death occurred in 162 of 599 patients (27%) with ischemic cardiomyopathy and in 59 of 295 patients (20%) with non-ischemic cardiomyopathy (p<0.05).
Conclusion: Our results showed that while the prevalence of appropriate shocks was similar in patients with ischemic and non-ischemic cardiomyopathy, patients with ischemic cardiomyopathy had a higher mortality than patients with non-ischemic cardiomyopathy.

METABOLIC AND BASIC ASPECTS OF HEART FAILURE

P1671 Archaeal gene-encoded organelles in association with asymptomatic form of Chronic Chagas disease

M.L. Higuchi, J. Kawakami, M.M. Reis, J.M. Silvestre, E.A. Bocchi, N. Stolf. *Heart Institute (InCor) of Sao Paulo University, Sao Paulo, Brazil*

Introduction: T.cruzi is the aetiological agent of Chagas'disease. 30% of the infected patients develop Dilated Cardiomyopathy related to an autoimmune myocarditis. Proteasomes are organelles that rid the cells of abnormal proteins and trypanosoma was discovered to carry proteasomes from archaea probably by evolutionary endosymbiotic mechanism. We observed by electron microscopy electron dense lipidic (ED) organelles containing archaeal DNA in chagasic endomyocardial biopsies (EB). Objective: To analyze if ED organelles encoding archaeal DNA are present in different amount in EB from chagasic patients with heart failure (HF) compared with asymptomatic indeterminate form (IF) pts.
Material and Methods: EB from 5 HF and 4 IF patients were studied by in situ hybridization with electron microscopy, using the ARC 915 bio sequence, detected with 10nm gold particles. Mean numbers/electron micrography of ED organelles and DNA positive dots in and outside of the organelles were counted analyzing 10 electron micrographies with 17.500x magnification of each case.
Results: Using Student T test we observed lower numbers of ED organelles (0.26±0.91) in HF group compared with IF (0.6±1.08) p=0.004. HF group had lower numbers of archaeal DNA dots in these organelles (0.19±0.94) than IF cases (1.64±2.38) p<0.001. There was a significant negative correlation between numbers of ED organelles vs amount of archaeal DNA dots outside of ED in IF (r=-0.46), and lack of correlation in HF group (r= -0.11).
Conclusion: Archaeal gene encoded organelles are associated with IF in patients carrying T.cruzi infection. These findings suggest that patients with an "autoimmune" myocarditis may have a lack of these organelles which would have the function of ridding abnormal proteins.



Archaeal encoded ED organelles

P1672 Electrophysiological and electroanatomical mapping of the right atrium in patients with dilated cardiomyopathy: relation to the collagen turnover and to increased propensity for atrial fibrillation

E.M. Kanoupakis[1], H.E. Mavrakis[1], C.A. Goudis[1], N.E. Malliaraki[2], M. Milathianaki[2], K. Stokkos[1], E.G. Manios[1], P.E. Vardas[1]. *[1]Cardiology Dept. Heraklion University Hospital, Heraklion, Greece; [2]Dept. of Biochemistry, Heraklion, Greece*

Purpose: Atrial fibrosis and heterogeneities in electrophysiological properties may contribute to the development of atrial fibrillation (AF) in patients with nonischemic dilated cardiomyopathy (DCM). We investigated whether the electrophysiological properties and endocardial voltage in different regions of the right atrium as well as the serum markers of collagen turnover differed between patients suffering from DCM with or without a history of paroxysmal AF.
Methods: We studied nineteen patients with left ventricular dysfunction (LVEF<30%) due to DCM, nine of whom have a history of paroxysmal AF. The following parameters were evaluated in all patients: effective refractory periods (ERPs) from the high and low lateral right atrium (LRA), high septal right atrium, and distal coronary sinus (CS); conduction time along the CS and LRA. Regional endocardial voltage measurements were made by means of electroanatomical mapping.
Serum procollagen type 1 aminoterminal propeptide (P1NP), tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) and C-terminal telopeptide of collagen type I (CITP) were assayed by ELISA with commercially available kits as markers of collagen synthesis and degradation.
Results: Patients with a history of paroxysmal AF demonstrated lower ERPs, a significant dispersion of refractoriness and an increase of atrial conduction time along the LRA and the CS compared with patients without AF. Electroanatomical mapping demonstrated regional voltage heterogeneity and lower voltage areas in patients with paroxysmal AF (1.9±0.4 mV vs. 1.1±0.2 mV, p<0.05). CITP levels were significantly lower in patients with paroxysmal AF (0.60±0.20 ng/ml vs. 0.41±0.08 ng/ml, p<0.05).
Conclusions: In patients with DCM, heterogeneities in electrophysiological properties of the right atrium in conjunction with abnormalities in serum markers of cardiac fibrosis may be responsible for the increased propensity for AF in some patients.

P1673 Intermittent fasting reduces mortality and attenuates post-infarction ventricular remodeling in rats

K. Okoshi, M.A.M. Polin, J.R. Paladino Junior, P.F. Martinez, L.L. Rodrigues, C.M. Rosa, C. Bonomo, L.A. Zornoff, L.S. Matsubara, M.P. Okoshi. *Sao Paulo State University, Botucatu Medical School, Botucatu, Brazil*

Purpose: Few reports have shown that intermittent fasting (feeding every other day) is beneficial in post-myocardial infarction rats. This study aimed to investigate the effects of intermittent fasting (IF) on mortality and in vivo and in vitro left ventricular structure and function in rats with myocardial infarction.
Methods: Male 65-day old Wistar rats were divided into two groups: control (C, n=60, rat chow and water ad libitum); and IF (n=60, rat chow every other day and water ad libitum). After 12 weeks, all rats were subjected to surgical occlusion of the left coronary artery. Twelve weeks later, surviving animals were submitted to echocardiography and isolated perfused heart study (Langendorff). Infarct size was measured by histology. Data were compared using Student's t test, and mortality analyzed by Chi-square test.

Results: Twelve weeks after infarction, mortality rate was lower in the IF group (C: 72.2%; IF: 48.5%; $p<0.05$) as was infarct size (C: 54.9±8.3%; IF: 31.7±5.5%; $p<0.05$). Echocardiographic and isolated perfused cardiac study results are presented in the table. No difference between groups was observed on left ventricular systolic and diastolic functional indices in both in vivo and in vitro studies.

	Control	Intermittent Fasting
Body weight (BW, g)	477±50	387±29
LVDD/BW (mm/kg)	24.5±2.56	27.8±2.46*
LAD/BW (mm/kg)	18.2±3.40	20.0±3.50
LV area change (%)	31.6±8.81	33.5±7.74
LV mass (g)	1.05±0.12	0.99±0.13
LV mass/BW (g/kg)	2.28±0.13	2.54±0.32*
LV volume (ml)	0.41±0.05	0.28±0.05*
LV volume/BW (ml/kg)	0.90±0.10	0.73±0.13*
LV mass/LV volume (g/ml)	2.57±0.41	3.53±0.52*

Mean ± SD; LVDD: left ventricular diastolic diameter; LA: left atrial diameter; LV area change: LV cavity area change from diastole to systole; LV volume: LV volume at diastolic pressure of zero. *$P<0.05$ vs. Control.

Conclusions: Intermittent fasting reduces infarct size and improves survival and post-infarction ventricular remodeling in rats.

P1674 Increased production of CXCL16 in experimental and clinical heart failure; a possible role in extracellular matrix remodeling

C.P. Dahl, C. Husberg, L. Gullestad, A. Waehre, A.V. Finsen, B. Halvorsen, P. Aukrust, E. Oie, A. Yndestad, G. Christensen.
University of Oslo, Oslo, Norway

Background: Although both experimental and clinical studies indicate a role for inflammation in the development of myocardial failure, knowledge about the production and functional role of the different inflammatory actors in heart failure (HF) remains incomplete. Based on its combined role in inflammation and vascular remodeling, we hypothesized a role for CXCL16 in the pathogenesis of HF.
Methods and Results: Our main findings were: (i) Patients with chronic HF (n=188) had significantly raised plasma levels of CXCL16 as compared with healthy controls (n=20), that significantly correlated with the degree of disease severity. (ii) Left ventricular (LV) tissue from patients with severe HF (n=8) showed enhanced production of CXCL16 compared to non-failing LV (n=6) as assessed by Western blotting. (iii) In mice exposed to pressure overload we found enhanced CXCL16 mRNA levels in the LV, with particularly high levels in those with decompensated hypertrophy. In mice with post-myocardial infarction (post-MI) HF, expression of CXCL16 was increased both in the infarcted and the non-infarcted areas of LV 3 and 7 days after coronary artery ligation, indicating early onset of increased CXCL16 production. The increase in CXCL16 in the tissue at 7 days post-MI was associated with increased CXCL16 levels both in cardiomyocytes and in non-cardiomyocytes (i.e., endothelial cells and fibroblasts). (iv) In vitro experiments showed that CXCL16 induces enhanced protein synthesis in neonatal rat cardiomyocytes, and promotes proliferation and matrix metalloproteinase (MMP) activity in myocardial fibroblasts accompanied by a significant increase in gelatinolytic activity. Furthermore, CXCL16 induced increased MMP activity in cardiomyocytes, primarily reflecting increased MMP-2 levels. (v) Using specific inhibitors in cell experiments, we showed that the effect of CXCL16 on fibroblasts involved activation of the c-Jun N-terminal kinases.
Conclusion: We demonstrate enhanced myocardial expression of CXCL16 in both experimental and clinical HF. The combined effect of CXCL16 on cardiomyocytes and myocardial fibroblasts suggest a role for CXCL16 in extracellular matrix remodeling and ultimately also in the development of HF.

P1675 Adaptive servoventilation improves respiratory stability and exercise capacity in patients with congestive heart failure and Cheyne-Stokes respiration

R. Lehmann[1], T. Bitter[2], S. Korte[1], A. Schmidt[1], C. Prinz[2], C. Langer[2], D. Horstkotte[2], O. Oldenburg[2]. *[1]Cardiac Research Unit, Bad Oeynhausen, Germany; [2]Department of Cardiology, Heart and Diabetes Centre North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany*

Purpose: Respiratory instability with increased VE/VCO2 slope during cardiopulmonary exercise testing and low CO2 arterial partial pressure is a strong prognostic predictor in patients (pts) with congestive heart failure (CHF) and nocturnal Cheyne – Stokes respiration (CSR). Nocturnal adaptive servoventilation (ASV) has recently been shown to improve cardiac function in these pts. Aim of this study was to investigate potential markers of respiratory stability in CHF pts with CSR and nocturnal ASV treatment.
Methods: ASV therapy was initiated in a total of 114 pts with CHF (NYHA ≥ II, LV-EF ≤ 40%) medically treated according to current guidelines with moderate to severe nocturnal CSR (apnoea-hypopnoea-index [AHI] ≥ 15/h).
Results: During a follow-up period of 3.1±0.8 months, 5 pts died and 2 stopped ASV treatment. In the remaining 107 pts (98 male, 64.4±12 years) AHI decreased from 39±17/h to 7±11/h ($p<0.001$), NYHA function class improved (2.5±0.8 to 2.1±0.9, $p<0.001$), left ventricular ejection fraction (28.9±6.4% to 33.0±9.5%, $p<0.001$) as well as peak oxygen uptake during cardiopulmonary exercise (CPX) testing increased (14.6±4.1 to 16.0±4.8, $p<0.01$). These improvements were accompanied by an increased daytime pCO2 (35.5±3.9mmHg to 36.8±3.7mmHg, $p<0.01$) and VE/VCO2 slope during CPX testing (34.2±4.9 to 32.7±4.7, $p<0.05$). Sensitivity of central CO2 receptors, as measured by hyperoxic-hyercapnic ventilatory response (HCVR) according to Read, decreased from 4.1±2.3l/min/mmHg to 2.3±1.2l/min/mmHg ($p<0.01$).
Conclusion: In selected heart failure pts with CSR, ASV is able to improve cardiac function and respiratory stability. Whether the improvement in prognostic surrogate markers like VE/VCO2 slope or pCO2 by ASV treatment leads to a decline in heart failure mortality needs to be determined.

P1676 Mitochondrial protection by post-conditioning during hindlimb ischemia-reperfusion is associated with reduced oxydative stress

A.S. Guilbert, A.L. Lang, J. Zoll, J. Bouitbir, Z. Mansour, A.P. Di Marco, S. Talha, F. Piquard, B. Geny. *Hopital Civil de Strasbourg, Strasbourg, France*

Objectives: After aortic clamping, free radical production originating from the ischemic lower limb skeletal muscles leads to a systemic response during reperfusion and explains remote organ impairments. Our objectives are to determine whether ischemic post-conditioning might decrease skeletal muscles mitochondrial respiratory chain injuries through a reduced oxidative stress.
Methods: twenty-eight rats were divided in three groups. The ischemia reperfusion group (IR group, n=8) was subjected to 3 hours ischemia induced by aortic clamping and collateral vessels ligation followed by 2 hours reperfusion. The post-conditioning groups had three bouts of ischemia-reperfusion (1,2 and 4 min ischemia and 5 min reperfusion) before reperfusion (PC group, n=9) and the control group had surgery without aortic clamping (Sham group, n=11).
Maximal oxidative capacities (Vmax) of the muscle and complexes I, II and IV of the mitochondrial respiratory chain were determined using glutamate-malate (Vmax), succinate (Vs) and TMPD-ascorbate, as substrates. Muscle oxidative stress was determined by measuring reduced glutathion (GSH). GSH was measured in gastrocnemius by monitoring the reduction of 5,5'-dithio-bis-(2-nitrobenzoic acid) to 5-thio-2-nitrobenzoate (TNB) by GSH at 412 nm.
Results: Physiological characteristics were similar in the three groups. Ischemia reduced Vmax (-27%, 6.5±0.4 vs. 4.8±0.5 μmol O2/min/g dry weight, $p<0.05$), Vs (-35%, 5.9±0.7 vs. 3.8±0.4 μmol O2/min/g dry weight, $p<0.03$) and partly TMPD ascorbate (19.2±1.8 vs. 14.2±1.7 μmol O2/min/g dry weight) in IR in comparison with SHAM, showing impairments of mitochondrial complexes I, II and IV activities. Ischemic post-conditioning reduced ischemia-induced mitochondrial dysfunction. Indeed, Vmax (5.9±0.3), Vs (5.9±0.4 μmol O2/min/g dry weight) and TMPD ascorbate values were similar to that of controls.
Ischemia-reperfusion induced decrease in reduced muscular glutathion was blunted after post-conditioning (0.63±0.05, 0.45±0.04* $p<0.05$, 0.58±0.09 GSH/g in SHAM, IR and PC groups, respectively).
Conclusions: Ischemic post-conditioning counteracted ischemia-induced mitochondrial complexes I, II and IV impairments and reduced skeletal muscle oxidative stress. Thus, post-conditioning might be an interesting approach to reduce muscular injuries in the setting of aortic clamping, possibly allowing to reduce peri-operative morbidities.

P1677 Impact of exercise training on myostatin expression in the myocardium and skeletal muscle in a chronic heart failure model

K. Lenk, V. Adams, A. Linke, R. Schur, S. Erbs, G. Schuler.
Herzzentrum der Universitaet Leipzig, Leipzig, Germany

Background: In chronic heart failure (CHF) elevated pro-inflammatory cytokines and muscle wasting are associated with the terminal stage of this syndrome. It has been shown that the expression of myostatin, a key regulator of skeletal muscle mass, is increased in a variety of cachectic states.
Aims: Aim of the present study was to investigate the expression of myostatin in an animal model of CHF and the influence of exercise training. Furthermore the role of pro-inflammatory cytokines was analyzed in cell culture.
Methods and Results: In an animal model of CHF (LAD ligation model), the content of myostatin protein was elevated more than 4fold in the heart (Co: 2.5±0.7 vs. CHF: 11.7±3.4; $p<0.01$) and 2.4-fold in skeletal muscle (Co: 0,87±0,1 vs. CHF: 2,09±0,5; $p<0,01$). Exercise training on a treadmill over 4 weeks led to a significant reduction in myostatin protein expression in the skeletal muscle and the myocardium of CHF animals, with values returning to baseline levels. To elucidate the impact of pro-inflammatory cytokines on myostatin expression, C2C12 myocytes were incubated with IL1-β, IL-6 and TNF-α. Only TNF-α induced the expression of myostatin through a p38MAPK-dependent pathway under participation of NF-κB. The increased TNF-α mRNA levels in skeletal muscle of CHF animals correlated significantly with myostatin expression ($r=0,57$; $p<0,01$).
Conclusion: These alterations of myostatin expression in the skeletal muscle might be one reason for the devastating process of muscle wasting in chronic heart failure.

P1678 Combined hydrotherapy/endurance training compared to endurance training alone in elderly patients with chronic heart failure. Clinical and hemodynamic effects

G. Caminiti, M. Volterrani, G. Marazzi, A. Cerrito, R. Massaro, S. Bovone, A. Franchini, M. Beato, A. Carluccio, G. Rosano. *IRCCS San Raffaele Hospital, Rome, Italy*

Purpose: To asses if a combined training of hydrotherapy (HT) added to endurance training (ET) is more effective than ETT alone in improving exercise tolerance and clinical status of elderly patients with chronic heart failure (CHF).
Methods: Twenty-one patients with stable CHF, median age 68±4 years; ejection fraction 32±9. NYHA functional class II-III were enrolled. Eleven pts were randomized to group A performing a combined training (HT+ET) and 10 patients to group B (ET only), both on top of maximal medical therapy. At baseline and after 12 weeks all patients underwent 6-minute walking test (6MWT), assessment of quadriceps maximal isometric voluntary contraction (MVC) and peaktorque (PT) blood pressure and herart rate (HR) and non invasive hemodynamic evaluation (Innocor, Innovision DK) with assessment of cardiac output (CO), stroke volume (SV) and peripheral vascular resistances (PVR). AT was performed 3 times/week in upright position at a water height of 1.40 m at temperature of 31°C. consisted of slow walking and exercises involving muscle groups of the lower and the upper limbs and torso with progressive increase in intensity. ET was performed 3 times/week and consisted on ciclying or walking at 60% of VO2.
Results: Exercise training was well tolerated. No patients had adverse events during water immersion. No patients withdrawn during the study period. Distance walked at 6mwt improved in both groups (Gr A: 150±32m; Gr B: 105±28 m) with significant intergroups differences (p 0.032). Diastolic BP and rest HR significantly decreased in the A group while remained unchanged in the B group (-14 mmHg±2, p 0.04; e – 12 bpm, p 0.03; respectively) CO and SV had a relative despite no significant increase in Gr A. PVR significantly decreased in A group (-38±7 mmHg/l/m; p 0.015) while remained unchanged in B group. Patients of A group had a significantly higher increase of both MVC and PT than B group. Conclusions: We demonstrated that HT added to ET, significantly increases exercise tolerance and hemodinamyc profile of patients with CHF.

P1679 Impaired energy metabolism in skeletal muscle and fat tissue of patients with chronic heart failure - interstitial metabolites assessed by microdialysis technique

T. Szabo[1], M. Boschmann[2], E. Postrach[2], A. Maehler[2], S.D. Anker[1], W. Doehner[1]. *[1]Charite - Campus Virchow-Klinikum, Berlin, Germany; [2]Charite - Campus Buch, Franz-Volhard-klinik, HELIOS Klinikum, Berlin, Germany*

Background: Impaired insulin sensitivity (SI) is a common finding in chronic heart failure (CHF) even in non-diabetic patients. Impaired SI as an indicator of abnormal energy metabolism, relates to exercise capacity, skeletal muscle strength and predicts survival. Using microdialysis technique, we assessed at tissue interstitial level metabolites of glucose and fat metabolism in adipose and muscle tissue at fasting and after oral glucose challenge.
Methods: Patients with CHF and healthy controls (con) were studied (both n=4). After an overnight fast (12h), microdialysis probes were implanted into the right M. quadriceps vastus lateralis and abdominal subcutaneous fat tissue. Dialysates (15 min fractions) were analyzed for interstitial glucose (glu), lactate (lac), pyruvate (pyr) and glycerol (gly) at baseline and during oral glucose tolerance test (OGT) in order to assess glycolysis and lipolysis.
Results: Interstitial concentrations in skeletal muscle of lac, glu and pyr were similar at baseline in both groups (lac: 1.00±0.08 vs. 1.06±0.13mmol/L, p=0.07; glu: 1.92±0,26 vs. 1.61±0.09mmol/L; p=0.31; pyr: 36.00±4.08 vs. 18.75±1.80μmol/L; p=0.08; all CHF vs. con). Lac increased rapidly after OGT in CHF but not in con (%change at 30 min: CHF 57.79±15.98%, con: 5.74±2.56%; p=0.018) and remained significant until 120 minutes (%change 120min: CHF 68.69±2.73%, con: 22.01±4.06%; p<0.0001). The ratio of lactate to pyruvate, indicating the balance of oxidative and non-oxidative metabolism, showed an up-regulated non-oxidative metabolism in CHF after OGT (120min %change: +66.63±23.60%). In contrast, an inverse relation was observed in controls representing the physiologic increase in oxidative metabolism after glucose challenge (120min %change: -65.34±5.05%; p=0.0016). Fat tissue interstitial glycerol concentrations indicating lipolysis decreased rapidly (60min) by
-57.68±6,16% in CHF patients to the levels of controls after OGT. In turn, no significant decreased in lipolysis was observed in controls after OGT (6.88±10.91%; p for CHF vs. con: 0.0021).
Conclusion: Our study shows from tissue interstitial metabolites of fat and muscle tissue that the oxidative/non-oxidative metabolic balance is impaired in CHF. The normal rapid up-regulation of oxidative metabolism upon glucose challenge is blunted in CHF. In contrast, non-oxidative metabolism is elevated in CHF skeletal muscle. In fat tissue our data suggest that elevated lipolysis in CHF is rapidly suppressed after OGT retuning to control values.

P1680 Low Triiodothyronine predicts impaired functional capacity in systolic heart failure patients

M. Fontana[1], M. Emdin[1], R. Poletti[1], L.E. Pastormerlo[2], G. Vergaro[2], A. Valleggi[1], A. Giannoni[1], C. Passino[1]. *[1]Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [2]Scuola Superiore Sant'Anna, Pisa, Italy*

Purpose: The aim of this study was to evaluate the relationship between thyroid function and reduced exercise capacity in chronic heart failure (HF). Cardiopulmonary exercise test has a prominent value in assessing clinical severity and prognosis in HF patients. Thyroid hormone (triiodothyronine - T3) has multiple actions on the cardiovascular system and on skeletal muscles and low-T3 status holds a negative prognostic value in HF.
Methods: 240 consecutive patients with systolic HF, free from thyroid diseases or drugs affecting thyroid function (79% males; age 62±12 years, mean±SD; left ventricular ejection fraction, EF, 30±9%) underwent a cardiopulmonary stress, clinical and neurohormonal characterization (assay for plasma brain natriuretic peptide, BNP, norepinephrine, aldosterone, renin activity, freeT3, freeT4, thyroid-stimulating hormone).
Results: At univariate analysis, peak oxygen consumption (peak VO2) correlated significantly (all P<0.001) with age (R=-0.51), estimated creatinine clearance (R=0.32), hemoglobin (R=-0.38), EF (R=0.26), fT3 (R=-0.24), BNP (R=-0.48), norepinephrine (R=-0.301). At multivariate analysis, age, gender and EF were the only independent predictors of peak VO2, whereas in patients with severe functional impairment (peak VO2 <14 mL/min/kg) fT3 resulted as independent predictor of peak VO2, together with gender and BNP level.
Conclusions: Low T3 level has an independent negative correlation with functional capacity in severe HF, representing, per se, a possible therapeutic target.

P1681 Attenuated expression of skeletal muscle IGF-1 splice variants in heart failure patients after high resistance exercise

H.K. Rasmusen[1], J.F. Hansen[1], S.D.R. Harridge[2], V. Backer[1], B. Larsson[3], M. Kjaer[1]. *[1]Copenhagen University Hospital, Bispebjerg, Copenhagen, Denmark; [2]King's College Hospital, London, United Kingdom; [3]Team Denmark, Copenhagen, Denmark*

Chronic heart failure (CHF) is characterized by exercise intolerance, which may partly be due to peripheral muscle wasting, potentially mediated via elevated tumor necrosis factor alfa (TNF-α) levels inhibiting muscle satellite cell differentiation. We studied the response of insulin-like growth factor-I (IGF-I) gene splice variants, (IGF-IEa and Mechano Growth Factor (MGF)) in skeletal muscle to high resistance exercise in CHF (n=9, 57-81 [range] yrs, LVEF 15-40%, NYHA class II-III) and in patients with moderate chronic obstructive lung disease (COPD) (n=8, 55-77 yrs, LVEF ≥ 55%, FEV1/FVC 51±4%). Physical fitness was low, and similar in CHF and COPD (maximal oxygen uptake: 17±1 (mean ± SE) and 15±2 ml/min/kg; 1 repetition max (1RM): 36±4 and 38±3 kg, respectively). All subjects completed 10 sets of six repetitions of single legged knee extensor exercise at 80% of 1RM. Muscle biopsy samples were obtained from the quadriceps muscle from both legs 2.5 h after exercise. IGF-I mRNA expression was determined by real-time quantitative RT-PCR. Plasma concentrations of TNF-α was significantly (P<0.05) higher in CHF (4.3±0.4 pg/ml) compared with COPD (2.3±0.4 pg/ml), while interleukin-6 (IL-6) was similar (3.5±0.8 and 3.7±1.0 pg/ml, respectively). IGF-IEa and MGF mRNA expression was similar in CHF and COPD before exercise, and in COPD (but not in CHF) a significant increase (+70±42%, P<0.05) in MGF mRNA levels was seen after exercise. IGF-IEa mRNA did not change with exercise in either group.
Conclusion: Physical deconditioning in CHF may be due to inadequate muscle growth response to exercise mediated by an inhibitory effect of TNF-α, while IL-6 does not seem to be important.

P1682 Associations between the severity of left ventricular impairment and circulating levels of resistin, adiponectin and leptin in patients with heart failure

A.S. Antonopoulos, C. Antoniades, D. Tousoulis, A. Drolias, N. Koumallos, K. Marinou, C. Bakogiannis, C. Psarros, A. Trikas, C. Stefanadis. *University of Athens, Athens, Greece*

Purpose: Adiponectin is an adipokine with a protective role in cardiovascular system, while resistin and leptin are adipokines with a pro-inflammatory effect. Despite the importance of adipokines in cardiovascular disease, the role in end-stage heart failure (HF) or stable coronary artery disease (CAD) is unclear. We compared the expression of adiponectin, resistin and leptin between patients with HF, CAD and healthy individuals, and we examined their association with left ventricular function.
Methods: The study population consisted of 268 individuals: 147 patients with HF (ejection fraction of the left ventricle (EF) 32.5±0.5%, 137 with CAD and normal EF (54.4±0.5%) and 80 healthy individuals matched for age, gender and risk factors for atherosclerosis. EF was measured by ultrasound and serum adiponectin, resistin and leptin were measured by ELISA.
Results: Serum resistin was significantly higher in HF (8.6±0.35 ng/ml) compared to CAD (6.5±0.3 ng/ml p<0.001) or healthy controls (7.0±0.4ng/ml,

p<0.001), while there was an inverse association between resistin and EF (rho=-0.294, p=0.0001). Adiponectin levels were also significantly greater in patients with HF (26.5±2.1 μg/ml) compared to either patients with CAD (14.8±0.9μg/ml, p<0.001) or healthy individuals (9.95±0.8μg/ml, p<0.001 vs HF and p=NS vs CAD), and adiponectin was negatively correlated with EF (rho=-0.245, p=0.0001). Importantly, serum leptin was significantly lower in HF (10.9±0.7 ng/ml) compared to CAD (14.4±1.5ng/ml p<0.05) or healthy individuals (13.6±0.7ng/ml, p<0.05), but there was no linear association between leptin and EF. In linear regression, the associations between EF and either resistin or adiponectin lost significance when body weight was introduced into the regression models.

Conclusions: Heart failure is associated with elevated resistin and adiponectin but decreased leptin levels. Resistin and adiponectin are both inversely associated with the degree of ejection function, but this effect is dependent on body weight.

P1683 Cardiotrophin-1 induces Interleukin-1b in human peripheral mononuclear cells via nuclear factor kappa B activation

M. Fritzenwanger[1], K. Meusel[1], C. Jung[1], M. Franz[1], Z. Wang[2], M. Foerster[1], H.R. Figulla[1]. *[1]Universitaetsklinikum Jena, Jena, Germany; [2]Second Affiliated Hospital of Fujian Medical University, Fujian, China, People's Republic of*

Background: Patients with congestive heart failure (CHF) have elevated concentrations of several proinflammatory cytokines, for example interleukin-1β (IL-1β) and cardiotrophin-1 (CT-1) - a member of the interleukin-6 family. As in CHF peripheral blood cells are able to produce proinflammatory cytokines we examined whether CT-1 induces IL-1β in peripheral mononuclear cells and examined the underlying responsible.

Methods: PBMC of healthy volunteers were stimulated with various concentrations of CT-1 for different periods. Protein concentrations in the supernatant were determined by ELISA and mRNA by polymerase chain reaction. Inhibition of RNA synthesis was done by actinomycin D, of intracellular protein transport by brefeldin A and of nuclear factor kappa B (NFkB) by parthenolide.

Results: CT-1 caused a concentration- and time-dependent increase of IL-1β mRNA with maximum induction after 3 h with 100 ng/ml (1,73±0,79 compared to unstimulated PBMC). Actinomycin D an inhibitor of mRNA synthesis inhibited CT-1 induced IL-1β mRNA induction indicating that CT-1 caused new mRNA synthesis. On protein level CT-1 caused a concentration- and time-dependent increase of IL-1β protein in the supernatant. Maximum IL-1β induction was achieved after 6-16 h (about 8-fold compared to unstimulated PBMC). Brefeldin A an inhibitor of intracellular protein transport diminished IL-1β protein in the supernatant to about 50%, indicating that intracellular transport is involved in IL-1β protein induction in the supernatant. Because parthenolide could completely inhibit IL-1β protein in the supernatant nuclear factor kappa B (NFκB) is important in CT-1 induced IL-1β induction.

Conclusion: Our data show that elevated concentrations of IL-1β in CHF may not only produced by the failing heart but also from CT-1 stimulated PBMC.

P1684 Ventricular tachyarrthythmias in advanced CHF are linked to recent weight loss and reduced body fat concent

M. Kotrc, I. Nemcova, L. Necasova, D. Hackajlo, I. Malek, J. Kautzner, V. Melenovsky. *Institute of clinical and experimental medicine (IKEM), Prague, Czech Republic*

Background: factors that lead to electrical instability in patients with chronic heart failure are incompletely understood. This retrospective study aimed to identify clinical characteristics associated with history of documented life-threatening ventricular tachyarrhythmia (VTA) in a cohort of pacients with chronic heart failure (CHF).

Methods: 126 patients with advanced CHF (57±10y, NYHA 2.7±0.5, LVEF 26±10%) underwent elective in-hospital assessment consisting of lab tests, MLHF quality of life questionaire, echocardiography, right heart cath and anthoropometry including body fat content estimation from thickness of 4 skinfolds (Best caliper, Womersley equation).

Results: 33 patients (26%) had history of VTA (VF or sustained VT). VTA+ patients tended to have more often CAD (60% vs 47%, p=0.17) and male gender (94% vs 80%, p=0.07). CHF duration (6.6 vs 6.9y, p=0.8) and severity (NYHA, MLHF score 48 vs 45, p=0.5) were similar, as well as frequency of comorbitidies (hypertension, DM, COPD, anemia). There was no difference in PA-derived hemodynamics, echo parameters, BNP (910 vs 876 pg/ml, p=0.8) or medication use (statins, ACE, ARB, BB) between groups. VTA+ patients had higher concentration of CRP (10 vs 5 mg/l,p=0.03) lower plasma sodium (138 vs 139, p=0.03) and more often small elevation of troponin I (p=0.04). Despite no difference in body weight or body mass index (BMI: 27 vs 28 kg/m^2, p=0.4) between groups, VTA+ subjects had significantly lower body fat content (19±8% vs 24±10%, p=0.01). VTA+ patients also more often reported weight loss >6% in the past 6 month period (in 48% vs 15%, p=0.002, by -4.5±8 vs -0.7±8 kg, p=0.05).

Conclusion: history of recent weight loss or reduced body fat concent, not evident from BMI, is associated with increased risk of ventricular tachyarrthitmia in patients with advanced heart failure.

P1685 Prediction of short-term course of heart failure in clinically stable heart transplant candidates with dilated cardiomyopathy

M. Dandel, R. Jasaityte, H.B. Lehmkuhl, C. Knosalla, R. Hetzer. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Background: With increasing heart transplant (HTx) waiting-times, anticipation of short-term cardiac worsening, and finding predictors of short-term outcome without HTx or the necessity of ventricular assist device implantation (VADs) are major goals.

We assessed the predictive value for clinical worsening of echocardiography, NT-ProBNP levels and exercise tolerance in patients with idiopathic dilated cardiomyopathy (IDCM) referred for HTx in order to provide more information with potential usefulness in guiding HTx listing procedures.

Methods: IDCM patients referred for HTx who where hemodynamically stable at their first clinical control performed after January 2006 were selected for the study. Exclusion criteria were LVEF ≥ 30%, NYHA class < III, atrial fibrillation and clinical instability during the last 2 months (with or without the need of inotropic support).

At inclusion into the study NT-ProBNP plasma levels were measured and the patients underwent comprehensive echocardiography (including 2D-strain imaging) and exercise testing. Patients' inclusion into the study ended on June 2007. Initially obtained parameters were tested for ability to predict further clinical course of heart failire (HF) during the next 6 months. Sudy endpoint was the 6 months survival without HTx or the necessity of VAD support.

Results: During the first 6 months, 20 (52.6%) of 38 evaluated patients showed cardiac deterioration (6 died, 16 received VADs).

Comparing the initial parameters of these patients with those of the 18 stable remained patients, we found no differences either in exercise tolerance (including VO2 max) or LV enddiastolic volume (285±98ml vs. 270±74ml) and ejection fraction (22±4% vs. 20±5%).

However, patients with subsequent clinical worsening had initially more altered transmitral flow profiles (shorter E-wave deceleration time, higher E/A ratios) and higher NT-ProBNP levels (p<0.05). Also 2D-strain imaging of the LV (easy to perform and not time consuming) revealed higher systolic dyssynchrony, lower late diastolic strain rate (DSRA) and higher diastolic DSRE/DSRA strain rate ratios (p<0.05).

At certain cut-off values, the transmitral E/A ratio, the DSRA and the ratio between transmitral E wave and DSRA showed high positive and negative predictive values for cardiac stability during the next 6 months (80%-90% and 90-91%, respectively).

Conclusions: In apparently clinically stable HTx candidates with IDCM, the transmitral flow profile and certain 2D-strain imaging parameters are predictive for the short-term (6 month) course of HF and may therefore be valuable in guiding listing procedures for HTx.

ASPECTS OF HEART FAILURE

P1686 Induction of mitogen activated protein kinases in response to pressure overload: a novel possible biomarker for uncontrolled human hypertension

A. Franzone, G. Esposito, G. Capretti, G. Schiattarella, A. Cannavo, G. Pironti, L. Di Serafino, C. Perrino, M. Chiariello. *Azienda Ospedaliera Universitaria Federico II, Naples, Italy*

The hypertrophic response to in vivo pressure overload has been associated with the activation of mitogen activated protein kinases (MAPKs) and re-induction of fetal genes such as the atrial natriuretic factor (ANF). However, whether the activation of these signalling pathways is dependent on the degree of pressure overload and might be used as a molecular biomarker of uncontrolled hypertension is currently unknown. In order to test the sensitivity of these different signalling pathways to pressure overload, we assayed the activity of MAPKs ERK, JNK and p38 in aortic banded mice with varying levels of load, ranging from a trans-stenotic gradient of 5 to 125 mmHg. In separated mice we measured ANF mRNA levels by Northern blotting. The fold induction in kinase activities (vs. sham mice) and ANF mRNA levels (normalized to GAPDH) were plotted against the transstenotic systolic pressure gradient and the left ventricular mass expressed by left ventricular weight (LVW)/body weight (BW) ratio. Although a significant induction of ANF mRNA levels was observed after aortic banding, it occurred only with systolic pressure gradients > 55 mmHg. In contrast, over a wide pressure gradients range, a significant linear correlation was observed for all MAPKs activity and pressure overload. To test whether ERK activation might reflect uncontrolled blood pressure levels in humans, we assayed ERK phosphorylation in isolated leucocytes from healthy normotensive volunteers (CON), hypertensive patients with controlled blood pressure values (CHT) or hypertensive patients with uncontrolled blood pressure values (UHT). Interestingly, ERK phosphorylation was increased in UHT patients compared to healthy volunteers. Furthermore, in hypertensive patients with drug-controlled arterial pressure levels ERK phosphorylation was normalized. Taken together, these results suggest that MAPKs activity is a sensitive sensor of pressure overload and that ERK activation in peripheral blood cells might be used as a novel surrogate biomarker of uncontrolled human hypertension.

P1687 Peptidomic profiles of plasma from post myocardial infarction rats using affinity capture Matrix Assisted Laser Desorption Ionisation Time of Flight (MALDI-ToF) mass spectrometry

B. Wang[1], S. Reisman[2], M. Ayhan[2], A. Kompa[1], H. Krum[1], G. Rice[2]. [1]*Monash University, Melbourne, Australia;* [2]*Baker IDI Heart and Diabetes Institute, Melbourne, Australia*

Objectives: The aim of this study was to utilise mass spectrometry-based peptide profiling to identify and characterise changes in the peptidomic profiles of blood in association with myocardial infarction (MI) and heart failure (HF).
Methods: One week after MI, Sprague Dawley rats were randomised to received either an angiotensin converting enzyme inhibitor ramipril (Ram – 1mg/kg), or vehicle (Veh - 0.5% methylcellulose, n=8/group) for 12 weeks. Echocardiogram and hemodynamic measurements were made before sacrificing and plasma collection. High abundance proteins were depleted and peptides were extracted from plasma before profiling analysed using MALDI ToF mass spectrometry. Differentially expressed peptide ions were identified using proprietary software ClinProtTools.
Results: MI increased heart/body weight (18%), lung/body weight (56%), and left ventricular (LV) end diastolic pressure (LVEDP-247%); and significantly reduced percentage fractional shortening (FS-75%) and rate pressure rise in the LV (dP/dtmax-20%). Ramipril treatment significantly attenuated the changes in LVEDP (61%) and FS (27%). Mass spectra analysis revealed that peptide ions at 1271, 1955, 2041, 2254 m/z were consistently decreased by Ram compared MI+Veh rats ($p < 0.001$), and are likely to be associated with therapeutic effects. The peptide at 2281 m/z was significantly higher in MI+Ram than MI+Veh and therefore may be associated with drug-stimulated effects.

	Sham	MI+Veh	MI + Ram
Heart/Body weight (mg/g)	3.2±0.1	3.8±0.3*	3.3±0.1
Lung/Body weight (mg/g)	3.63±0.1	5.7±0.9*	4.0±0.4
Fractional Shortening (%)	38.6±2.1	9.8±1.3***	17.23±1.99#
LVEDP (mmHg)	2.8±0.7	9.7±1.1***	5.5±0.8#
dP/dt_{max} (mmHg)	5898±165	4819±274*	5156±115

Data are expressed as mean ± SEM. *P<0.05, ***P<0.001 compared to sham animals; #P<0.05, compared to MI+Veh animals.

Conclusions: The data obtained from this study is of utility as: (i) components within a multivariate classification model that may be used as a prognostic or diagnostic test; and because the identity of the contributing peptides can be determined, (ii) specific multiplex immunoassays may be developed to provide quantitative endpoints, and (iii) to increase our understanding of the aetiology of cardiovascular disease complications.

P1688 Genetic polymorphisms of beta-adrenergic and RAA systems in chronic heart failure: relation with remodeling and LV systolic function

C. Bergamini, M. Cicoira, A. Rossi, M. Rigolli, F. Vassanelli, D. Cassater, L. Zanolla, C. Vassanelli. *Univ. of Verona, Verona, Italy*

Objectives: To assess whether the genetic background of maximally treated patients with stable chronic heart failure (CHF) predicts variations in left ventricular systolic function and volumes.
Background: Neurohormonal systems play an important role in the pathophysiology of CHF. Due to inter-individual heterogeneity in the benefits of therapy, it may be hypothesized that polymorphisms of neurohormonal systems may affect left ventricular remodeling and systolic function.
Methods: We prospectively studied 131 CHF outpatients on optimal treatment for at least six months. Complete echocardiographic evaluations were performed at baseline and after 12 months of follow-up. Genotype analysis for ACE I/D, β1adrenergic receptor (AR) Arg389Gly, β2AR Arg16Gly and β2AR Gln27Glu polymorphisms was performed.
Results: No differences in baseline characteristics were detected among genotype subgroups. ACE II genotype was a significant predictor of improvement of LVEDV and LEVSV over time (p=0.003 and p=0.002, respectively) but not of left ventricular ejection fraction (LVEF); β1AR389 GlyGly was related to an improvement in LVEF (p=0.02) and of LVESV (p=0.01), while β2AR 16 and β2AR 27 were not associated with significant changes in left ventricular function and volumes. The predictive value of these polymorphisms remained after adjustment for other clinically significant predictors at multivariate analysis ($p<0.05$ for all).
Conclusions: ACE I/D and β1AR Arg389Gly polymorphisms are independent predictors of reverse remodeling and systolic function recovery in CHF patients under optimal treatment.

P1689 Recirculating delivery of AAV-BARKct for the treatment of heart failure in a large animal model

M. Byrne[1], R. Idrizi[1], G. Akita[2], R. Kelly[2], J. Power[1], D.M. Kaye[1]. [1]*Baker IDI Heart Research Institute, Melbourne, Australia;* [2]*Genzyme Corp, Boston, United States of America*

Purpose: Whilst much is known about the basic molecular mechanisms that underly heart failure, many currently available drugs do not specifically targets these defects. Gene theray offers the promise of providing a means for selective molecular manipulation. Amongst these changes, abnormalities in the expression and regulation of G-protein coupled receptors (GPCRs) are well known. Previous studies in small animals indicate that manipulation of regulatory kinases may improve cardiac function. The purpose of this study was to evaluate the effects of percutanous deivery of BARKct a small peptide inhibitor of GRK2 in an ovine animal model of tachycardia induced heart failure (HF).
Methods: A total of 14 animals underwent rapid right ventricular pacing (180bpm) for 28 days to induce HF. BARKct was expressed in an adeno-associated virus (AAV). Percutaneous delivery of AAV-BARKct (n=8) or saline (n= 6) was performed by coronary arterial delivery, with coronary sinus blood collection and recirculation using a a pump-oxygenator for 10 minutes. Sheep were then continually paced for a further 28 days after administration. In all cases, left ventricular (LV) pressure derivatives (+dp/dtmax, -dp/dtmax) and echocardiographic parameters (ejection fraction, EF and fractional shortening, FS) were measured prior to delivery (baseline) and at study completion. Results are shown as change from baseline.
Results: Animals that recieved AAV-BARKct showed a significant improvement in echocardiographic parameters: change in LVEF (AAV-BARKct 13.4±3.3; cont -9.6±2.5; $p<0.05$) and change in LVFS (AAV2-BARKct 7.8±2.1; cont -5.6±1.3; $p<0.05$). In conjunction, both the change in LV +dp/dtmax, (AAV-BARKct 28±90; cont -306.4±84.5; $p<0.05$) and LV -dp/dtmax (AAV-BARKct 328.8±132.1; cont -443.8±219.3; $p<0.05$) reflected an improvement in cardiac function in AAV-BARKct treated animals compared to a decline in saline treated HF animals.
Conclusions: This study demonstrates a favorable effect of BARKct in the failing large animal heart, when delivered using an AAV in conjunction with recirculating intracoronary delivery.

P1690 Evidence for contractile dysfunction and heart failure in pressure-overloaded wild-type mice - does the PGC-1alpha story hold true?

G. Faerber[1], H.F. Barreto-Pereira[2], R. Gilsbach[2], M. Schoepe[1], M. Schwarzer[1], L. Hein[2], T. Doenst[1]. [1]*Herzzentrum der Universitaet Leipzig, Leipzig, Germany;* [2]*Universitaetsklinikum Freiburg, Freiburg im Breisgau, Germany*

The metabolic master regulator, PGC-1α has been implicated in the development of pressure overload heart failure. Its downregulation is thought to limit mitochondrial ability to generate ATP. However, the standard model for pressure overload in mice, transverse aortic constriction (TAC), does not generate heart failure and direct evidence supporting the suggested mechanism in non-transgenic animals is scarce. Objective: We assessed the ability of modified minimally-invasive TAC to induce heart failure in C57/Bl6-mice and characterized metabolic gene expression and mitochondrial respiratory capacity.
Methods: TAC was performed through a mini-sternotomy without intubation (n=156, sham n=24). Hypertrophy was assessed by heart/body-weight-ratios (H/BW), and contractile function by intracardiac Millar pressure measurements. Metabolic genes were assessed with RT-qPCR and Western blot and the respiratory capacity of isolated mitochondria was measured with a Clark-electrode.
Results: Perioperative survival was 75%. Within 7 weeks, TAC induced significant hypertrophy (H/BW:TAC9.15±0.31mg/g vs. sham:4.47±0.07mg/g, $p<0.01$). 25% of TAC mice displayed signs of heart failure (pleural effusions, dyspnea, weight loss). All of them had H/BW>10 and >10-fold increases in BNP-, ANP- and β-MHC-expression. TAC mice with H/BW from 5-10 demonstrated compensated hypertrophy with normal dp/dtmax (6621±774mmHg/sec) and no failure signs. Rate-pressure-products (mmHg/min/mgBW) were 508±38 in sham, 446±30 in hypertrophied (n.s.), and 157±64 in failing hearts ($p<0.01$). mRNA and protein expression of PGC-1α, PPARα and fatty acid oxidation genes was significantly reduced in failing hearts, and was associated with reduced respiratory capacity of isolated mitochondria with various substrates (nAO/min/mg using palmitoylcarnitine: sham 322±42, hypertrophy 278±34, heart failure 155±26, $p<0.01$). Respiratory chain protein was normal in both hypertrophied and failing hearts.
Conclusions: Heart failure can be induced in wild-type mice by minimally invasive aortic constriction. This pressure-overload-induced heart failure is indeed associated with decreased PGC-1α expression and impaired respiratory capacity and fatty acid oxidation.

P1691 Regulation of cAMP-release by adenylylcyclase in the unloaded terminal failing human heart

A. Kassner[1], K. Toischer[2], M. Morshuis[1], D. Roefe[1], A. El-Banayosy[3], H. Milting[1]. [1]*Herz und Diabeteszentrum NRW, Bad Oeynhausen, Germany;* [2]*Georg-August Universität, Abteilung Kardiologie und Pneumologie, Göttingen, Germany;* [3]*Penn State Milton S. Hershey Medical Center, Pennsylvania, Hershey, United States of America*

Purpose: In terminal heart failure (HF) signal transduction of the β-adrenergic system is decreased due to receptor downregulation and uncoupling. The improved responsiveness of the myocard to inotropes after ventricular assist device (VAD) support is claimed to be due to the upregulation of the β1-adrenergic receptor (β1-AR). In addition, selective stimulation of the β2-AR was used for the induction of cardiac regeneration in VAD-patients. However, little is known on a)

AC-regulation itself and b) the β2-AR coupling to the cAMP pathway after VAD. Thus, we analysed regulation of the AC-activity in VAD-supported and non-failing (NF) control myocardium.
Methods: Myocardial membrane preparations from 8 NF and 17 paired VAD-samples pre and post VAD were analysed for AC-activity in the presence of catecholamines or Forskolin. cAMP-release was determined with a cAMP-ELISA and given as specific activity [pmol/mg min]. Total RNA expression was determined by Taqman. Organ bath experiments were done with trabeculae from both ventricles.
Results: Isoprenaline-induced AC-activity was decreased ($p<0.05$) in HF-samples and increased significantly ($p<0.05$) after VAD-support (NF, preVAD, postVAD, means ± SD): 47.9±14.9, 24.4±13.3, 50±50.3. Direct AC-stimulation by Forskolin revealed a significant upregulation postVAD- compared to NF-samples (NF, preVAD, postVAD, means ± SD): 192.1±68.7, 191.1±60.4, 281.5±133. Thus, the relative stimulation by isoprenaline in relation to the increase of AC-activity by Forskolin was comparable in all groups. The mRNAs of the most abundant ACs in the heart: AC5 and AC6 were not regulated. The combination of Clenbuterol (β2-AR-agonist) and Bisoprolol (β1-AR-blocker) lead to 25-30% increase in AC-activity in all groups. However, selective stimulation of β2-AR by Clenbuterol did not reveal change of β2-AR-AC coupling after VAD. Stimulation of ventricular trabeculae pretreated by bisoprolol with increasing concentrations of clenbuterol revealed negative inotropic responses at high concentrations.
Conclusions: Regeneration of catecholamine response in VAD-supported myocardium is not directly related to upregulation of β1-AR but due to an increased sensitivity of AC-activity. Measurement of AC-mRNA does not correlate to the AC-activity. There is no evidence that β2-AR coupling to AC-stimulation is influenced by VAD, since the negative ionotropic responses to high Clenbuterol concentration support the notion of a sustained coupling of β2-AR to the Gi-alpha-pathway.

P1692 Recombinant periostin peptide improves myocardial function in a preclinical infarct model

D. Ladage[1], Y. Kawase[1], S. Shapiro[1], M. Garcia[1], R. Hajjar[1], B. Kuhn[2]. [1]*Mount Sinai Hospital, New York, United States of America;* [2]*Harvard University, Boston, United States of America*

The goal of conventional heart failure therapy is to improve the function of cardiomyocytes, the contractile cells of the heart. Replacing lost cardiomyocytes using biological strategies would revolutionize heart failure therapy. We previously demonstrated that administration of recombinant periostin induces cardiomyocyte replacement and improves myocardial function in a rat infarct model. Here, we report the results of a pre-clinical trial of periostin peptide administration in a porcine model.
We induced myocardial infarction (MI) in female Yorkshire swine by deploying a coil in the left anterior descending coronary artery. Using a pericardiocentesis approach, we applied periostin fasciclin I-only polypeptide with a Gelfoam-based system for long-term delivery into the pericardial space 2 days after MI. We determined the effect on cardiac function over 3 months after initiation of therapy.
Control (n = 5) and treatment groups (n = 5) were comparable in their hemodynamic parameters before beginning of therapy. Ejection fraction (EF) improved in periostin-treated animals by 13.9±4.5%, while decreasing in control animals after one month (Tab. 1). Left ventricular catherization showed a significantly increased dP/dt in periostin-treated animals after one month with a sustained effect after 3 months. In treated swine, cardiac index was increased at one month compared with 48 hr after the MI, while decreasing in untreated animals. Gain of function in the periostin group was preserved over the three months observation period. Echocardiography showed significantly increased EF at one month after periostin administration (48.0±16.7%) compared to control (38.5±7.9%, $P < 0.05$).

Table 1. Selected hemodynamic parameters

	1 month			3 months		
	EF (%)	dP/dt_{max} (mmHg/s)	CI (mL/kg/min)	EF (%)	dP/dt_{max} (mmHg/s)	CI (mL/kg/min)
Periostin	44±5	1709±257	114±16	45±4	1855±239	98±24
Control	32±7	1355±221	99±22	38±8	1480±176	83±17

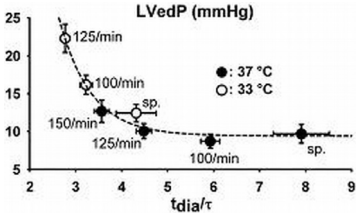
EF determined by left ventriculogram; Cardiac Index (CI) by thermodilution. All presented parameters differ significantly (ANOVA) between groups.

In summary, minimally invasive application of cardiac regeneration factors is biologically effective and safe. Periostin peptide induced sustained improvement of cardiac function after MI. Overall, inducing myocardial regeneration with recombinant periostin represents a promising and innovative strategy for the treatment of ischemic heart disease.

P1693 Mild hypothermia: An experimental proof for an increase of left ventricular end-diastolic pressure by slowed left ventricular relaxation

H. Post[1], J.D. Schmitto[2], J. Christoph[2], R. Holland[2], P. Steendijk[3], F.A. Schoendube[2], B. Pieske[1]. [1]*Medical University of Graz, Graz, Austria;* [2]*Medical University of Goettingen, Goettingen, Germany;* [3]*Leiden University Medical Center, Leiden, Netherlands*

Background: Isolated left ventricular (LV) dysfunction is characterized by an increase of LV end-diastolic pressure (LVedP) at preserved contractility and normal LV dimensions. Whether or not this occurs only secondary to altered passive LV properties or also can be induced by slowed active LV relaxation is still a matter of debate.
Methods: We previously demonstrated that during mild hypothermia (MH 33°C) in anaesthetized pigs (n=10), LV inotropy is increased (leftward shift of pressure-volume loops), while a decreased dP/dtmin and an increased time constant of isovolumic LV relaxation (tau) indicate slowed active relaxation. Here, we correlated LVedP with the ratio of absolute diastolic time (tdia) and tau. Data were obtained at normothermia (37°C) and MH, and heart rate was altered by right atrial pacing.
Results: Spontaneous heart rate decreased during MH (74±4 vs 85±5 bpm, $p<0.05$), while tau increased markedly (100±15 vs 50±2 ms). The ratio tdia/tau was lower at a given heart rate during MH. LVedP could be predicted accurately from tdia/tau by an exponential equation ($r^2=0.98$).



Conclusion: We show that slowed LV relaxation can indeed increase LVedP. The induction of MH should be performed with caution in patients with pre-existing diastolic dysfunction.

P1694 Incidence of left ventricular dysfunction after anthracycline chemotherapy in an elderly population

C. Lestuzzi[1], E. Viel[1], L. Tartuferi[1], D. Crivellari[2], D. Lombardi[2], G.M. Miolo[2], L. Fratino[2], N. Meneguzzo[1]. [1]*Cardiology, Centro di Riferimento Oncologico, National Cancer Institute, Aviano (Pn), Italy;* [2]*Oncology, Centro di riferimento Oncologico, National Cancer Institute, Aviano (Pn), Italy*

Purpose: Age >65 is considered a risk factor for anthracycline (ANTHRA) cardiotoxicity. We report our experience in an elderly population evaluated by echocardiography after chemotherapy (CT) with Adriamycin (ADM), EpiADM or other ANTHRA
Methods: We studied clinically and by echocardiography 224 consecutive patients (pts), 43 males, 181 females, who had undergone CT with ANTHRA at age >65. Hypertension was present in 103 pts, diabetes in 26, four had angina, 82 on cardiovascular drugs. An echocardiogram (echo) before CT was available in 167 pts (including 37 pts who had been previolusy treated with ANTHRA). One more follow-up echo 4-17 months later was obtained in 82 (in 27 after receiving further CT with ANTHRA or trastuzumab). Significant left ventricular (LV) dysfunction was classified as LV ejection fraction (EF) below 50% or drop of absolute value >10% compared to pre- CT echo. Dosage of EpiADM and other ANTHRA were calculated as ADM equivalent to compare ANTHRA with different cardiotoxic power.
Results: The pts were aged 65 to 86 (mean 69) when starting CT and 68 to 87 (mean 75) at last follow-up. They received 69-928 (mean 284, median 248) mg/m^2 of ADM or equivalent. Among the 224, a significant LV dysfunction after CT was observed in 15. One had an EF of 48% before CT, unchanged after it; in 2 pts LV dysfunction developed after acute myocardial infarction. Only 12 pts (5%), then, were classified as having true ANTHRA cardiotoxicity. They were 2 men and 10 women aged 65 to 73 (mean 68) at the time of CT, and received 110-606 mg/m^2 (mean 358) of ADM or equivalent. Two pts were diabetic and/or hypertensive, 10 had no known cardiovascular risk factor (one had an ischemic heart disease diagnosed during follow-up). In five of the 12 LV dysfunction was detected at first follow-up, in 7 later on (in 3 after further CT, in one after atrial fibrillation). The interval between start of first CT and detection of LV dysfunction was 3-130 months (mean 37). Ten pts had a follow-up after LF dysfunction diagnosis: under therapy with ACE-inhibitors, beta-blockers and diuretics a clinical improvement was observed in all, and recovery of LV function in 9 (up to EF >50% in 6). At last follow-up the EF was 38% to 58% (mean 49%) and all pts were in NYHA class 1 or 2.
Conclusions: Incidence of ANTHRA cardiotoxicity was rather low (about 5%) in this elderly population. LV dysfunction may be delayed, and sometime linked to other cardiac events (arrhythmias, ischemic heart disease). Clinical and functional partial or complete recovery is possible, with usual treatment for dilated cardiomyopathy.

P1695 Cardiotoxicity of imatinib mesylate: a rare adverse effect?

M.S. Marcolino[1], N.C.D. Clementino[1], H.N.S. Bittencourt[1], M.M. Barbosa[2], M.C.P. Nunes[1], M.H.C.R. Silva[1], A.L.P. Ribeiro[1]. [1]*Universidade Federal de Minas Gerais, Belo Horizonte, Brazil;* [2]*Hospital Socor, Belo Horizonte, Brazil*

Objective: Imatinib mesylate (IM) is the first line therapy for chronic myeloid

leukemia (CML) patients. Clinical findings of congestive heart failure have been described in ten patients treated with IM. Therefore, retrospective studies have not confirmed the existence of cardiac toxicity. Thus, it remains a controversial issue. The objective of this study is to assess the cardiotoxicity of IM in CML patients in a tertiary academic hospital.
Methods: We included 103 patients with CML on treatment with IM for a median time of 844 days and 56 patients with myeloproliferative disorders not treated with IM as a control group. All of them underwent complete clinical evaluation (interview and physical examination), B-type natriuretic peptide (BNP) plasma measurement, electrocardiogram and echocardiogram.
Results: IM group showed younger patients (median 48 vs. 54 years, p=0,025) and a higher frequency of edema (26% vs. 11%, p=0,025), but groups were similar regarding gender distribution and cardiac risk factors, except for hypertension (lower prevalence in IM group: 27% vs. 46% in controls, p=0,002). The frequency of other cardiovascular signs and symptoms, electrocardiographic abnormalities, ejection fraction [median 69 (64-73)% vs. 68 (65-74)%, p=0,67], left ventricle (LV) diastolic dimension, diastolic function and BNP measurements [median 11 (interquartile range 8-22) vs. 13 (8-27) pg/mL, p=0,213] were not different between groups.
Four patients had BNP levels above 100 pg/mL, all of them in IM group. A 48-year-old accelerated phase CML male without other recognized risk factors for heart disease was observed to have a reduced LV ejection fraction (38%) and a BNP of 190 pg/mL. This patient has been taking 600 mg of IM for 272 days and he has no history of previous usage of interferon alpha. He has been submitted to endomyocardial biopsy. Immunohistochemistry staining showed that NADH, SDH and COX oxidation reactivity were increased. Transmission electron micrographs showed cardiomyocytes with degenerative changes and pleomorphic mitochondria with effaced cristae and vacuoles. Some sarcomeres appeared disorganized. These biopsy findings were similar to what was observed by other authors.
Conclusions: We studied the cardiac effects of imatinib using sensitive non-invasive methods. Our findings have indicated absence of systematic cardiac toxicity, which confirms and extends some previously published reports. However, the patient with decreased ejection fraction and biopsy abnormalities, who had no cardiovascular risk factors, point out a possibility of isolate cases of cardiotoxicity.

P1696 The effects of early aldosterone blockade on myocardial fibrosis and contractility in rats with ascending aortic stenosis

M.P. Okoshi, D.H.S. Campos, P.F. Martinez, A.R.R. Lima, M.D.M. Cezar, L.S. Matsubara, L.C.O. Costa, A.A. Guimaraes, A.C. Cicogna, K. Okoshi. *Botucatu Medical School, UNESP, Botucatu, Brazil*

Purpose: Aldosterone antagonists improve survival in severe heart failure patients. The issue as to whether early aldosterone antagonism can modulate myocardial remodeling and function in chronic and persistent pressure overload-induced heart failure is unresolved. This study investigated the effects of early treatment with spironolactone, a mineralocorticoid receptor blocker, on myocardial fibrosis and function in rats with ascending aortic stenosis (AAS).
Methods: Aortic stenosis was created in weaning rats (body weight 60 to 70 g). Three days later, rats with aortic stenosis were randomized to receive aldosterone blocker spironolactone (AAS-SPR, 20 mg/kg/d, n=12) or no drug (AAS, n=18) for 18 weeks, and compared with sham-operated rats (n=13). Myocardial function was studied in isolated left ventricular (LV) papillary muscle under isometric contraction in basal condition (1.25 mM extracellular calcium concentration) and after inotropic stimulation. Myocardial collagen volume fraction (CVF) and hydroxyproline concentration (HOP) were evaluated in the LV free wall. Statistics: ANOVA and Tukey's test.
Results: Data are shown in the table as mean ± standard deviation. After inotropic stimulation with post-rest contraction, increase of extracellular calcium concentration, or β-adrenergic stimulation with 1 μM isoproterenol, +dT/dt was lower in AAS and AAS-SPR groups than Sham ($p<0.05$) and there was no difference between AAS and AAS-SPR groups.

	Sham	AAS	AAS-SPR
LV/BW (mg/g)	1.79±0.13	2.80±0.25*	3.31±0.39*#
RV/BW (mg/g)	0.54±0.06	0.76±0.33	0.89±0.31*
+dT/dt (g/mm^2/s)	65±14	46±13*	46±13*
HOP (μg/mg dry tissue)	2.62±0.57	5.27±1.58*	3.29±0.26
CVF (%)	2.29±0.77	5.13±3.37*	3.14±3.25

LV/BW: left ventricle weight/body weight ratio; RV/BW: right ventricle weight/body weight ratio; +dT/dt: maximum rate of tension development; *$p<0.05$ vs Sham; #$p<0.05$ vs AAS; ANOVA and Tukey.

Conclusion: Aldosterone blocker spironolactone attenuates myocardial fibrosis and induces further cardiac chambers hypertrophy without changing myocardial function in rats with ascending aortic stenosis.

P1697 Urocortin 2 treatment reduces genes involved in cardiac remodelling in an ovine model of heart failure

L. Ellmers, E. Carter, N.J.A. Scott, A.M. Richards, V.A. Cameron, M.T. Rademaker. *University of Otago, Christchurch, Christchurch, New Zealand*

Purpose: To investigate the impact of Urocortin 2 on the genes involved in cardiac remodelling in an ovine model of heart failure.
Methods: Gene expression levels of known markers of cardiac remodelling (β-MHC, Gata 4,TGFβ and Collagen 1) were investigated by quantitative real-time PCR in cardiac left ventricle tissue from sheep in pacing-induced heart failure (225bpm for 7 days) receiving either Urocortin 2 (n=4) or a vehicle control (n=3) over a 4 day infusion period. Ventricle tissue from non-paced animals was used as a control (n=4).
Results: Urocortin 2 treatment reduced gene expression of Gata 4 in Urocortin 2 treated sheep similar to those seen in non-paced, non-failing hearts (0.019±0.04 versus 0.019±0.09 pg/μg RNA), in comparison to the paced, control sheep, where Gata 4 levels were highly upregulated (0.31±0.01 pg/μg RNA). The same trend was seen in Collagen 1, with expression levels in the Urocortin 2 treated group actually lowering to below the levels seen in the non-paced control group (0.57±0.33 versus 0.94±0.6 pg/μg RNA), in contrast to the paced, control sheep, where Collagen 1 levels were increased (2.51±1.6 pg/μg RNA). Likewise, TGF-β and β-MHC gene expression levels were observed to have been lowered in the Urocortin 2 treated group compared with the paced, control group, but not to the extent of Gata 4 and Collagen 1. Interestingly, ANP and BNP (cardioprotective natriuretic peptides that are sensitive markers of cardiac damage) levels were found to be raised well above control groups in the Urocortin 2 treated group (ANP; 2.09±1.18 versus 1.61±1.19 pg/μg RNA), with BNP levels being double that of the paced, control heart failure group (3.94±2.6 versus 1.99±0.93 pg/μg RNA). The reductions observed in Gata 4 and β-MHC in the Urocortin 2 treated group indicate a reduction in cardiac hypertrophic drive compared to the paced, control group, while the decreases in TGF-β and Collagen 1 in the Urocortin 2 treated group imply a decrease in the degree of cardiac fibrosis compared with the paced, control group.
Conclusions: Urocortin 2 treatment may have beneficial tissue/molecular effects on cardiac hypertrophy and fibrosis in heart failure. The rise in both ANP and BNP in response to Urocortin 2 treatment compared with control suggests a novel interaction of this peptide with a well characterised cardioprotective system.

P1698 Clinical profile of patients affected by dominant desmosomal arrhythmogenic right ventricular cardiomyopathy

A. Tsatsopoulou[1], L. Antoniades[2], A. Anastasakis[3], P. Syrris[4], A. Asimaki[4], G. Daniel[2], A. Vouliotis[3], C. Stefanadis[3], N. Protonotarios[1]. *[1]Yannis Protonotarios Medical Center of Naxos, Naxos, Greece; [2]Nicosia General Hospital, Nicosia, Cyprus; [3]University of Athens, Athens, Greece; [4]University College London, London, United Kingdom*

Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) due to dominant desmosomal mutations is the most frequent form of the disease. In this study we aimed to evaluate the clinical profile of patients with dominant desmosomal ARVC diagnosed with the recently revised Task Force criteria (TFC).
Methods: The study population included 40 ARVC patients carrying a pathogenic dominant desmosomal mutation (19 males, 21 females; mean age 41±16 years). Repolarization abnormalities (T-wave inversion in leads V1 and V2 or beyond) and depolarization abnormalities (epsilon waves and QRS terminal activation duration ≥55ms in leads V1 or V2 or V3) on standard 12-lead ECG as well as right ventricular (RV) structural/functional abnormalities on 2-dimensional echocardiography (akinesia, dyskinesia or aneurysm and outflow tract diameter ≥29mm) according to revised TFC were evaluated. Ventricular arrhythmias (ventricular extrasystoles >500/24hour or ventricular tachycardia) were searched on 24-hour Holter monitoring and ECG recordings. The diagnosis of ARVC was based on 2 major or 1 major plus 2 minor or 4 minor TFC. Arrhythmic events (unexplained syncope, episodes of sustained ventricular tachycardia and sudden death) were recorded. Heart failure was classified according to NYHA functional class.
Results: ECG abnormalities were present in 100% of patients; in 41% on repolarization, in 10% on depolarization and in 49% on both. On 2-dimensional echocardiography, RV structural/functional alterations were detected in 85%; diagnostic according to TFC in 59% and non-diagnostic in 26%. Left ventricular alterations were detected in 24% of patients. Ventricular arrhythmias were recorded in 89%. Up to the age of 44±16 years, at the end of follow-up, arrhythmic events appeared in 55% of patients (unexplained syncope in 15%, sustained ventricular tachycardia in 33%, and sudden death in 20%). Mean age at first event was 34±16 years. Heart failure was developed in 13% of patients.
Conclusions: Dominant desmosomal ARVC is mainly an arrhythmogenic disorder always presenting with ECG abnormalities, while diagnostic structural/functional abnormalities on 2-dimensional echocardiography are detected in slightly more than half of affected carriers. Thus, family screening with standard 12-lead ECG would indicate all affected carriers facilitating further evaluation towards ARVC diagnosis.

P1699 The role of chemokine in enterovirus positive myocarditis- possible mechanism for the determination of inflammatory acuity

F. Escher[1], U. Kuehl[1], D. Lassner[2], D. Westermann[1], H.P. Schultheiss[1], C. Tschoepe[1]. *[1]Charite - Campus Benjamin Franklin, Berlin, Germany; [2]IKDT, Berlin, Germany*

Background: Based on the ability of fractalkine (CX3CL1) to promote leucocyte infiltration into vessel wall, we analyzed the role of CX3CL1 and its receptor (CX3CR1) on chemotactic and the adhesive properties of peripherial blood mononuclear cells (PBMCs), as well as the release of monocyte chemoattractant protein-1 (MCP-1) in patients with enterovirus (EV) positive myocarditis.
Methods and Results: We studied n=10 EV myocarditis patients, which underwent endomyocardial biopsies (EMBs). Healthy sex- and age-matched donors served as controls (n=10). We examined plasma levels by enzyme immunoassay and intramyocardial expression by immunohistochemistry of CX3CL1 and MCP-1. Expression of CX3CL1 were significant increased in patients with EV myocarditis (CX3CL1-Area fraction (AF) % 0.078+0,012 vs. 0.009+0,003 $p<0.05$; MCP-1-AF % 0.093+0.023 vs. 0.011+0.009). We also examined CXCR3-mediated chemotaxis as well as the effects of CX3CL1 on MCP-1 levels in peripherial blood mononuclear cells (PBMCs) supernatants. CX3CL1 induced chemotaxis was significantly higher in PBMCs from EV positive patients as compared with healthy controls (6.6+2.0 vs. 3.4+2.6% migrated PBMCs/field, $p<0.05$). The MCP-1 secretion was significantly higher in PBMCs from EV positive patients as compared with controls (1020+254.6 vs 325.5+106.2 pg/ml $p<0.05$), and this elevation was further increased by CX3CL1 in EV positive patients (1690.1+84.8 pg/ml). No significant CX3CL1-mediated MCP-1 increase was seen in PBMCs from healthy controls (175.0+77.78 pg/ml).
Conclusion: In EV positive myocarditis patients enhanced CX3Cl1, MCP-1 expression within the failing human heart is associated with a marked increase in serum levels of this chemokine, accompanied of enhanced expression of the corresponding receptor, CX3XR1, in PBMC. This up-regulation affected the functional potential of PBMCs as shown by enhanced chemotactic, and other inflammatory responses (i.e. increased MCP-1 secretion) to CX3CL1 stimulation.

P1700 Prevalence of viral genomes and coinfection in the myocardium of adults with iiopathic left ventricular dysfunction

A. Gkouziouta, G. Karavolias, G. Saroglou, S. Adamopoulos, V. Voudris. *Onassis Cardiac Surgery Center, Athens, Greece*

Purpose: Enteroviruses have been considered to be the most common cause of acute viral myocarditis (VM), with possible transition from myocarditis to dilated cardiomyopathy (DCM). Other viruses are also frequently encountered in (VM) patients, suggesting that persistence of various virus species may play a pathogenic role in the transition from myocarditis to DCM.The purpose of this study was to screen endomyocardial biopsies (EMBs) from patients with "idiopathic" DCM for the presence of viral genomes by using polymerase chain reaction (PCR) to assess the frequency of cardiac viral infections that may be involved in the pathogenesis of the disease.
Methods: Between September 2006 and December 2008, 80 patients with clinically suggested DCM underwent EMB in our institution after angiographic and echocardiographic exclusion of coronary artery disease and other causes of cardiac dysfunction. The clinical diagnosis of DCM was taken into consideration in all patients who presented with idiopathic global or regional LV dysfunction and/or dilated LV in association with symptoms of heart failure (NYHA functional class II–IV) in spite of medication. 84%of the patients presented with reduced systolic LVEF (<35%) and increased LV diametres, whereas in 16% of patients LV function was preserved.
Results: PCR and reverse transcription-PCR were performed to detect the genomic sequences of enterovirus (EV), adenovirus (ADV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6), parvovirus B19 (PVB19), influenza A and B viruses, Chlamydia (trachomatis, psittackie, pneumoniae) and Coxiella burnetii. Myocardial inflammation was assessed by histological and immunohistological analyses. Viral genomes could be amplified from EMBs of 24 (30%) of the 80 DCM patients. EMBs were positive for Chlamydia trachomatis 8 (33.3%), Chlamydia psittackie 1 (4.16%), HSV6 1 (4.16%), Coxsackie B3: 2 (8.3%) and CMV 1 (4.16%). Coinfections with Chlamydia trachomatis and HSV1/HSV2/HHV6 were present in 10 (41,6%) biopsy specimens while coinfection with ParvoB-19 and HSV1/HSV2 in 1 (4.25%). Active or borderline myocarditis according to the Dallas classification did not exist in any case. Four of the 24 patients with coinfection (Chlamydia trachomatis and HSV1/HSV2) due to deterioration of their status were supported with ventricular assist devices and transplanted.
Conclusions: Viral genomes were frequently detected in EMBs of patients with systolic left ventricular dysfunction. Our data suggest that myocardial persistence of various viruses, often presenting as multiple infections, may play a role in the pathogenesis of DCM.

P1701 Cellular mechanisms of cardioprotective exercise training in heart failure

A. Schmidt, K. Wagner, B. Pieske. *Medical University of Graz, Department of Cardiology, Graz, Austria*

Background: Moderate exercise training not only improves functional capacity but may also result in lower mortality in patients suffering from heart failure. The underlying cellular mechanisms of this favorable outcome are largely unknown. The present study examines the hypothesis, that moderate exercise training modulates the expression of SERCA2a, a key calcium handling protein, via the Akt-/GSK-3β-signaling pathway.
Methods and Results: Over a period of four weeks, 24 adult FVB/N mice (EX) underwent submaximal exercise training on a treadmill (22 m/min, 2x1h/d) and were analyzed in parallel with age-matched sedentary control animals (SG; n=24). Echocardiographically, gravimetrically and histopathologically, a mild but highly significant degree of training-induced cardiac hypertrophy was found (112.2%). Induction of this physiological form of hypertrophy was paralleled by an increase in the activity of Akt in cardiac homogenates (159% phospho-Akt/Akt ratio). Akt-activation resulted in increased phosphorylation and thereby inactivation of its downstream target glycogen synthase kinase (GSK)-3β (183%,$p<0.05$). The activation of p38, known to be involved in pathological cardiac remodeling, was suppressed selectively in exercised mice. Interestingly, we also found increased SERCA2 levels in trained animals compared to sedentary controls (133%,$p<0.05$). These exercise-induced changes were associated with a significant reduction in mortality due to acute Doxorubicin-induced cardiomyopathy (20 mg/kg) (survival rate EX: 58% vs. SG: 29%,$p<0.05$).
In human heart failure samples, an significant increase in Akt-activation (145%, $p<0.05$) was found in left ventricular biopsies from "compensated" hypertrophied hearts (obtained during aortic valve replacement due to aortic stenosis, EF>50%,n=8), whereas in explanted "decompensated" failing hearts (obtained from patients undergoing heart transplantation, EF<30%, n=15), a significant drop in Akt phosphorylation (53%) was found compared to non-failing myocardium (100%, n=15). This was paralleled by a decrease in GSK-3β phosphorylation and SERCA2 expression levels (73%, $p<0.05$).
By using IGF-1, a stimulator, and wortmannin, an inhibitor of the PI3-K-/Akt-/GSK-3β-signaling pathway, we were able to show that SERCA-expression is modulated in an Akt-/GSK-3β- dependent manner in cultured adult rabbit cardiomyocytes.
Conclusion: Induction of physiological hypertrophy by submaximal exercise training is associated with activation of Akt-dependent cellular survival pathways in the heart, which may be beneficial in restoring depressed SERCA2a levels in human heart failure.

P1702 Chronic heart failure induces atrophy and myogenin downregulation in rat skeletal muscle

P.F. Martinez[1], K. Okoshi[1], L.A.M. Zornoff[1], R.F. Carvalho[2], S.A. Oliveira Junior[1], D.H.S. Campos[1], A.R.R. Lima[1], C.R. Nogueira[1], M. Dal Pai-Silva[2], M.P. Okoshi[1]. *[1]Botucatu Medical School, UNESP, Botucatu, Brazil; [2]Botucatu Biosciences Institute, UNESP, Botucatu, Brazil*

Purpose: Although intrinsic skeletal muscle abnormalities can influence exercise intolerance during heart failure (HF), the factors responsible for muscle changes are not completely defined. This study evaluated the expression of myogenic regulatory factors (MRF), myosin heavy chain (MyHC) isoforms, and fiber trophism in the soleus muscle of rats with myocardial infarction (MI) during compensated left ventricular (LV) dysfunction and clinical HF. As cytokines may play a role in HF-induced myopathy, tumor necrosis factor-α (TNF-α) serum concentration was also determined.
Methods: A coronary ligation model was employed to induce HF. Six months after surgery, three groups of rats were studied: Sham; infarcted rats without HF (MI/HF-, n=11); and infarcted rats with HF (MI/HF+, n=11, which presented tachypnea, pleural effusion, and right ventricular hypertrophy). Cardiac structure and function were evaluated by transthoracic Doppler echocardiogram. Infarct size was measured by histological analysis. MRF MyoD, myogenin, MRF4, and cyclophilin A (housekeeping gene) expression was assessed by reverse transcription-polymerase chain reaction in the soleus muscle. Poliacrylamide gel electrophoresis was performed to evaluate MyHC isoforms (I and IIa). Histochemical analysis with myofibrillar ATPase was employed to analyze muscle fiber type and cross sectional fiber areas. TNF-α serum concentration was measured by ELISA. Statistics: ANOVA and Tukey test; Pearson correlation.
Results: MI size was greater in MI/HF+ than MI/HF- (P=0.001; Student's t test). Infarcted groups presented left cardiac chamber dilation and LV dysfunction compared to Sham. Cardiac alterations were more pronounced in MI/HF+ than MI/HF-. MI/HF+ had atrophy of type I, IC/IIC, and IIA fibers compared to Sham. Myogenin gene expression was similar in MI/HF- and MI/HF+ and lower than Sham ($P<0.001$). There was a trend for MyoD expression to be higher in MI/HF+ group (P=0.078). MRF4 expression and MyHC distribution did not differ between groups. TNF-α serum concentration was significantly higher in MI/HF+ than Sham (Sham: 3.26±1.25; MI/HF-: 4.78±1.63; MI/HF+: 6.28±2.49 pg/mL; P=0.009). Myogenin expression was negatively correlated with left atrium diameter-to-body weight ratio, TNF-α serum concentration, and types I and IIA fiber areas.
Conclusion: Chronic heart failure reduces myogenin gene expression and in-

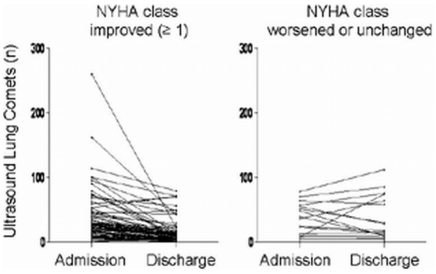
duces skeletal muscle atrophy. Changes in gene expression can occur early during HF development.

ECHOCARDIOGRAPHY AND HEART FAILURE EPIDEMIOLOGY

P1703 Ultrasound Lung Comets for serial assessment of pulmonary congestion in heart failure

L. Gargani[1], M.C. Scali[1], M. Agrusta[2], P. Tesorio[2], E. Poggianti[1], F. Frassi[1], R. Sicari[1], M. Mottola[2], E. Picano[1]. [1]*CNR Istituto di Fisiologia Clinica, Pisa, Italy;* [2]*Clinica Cardiologica "Montevergine", Mercogliano, Italy*

Background: Serial chest radiographs are too insensitive and therefore not recommended for monitoring pulmonary congestion in heart failure patients (AHA/ACC guidelines 2006). Ultrasound lung comets (ULC) are a simple, quantitative chest sonography sign of pulmonary congestion, and might represent a convenient alternative to chest x-ray in this clinical setting. Aim: To assess whether dynamic changes in ULC could mirror variations in clinical status.
Methods: 120 patients (31 females; age 70±11 years) admitted with dyspnoea (NYHA class ≥II) to a Cardiology or Emergency Department were evaluated. NT-proBNP assessment and ULC were independently performed at admission and before discharge. Body weight and diuresis were recorded every day during hospitalization. A patient ULC score was obtained by summing the number of ULC found on anterior and lateral chest. Patients were considered "responders" to therapy when NYHA class decreased ≥1 grade at discharge.
Results: Responders (group I, n=100) and non-responders (group II, n=20) had similar NT-proBNP (I=5668±7356 vs II=3587±3556 ng/l, p=0.23), and ULC number (I=36±38 vs II=32±25, p=0.66) at admission. At discharge, responders had lower ULC (I=13±17 vs II=32±33, p<0.001, see figure) but similar NT-proBNP (I=3921±5954 vs II=3151±3187 ng/l, p<0.59), when compared to non-responders. No significant difference was found in total diuresis from admission to discharge (I=5076±5894 vs II=3748±4600 cc, p=0.49), and body weight variation (I=-1.9±2.5 vs II=-2.5±3.3 kg).



Conclusions: ULC variations mirror changes in clinical functional class in patients hospitalized with acute dyspnoea. ULC represent an objective parameter of clinical improvement, useful for serial assessment of extra-vascular lung water in patients admitted with acute dyspnoea.

P1704 Echocardiography signs of early myocardial impairment in patients with breast cancer and Trastuzumab therapy

S.A. Lange[1], B. Ebner[2], A. Wess[1], T. Hitschold[3], J. Jung[1]. [1]*Medizinische Klinik I, Kardiologie und Angiologie, Klinikum Worms, akademisches Lehrkrankenhaus der, Worms, Germany;* [2]*Dresden University of Technology, Dresden, Germany;* [3]*Frauenklinik, Brustzentrum-Perinatalzentrum, Klinikum Worms, Worms, Germany*

Objective: Recent studies in patients with breast cancer and Trastuzumab therapy (Herzeptin®) showed a development of a toxic cardiomyopathy as a severe complication.
The aim of this study was to discover the early changes in myocardial function and structure measured by echocardiography.
Methods: We studied 20 female patients with Her-2-neu over expression in mamma carcinoma by echocardiography before and three month after beginning of the therapy with Herzeptin®.
Results: After three months of the therapy with Trastuzumab we discovered a significant increase of the diastolic and systolic left ventricle volume index (LV-DVI 35.33±1.44ml/m^2 vs. 40.85±1.53ml/m^2, p<0.01 and LV-SVI 13.53±0.74ml/m^2 vs. 16.78±1.31ml/m^2, p<0.05) and an increase of the end-systolic LV diameter (LVESD 29.69±0,88mm vs. 32.06±1.44mm, p<0.05). We obtained also a reduced systolic ventricle function measured by Tissue Doppler Imaging at the mitral valve annulus (s' 8.95±0.41cm/s vs. 7.59±0.33cm/s, p<0,001) and by determining of the Fractioning shortening (FS 38.50±1.33% vs. 32.60±1.56%, p<0.001), while the biplane Simpson Ejection fraction differed not significantly (Si-bp EF. 62.45±1.07% vs. 59.25±2.06, p=0.17). There were also an increase of the left atrium volume index (LA-VI 20.79±1.38ml/m^2 vs. 26.01±1.98ml/m^2, p<0.001) and an increase of the mitral valve insufficiency degree (0.53±0.15° vs. 0.85±0.20°, p<0.05).
We could not show a significant increase in diastolic dysfunction. Also the right heart diameters and function did not change significantly. Most of all patients stayed in an asymptomatic stage of cardiac disease, only one patient developed a dyspnea NYHA I and three patients described palpitations. (All values were mean value ± standard error of mean).
Conclusion: The blockade of Her 2-neu receptors with trastuzumab in patients with breast cancer led to a measurable alteration of systolic function and an increase of left heart volume already after three months treatment.

P1705 Subepicardial and subendocardial left ventricle rotational mechanics in heart failure patients: relation to left ventricular dimensions and mechanical activation

M. Bertini[1], N. Ajmone Marsan[1], V. Delgado[1], G. Nucifora[1], R.J. Van Bommel[1], C.J.W. Borleffs[1], G. Boriani[2], M. Biffi[2], M.J. Schalij[1], J.J. Bax[1]. [1]*Leiden University Medical Center, Leiden, Netherlands;* [2]*Univ. di Bologna - Istituto di Cardiology, Bologna, Italy*

Purpose: Myofibers have a right- and left-handed orientation at the subepicardial and subendocardial layers, respectively. At present, minimal data are available on subepicardial and subendocardial left ventricular (LV) twist. The aim of the study was to explore LV twist behavior in both layers in heart failure (HF) patients.
Methods: A total of 118 consecutive HF patients and 45 consecutive normal subjects were included. Real-time three-dimensional echocardiography was performed in the overall study population to assess LV volumes, LV ejection fraction (EF) and systolic dyssynchrony index (SDI). Speckle tracking analysis was applied to LV basal and apical short axis images to assess subepicardial and subendocardial rotation. Consequently, subepicardial and subendocardial LV twist were calculated.
Results: LV rotational parameters are presented in Table. Peak subepicardial LV twist was significantly lower as compared to peak subendocardial LV twist (p<0.001), either in HF patients and in normal subjects. In order to identify the independent determinants of subepicardial LV twist, a multivariable linear regression analysis was performed. SDI resulted the only independent determinant of subepicardial LV twist (β=-0.43, p<0.001). LVESV index (β=-0.38, p<0.001) and SDI (β=-0.26, p=0.002) were both independent determinants of subendocardial LV twist at multivariable linear regression analysis.

Characteristics of the study population

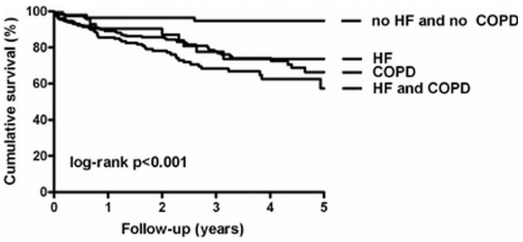
	HF patients (n=118)	Normal subjects (n=45)	p-value
Age (years)	61±20	41±15	<0.001
LVEDV index (ml/m^2)	95±29	46±12	<0.001
LVESV index (ml/m^2)	69±24	18±7	<0.001
LVEF (%)	28±6	62±4	<0.001
SDI (%)	7.9±2.7	2.3±1.2	<0.001
Peak subepicardial LV twist (°)	2.7±2.4	9.9±2.5	<0.001
Peak subendocardial LV twist (°)	4.7±3.6	15.7±3	<0.001

Conclusions: In HF-patients, subepicardial and subendocardial LV twist are significantly reduced. Subepicardial LV twist is strongly related to SDI reflecting the close link between rotational mechanics and electromechanical activation. Conversely, subendocardial LV twist is better related to LV dimension underscoring the influence of LV volumes on subendocardial rotation.

P1706 Prognostic value of heart failure screening with echocardiography in patients with chronic obstructive pulmonary disease undergoing major vascular surgery

W.J. Flu[1], Y.R.B.M. Van Gestel[1], J.P. Van Kuijk[1], S.E. Hoeks[1], R. Kuijper[1], O. Schouten[1], T.A. Winkel[1], D. Goei[1], J.J. Bax[2], D. Poldermans[3]. [1]*Erasmus, Rotterdam, Netherlands;* [2]*Leiden University Medical Center, Leiden, Netherlands;* [3]*Erasmus MC - Thoraxcenter, Rotterdam, Netherlands*

Purpose: Both heart failure (HF) and chronic obstructive pulmonary disease (COPD) are associated with increased mortality. The current study evaluated the influence of HF and COPD on long-term outcome of vascular surgery patients.
Methods: Echocardiography and pulmonary function tests were performed preoperatively in 632 vascular surgery patients. HF with a reduced ejection fraction (HFREF) was defined as a left ventricular ejection fraction (LVEF) <40%. HF with a preserved ejection fraction (HFPEF) (LVEF>40%) was defined as an E/A-ratio >2 plus a deceleration time <150ms or an E/A ratio <1. Moderate or severe COPD was defined according to the GOLD guidelines. The study endpoint was 5-year all cause mortality. Patients were classified as having 1) no HF and no COPD, 2) COPD, 3) HF or 4) COPD and HF.
Results: Mortality rates in patients with 1) no HF and no COPD, 2) COPD, 3) HF or 4) COPD and HF were 4%, 17%, 20% and 28%, respectively (p<0.001). After adjusting for other risk factors, patients with COPD, HF or a combination of COPD and HF had an increased risk for long-term mortality compared to patients without HF and COPD (HR: 3.6; 95%CI: 1.2-10.8, HR: 4.2; 95%CI: 1.7-10.7 and



Cumulative long-term survival

HR: 5.4; 95%CI: 2.1-13.8), respectively. Furthermore, COPD patients with HFPEF or HFREF had comparable risks for long-term mortality (HR: 2.5; 95%CI: 1.3-4.9 and HR: 2.7; 95%CI: 1.2-5.7).

Conclusions: Patients with HF or COPD have an increased risk for long-term mortality after vascular surgery. However, the strongest association was observed in patients with both COPD and HF. Furthermore, HFPEF or HFREF in addition to COPD leads to an increased risk for long-term mortality. These data promote standard preoperative evaluation of left ventricular function with echocardiography in COPD patients undergoing vascular surgery.

P1707 Assessment of right ventricular strain in patients with and without pulmonary hypertension

A. Meris[1], C. Conca[1], C. Klersy[2], A. Evangelista[1], J. Klimusina[1], M. Averaimo[1], A. Auricchio[1], F. Faletra[1]. [1]*Fondazione Cardiocentro Ticino, Lugano, Switzerland;* [2]*Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

Purpose: Assessment of right ventricular (RV) function is of paramount importance in many cardiovascular diseases, and it is usually done using RV tricuspid annular plane systolic excursion (TAPSE) or RV fractional area change (RV-FAC). Whether strain by using 2D speckle tracking can be equally applied to RV has been evaluated to a minimum extent.

Methods: We evaluate RV function using TAPSE, RV-FAC, and RV strain by using 2D speckle tracking in 76 patients with RV dysfunction. Group A consisted of 31 patients with pulmonary hypertension defined as pulmonary systolic artery pressure $\geq$ 35 mmHg, and Group B (45 patients) without pulmonary hypertension. Analyses of RV strain were performed using conventional 2D echo grey scale apical four-chamber images, setting the frame rate between 70 and 80 Frames-Per-Second. Longitudinal peak strain (LPS), defined as percentage of maximum shortening in systole (negative values) for 6 RV segments (basal, mid, and apical segments of the RV free wall and septum) and global RV strain, defined as the average of LPS in the 6 segments, were measured.

Results: Overall, mean RV strain amount was significantly lower in group A (Table). Similarly, a significantly lower TAPSE and RV-FAC was found in group A patients. The regional distribution of amount of strain did not differ between the 2 groups; in contrast, some differencies were found in regional distribution of LPS.

	Group A	Group B	p value
Global strain (%)	-12±4	-14±3	0.038
LPS - basal free wall	-19±7	-19±7	0.913
LPS - mid free wall	-16±6	-19±6	0.030
LPS - apical free wall	-15±6	-17±6	0.183
LPS - basal septum	-9±5	-10±5	0.149
LPS - mid septum	-8±4	-9±4	0.105
LPS - apical septum	-9±7	-11±5	0.129
TAPSE (cm)	1.3±0.3	1.4±0.2	0.047
RV-FAC (%)	28.3±7.1	32.7±6.8	0.008

Conclusions: RV global strain but not longitudinal peak strain is reduced in patients with RV dysfunction and pulmonary hypertension. Thus, global strain might be used as a tool to identify patients with pulmonary hypertension.

P1708 Echocardiographic detection of congestive heart failure in postinfarction rats

P.F. Martinez[1], K. Okoshi[1], L.A.M. Zornoff[1], S.A. Oliveira Junior[1], D.H.S. Campos[1], A.R.R. Lima[1], R.L. Damatto[1], C.R. Padovani[2], A.C. Cicogna[1], M.P. Okoshi[1]. [1]*Botucatu Medical School, UNESP, Botucatu, Brazil;* [2]*Botucatu Biosciences Institute, UNESP, Botucatu, Brazil*

Purpose: In experimental studies of congestive heart failure (CHF) treatment, it is important to select animals with a similar degree of cardiac functional impairment. However, this is difficult to establish in postinfarction-induced CHF without hemodynamic evaluation. This study aimed to determine echocardiographic criteria for CHF in long-term follow-up postinfarction rats with J-tree cluster analysis using structural and functional parameters.

Methods: Myocardial infarction (MI) was induced by left coronary occlusion. Sham-operated animals were used as controls. Six months later, survival animals were subjected to transthoracic Doppler echocardiography, and euthanized the next day. At euthanasia, we looked for clinical and pathologic features of CHF, including tachypnea/labored respiration, pleuropericardial effusions, ascites, left atrial thrombi, hepatic congestion, and right ventricular hypertrophy (right ventricular weight/body weight $>$0.8 mg/g). Infarct size was measured by left ventricle histological analysis. Six echocardiographic variables were used in the J-tree cluster analysis: left ventricular systolic dimension (LVSD), left ventricular diastolic dimension-to-body weight ratio (LVDD/BW), left atrium diameter-to-body weight ratio (LA/BW), posterior wall shortening velocity (PWSV), early diastolic mitral inflow (E wave), and isovolumetric relaxation time (IVRT).

Results: Cluster analysis joined the rats into one Sham and two MI groups. One MI cluster had clinical and pathological features of CHF (MI/CHF+ group, n=24, infarct size: 42.7±5.8%). Right ventricular hypertrophy was present in all rats from this group; pleuropericardial effusion in 75%, and tachypnea/labored respiration in 37.5%. In the other MI cluster (MI/CHF- group, n=11, infarct size: 32.3±9.9%), only one of the rats had right ventricular hypertrophy; two had pleuropericardial effusion, and two tachypnea/labored respiration. Three rats with small infarct size (21.6±2.2%) presented mild cardiac alterations and were placed in the Sham group.

Conclusion: Echocardiographic structural parameters and systolic and diastolic functional indices can be used to separate postinfarction rats with CHF from those with compensated left ventricular dysfunction.

P1709 Evaluation of systolic long-axis left ventricle function in patients with heart failure with normal ejection fraction diagnosed by the new criteria of European Society of Cardiology Guidelines

A.J. Lagoeiro Jorge[1], E.T. Mesquita[1], M.L.G. Rosa[1], L.C.M. Fernandes[1], M.L. Ribeiro[1], F.V. Licio[2]. [1]*Universidade Federal Fluminense, Niterói, Brazil;* [2]*Universidade Federal do Rio de janeiro, Rio De Janeiro, Brazil*

Purposes: To investigate the presence of systolic long-axis left ventricle (LV) dysfunction evaluated by the peak systolic annular velocity (S') in outpatients with suspected of heart failure with normal ejection fraction (HFNEF) and to correlate with the levels of BNP and diastolic dysfunction evaluated by the peak early diastolic annular velocities (E'), and E/E' ratios.

Methods: The study population consisted of 88 outpatients (mean age 69.3±12.3 years) with clinical suspected of HF and ejection fraction (LVEF) $\geq$ 50% which were submitted to tissue Doppler image (TDI) for evaluation of systolic and diastolic long-axis LV function and dosage of BNP. Patients were classified, in accordance with the criteria, in two groups one confirmed HFNEF and another excluded HFNEF.

Results: HFNEF was confirmed in 29 patients (33%)who presented increased volume of the left atrium and diastolic abnormalities (table1). No significant intergroup differences in LVEF were observed. The average values of S' in the group with HFNEF was 7.8 cm/s, while patients without HFNEF had average values of S' of 9.6 cm/s (p 0.003). The average of BNP in patients with and without HFNEF was 131 pg/ml (median 95.1) and 21 pg/ml (median 16.1) (p $<$0,0001) respectively. Systolic long-axis LV function was correlated with the diastolic function assessed by E' and E/E' ratio (r = 0.46 and r= (-) 0.43; p $<$ 0.0001), however values of BNP were not correlated (r = (-) 0.18; p 0,102).

Clinical characteristics, tissue Doppler

	Total (n=88)	No HFNEF (n=59)	HFNEF (n=29)	p
Age (years)	69.3±12.3	66.1±10.9	75.7±12.7	0.527
Female gender (%)	72.1	70.2	75.9	0.578
Arterial hypertension (%)	90.7	87.7	96.6	0.182
LVEF	72.6±8.3	72.8±7.5	72.1±9.9	0.659
S' (cm/s)	9.0±2.0	9.6±3.0	7.8±2.0	0.003
E/E'	9.8±5.2	7.3±2.0	14.6±6.1	$<$0.0001
E' (cm/s)	8.9±3.0	9.5±2.0	7.6±3.0	0.002
LAV-Indexed (ml/m^2)	33.6±13.9	29.0±8.9	42.8±17.0	$<$0.0001

LAV-I, Left atrial volume; Independent Samples Test; Pearson Chi-Square.

Conclusions: Our results show a decrease of S' values in patients who had the diagnosis of HFNEF in relation to the group where the diagnosis wasn't confirmed. A linear correlation was noted between the E/E' ratio and E' with the worsening of systolic long-axis LV function.

P1710 Mitral annular motion as a surrogate for left ventricular function: correlation with brain natriuretic peptide levels

M.F. Elnoamany, A. Kilany. *Menoufyia Faculty of Medicine, Shebeen Elkom, Menoufyia, Egypt*

Background: Pulsed-wave (PW) Doppler tissue velocities of the mitral annulus correlate well with Left Ventricular (LV) diastolic (D) and systolic (S) functions. Brain natriuretic peptide (BNP) levels have been shown to be elevated in patients with symptomatic LV dysfunction (Dys) and correlate to the severity of symptoms and prognosis.

Objectives: To validate the accuracy of mitral annular motion (MAM) assessed by Doppler Tissue Imaging (DTI) & M-mode Echocardiography (MME) as a surrogate for determination of LV function in comparison with BNP.

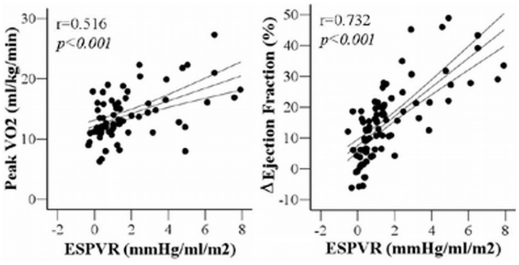
Methods: A series of 133 patients with a variety of cardiac pathologies referred

for echocardiography and 20 healthy age & sex matched volunteers as a control group were included the study. Ejection fraction (EF) of LV, Doppler recordings of the mitral inflow, MME and PWDTI data (from each of 4 mitral annular sites, inferior, anterior, septum and lateral) were obtained. Mean peak (S) MAM velocity (Sm), mean annular early (D) velocity (Em) by PWDTI and mean mitral annular plane (S) excursion (MAPSE) by MME were calculated by averaging of values measured at each annular site. BNP levels were measured by a rapid immunoassay and blinded to cardiologist making the assessment of LV function.
Results: MAPSE <12 mm determined by MME has 90% sensitivity, 88% specificity & 89% accuracy for detection of LVEF <50%, while these values were 94%, 93% & 94% respectively for (Sm) < 8 cm/s determined by PWDTI. BNP level >75 pg/ml has 98% sensitivity, 90% specificity & 97% accuracy for detection of LV Dys either (S, D or both). BNP levels were significantly higher in patients with combined (S & D) Dys. than those with only (S) Dys, the later group had significantly higher BNP levels than those with only (D) Dys. (1054.5±202.3 pg/ml vs. 500±39.9 pg/ml & 500±39.9 pg/ml vs. 215.3±100.9 pg/ml respectively, $p<0.001$) & each were significantly higher than control group (12.3±5.7 pg/ml, $p<0.001$). Significant correlations ($p<0.001$ for all) were found between BNP levels and Em (r= -0.82), Sm (r= -0.7), early transmitral (E) to Em ratio (r=0.61), MAPSE (r= -0.54), LVEF (r= -0.64) & LV end D dimension (r=0.63).
Conclusion: MME and PWDTI used for assessment of MAM are useful methods for evaluation of LV function but parameters measured by PWDTI correlate more strongly with plasma BNP levels than those measured by MME and provide a simple, sensitive, accurate and reproducible tool for early diagnosis of LV dysfunction.

P1711 Pressure-volume relationship during stress echo predicts exercise tolerance in patients with congestive heart failure

Q. Ciampi[1], L. Pratali[2], T. Bombardini[2], M. Della Porta[1], B. Villari[1], E. Picano[2], R. Sicari[2]. *[1]Ospedale Fatebenefratelli, Cardiology Division, Benevento, Italy; [2]Fondazione G Monasterio, Pisa, Italy*

Background: Dobutamine stress echocardiography (DSE) is widely used for evaluation of myocardial contractile reserve in patients with congestive heart failure (CHF). End-systolic pressure-volume relationship (ESPVR) is a useful method to evaluate LV myocardial contractility during stress. Aim or our study is to evaluate the relationship between ESPVR, systolic and diastolic function, BNP levels, and aerobic exercise capacity in CHF patients.
Methods: 84 CHF patients (age 68±9 years, 56% with an ischemic etiology), underwent high dose of DSE (up to 40 mcg/kg/min). ESPVR was determined as difference of the ratio between systolic cuff pressure/end-systolic volume (biplane using a Simpson rule), assessed at baseline and at peak DSE. 66 CHF patients underwent, also, cardiopulmonary exercise test with expired gas measurement.
Results: ESPVR was significantly lower in CHF patients with NYHA >2 (2.17±1.99 vs 0.91±0.72 $p<0.001$). ESPVR was inversely related to end-diastolic and end-systolic diameters (r=-0.333, p=0.002 and r=-0.385, $p<0.001$), to end-diastolic and end-systolic volumes at rest (r=-0.358, p=0.001 and r=-0.412, $p<0.001$) and at peak DSE (r=-0.497, $p<0.001$ and r=-0.608, $p<0.001$), to WMSI at rest (r=-0.309, p=0.019) and at peak DSE (r=-0.524, $p<0.001$), to E/Ea ratio (r=-0.326, p=0.011) and lgBNP (r=-0.557, $p<0.001$). ESPVR was directly related to ejection fraction at rest (r=0.529, $p<0.001$) and at peak DSE (r=0.843, $p<0.001$, Figure), to mitral annulus peak systolic velocity (r=0.480, $p<0.001$) and to peak oxygen consumption (Figure).

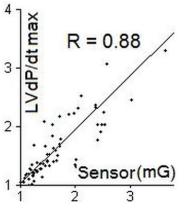


Conclusions: In patients with CHF, impaired non-invasive myocardial contractility is related to impaired systolic function at rest and at peak DSE, higher BNP levels and poorer exercise tolerance.

P1712 Operator-independent force-frequency relation monitoring with a new transcutaneous cardiac force sensor in pacing induced heart failure

V. Gemignani[1], E. Bianchini[1], F. Faita[1], M. Campan[2], V. Lionetti[2], F. Recchia[2], E. Picano[1], T. Bombardini[1]. *[1]Fondazione G Monasterio, Pisa, Italy; [2]Scuola Superiore Sant'Anna, Pisa, Italy*

Background: The inherent ability of ventricular myocardium to increase its force of contraction in response to an increase in contraction frequency is known as the cardiac force-frequency relation (FFR). When measured in explanted myocardial strips, the FFR is upsloping in normal while flat-negative in failing hearts.
Aim: To evaluate the feasibility of the FFR measurement by a precordial cutaneous sensor.
Methods: A microelectromechanical accelerometer was positioned in the precordial region of 6 chronically instrumented minipigs. The cardiac force was measured as the myocardial vibrations amplitude in the isovolumic contraction period (generating the first cardiac sound), and plotted versus the cardiac frequency. Left ventricular pressures and LV dP/dt max were continuously measured by a Millar catheter. Heart failure was induced by pacing the left ventricular (LV) free wall at 180 beats/min for three weeks. Pigs were considered in severe HF when LV end-diastolic pressure was ≥20mmHg. The FFR was measured at baseline and in HF, with the pacemaker turned off, during Dobutamine infusion (up to 40 mg/kg).
Results: The FFR was upsloping in all pigs at baseline (slope = 2.62±0.72 mG/bpm). After pacing induced HF, the FFR was flat both with the sensor (slope = 0.10±0.54 mG/bpm) and LV dP/dt max measurements (slope = 0.31±0.47 mmHg/sec -1/bpm), $p<0.05$ vs baseline. Sensor based cardiac force changes were significantly related to positive peak LVdP/dt changes during dobutamine stress (r=0.88, $P<0.001$): see figure.



Conclusions: The cardiac force-frequency relation can be continuously and reliably measured by a cutaneous accelerometer in normal and failing hearts, with accuracy comparable to invasive measurements.

P1713 Prognostic implications of indexed left ventricular end-diastolic diameter by echocardiography to outpatients with chronic systolic heart failure: application of ASE/ESC guidelines

F. Bursi, A. Barbieri, C. Leuzzi, L. Reggianini, C. Manicardi, S. Copelli, M.G. Modena. *Ospedale Policlinico, Modena, Italy*

Objectives: This study sought to understand the prognostic implications of increased left ventricular (LV) end-diastolic diameter indexed to body surface area (EDDi) measured by echocardiography both at baseline and after optimization of medical and device therapy in a large population of outpatients with chronic heart failure (CHF).
Background: The American Society of Echocardiography/European Society of Cardiology (ASE/ESC) recommended indexing linear measurements and recently published sex-based cut-offs to qualify LV dilatation that have not been clinically validated in the CHF setting.
Methods: We evaluated the prognostic value of EDDi on mortality and heart transplantation. The only exclusion criteria for this study was LV ejection fraction >45%. Clinical state and medications had been stable for at least 1 month in all patients. Patients had echocardiograms performed during their index visit, at 6 months, following β-blocker uptitration and at yearly intervals. The first (baseline) and last available echocardiograms were considered. The EDDi were calculated. The published cut-offs (EDDi ≤3.2 cm/m^2 for women and ≤3.1 cm/m^2 for man) were used to classify patients with normalized LV.
Results: In 332 CHF patients (age, 64±13 years; LV ejection fraction, 30.0±7.5%; NYHA class, 2.2±0.7) mean EDDi was 6.03±3.67 cm/m^2 at baseline and 5.95±3.49 cm/m^2 at the last echocardiogram. During 3.7±4.2 years of follow-up, 96 patients had an event, of whom 91 patients died and 5 patient had heart transplantation. The risk of the composite end point increased with abnormal baseline EDDi (for each 0.1cm/m^2 increase HR 1.06, 95% CI: 1.02-1.09; p=0.002), even after adjusting for baseline clinical and echocardiographic covariates including LV ejection fraction (adjusted HR 1.05, 95%CI: 1.01-1.09; p=0.017). 322 patients had EDDi measured at follow-up. Larger EDDi after therapy optimization was associated with increased risk of events (HR 1.10 95% CI:1.06-1.34; $p<0.001$). According to the ASE/ESC cut-offs 81 patients (25%) were classified as having normalized LV. These patients had a significantly reduced risk of death and heart transplantation (HR 0.22 95%CI 0.10-0.49, $p<0.001$). Decreased risk associated with EDDi normalization was independent of other potential confounders (p=0.001).
Conclusion: In a large population of outpatients with systolic CHF, larger EDDi is associated with a significantly higher risk of death and heart transplantation. EDDi normalization after optimized therapy occurs in about a quarter of the cases and it represents a strong prognostic indicator of better outcome.

P1714 Reduced left atrial function and normal ejection fraction in hypertensive patients with dyspnoea

Y.T. Tan[1], F. Wenzelburger[1], E. Lee[2], G. Heatlie[2], F. Leyva[1], M. Frenneaux[1], J.E. Sanderson[1]. *[1]University of Birmingham, Birmingham, United Kingdom; [2]University of North Staffordshire, Stoke-On-Trent, United Kingdom*

Background: There is a high incidence of hypertension and atrial fibrillation in patients diagnosed with heart failure and normal ejection fraction (HFNEF). Little is known about the atrial function of these patients who are still in sinus rhythm. We hypothesize that hypertensive patients who are diagnosed with HFNEF have reduced atrial function and this is more apparent on exercise.
Methods: 40 HFNEF patients with hypertension and sinus rhythm (72±7 years, 30 female), and 25 age-matched healthy controls (69±7years, 19 female) were recruited. Rest and submaximal supine exercise echocardiography was performed to comparable heart rates and images were analysed off-line (Echopac). Early (Em) and late diastolic annular velocities (Am) were assessed by Colour Tissue Doppler Imaging at the mitral annular level from the septal and lateral walls at rest and on exercise. The averaged value of the two walls was used to calculate the atrial functional reserve index with the following equation: (Am on exercise – Am at rest) × [1 – (1/Am at rest)]. Left atrial volume index (LAVI) and left ventricular mass index (LVMI) were derived from M-Mode.
Results: Am was significantly reduced at rest in patients compared to controls (6.9±1.6cm/s vs 7.8±1.7cm/s, p=0.033). This difference became more apparent on exercise (8.1±1.7cm/s vs 10.0±2.3cm/s, $p<0.001$) resulting in a significantly lower left atrial (LA) functional reserve index in patients (0.98±1.44 vs 1.92±1.47, p=0.033). LAVI and LVMI were significantly higher in patients (LAVI 31.6±9.8ml/m^2 vs 23.9±8.7ml/m^2, p=0.002; LVMI 92.6±34.4g/m^2 vs 77.9±19.3g/m^2, p=0.04). Am on exercise was found to have a negative correlation with LAVI (r=-0.317, p=0.006), LVMI (r=-0.351, p=0.004) and the ratio of early mitral inflow velocity to Em on exercise, E/Em (r= -0.540 $p<0.001$).
Conclusion: Left atrial function is reduced in HFNEF patients with hypertension and in sinus rhythm. LA functional reserve is reduced with increased LAVI and mean LA pressure as measured by E/Em. LA function plays an important role in late LV filling particularly when filling time is shorten on exercise and delayed in hypertensive patients with symptoms of heart failure. Progressive rise in mean LA pressure and change in LA dimension lead to impaired LA function which is more apparent on exercise.

P1715 Investigation of left atrial function by strain imaging: comparative study in controls and coronary patients

P.M.J. Claessens[1], C.W.F. Claessens[2], M.M.M. Claessens[3], J.E.J. Claessens[1], M.C.F. Claessens[4]. *[1]AZ Monica, Antwerpen, Belgium; [2]AZ Sint Jozef Turnhout, Turnhout, Belgium; [3]Heilig Hart Ziekenhuis Roeselare, Roeselare, Belgium; [4]Kloppend Hart Essen, Essen, Belgium*

Hypothesis: Frequent complications in patients with severe coronary artery disease (CAD) are arrhythmias, thrombo-embolic events and heart failure. In all these problems left atrial function is of primordial importance.
Methods: Echocardiographic exploration including strain imaging was performed in 330 patients, equally divided in 2 groups with comparable age, heart rate and performance capacity: I normal controls and II: patients with CAD treated with stent implantation or surgical myocardial revascularization For the contractile function of the left atrium we assessed by means of strain measurements the reservoir function (RF), the conduit function (CF) and the booster pump function (BPF) at the atrial free wall, at the roof and at the interatrial septum. All subjects of both groups were in sinus rhythm and maintained a normal physical activity.
Results: The body mass index was identical in the two groups (I:26.1; II:26.5). The systolic left ventricular function was normal in the two groups without difference in the peak systolic ventricular strain: at the lateral wall of the left ventricle: -21 in I and -20.4 in II. The RF was significantly decreased in CAD ($p<0.001$) with a peak strain left atrial RF at the free wall of 91 in I and 73 in II; at the roof: 88 in I and 70 in II; at the interatrial septum: 92 in I and 74 in II. The left atrial CF was markedly reduced in group II ($p<0.001$) with a strain value of 52 in I and 49 in II. We noted a little decrease of the left atrial BPF with a reduced strain rising during atrial contraction in the CAD patients: at the free wall of the LA strain values of 34 in I and 32 in II, at the roof: 34 in I and 31 in II and at the interatrial septum 29 in I and 27 in II.
Conclusions: Notwithstanding all examined subjects maintained a normal exercise capacity and notwithstanding both groups were free of complaints with a normal ejection fraction and a normal contractility of the left ventricle, we noted a statistically significantly different behaviour of the LA in the two groups. In the presence of CAD the left atrial function was impaired with a decreased RF, a reduced CF and a diminished BPF, indicating a decreased contractile force and a reduced elongation capacity resulting in a higher risk for heart failure.

P1716 Prevalence of echocardiographic criteria of noncompaction in a non selected population

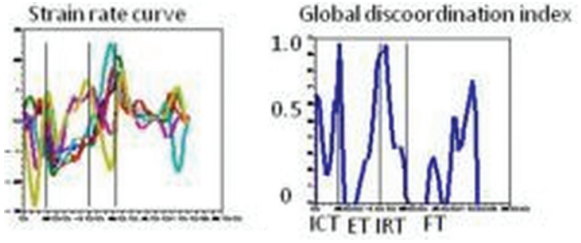
J.-C. Eicher[1], F. Schaad[2], G. Habib[3], O. Barthez[2], J.-E. Wolf[2]. *[1]Centre Hospitalier Universitaire de Dijon, Dijon, France; [2]CHU-Hôpital du Bocage, Dijon, France; [3]AP-HM - Hopital de la Timone, Marseille, France*

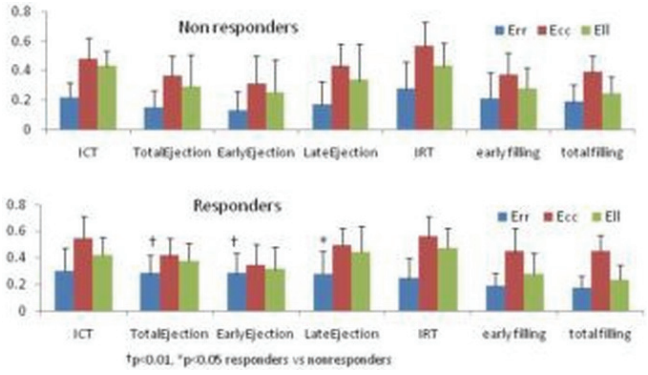
Background: Left ventricular noncompaction (LVNC) has been recently included in the 2006 classification of cardiomyopathies as a genetic cardiomyopathy. The diagnosis is usually based on the echocardiographic criteria defined by Jenni et al., including multiple trabeculations of the left ventricular (LV) wall, deep intertrabecular recesses perfused from the LV cavity, and a 2-layered structure of the endomyocardium with a noncompacted to compacted ratio (NC/C) ≥ 2 in systole. Once overlooked, this disease might be today overdiagnosed.
Purpose: To look for the presence of LVNC criteria in a non selected population referred for echocardiography.
Methods: 170 consecutive patients were prospectively studied. Multiple echocardiographic views were recorded, looking for LVNC criteria in a 17-segment model. These patients were compared with a group of 15 patients included in the French Noncompaction Registry in which the diagnosis of LVNC was established by an expert committee.
Results: 2 patients were excluded for poor imaging quality. Echocardiographic diagnosis was: normal 54 pts (32.1%), valve disease 52 pts (31.0%); dilated cardiomyopathy 26 pts (15.5%); ischemic heart disease (IHD) 18 pts (10.7%); hypertrophic cardiomyopathy 12 pts (7.1%); restrictive cardiomyopathy 6 pts (3.6%). Sixty% of patients had at least 1 LVNC criterion, particularly among those with dilated and restrictive cardiomyopathy, IHD, and aortic stenosis. Each single criterion showed a sensitivity of 100%, but poor specificity except for the NC/C ratio (85%). Presence of all criteria together yielded a specificity of 81%, and a positive predictive value (PPV) of 32%. The mean number of involved segments was 4.1±2.4 compared to 7.2±2.0 in the LVNC population. Considering the affected segments, the mean NC/C ratio was 1.8±0.4 vs 2.3±0.2 in the LVNC group. Preferentially affected segments were apex, and lateroapical and inferoapical segments, involvement of medial segments were more specific of established LVNC. Using modified diagnostic criteria: 1) multiple trabeculations, 2) intertrabecular recesses perfused from the cavity, 3) a NC/C ratio ≥2.1, and 4) involvement of at least 5 segments, including at least 2 medial segments, specificity improved to 92% and PPV to 54% without lowering sensitivity.
Conclusion: Some echocardiographic criteria of LVNC are frequently found in patients with various types of heart disease, as well as in normal patients. It raises the question of whether LVNC is a specific disease, or a phenotypic adaptation. We tried to improve the specificity of echocardiography by proposing modified criteria.

P1717 Presence of radial discoordination during ejection phase is a major determinant for reverse remodeling after cardiac resynchronization therapy

T. Arita, K. Ando, Y. Soga, M. Goya, M. Iwabuchi, M. Nobuyoshi. *Kokura Memorial Hospital, Kitakyushu, Japan*

Background: Mechanism of reverse remodeling by cardiac resynchronization therapy (CRT)is yet to be examined.
Methods: Fifty-seven patients with advanced heart failure (Age 69.2±10.6, Male 33/57, Ischemic 20/57, Sinus rhythm 52/57, LVEDV 199.5±55.3ml, EF 24.6±5.81%, QRS 154.1±26.7ms) underwent CRT. At pre and 3 -6 months post CRT, echocardiography (GE, Vivid7, Norway) was obtained. Radial/circumferential/longitudinal strain curve were obtained by speckle tracking analysis of two dimensional echocardiogram from mid short axis view and apical four chamber view. Global discoordination index (GDI=ISR/(GSR+ISR), where ISR (internal strain rate)=$\int(\Sigma|S'(n)|-|\Sigma S'(n)|)dt)/2$, GSR=global strain rate) as a function of time was calculated for spatial nonuniformity. Standard deviation of time to 10, 20, 50, 80, 100% of peak strain as systolic asynchrony and time to 30% completion of lengthening as diastolic asynchrony on each strain curves were calculated for temporal nonuniformity.Reduction of LVESV>15% is defined as responder.
Results: None of the temporal nonuniformity parameters showed significant difference between responders and nonresponders. As regards spatial nonuniformity, only radial discoordination index during ejection phase showed significant difference (GDI during total ejection phase, 0.14±0.11 vs 0.28±0.13, $p<0.005$). Circumfenrential/longitudinal discoordination index were not significantly different between two groups. Comparison among discoordination in each axis showed





radially more coordinated ($p<0.01$) and circumferentially/longitudinally more discoordinated deformation in both groups.
Conclusion: CRT responders showed more radially discoordinated deformation than non responders. Both groups showed more circumferential and longitudinal discoordination to similar degree.

P1718 Specific features of heart failure in elderly patients. Results from the DEVENIR study

M. Guenoun[1], P. Assyag[2], C. Contre[3], I. Leurs[3], P. Poncelet[4], P.L. Prost[5], J.F. Thebaut[6], A. Cohen-Solal[7]. *[1]Private Cardiologist, Plan De Cuques, France; [2]AP-HP - Hopital St Antoine, Paris, France; [3]MENARINI, Rungis, France; [4]Polyclinic, Henin Beaumont, France; [5]Dicovery Cascade, Paris, France; [6]Private Cardiologist, Sarcelles, France; [7]Lariboisiere Hospital (AP-HP), Paris, France*

Rationale: Due to the growing part of the elderly pts in the french population, Heart Failure is now frequently encountered in pts more than 80-year-old. Furthermore, (HF) could be classified in 3 groups according to LVEF (LVEF 40-50% known as "grey zone"). Mechanisms, baseline characteristics, prognosis and treatment recommendations are different between these groups.
Objectives: to describe the proportion of pts more than 80-year-old in the population of pts treated for HF by outhospital cardiologists in France.
Methods: Cross sectional observational survey with retrospective collection of data at hospital discharge. Pts must have been diagnosed with HF and have been hospitalised for HF within the previous 18 months. Pts are classified according to the LVEF at hospital discharge.
Results: 412 French outhospital cardiologists entered 1 452 patients meeting the inclusion criteria. FEVG at hospital discharge was known for 1408 pts. 355 (25%) were more than 80-year-old.

Characteristics according to age

	>80 years old	≤80 years old	p
LVEF <40%	165 (47%)	627 (60%)	
LVEF 40-50%	94 (27%)	270 (26%)	<0.0001
LVEF >50%	96 (27%)	156 (15%)	
Men	176 (50%)	762 (72%)	<0.0001
Ischemic etiology	195 (55%)	532 (51%)	0.15
Hypertensive etiology	163 (46%)	419 (40%)	0.04
Valvular etiology	81 (23%)	138 (13%)	<0.0001
Dilated cardiomyopathy	78 (22%)	384 (36%)	<0.0001
COPD/asthma	54 (12%)	204 (19%)	0.08
Renal dysfunction	165 (46%)	322 (31%)	<0.0001
Diabetes	82 (23%)	356 (34%)	0.0002
Cognitivetroubles/Dementia	37 (10%)	33 (3%)	<0.0001
Anaemia	43 (12%)	76 (7%)	<0.004

$p = \chi^2$.

Conclusion: 25% of the French HF patients are more than 80 years old. HF with preserved LVEF is more frequent in elderly patients than in younger patients. However LVEF is less than 40% in 47% of elderly patients and comorbidities are more frequent in this group.

P1719 Prevalence of heart failure in the community: preliminary results of an epidemiological survey in the elderly population in Italy. The PREDICTOR Study

G.F. Mureddu[1], V. Rizzello[1], N. Agabiti[2], G. Cacciatore[1], G. Cesaroni[2], F. Forastiere[2], R. Latini[3], S. Masson[3], C.A. Perucci[2], A. Boccanelli[1] on behalf of PREDICTOR Study Group. *[1]San Giovanni-Addolorata Hospital, Rome, Italy; [2]Department of Epidemiolgy ASL RM/E, Rome, Italy; [3]The Mario Negri Institute for Pharmacological Research, Milan, Italy*

Purpose: To evaluate the prevalence of heart failure (HF) in the elderly community in Italy. Epidemiological data are needed to direct preventive interventions.
Methods: A representative random sample of 65-84 year old residents in the Lazio Region (five million inhabitants) were identified from regional population registries. A total of 2459 persons (out of 4500 eligible residents) were invited and 1033 entered the study. All subjects underwent physical examination, biochemistry/NT-proBNP determinations, 12-lead EKG, and color-Doppler echocardiography. Clinical diagnosis of HF was made according to the European Society of Cardiology criteria. Echocardiograms were centrally analysed by two blinded readers. Systolic left ventricular dysfunction (LVD) was defined as left ventricular ejection fraction (LVEF) < 50% or midwall fractional shortening (MFS) <15%. Diastolic LVD was defined by a Doppler-derived multiparametric algorithm.
Results: Among the 553 study participants enrolled so far (mean age: 73.4±5.1 years; 51% females), 21 (4.1%) showed LVEF<50%, 137 (31.7%) MFS <15%, and 176 (31.8%) had diastolic LVD. Prevalence of HF with depressed systolic function (LVEF<50%) was 2.7% (12/452; 1.3% NYHA III class) whereas HF with preserved LVEF was found in 21.2% of cases (96/452). Overall, 10.6% subjects had depressed MFS and 9.3% diastolic LVD (7.5% mild and 2.8% moderate to severe). Among the 96 subjects with clinical HF but with normal LVEF, 37 (38.5%) showed isolated diastolic LVD (33.3% mild and 5.2% moderate-to-severe). NT-pro BNP was significantly higher in subjects with LVEF <50% (median: 443 pg/ml; range 210-1307) compared to LVEF ≥50% (median: 114 pg/ml; range: 60-207; p<0.0001) and in subjects with HF with reduced LVEF (median: 1307 pg/ml; range: 96-6702 pg/ml) as compared to those with HF and preserved LVEF (median: 320 pg/ml; range: 43-700 pg/ml, p<0.001). Among subjects with HF, subjects with NYHA class III showed higher NT-pro BNP values (median: 1233 pg/ml; range: 935-1622) as compared to subjects with NYHA class I (median: 85 pg/dl; range: 49-192; p<0.0001). ROC curve analysis showed that the cut-off value of 186,5 pg/ml for NT-proBNP had the highest sensitivity/specificity ratio to detect LV dysfunction (sensitivity 86%, specificity 72%, AUC: 0.87, negative predictive value 99%, positive predictive value 12%).
Conclusions: In the community, HF is frequently present in elderly individuals with and without overt systolic dysfunction. These preliminary results underline the importance of diagnostic testing in elderly individuals at risk of HF at population level.

P1720 Characteristics of male and female patients at the time of first data entry into the canadian heart failure network longitudinal database 1999 to 2008

M. Arnold[1], A. Ignaszewski[2], H. Haddad[3], J. Howlett[4], M.-H. Leblanc[5], P. Staples[6], E. Azevedo[7], R. Gutierrez[8], S. Roth[9], G. Marchiori[1] on behalf of Canadian Heart Failure Network. *[1]University Hospital, London, Canada; [2]St. Paul's Hospital, Vancouver, Canada; [3]Ottawa Heart Institute, Ottawa, Canada; [4]QE II Hospital, Halifax, Canada; [5]Institut de Cardiologie de Quebec, Quebec City, Canada; [6]Hotel Dieu Hospital, Kingston, Canada; [7]Mount Sinai Hospital, Toronto, Canada; [8]Royal Alexandra Hospital, Edmonton, Canada; [9]Scarborough General Hospital, Scarborough, Canada*

Purpose: The Canadian Heart Failure Network provides a longitudinal electronic database for specialized heart failure clinics across Canada to record patient demographics and disease variables to allow analysis of referral practice patterns and outcomes. Centers enter data that are helpful to them for patient management, clinical letters, and trend analyses. The purpose of this analysis was to compare patient characteristics of male and female heart failure patients at the time of first national database entry.
Methods: A retrospective analysis of the Canadian Network database was performed using standard statistical techniques and data are described as population means or percentages.
Results: From January 1999 to December 2008, data on 16,199 patients have been entered into this national database. At first database entry, 68.9% of patients were male and 31.1% were female. The mean age of the population was 67.3±14.5 (sd) yrs [66.6±13.9 (sd) yrs in males and 68.9±15.4 yrs in females (P<0.001)]. An ischemic etiology was attributed in 59.1% of males vs 42.5% of females (P<0.001). Males were less likely to be NYHA class III (P<0.001) and more likely to be NYHA class I/II (P<0.001) compared to females. There was no difference for NYHA class IV. Dyspnea, as the principal limiting symptom, occurred in 54.8% in males vs 58.3% of females (P=0.008). The following comorbidities were documented (males vs females): systemic hypertension 37.2 vs 40.3% (P<0.001); dyslipidemia 35.3 vs 27.6% (P<0.001); current smoker 12.5 vs 9.0% (P<0.001); valve disease 12.0 vs 15.2% (P<0.001); cerebrovascular disease 13.6 vs 12.6% (P=NS); renal dysfunction 16.6 vs 13.3% (P<0.001); atrial fibrillation 23.8 vs 21.7% (P<0.004); COPD 11.6 vs 11.2% (P=NS); arthritis 10.9 vs 18.4% (P<0.001); cancer 6.5 vs 10.6% (P<0.001).
Conclusions: While males are predominantly referred to these outpatient clinics across Canada, the differences in presentation at entry and prevalence of comorbidities should reinforce the need for clinic management algorithms and patient educational materials to reflect the differences between male and female heart failure patients.

P1721 Analysis of a population with MADIT II-like criteria in a multidisciplinary Heart Failure Unit

R. Villuendas, C. Pajuelo, C. Bosch, F. Pons, J. Perez-Rodon, X. Carrillo, B. Gonzalez, A. Urrutia, J. Lupon, V. Valle. *Hospital Universitario Germans Trias I Pujol, Badalona, Spain*

Introduction: The MADIT (Multicenter Automatic Defibrillator Implantation Trial)-II study demonstrated the benefits of the implantable cardioverter-defibrillator

(ICD) in decreasing mortality of patients with previous myocardial infarction (MI) and left ventricular ejection fraction (LVEF) ≤ 30%. This type of patients may represent an important proportion of the overall patients treated in a heart failure (HF) Unit.

Objectives: To assess the prevalence, clinical characteristics, outcome, and causes of death of patients that satisfied MADIT II-like criteria for prophylactic ICD implantation in a multidisciplinary HF Unit.

Results: From August 2001 to December 2008, 960 patients were admitted to our HF Unit. A total of 240 (25%) had history of previous MI and LVEF ≤ 30% at the admission. The patient characteristics of this group were: 80.5% men, mean age 67±10.7 (32-88 year-old), median LVEF 24% (8-30%). They were mainly in functional class II-III (I: 3.8%, II 57.9%, III 35.8% and IV 2.5%). Fifty-seven percent had renal insufficiency (creatinine clearance < 60 ml/min), 48.3% were diabetic, 56.3% had hypertension, 36.8% had anemia (Hb < 12 mg/dl), 22.1% suffered from peripheral vasculopathy and 20% from chronic pulmonary obstructive disease. Twenty-six patients (10.8%) were in atrial fibrillation; the median QRS duration was 120 msec (60-210) with 34.2% having a QRS > 120 msec. Twenty-two patients had an ICD already implanted at the first visit (9.2%). Median follow-up was of 35.3 months (range 0-91), during which 15 new ICD were implanted (6.2%). At the end of follow-up, mortality rate was 41.6% (100 P). The causes of death were: 34% HF, 18% sudden death, 7% acute MI, 6% dead from other cardiovascular causes, 16% from non-cardiovascular and 19% dead from an unknown cause.

Conclusions: The fourth part of all patients attended in our HF Unit fulfilled the main inclusion criteria of MADIT II study, which represents a substantial amount of patients. Although ICD implantation rate was low in this group of patients, 82% of mortality was not due to sudden death.

P1722 U-shaped relationship between left ventricular ejection duration and mortality in patients undergoing coronary angiography

T. Weber, M. Ammer, M. Rammer, E. Lassnig, B. Eber. *Klinikum Wels-Grieskirchen, Wels, Austria*

Purpose: We previously found a shortening of mechanical systole in impaired systolic function and a prolongation of mechanical systole in diastolic dysfunction. Whether this implies a worse prognosis is not known.

Methods: We prospectively measured left ventricular ejection duration from the radial waveform, using high-fidelity applanation tonometry (SphygmoCor, AtCor medical), in 845 patients undergoing coronary angiography for suspected coronary artery disease (CAD). Exclusion criteria were atrial fibrillation and valvular heart disease. Left ventricular ejection time was normalized for heart rate, according to Weissler (LVETI). Statistics were log-rank test and Cox proportional hazards models.

Results: Mean age was 64.7 (SD 10.7) years, 60.8% were male. 70.2% had coronary artery disease (CAD), 28.6% impaired systolic function, and 35.3% heart failure. Mean LVETI by tertile (T) was 375 (SD 13) (T1), 401 (SD 5) (T2), and 427 (SD 13) (T3) msec. There was a positive relationship between LVETI and systolic/mean/diastolic blood pressure/pulse pressure across all tertiles of LVETI, and there were more patients with impaired systolic function in T1, as compared to T2 and T3. In contrast, other baselines characteristics and presence and extent of CAD did not differ between tertiles. After a follow-up of 49.7 (SD 12.4) months, 95 patients died (50 of cardiovascular causes). The incidence of all-cause mortality demonstrated a U-shaped relationship to LVETI (HR T1 1.74; 95% CI 1.05-2.88; p=0.03); T2 reference; HR T3 1.76; 95% CI 1.03-2.99; p=0.04). Likewise, the incidence of cardiovascular mortality demonstrated a U-shaped relationship to LVETI (HR T1 2.72; 95% CI 1.33-5.56; p=0.006); T2 reference; HR T3 2.78; 95% CI 1.31-5.93;p=0.008). After adjustment for age, gender, extent of CAD, mean blood pressure,systolic function, presence of heart failure, nt-proBNP, and heart rate, the adjusted RR for T3 for all cause mortality was 2.0; 95% CI 1.12 – 3.57; p=0.02),as compared with T2. In contrast, the adjusted RR for T1 for all cause mortality was 1.27; 95% CI 0.95 – 1.69; p=0.11), as compared to T2. The U-shaped relationship between LVETI tertiles and cardiovascular mortality remained significant after multivariable adjustments.

Conclusion: A shortening of LVETI is associated with increased all cause and cardiovascular mortality. This can be attributed partially to the inverse relationship between LVETI and systolic function. A prolongation of LVETI is associated with increased all cause and cardiovascular mortality as well. This is accompanied by, but independent of higher blood pressures.

CARDIOVASCULAR PHARMACOLOGY

P1723 Both levosimendan and dobutamine are equally effective in improving LV systolic functions in heart failure patients receiving beta blocker therapy: a radionuclide ventriculographic study

Y. Cavusoglu, A. Beyaztas, E. Entok, M. Tek, I. Uslu, C. Demirustu, A. Birdane, A. Unalir, B. Gorenek, N. Ata. *Eskisehir Osmangazi University, Eskisehir, Turkey*

Purpose: Levosimendan (LEVO) has been reported to have better hemodynamic effects on the increase in cardiac output and the decrease in pulmonary capillary wedge pressure in patients receiving beta blockers as compared to dobutamine (DOB). However, it is not clear whether hemodynamic advantages of LEVO over DOB are result from its better inotropic effect or vasodilatory action. Also, beta blockade is thought to attenuate the effects of DOB. Therefore, we tested the effects of LEVO and DOB on left ventricular (LV) systolic functions in heart failure patients under beta blocker therapy by means of radionuclide ventriculography (RNV).

Methods: The study population consisted of 42 advanced heart failure patients with LV ejection fraction (EF) <0.35 who were on beta blocker therapy. All patients underwent RNV and LV EF, peak ejection rate (PER) and time to peak ejection rate (TPER) were used to measure for LV systolic functions. Cardiac blood pool images were accomplished at rest (basal-1) and at the end of the administration of DOB infusion (10 microg/kg/min) for 15 min. Subsequently, DOB was discontinued for 15 min and RNV measurements were repeated before the initiation of LEVO infusion (basal-2). A bolus dose of LEVO (24 microg/kg) was administered over 10 min followed by a constant infusion of 0.2 microg/kg/min for 30 min. and RNV was repeated.

Results: Basal LV EF, PER and TPER before LEVO infusion were similar to those before DOB infusion. LV systolic (LV EF, PER, TPER) indexes have been found to be significantly improved with both LEVO and DOB administrations as compared with their basal values (table). However, no significant difference was observed in LV EF, PER and TPER between DOB and LEVO administrations.

Radionuclide ventriculography

	Basal-1	DOB	p	Basal-2	LEVO	p
LVEF, %	30.11±1.5	33.29±1.7	0.001	30.62±1.5	32.98±1.5	0.004
PER, edc/msc	1.59±0.07	1.99±0.09	0.001	1.69±0.07	1.87±0.08	0.015
TPER, ms	169±7.23	139±5.25	0.001	153±4.26	127±4.74	0.001

No significant difference between Basal-1 and Basal-2, and also between DOB and LEVO data. LVEF: left ventricular ejection fraction, PER: peak ejection rate, TPER: time to peak ejection rate.

Conclusions: In contrast to previous results, this study suggest that both LEVO and DOB are almost equally effective in improving LV systolic functions in heart failure patients receiving beta blocker therapy.

P1724 Hypertension-related hypoalgesia: a retrospective cohort study in a hypertensive population under pharmacologic treatment

E. Koch[1], T. Romero[2], D. Sandoval[1], C. Romero[1], M. Bravo[1], I. Segovia[1], O. Henriquez[1], L. Urrutia[1]. *[1]Department of Family Medicine, Faculty of Medicine, University of Chile, Santiago, Chile; [2]Sharp Health Care, San Diego, United States of America*

Background: An inverse relationship between pain sensitivity and arterial hypertension has been previously reported and described as hypertension-related hypoalgesia. However, it is unclear whether this relationship persists in hypertensive populations under anti-hypertensive treatment.

Methods: 1194 patients were randomized from a population of 392,000 hypertensive individuals in 133 primary care clinics and 52 districts in the city of Santiago, Chile. Using a retrospective cohort design their medical records were reviewed through a period of 12 consecutive months. Episodes of muscle-skeletal pain lasting ≥1 month were identified in this fashion. Systolic blood pressure (SBP) was evaluated during routine check-ups for BP control. Odds ratio with 95% confidence intervals were calculated, utilizing the lowest SBP level as the reference and controlling for confounders in logistic regression models.

Results: The prevalence of muscle-skeletal pain episodes in a 12-month period was 32.5%, higher in women than men (35.3% vs 26.2%, p<0.01). A graded inverse association between SBP and risk of muscle-skeletal pain lasting ≥1 month was observed which persisted after adjustment for confounders including anti-hypertensive, analgesic and anti-inflammatory treatments and diabetes (Table). The highest SBP group had a 34% lower risk of muscle-skeletal pain compared with the lowest group.

Table 1

Systolic BP (mmHg)	Odds Ratio (95% Confidence Interval)		
	Crude risk	Age- and sex adjusted	Full model†
<130 (reference)	1,00	1,00	1,00
130–160	0,99 (0,97-1,01)	0,92 (0,90-94)	0,88 (0,87-0,90)
>160	0,84 (0,82-0,87)	0,72 (0,70-0,74)	0,66 (0,64-0,68)

†Model adjusted for age, sex, BMI, physical activity level, smoking, alcohol consumption, diabetes status, psychological health, education and analgesic, anti-inflamatory and anti-hypertensive treatment.

Conclusion: Our results corroborate the hypothesis that SBP is inversely related to pain sensitivity. The inverse relationship persists after adjusting for confounders and anthipertensive treatment, suggesting a neurobiological mechanism common to both pain and blood pressure regulatory systems. The clinical implications of a plausible higher threshold to pain in hypertensive patients need further research and definition.

P1725 Experimental orthostasis elicits hypertension which can be prevented by antihypertensive drugs

- Cseko[1], - Raffai[2], - Monos[2]. [1]*Department of General Pharmacology, Gedeon Richter Plc, Budapest, Hungary;* [2]*Institute of Human Physiology and Clin. Exp. Research, Semmelweis University, Budapest, Hungary*

Orthostatic hypertension (OHT) develops in about 5% of population in response to orthostatic stress, but it is more prevalent in borderline hypertension and autonomic neuropathies. We have recently shown that sustained orthostasis elicits hypertensive response in conscious rat at least for 2 hours via sympathetic activation. The aim of this study was to investigate the effect of two, differently acting antihypertensive drugs and their combination on OHT in our rat model.

Normotensive freely moving conscious rats were used and the effects of orally administered antihypertensive drugs (added 2 hours before tilting) on cardiovascular responses to 45° head-up tilt (HUT) for 2 hours were investigated: 1) the Ca^{2+}-antagonist amlodipine (5 mg/kg), 2) the ACE inhibitor lisinopril (10 mg/kg) and 3) their combination. Arterial blood pressure (BP) and heart rate (HR) were monitored continuously by telemetry, while their spectral properties {low (LF) and high (HF) frequency components of HR} and spontaneous baroreflex sensitivity (sBRS) were computed.

The changes elicited by HUT were compared to the last point measured in the horizontal position. The OHT (+10.1±2.1 mmHg) elicited by HUT was slightly decreased by amlodipine (+5.35±0.7 mmHg) and lisinopril (+5.15±1.3 mmHg), while their combination synergistically decreased OHT (+0.29±2.5 mmHg). HUT induced tachycardia (+65±14 BPM) wasn't further increased by amlodipine and lisinopril, or by their combination (+45±9.3; +56±12; +53±11 BPM respectively). Amlodipine slightly while lisinopril and the combination significantly reduced LF and LF/HF ratio. Amlodipine decreased sBRS (from 0.8 ms/mmHg to 0.35 ms/mmHg), while lisinopril and co-administration enhanced it (from 0.8 ms/mmHg to 0.92 and 0.89 ms/mmHg respectively).

In conclusion, both antihypertensive drugs decrease experimental OHT, while their combination has positive synergistic effect in blood pressure lowering. Amlodipine slightly, while lisinopril and the combination significantly reduce sympathetic tone. Amlodipine suppresses, while lisinopril and the combination enhance sBRS. In OHT patients the combination of Ca^{2+}-antagonist amlodipine and ACE inhibitor lisinopril can be useful through the synergistic blood pressure lowering effect and the beneficial influence on sympathetic tone and sBRS.

P1726 Efficacy of combination therapy using nebivolol and trimetazidine in patients with isolated systolic hypertension and stable effort angina

S. Vatinian, S. Gurgenyan, K. Nikoghosyan on behalf of Institute of Cardiology. *Institute of Cardiology, Yerevan, Armenia*

Background: Arterial hypertension and stable, effort-induced angina contribute synergistically to high cardiovascular risk. The aim of this study was to evaluate the efficacy of beta-blocker nebivolol alone or in combination with metabolic agent trimetazidine in patients with isolated systolic hypertension (ISH) and stable effort angina (SEA).

Methods: Sixty six patients with mild to moderate ISH, SEA and documented coronary artery disease (CAD), aged 57–65 years, were randomly assigned to nebivolol 5 mg daily (group A - 33 patients) and nebivolol 5 mg daily with trimetazidine MR 35 mg twice daily (group B - 33 patients). Echocardiography and treadmill exercise tests were performed at baseline and after 6 months of therapy. The parameters of left ventricular (LV) hypertrophy were evaluated.Differences in the efficacy parameters were analysed using 2-tailed Student's t test for quantitative parameters.

Results: At the end of the study systolic blood pressure was lowered in both groups to less than 140 mm Hg.LV mass index reduced from 156,1±6,8 to 124,5±3,1 g/m^2 with nebivolol and from 157,5±6,3 to 123,8±3,4 g/m^2 with nebivolol and trimetazidine MR in combination ($p<0,05$ for both groups). The decrease in LV mass was essentially caused by a reduction of ventricular wall thickness and diameter. At baseline there were no significant differences between the groups with respect to exercise test duration, total workload, time to 1 mm ST segment depression, time to onset of angina, maximum ST segment depression, grade of anginal pain, anginal attacks per week. At the end of the study time to 1 mm ST segment depression compared to baseline increased by 10,9% in group A ($p<0,01$) and by 20,8% in group B ($p<0,001$). Time to onset of angina increased by 11,3% in group A ($p<0,01$) and by 19,1% in group B ($p<0,001$). Maximum ST segment depression compared to baseline passed by 5,8% in group A ($p<0,01$) and by 14,7% in group B ($p<0,001$). Mean number of anginal attacks per week decreased by 21,8% in group A ($p<0,01$) and by 36,5% in group B ($p<0,001$). There was no significant difference between two groups for grade of anginal pain.

Conclusions: Therapy with beta-blocker induced qualitative antihypertensive effect and qualitative effect on the parameters of LV hypertrophy in patients with ISH and CAD. Combination treatment using beta-blocker and metabolic agent produced significant improvements in exercise stress tests and reduced clinical symptoms compared to beta-blocker alone.

P1727 Increased thromboxane production in preeclampsia, influence of aspirin treatment

C. Perneby[1], K.B. Bremme Katarina[2], M.V. Marie Vahter[3], M.D. Maud Daleskog[1], P.H. Paul Hjemdahl[1] on behalf of PaulHjemdahl. [1]*Inst of Medicin Clinical Pharmacology Unit Karolinska Institute, Stockholm, Sweden;* [2]*Dept of Womens Health Karolinska Institute, Stockholm, Sweden;* [3]*Institute Environmental Institute Karolinska Institute, Stockholm, Sweden*

Introduction: Preeclampsia occurs in 2-8% of all pregnancies, and is one of the most common causes of mortality and morbidity in mothers and children. There is some evidence that platelets are involved in preeclampsia. Aspirin (ASA) selectively inhibits the production of thromboxane from platelets at low dosages (<160 mg daily). We thus investigated the thromboxane production in patients at high risk for suffering preeclampsia and healthy women, as well as effects of ASA treatment during pregnancy.

Material and methods: 28 women at high risk for having preeclampsia and 22 healthy pregnant women without any pregnancy complications, and without ASA treatment were included in the study. ASA (Trombyl®, Pfizer; 75 mg/day) treatment of patients with a high risk of suffering preeclampsia commenced between gestational week 6-14 and stopped 2 weeks before delivery. Urine samples were collected before ASA treatment, after two weeks of ASA treatment, in pregnancy week 28-32 and 3-9 days post partum. Urinary 11-dehydro-TxB2 (TxM) was determined by enzyme immunoassay (Cayman Chemicals, Ann Arbor, MI, USA).

Results: Urinary TxM excretion increased with the duration of normal pregnancy. The highest levels were seen 3-9 days post-partum, 250±30 ng/mmol creatinine compared to 90±12 ng/mmol creatinine before gestational week 13 ($p<0.0001$). The urinary excretion of TxM was significantly higher in patients at high risk for developing preeclampsia compared to the control group 129.±12 vs 90.±12. ng/mmol creatinine ($p<0.05$) at gestational week 13. After 2 weeks of ASA treatment U-TxM had decreased by 79±2% ($p<0.001$) to 23.7±1.8 ng/mmol creatinine in the high risk group. Five of the 28 high risk patients developed preeclampsia. These patients had a higher excretion of TxM before pregnancy week 13 than patients without complications (191±32 vs 118±11 ng/mmol creatinine; $p<0.05$).

Conclusions: TxM excretion increases during normal pregnancy, with the highest levels 3-7 days postpartum. Patients at high risk for having preeclampsia have increased TxM excretion before gestational week 13 compared to normal pregnancy. Low-dose aspirin effectively inhibits thromboxane production during pregnancy, also among patients developing preeclampsia.

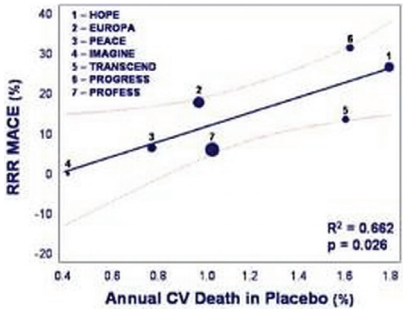
P1728 The benefit of RAS inhibition in vascular disease without heart failure is strongly correlated to the cardiovascular risk

P.J. Sousa, J. Ferreira, C.T. Aguiar, J.A. Silva. *Hospital de Santa Cruz - CHLO, Lisbon, Portugal*

Purpose: In patients with vascular disease and no evidence of heart failure (HF) the benefit of renin-angiotensin system (RAS) inhibitors in the reduction of major adverse cardiovascular events (MACE) is challenged by some clinical trials. We evaluated the relation between the reduction of MACE and the annual rate of cardiovascular (CV) death in the placebo treated patients, as a measure of the population's CV risk, in trials comparing RAS inhibitors and placebo in patients with vascular disease and no HF.

Methods: Using data from seven randomized trials (64,721 patients) identified by systematic search of electronic databases, we extracted reported data on CV death and MACE (combined incidence of CV death or myocardial infarction or stroke). Linear regression analysis was applied to assess the relation between the relative risk reduction (RRR) of MACE observed with RAS inhibition versus placebo and the annual rate of CV death observed in the placebo treated patients.

Results: There was a direct strong linear correlation between the RRR of MACE induced by RAS inhibitors and the placebo's annual rate of CV death (R2=0.662; p=0.026)



Conclusions: In trials comparing RAS inhibitors and placebo in patients with vascular disease and no evidence of heart failure, the reduction of MACE induced by RAS inhibitors was significantly correlated to the annual rate of CV death in the placebo treated patients.

P1729 Five years two center retrospective analysis of patients with digoxin toxicity

R. Kockova[1], J. Skvaril[1], M. Cernohous[1], M. Zavoral[1], V. Kocka[2], T. Palecek[3], A. Praveckova[3], A. Linhart[3]. *[1]Central Military Hospital and Charles University, Prague, [2]Královské Vinohrady University Hospital and Charles University, Prague, [3]General Teaching Hospital, Second Department of Internal Medicine and Charles University, Prague, Czech Republic*

Aims: Digoxin is a therapeutic agent known over 200 years with narrow therapeutic window. Digoxin indications have narrowed during last decade but its use is still common in modern cardiology especially for patients with heart failure and atrial fibrilation. The aim of our analysis was to characterize patient population with toxic serum digoxin level with special interest in the role of drug interactions.
Methods and results: Databases of two large teaching hospitals in Prague, CZ were retrospectively reviewed from 2001 till 2006. There were 116.276 patients admitted and 222 (0.2%) patients with serum digoxin level ≥3.0 ng/ml were identified. Medical records were analyzed in detail by qualified cardiologist (including creatinin clearance, dose of digoxin, route of administration, concomitant medication, ECG review, therapy, survival till hospital discharge). The average age of patients was 78 years, 41% were male and 59% were female. 27% of patients had normal blood level of creatinine but only 14% had creatinine clearance ≥60ml/min. 50% of patients were prescribed at least one medication with known pharmacokinetic interaction with digoxin, most common interaction being with amiodarone in 23% of patients. Average daily dose of digoxin was 0.195mg. Admission ECG demonstrated bradycardia in 16%, tachycardia in 11%, typical ST segment scooping was present in 29%. 4% of patients required temporary pacing, only 1 patient was treated with Digoxin-specific Fab antibody fragments. Hospital mortality was 8%. Statistically significant predictors of mortality were low creatinine clearance (p=0.01), i.v. administration of digoxine (p=0.02), concomitant use of ACEI/ARB was protective (p=0.01). There was borderline association between mortality and low ejection fraction of left ventricle (P=0.07) and with low body weight (P=0.08). Digoxin dose, serum digoxin level, potassium level or age did not have any influence on mortality.
Conclusion: Digoxin toxicity is rare in current medicine. Typical patient with digoxin toxicity is elderly woman with renal impairment and polypragmasia. The most common medication with known interaction is amiodarone. Hospital mortality is high at 8%. Markers of poor prognosis are low creatinine clearance, i.v. administration of digoxine and possibly low ejection fraction of left ventricle and low body weight. Interestingly treatment with ACEI and/or ARBs appears to have a protective effect.

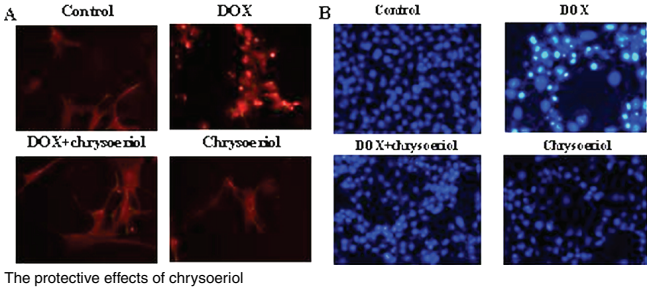
P1730 Protective effects of chrysoeriol against doxorubicin-induced cardiotoxicity in vitro

Z. Liu, X.D. Song, Y. Xin, X.J. Wang, H. Yu, Y.Y. Bai, J.H. Liu, C.N. Zhang, R.T. Hui. *Fuwai Hospital and Cardiovascular Institute, Beijing, China, People's Republic of*

Purpose: The aim of this study was to evaluate the protective effects of chrysoeriol, a flavone compound, against doxorubicin (DOX)-induced apoptosis and death in H9c2 cells and find out its preliminary mechanism. Methods We used 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl-2H-tetrazolium bromide (MTT) assay, Hoechst33258 staining and measurement of lactate dehydrogenase (LDH) release to evaluate the protective effects of chrysoeriol against DOX-induced apoptosis and death in H9c2 cells. To find out the mechanism of this protective effects, the immunofluorescence of intracellular ROS was observed and the activities of malondialdehyde (MDA), superoxide dismutase (SOD) and Glutathione Peroxidase (GPx) were measured.
Results: Chrysoeriol significantly reduced doxorubicin-induced apoptosis and cell death. Chrysoeriol at a dose of 20 μg/ml notably reduced intracellular ROS, decreased the concentration of MDA and raised SOD and GPx activities to their normal levels. Furthermore, the addition of chrysoeriol did not affect the antitumor activity of DOX.

The protective effects of chrysoeriol

	LDH (U/mL)	MDA (U/mL)	SOD (U/mL)	GSH-Px (mU/mL)
Control	644.2	0.35	20.46	0.76
DOX	1181.4	0.87	12.04	0.35
DOX+Chrysoeriol	791.7	0.51	18.26	0.66
Chrysoeriol	606.7	0.26	21.02	0.79



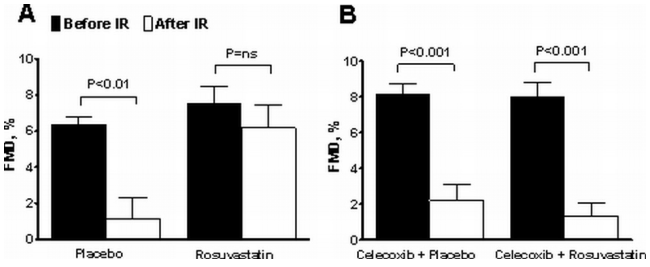
The protective effects of chrysoeriol

Conclusion: Chrysoeriol could potentially serve as a novel cardioprotective agent against DOX-induced cardiotoxicity without affecting the antitumor activity of DOX.

P1731 Single-dose rosuvastatin prevents endothelial dysfunction induced by ischemia and reperfusion via a COX-2 dependent mechanism, an effect that is independent of lipid lowering: a human in vivo study

A. Liuni[1], M. Luca[1], T. Gori[2], J.D. Parker[1]. *[1]Mount Sinai Hospital/University Health Network, Toronto, Canada; [2]Medizinische Klinik, University of Mainz, Mainz, Germany*

Purpose: Animal studies have demonstrated that rosuvastatin (RSV) can limit myocardial and vascular damage induced by ischemia-reperfusion (IR), an effect that may be mediated by the lipid-independent activation of cyclooxygenase-2 (COX-2). It is unknown whether RSV can also prevent the impairment in endothelium-dependent vasodilation induced by IR via a similar mechanism in humans.
Methods and Results: In a double-blinded, parallel design, 20 healthy volunteers were randomized to oral RSV (40 mg) or placebo. 24 hours later, endothelium-dependent, flow-mediated dilation (FMD) of the radial artery was measured before and after IR (15 minutes of upper-arm ischemia followed by 15 minutes of reperfusion). Pre-IR FMD was similar between groups (P=NS). IR did not modify baseline or peak hyperemic blood flow during FMD (P=NS). After placebo administration, IR significantly blunted FMD (pre-IR: 6.4±0.4%; post-IR: 1.1±1.2%, P=0.002). RSV prevented this impairment (pre-IR: 7.5±1.0%; post-IR: 6.2±1.2%, P=NS; P<0.01 compared with placebo; figure, A). In a separate protocol, pretreatment with celecoxib (COX-2 inhibitor, 200mg BID/5 days) completely abolished RSV's protective effect (pre-IR: 8.0±2.2%; post-IR: 1.4±2.0%, P<0.001; P=NS compared with placebo; figure, B). There were no differences in baseline lipid levels between groups nor was there a lipid-lowering effect of RSV over the 24-hour period in either protocol.



Conclusions: The present findings demonstrate, for the first time in humans, the ability of RSV to pharmacologically prevent the development of IR-induced endothelial dysfunction via a COX-2 dependent mechanism, independent of lipid lowering. These data provide a mechanistic background to the evidence that statin therapy reduces myocardial injury in the setting of primary angioplasty.

P1732 TNF-alpha antagonists improve arterial stiffness in patients with inflammatory arthropathies: Results from a controlled study

K. Angel[1], S.A. Provan[2], T.K. Kvien[2], D. Atar[1]. *[1]Oslo University Hospital, Oslo, Norway; [2]Diakonhjemmet Hospital, Oslo, Norway*

Purpose: The chronic inflammatory state of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) contributes to the accelerated atherosclerosis associated with these diseases. The aim of this comparative study was to evaluate the effect of one year treatment with Tumor Necrosis Factor (TNF)-α antagonists on arterial stiffness in patients with RA, AS and PsA.
Methods: 36 patients (RA=15, AS=14 and PsA=7) who started with anti-TNF-α therapy (adalimumab=11, etanercept=16, infliximab=9) and a non-treatment group of 16 patients (RA=9, AS=5 and PsA=2) underwent measurements of aortic Pulse Wave Velocity (aPWV) and Augmentation Index (AIx) at baseline and after one year (Sphygmocor). Patients in the non-treatment group had the same indications for anti-TNF-α therapy, but had to postpone their initiation due to positive Mantoux-test or planned operations.

Baseline and change in key variables

	Baseline			Change		
	Anti-TNF (n=36)	Control (n=16)	p-value	Anti-TNF (n=36)	Control (n=16)	p-value
PWV m/s	7.5	7.3	0.64	-0.53	0.08	0.001
AIx %	20.5	23.0	0.41	0.1	0.2	0.95
CRP mg/l	12.5	10.9	0.73	-8.63	0.88	0.001
DAS28*	3.92	4.20	0.47	-1.10	-0.20	0.02
MAP** mmHg	98.5	95.9	0.78	-3.2	-2.7	0.85
HR b/min	64	65	0.93	-0.3	1.4	0.45

*RA patients only, **Mean Arterial Pressure.

Results: Mean (SD) age in the treatment/control group was 46.2 (12.2)/49.0 (14.1) years, 42.9/50.0% (p=0.63) were females and disease duration was 11.0 (9.6)/11.6 (10.1) years. Patients who started anti-TNF-α therapy had a significant decrease in aPWV whereas the patients in the control group had no change. AIx did not change in any of the groups. CRP and Disease Activity Score 28 joints (DAS28) were significantly reduced in the treatment group but did not change in the control group.
Conclusion: The present study shows for the first time in a comparative design that long term anti-TNF-α therapy improves aPWV in patients with RA, AS and PsA. These findings lend support to the idea that the atherosclerotic process is amenable to pharmacologic intervention.

P1733 Lipid-altering efficacy and tolerability of ER niacin/laropiprant in type 2 diabetes mellitus patients

A. Maclean[1], J. Mckenney[2], R. Scott[3], E. Brinton[4], H. Bays[5], H. Giezek[1], R. Ruck[1], K. Gibson[1], C. Mccrary Sisk[1], D. Maccubbin[1]. *[1]Merck Research Laboratories, Rahway, United States of America; [2]National Clinic Research, Richmond, United States of America; [3]Christchurch School of Medicine, Canterbury, New Zealand; [4]University of Utah School of Medicine, Salt Lake City, United States of America; [5]L-Marc, Louisville, United States of America*

Niacin is underutilized, mainly due to flushing, a process mediated by PGD2. The PGD2 receptor (DP1) antagonist, laropiprant (LRPT), reduces flushing with extended release niacin (ERN). We evaluated the lipid-altering efficacy and tolerability (specifically, effects on glycemic control) of ERN/LRPT (a tablet containing 1g ERN and 20mg LRPT) vs placebo (PBO) in patients with type 2 diabetes mellitus (DM-2). In this multicenter, double-blind, PBO-controlled, 36-week study, DM-2 patients (n=796) were randomized 4:3 to ERN/LRPT or PBO. After 4 weeks at 1g/d, ERN/LRPT was doubled to 2g/d (2 tablets) for the remainder of the study. Lipid efficacy at week 12 and safety/tolerability at week 36 were evaluated. ERN/LRPT produced significant beneficial lipid/lipoprotein changes vs PBO ($p \leq 0.001$ for all; Table) and was generally well tolerated. AEs leading to discontinuation were higher in the ERN/LRPT group vs PBO (22.5% vs 9.4%), with the most common being pruritus (3.6% vs 0), flushing (2.0% vs 0.9%), diarrhea (1.8% vs 0.6%), rash (1.8% vs 0.3%) and vomiting (1.1% vs 0). There were no cases of myopathy or CK elevations ≥10xULN. The incidence of consecutive ≥3xULN ALT/AST elevations was 0.7% vs 0.3% (p=0.635). Consistent with known effects of niacin, mean increases in fasting plasma glucose and HbA1c were greater in the ERN/LRPT group vs PBO [9.7 vs 3.2 mg/dL; difference (95% CI): 6.6 (1.1, 12.0)] and [0.34 vs 0.16%; difference (95% CI): 0.18 (0.08, 0.28)], respectively.

LS mean % change (95% CI) to Week 12

Efficacy Parameter	ERN/LRPT (n=432)	PBO (n=336)	Difference vs. PBO
LDL-C	-15.8 (-18.4, -13.2)	2.1 (-0.3, 4.6)	-17.9 (-21.4, -14.4)
HDL-C	25.4 (23.4, 27.5)	2.2 (0.6, 3.8)	23.2 (20.7, 25.7)
TG, median	-22.2 (-25.5, -18.8)	2.3 (-1.6, 6.2)	-23.1 (-27.2,-18.9)
TC/HDL-C ratio	-21.9 (-23.8, -20.1)	1.0 (-0.8, 2.8)	-22.9 (-25.4, -20.4)
LDL-C/HDL-C ratio	-30.8 (-33.4, -28.2)	1.2 (-1.4, 3.7)	-32.0 (-35.5, -28.4)
Apo B	-14.5 (-16.3, -12.7)	2.6 (0.6, 4.6)	-17.1 (-19.7, -14.5)
Apo A-1	9.3 (8.0, 10.6)	1.1 (-0.4, 2.6)	8.2 (6.3, 10.2)

Significantly more patients required intensified anti-hyperglycemic therapy in the ERN/LRPT group vs PBO (17.6% vs 8.2%; $p \leq 0.001$). In DM-2 patients, ERN/LRPT produced significant, durable improvements in all major lipids/lipoproteins. ERN/LRPT was generally well-tolerated, with manageable glycemic effects in most patients.

P1734 Achievement of LDL target level with three different drug strategies after failure of simvastatin 40mg

P.J. Robinson[1], M.D. Blagden[2], R.A. Chipperfield[3], R.M.C. Gaunt[4], P.R. Harvey[5], T. McCormack[6], C. Mellon[1]. *[1]Merck Sharp & Dohme Ltd, Hoddesdon, United Kingdom; [2]Avondale Surgery, Chesterfield, United Kingdom; [3]Schering Plough Ltd, Welwyn Garden City, United Kingdom; [4]Rowden Surgery, Chippenham, United Kingdom; [5]Crouch Oak Practice, Addlestone, United Kingdom; [6]Spring Vale Medical Centre, Whitby, United Kingdom*

Purpose: N.I.C.E. guidelines recommend simvastatin (S) 40mg as first line lipid-lowering therapy, after lifestyle modification, in most patients with or at high risk of cardiovascular disease (CVD). When this is not sufficient, increasing the statin dose, switching to a more potent statin or adding a complementary therapy such as ezetimibe (E), can be considered. The addition of E to stable, ongoing S was compared with switching to atorvastain (A) or rosuvastatin (R) in this randomised, double-blind clinical trial.
Methods: Patients with CVD, diabetes or 10-yr CVD risk >20% were screened during a 6 wk run-in on S 40mg at 34 UK primary care sites. 786 patients with LDL-C ≥2mmol/l (but <4.2mmol/l) were randomised to E 10mg + S 40mg, A 40mg or R 5-10mg (according to UK label). Primary endpoint was % patients reaching LDL-C <2mmol/l after 6 wks.
Results: Mean age 64 yrs; M:F 2:1; diabetes (13%); CVD (52%). 28% qualified for R 5mg. Significantly more patients achieved LDL<2mmol/l with E+S than with A or R alone (table). E+S also reduced LDL-C, TC, non-HDL-C and ApoB/A1 significantly more than A and R. There was a small but significant reduction in HDL-C with E+S and A but no significant differences between treatments. E+S, A and R were generally well tolerated, with few discontinuations due to adverse events (2.7%, 1.9%, 3.4% respectively) or drug-related AEs (8.1%, 6.2%, 8.0% respectively).
Conclusion: Adding E 10mg to S 40mg significantly improved several lipid parameters and attainment of LDL-C <2mmol/l compared with switching to A 40mg or to R 5-10mg. The combination of cholesterol absorption inhibitor E 10mg + S 40mg offers an effective and well-tolerated means of achieving desired lipid levels.

P1735 Serial assessments of coronary remodeling from the approach trial (assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history)

H.M. Garcia-Garcia[1], P.W. Serruys[1], H.C. Gerstein[2], C.P. Cannon[3], G.A. Van Es[4], N.S. Kolatkar[5], B.G. Kravitz[5], D.M. Miller[5], C. Huang[5], R.W. Nesto[6]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]McMaster University, Hamilton, Canada; [3]Brigham and Women's Hospital, Boston, United States of America; [4]Cardialysis, Rotterdam, Netherlands; [5]GSK, Philadelphia, United States of America; [6]Lahey Clinic, Burlington, United States of America*

Background: Patients with type 2 diabetes (T2DM) have impaired vascular remodeling as demonstrated by intravascular ultrasound (IVUS). Thiazolidinediones, which improve insulin sensitivity and have effects on cardiovascular biomarkers, may reduce expansive remodelling thereby contributing to plaque stabilization.
Methods: Serial IVUS changes were assessed in 462 patients with T2DM randomized to rosiglitazone or glipizide for up to 18 months in the APPROACH trial. The relationship between change in atheroma volume and changes in vessel and lumen volumes was determined to characterize the pattern of coronary remodeling.
Results (see table p. 299): Glycemic control and use of background cardiovascular medications did not differ between groups. Treatment with rosiglitazone was associated with a significant reduction from baseline in vessel volume (-8.1 mm^3 95% CI -14.90, -1.32, p=0.02), which correlated with change in atheroma volume (r=0.39, p<0.0001), consistent with a constrictive remodeling pattern. No significant change in vessel volume was seen in patients treated with glipizide (-4.6 mm^3 95% CI -11.40, 2.27, p=0.19) and the relationship with change in atheroma volume was modest (r=0.15, p=0.03). Luminal dimensions did not significantly change in either group and change in lumen volume was highly related to change in atheroma volume in both groups (rosiglitazone r=-0.26, p<0.0001; glipizide r=-0.36, p<0.0001).
Conclusion: Treatment with rosiglitazone, was associated with a favorable effect on atheroma volume, and with a functional constrictive remodelling without a non significant reduction in lumen size. In the glipizide group, despite an absence of reduction in atheroma volume, a trend towards constrictive remodelling was observed.

P1736 High-dose N-acetylcysteine for the prevention of contrast-induced nephropathy

G. Marenzi[1], H. Trivedi[2], S. Daram[2], A. Szabo[2], A.L. Bartorelli[1]. *[1]Centro Cardiologico Monzino, Milan, Italy; [2]Medical College of Wisconsin, Milwaukee, United States of America*

Purpose: Several studies have been focused on the use of N-acetylcysteine (NAC) as a measure to attenuate contrast-induced nephropathy (CIN). Whether NAC is beneficial, however, is still uncertain. Indeed, numerous large meta-analyses have shown significant heterogeneity of NAC effect. We hypothesized that prophylaxis with high-dose NAC decreases the incidence of CIN.

Abstract P1734 – Table 1

% Patients LDL-C<2mmol	E+S (N=255) 67.5		A (N=259) 36.3		R (N=258) 17.4		Between-group difference OR 4.5 E+S vs A† OR 13.6 E+A vs R†	
	Baseline	%Change	Baseline	%Change	Baseline	%Change	E+S vs A	E+S vs R
LDL-C mmol/l	2.6 (0.4)	-26.2†	2.6 (0.4)	-11.1†	2.5 (0.4)	-3.0*	-15.1†	-23.2†
TC mmol/l	4.7 (0.6)	-16.3†	4.7 (0.6)	-8.3†	4.7 (0.6)	-2.5‡	-8.0†	-13.8†
HDL-C mmol/l	1.4 (0.3)	-1.4*	1.4 (0.3)	-2.3‡	1.4 (0.3)	-0.1	0.8	-1.3
non HDL-C mmol/l	3.3 (0.5)	-21.1†	3.1 (0.5)	-10.5†	3.5 (0.5)	-3.1*	-11.7†	-19.0†
Apo B/A1	0.6 (0.1)	-15.4†	0.6 (0.1)	-3.8‡	0.6 (0.1)	-3.1*	-11.6†	-12.3†

*p<0.05; ‡p<0.01, †p<0.001 OR=Odds Ratio analysed by logistic regression; % change from baseline analysed by Least Squares Mean.

Abstract P1735 – Table 1

IVUS Measurement	Glipizide			Rosiglitazone			Treatment Difference
Mean (SD), mm^3	Baseline	Follow-up	Change (95% CI)	Baseline	Follow-up	Change (95% CI)	(95% CI)
Total atheroma volume	249.7 (150.4)	249.6 (149.7)	1.0 (-3.0, 4.9)	222.4 (137.4)	218.6 (134.3)	-3.6 (-7.5, 0.3)	-4.6 (-9.5, 0.4)
Total vessel volume	609.4 (311.8)	603.1 (304.3)	-4.6 (-11.4, 2.3)	555.1 (298.0)	547.2 (298.2)	-8.1 (-14.9, -1.3)	-3.6 (-12.2, 5.0)
Total lumen volume	359.7 (195.7)	353.5 (192.2)	-4.9 (-11.9, 2.1)	332.7 (192.4)	328.7 (191.9)	-4.6 (-11.5, 2.3)	0.3 (-8.4, 9.1)

Methods: We conducted a meta-analysis to evaluate the efficacy of high-dose NAC for the prevention of CIN. Our pre-specified inclusion criteria were: 1) adult subjects; 2) english language literature; 3) administration of high-dose NAC a priori defined as a daily dose greater than 1200 mg or a single peri-procedural dose (within 4 hours of contrast exposure) greater than 600 mg; 4) prospective studies of individuals randomized to NAC, administered orally or intravenously, versus a control group; 5) studies that included the end-point of the incidence of CIN. Trials that compared N-acetylcysteine with another active treatment were excluded.
Results: Sixteen comparisons of patients randomized to high-dose NAC versus controls met our pre-specified inclusion criteria with a total sample size of 1677 subjects (842 assigned to high-dose NAC, 835 to the control arm). The weighted mean baseline creatinine of the overall population was 1.58 mg/dL. The results of the Breslow-Day test showed no significant heterogeneity (Chi-square=22.74; degree of freedom=15; P=0.09; I2=34%). The overall effect size assuming a common odds ratio derived using the exact Mantel-Haenszel test revealed an odds ratio of 0.46 (95% CI:0.33 0.63; P<0.0001) for the occurrence of CIN with the use of high-dose NAC. The results of the more conservative random effects approach were similar (OR=0.52; 95% CI:0.34 0.78; P=0.0018). There was no evidence of publication bias (P=0.34).
Conclusions: Our results suggest high-dose N-acetylcysteine decreases the incidence of contrast-induced nephropathy.

P1737 Fibrinolysis and Insulin Sensitivity in Imidapril and Candesartan recipient (FISIC)

R. Fogari, I. Ferrari, T. Santoro, S. Salvadeo, A. Zoppi, P. Lazzari, G. Derosa. *Department of Internal Medicine - University of Pavia, Pavia, Italy*

Purpose: to compare the effect of imidapril and candesartan on insulin sensitivity evaluated through the euglycemic hyperinsulinemic clamp, and on fibrinolysis, evaluated through the plasma PAI-1 antigen and t-PA activity, in mild to moderate hypertensive patients.
Methods: fifty-six outpatients aged 18-65 years with mild to moderate hypertension (DBP > 90 < 105 mmHg and SBP ≥ 140 < 180 mmHg) and normal BMI (≤ 25 kg/m^2) were enrolled in a parallel arm PROBE study. After 2 weeks placebo period the patients were randomized to imidapril 5mg or to candesartan 8mg for 12 weeks. In non responder patients doses were titrated every 2 weeks. Clinical BP as well as plasma PAI-1 antigen and t-PA activity have been evaluated after 1, 2, 4, 8, and 12 weeks of treatment. At the end of the placebo period and of each treatment period, the patients performed an euglycemic hyperinsulinemic clamp (insulin sensitivity has been evaluated by glucose infusion rate [GIR] during the last 30 minutes of the clamp) and a desmopressin test (with desmopressin infusion in brachial artery) to evaluate the endothelial ability to release t-PA.
Results: both imidapril and candesartan induced a significant and similar SBP/DBP reduction (-16.0/12.6 mmHg and -15.9/12.2 mmHg, p< 0.001, respectively). Imidapril significantly increased GIR (+1.14 μmol/min/kg, p< 0.001 vs baseline) while candesartan did not substantially change it (+ 0.16 μmol/min/kg, ns vs baseline, p< 0.05 vs imidapril). PAI-1 showed a progressive decrease in imidapril from 21.8±10.7 ng/ml to 15.3±6.7 ng/ml at week 12 (p< 0.001 vs baseline), while with candesartan at week 12 it was increased from 20.9±10.9 ng/ml to 24.5±10.3 ng/ml (p< 0.05 vs baseline, p< 0.001 vs imidapril). t-PA activity showed a small increase with imidapril (from 0.47±0.1 IU/ml to 0.49±0.1 IU/ml, p< 0.05) and a decrease with candesartan (from 0.48±0.1 IU/ml to 0.42±0.1 IU/ml, p< 0.01 vs baseline, p< 0.05 vs imidapril). t-PA activity response to desmopressin test showed an increase of 1.27 IU/ml with candesartan (p< 0.001) and of 3.08 IU/ml with imidapril (p< 0.001 vs baseline, p< 0.001 vs candesartan).
Conclusions: these results indicate that in normal weight hypertensive patients, imidapril significantly improved insulin sensitivity as well as fibrinolytic balance, while candesartan did not induce any clinically relevant change, despite similar BP reduction. It suggests that ACE-I action on insulin sensitivity and fibrinolysis is mediated by specific mechanisms independent of their antihypertensive effect.

P1738 Healthcare costs and resource utilization of patients receiving combination treatments of angiotensin receptor blocker with chlorthalidone or with hydrochlorothiazide

S. Sun[1], A. Yu[2], K. Chen[2], M. Mattson[2], Y. Xu[1], O. Dabbous[1].
[1]Takeda Pharmaceuticals North America, Inc., Deerfield, Illinois, United States of America; [2]Analysis Group, Inc., Boston, Massachusetts, United States of America

Background: Angiotensin receptor blockers (ARB) and diuretics are frequently prescribed as combination treatment for hypertension (HTN). The most frequently used diuretic in such combination therapy is hydrochlorothiazide (HCTZ). Chlorthalidone (CLD) is considered therapeutically interchangeable with HCTZ.
Purpose: The purpose of this study was to compare healthcare costs and resource utilization between ARB+CLD and ARB+HCTZ treatment groups.
Methods: Using the Integrated Health Care Information Services Database (1999–2007) we selected patients with a diagnosis of essential HTN (ICD-9 CM: 401) 6 months prior to the first study drug fill date, at least one refill of the ARB and CLD or HCTZ, and continuous enrollment for 6 months prior to and at least 12 months after the index date (the date the first prescription was filled for any study drug). Costs were compared between treatment groups using a Wilcoxon test and were adjusted for differences in demographics, baseline comorbidities, medication use, and resource utilization using a generalized linear model with log-link function and gamma distribution. Medical, pharmacy and total costs (medical plus pharmacy) were calculated from one-year cumulative claims. All costs were adjusted to year 2007 dollars. Resource utilization rates including hospitalization and urgent care use were estimated and compared using a Kaplan-Meier method with log-rank test and a Cox Proportional Hazards model. Data were censored at the end of availability with a maximum availability of 3 years.
Results: The analysis included 836 patients who received ARB+CLD and 16,939 who received ARB+HCTZ. ARB+CLD patients incurred lower annual medical costs ($5,374 vs. $6,064, P<0.001) and lower total costs ($7,927 vs. $8,869, P<0.0001) than ARB+HCTZ patients. After adjusting for covariates, ARB+CLD patients were shown to have incurred lower annual medical costs ($5,327 vs. $6,156, P=0.0018) and total costs ($7,916 vs. $8,974, P<0.001) than ARB+HCTZ patients. For healthcare resource utilization, ARB+CLD patients had significantly lower hospitalization (P=0.048) and urgent care (P<0.001) rates than ARB+HCTZ patients. Similarly, the Cox Proportional Hazards model showed that ARB+CLD patients had a lower risk of hospitalization [HR = 0.85, 95% CI = (0.73, 0.98), P=0.029] and urgent care use [HR=0.86, 95% CI = (0.77, 0.96), P=0.010] compared to ARB+HCTZ patients.
Conclusions: Our results demonstrated that patients who received ARB+CLD had lower hospitalization and urgent care utilization rates in addition to lower medical and total health care costs than patients who received ARB+HCTZ.

P1739 Pharmacogenetically determined treatment's influence on lipids profile and insulin resistance (IR) in relation to polymorphisms of ACE, AGTR1, eNOS, PPAR-g2, ADRB1 genes in hypertensive (EAH) patients

L. Sydorchuk[1], K.M. Amosova[2], R.I. Sydorchuk[1], I.I. Sydorchuk[1].
[1]Bukovinian State Medical University, Chernivtsi, Ukraine; [2]National State Medical University, Kyiv, Ukraine

Objective: To evaluate lipids profile and IR changes in EAH patients under the treatment depending on I/D polymorphism in ACE gene, A1166C in AGTR1 gene, T894G in eNOS gene, Pro12Ala in PPAR-γ2, Arg389Gly in ADRβ1 gene.
Design/Methods: 249 patients (EAH I – 26.5%; EAH II – 45.8%; EAH III – 27.7%; women – 48.2%, men – 51.8%, mean age 50.5±10.4 yrs) underwent combination therapy depending on genes' polymorphism ((hydrochlorothiazide (HCTZ)+angiotensin II receptor (ARB) blocker), HCTZ+β1-blockers (BB), HCTZ+ACE inhibitor (ACEI), calcium antagonists (CA)+ARB, CA+BB, CA+ACEI). Lipids profile – plasma levels of total Cholesterol (TC), Low- and High density Cholesterol levels (LDL-C, HDL-C). IR – plasma level of C-peptide, Fasting glucose (FG), IRI and HOMA-IR. Efficacy criteria – TC <5.0 mmol/l, LDL-C <3.0 mmol/l, FG <6.1 mmol/l, HOMA-IR <3.0 (ESC/ESH 2007).
Results: Target TC and LDL-C patients' amount increased by 24.4% and 26.4% (p<0.001) and lower than "threshold" FG and HOMA-IR patients' amount grew by 8.0% and 13.9% (p<0.001). HCTZ+ARB lead to LDL-C, FG and HOMA-IR patients' increased by 23.3%, 28.3% (p<0.001), 13.3% (p=0.041) and 31.6% (p<0.001) accordingly: reliable in II (ACE) (p<0.001), AA (AGTR1) (p<0.001), G-allele of eNOS gene (p≤0.009), Pro-allele (PPARγ2) (p≤0.014) and ArgArg (ADRβ1) (p<0.001). HCTZ+BB and CA+BB didn't cause reliable changes in FG and HOMA-IR. HCTZ+BB combo caused target 'TC patients increase by 14.7% (p=0.05): reliable in ID (ACE) (p=0.05), AA (AGTR1) (p=0.037) and ArgGly (ADRβ1) (p=0.045), without authentic changes of LDL-C "threshold" patients amount. HCTZ+ACEI increased "target" TC and LDL-C patients amount by 20.0% and 28.0%, p<0.001: reliable in ID (ACE) (p<0.001), A (AGTR1), G (eNOS), Pro-allele carriers (PPARγ2) and Arg (ADRβ1) (p≤0.025). CA+ARB combo is better according to "target" TC and LDL-C, than HCTZ+ACEI (p=0.008 and 0.012) and HCTZ+BB (p<0.001). HCTZ+ACEI was reliable better in the rate of "target" TC and LDL-C plasma level achievement, than CA+BB (p=0.039 and p=0.04). Reliable advantage on glucose metabolism changes in patients with EAH have ACEI+CA (or HCTZ) and ARB+CA (or HCTZ), than CA (after FMD increasing – better CA+ACEI), than HCTZ+BB (p<0.05) in D-allele (ACE gene). HCTZ+BB and CA+BB did not cause reliable changes in "threshold" FG rate and HOMA-IR.

Conclusions: Efficacy of CA+ACEI (ARB) and HCTZ+ACEI (ARB) on lipids profile and IR changes is dependent on polymorphisms of ACE (I/D), AGTR1 (A1166C), eNOS (T894G), PPAR-γ2 (Pro12Ala), ADRβ1 (Arg389Gly) genes.

P1740 High efficacy and metabolic safety of carvedilol in the treatment of hypertension in common clinical out-patient practice. Results of phase 4 clinical trial

M. Gajdos. *Slovak Medical University, Bratislava, Slovak Republic*

Purpose: Raised doubts about therapeutic benefits and safety of classic β-blockers, mainly due to their vasoconstriction and nonfavourable metabolic effects, are widely discussed. Combined carvedilol (non-selective β- and α1-blocker) mechanism of action offers ideally balanced advantageous hemodynamic and metabolic effects for patients with hypertension and other cardiovascular diseases. Its declared antihypertensive efficacy and metabolic safety in common clinical practice was evaluated.
Methods and patients: Blood pressure (BP) and selected biochemical parameters changes after 6 months carvedilol (C) therapy (25 mg daily dose, increased after the 1st month therapy to 50 mg in these, who did not reach BP target values ≤140/90 mm Hg for low or ≤130/80 mm Hg for high risk patients) in 1878 hypertensive patients (age 63.2±11.9 years, 1009 women, BMI 28.8±4.4, 369 smokers, 654 diabetics, 1185 with clinical equivalent of atherosclerosis, 391 with kidney disease, 577 on C mono-therapy) were evaluated (Student t-test). Regional Ethics Committee approved the protocol.
Results: Initial C therapy decreased BP from 159/95.6 to 138.2/84 mm Hg, what led to target BP values in 30.1% of high and 62.5% of low risk patients. Next C dose enhancement led to final BP 129.1/79.4 mm Hg with reached BP target values in 60% of high and 79.7% of low risk patients. Glycemia and evaluated lipid parameters (except HDL-C) decreased after 6 months C therapy significantly, the changes were more intensive in subgroup of diabetics if evaluated alone (table).

Biochemical parameters

Parameter (mean ± SD)	Month 0 AP	Month 6 AP	p ≤	Month 0 D	Month 6 D	p ≤
Glycemia (mmol/l)	6.3±2.1	6.0±1.7	0.001	8.1±2.4	7.4±2.2	0.001
Total-C (mmol/l)	5.5±1.0	5.2±0.7	0.001	5.6±1.1	5.2±0.8	0.001
LDL-C (mmol/l)	3.2±0.8	2.9±0.7	0.001	3.3±0.8	2.9±0.7	0.001
HDL-C mmol/l	1.3±0.4	1.3±0.3	ns	1.2±0.3	1.3±0.3	0.001
Triglycerides (mmol/l)	1.9±0.8	1.8±0.7	0.001	2.2±0.9	1.9±0.7	0.001
Creatinine (umol/l)	87.6±28.2	87.0±26.6	ns	91.7±27.5	90.1±27.1	ns

AP - all patients, D - diabetics, C - cholesterol.

Conclusions: Antihypertensive effectiveness and favourable metabolic effects predetermine carvedilol as drug of choice for mono- and combined therapy in hypertensive patients indicated for β-blockade, included these with dyslipidemia, glucose intolerance or diabetes.

P1741 Levosimendan neither improves nor worsens mortality in patients with cardiogenic shock due to ST-elevation myocardial infarction

E. Omerovic, T. Ramunddal, P. Albertsson, L. Grip, G. Matejka. *Sahlgrenska University Hospital, Gothenburg, Sweden*

Introduction: The role of inotropic therapy in the treatment of cardiogenic shock (CS) has not been adequately tested in randomized clinical trials. The aim of this study was to evaluate the effect of levosimendan, on short-term and long-term mortality in CS after ST elevation myocardial infarction (STEMI).
Methods: Data were obtained from the SCAAR (Swedish Coronary Angiography and Angioplasty Register) and the RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive Care Admission registries) about ninety-four consecutive patients (pts) with CS due to STEMI at a Sahlgrenska University Hospital (SU). Upon diagnosis of CS in Gothenburg area and at seven primary hospitals in Västra Götaland region, the pts were transported for acute angiography, percutaneous coronary intervention (PCI) and intensive care. The pts were divided into two cohorts (levosimendan and control) subjected to the two different treatment strategies. Inotropic support with levosimendan was mandatory in all patients between January 2004 and December 2006, n = 46. After presentation of SURVIVE and REVIVE II studies, levosimendan was considered contraindicated in CS and was not used in the last consecutive pts, n = 48. During this time, the routine use of inotropes in CS was discouraged. The use of intra-aortic balloon pump (IABP) was mandatory in all pts. Adjusted short- (30-days) and long-term (one-year) mortality was compared using Cox-regression.
Results: The cohorts were balanced in terms of baseline characteristics (~65 years old, ~30% women) and had similar pharmacological treatment. Multi-vessel disease was present in ~75% of pts and 16% had significant lesion of the left main. There was no difference between the groups regarding the severity of coronary lesions, revascularization success or completeness of revascularization. While levosimendan was administered to all patients in the first cohort, inotropy was used only in 54% of pts in the second cohort. The use of thrombolytics, intra aortic balloon contra-pulsation, stents and GP IIa/IIIb blockers were similar in both groups. There was no difference in the length of stay at the coronary care unit. There was no difference in the incidence of neither new-onset atrial fibrillation nor in-hospital cardiac arrest. There was no difference in mortality at 30-days and at one year.
Conclusion: The use of levosimendan neither improves nor worsens mortality in patients with CS due to STEMI. Well-designed randomized clinical trials are needed to define whether inotropic therapy may improve or worsen morbidity and mortality in CS pts.

P1742 The effect of darapladib, a direct inhibitor of lp-pla2, on necrotic core volume by ldlc level: a subgroup analysis of the integrated biomarker and imaging study-2 (ibis-2)

P.W. Serruys[1], H.M. Garcia-Garcia[1], E.A. Tarka[2], T.M. Trivedi[2], R. Davies[2]. *[1]Erasmus MC - Thoraxcenter, Rotterdam, Netherlands; [2]GSK, Philadelphia, United States of America*

Purpose: The IBIS-2 study showed that darapladib (an oral Lp-PLA2 inhibitor) prevented expansion of necrotic core volume in patients with coronary artery disease (CAD). The purpose of this analysis was to further evaluate the effects of Lp-PLA2 inhibition on necrotic core volume by baseline and achieved low density lipoprotein (LDL) levels.
Methods: The 1-year effects of darapladib 160 mg daily (n = 172) vs. placebo (n = 151) on progression of necrotic core volume were assessed by quantitative IVUS-radiofrequency (RF) analysis. Patients were stratified into tertiles according to baseline LDL level and end-of-study achieved LDL level and the treatment effect on necrotic core volume was assessed.
Results: There was a high level of adherence to guideline-mandated treatment including use of anti-platelet agents and statins in >99% and 90% of patients, respectively. There was no difference in mean achieved LDL values between groups (placebo 2.29±0.08 mmol/L; darapladib 2.23±0.07 mmol/L; p=0.54). Sample size by treatment group and tertile ranged from approximately 30-40 per group.

LDL (mg/dL)	Mean adjusted difference (mm^3) darapladib vs. placebo	95% CI	p-value
Change from Baseline in IVUS-VH Necrotic Core Volume at the End of Study by Baseline LDL Tertile Value			
<87 (<2.24 mmol/L)	-8.53	-16.28, -0.77	0.03
87 to <11 7 (2.24 to <2.99 mmol/L)	-7.13	-15.01, 0.75	0.08
≥117 (≥2.99 mmol/L)	-0.82	-8.54, 6.90	0.83
Change from Baseline in IVUS-VH Necrotic Core Volume at the End of Study by Achieved LDL Tertile Value			
<72 (<1.85 mmol/L)	-6.23	-13.52, 1.06	0.09
72 to <92 (1.85 to <2.36 mmol/L)	-13.55	-22.21,-4.89	0.003
≥92 (≥2.36 mmol/L)	-5.94	-13.87, 1.99	0.14

Based on an ANCOVA model with terms for ACS status, pooled country, matched segment length, baseline necrotic core volume, and treatment group.

Conclusions: Darapladib reduced necrotic core volume in patients with CAD across all achieved LDL tertiles and the lower LDL tertiles at baseline, compared with placebo.