Monday, 5 September 2005

MANAGEMENT OF VALVE DISEASE

1303 Percutaneous closure of mitral and aortic perivalvular leaks with Amplatzer Duct occluder

E.J. Garcia Fernandez, G. Bocuzzi, J. Pinto, L. Garcia Nielsen, M. Moreno, M.A. Garcia Fernandez. *Hospital Universitario Gregorio Maranon, Department of Interventional Cardiology, Madrid, Spain*

Objectives: This study was done to assess the immediate and mid-term results of percutaneous closure of prosthetic perivalvular leak using the Amplatzer Duct occluder.
Background: The incidence of primary perivavalvular leak after cardiac valve replacement varies from 2 to 17%. Surgical reintervention is the treatment of choice for a vast majority of patients. However, in high risk patients the operative mortality and the risk of recurrence remains elevated.
Methods: Between February 2003 and November 2004, 17 patients who were believed to be poor operative candidates underwent attempted device closure of perivalvular leak. An aortic perivalvular leak was present in six of the 15 patients, the remaining nine had a mitral leak.
Results: Successful implantation of the device was achieved in all patients with perivalvular aortic leak and in 8 of 11 patients with perivalvular mitral leak. Mean diameter of the device was 8.5±1.4mm. Procedure related complications were: blood loss or haematoma requiring blood transfusion in 6 patients, transient worsening of haemolytic anemia in two patients. At clinical follow up (180 median of days) a variable decrease in transfusion requirement and a clinical improvement was observed after successfull percutaneous closure. One patient, in which a second procedure to close a small persistent periprothetic mitral valve leak was attempted, died due to the worsening of congestive heart failure.
Conclusions: We conclude that transcatheter closure of perivalvular leak using the Amplatzer Duct occluder appears to be a reasonable "first-step" alternative in patients who are poor operative candidates. In addition due to the high rate success and to the relative simplicity, percutaneous closure of perivalvular aortic leak should be offered even in low risk patients.

1304 Current indications and clinical outcome of percutaneous aortic balloon valvuloplasty for severe degenerative aortic valve stenosis

F. Saia, C. Marrozzini, P. Ortolani, T. Palmerini, S. Silenzi, S. Gianstefani, A. Branzi, A. Marzocchi. *University of Bologna, Institute of Cardiology, Bologna, Italy*

Purpose: To assess current indications and clinical outcome of percutaneous aortic balloon valvuloplasty (PABV) for degenerative aortic stenosis.
Methods: From 1998 to January 2005, 60 consecutive patients underwent PABV for critical aortic stenosis at our institution. Follow-up was obtained from analysis of clinical records and telephone contact. The cumulative incidence of death, acute myocardial infarction, repeat PABV and aortic valve replacement during follow-up was estimated according to the Kaplan-Meier method.
Results: Average age was 78.5±7.6 years. Overall, 52% of the patients were female, 37% were diabetics, 32% had moderate to severe chronic renal failure (3% requiring dialysis), and 43% had concomitant coronary artery disease. Previous myocardial infarction was present in 30% of the patients, and prior coronary bypass intervention in 17%. Most of the patients (41, 68%) presented dyspnea NYHA class III and IV, 19 (32%) had acute coronary syndrome at admission, and 3 (5%) acute myocardial infarction. Indication to the procedure was permanent contraindication to aortic valve replacement due to severe comorbidity in 48 (80%), bridge to cardiac surgery because of temporary contraindication in 7 (12%), and cardiogenic shock in 5 (8%). At baseline echocardiography, average left ventricular ejection fraction was 47±18%, peak transvalvular gradient 71±31 mmHg and aortic valve area 0.6±0.1 cm^2. All the procedures were performed via the femoral retrograde approach. Four patients (6.7%) died during the procedure or shortly after; 2 of them had cardiogenic shock at admission. Post-procedure echocardiography showed an average increase of aortic valve area of 0.23±0.16 cm^2, a reduction of peak transvalvular gradient of 29±27 mmHg. Significant aortic regurgitation developed in 4 patients (6.7%), and only in 1 case it was of severe entity. Cumulative 1-year survival was 83%, whilst 5-year survival was 36%. Survival free from myocardial infarction, aortic valve replacement and repeat PABV was 70% at 1-year and 10% at 5 years.
Conclusions: PABV is mainly a palliative procedure to treat patients with severe degenerative aortic stenosis not suitable to undergo aortic valve replacement. In addition, it might represent a life-saving option for patients presenting with cardiogenic shock and for those with temporary contraindications to cardiac surgery. Recently developed alternative strategies such as percutaneous aortic valve replacement should favourably compare with PABV before introduction into clinical practice.

1305 Update in percutaneous aortic valve replacement for compassionate patients with severe aortic stenosis

H. Eltchaninoff[1], F. Bauer[2], C. Tron[2], C. Agatiello[2], D. Nercolini[2], F. Vochelet[2], V. Babaliaros[2], A. Cribier[2]. *[1]C.H.U. Charles Nicolle, Service de Cardiologie, Rouen cédex, France; [2]Charles Nicolle, Cardiology Dept., Rouen, France*

First human implantation of a percutaneous heart valve (PHV) was performed in april 2002 in a patient (Pt) with severe calcific aortic stenosis (AS). Since then, this technique was applied to 27 Pts in 3 consecutive monocentric series including exclusively compassionate cases: pilot (4 Pts), I-REVIVE study (16 Pts) and RECAST study (7 Pts; ongoing study). The aim of these studies was to evaluate the feasibility, safety of PHV implantation and short-term clinical follow-up (F-U).
The PHV (Percutaneous Valve Technologies-Edwards Lifescience) is a tricuspid bioprosthetic valve made of 3 leaflets of equine pericardium sutured in a 23-mm diameter stent. Crimped over a 22-mm balloon catheter, the PHV is inserted percutaneously (24-F sheath) under local anesthesia and implanted within the native aortic valve after balloon aortic predilatation. Major inclusion criteria were as follows: aortic valve area (AVA) < 0.7 cm^2; annulus 19-23 mm in diameter; NYHA class IV; Pts declined by surgeons. Mean age was 76±8 years and 52% were male. PHV was successfully deployed in 21 Pts using the retrograde approach in 4 and the antegrade transeptal approach in 17. Reasons for failure were: death before PHV (2), unstable hemodynamics (1), immediate balloon-valve assembly migration (1), failure of retrograde approach (2). Valvular function was dramatically improved in all successfull cases with an increase in AVA from 0.56±0.10 to 1.67±0.36 $cm^2$and a decrease in mean gradient from 39±12 to 9±0.5 mm Hg. Coronary arteries were patent in all cases and $>$ grade 2 angiographic paravalvular leak was noted in 6. One Pt died from crushing syndrom 30' after successfull PHV implantation. Pacing lead and transeptal catheterization related tamponade occurred in 2 Pts and one Pt had a stroke during the diagnostic procedure. PHV function remained unchanged in all Pts during F-U on sequential echographic assessment. Twelve Pts died during F-U from PHV not related death (cancer, renal insufficiency, post-extracardiac surgery, etc.). In the I-REVIVE study, 3 implanted Pts are alive at 13, 15 and 17 months respectively with unchanged PHV function and return to normal life. In the ongoing RECAST study, 5 Pts are alive at a longest F-U of 2 months.
Conclusion: This early experience demonstrates that PHV implantation is feasible offering remarkable improvement in valvular function, no impairement of coronary arteries and lasting valvular function in survivors. Multicentric studies are up to start in Europe and USA to further assess this alternative technique for non operable Pts with aortic stenosis.

1306 Management, and one-year outcome of patients with valvular heart disease in NYHA class IV

B. Iung[1], D. Messika-Zeitoun[2], P. Tornos[3], F. Delahaye[4], G. Baron[5], A. Nicoud-Houel[2], C. Gohlke-Barwolf[6], A. Vahanian[2] on behalf of the Scientific Committee. *[1]Hopital Bichat, Service de Cardiologie A, Paris Cedex 18, France; [2]Bichat Hospital, Cardiology, Paris, France; [3]Vall d'Hebron Hospital, Cardiology, Barcelona, Spain; [4]Cardiology Hospital, Cardiology, Lyon, France; [5]Bichat Hospital, Epidemiology and Biostatistic, Paris, France; [6]Heart Centre, Cardiology, Bad Krozingen, Germany*

Purpose: Decision making is particularly difficult in patients with valvular heart disease (VHD) in NYHA class IV, since they have a poor spontaneous prognosis as well as a high operative risk. To address this issue, we studied characteristics, management, and one-year outcome of patients in NYHA class IV in the Euro Heart Survey on VHD.
Methods: Among the 5001 pts included in the Euro Heart Survey on VHD between April and July 2001, 412 were in NYHA class IV: 316 with native VHD and 96 with previous cardiac surgery.
Results: Mean age was 67±12 years and 214 (52%) were female. The frequency of comorbidity was as follows: previous myocardial infarction 20%, carotid atherosclerosis 6%, renal failure 8%, chronic obstructive pulmonary disease 23%, neurological dysfunction 10%. At least one comorbidity was present in 49% of patients. Mean left ventricular ejection fraction was 49±16%.
During the study period, 169 patients (41%) in this study group were operated on (42% of native VHD and 38% of previously operated patients, p=0.37), accounting for 13% of the 1269 operated patients in the entire survey. Associated coronary bypass was performed in 24% of patients.
Operative mortality was 5.9%. One-year survival was 93±2% in operated patients vs. 81±3% in non-operated ($p<0.0001$). Non-operated patients had a higher risk profile than operated patients, as attested by a higher Euroscore (8.5 ± 3.2 vs. 6.9 ± 3.1, $p<0.0001$).
In a multivariate Cox model, the absence of valve intervention was a stong predictor of one-year mortality (Relative risk (RR)=2.8, p=0.001), the other predictors being older age (RR=1.6 per 10-year increment, $p<0.0001$), male gender (RR=2.4, p=0.0005), and renal failure (R=2.0, p=0.03).
Conclusion: In this contemporary survey, patients with VHD in NYHA class IV: 1) Still account for 13% of operated patients. 2) Frequently have comorbidity. 3) Have a low operative mortality, which may be partly related to patient selection, since only 41% were operated on. 4) Had a better one-year outcome after valve intervention, even when adjusting for differences in patient characteristics, suggesting that surgery should be considered more frequently in these high-risk patients.

1307 Are there gender-related differences in the presentation and management of patients with severe aortic stenosis?

A. Cachier[1], B. Iung[2], D. Messika-Zeitoun[1], C. Gohlke-Barwolf[3], G. Baron[4], F. Delahaye[5], D. Himbert[1], A. Vahanian[1] on behalf of the Scientific Committee. *[1]Bichat Hospital, Cardiology, Paris, France; [2]Hopital Bichat, Service de Cardiologie A, Paris Cedex 18, France; [3]Heart Centre, Cardiology, Bad Krozingen, Germany; [4]Bichat Hospital, Epidemiology and Biostatistic, Paris, France; [5]Cardiology Hospital, Cardiology, Lyon, France*

Purpose: Aortic stenosis (AS) is the most frequent valvular heart disease in Western Countries. However, little is known on the impact of gender-related differences in the presentation and management of patients with severe AS. We compared patient characteristics and decision for surgery in men and women with severe AS in the Euro Heart Survey on valvular heart disease.
Methods: Of the 5001 patiens included between April and July 2001; 1197 had AS, among whom 809 had severe AS, defined as indexed valve area (VA) $\leq$0.6 cm/m^{2}body surface area or mean gradient $\geq$50 mmHg.
Results: Characteristics of men and women with severe AS are detailed in the table.

Table 1. Comparison of men and women with severe AS

	Women (n=347)	Men (n=462)	p
Age (years)	72±10	68±12	<0.001
≥80 years (%)	20	9	<0.001
NYHA III-IV (%)	48	37	0.002
Angina (%)	45	49	0.26
≥ 1 comorbidity (%)	30	40	0.002
Coronary disease (%)	35	48	<0.001
LV ejection fraction	0.60±0.12	0.56±0.14	<0.001
Indexed VA (cm^2 /m^2)	0.41±0.19	0.41±0.10	0.49

LV: left ventricle

A decision to operate was taken in 73% of women and 76% of men (p=0.38). In multivariate analysis, a decision for not to operate was associated with age ≥80 years (p<0.0001), NYHA class I-II (p<0.01), the presence of at least one comorbidity (p=0.03), and LV ejection fraction <50% (p=0.04), but not with gender (p=0.59).
Of the 512 pts who had undergone surgery during the study period, 30-day mortality was 2.4% in women and 3.7% in men (p=0.38).
Conclusion: This contemporary survey shows that 1) Women with severe AS present at an older age and with more severe symptoms, while men have more frequent comorbidity and coronary disease. 2) The severity of AS does not differ according to gender. 3) Gender has no impact on the decision to operate, even when adjusting for differences in patient characteristics.

1308 Clinical presentation and management of patients with severe mitral regurgitation: are there differences between men and women? Lessons from the Euro Heart Survey

A. Cachier[1], D. Messika-Zeitoun[1], B. Iung[2], P. Tornos[3], D. Himbert[1], E. Butchart[4], G. Baron[5], A. Vahanian[1] on behalf of the Scientific Committee. *[1]Bichat Hospital, Cardiology, Paris, France; [2]Hopital Bichat, Service de Cardiologie A, Paris Cedex 18, France; [3]Vall d'Hebron Hospital, Cardiology, Barcelona, Spain; [4]University Hospital, Cardia Surgery, Cardiff, United Kingdom; [5]Bichat Hospital, Epidemiology and Biostatistic, Paris, France*

Purpose: It is not known whether clinical presentation and management of patients with severe mitral regurgitation (MR) differs according to gender. We used the data of the Euro Heart Survey on valvular heart disease, in order to compare patient characteristics and decision for surgery in men and women with severe MR.
Methods: Between April and July 2001, 5001 patients were included in the Euro Heart Survey; 877 had MR, among whom 546 had severe MR, defined as MR grade ≥ 3/4.
Results: Characteristics of men and women with severe MR are compared in the table.

Table 1. Comparison of men and women with severe MR

	Women (n=254)	Men (n=292)	p
Age (years)	67±14	64±14	0.07
NYHA III-IV (%)	56	44	0.005
Congestive heart failure (%)	32	25	0.04
Atrial fibrillation (%)	38	25	0.001
Degenerative MR (%)	57	59	0.57
LV ejection fraction	0.54±0.14	0.52±0.16	0.10
Indexed LV ESD (mm/m^2)	22±5	22±5	0.47
Coronary disease (%)	35	50	0.01
Decision for surgery			
All pts (%)	42	48	0.17
Pts in NYHA I-II (%)	32	48	0.01
Pts in NYHA III-IV (%)	50	48	0.80

LV: left ventricle, ESD: end-systolic dimension

Of the 155 patients who had undergone surgery during the study period, valve repair was performed in 37% of the women and 53% of the men (p=0.04). Thirty-day mortality was 6.6% in women and 2.2% in men (p=0.17).
Conclusion: Significant differences exist between men and women with severe MR 1) Women are referred at a more advanced clinical stage than men, although LV function does not differ. 2) Overall, decision for surgery does not differ according to gender. However, in patients with few or no symptoms, a decision to operate is taken less frequently in women. 3) In women, valve repair is less frequently performed and operative mortality tends to be higher than in men.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION: DIAGNOSIS AND MEDICAL TREATMENT

1309 N-terminal fragment of proBNP as marker of persistent pulmonary hypertension in survivors of acute pulmonary embolism

A. Kaczynska[1], M. Szulc[2], A. Bochowicz[2], G. Styczynski[2], M. Kostrubiec[2], A. Kuch-Wocial[2], P. Pruszczyk[2]. *[1]Medical University of Warsaw, Int. Dis., Angiology and Hypertension, Warsaw, Poland; [2]Medical University of Warsaw, Int. Dis., Angiology and Hypertension, Warsaw, Poland*

Background: In some pts with APE despite 6-month anticoagulation pulmonary artery clots are not completely resolved. We tried to assess if biochemic marker of myocardium strain - N-terminal fragment of proBNP (NTproBNP) is helpful to define pts with persistent right ventricle (RV) overload due to pulmonary arteries occlusion, who may benefit from prolonged treatment.
Examined group and methods: We observed 41 pts (32 F, 9 M) aged 62,7 ± 17,1 yrs with confirmed APE. On admission and after 6 months of treatment transthoracic echocardiography was performed to assess RV overload-examined were RV/LV ratio, tricuspid peak systolic gradient (TVPG), acceleration time of pulmonary ejection (Act) and RV hypokinesis as well as serum NTproBNP was measured quantitatively (ECLIA, Roche).
Results: On admission NTproBNP was elevated above reference value in 85% pts and correlated with all echocardiographic parameters of RV overload (RV/LV ratio r =0,6, p= 0,0004, Act r = - 0,6, p= 0,0001, TVPG r =0,4, p=0,03). After 6 months NTproBNP decreased significantly (tab.). It correlated only with TVPG (r = 0,7, p = 0,04) and all 6 pts with NTproBNP elevated above reference value had also TVPG > 30 mmHg (p =0,002).

Echocardiography and NTproBNP

	admission	6th month	p*
RV (mm)	31 (22-46)	26 (16-36)	0,001
RV/LV	0,8 (0,4-1,5)	0,6 (0,3-1)	0,0004
Act (ms)	60 (35-120)	110 (60-190)	0,00003
TVPG (mmHg)	42 (5-71)	25 (0-60)	0,00004
NTproBNP (pg/ml)	1888,5 (43,9-33340,0)	285,4 (26,9-1568,0)	0,001

* Wilcoxon's test

Conclusion: NTproBNP as marker of myocardium strain correlates with echocardiographic parameters of RV overload in APE. In patients after PE episode elevated NTproBNP may reflect persistent pulmonary hypertension.

1310 Alternative and additional diagnoses in multislice CT in patients suspected of pulmonary embolism

E. Czekajska-Chehab[1], A. Trojanowska[1], J. Przegalinski[2], A. Tomaszewski[2], M. Wojcik[2], L. Grzycka-Kowalczyk[1], T. Widomska-Czekajska[2], A. Drop[1]. *[1]Skubiszewski Medical University, Department of Radiology, Lublin, Poland; [2]Skubiszewski Medical University, Department of Cardiology, Lublin, Poland*

Multi-slice computed tomography pulmonary angiography (MSCTPA) has become the basic kind of examination in patients suspected of having pulmonary embolism (PE).
The aim of the study was to present the results of MSCTPA in patients with the clinical suspicion of PE, particularly the possibilities of detection of concomitant changes and alternative diagnoses explaining the cause of clinical manifestations.
Methods: The results of MSCTPA performed with the 8-row tomograph LightSpeed Ultra-GE (collimation 1.2mm, interval 0.6mm; i.v. Ultravist 370-4ml/s, delay time in Smart Prep or test bolus technique) were analysed in 182 consecutive patients with the clinical suspicion of PE. In 25 cases two-phase scanning was used.
Results: The embolic material was visualized in 93 examinations (51%); in 71 cases (39%) the signs of acute and subacute PE were dominant. In 8 cases, the type of changes was that of chronic or recurrent PE. In 47 examinations (26%), including 6 with PE, some other types of changes were found, which could explain clinical symptoms. These included: pneumonia and/or pleuritis-20 cases (11%), circulatory failure- 9 cases (5%), pulmonary fibrosis and neoplasms-4 cases each, bronchiolitis obliterans- 3 cases, ARDS or PAPVR- 2 cases each, alveolitis allergica, interventricular septum dissection, patent ductus arteriosus with pulmonary hypertension-1 case each. In 79 cases (43%) the following concomitant abnormalities were observed: enlargement of mediastinal or hilar lymph nodes- 22 cases (12%), limited emphysematous or post-inflammatory lesions

in the lungs and pleura-19 cases (10%), single pulmonary nodules 3-15mm in diameter- 10 cases, hiatus hernia- 7 cases, retrosternal goitre – 6 cases, vascular anomalies – 4 cases, fluid in the pericardial sac, post-radiation pulmonary lesions, neoplasm recurrence - 3 cases each, and others- 5 cases.
Conclusion: Multi-slice computed tomography pulmonary angiography is a useful and quick method to diagnose pulmonary embolism and assess its nature and severity. In about 25% of patients the PE examination enables an alternative diagnosis and in more than 40% provides additional information about concomitant changes.

1311 New method for differentiation of chronic thromboembolic from idiopathic pulmonary hypertension

J. Endrys[1], J. Stasek[2], J. Bis[3]. *[1]Hradec Kralove, Czech Republic; [2]University Hospital, 1st Department of Medicine, Hradec Kralove, Czech Republic; [3]University Hospital, 1st Department of Medicine, Hradec Králové, Czech Republic*

Introduction: Pulmonary angiography and recently spiral CT are considered as a golden standard for differential diagnosis of chronic tromboembolic (CTPH) and idiopathic pulmonary hypertension (IPH). According to Braunwald it might be sometimes difficult to rule out CTPH as a cause of pulmonary hypertension since in advanced stages recanalization takes place and typical pattern of vascular occlusions disappears and on the other hand in IPH local thrombosis of pulmonary artery branches can develop. After finding that CTPH constantly cause extensive bronchopulmonary collaterals (BPC) while in IPH they are missing (Endrys at al. Heart 78: 171-6, 1997) we tried to utilize it for reliable differentiation of CTPH and IPH and simultaneously reduce the risk of pulmonary angiography.
Methods: We have investigated 22 patients with IPH and 12 patients with CTPH. The presence of BPC was proved by measurement of BPC flow using dye dilution method, which we developed for such purpose and/or by selective bronchial arteriography and aortography. Recently BPC were visualized by reconstruction of spiral CT noninvasively.
Results: In the group of CTPH we found high values of BPC flow: 0.93 (range 0.4-1.8) l/min, while in patients with IPH only traces were measured in 4 and in 12 BPC flow was not measurable at all. Aortography or bronchial arteriography showed extensive BPC in all patients with CTPH, frequently with the opacification of the peripheral branches of the centrally occluded pulmonary arteries. On the other hand in IPH just normal, hardly visible normal bronchial arteries were identified.
Conclusions: Presence of BPC sharply differentiated patients with CTPH from patients with IPH. Regarding to the diffuse process of embolization in CTPH the most simple method how to prove BPC is just a selective bronchial arteriography close to the tracheal bifurcation. It is easy to do and using just few ml of contrast dye is much safer than pulmonary arteriography. In the last 3 patients spiral CT was also used for visualization of BPC.

1312 Primary pulmonary artery sarcomas misdiagnosed as chronic thromboembolic pulmonary hypertension

H. Gutierrez Garcia[1], P. Escribano[2], F. Hernandez[2], J. Cortina[3], R. Tello[2], T. Sotelo[4], J. Delgado[2], M.A. Gomez Sanchez[2]. *[1]Madrid, Spain; [2]Hospital 12 de Octubre, Cardiology, Madrid, Spain; [3]Hospital 12 de Octubre, Cardiac Surgery, Madrid, Spain; [4]Hospital 12 de Octubre, Patology, Madrid, Spain*

Background: primary pulmonary artery sarcomas (PPAS) are rare tumours that are frequently misdiagnosed as chronic thromboembolic pulmonary hypertension (CTEPH). Therapeutic approach and prognosis are quite different between the two entities.
Objectives: to review the main clinical and imaging-techniques differences between CTEPH and PPAS.
Methods: we retrospectively reviewed clinics and imaging-technique characteristics of all cases referred to our Unit with suspected CTEPH.
Results: Among 214 patients evaluated in our Unit between 1990 and 2005, 26 were referred with suspicion of CTEPH. In 4 patients, the final diagnosis was PPAS. In all patients, clinical evaluation, transthoracic echocardiography, lung perfusion scintygraphy, multislice computed tomography and right heart catheterization with pulmonary angiography were performed as standard evaluation. In two patients with high suspicion of PPAS, biopsy of the intravascular mass during angiography was performed before surgery. The main clinical and imaging-techniques differences are shown in the table.

Main differences between CTEPH and PPAS

	CTEPH	PPAS
Symptoms progression (dyspnoea)	Slow	Quickly, < 1 year
Intense pulmonary murmur	Rare	Frequent
Visualisation with echocardiography	Rare	Frequent (inhomogeneous)
Multislice Computed Tomography	Bilateral masses in pulmonary arteries	Unique mass in main pulmonary arteries
Peripheral defects in angiography	Frequent, in both lungs	Rare, same lung as the mass
Progression despite anticoagulation	Rare	Frequent

Conclusions: Quickly clinical progression and the presence of unique mass in main pulmonary arteries are highly suspicious of PPAS in patients with likelihood CTEPH. The biopsy of the intravascular mass seems to be useful to set the diagnosis before surgery.

1313 Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension

D. Bondermann[1], R. Nowotny[2], N. Skoro-Sajer[2], J. Jakowitsch[2], C. Adlbrecht[2], M. Kneussl[2], I.M. Lang[2]. *[1]Wien, Austria; [2]General Hospital, Cardiology, Vienna, Austria*

Background: Bosentan, a dual endothelin-1 receptor antagonist that can be administered orally, has been shown to be effective in the treatment of idiopathic pulmonary arterial hypertension. The aim of the present study was to evaluate its safety and efficacy in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).
Methods: This was a prospective uncontrolled cohort study. The effect of bosentan therapy was tested in 16 patients (9f/7m, mean age 70±13years) with inoperable CTEPH. After six months, changes from baseline in 1) liver enzymes, 2) NYHA functional class, 3) six-minute-walking distance and 4) NT brain natriuretic peptide (pro-BNP) were evaluated.
Results: NYHA functional class improved by one class in 11 patients. Six-minute walking distances increased from 299±131m to 391±110m (p=0.01). In parallel, proBNP decreased from 3365±2923pg/ml to 1755±1812pg/ml (p=0.01). Neither AST (25±2 versus 25±2U/l, p=0.25) nor ALT (23±12 versus 24±9U/l, p=0.57) showed significant changes.
Conclusions: Our initial experience with bosentan therapy in patients with inoperable CTEPH is promising and urges the need for a randomized, placebo-controlled trial.

1314 Survival in patients with chronic thromboembolic pulmonary hypertension

D. Bondermann[1], R. Nowotny[2], C. Adlbrecht[2], J. Jakowitsch[2], S. Lehr[3], I.M. Lang[2]. *[1]Wien, Austria; [2]General Hospital, Cardiology, Vienna, Austria; [3]Computer Science, University of Vienna, Vienna, Austria*

Background: A series of medical conditions have recently been identified as risk factors for the development of chronic thromboembolic pulmonary hypertension (CTEPH). The impact of these medical conditions on prognosis is unknown.
Methods: 129 consecutive CTEPH patients diagnosed between 1994 and 2003 (67f/62m) were studied. Prior splenectomy, ventriculo-atrial shunt (VA-shunt), chronic inflammation, elevated plasma factor VIII and anti-cardiolipin-antibodies/lupus anticoagulant were considered risk factors. Kaplan-Meier estimates of the survival distribution were performed. The influence of pulmonary thromboendarterectomy (PEA) on survival was tested by the Cox proportional hazards model.
Results: Mean patient age at diagnosis was 55±16 years. Median observation time was 56 months. In 85 patients (66%) an underlying medical condition was identified (splenectomy, n=12, VA-shunt, n=7, inflammatory bowel disease (IBD), n=8, elevated plasma factor VIII, n=42, and APL, n=16). Right heart hemodynamics were not significantly different in the patients with and without associated risk factors (pulmonary vascular resistance: 906±426 dynes s^{-1} cm^{-5} versus 888±427 dynes s^{-1} cm^{-5}, p=0.2). Because of distal thrombus localization only 4 patients with splenectomy or IBD underwent PEA. PEA reduced the risk to die by 62% (HR=0.38; 95% CI: [0.16-0.87], p=0.025). Patients died from right heart failure (n=21), malignancy (n=1) or after PEA (n=12). While the overall median survival time was 113 months, survival time in patients with splenectomy or IBD (n=20) was significantly shorter (55 months, p=0.015).
Discussion: The data show that there exist several CTEPH entities. CTEPH associated with splenectomy or IBD carries the worst prognosis. The predominantly distal thrombus localization and associated pulmonary vascular disease in these patients may account for this observation.

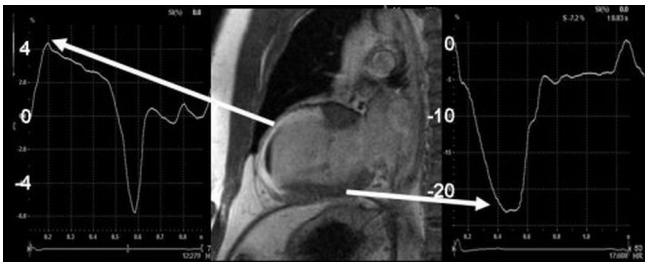
STRAIN AND STRAIN RATE FOR QUANTITATIVE DIAGNOSIS OF ISCHAEMIA

1365 The extent of myocardial scarring assessed by strain Doppler echocardiography – validated by magnetic resonance imaging

T. Vartdal[1], E. Pettersen[2], H. Brunvand[2], E. Lyseggen[3], H.J. Smith[4], H. Ihlen[2], O.A. Smiseth[2], T. Edvardsen[2]. *[1]Rikshospitalet University Hospital, Department of Cardiology, N-0027 Oslo, Norway; [2]Rikshospitalet University Hospital, Department of Cardiology, Oslo, Norway; [3]Rikshospitalet University Hospital, Institute for Surgical Research, Oslo, Norway; [4]Rikshospitalet University Hospital, Department of Radiology, Oslo, Norway*

Objectives: late gadolinium enhancement cardiovascular magnetic resonance (CMR) can determine myocardial scar after myocardial infarction with great accuracy. Strain Doppler echocardiography (SDE) show promising results regarding assessment of myocardial function. The aim of this study was to test if SDE dur-

ing the acute phase of myocardial infarction could predict the extent of myocardial scar after left ventricular (LV) remodeling.
Methods and Results: thirty-one patients with acute anterior myocardial infarction who underwent percutaneous coronary intervention (PCI) were included. SDE was performed within the first two hours after PCI and peak strain in 12 LV segments were analysed. Figure shows myocardial lengthening in the scarred area (left) and normal shortening in the remote area (right). Peak cardiac enzymes (SGOT, TnI, CK-MB), duration of ischaemia, ejection fraction (EF) by echocardiography and Selvester QRS Scoring System (SSS) were measured. A follow-up CMR scan was performed after 6 months with assessment of total LV infarct size and the scar extent in each of the 12 LV segments. Peak strain correlated well with the transmurality of the myocardial scar in each segment (r= 0.71, $p<0.001$). The total LV infarct size by CMR was compared to strain averaged from all LV segments, cardiac enzymes, SSS and EF by echocardiography in a stepwise multiple regression model. Averaged strain was found to be the best predictor of LV infarct size (β=0.50, p=0.004) followed by SGOT (β=0.43, p=0.010). Peak Tn I, CK-MB mass, SSS, EF and the ischemic time were less accurate in predicting infarct size.



Gadolinium enhanced MR and strain traces

Conclusion: SDE performed immediately after PCI can predict the extent of myocardial scar better than cardiac enzymes, adding important diagnostic and therapeutic implications.

1366 Impact of age and haemodynamics on strain rate during dobutamine stress echocardiography: is designation of a normal range feasible?

C. Bjork Ingul[1], S.A. Slordahl[1], H. Torp[1], T.H. Marwick[2]. [1]*Norwegian University of Science and Technolog, Trondheim, Norway;* [2]*University of Queensland, Brisbane, Australia*

Background: Recent developments have improved the feasibility of strain rate using tissue Doppler or speckle tracking to quantify dobutamine stress echocardiography (DSE). We sought the effects of clinical (age, beta-blockade) and hemodynamic factors (heart rate (HR), systolic blood pressure (SBP)) and regional variation on peak systolic strain rate (SRs) at rest and peak stress.
Methods: SRs were obtained in 50 patients with normal coronary angiography and 60 patients with a low risk Framingham score (<1%/year), who had a normal response to a standard DSE protocol. SRs was measured simultaneously in each segment, using customized software (GCmat, GE Vingmed Horten, Norway) for automated measurements. A dynamic region of interest was placed automatically in the centre of the segment at end-diastole, and the mid point of the segment was tracked throughout the cardiac cycle. Longitudinal motion was measured by tissue Doppler velocity and lateral motion by speckle tracking in the grey scale images. SRs was calculated from the velocity gradient along the ultrasound beam.
Results: In these normal patients, the average rest SRs was -1.4 $\pm$ 0.4 1/s and at peak was -2.6 $\pm$ 0.7 1/s. There were no differences in SRs for the different walls at rest; septum (-1.3 1/s), lateral (-1.4 1/s), inferior (-1.4 1/s) and anterior (-1.4 1/s)(p=NS). At baseline there were no significant differences in SRs in the subgroups of HR (<60, 60-70, 70-80, >80 beats/min), SBP (<120, 120-140,140-160,>160 mmHg), age (<30, 30-40, 40-50, 50-60, 60-70, >70 years) and use of beta-blocker. At peak stress the following subgroups; age >70, SBP >160, HR <140, use of beta-blocker therapy; had significantly lower SRs (Table). However, beta-blockade was the only independent predictor of SRs (Table).

SRs at peak for different variables

Variable	Subgroups with sign. different SRs	SRs for these subgroups vs. the others	Multivariate
Age	> 70 years	-2.3 vs. -2.6 1/s (p=0.009)	F=3.4, p=0.06
Systolic blood pressure	> 160 mmHg	-2.4 vs. -2.7 1/s (p=0.001)	F=1.4, p=0.24
Heart rate	< 140 beats/min	-2.4 vs. -2.6 1/s (p=0.007)	F=1.2, p=0.27
Beta-blocker	beta-blocker use	-2.4 vs. -2.7 1/s (p=0.000)	F=4.4, p=0.03

Conclusion: At peak dobutamine stress, the normal SRs was 2.6 $\pm$ 0.7 1/s in most age groups and under most hemodynamic conditions. A different normal range (-2.4 $\pm$ 0.7 1/s) should be considered for patients on beta-blockers.

1367 Selection of optimal strain rate imaging parameter for the diagnosis of coronary artery disease during dobutamine stress echocardiography. An angiographic comparison

L. Hanekom, S. Moir, L. Jeffries, D. MacNab, T.H. Marwick. *University of Queensland, Department of Medicine, Brisbane, Australia*

Background: Several small studies have suggested that strain rate imaging (SRI) may improve the accuracy and reliability of wall motion scoring (WMS) at dobutamine echo (DSE). However, physicians wishing to apply SRI may be deterred by a bewildering variety of parameters.The goal of this study was to identify the optimal parameter for DSE in a large angiographic comparison.
Methods: We studied 2 groups - a consecutive group of 170 pts (63 female, age 64$\pm$8yrs) with known or suspected CAD, undergoing DSE and angiography to define sensitivity and specificity (CAD defined as QCA measurement >50%), and 37 pts at low probability of CAD. Pts with previous CABG, LBBB on ECG and PPM were excluded. Cut-off values for SRI were analyzed in 134 pts (2145 segts) without previous MI. The accuracy of SRI in the prediction of CAD was also assessed in all pts, and compared with conventional WMS.
Results: Feasibility of SRI was 94% at rest and 91% at peak stress. At peak stress, ischemic and abnormal segments had significantly lower SR ($p<0.0001$), end-systolic strain (ESS; $p<0.0001$) and higher SR increment ($p<0.0001$), post-systolic index (PSI; 0.4$\pm$0.7 vs. 0.3$\pm$0.3) and time to end of systole (tes, $p<0.0001$) compared with normal and non-ischemic segts. Sensitivity and specificity of WMS showed typical post-test referral bias picture (Table) but usual values for normalcy. SRI did not alter sensitivity in either group, but specificity was most improved by PSR. ESS and TES were as sensitive but less specific, and PSI was specific but insensitive. SRI did not improve the performance of DSE in assessment of single and multivessel CAD.

SRI parameters

		Group 1 (134pts)				
		WMS	psr<-0.95	ESS<-10	tes>0.21	psi>0.25
CAD	Sens (%)	91	96	87	90	50
	Spec (%)	37	62*	37	35	67
	AUC	0.64	0.8**	0.63	.62	.58
	Normalcy(%)	91	96			
LAD	Sens	72	94*	85	81	46
Posterior	Sens	81	89	62	78	32
		Group 2 (170pts)				
		WMS	psr<-0.95	ess<-10	tes>0.21	psi>0.25
CAD	Sens (%)	93	97	91	93	59
	Spec (%)	34	57*	34	32	63
	AUC	0.64	0.78**	0.62	0.62	0.61
	Normalcy(%)	93	97			
LAD	Sens	75	93*	87	87	52
Posterior	Sens	88	92	74	82	32

**p<0.0001, *p<0.05

Conclusions: Use of SRI during DSE is feasible and may improve specificity of DSE. Peak SR appears to be the optimal parameter.

1368 Assessment of left ventricular segmental function after autologous bone marrow stem cells transplantation in patients with acute myocardial infarction by tissue tracking and strain imaging

W. Ruan[1], X.H. Shu[2], C.Z. Pan[1], Y.L. Li[1], J.B. Ge[1], H.Z. Chen[1]. [1]*Zhongshan Hospital, Fudan University, Department of Cardiology, Shanghai, China;* [2]*Zhongshan Hospital, Department of Cardiology, Shanghai, China*

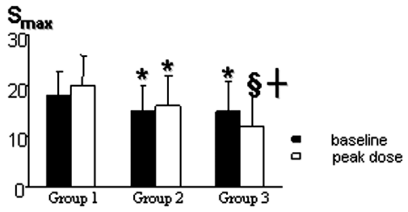
Objective: Using tissue tracking and strain imaging to assess left ventricular (LV) segmental function after autologous bone marrow stem cells (BMCs) transplantation in patients with acute myocardial infarction.
Methods: Twenty patients who had acute myocardial infarction and anterior descending coronary artery occlusion proven by angiography were double-blindedly randomnized into either bone-marrow-cell (Group A, n=10) or control (Group B, n=10) groups. Within 2h after percutaneous intervention (PCI), group A patients were treated with intracoronary injection of BMCs, while control patients were injected diluted serum. GE vivid 7 and Q-analyze software were used to perform echocardiogram in both groups for 1 week, 3 months and 6 months follow-up. Apical 4-, 3- and 2-chamber views of tissue Doppler imaging were acquired to measure peak systolic displacement (Ds) and peak systolic strain (Smax) from 12 segments of LV walls to evaluate the segmental contractile function. LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (LVEF) were obtained by 2D echocardiography to assess LV global function and volume.
Results: (1) 3 months later, Ds and Smax at the infracted region clearly increased in the BMCs group (Ds: 3.31 $\pm$ 3.04 mm vs 6.25 $\pm$ 3.64 mm; Smax: -11.97 $\pm$ 5.77% vs -17.10 $\pm$ 6.37%, $P<0.01$), but not in the control group (Ds: 4.38 $\pm$ 2.32 mm vs 5.33 $\pm$ 2.96 mm; Smax: -13.44 $\pm$ 6.12% vs 14.03 $\pm$ 7.32%, $P>0.05$). Moreover, Ds of the non-infarcted region also increased in both groups ($P<0.05$ or $P<0.01$), but the amount of Ds enhancement was much greater in the BMCs group than that in the control group (2.72$\pm$2.80 vs 1.08$\pm$2.05 mm, $P<0.001$). The parameters didn't present significant difference between 3-month and 6-month follow-up in both groups ($P>0.05$). (2) LVEF at baseline (1-week

after PCI) was 52.6±8.9% and 52.1±5.5% in the treated and control group respectively(P>0.05). After 6 months, mean LVEF had increased by 6% in the BMCs group, but decreased by 2% in the control group. (3) Mean end-diastolic and end-systolic volume remained almost constant in Group A after stem cell transplantation, but continued to increase in Group B post-treatment (P>0.05).
Conclusions: Transplantation of autologous BMCs in patients with acute myocardial infarction helps to improve global and regional contractility and attenuate post-infarction left ventricular remodeling. Tissue tracking and strain imaging provide quick, simple and noninvasive methods for clinical assessment of left ventricular segmental function.

1369 Strain rate imaging during dobutamine stress echocardiography accurately differentiates mild from severe transplant vasculopathy

E. Eroglu, J. D'hooge, A. Marciniak, D. Thijs, W. Droogne, B. Bijnens, J. Vanhaecke, G.R. Sutherland. *University Hospital Gasthuisberg, Department of Cardiology, Leuven, Belgium*

Background: The incidence and severity of transplant vasculopathy (Tx-CAD) is usually underestimated with coronary angiography. Dobutamine stress echocardiography (DSE) has been shown to be a sensitive non-invasive method for the diagnosis of Tx-CAD. We sought to determine whether strain rate imaging (SRI) during DSE could identify inducible ischemia at an earlier stage of the disease.
Methods: 26 post-Tx patients were prospectively enrolled. DSE using SRI (max dose 20μg/kg/min) was performed 24h before routine control angio. Data were acquired (GE Vivid7; frame rate>180Hz) from apical 4-, 3- and 2-chamber views at baseline and incremental dobutamine infusion levels. Maximal systolic velocity (Vmax), strain rate (SRmax) and strain (Smax) were estimated for each segment. Segments were assigned to a presumed perfusion territory based on angio by a blinded reader and 3 groups were defined according to the severity of the luminal stenosis of the perfusing arteries: 1) normal, 2) focal stenosis<50% and/or minor diffuse irregularities, 3) focal stenosis>50% and/or diffuse significant irregularities. Differences between the groups were tested using a one-way ANOVA with a Tukey-Kramer post-hoc.
Results: Vmax was not different between the groups at baseline but was reduced at peak dose for groups 2 and 3 (p<0.01). SRmax and Smax were significantly reduced for Group 2 and 3 at both baseline and peak dose (Fig 1). Finally, at peak dose Smax was significantly different between all 3 groups and enabled to detect severe Tx-CAD with a 86% sensitivity, 82% specificity and 93% negative predictive value using a cut-off of Smax<9%.



* P< 0.05; group 2 vs group1, group 3 vs group 1, § p<0.01; group3 vs group 1,
+ p< 0.05; group 3 vs group 2

Figure 1

Conclusion: SRI during DSE can accurately differentiate mild from severe Tx-CAD and showed a high accuracy in the detection of severe Tx-CAD.

1370 Peak strain delay post adenosine is related with respective flow reserve: evidence in left anterior descending artery territory

G. Athanassopoulos[1], Y. Zhu[2], G. Hatzigeorgiou[2], G. Karatasakis[2], E. Papadakis[2], D.V. Cokkinos[2]. *[1]Pireas, Greece; [2]Onassis Cardiac Surgery Center, 1st Cardiology Department, Athens, Greece*

Introduction: left ventricular post systolic strain has been shown to be an accurate index of underlying ischaemia post dobutamine stress. However, there are no data concerning the effect of adenosine (AD) on the timing of peak strain (t-Pstr) nor its correlation with regional flow reserve (CFR).
We assessed the effect of AD on the timing of peak strain and the potential relationship with the respective flow reserve in the territories supplied by the left anterior descending artery (LAD) in chronic coronary artery disease (CAD).
Patients/Methods: 30 patients were studied (age 61±9, 1 female). None had akinesis in the LAD territory. 8/30 pts had a >50% LAD diameter stenosis. LAD CFR was estimated by AD 140μg/kg/min for 4 min by transthoracic echo. LAD flow was interrogated (nearby the apex) by a 7 MHz transducer (modified 2-chamber apical view). The time (t-AVC: msec) from the onset of QRS to aortic valve closure (AVC) and the respective to the peak strain (t-Pstr) were measured by Doppler tissue imaging (DTI) in the territories supplied by LAD (mid-apical anterior and septal wall from 2/4 chamber apical views respectively).
The difference (dt) between the maximum t-Pstr and t-AVC was calculated as well as it ratio to the respective RR interval (dt/RR) both at rest (R) and during AD.
Results: pts with >50% LAD had prolonged t-Pstr at apical A at R and more pronounced during AD (R: 384±50 vs 351±30, p=0.06, AD: 391±52 vs 337±31, p=0.014). However, dt-AD or dt/RR –AD was similar among pts with or without >50% LAD stenosis.
The dt/RR-AD had a linear inverted relationship with CFR LAD (r=0.54, p=0.002: regression equation: dt/RR-AD=0.02+0.02*CFR).
When ROC analysis was performed for dt/RR-AD to predict CFR LAD<2, the best cut off value was 0.38: (area under curve=0.81, p=0.043, sens/spec 0.8/0.93).
Conclusion: in chronic CAD, AD infusion induces delay to the onset of peak strain in LAD territories. The relative differences of this delay to the AVC detected by DTI are affected by the LAD flow reserve and might used as an index of flow adequacy in the relevant myocardial territory.

ASSESSING ASYNCHRONY: THE ADDED VALUE OF ECHOCARDIOGRAPHY

1371 Measuring ventricular dyssynchrony using standard echocardiography or tissue Doppler imaging: do the results agree?

H. Burri[1], H. Muller[2], H. Sunthorn[2], D. Shah[2], R. Lerch[2]. *[1]University Hospital of Geneva, Cardiology, Geneva, Switzerland; [2]University Hospital, Cardiology, Geneva, Switzerland*

Background: Ventricular dyssynchrony may affect response to biventricular pacing. Dyssynchrony may be measured using either standard echocardiography with pulsed-wave Doppler (PWD) and M-mode (MM), or pulsed-wave tissue Doppler imaging (TDI). Our aim was to evaluate whether these methods provide concordant results.
Material and Methods: 40 consecutive patients (27 males, age 67± 15 years) with a LVEF of < 0.35 were included. Inter-ventricular dyssynchrony was evaluated by PWD by difference in pulmonary and aortic pre-ejection intervals, and by TDI by calculating the maximal difference between Q-Sm intervals at the basal right ventricular free wall and any of 4 basal segments of the left ventricle. Intra-ventricular dyssynchrony was evaluated using MM by evaluating delayed contraction of the posterior basal wall after onset of ventricular filling, and by TDI by the maximal difference of Q-Sm intervals between 4 basal segments of the left ventricle. A control group of 39 subjects with normal systolic function was also studied in order to determine cut-off values for these parameters.
Results: Interventricular dyssynchrony was present in 9/40 (23%) of patients using PWD, and in 17/40 (43%) of patients using TDI (k=0.35). Intra-ventricular dyssynchrony was not detected by MM in any of the patients, whereas TDI showed evidence of dyssynchrony in 15/40 (38%) of patients.

Comparison of standard echo and TDI

Inter-ventricular asynchrony			Intra-ventricular asynchrony		
n	TSI+	TDI–	n	TSI+	TDI–
PWD+	7	2	MM+	0	0
PWD–	10	21	MM–	15	25

Conclusions: Results differ considerably according to evaluation of dyssynchrony by standard echocardiography or by TDI. Standard echocardiography is less likely to show evidence of dyssynchrony, especially as concerns intra-ventricular dyssynchrony. This may have implications for patient selection for cardiac resynchronization therapy.

1372 Prognostic value of ventricular asynchrony in patients with LBBB and heart failure

R. Citro[1], A. D'Andrea[2], V. Ducceschi[3], G. Bottiglieri[3], M.M. Patella[3], F. Gatto[3], M. Scherillo[2], G. Gregorio[3]. *[1]San Luca Hospital, Department of Cardiolgy, Vallo della Lucania, Italy; [2]G. Rummo Hospital, Interventional Cardiology, Benevento, Italy; [3]San Luca Hospital, Department of Cardiology, Vallo della Lucania, Italy*

Purpose: The mechanical consequence of LBBB is an altered ventricular synchronization with an unfavorable effect on global LV performance. Tissue Doppler echocardiography (TDE) has been shown a useful tool to evaluate ventricular asynchrony. Aim of the study was to evaluate the prognostic significance of TDE assessed myocardial systolic activation delay of both left (LV) and right (RV) ventricle in patients with left bundle branch block (LBBB) and clinical signs of heart failure. Population and methods: 55 patients (mean age 66±13yy; 33 male) with complete LBBB (QRS >120 msec) and in II NYHA class underwent standard Doppler echo and pulsed TDE. Myocardial activation delay (MAD) from the beginning of Q wave of ECG to the onset of systolic myocardial velocity wave was evaluated in 5 different basal myocardial segments (LV anterior, inferior, septal, lateral walls - RV lateral wall). Intraventricular activation delay (IntraV-del) was calculated by the difference of MAD of each LV myocardial segments. Interventricular activation delay (InterV-del) was calculated by the difference of MAD between the most delayed LV segment and RV lateral wall. An index of global ventricular asynchrony (GVA) was obtained by the sum of IntraV-del and InterV-del. Patients were followed and cardiac events such as death, hospitalization (Hosp), congestive

heart failure (CHF) and need of cardiac resynchronization therapy (CRT) were recorded.
Results: The mean value of EF was 40,4±11,9 and of Inter V-del, IntraV-del and GVA was respectively (97.4±46,7; 57.9±35.5; 152.58±82.4 msec). All these parameters resulted inversely related to EF(r=-0.68. p<0.001; r= -0.56 p<0.001; r= -0.96 p<0.0001) During the follow-up (26.2 months, range 11.4 to 37.1) cardiac events were recorded in 36 (65%) patients (death 10 pts, CHF 23 pts; Hosp 31 pts; CRT 4 pts). Cox's proportional hazard multivariate analysis showed that age, GVA and InterV-del (HR=1.0196; 1.0004; 1.0391; p<0.05) were independent predictors of mortality. ROC analysis showed that a cut off value of InterV-del >100 msec (AUC= 0.86; p<0.001) predicted mortality, CHF and Hosp with sensitivitiy and specificity respectively of 81% and 84%; 75% and 90%; 70% and 95%.
Conclusion: Interventricular asynchrony represents a prognostic indicator of mayor cardiac events at two years follow up in patients with LBBB and HF. Our data could have implications for selecting patients suitable for cardiac resynchronization therapy.

1373 Improvement of left ventricular longitudinal systolic function by biventricular pacing is related to changes of dysynchrony induced by low dose dobutamine before pacing

G. Athanassopoulos[1], K. Papadopoulos[2], S. Karagiannis[2], Y. Zhu[2], T. Maounis[2], G. Karatasakis[2], E. Papadakis[2], D.V. Cokkinos[2]. *[1]Pireas, Greece; [2]Onassis Cardiac Surgery Center, 1st Cardiology Department, Athens, Greece*

Introduction: Left ventricular (LV) resynchronisation (BIV) is a new modality of heart failure treatment. Evaluation of LV dysynchrony is based upon only resting time delays of peak systolic velocities and there are no data about delays post dobutamine (DOB). We assessed the dynamic changes of regional time delays post DOB and related them to LV longitudinal function by Doppler tissue imaging (DTI) post BIV.
Methods: 20 consecutive patients who underwent BIV were studied (age:46-70 years, EF: 26±8%). Using DTI, time delays (dt:sec) from QRS to the peak of systolic velocities were measured at the basal (1), mid (2) and apical (3) regions of septal (S) and lateral (L) wall, using 4 chamber apical view, at baseline (No pace) and during BIV. The respective dt (sec) was measured at rest (R) and post low dose (5 min stages of 5 and 10μg/kg/min) DOB.
Time differences (Dif dt) between DOB and R for each region at NoPace and BIV, as well as between BIV and NoPace were calculated.
Peak Velocities (Vel), strain (S) and strain rate (SR) were measured in these 6 LV regions.
Results: At NoPace, DOB decreased dt compared to R in S1 (0.015±0.034, p=0.05) and in L3 (0.032±0.055, p=0.036).
D-dt between DOB/R at NoPace were increasing from base to apex of lateral wall (L1: -0.0089±0.048, L2: -0.0139±0.056, L3:-0.0318±0.055, p=0.022), where it was unaltered from basal/mid to apical regions of S.
During BIV the following increases (.%d:) in DTI indices were found compared to NoPace: In Vel: S1: 0.53±0.9, p=0.023, S2: 0.54±0.9, p=0.03, S3: 0.52±0.7, p=0.006.
In S: S1: 0.41±0.83, p=0.044, S2: 0.59±0.84, p=0.009, S3 0.65±0.78, p=0.003.
In SR: S1: 0.66±1.17, p=0.024, S2: 0.58±0.88, p=0.01, S3: 0.87±1.98, p=0.07, L3: 1.01±1.58, p=0.02.
At BIV, further increases were found at DOB compared to R: In: Vel: S1: 0.30±0.43, p=0.01, S2: 0.25±0.53, p=0.05, L1: 0.74±1.5, p=0.048, L3: 1.66±2.5, p=0.029.
In SR: L2: 0.15±1.16, p=0.035.
When the Dif dt between DOB/R at NoPace was considered, then the following relationships were found between respective Dif dt and increase of DTI indices post BIV: Vel S3: r=-0.65, p=0.002, Vel S2: r=-0.40, p=0.09, SR S2: r=0.55, p=0.01.
Conclusion: The improvement of septal DTI indices of LV longitudinal function post BIV is strongly related with the decrease induced in septal dyssynchrony by DOB. This test can probably be used to predict post BIV improvement of LV longitudinal function.

1374 Discrepancies in the prevalence of ventricular asynchrony in patients with systolic dysfunction by using different methods to evaluate intraventricular asynchrony

L. Perez de Isla, J. Zamorano, C. Almeria, J.L. Rodrigo, A. Aubele, L. Hernando, M. Quezada, C. Macaya. *Hosp.Clinico San Carlos, Istituto Cardiovasc., Unidad de Imagen Cardiovascular, Madrid, Spain*

Some recent studies showed that the EKG is not sensitive enough for reliable identification of patients with correctable mechanical asynchrony. Echo-Doppler provides non-invasive insights into regional asynchrony and may help to improve asynchrony detection. Nevertheless, a large number of methods have been described. Our aim was to assess the prevalence of echocardiographically detected ventricular asynchrony by using different methods.
Methods: we have designed a prevalence registry (RAVE registry) in order to evaluate this issue. 316 consecutive patients referred for an echo study in 13 hospitals comprised the study group. All of them had a left ventricular ejection fraction <40%. We also enrolled 29 control patients without systolic dysfunction. Intraventricular asynchrony was evaluated using four different methods: a) septal-to-posterior wall motion delay (SPWMD) obtained by M-mode (cut-off point=130 ms); b) difference between time from Q wave to left ventricular ejection end as assessed by pulsed Doppler and time from Q wave to the end of the systolic wave of the most delayed basal segment as assessed by pulsed DTI (ejection-DTI time; cut-off point: 50 ms); c) Standard deviation of the time from the Q wave to the end of the systolic wave of all 4 segments (Systolic SD; cut-off point=> 2SD of the control group) and d) the maximum difference in the time from the Q wave to the end of the systolic wave of all 4 segments (Systolic Max; cut-off point > 100 ms).
Results: Mean age was 62.14±13.5 years (75.7% men). Clinical and echocardiographic baseline characteristics were similar in both groups of patients with systolic dysfunction. The prevalence of intraventricular asynchrony is shown in the table below.

Table

	Controls	Narrow QRS	Wide QRS
SPWMD>130 ms	0	75 (40.3%)	56 (60.9%)
Ejection-DTI time>50 ms	0	73 (38.4%)	41 (39.8%)
Systolic Max>100 ms	0	40 (20.8%)	27 (26.2%)
>+2 systolyc SD of controls	0	136 (72.8%)	82 (79.6%)

Prevalences of asynchrony wuth different methods

Conclusion: The prevalence of intraventricular asynchrony depends on the method and criteria that we use to evaluate it. Further studies are needed to establish the most accurate echocardiographic marker of asynchrony to predict which patient is going to respond to CRT.

1375 Tissue Doppler velocity is superior to the displacement or strain mapping in predicting a favourable response after cardiac resynchronisation therapy

Q. Zhang[1], J.W.H. Fung[1], H. Lin[1], Y.S. Chan[1], H.C.K. Chan[2], Y. Zhang[1], Y.Y. Lam[1], C.M. Yu[3]. *[1]The Chinese University of Hong Hong, Department of Medicine & Therapeutics, Hong Kong, China; [2]Alice Ho Miu Ling Nethersole Hospital, Department of Medicine, Hong Kong, China; [3]The Chinese University of Hong Kong, Div.Cardiology, Dept Medicine & Therapeutics, Shatin, Hong Kong*

Background: Direct assessment of systolic asynchrony by echocardiography appears useful to predict a favorable response after cardiac resynchronization therapy (CRT). This study compared the predictive values of 3 different forms of tissue Doppler imaging (TDI) signals.
Methods: Echocardiography with TDI was performed at baseline and 3-month after CRT in 55 patients (66±11 yrs, 72.7% male). During off-line TDI analysis, the time to peak myocardial systolic velocity in ejection phase (Ts), the time to peak myocardial displacement and the time to peak systolic strain were measured in a 6-basal, 6-mid segmental model. Parameters of systolic asynchrony derived by velocity, displacement and strain mapping were calculated as standard deviation of 12 (SD-12) and 6 basal segments (SD-6), basal septal-to-lateral segmental difference (sept-lat) and basal septal-to-posterior segmental difference (sept-post). These parameters were correlated with percentage reduction in left ventricular end-systolic volume (DeltaLVVs) and absolute gain in ejection fraction (DeltaEF).
Results: There was a reduction of LV volume (End-diastolic: 179±75 vs 156±72cm^3; End-systolic: 136±68 vs 107±61cm^3) and improvement of EF (26±9 vs 34±11%) after CRT for 3 months (all p<0.001). Among the 3 TDI techniques for systolic asynchrony, all of velocity parameters, but only 2 of the displacement parameters and none of strain parameters correlated significantly with LV reverse remodeling and gain in EF (Table), in which Ts-SD-12 remained the best.

Table

		SD-12	SD-6	Sept-lat	Sept-post
For Ts	DeltaLVVs	-0.82**	-0.70**	-0.61**	-0.50**
	DeltaEF	0.65**	0.55**	0.42*	0.37*
For Displacement	DeltaLVVs	-0.36*	-0.26	-0.16	-0.07
	DeltaEF	0.28*	0.21	0.07	-0.04
For Strain	DeltaLVVs	-0.17	-0.13	0.11	0.08
	DeltaEF	0.23	0.22	0.03	-0.02

**p<0.001, *p<0.05

Conclusion: Parameters of systolic asynchrony derived from tissue velocity is superior to those from displacement and strain mapping in predicting LV reverse remodeling and gain in EF after CRT. Furthermore, it is suggested to measure multiple segments for more comprehensive evaluation.

1376 Evaluation of intraventricular mechanical asynchrony using real time 3D echocardiography

E. Liodakis, O. Al Sharef, D. Dawson, P. Nihoyannopoulos. *Hammersmith Hospital, Echocardiography Department, London, United Kingdom*

Introduction: Mechanical asynchrony (MA) assessed with Real-Time Transthoracic 3-D echocardiography (RT3DE) is a major observation in patients with left

ventricular dysfunction. This asynchrony, observed in the 16 regions, can be measured using the Dysynchrony Index (DI), which derives by calculating the standard deviation of the time for each of the segments to reach its minimum volume
Hypothesis: MA measured using the DI may be correlated to the ejection fraction (EF) and to the length of the QRS complex in patients suffering from heart failure.
Methods: We investigated 40 heart failure patients who were paired with 40 normal subjects. RT3D scanning was performed using the SONOS-7500. TomTec software was used for the offline analysis.
Results: From the 40 patients that were investigated 38% had mild, 40% moderate and 22% severe systolic dysfunction. The DI was 10.5±1.3, 13.8±2.2 and 19.5±1.4 respectively (fig2)which was statistically significant higher than that observed in the normal subjects (6.6±0.9 t test $p<0.001$). A strong negative correlation between the EF and DI was found.($r=-.78$ n=40 $p<0.01$fig1)The length of the QRS complexes was <120ms in 27%, between 120-140ms in 30% and >140ms in 43% of the patients. The DI was 7.3±1.2, 13.8±1.6 and 17.2±1.4 respectively. There was a positive correlation between the length of the QRS complex and the DI. ($r=.52$ n=40 $p<0.001$). Excellent Inter- and Intraobserver agreement was found in the calculation of DI using the Interclass Correlation Coefficient.(0.94 and 0.95 respectively)

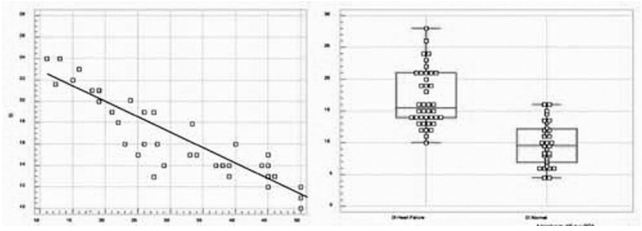


Fig 1 and 2

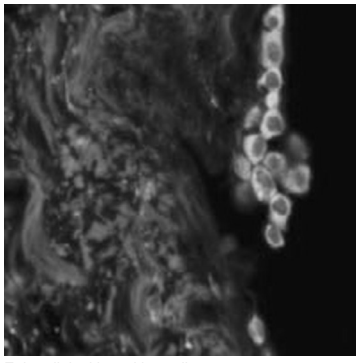
Conclusions: RT3DE is an effective and reproducible tool for quantifying mechanical asynchrony. DI is strongly correlated with systolic dysfunction and could be a valuable parameter in the assessment of heart failure patients.

PAEDIATRIC CARDIOLOGY: COMPLEX QUESTIONS, DIFFICULT ANSWERS

1385 Epicardium contains a population of c-kit positive cells that may contribute to myocardial regeneration

C. Castaldo[1], D. Nurzynska[1], F. Di Meglio[1], S. Vitale[1], D. Cesselli[2], A.P. Beltrami[2], P. Muller[3], S. Montagnani[1]. *[1]Universita' "Federico II", Scienze biomorfologiche e funzionali, Napoli, Italy; [2]Università di Udine, Ricerche Mediche e Morfologiche, Udine, Italy; [3]Universitat des Saarlandes, Departments of Innere Medizin III, Homburg/Saar, Germany*

On the basis of the previous studies which described in the myocardium the presence of primitive cells that in vitro differentiate in the myocardial lineages, we identified by immunofluorescence in the adult hearts of healthy donors (n=10) and diseased hearts (ischemic and dilated cardiomyopathy, n=7) the population of c-kit (+) cells whose localization and phenotype differed between the groups. In the normal hearts c-kit(+) cells were observed mainly in the epicardial layer of ventricles. These cells were expressing transcription factors GATA-4 and MEF2C and were negative for alpha-sarcomeric actin. Confocal microscopy revealed the co-localization of alpha laminin and alpha4 integrin chain on these cells, but the western blot analysis showed the differences in the laminin expression between normal and pathological hearts: in the latter the level of expression was significantly higher and interestingly isoform 1 of laminin (characteristic for fetal, developing heart) was present. In the pathological hearts the c-kit(+) cells were not longer found in the epicardial region, but their presence was evidenced in the main myocardium. These cells also expressed MEF2C and GATA-4, but, in contrast with those found in the epicardial region of normal hearts, were alpha-sarcomeric actin positive.



Epicardial c-kit positive cells

We hypothesize that the epicardial c-kit(+) cells constitute the population of residual progenitors which respond to pathological conditions and changes in the extracellular matrix and migrate into the myocardium contributing to the regeneration of cells of cardiac lineages.

1386 Developmental changes of the right ventricular function using color tissue Doppler and strain echocardiography

M. Hajikano[1], Y. Katsube[2], S. Ogawa[3], R. Fukazawa[3], M. Kamisago[3], Y. Kuramochi[3], Y. Uchikoba[3], E. Ikegami[3]. *[1]Nippon Medical School 2nd Hospital, Pediatrics Department, Kawasaki, Japan; [2]Nippon Medical School 2nd Hospital, Pediatrics, Kawasaki, Japan; [3]Nippon Medical School Hospital, Pediatrics, Tokyo, Japan*

Introduction: cardiac function changes during development. However, to evaluate the changes, especially right ventricular function is difficult by using conventional echocardiography. Recently, color tissue Doppler echocardiography was developed and the efficacies for evaluation of cardiac function in adult have been reported. Purpose: in the present study, we investigated the developmental changes from neonate to adolescent of the right ventricular function by color tissue Doppler echocardiography.
Methods: we classified 45 healthy children to following six groups and performed color tissue Doppler echocardiography; day 0 (group A, n=9), day 5 (group B, n=6), 1 month (group C, n=7), 1 year-old (group D, n=6), 6-7 year old (group E, n=9), and 12-13 years old (group F, n=7). Measurement of peak early diastolic value on flow pattern of tricuspid valve (E), peak strain value of right ventricular free wall from apical 4-chamber view, peak systolic tissue velocity (Sw), and peak early diastolic value (Ew) were determined as parameters of systolic and diastolic function. In addition, we calculated Tei index (index of combined systolic and diastolic ventricular myocardial performance) calculated from flow pattern of tricuspid valve and pulmonary artery.
Results: representative parameters (M±SE) are in the table (# $p<0.05$ vs. B). Summaries: there were significant changes in parameters of right ventricular systolic and diastolic function from early neonate to 1 year of age, and no remarkable changes to adolescent.

	B	D	E
strain (%)	16.5±2.0	34.9±2.9 #	28.3±1.8 #
Sw (cm/s)	3.06±0.26	8.81±0.76 #	10.32±0.36 #
E (cm/s)	0.5±0.04	0.66±0.04	0.53±0.02
Ew (cm/s)	3.98±0.78	13.18±0.84 #	10.82±0.48 #
E/Ew	0.15±0.03	0.05±0.01 #	0.05±0.01 #
Tei index	0.18±0.05	0.15±0.02	0.13±0.16 #

Conclusion: there were significant changes in parameters of right ventricular systolic and diastolic function from early neonate to 1 year of age, and no remarkable changes to adolescent.

1387 Analysis of intercalated disc remodelling in explanted hearts from children with congenital heart diseases or dilated cardiomyopathy

P. Francalanci[1], A. Tessa[2], F.M. Santorelli[2], F. Diomedi Camassei[1], F. Parisi[3], R. Di Donato[3], F. Callea[1]. *[1]Children's Hospital Bambino Gesu, Pathology, Rome, Italy; [2]Children's Hopital Bambino Gesù, Molecular Medicine, Rome, Italy; [3]Children's Hospital Bambino Gesù, DMCC, Rome, Italy*

Purpose: The cadherin family of trans-membrane proteins mediates mechanical junctions at the level of intercalated discs (ID) where the ends of thin and intermediate filaments are anchored to polar sarcolemma via adherents junctions and desmosomes, respectively. In the adherens junctions, the barb ends of actin of terminal sarcomeres are believed to link N-cadherin through binding to alfa-actinin or vinculin, which joins a-catenin, which links beta- or gamma-catenin.
Previous study in hamster and human hypertrophic cardiomyopathy demonstrated a remarkable accumulation of N-cadherin and beta-catenin in disarrayed ID and that the alteration of this pathway could play a key role in modulation of genes directly related to the onset of the hypertrophic phenotype.
Aim: Aim of this study is to evaluate whether in end-stage cardiac hypertrophy due to dilated cardiomyopathy (DCM) or congenital heart disease (CHD) the ID remodelling is associated with abnormal expression of cadherin/catenin complex (adhesion junctions) as well as of connexin 43 (Cx43) in gap junction (GJ).
Methods: Ventricular samples of explanted hearts obtained from 8 children (aged 1-15 years) with DCM and from 6 children (aged 9-15 years) with CHD were studied by light microscopy, immunohistochemistry and Western blot analysis.
Results: Both DCM and CHD displayed hypertrophic and disarrayed myocells with disorganized morphology of the IDs. In disarrayed ID, beta-catenin immunostaining was increased and fragmented in all samples, while gamma-catenin stain was almost regular in DCM and faint in CHD. Cx43 expression was abnormal in all, showing a distribution over the entire surface of the myocytes, consistent with neonatal distribution. By Western blotting analysis, beta-catenin was significantly increased in 10 samples, 6 DCM (+ 53%) and 4 CHD (+31%). Contrariwise, gamma-catenin expression was unchanged in DCM, whereas it was reduced (25%) in 4/6 patient with CHD. Cx43 was normal.
Conclusions: This study suggests that beta-catenin deposits occur at the ad-

hesions junctions in end-stage hypertrophic ventricular myocytes, regardless of the primitive heart pathology, either structural cardiomyopathy (DCM) or congenital malformation (CHD). This seems not associated with simultaneous down-regulation of gamma-catenin, at least in DMC. Remodelling of adhesions junctions does not lead to a quantitative changes of Cx43, although the expression of this protein can be abnormal.

1388 Natural history of Wolff-Parkinson-White syndrome

C. Pappone[1], F. Manguso[2], R. Santinelli[2], P. Mazzone[2], G. Vicedomini[2], G. Augello[2], I. Isabelle[2], V. Santinelli[2]. [1]*HSR Fondazion S.Raffaele, Reparto di Aritmologia, Milan, Italy;* [2]*San Raffaele University Hospital, Electrophysiology and Cardiac Pacing, Milan, Italy*

Background: The natural history of asymptomatic ventricular preexcitation remains largely unknown and information pertaining to risk stratification is insufficient.
Methods: From 1990 to 2004, we collected clinical and electrophysiologic data in 477 asymptomatic untreated subjects with Wolff-Parkinson-White syndrome.
Results: In a total observation time of 2,070 patient-years, 80 patients (16.8 percent) presented an arrhythmic event. Supraventricular tachycardia was documented in 55 (11.5 percent), atrial fibrillation in 18 (3.8 percent), and ventricular fibrillation in 6 patients (1.3 percent). Symptoms began between 12 and 25 years and, after 35 years, there was little risk of having a first arrhythmic episode. Independent predictors were age (P=0.001), inducibility (P<0.001) and presence of multiple pathways (P<0.001). Syncope, cardiac arrest, or sudden death occurred in 26 patients (5.5 percent) and were predicted by age (P=0.02), inducibility (P=0.01) and multiple pathways (P<0.001). Ventricular fibrillation was only predicted by multiple pathways (P=0.04). By combining these risk factors, we stratified patients into low (70.2 percent of the studied population), moderate (10.2 percent), and high-risk (23.4 percent) groups.
Conclusions: The natural history of asymptomatic Wolff-Parkinson-White syndrome is not as benign as previously believed. Inducibility, multiple pathways and young age are independent predictors of arrhythmic events and can be used to stratify asymptomatic population into low, moderate and high-risk groups. Prophylactic catheter ablation can be offered to subjects who are in the high-risk group. It will be beneficial to address the role of invasive testing in future guidelines.

1389 Neonatal electrocardiographic screening of genetic arrhythmogenic disorders and congenital cardiovascular diseases: prospective data from 31,000 infants

K. Goulene[1], M. Stramba-Badiale[1], L. Crotti[2], S.G. Priori[3], P. Salice[4], S. Mannarino[5], E. Rosati[6], P.J. Schwartz[2]. [1]*IRCCS Istituto Auxologico Italiano, Cardiology Dpt., Milano, Italy;* [2]*University of Pavia, Dept of Cardiology, Pavia, Italy;* [3]*IRCCS Fondazione Maugeri, Molecular Cardiology, Pavia, Italy;* [4]*ICP, Pediatric Cardiology, Milano, Italy;* [5]*IRCCS Policlinico San Matteo, Pediatrics, Pavia, Italy;* [6]*Ospedale A Perrino, Neonatology, Brindisi, Italy*

Our prospective study on 34000 newborns (NEJM 1998) showed an increased risk for Sudden Infant Death Syndrome (SIDS) among infants with a prolonged QT interval. Our subsequent molecular studies in large SIDS populations have indicated that mutations in the long QT Syndrome (LQTS) genes can be present in 10-15% of SIDS victims. As sudden death is often the first manifestation of LQTS and as effective therapies available, these findings have raised the controversial issue of neonatal ECG screening. To assess prevalence and clinical significance of neonatal ECG abnormalities, we initiated a prospective study of 50,000 consecutive neonates, following the guidelines of the European Society of Cardiology (EHJ 2002). In this way we tested the feasibility of widespread neonatal ECG screening. ECGs are recorded between the 15th and 25th day of life in 16 Italian centers and then transmitted to the coordinating center for analysis together with demographic and clinical variables. As of February 10th 2005, we recorded ECGs in 31,313 infants: 430 (1.4%) had a QTc > 440 ms and 31 (1/1,000) had a QTc > 470 ms, our cut-off value for molecular screening of LQTS genes. So far, genotyping has been completed in 8/20 and identified LQTS mutations in 6 infants (4 on KCNQ1 and 2 on HERG). One case was a de novo mutation while in the remaining 5 the finding led to the unsuspected diagnosis of LQTS in other family members. Additional significant ECG abnormalities were found in 155 neonates. In 4 asymptomatic neonates ECG abnormalities led to additional investigations which revealed coarctation of the aorta with cardiac involvement in 3 and anomalous origin of the left coronary artery in one: this allowed successful surgical correction in all 4 infants. Thus, an ECG performed in the first month of life identifies abnormalities associated with cardiovascular risk. LQTS can be diagnosed very early, allowing preventive measures not only in the neonate but also in the affected family members. Also, still asymptomatic infants with cardiovascular malformations can be diagnosed thus allowing therapeutic interventions, including surgery, prior to the development of irreversible or severe cardiac damage.

1390 Radiofrequency catheter ablation of intracardiac masses in childhood

M. Emmel[1], N. Sreeram[1], J.V. DeGiovanni[2], K. Brockmeier[1]. [1]*Univ. Hospital of Cologne, Department of Pediatric Cardiology, Köln, Germany;* [2]*Birmingham Children's Hospital, Paediatric Cardiology, Birmingham, United Kingdom*

Introduction: Intracardiac rhabdomyomas resulting in haemodynamically significant obstruction or recurrent arrhythmias, have hitherto been managed by open heart surgery. Hypertrophic cardiomyopathy (HOCM) with symptomatic left ventricular outflow obstruction (LVOTO) in young children has also been treated by surgical myectomy. We present our experience with radiofrequency catheter ablation (RFA) in two infants with intracardiac rhabdomyomas and in two children with HOCM.
Methods: Of the two patients with rhabdomyoma, in both the rhabdomyoma was located on the mitral valve. The first, aged 7 months, had recurrent reentrant supraventricular tachycardia, which was resistant to drug therapy. At invasive electrophysiologic study, the accessory pathway was confirmed to be the rhabdomyoma, which was successfully ablated. Within 24 hours, the tumour showed liquefaction necrosis, with further shrinkage within 6 weeks of ablation. The second patient, a neonate with a large supramitral rhabdomyoma, had clinically significant mitral valve inflow obstruction and a large left to right shunt at atrial level. Via a venous approach, the tumour was ablated using RF energy, with resultant tumour shrinkage and resolution of symptoms. The infant was discharged from hospital 7 days post-ablation.
The HOCM patients, aged 4 years and 11 years respectively, had severe symptomatic LVOTO with Doppler gradients of 70 mmHg and 80 mmHg. At invasive electrophysiologic study, sequential AV temporary pacing using varying AV intervals did not influence the pullback gradient in either of the patients. The extent of the septal obstruction was delineated by left ventricular angiography. Transcatheter septal ablation was then performed, using a 7F cooled tip ablation catheter (Sprinklr, Medtronic) introduced retrogradely via the femoral artery, taking care to stay away from the His bundle. A series of lesions was applied, beginning distally, and working towards the aortic valve. Transient junctional rhythm during RF application necessitated constant atrial pacing, to confirm the integrity of AV conduction. The extent of myocardial necrosis was documented by serum Troponin T and CK-MB levels. At 6 week follow-up, symptoms had improved, the minimal LVOT diameter had increased, and the peak Doppler gradient had decreased to 20mm Hg and 40 mmHg respectively.
Conclusions: RFCA is an excellent alternative to surgery in selected symptomatic patients with intracardiac masses such as rhabdomyomas or with HOCM. It is possible to alleviate the obstruction and relieve symptoms, while preserving AV conduction.

SPECIFIC ISSUES IN GROWN-UP CONGENITAL PATIENTS: AN INCREASING PROBLEM?

1391 Prevalence of cardiovascular risk factors in adults with congenital heart disease

P. Moons[1], K. Van Deyk[2], D. Dedroog[2], E. Troost[2], W. Budts[2]. [1]*Catholic University of Leuven, Center f. Health Services & Nursing Res., Leuven, Belgium;* [2]*University Hospitals of Leuven, Division of Congenital Cardiology, Leuven, Belgium*

This study assessed the presence of risk factors for ischaemic heart disease in a large sample of adults with congenital cardiac anomalies.
Methods: At our outpatient clinic, all patients are examined by an advanced practice nurse and a congenital heart disease cardiologist. Data on smoking behaviour, sport participation, blood pressure, body mass index, and the diagnosis of diabetes are recorded systematically. In a 4-years period, we harvested data of 1976 individual patients (54% male) with a median age of 26 years.
Results: Table 1 describes risk factors in males and females with congenital heart

Table 1

Risk factor		Males	Females	p-value
Smoking				<0.001
	No	77.0%	85.0%	
	Occasionally	1.9%	1.8%	
	Regularly	21.2%	13.1%	
Participation in sport				0.011
	No	35.2%	40.8%	
	Occasionally	13.0%	14.1%	
	Regularly	51.8%	45.1%	
Blood pressure				0.001
	Systolic blood pressure < 140 mmHg + diastolic blood pressure < 90 mmHg	62.1%	70.1%	
	Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg	37.9%	29.9%	
BMI				<0.001
	<20 kg/m^2	19.2%	19.5%	
	20-25 kg/m^2	47.7%	49.6%	
	>25-30 kg/m^2	26.4%	19.7%	
	>30 kg/m^2	6.7%	11.2%	
Diabetes		0.9%	0.6%	0.24

disease. Only 20.4% men and 21.0% women have a fully heart-healthy lifestyle, as they presented without any risk factor.
Conclusion: A substantial amount of patients had one or more cardiovascular risk factors. Hence, primary prevention by strenghtening educational efforts, becomes critically relevant in patients with congenital heart disease to avoid the additional burden of coronary events in this growing population of patients.

1392 Systematic, early surgical repair throughout the last 30 years has substantially made to decline the overall prevalence of Eisenmenger reaction in simple congenital heart disease

J.M. Oliver[1], E. Diaz Caraballo[1], P. Gallego Garcia De Vinuesa[2], A. Gonzalez[1], J. Ruiz Cantador[1], M. Mateos[1], A. Sanchez Recalde[1], A. Aroca[1]. *[1]La Paz University Hospital, Adult Congenital Heart Disease Unit, Madrid, Spain; [2]Virgen Macarena University Hospital, Seville, Spain*

Background: A multicentric European study has recently noted that more than two thirds of the adults with Eisenmenger reaction (ER) had a simple congenital heart disease (CHD) and it is recommended to correct these defects before ER developes. However, whether the early surgical approach of these simple CHD throughout the last 30 years modifies the prevalence of ER in adults still remains unclear.
Methods: In 2,568 consecutive patients >15 years with CHD, we identified those who fulfilled the following criteria: 1) right ventricular systolic pressure at systemic level; 2) no right ventricular outflow tract stenosis; and 3) a nonrestrictive communication at any level with predominant right-to-left shunt. According to the related CHD, they were classified into two groups: simple CHD (isolated atrial or ventricular septal defect and patent ductus arteriosus; ASD, VSD and PDA respectively) and complex CHD. The overall prevalence and the prevalence of ER in the group of simple CHD were analysed.
Results: A total of 41 adults with ER made up the study population. Mean age was 35 + 12 years (range 16-81) and 23 (56%) were female. Thirteen patients (32%) had a simple CHD (ASD: 2; VSD: 10; PDA: 1) and 28 (68%) with a complex CHD (atrioventricular septal defect: 14; univentricular heart: 6; truncus arteriosus: 3; D-TGA with VSD: 2; and others complex CHD: 3). The overall prevalence of ER was 1.6% in the whole group of adults with CHD while it was 0.4% among 478 patients with ASD; 1% among 105 patients with PDA; and 2.6% among 380 patients with VSD. All patients with simple CHD and ER were older than 30 years or had a severe chromosomal abnormality.
Conclusions: Eisenmenger reaction is nowadays an uncommon complication in adults with CHD. The overall prevalence of ER in adults with a simple CHD has changed appreciably with time. This decrease may be a result of the systematic and early surgical approach throughout the last 30 years.

1393 Rate of deterioration of right ventricular function in relation to conduction disturbances in adult patients after atrial repair for transposition of the great arteries

R.W.C. Scherptong[1], H.B. Grotenhuis[2], A. de Roos[2], M.J. Schalij[3], E.E. van der Wall[3], H.W. Vliegen[3]. *[1]Leiden University Medical Centre, Department of Heart Disease, Leiden, Netherlands; [2]Leiden University Medical Centre, Department of Radiology, Leiden, Netherlands; [3]Leiden University Medical Centre, Department of Heart Disease, Leiden, Netherlands*

Background: Adults after atrial repair for transposition of the great arteries (TGA) are prone to a decline in right ventricular (RV) function. The rate of deterioration of ventricular function over time and the relation to ECG parameters is unclear.
Aim: To quantify the rate of deterioration in RV function over time, and to analyse QRS and QT duration as a predictor of decline in ventricular function.
Methods: 22 adult (18-39 yrs) pts underwent serial MRI and ECG examination during regular follow-up. Right ventricular volumes and ejection fraction were measured using MRI. QRS and QT duration were measured manually using computerized ECG's.
Results: Over a mean follow-up period of 4.9 ±2.5 yrs, mean RV end diastolic volume increased from 159 ±49ml to 238 ±99ml, P< 0.001 (Fig. 1). Mean end systolic volume increased from 75 ±27ml to 136 ±80ml, P<0.001. Mean Ejection Fraction decreased from 53 ±8% to 43 ±9%, P=0.001. Initially QRS duration was positively correlated to end diastolic volume (R=0.78, P<0.01) and remained correlated to end diastolic volume at follow-up (R=0.55, P<0.01). Correlation between QT duration and end diastolic volume was initially not significant (R=0.41, P=0.06), but reached significant levels at follow-up (R=0.46, P=0.03). During follow up mean QRS duration increased from 101 ±18ms to 106 ±20ms, P=0.105. Mean Bazett corrected QT duration increased from 417 ±36ms to 425 ± 33ms, P=0.063.
Conclusion: Pts late after Mustard or Senning repair show a remarkable decline in RV function over a time period of 5 years. QRS and QT duration are related to RV volume and show a trend towards increasing over time.

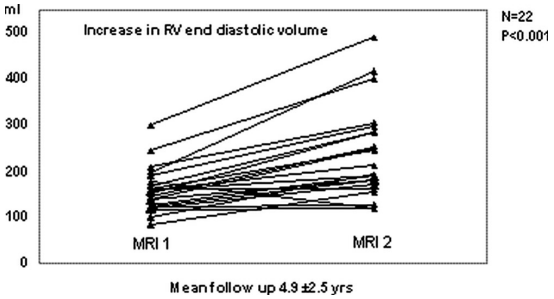


Figure 1

1394 Evaluation of aortic stiffness and wave reflections in patients after successful coarctation repair

S. Brili, I. Dima, N. Ioakeimidis, N. Alexopoulos, C. Vlachopoulos, C. Antoniades, D. Tousoulis, C. Stefanadis. *Athens Medical School, Hippokration Hospital, 1st Cardiology, Athens, Greece*

Introduction: We have previously shown that normotensive patients with successful coarctation repair (SCR) have decreased distensibility of the upper body and increased distensibility of the lower body arteries. Aortic stiffness and wave reflections are implicated in the pathogenesis of hypertension. In this study we aimed at assessing whether aortic stiffness and wave reflection indices are influenced in this category of patients.
Methods: 19 normotensive, asymptomatic patients 26±7 years old, and age at surgery 15±9 years with SCR and gradient <25mmHg, and 19 age, gender, height, weight, smoking status, lipid profile adjusted controls were studied. Carotid-femoral pulse wave velocity (PWV) was measured as an index of the stiffness of the whole aorta using a validated non-invasive device (Complior®). Wave reflections resulting from the whole body were studied using a validated system (Sphygmocor®) that employs high-fidelity arterial tonometry for the non-invasive registration of radial pulse waveform and appropriate computer software for pulse wave analysis. Aortic pressure waveform was synthesized from the radial waveform using a generalized transfer function. Augmentation index (AIx) was measured as an index of wave reflections.
Results: SCR patients had higher systolic, pulse and mean pressure than controls, while diastolic pressures did not differ. PWV and AIx were not different among the two groups (table)

	Postcoarctectomy patients	Controls	P value
Age, years	26.5 (7.3)	27.5 (5.8)	NS
SP, mmHg	130.6 (14.9)	116.9 (14.6)	<0.01
DP, mmHg	71.7 (8.7)	68.6 (8.3)	NS
PP, mmHg	58.9 (13.2	48.3 (10.4)	<0.01
MeanP, mmHg	90.7 (10.0)	83.4 (10.2)	<0.05
Heart rate, bpm	70.5 (11.1)	70.7 (11.2)	NS
PWV, m/sec	5.2 (0.9)	5.5 (0.9)	NS
AIx, %	11.1 (13.7)	9.3 (9.2)	NS

Conclusions: Despite the fact that SCR patients had higher systolic and pulse pressures, PWV and AIx were not different than controls, possibly because these indices are influenced by the elastic properties of both the pre- and post-coarctation part of the arterial tree.

1395 Clinical experience with bosentan for the treatment of pulmonary hypertension associated with congenital heart disease

J. Carlsen[1], M. Humbert[2], D.G. Kiely[3], C. van Lierop[4], B. Schwierin[4], M.M. Hoeper[5]. *[1]Charlottenlund, Denmark; [2]Hopital Antoine Beclere, Service de Pneumologie, Clamart, France; [3]Dept. of Respiratory Medicine, Royal Hallamshire Hospital, Sheffield, United Kingdom; [4]Actelion Pharmaceuticals, Medical Department, Allschwil, Switzerland; [5]Hannover Medical School, Dept. of Respiratory Medicine, Hannover, Germany*

Congenital heart diseases (CHD) including systemic-to-pulmonary shunts are complicated in about 15% by pulmonary arterial hypertension (PAH), resulting in reduced exercise capacity and increased mortality. The oral dual ETA/ETB antagonist bosentan is the only approved oral therapy for PAH and is regarded as cornerstone therapy according to recently published guidelines. However, treatment experience with bosentan in PAH-CHD is limited.
In agreement with the European Agency for the Evaluation of Medicinal Products (EMEA), a postmarketing surveillance program (TRAX) was established in May 2002 to monitor the safety of bosentan irrespective of disease etiology (including the PAH-CHD subgroup) under clinical practice conditions. There was focus on liver function, because in the pivotal trials elevations of liver aminotransferases (ALT/AST) were observed in 11.2% of patients.
TRAX was a web-based interactive database in 18 countries to (1) provide treatment and drug monitoring algorithms for the prescriber and (2) collect signals: potential safety signals (stipulating a complete drug reaction form) such as adverse events, specific categories of signals including elevations of ALT/AST, other abnormal lab values, death, and hospitalization; non-safety signals including reasons for discontinuation such as patient request, non-medical reason, or lost to follow up.
Until 19 November 2004, a total of 579 patients with PAH-CHD (65.3% females,

≤ 5 years of age: 5.0%, 6-11 yrs: 8.1%, 12-17 years: 10.2%, ≥ 18 years: 76.8%) were included. 16.4% of patients were in NYHA class II, 67.7% in class III, and 10.9% in class IV. Concomitant medications at baseline included anticoagulants in 58.0% and prostanoids in 14.9%. Mean exposure to bosentan was 38.6 (± 32.2) weeks. 176 patients (23.9%) were treated with bosentan for at least 1 year. Potential safety signals were recorded in 19.7%, which was substantially lower than in patients with idiopathic PAH (IPAH: 36.7%). Elevated ALT/AST values after bosentan initiation were recorded in 2.8% (IPAH: 8.4%), with the following breakdown: ≤ 3 x upper limit of normal [ULN]: 0.2%; >3 x ULN to ≤ 5 x ULN: 1.2%; > 5 x ULN to ≤ 8 x ULN: 0.9%; > 8 x ULN: 0.2%; unknown values: 0.3%. Median time to onset of ALT/AST elevations was 55.5 days. There were no cases of fatal or permanent liver injury associated with bosentan.
Long-term bosentan was safe in the PAH-CHD subgroup, as indicated by the lower number of potential safety signals and low rate of LFT elevations compared to the IPAH subgroup and the safety profile derived from clinical trials.

1396 Fenestrated ASD closure in adults with ASD and pulmonary hypertension or right heart failure

L. Bruch, F. Scherf, A. Winkelmann, S. Rux, M.O. Grad, F.X. Kleber.
ukb and charite medical school, Berlin, Germany

Background: Atrial Septal Defects (ASDs) with a pulmonary to systemic flow ratio (Qp/Qs) above 1.5 are usually considered candidates for interventional or surgical closure to reduce right ventricular failure due to volume overload, development of pulmonary hypertension and development of arrhythmias. However, up to 30% of patients have either persistent pulmonary hypertension or right ventricular enlargement after ASD closure in adulthood and cases with right and left heart failure after ASD closure have been reported by several investigators.
Methods: In our own series we found 12% of patients developing acute right or left heart failure after complete closure. A partial closure with a fenestrated ASD closure device offers the opportunity to reduce volume overload to the RV and simultaneously limits pressure increases in both atria by using the atrium with the lower pressure as an overflow reservoir.
Results: We evaluated 14 patients after partial ASD closure, 12 with fenestrated umbrella devices (AGA Medical), 1 by leaving a second small atrial communication untreated and one with incomplete surgical closure. The patients mean age was 64.6 years. All had pulmonary hypertension (mean PAPm 34 mmHg), mean Qp/Qs was 2.74. Stretch size of the ASD was 18-38 mm. We used Amplatzer ASO-devices with a 6 to 8 mm fenestration.
So far repeat cardiac cath was performed 5-11 months after the intervention in 12 patients, echo and CPX follow up in 13 patients. Despite the considerable residual shunt (Qp/Qs 1.4) the following favourable changes were seen: see table 1.
No patient developed signs or symptoms of left or right heart failure on follow up.

Table 1

	Pre	Post (3-12 months)	
Mean NYHA	2.5	1.3	
VO2max.	16.0	19.6	ml/kg/min.
VE vs. VCO2 slope	37	30	
RVEDD	46 ± 6	40 ± 5	mm
PAPsys (echo)	53 ± 6	39 ± 7	mmHg

p<0.05 for changes in all parameters

Conclusions: We conclude, that incomplete closure of ASD in patients with right heart failure or PHT is appropriate and yields a low complication rate. It might be the preferred way of therapy in selected patients. Randomized protocols should be performed.

GENDER INFLUENCES ON CORONARY DISEASE

1429 Serum creatinine is a strong independent predictor of vascular events in women undergoing coronary angiography

C.H. Saely[1], S. Aczel[1], T. Marte[1], P. Langer[2], H. Drexel[1].
[1]Landeskrankenhaus Feldkrich, Department of Medicine and VIVIT, Feldkirch, Austria; [2]VIVIT-Institute, Feldkirch, Austria

Objective: To evaluate the association of serum creatinine with angiographic coronary artery disease (CAD) and with the incidence of vascular events in women undergoing coronary angiography.
Methods: We enrolled 243 women undergoing coronary angiography for the evaluation of established or suspected coronary artery disease (CAD). With respect to serum creatinine we built three groups of patients: women with low serum creatinine <1.0 mg/dl (group 1; n = 110), women with serum creatinine ≥1.0 mg/dl, but within the normal range, i.e. <1.2 mg/dl (group 2; n = 96), and women with mildly elevated serum creatinine above the normal range, but =<3 mg/dl (group 3; n = 36). Women with serum creatinine >3 mg/dl (n = 1) were excluded. Over a mean follow-up period of 2.3 ± 0.4 years the incidence of vascular events was recorded.
Results: The prevalence of significant coronary stenoses ≥50% increased from group 1 (34.5% [38 of 110]) over group 2 (50.0% [48 of 96]) to group 3 (61.1% [22 of 36]), p for trend = 0.002. Also, the incidence of vascular endpoints increased significantly from group 1 (2.7% [3 of 110]) over group 2 (11.4% [11 of 96]) to group 3 (13.9% [5 of 36]), p for trend = 0.004. In Cox regression analyses adjusting for age, gender, diabetes status, hypertension, smoking, and serum cholesterol serum creatinine proved independently predictive for vascular events, with adjusted odds ratios of 5.88 (1.48-23.31); p = 0.012, and 7.57 (1.55-37.05); p = 0.012) for groups 2 and 3 versus group 1.
Conclusions: Among women undergoing coronary angiography, serum creatinine is associated with angiographic CAD and is a strong independent predictor of vascular events. Even slight elevations of serum creatinine within the normal range are associated with an increased prevalence of angiographic CAD and with an increased incidence of vascular events.

1430 Age and sex specific trends in short and long-term case fatality following a first myocardial infarction 1990-2000

N.F. Murphy[1], K. MacIntyre[2], J. Chalmers[3], S. Frame[3], A. Redpath[3], S. Stewart[4], S. Capewell[5], J.J.V. McMurray[1]. *[1]Western Infirmary, Department of Cardiology, Glasgow, United Kingdom; [2]University of Glasgow, Glasgow, United Kingdom; [3]ISD, Edinburgh, United Kingdom; [4]University of South Australia, Adelaide, Australia; [5]University of Liverpool, Liverpool, United Kingdom*

Introduction: Studies have shown that case fatality following hospitalisation with a first myocardial infarction is improving. However it is not known whether these trends are similar in men and women and in different age groups. Little is known about contemporary trends in short and longer term prognosis of men and women in different age groups following hospitalisation with a first myocardial infarction. The aim of this study was to describe and compare trends in short and longer term case-fatality following hospitalisation with a first myocardial infarction, in men and women and in different age groups between 1990 and 2000.
Methods: Using the Scottish Linked Morbidity Record Database we identified all patients hospitalised with a first myocardial infarction between 1990 and 2000. We calculated sex specific case fatality at 30 days, one year and five years. We used multivariate modelling at 30 days, one year and 5 years to examine factors affecting prognosis and to determine trends over time in men and women separately and in different age groups.
Results: Between 1990 and 2000 there were 110,226 hospitalisations with a first myocardial infarction. During this time crude 30 day case fatality fell by 19% in men and 8% in women and five year case fatality by 9% in men and 5% in women. Falls in adjusted 30 day case fatality following a first myocardial infarction were greater in younger than in older individuals and in men than in women (59% decline in men and 47% in women aged <65 years). Falls in adjusted one year and five year case-fatality excluding 30 days were similar in men and women but greater in younger than in older individuals.
Conclusion: There have been greater improvements in short term than in longer term survival following a myocardial infarction. Decline in short term case fatality has been greater in men. Improvements in survival have been more marked in younger age groups. This may reflect differences in treatment and in secondary prevention between different age groups and men and women.

1431 Apparent gender bias in the treatment of women with an acute coronary syndrome. The global registry of acute coronary events

S. Dey[1], K.A.A. Fox[2], E.P. Gurfinkel[3], F.A. Anderson[4], N. Gowda[4], D. Brieger[5], K.A. Eagle[1] on behalf of The GRACE Investigators.
[1]University of Michigan Health System, Cardiovascular Center, Ann Arbor, United States of America; [2]The University of Edinburgh, Edinburgh, United Kingdom; [3]ICYCC Favaloro Foundation, Buenos Aires, Argentina; [4]UMASS Medical School, Worcester, United States of America; [5]Concord Hospital, Sydney, Australia

Introduction: Studies suggest a gender bias in the diagnosis and treatment of acute coronary syndromes (ACS). We aimed todetermine whether there is a bias in treating women with ACS or if women present with different symptoms and angiographic ACS and thus are treated less aggressively.
Methods: 2,982 women and 7,581 men underwent angiography and were included in the GRACE registry. We compared history, presenting symptoms, coronary anatomy, treatment and in-hospital and 6-month outcomes. Normal vessels/mild disease was defined as stenosis in <50% of ALL epicardial vessels.
Results: Women were on average older, had higher rates of angina, heart failure, diabetes and hypertension but were less likely to smoke, have a prior MI, stroke, or prior PCI compared to men (P<0.05). Men and women had similar levels of cardiac enzymes. Among patients with MI (STEMI/NSTEMI), women were significantly more likely to present with (pre)syncope, dyspnea, palpitations, jaw pain and nausea, while men presented with classic chest pain and diaphoresis (P<0.05). Women were twice as likely to have normal/mild CAD on angiography as men (8% vs 4%, P<0.05) and were less likely to undergo PCI or CABG. Men and women with normal/mild disease were less likely to undergo interventional and medical therapy than patients with more advanced epicardial disease. Women with normal/mild disease were less likely to receive aspirin, beta-blockers, statins and ACE inhibitors than men with similar angiographic disease. There were no differences in rates of PCI and or CABG among men and women with

advanced CAD. At 6 months, the combined endpoint of death, MI, stroke and rehospitalization was similar in women and men. Among patients with advanced disease undergoing PCI, women showed an increased trend towards worse outcomes compared to men. Women with normal/mild disease showed a trend towards better outcomes than men, and thus appeared to derive more benefit from medical therapy. These observations are consistent with the general bservation that ACS in women is more diffuse (less segmental) when compared to men.
Conclusions: Among MI patients, women presented with different symptoms and were more likely to have normal/mild disease than men. This difference explains the apparent gender bias for revascularization where women with ACS were less likely to receive in-hospital PCI or CABG. Women with normal/mild CAD were less likely to receive preventative medications at discharge than men with equivalent disease. Reasons for this discrepancy are not entirely clear.

1432 Gender differences in baseline characteristics, management and outcomes in acute coronary syndromes. Data from the FACT nationwide French registry

G. Montalescot[1], Y. Cottin[2], B. Chevalier[3], N. Danchin[4], A. Furber[5], P. Goldstein[6], P. Ravaud[7], P.G. Steg[8] on behalf of enquete FrAncaise observationnelle sur la prise en Charge des patients. *[1]Hôpital Pitié-Salpétrière, Paris, France; [2]CHU, Dijon, France; [3]CCN, Saint-Denis, France; [4]Hôpital Européen Georges Pompidou, Paris, France; [5]CHU, Angers, France; [6]SAMU Régional, Lille, France; [7]Hôpital Bichat-Claude Bernard, Paris, France; [8]Hopital Bichat-Cl.Bernard, Service de Cardiologie, Paris Cedex 18, France*

Background: gender is suspected to impact on the management and outcomes of acute coronary syndromes (ACS)
Methods: FACT is a french ACS registry collected in January 2003 in 361 cardiology units in France.
Results: data from 3485 pts are in shown in Table. Women received less aggressive pharmacologic and revascularisation therapy, despite being older and at higher risk of death. Analysis of discharge prescriptions (not shown) demonstrated less use of evidence-based therapies in women.
Outcomes were markedly worse for women and this difference persisted after adjustment for baseline differences: after multivariate analysis, the OR for in-hospital death in women relative to men was 1.526 [1.046-2.225], p=0.03.

Results

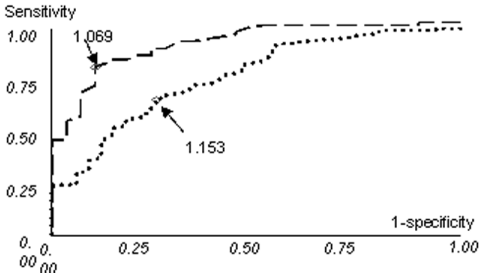
	Men	Women	p
N	2464	1021	
%	70.7	29.3	
Mean age (years)	63.6	72.4	0.001
Current smokers	34.6	12.5	0.001
Hypercholesterolemia	52.3	46.8	0.004
Hypertension	47.1	65.6	0.001
Diabetes	21.5	26.8	0.001
Hx of MI	20.5	15.6	0.001
Aspirin in the first 24 h	94.1	92.3	0.046
Beta blockers in first 24h	71.7	60.8	0.001
GpIIb/IIIa blockers	24.2	7.6	0.001
angiography	86.7	72.5	0.001
PCI	65.5	48.1	0.001
CABG	7.0	5.5	NS
in-hospital death	3.9	.7	0.001
in-hospital CHF	15.6	26.5	0.001

Conclusion: there are major gender differences in baseline characteristics, management and outcomes. Despite an aggressive use of interventions and evidence-based therapies in this contemporary cohort, there were markedly worse outcomes among women. This underscores the need to focus specific attention to ACS in women, in order to improve their outcomes.

1433 Gender differences in carotid intima-media thickness in patients with suspected coronary artery disease

A. Kablak-Ziembicka[1], T. Przewlocki[2], W. Tracz[2], P. Pieniazek[2], P. Musialek[2]. *[1]Institute of Cardiology, Collegium Medicum, Dept. of Cardiac and Vascular Diseases, Krakow, Poland; [2]Institute of Cardiology, CM UJ, Dept of Cardiac and Vascular Diseases, Krakow, Poland*

Background: Patients selection for angiography with suspected coronary artery disease (CAD) is still a challenge in some specific subgroups. E.g. women have often atypical symptoms and false-positive non-invasive tests. Study aimed to evaluate gender differences and clinical value of carotid intima-media thickness (IMT) in predicting CAD.
Methods: We evaluated 558 consecutive symptomatic patients who underwent coronary angiography, including: 91 women (aged 61.2±9.5) with CAD (at least 1 lesion >50% in coronary artery); 29 women (aged 58.3±6.0) without CAD; 372 men (aged 58.9±9.2) with CAD; and 66 men (aged 54.6±8.7) without CAD. Maximal IMT was assessed bilaterally at common carotid, bulb and internal carotid arteries and expressed as a mean-IMT for each patient.
Results: In patients without CAD, women had lower mean-IMT values than men (0.93±0.15 vs. 1.05±0.19;p<0.001). This gender difference, was not seen in CAD patients (1.3±0.31 vs. 1.31±0.31;p=0.92). For both genders, those with CAD had greater IMT values than those without CAD. Multivariable regression analysis showed that age, CAD, hypertension, smoking and diabetes have the strongest impact on IMT values in both genders. ROC analysis showed that women have significantly lower IMT threshold for CAD likelihood (p<0.001): mean-IMT of 1.069 mm was highly predictive of concomitant CAD (sensitivity 79%, specificity 90%, PPV 96%) with 7.65-fold increase in relative risk of CAD. While for men mean-IMT threshold was 1.153 mm (sensitivity 66%, specificity 74%, PPV 93%) with 2.58-fold relative risk of CAD.



ROC curves for women (up)and men(below)

Conclusion: Carotid IMT might be valuable tool in patient selection for coronary angiography, predicting CAD likelihood. This concerns particularly women in whom sensitivity and specificity of mean-IMT is high.

1434 ST-elevation myocardial infarction: is female gender (still) a risk factor?

P.F. Monteiro on behalf of the Portuguese Registry of Acute Coronary Syndromes Investigators. *Coimbra University Hospital, Cardiology Dept., Coimbra, Portugal*

Introduction: Female are classically presented as having a worse prognosis if undergoing ST-elevation myocardial infarction (STEMI). Is this still true, despite recent developments in STEMI therapy?
Aim: To evaluate, in a population of patients admitted for STEMI, which are the epidemiological, clinical and therapeutic parameters that differ between male and female patients, in order to determine in gender independently influenced post-STEMI prognosis.
Population and Methods: Retrospective analysis of a nationwide database containing data from 6061 patients admitted since 2002 in Coronary Care Units or Cardiology wards for STEMI. This population was subdivided according to the gender; 4365 patients (group A) were male and 1696 were female (group B). Both groups were analyzed regarding demographic, epidemiological and clinical parameters.
Results: Female had a worse risk profile and previous coronary artery disease (CAD). They were less frequently in Killip class I (78.8% vs 97.6%; p<0.05) and were less submitted to reperfusion therapy (52% vs 65.6%; p<0.05) and, both during the hospital stay and at discharge, they were less treated with cardiovascular drugs; they a more frequent pattern of "de novo" left bundle branch block in the admission ECG. Regarding left ventricular (LV) function, female patients had less frequent preserved LV dysfunction (45.1% vs 49.1%; p<0.05) and had a worse in-hospital outcome (death rate: 14.9% vs 6.6%; p<0.05). They had a lower rate of coronary angiography (44.8% vs 55.7%; p<0.05), and were less submitted to angioplasty (31.8% vs 40.1%; p<0.05). During the 6-month clinical follow-up, the mortality rate was significantly higher in females (11.1 vs 6.6%; p<0.05). The multivariate analysis of the causes for a higher in-hospital mortality in women showed that the gender was not an independent predictor of prognosis; the factors of good prognosis found were: use of beta-blockers and angiotensin converting enzyme inhibitors and performance of coronary angiography, while age higher than 72 years, previous diabetes, use of catecholamines and severe LV dysfunction were related with a worse prognosis. Regarding 6-month mortality, gender was, once again, not an independent determinant of prognosis, unlike age higher than 74.5 years and use of calcium channel antagonists at discharge.
Conclusion: In female patients with STEMI, the worse in-hospital and 6-month prognosis is due, not to gender itself, but to the treatment received, that influences LV function, an important prognostic factor in coronary patients.

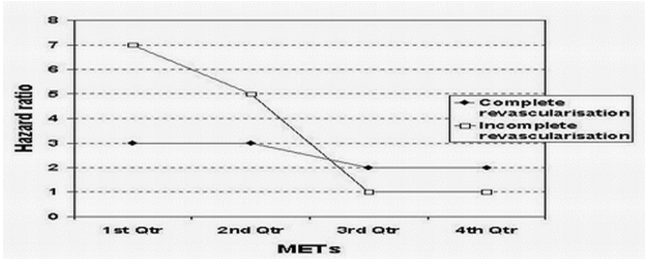
UPDATE ON EXERCISE TESTING IN CORONARY HEART DISEASE

1435 Prognostic importance of exercise capacity in patients with myocardial infarction treated with primary PCI. A DANAMI-2 sub-study

N. Valeur[1], P. Clemmensen[2], P. Grande[2], K. Saunamaki[2]. *[1]Rigshospitalet, Department of Cardiology, Copenhagen, Denmark; [2]Rigshospitalet, Department of Cardiology, Copenhagen, Denmark*

Aim: To determine the prognostic importance of exercise test variables in relation to the degree of revascularisation following primary PCI.

Methods: In the DANAMI-2(the 2nd DANish trial in AMI) trial patients with ST-elevation AMI(STEMI) were randomised to primary angioplasty(PCI) or fibrinolysis. Of 790 patients randomised to primary PCI 572 performed an ET (exercise testing).Of these 310 patients had complete and 216 had incomplete revascularisation. Complete revascularisation was defined as TIMI 3 flow in the infarct related artery at the end of the procedure, and nowhere else greater than 30% stenoses. The primary endpoint was a composite of death and reinfarction and follow-up was up to 3 years.
Results: Patients with incomplete revascularisation had a lower exercise capacity (6.5 [1.9-12.8] METs versus 7.0 [2.1-14.0], p=0.0004) and more frequently ST-segment depression (43 (20%) versus 39 (13%), p=0.02) compared to patients with complete revascularisation. Exercise capacity was of prognostic importance for death and/or reinfarction, (hazard ratio per one MET increase was 0.69 (0.49-0.98), p=0.04) and for death alone (0.76 (0.60-0.97), p=0.03) in patients with incomplete revascularisation, but not in patients with complete revascularisation (hazard ratio 1.08 [0.64-1.83], p=0.77 and 1.16 [0.88-1.53], p=0.30, respectively). ST-segment depression had no prognostic importance in either group.



Death and reinfarction

Conclusion: Exercise capacity is long term prognostic of death and death and/or reinfarction in patients with incomplete revascularisation, but not in patients with complete revascularisation.

1436 Prognostic value of early exercise testing after coronary stent implantation

P. Wenaweser[1], J.-F. Surmely[2], M. Roffi[3], C. Rey[2], S. Cook[2], S. Windecker[2], O.M. Hess[2], B. Meier[2]. [1]*Bern, Switzerland;* [2]*Swiss Cardiovascular Center Bern, Bern, Switzerland;* [3]*University Hospital Zurich, Cardiology, Zurich, Switzerland*

Background: We have shown that exercise testing the first day after coronary stenting is safe. However, the value for the long-term follow-up remains to be determined. We aimed to assess a possible prognostic impact of early exercise testing after coronary stenting.
Methods and Results: Between September 1997 and June 2001, a total of 1000 unselected patients were randomized to a symptom-limited exercise stress test (498 patients) or no stress test (502 patients) the day after coronary stenting; 52 in the exercise group had contraindications for the test. Of the remaining 446 patients undergoing stress test 102 patients (23%) had a pathologic (either subjective or objective signs for ischemia, ST +), 314 patients (70%) a normal (ST -) and 30 patients (7%) a nonconclusive (insufficient double product) result. The latter were excluded from the analysis. Follow-up was obtained in 92%. Baseline demographics and state of revascularization at the time of stress test were comparable in the two groups. Major adverse cardiac events (MACE: death, MI, revascularization) in the long-term follow-up (45 $\pm$ 19 months) were assessed and compared between the two groups (table). Death occurred significantly more often in the ST+ group. There was a trend to more myocardial infarction and repeated revascularization procedures in patients with pathologic stress test.

MACE

	ST + (n=102)	ST- (n=314)	p-value
Death, %	9.3	3.9	0.04
- cardiovascular, %	4.1	1.1	0.05
Myocardial infarction, %	7.2	4.6	ns
Repeat angioplasty, %	32.0	26.7	ns
Bypass surgery, %	5.2	6.3	ns
Combined MACE, %	45.4	35.4	0.08

Conclusion: A pathologic stress test early after stent implantation is associated with a higher mortality rate and a trend to more repeat revascularization procedures. A more aggressive revascularization strategy should be considered in this high risk patient population.

1437 The role of physical fitness in predicting long-term prognosis in middle-aged women surviving acute coronary syndrome

F. Al-Khalili[1], I. Janszky[2], A. Andersson[3], B. Svane[4], K. Schenck-Gustafsson[3]. [1]*Dept. of Internal Medicine, Cardiology Unit, Stockholm, Sweden;* [2]*Karolinska institutet, Preventive medicine, Stockholm, Sweden;* [3]*Karolinska Hospital, Department of Cardiology, Stockholm, Sweden;* [4]*Karolinska Hospital, Department of Thoracic Radiology, Stockholm, Sweden*

Aim: To evaluate the importance of exercise testing parameters and sedentary lifestyle in relation to long term prognosis in middle aged women with acute coronary syndrome (ACS).
Methods and results: Women aged <66 years in the greater Stockholm area in Sweden recently hospitalized for ACS were recruited. All underwent an extended baseline clinical examination including exercise testing (ET) and then were followed up for 9 years. Physical activity during leisure time was assessed based on a questionnaire according to the WHO criteria. Non-participation in ET had a hazard ratio (HR) of 4.26 (95% confidence interval (CI) 2.02-8.95) for total mortality, and 3.03 (95% CI 1.03-8.91) for cardiovascular mortality. All ET parameters were significantly different between survivors than non-survivors except ET induced angina pectoris and ST segment depression. Sedentary lifestyle (SLS) and ET parameters were related to total mortality and cardiovascular mortality in a multivariate analysis adjusting for age, index event and many coronary risk factors including the left ventricular function. Predictors of total mortality were SLS, HR 2.59 (95% CI 1.14-5.88), exercise time, HR 1.17 (95% CI 1.02-1.34), and the difference in pulse and systolic pressure between rest and exercise, HR 0.98 (95% CI 0.97-0.99). Parameters that predicted cardiovascular mortality were SLS, HR 3.06 (95% CI 1.05-8.91) and difference in systolic blood pressure between rest and exercise, HR 0.97 (95% CI 0.94-1.00).
Conclusion: In female patients <66 years surviving ACS, independent predictors of poor long-term prognosis were sedentary life style, non participation in exercise testing, and haemodynamic parameters during exercise test.

1438 Chest pain in the setting of negative exercise echocardiography is an independent predictor of adverse cardiac outcomes

M. Al-Mallah[1], F. Alqaisi[2], A. Arafeh[2], R. Al-Tamsheh[2], K. Ananthasubramaniam[2]. [1]*Dearborn, MI, United States of America;* [2]*Henry Ford Hospital, Detroit, MI, United States of America*

Purpose: Exercise stress echocardiogram (SE) is a widely utilized test to evaluate patients with suspected coronary heart disease. However, the prognostic value of chest pain suggestive of angina during negative SE continues to be controversial and not well established. We tested the hypothesis that chest pain during negative SE is an independent predictor of major adverse cardiac events (MACE).
Methods: Retrospective study of consecutive patients referred for SE between 1/1997 and 12/1997. Patients were divided into 2 groups based on the development of chest pain during exercise. Baseline demographics and SE variables were obtained through review of the medical record and the SE report. Patients were followed up for a median duration of 73 months for the incidence of MACE (angina, myocardial infarction, coronary angioplasty or bypass surgery, cerebrovascular accidents or death). Group comparisons were conducted for baseline demographics and MACE using chi-square testing and student t-test. Multivariate logistic regression was used to identify independent predictors of MACE.
Results: Of 683 patients who had negative SE, 28 (4.1%) patients reported chest pain at peak stress. There were no differences between the two groups in mean age, gender, race, cardiac risk factors, prior coronary disease or previous medications. Over a median follow up of 73 months, patients with chest pain had more MACE (21.4% vs. 5.6%, p=.001), coronary angioplasty (7.1% vs. 1.4%, p=.018), and bypass surgery (7.1% vs. 1.1%, p=.006). After adjusting for confounding variables, the degree of METS achieved and chest pain during negative SE were independent predictors of MACE (Adjusted OR for chest pain 4.1, 95% CI 1.3-12.9, p=.015).
Conclusion: Chest pain suggestive of angina at peak stress is an independent predictor of MACE in patients with negative SE. This reemphasizes the importance of simple clinical data providing powerful prognostic predictive value despite a negative SE. Such patients need aggressive risk factor modification and may warrant additional diagnostic testing to prevent long term cardiovascular events.

1439 Negative exercise ECG: is it time to re-examine the concept?

R. Bigi[1], L. Cortigiani[2], D. Gregori[3], D. De Chiara[1], C. Fiorentini[1]. [1]*University School of Medicine, Cardiology Unit, Dpt. of Medicine and Surgery, Milan, Italy;* [2]*"Campo di Marte" Hospital, Cardiology Dept., Lucca, Italy;* [3]*University Medical School, Dpt. of Public Health and Microbiology, Turin, Italy*

Background: The Stress-Recovery Index (SRI) is known to add incremental diagnostic and prognostic information in patients with known or suspected coronary artery disease. We sought to verify whether it may improve prognostic accuracy in patients with negative exercise ECG.

Methods: SRI, defined as the absolute difference between the areas designated by heart rate-adjusted ST depression during exercise and recovery, was derived in 700 consecutive patients with negative (ST depression <0.1 mV) exercise ECG who were prospectively followed-up for the combination of death and nonfatal infarction. To assess whether it added significantly to routinely obtained information, clinical and exercise testing data were entered into a sequential Cox's model (model 1); SRI was entered last (model 2). Model validation was performed by bootstrap adjusted by the degree of optimism in estimates. Survival curves were set up using Kaplan-Meier method and compared by the log-rank test.
Results: during a median follow-up of 3.0±1.5 years, 22 deaths and 40 nonfatal infarctions occurred. Hypertension (HR 1.7, 95%CI 1.04-2.9), age (HR 1.6, 95%CI 1.14-2.3 for interquartile difference in years), and SRI (HR 0.52, 95%CI 0.28-0.56 for interquartile difference) were independent predictors of outcome. Area under the ROC curve of the risk function was 0.69 (95% CI 0.57-0.80) for model 1 and 0.84 (95% CI 0.77-0.90) for model 2 (p=0.001). Log-rank test for trend showed a significant (p<0.001) difference in event-free survival by SRI quartiles
Conclusion: SRI analysis provides additional prognostic discrimination on top of clinical and exercise testing variables and significant discrimination of survival in patients with a negative exercise ECG.

1440 Is there a better way to predict death than heart rate recovery?

D. Gorelik, D. Hadley, J. Myers, V. Froelicher. *Stanford University VAPAHCS, Cardiology, Palo Alto, United States of America*

Purpose: Heart rate recovery (HRR) during exercise testing is a marker demonstrating the role of the autonomic nervous system on the heart. The prognostic value of HRR at two minutes versus computational analysis of HRR as a function of resting and maximum heart rate during exercise testing has not been determined in a clinical population. We aimed to demonstrate the predictive value of heart rate recovery (HRR) at two minutes from the end of exercise to predict mortality compared to exercise testing variables, HRR at different time frames, and computational analyses of HRR.
Methods: A total of 2,193 patients who underwent exercise testing were followed for 10.2 ± 3.6 years. These patients were analyzed with respect to angiographic disease, clinical variables, use of medications,ECG abnormalities, and exercise testing markers. Natural log and log determination of HRR as a function of maximum heart and resting heart rate were analyzed. Those who survived versus died were analyzed by t-test and Chi square. Cox hazard regression analysis was performed to determine the mortality risk for exercise testing parameters, clinical variables, the drop in heart rate from end exercise at different time frames, and computational models of HRR.
Results: A drop in heart rate less than 22 bpm from end exercise was present in 250 patients (11%); during follow-up, 193 died. An abnormal heart rate recovery at two minutes was a better predictor of mortality (HR 0.97, CI 0.96-0.98, P<0.001) than HRR at 1, 3, or 5 minutes. HRR at two minutes predicted mortality better than computational models of HRR relating HRR as a function of maximum and resting heart rates. After adjusting for other significant predictors of mortality including age, standing HR, maximum HR, maximum SBP, heart rate change, METs, the double product at rest and exercise, and the difference between the two variables, HRR was a better predictor of death (HR 0.97, CI 0.96-0.97, P<0.001) than age (HR 1.04, CI 1.03-1.05, P<0.001), METs (HR 0.85, 0.82-0.88, P<0.001), and maximum heart rate (HR 1.01, CI 1.00-1.01, P<0.001).
Conclusion: The simple determination of heart rate drop at two minutes post exercise is an excellent indicator of mortality versus computation models of HRR and the determination of HRR at different time intervals. HRR at two minutes outperformed age, METs, and maximum heart rate achieved during exercise in determining the risk of death.

STEM CELL THERAPY IN MYOCARDIAL INFARCTION: ALMOST THERE?

1449 A comparison of 3 methods of mesenchymal stem cell delivery following transmural myocardial infarction in a porcine model

R.L. Wilensky[1], T. Freyman[2], G.M. Polin[1], H. Osman[1], J. Crary[2], M. Palasis[2]. *[1]Hosp. & Univ. of Pennsylvania, Division of Cardiology, Philadelphia, United States of America; [2]Boston Scientific Corp, Natick, United States of America*

Background: Cellular cardiomyoplasty is a novel technique to treat impaired myocardium after myocardial infarction (MI). However, the optimal delivery method of mesenchymal stem cells (MSC) is unknown. We conducted a randomized study to evaluate the efficiency of successful MSC engraftment at 2 weeks following a transmural MI utilizing 3 commonly used delivery approaches: intravenous (IV), intracoronary (IC), and percutaneous endocardial injection (EC).
Methods: Female Yorkshire pigs weighing 27-40kg (n=18) underwent transmural MI of the distal septal and anterolateral apical walls by a 60 min balloon occlusion of the mid left anterior descending artery. Following a 15 min recovery, $5x10^7$ MSCs containing iridium particles were administered via IV, IC, or EC routes in 6 pigs/group. The Stiletto catheter, (Boston Scientific) was used for EC delivery. Two weeks later infarct size was determined and cell engraftment was assessed within the infarct, the liver and the lung by quantifying the presence of intracellular iridium through neutron activation. Iridium particles are present in viable cells (lower limit of detection <25,000 cells).
Results: There was no difference in infarct size between groups (table). The mean number of engrafted MSCs and mean MSCs/gram infarct tissue was higher in the IC compared to EC (p=0.01, p=0.02 respectively) and IV groups (p< 0.003, p< 0.002). There was increased engraftment in the liver and lung in the IV and IC groups compared to the EC group. While no adverse events were noted in the IV and EC groups, 3 of 6 IC pigs had decreased distal blood flow after MSC infusion. Fluorescent in-situ hybridization (FISH) at 2 weeks showed engraftment of male cells within the infarct and border zones of the female hearts.

MSC uptake

	Infarct Size (% LV mass)	Total MSCs in infarct zone	MSC/g Infarct	MSC/g Liver	MSC/g Lung
IC	26.3±4.1	2,863,680±982,722	105,855±43,543	1,455±1,240	10,550±2,345
EC	25.8±4.9	1,392,903±618,470	50,791±24,340	668±717	4,127±3,338
IV	26.0±2.5	not detected	not detected	9±21	12,827±2,470

Conclusions: 1. IC injection of MSCs post-MI resulted in increased infarct engraftment compared to IV and EC delivery, 2. IC and IV delivery were associated with greater remote engraftment than EC and 3. IC was associated with decreased blood flow following delivery, which may translate into a larger myocardial injury.

1450 Assessment of cardiac function and cell tracking after bone marrow cell transplantation in pigs with myocardial infarction

J. Mueller-Ehmsen[1], L. Baisch[1], P. Tossios[2], K. Schomaecker[3], J.H. Fischer[4], W. Bloch[5], U. Mehlhorn[2], R.H.G. Schwinger[1]. *[1]University of Cologne, Dept. of Internal Medicine III, Cologne, Germany; [2]University of Cologne, Dept. of Cardiac Surgery, Cologne, Germany; [3]University of Cologne, Dept. of Nuclear Medicine, Cologne, Germany; [4]University of Cologne, Inst. of Experimental Medicine, Köln, Germany; [5]German Sport University, Inst. for Circulatory Research, Cologne, Germany*

Bone marrow derived cells may support cardiac regeneration as putative therapy for myocardial infarction (MI). In most clinical studies simultaneous revascularization is performed, hampering conclusions on the specific effect of cell therapy. Therefore, we investigated the impact of mononuclear bone marrow cell (MNC) injection on cardiac function in pigs with MI but no revascularization.
MI was induced in 16 male domestic pigs (2 months, 28-32 kg) by catheter guided coil occlusion of the LAD. 2 weeks later, MNC (ficoll gradient) were injected into the infarcted area (border zone, 6 animals, 12 injections, 200 µl each, 4 x 10^7 MNC). 4 animals were medium injected for control. Laevocardiography was performed before MI, 2 wks after MI (before cell injection), and 2 wks after cell injection. In 2 animals cells were labeled with In-111, and cells were tracked scintigraphically at 0h, 0.5h, 2h and 24h after injection. 4 animals were used histological analysis (2, 4 and 8 wks after cell injection, cells labeled with Hoechst dye and colloidal gold).
As expected, LVEF was decreased 2 wks after MI vs. baseline in both groups (cell therapy: RAO 56.4±5.2 vs. 64.0±2.1%, P=0.18; LAO 46.4±3.8 vs 57.0±3.0%, P=0.04; medium injection: RAO 57.0±5.4 vs. 74.2±3.4%, P=0.11; LAO 56.5±2.1% vs. 69.0%±3.7, P=0.07). After cell therapy, there was a trend towards increased LVEF (RAO 61.2±5.5%, P=0.34; LAO 55.8±2.7%, P=0.08), which was not observed in medium injected animals (RAO 56.7±7.2, P=1.0; LAO 49.8±4.7%, P=0.14). Regional LV function as assessed by gravity wall motion analysis remained unaffected by cell therapy. In scintigraphy, at 0.5h after injection 84-87% of the cells were detected in the heart, 4-6% in the lungs and 3-5% in the liver. At 2h the numbers were 85%, 4% and 6%, at 24h they were 76-77%, 5-6% and 11-14%, and at 48h 77%, 7% and 11%. In histology, grafted cells were readily identified, some were longitudinal in shape and adjacent to cardiomyocytes. However, most cells were monocyte- or macrophage-like in morphology. They stained positive for p-connexin and CD45, but not for alpha- actinin.
In conclusion, there is evidence for high grafting efficacy and persistence of MNC after needle injection into myocardial infarction. Global LV function shows a trend for improvement by cell therapy, but no effect on regional wall motion was seen. In histology, the labeled cells were readily identified for up to 8 weeks. However, no evidence for myocardial differentiation was found.

1451 Effects of mesenchymal stem cells transduced with Akt on porcine myocardial infarction

Y. Ahn, S.Y. Lim, M.H. Jeong, Y.S. Kim, K.I. Nam, M.C. Lee, H.C. Song. *Chonnam National University Hospital, Cardiology, Gwangju, Korea, Republic of*

Background: bone-marrow-derived Mesenchymal stem cells (MSCs) are self-renewing, clonal precursors of non-hematopoietic tissues and can differentiate into cardiac muscle in vitro and in vivo. However, transplantation of MSCs into infarcted porcine hearts yields only marginal improvement in cardiac function. This

study was designed to examine whether MSCs transduced with Akt, a serine-threonine kinase and potent pro-survival signal in many systems, are more resistant to apoptosis and enhance cardiac repair after transplantation into the ischaemic porcine heart.
Methods and Materials: we separated MSCs from hematopoietic cells based on their preferential attachment to polystyrene surfaces. We genetically engineered MSCs using ex-vivo myr-Akt-adenoviral gene transfer. MSCs were delivered by intracoronary injection to pigs after myocardial infarction (MI) [group I (control: n=5), media only; group II (n=5), MSCs only; group III (n=5), MSCs modified with Akt]. Myocardial SPECT was performed before and 4 weeks after MSC transplantation and pigs were sacrificed for immunocytochemical characterisation using CD34 (ICO115), integrin alphaV, Vimentin, and alpha-sarcomeric actin and further histologic analysis for apoptosis and fibrosis.
Results: mean LV ejection fraction (EF) was 44.8±16.6%, 29.8±7.6%, and 41.2±8.3% at first (each n=5) and changed to 29.8±8.5%, 39.0±9.5%, and 60.1±17.4% at 4 weeks after the MSC implantation in group I, II, and III respectively. Mean MI area was 17.6±9.2%, 35.0±11.8%, and 24.3±11.2% at first, and changed to 19.6±10.1%, 27.2±13.9%, and 7.4±5.3% in group I, II, and III respectively. Transplantation of ~107 cells into the ischemic porcine myocardium in group II increased the delta LV EF (-14.9±15.3% versus 9.0±8.6%, n=5 in each, p=0.016) and decreased the delta area of MI (2.1±1.3% versus -7.9±9.0%, n=5 in each, p=0.04) compared with control group and much more different in group III in delta LV EF (19.2±16.4%, p=0.006) and in delta area of MI (-16.3±6.4%, p=0.037).
Conclusion: MSCs transduced with Akt enhance repair of the injured area, prevent remodeling, and restore systolic performance in infarcted hearts.

1452 Enhanced ventricular remodelling after a myocardial infarction by augmented cell transplantation: bone marrow stromal cells overexpressing tissue inhibitors of metalloproteinase-3

D. Angoulvant[1], S. Fazel[1], P.W. Fedak[1], R.D. Weisel[1], T. Lai[1], C. Seneviratne[1], R. Khokha[2], R.-K. Li[3]. [1]*Toronto General Hospital, Cardiovascular Surgery, Toronto, Canada;* [2]*Ontario Cancer Institute, Toronto, Canada;* [3]*Toronto General Research Institute, Cardiovascular Surgery, Toronto, Canada*

Background: We have recently reported that timp-3-/- mice lacking Tissue Inhibitor of Matrix Metalloproteinase (TIMP)-3 serve as a model of dilated cardiomyopathy. We hypothesized that cell based gene therapy designed to restore regional TIMP-3 expression in timp-3-/- mice would prevent progression to overt heart failure following myocardial infarction (MI).
Methods: Bone marrow stromal cells (BMSC) from C57Bl6 mice were harvested and expanded before being transfected with murine TIMP-3 cDNA. Transfected BMSC (BMSC-T3) were injected in the anterior wall of timp-3-/- mice hearts immediately after coronary ligation. BMSC or media injections served as controls. Heart function was assessed by echocardiography measuring left ventricular (LV) area fractional change (AFC) at baseline, day 3, 7 and 28 after MI. Biochemical, histological and morphological analysis were performed at the same endpoints.
Results: In vitro, measurement of β-Galactosidase expression showed a 15±2% transfection efficiency at day 3. RT PCR, Western blot and gelatine zymography confirmed the overexpression and secretion of active TIMP-3 in BMSC-T3. In vivo, BMSC-T3 induced a significant reduction of myocardial matrix metalloproteinases (MMP)-9 and -2 activities and TNF-a levels over BMSC at day 3 (all $P<0.05$). Tunnel staining showed a significant reduction of apoptosis in the border zone 3 days after BMSC implantation that was significantly enhanced in the BMSC-T3 group ($P<0.05$). Confocal analysis of the remote myocardium at day 28 showed a significant preservation of collagen structure after BMSC implantation. TIMP-3 overexpression significantly enhanced the benefit of BMSC on collagen content and collagen fibrils length and diameter (all $P<0.05$). Functional and morphometric analysis showed significant LV dilatation and reduction of AFC (-54.09±2.73%) 28 days after MI in the medium group. BMSC implantation significantly reduced the LV infarcted volume (-51.45±9.9%, P=0.01) and preserved LV systolic function and geometry ($P<0.001$). TIMP-3 overexpression significantly enhanced the benefit of BMSC on LV systolic function ($P<0.05$).
Conclusion: These data show the significant benefit of BMSC implantation on post MI cardiac remodelling and systolic function. They demonstrate that TIMP-3 overexpression after MI reduces MMPs activities and TNF-a level resulting in significant reduction of apoptosis, extracellular matrix degradation, and systolic dysfunction. Our data demonstrate that gene enhanced cell therapy provides an efficient way of delivering beneficial cellular and extracellular signal after MI.

1453 Failure of short-term functional improvement after unselected bone marrow as well as mononuclear cell fraction administration in a porcine model of myocardial infarction

A.D. Moelker[1], T. Baks[1], W. Kerver[1], E.J. van den Bos[1], H.M.M. van Beusekom[1], G.P. Krestin[2], W.J. van der Giessen[1], D.J. Duncker[1]. [1]*Erasmus MC, Cardiology, Thoraxcenter, Rotterdam, Netherlands;* [2]*Erasmus MC, Radiology, Rotterdam, Netherlands*

Background: Regeneration of infarcted myocardium by transplantion of bone marrow derived cells into the infarct region has been proposed in both pre-clinical and clinical studies to prevent heart failure via angio- and/or myogenesis. We studied the effect of intracoronary administration of both unselected, crude bone marrow (BM) as well as injection of bone marrow derived mononuclear cells (MNC) in a porcine model of myocardial infarction (MI) induced left ventricular (LV) remodeling.
Methods: In 18 domestic swine, the proximal left circumflex coronary artery was balloon-occluded for two hours followed by reperfusion. Six other swine served as non-MI control. One week later, all swine underwent magnetic resonance imaging (MRI) to assess global and regional LV function. Then, 6 MI swine received intracoronary autologous unselected BM and 6 other MI swine received MNC, a total of ~ 5*10*8 cells, and 6 MI swine received medium, infused i.c. at the site of occlusion. Four weeks later all swine underwent a follow-up MRI.
Results: One week after MI, end-diastolic volume (EDV) and LV weight (LVW) were larger, while systolic wall thickening (SWT) of the MI area was lost, and ejection fraction (EF) was lower then in control swine. Injection of both unselected BM and MNC had no effect on the MI-induced changes.

Data=mean ± SEM		Control n=6	MI+medium n=6	MI+BM n=6	MI+MNC n=6
EDV (mL)	Baseline	63 ± 3	88 ± 4*	100 ± 6*	75 ± 3*
	Endpoint	80 ± 5	114 ± 10*	126 ± 6*	94 ± 6*
EF (%)	Baseline	57 ± 3	49 ± 3*	43 ± 1*	47 ± 1*
	Endpoint	62 ± 4	55 ± 4*	48 ± 2*	48 ± 3*
LVW (g)	Baseline	51 ± 4	62 ± 4*	63 ± 4*	55 ± 2
	Endpoint	75 ± 4	95 ± 8*	84 ± 5*	74 ± 3
SWT LCX area (%)	Baseline	56 ± 8	-15 ± 4*	-14 ± 3*	-13 ± 4*
	Endpoint	67 ± 8	-9 ± 13*	-19 ± 6*	-24 ± 6*

*P<0.05 vs. control

Conclusion: Contrary to earlier reports in small animal models, intracoronary injection of BM or MNC in swine one week after MI does not attenuate adverse LV remodeling or improve global or regional LV function 4 weeks later.

1454 Autologous transplantation of bone marrow cells in patients with acute myocardial infarction. The effect of the number of transplanted cells on the reduction of infarct size

J. Meluzin[1], L. Groch[2], S. Janoušek[3], J. Mayer[4], O. Hlinomaz[2], J. Prášek[5], M. Kamínek[6], J. Staníèek[7]. [1]*St. Anna Hospital, 1st. Department of Internal Medicine, Brno, Czech Republic;* [2]*St. Anna Hospital, 1st. Department of Internal Medicine, Brno, Czech Republic;* [3]*Brno University Hospital, Dept. of Internal Medicine-Cardiology, Brno, Czech Republic;* [4]*Brno University Hospital, Dept. of Internal Med.-Hematooncology, Brno, Czech Republic;* [5]*Brno University Hospital, Dept. of Nuclear Medicine, Brno, Czech Republic;* [6]*Olomouc University Hospital, Dept. of Nuclear Medicine, Olomouc, Czech Republic;* [7]*Masaryk Institute of Oncology, Dept. of Nuclear Medicine, Brno, Czech Republic*

Background: At present, it is not known whether the effect of autologous mononuclear bone marrow cell transplantation depends on the amount of implanted cells. The aim of this study was to assess the influence of the number of transplanted mononuclear bone marrow cells (MBMC) on myocardial function and perfusion in patients after acute myocardial infarction (MI).
Methods: The study comprised 35 patients with the first acute MI treated with coronary angioplasty and stent implantation (resultant TIMI III flow). Only patients with the evidence of irreversible damage of infarcted myocardium proved by dobutamine echocardiography, Tc-99m-sestamibi single photon emission computed tomography (SPECT), and positron emission tomography were included. The patients were randomized into 3 groups. Group A patients (n = 11) were transplanted with a higher number of MBMC (100 000 000 cells). Group B patients (n = 12) received a lower number of MBMC (10 000 000 cells). Twelve patients who were not treated with cell transplantation served as controls (Group C). Cell transplantation was performed by intracoronary catheter cell implantation 5-9 days after the onset of MI. Global and regional myocardial function and perfusion were determined by gated Tc-99m-sestamibi SPECT and Doppler tissue imaging of longitudinal myocardial contractions 1-4 days before the cell transplantation and 3 months later.
Results: Pre-transplant left ventricular ejection fractions did not change significantly with cell transplantation (from 38% to 43% in group A, from 40% to 44% in group B, and from 40% to 41% in group C, all p = NS). Peak systolic velocity of the longitudinal contraction of infarcted wall (Sa) increased from 4.18 cm/s to 4.99 cm/s in group A ($p < 0.01$), but did not change significantly in groups B (from 4.51 cm/s to 4.69 cm/s, p = NS) and C (from 4.83 cm/s to 4.56 cm/s, p = NS). The differences in pre- and post-transplant values of Sa differed significantly between groups A and B ($p < 0.05$) and A versus C ($p < 0.01$). The perfusion defect in infarcted area decreased from 52% to 41% in group A ($p < 0.01$), from 48% to 40% ($p < 0.01$) in group B, and from 47% to 38% ($p < 0.01$) in group C after cell transplantation, (p = NS among groups).
Conclusion: Intracoronary implantation of MBMC improves regional myocardial function of acutely infarcted myocardium in a dose-dependent manner.

CELLULAR THERAPY FOR THE FAILING HEART

1455 Effects of autologous bone marrow stem cell transplantation on beta-adrenoceptor density in a rabbit model of heart failure

S. Dhein[1], J. Garbade[1], D. Rouabah[1], G. Abraham[2], F.R. Ungemach[2], F.W. Mohr[1]. *[1]University of Leipzig, Klinik für Herzchirurgie, Leipzig, Germany; [2]Veterinary Pharmacology and Toxicology, Leipzig, Germany*

Introduction: Stem cell transplantation may provide a possible alternative therapy to classical therapies in the treatment of chronic heart failure. In order to assess whether a long-term improvement of cardiac function can be achieved it should be investigated whether the β-adrenoceptor (β-AR) downregulation in heart failure can be reversed.
Methods: White male New Zealand rabbits were treated with doxorubicine (3 mg/kg/week for 6 weeks) to induce a dilative cardiomyopathy. Thereafter, we obtained mononuclear fraction of autologous adult bone marrow stem cells (BMC) by Ficoll density gradient centrifugation, subcultivated the BMC for 4 days, and injected 1.5-2.0 Mio of these cells in 1 ml by infiltrating the myocardium via a left anterolateral thoracotomy. 4 weeks later the rabbits were investigated and the heart excised and processed for radioligand binding assay. A membrane protein preparation from the left ventricle, septum and right ventricle was incubated with (-)-125[I]-iodocyanopindolol for saturation binding assay. Unspecific binding was assessed with the unselective β-AR-antagonist CGP 12177, and the percentage of β1-AR and β2-AR by displacement with ICI 118,551.
Results: In the rabbit heart β1-AR predomninate with >80%. In doxorubicine treated rabbits β-AR density was significantly downregulated in left ventricle (control: 70±1; doxo.: 22±5 pMol/mg) and in ventricular septum (control: 93±2; doxo.: 64±16 pMol/mg), but not in right ventricle, thus, indicating a left ventricular failure. BMC transplantation lead to a significantly attenuated β–AR downregulation both in left ventricle (stem+doxo.: 52±9 pMol/mg) and in ventricular septum (stem+doxo.: 91±13 pMol/mg). Intracardiac pressure volume loops (in-vivo) showed that the β-AR downregulation in heart failure was accompanied by reduced contractility which was markedly less pronounced in BMC transplanted hearts.
Conclusions: Doxorubicine-induced heart failure results in β-AR downregualtion probably via chronic activation of the sympathoadrenal system. This is significantly antagonized by BMC transplantation. The results indicate that BMC transplantation improves sympathoadrenal dysregulation in heart failure. Thus, transplantation of adult autologous bone marrow stem cells may be an interesting new therapeutic approach.

1456 Simultaneous autologous transplantation of co-cultured mesenchymal stem cells and skeletal myoblasts improves ventricular function in a murine model of Chagas disease

L.C. Guarita Souza[1], K.A.T. Carvalho[1], C. Rebelatto[1], A. Senegaglia[1], P. Hansen[1], N. Miyague[1], J.R. Faria Neto[2], P.R.S. Brofman[1]. *[1]PUC-PR, Experimental Lab. of Cell Culture, Curitiba, Brazil; [2]Curitiba, Brazil*

Background: Cellular transplantation is emerging as a promising and feasible strategy for the treatment of postinfarction ventricular dysfunction. Whether its beneficial effects can be extended to other cardiomyopathies remains an unexplored question. We evaluated the histological and functional effects of simultaneous autologous transplantation of co-cultured stem cells (SC) and skeletal myoblasts (SM) in an experimental model of dilated cardiomyopathy due to Chagas disease, characterized by diffuse fibrosis and impairment of microcirculation.
Methods: Eighty Wistar rats weighing 200g were infected intraperitoneally with 15x10E4 trypomastigotes. After eight months, a 2-D echocardiographic study was performed for baseline assessment of left ventricle (LV) ejection fraction (EF,%), end diastolic volume (LVEDV,ml) and end systolic volume (LVESV,ml). Seventeen animals (21.25%) developed LV dysfunction (EF< 37%) and were selected for the study. Skeletal myoblasts isolated from muscle biopsy and mesenchymal stem cells from bone marrow aspirates were co-cultured in vitro for 12 days. Cell viability was >90%. Seven animals received autologous transplant of 5,4x10E6 ± 8,0x10E6 cells (300 mL) into the LV wall. The control group (n=8) received culture medium (300 mL). Cells were marked with vimentin and fast myosin. After 4 weeks, ventricular function was reassessed by echo and the animals were euthanized. For histological analysis, heart tissue was stained with H&E and immunostained for fast myosin, bromodeoxyuridine (BrdU) and factor VIII.
Results: After 4 weeks, cell transplantation significantly improved EF and reduced LVEDV and LVESV. No change has been observed in the control group (see table). Skeletal fibers and neoangiogenesis were identified within the myocardium of the transplanted group.

Table 1. Effects of cell transplantation

	Cell Transplant Group (n=7)			Control Group (n=8)		
	Pre	Post	p*	Pre	Post	p*
EF (%)	31.10±5.78	53.37±5.84	<0.001	36.21±3.70	38.19±7.03**	ns
LVEDV (ml)	0.83±0.08	0.64±0.16	0.005	0.68±0.12	0.72±0.16	ns
LVESV (ml)	0.56±0.06	0.30±0.10	0.001	0.43±0.08	0.45±0.14**	ns

*Pre vs. Post; **Control vs. Transplant

Conclusion: The co-transplant of SC and SM is functionally effective in the Chagas disease ventricular dysfunction.

1457 MRNA expression of stem cell markers are increased in left ventricular myocardium of humans and dogs with chronic heart failure

S. Rastogi, V.G. Sharov, M. Imai, H.N. Sabbah. *Henry Ford Health System, Detroit, MI, United States of America*

Background: Ataxin-1 (Sca1) and c-Kit are key stem cell markers that, when observed in tissue, provide evidence for the presence of bone marrow stem cells (BMSC). We previously showed that ongoing cardiomyocyte injury, degeneration and loss occurs in the failing left ventricle (LV). This ongoing myocardial injury creates an ideal substrate for colonization of the myocardium by circulating BMSC; the latter are decreased in dogs with chronic heart failure. In this study, we tested the hypothesis that mRNA gene expression for Sca1 and c-Kit may be increased in the failing LV myocardium in response to ongoing injury, degeneration and loss of cardiomyocytes.
Methods: mRNA gene expression for Sca1 and c-Kit was measured in LV myocardium of explanted failed human hearts due to ischemic cardiomyopathy (ICM, n=6), idiopathic dilated cardiomyopathy (IDC, n=6), normal donor human hearts which were deemed not suitable for transplantation (NL-Human, n=6), dogs with intracoronary microembolization-induced heart failure (HF-Dogs, n=6) and in LV myocardium of normal dogs (NL-Dogs, n=6). Tissue samples from all groups were used to extract RNA. mRNA gene expression for Sca1 and c-Kit was measured using reverse transcriptase polymerase chain reaction (RT-PCR) and bands obtained after ethidium bromide gel electrophoresis were quantified in densitometric units (du) Results: Data are shown in the table. mRNA gene expression for Sca1 and c-Kit was significantly increased in LV myocardium of patients with ICM and IDC compared to LV myocardium from NL-Human donor hearts. Similarly, mRNA gene expression for Sca1 and c-Kit was significantly increased in LV myocardium of HF-Dogs compared to NL-Dogs.

mRNA Expression of Sca1 and c-kit

	NL-Human	ICM	IDC	NL-Dogs	HF-Dog
Sca1 (du)	312 ± 15	564 ± 16*	519 ± 15*	4450 ± 254	8775 ± 235**
c-Kit (du)	85 ± 4	179 ± 4*	159 ± 4*	6651 ± 672	9764 ± 402**

*=p<0.05 vs NL-Human; **=p<0.05 vs NL-Dog

Conclusions: The results of this study indicate that in LV myocardium of explanted failed human hearts, regardless of etiology, as well in LV myocardium of dogs with experimentally-induced HF, mRNA gene expression for Sca1 and c-Kit are upregulated. This upregulation of key stem cell markers in HF suggest the possibility that colonization of the myocardium by circulating BMSC occurs in HF and may also explain the decrease in circulating BMSC observed in dogs with HF.

1458 Early tissue distribution of bone marrow mononuclear cells after transcoronary transplantation in human

M. Penicka[1], O. Lang[2], P. Widimsky[1], I. Kleisner[2], P. Kobylka[3], T. Kozak[4], T. Vanek[5], H. Trojanova[2]. *[1]3rd Medical School Charles University, Cardiocenter, Department of Cardiology, Prague, Czech Republic; [2]Charles University Hospital, Department of Nuclear Medicine, Prague, Czech Republic; [3]Hematology and Blood Transfusion, Prague, Czech Republic; [4]3rd Medical School Charles University, Department of Hematology, Prague, Czech Republic; [5]3rd Medical School Charles University, Cardiac Surgery, Prague, Czech Republic*

Our goal was to study early tissue distribution of bone marrow mononuclear cells (BMCs) after intracoronary injection in patients with acute myocardial infarction (AMI), chronic ischemic and idiopathic left ventricular (LV) dysfunction.
Methods: Study population consisted of six patients: two patients with large anterior AMI (LV ejection fraction < 40%), four patients with advanced heart failure (NYHA III, LV ejection fraction < 35%) due to chronic ischemic (n=2) or idiopathic (n=2) LV dysfunction. Bone marrow blood was aspirated from both iliac crests (mean $2.5x10^8$ BMCs). Twenty % of BMCs suspension was labeled with 20 mCi of 99mTc hexamethylpropylene amine oxime (HMPAO). Whole body and SPECT images were obtained at 2 and 20 hours after injection in the LAD perfusion territory.
Results: In patients with AMI, the estimated radioactivity uptake by the heart was 4% of the injected radioactivity at 2 hours and 1% at 20 hours after transplantation. In patients with chronic ischemic LV dysfunction, no radioactivity was observed in the LAD supplied myocardium at both 2 and 20 hours after injection. Both patients with idiopathic LV dysfunction did not tolerate event short LAD balloon occlusion and developed severe complications: malignant arrhythmias in one case and refractory LAD spasm demanding immediate bailout stenting in the other one. Of note, in these patients, no radioactivity remained in the myocardium at 20 hours after transplantation.
Conclusion: Succesfull BMCs myocardial engraftment was observed only in patients with AMI. Patients with idiopathic dilated cardiomyopathy do not tolerate even short balloon occlusion of their major coronary artery and are at risk of developing complications (not seen in patients with coronary artery disease) after intracoronary stem cell transplantation.

1459 Cardiac stem-progenitor cell activation and myocyte hyperplasia in response to acute and diffuse myocardial damage by isoproterenol

G.M. Ellison[1], D. Torella[2], S. Mendez-Ferrer[1], M. Rota[1], C. Indolfi[3], B. Nadal-Ginard[1]. [1]*Cardiovascular Research Insitute, Medicine, Valhalla, NY, United States of America;* [2]*Federico Ii University, Cardiology Dept., Naples, Italy;* [3]*Magna Graecia University, Cardiology, Catanzaro, Italy*

Purpose: recent studies have questioned the accepted dogma that the regenerative capacity of the heart following injury is limited. A distinct population of resident c-kit+ cardiac stem-progenitor cells (CSC) may have the potential to regenerate functional heart muscle. Our objective was to evaluate whether CSC activation and consequent myocyte regeneration participates in LV remodelling after diffuse myocardial injury in the presence of a patent coronary circulation.
Methods: male Wistar rats received a single subcutaneous injection of isoproterenol (ISO, 5mg kg-1) and were sacrificed 1, 3, 6, 14 and 28 days later. Immunohistochemistry and confocal microscopy were employed to assess myocyte and CSC apoptosis (hairpin 1) and proliferation (BrdU/ki67) in the LV.
Results: in comparison with controls (CON), LVEDP increased and LV + and - dP/dt decreased significantly in ISO-treated rats at 1 day, uncovering acute LV failure. Interestingly, these parameters started to improve at 3 days, becoming normal by 14 and remained sustained through to 28 days. The average myocyte volume markedly increased at 3 days, and then decreased progressively by 28 days. The fraction of apoptotic myocytes peaked at 1 day after ISO (0.4% vs. 0.01%) and decreased over time (0.05% at 28 days). Conversely, the number of cardiac c-kit+ cells increased 4, 5, 6, 4 and 2 fold compared to CON at 1, 3, 6, 14 and 28 days after ISO, respectively. Interestingly, ISO did not produce significant CSC apoptosis. Myocyte progenitors (c-kit+/GATA4+) and precursors (c-kit+/GATA4+/alpha-sarcomeric actin+) were identified at 3 through to 28 days after ISO. The fraction of newly-formed myocytes (BrdU+) in treated rats was 0.1% at 1 day (not different from CON) but significantly increased at 6 days (1.3%), reaching 5% by 28 days. Similar results but with slightly lower fractions were obtained counting ki67+ myocytes. Remarkably, real time RT-PCR and western blot analysis showed that c-kit+ CSCs do not express the SR Ca^{2+} release channel, ryanodine receptor (RyR2). Subsequently, they are characterised by an inversion of beta1/beta2 expression. These findings provide a possible explanation for CSC resistance to ISO-induced apoptosis, when compared to myocytes.
Conclusions: injection of isoproterenol causes acute heart damage with extensive myocyte death. The heart compensates for this damage initially through myocyte hypertrophy and secondary hyperplasia. The latter is produced by the activation and differentiation of c-kit+ cardiac stem-progenitor cells.

1460 Human atria are a feasible source of multipotent adult progenitor cells

D. Cesselli[1], P. Marcon[1], E. Puppato[1], S. Rigo[1], S. Burelli[1], N. Bergamin[1], A.P. Beltrami[2], C.A. Beltrami[1]. [1]*Policlinico Universitario, Cattedra di Anatomia Patologica, Udine, Italy;* [2]*Policlinico Universitario, Dip. Ricerche Mediche e Morfologiche, Udine, Italy*

Murine models appointed atria as the heart region with the highest frequency in cardiac stem cell niches. Respect to a left ventricle biopsy, an atrial biopsy is a safer procedure to be employed as a cell source for autologous transplantation.
Aim: To isolate, characterize and compare atrium-derived (Ad) and ventricle-derived (Vd) multipotent mesenchymal progenitor cells (MAPCs) obtained from explanted human hearts.
Methods and Results: Small cells ($<30\mu m$) were isolated from left atria and left ventricles of 15 explanted human hearts affected by ischemic cardiomyopathy, and grown in a medium selective for MAPCs. Cell lines were obtained from every isolated atrium and ventricle, although the cloning efficiency was almost ten times higher for atrium derived cells with respect to ventricle derived ones (1.7 ± 0.3vs15 ± 2.6). When compared with Vd cells, Ad cells were characterize by a shorter population doubling time (36 ± 3h vs 51 ± 6h).
Ad and Vd primitive cells share, instead, a similar mesenchymal immunophenotype: as evaluated by flow-cytometry (n=15), they were shown to be CD45-/CD34-/CD38-/CD117-/CD133-/HLA-DR-/CD29lo/KDRlo/CD90hi/CD13hi/CD49bhi.
Both Ad (n=10) and Vd(n=10) cell lines displayed a small but sharply defined population expressing high levels of MDR-1 and ABCG2; they were characterized by the presence, in vitro, of asymmetric cell divisions (n=6), as assessed by immunofluorescence and confocal microscopy, and they possessed telomerase activity(n=6).
Cell lines obtained from the two different cardiac region (n=6) did not differ ($p<0.001$) in cardiac-specific transcription factor expression, as evaluated by flow-cytometry and RT-PCR, displaying in both cases a small fraction (less than 10%) of cells positive for GATA-4, MEF2C, Nkx2.5 and Myocardin.
Moreover, when exposed to appropriate differentiation inducing conditions, both Ad(n=5) and Vd(n=5) cell lines, were able to differentiate along an adipogenic, osteogenic, endothelial, and myogenic fate. Specifically, when cells were cultured in myogenic medium, they became strongly positive to GATA4, SMA, Troponin T and alpha-sarcomeric actin.
Conclusion: In conclusion, 1. multipotent cells can be isolated and grown from both atria and ventricles of human hearts;
2. Ad primitive cells did not differ from the Vd ones in terms of phenotype, telomerase activity and multilineage differentiation capacity;
3. the highest cloning efficiency and shortest population doubling time displayed by Ad multipotent cells, appoint atria, respect to ventricles, as a more feasible cell source to be employed for autologous cell therapy.

e-POSTER SESSION 4

MODERATED e-POSTERS: ADAPTATION TO ISCHAEMIA

P1552 Alteration of sympathetic function in hibernating myocardium

A.S. John[1], C. Depre[2], O.E. Rimoldi[1], J.R. Pepper[3], D.E. Vatner[2], S.F. Vatner[2], D.J. Pennell[3], P.G. Camici[1]. [1]*Imperial College School of Medicine, MRC Clinical Sciences Centre, Faculty of Med., London, United Kingdom;* [2]*University of New Jersey, Cardiovascular Research Institute, New Jersey, United States of America;* [3]*Imperial College, NHLI, London, United Kingdom*

Background: Hibernating myocardium (HM) is defined as a chronic left ventricular (LV) dysfunction that improves after revascularization. HM responds to sympathomimetics, even though a global decrease of sympathetic effectors is known to occur in heart failure secondary to an increased sympathetic drive. To test the hypothesis that the β-adrenoceptor (β-AR) axis is affected, but still responsive in HM, presynaptic norepinephrine reuptake-1 (C11-hydroxyephedrine) and postsynaptic β-AR density (C11-CGP-12177), measured in vivo with positron emission tomography (PET), were correlated with the expression of intracellular regulators of the β-AR signalling axis in myocardial biopsies ex vivo.
Methods: Fourteen patients with coronary artery disease (CAD) and LV dysfunction (ejection fraction $38\pm11\%$) underwent function and viability assessment with cardiovascular magnetic resonance (CMR). PET data in patients were compared with those in 30 healthy controls. Dysfunctional, but viable segments subtended by stenosed coronaries were defined HM. Biopsies were taken at bypass surgery from HM and remote myocardium (RM) and processed for RNA extraction. Transcripts encoding β1-AR, β2-AR, Gs-a, and adenylate cyclase-6 were measured by quantitative PCR.
Results: Both norepinephrine re-uptake and total (β1+β2) AR density in vivo were significantly reduced ($p<0.05$) in HM compared to healthy controls, with no difference between HM and RM. However, β1- and β2-AR mRNAs were reciprocally regulated (β1-AR mRNA HM $>$ RM; β2-AR mRNA RM $>$ HM) while Gsa and adenylate cyclase mRNAs were significantly reduced in HM ($P<0.05$).
Conclusion: While there are no differences in pre-synaptic norepinephrine reuptake and β-AR density between HM and RM, significant differences are present in the expression of β-AR subtypes and intracellular signalling pathway, which might contribute to the dysfunction of HM.

P1553 Ischaemic postconditioning fails to protect hypertrophied myocardium

C. Reussner, C. Weinbrenner, D. Tillack, R.H. Strasser. *University of Technology, Dept. of Cardiology, Medical Clinic, Dresden, Germany*

Background: Preconditioning (brief ischemic stimuli prior to an infarction) limits myocardial damage in normal and also in hypertrophied myocardium. Recently it was demonstrated, that brief repetitive episodes of ischemia and reperfusion subsequently to an infarction also effectively reduce infarct size. The present study was performed to determine, whether this protection by postconditioning is also operative in hypertrophied myocardium from spontaneously hypertensive rats (SHR).
Methods and Results: Hemodynamic, morphometric, and infarct size data were obtained in WKY-rats (age-and body-weight-matched normotensive controls) and compared to SHR-rats (both aged 10-12 weeks). The mean arterial pressure was increased by 37% and the heart weight/body weight ratio was raised by 18% in SHR-rats compared to WKY-rats indicating that hearts from SHR-rats were hypertrophied.
Infarct size was measured using propidium iodide. Control hearts experienced 30 min of infarct ischemia and 30 min of reperfusion. Postconditioning was performed by 3 cycles of ischemia/reperfusion 30 seconds each subsequent to 30 min of infarction. Infarct size was comparable in control hearts from WKY- and SHR-rats ($50\pm2\%$ vs. $45\pm5\%$). Postconditioning significantly reduced infarct size by 30% in WKY-rats, however, in SHR-rats the infarct sparing effect of postconditioning was lost ($35\pm3\%$ vs. $48\pm6\%$).
Conclusion: Postconditioning effectively reduces infarct size making this protective mechanism very interesting for future clinical applications. Myocardial hypertrophy, which is found frequently in patients with CAD, inhibits the protection from postconditioning. The mechanism responsible for the failure to protect hypertrophied myocardium has to be elucidated further.

P1554 ATP sensitive K channel opener inhibits calcium overload of isolated porcine myocardial mitochondria induced by mimicked ischaemia-reperfusion

Y. Wakida[1], M. Fukuta[1], T. Iwa[1], H. Takasima[1], Y. Hotta[2], N. Ishikawa[2], T. Ito[1]. *[1]Aichi Med. University, Cardiology, Aichi, Japan; [2]Aichi Medical University, Pharmacology, Aichi, Japan*

Background: ATP sensitive K channel opner, Nicorandil, is a potent myocardial protective agent reducing reperfusion injury. The precise mechanisms of this action are not known. However, several studies have indicated indirectly it's relation with a mitochondrial function. Purpose: To have a direct evidence we studied the effect of nicorandil on Ca overload using an isolated porcine myocardial mitochondria. Methods and results: Isolated mitochondria from porcine myocardium were pre-loaded with fluoroprobes of fura-2 AM for measuring mitochondrial Ca concentration. Mimicking ischemia-reperfusion, lowering the Ca concentration (10μM to 100nM) or acidifying (pH7.4 to 6.5) in the perfusate, rapidly elevated the fura-2 Ca signal in mitochondria (Cam). Atractyloside(10^{-3}M), which opens mitochondrial permeability transition pore (MPTP), similarly elevated Cam. These elevation of Cam were inhibited by cyclosporine A (10^{-4}M), which inhibits MPTP. Ca and PH change-induced Cam increase was not affected by atractyloside nor FK506 (10^{-4}M). These observations indicated Cam elevation after Ca and PH change was caused by MPTP opening. Preloaded nicorandil inhibited these increase of Cam (Fig1., inhibited rate was 23.0±2.4% by 10^{-4}M, 14.6±11.2% by 10^{-6}M in Ca change, and 19.6±5.3% by 10^{-4}M, 31.8±9.0% by 10^{-6}M in PH change, each group n=5). Increased Cam induced by PH change was inhibited to 93.2±1.2% by 10^{-4}M or 88.2±1.0% by 3x10^{-4}M of nicorandil as well as 10^{-}4M of diazoxide, which inhibit KATP channel.

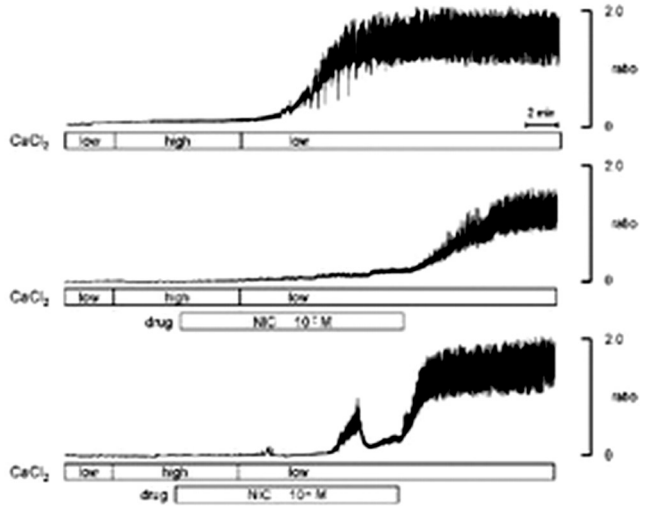


Figure 1

Conclusion: These results suggested that protective effect of nicorandil after reperfusion is attributed to an inhibiting Ca influx into mitochondria by inhibiting MPTP opening.

P1555 Reduced synchrony of sarcoplasmic reticulum Ca^{2+} release due to a reduction of T-tubule density in chronic ischaemic myocardium of pigs

L. Biesmans[1], F. Heinzel[1], V. Bito[1], J. Verheyden[1], M. Marciniak[2], P. Claus[2], J. D'hooge[2], K.R. Sipido[1]. *[1]K.U. Leuven, Lab of Experimental Cardiology, Leuven, Belgium; [2]KUL, Lab of Cardiac Imaging, Leuven, Belgium*

In heart failure due to chronic myocardial ischemia, contractile dysfunction is associated with structural and functional changes at the cellular level. In a model of chronic regional myocardial ischemia in pigs we have recently shown that contraction is slowed and reduced in cardiomyocytes isolated from the ischemic myocardium (Bito et al., 2004). In ventricular myocytes, T-tubules (TT) ensure spatial and temporal synchrony of Ca^{2+} release from the sarcoplasmic reticulum triggering contraction. Loss of TT has been observed in a canine model of pacing-induced heart failure. We investigated potential alterations in TT density with chronic ischemia and functional consequences. A copper-coated metal stent inducing intima proliferation was implanted in the circumflex coronary artery of pigs resulting in a >90% stenosis; dobutamine stress echo identified animals with reduced contractile function but viable myocardium (hibernation, HIB) and with myocardial infarction, as confirmed by pathology. We compared cardiomyocytes isolated 4-6 weeks after stent implantation from HIB or the infarct border zone (MI) to cells from the same heart region of healthy age-matched pigs (CTRL). TT density was quantified in stacks of confocal images by the fraction of signal-positive voxels within the cell after Di8-ANEPPS staining. In voltage-clamped cardiomyocytes Ca^{2+} release was recorded by epifluorescence and in confocal line scan images (Ca^{2+} indicator Fluo-3, voltage steps from -70 to 0 mV, 1 Hz). During chronic ischemia, mean TT signal decreased by 35%±5 in MI (n=5 pigs) and by 47%±4 in HIB (n=8) (both $p<0.05$ vs. CTRL, n=9). Loss of TT was associated with increased dyssynchrony of Ca^{2+} release along the longitudinal axis of the myocyte with fewer regions of early Ca^{2+} release (i.e. areas with locally half-maximal $[Ca^{2+}]_i$ reached in < 12 ms) in MI (31±6% of scan line vs. 56±6% in CTRL). Time to peak (TTP) of local transients in early areas was comparable in CTRL and MI (60±8 vs. 59±15 ms). However, the larger fraction of regions with delayed increase in $[Ca^{2+}]_i$ resulted in a slowed upstroke of the averaged whole-line transient in MI (TTP 132±19 ms vs. 73±4 ms in CTRL, $p<0.05$). Whole-cell averaged epifluorescence recordings confirmed a reduction in $[Ca^{2+}]_i$ in MI at an early timepoint (25 ms) despite unchanged peak $[Ca^{2+}]_i$. In conclusion, a loss of T-tubules during chronic ischemia is associated with dyssynchronous Ca^{2+} release, which may contribute to cellular contractile dysfunction in ischemic heart failure.

P1556 A single dose of metformin activates AMP-activated protein kinase (AMPK) in the rat heart and reduces myocardial infarct size 24 hours later

B. Loefgren[1], L.S. Jensen[2], J.M. Nielsen[1], S.B. Kristiansen[1], N. Jessen[2], T.T. Nielsen[1], H.E. Boetker[1], S. Lund[2]. *[1]Aarhus University Hospital, Skejby Sygehus, Department of Cardiology, Aarhus N, Denmark; [2]Aarhus University Hospital (ÅS), Medical Department M, Aarhus, Denmark*

Background: Treatment of type 2 diabetes with metformin is associated with a reduction in cardiovascular events and death compared to treatment with insulin or sulphonylureas. The mechanisms underlying this beneficial effect of metformin remain elusive. Metformin activates AMP-activated protein kinase (AMPK) which is recently found to play an important protective role in the ischemic heart. The aim of the present study was to investigate whether a single dose of metformin protects the heart against ischemia-reperfusion injury 24 hours after the treatment and whether the AMPK system was involved.
Methods: Male Wistar rats (~ 300 g) were allocated into two groups: A metformin group given a single oral dose of metformin (250 mg/kg body weight) and a control group given a single oral dose of vehicle (NaCl). After 24 hours the hearts were perfused in a Langendorff model and subjected to 45 minutes of regional ischemia and 120 minutes reperfusion. Infarct size was determined by tetrazolium staining and expressed as a percentage of the risk zone (I/R %). Isoform specific AMPK-alpha2 activity was measured 2 hours after administration of metformin or vehicle.
Results: Infarct size was significantly reduced in the metformin treated group (I/R %: 20±4% vs. 38±4%, $p<0.01$, n=10) compared to controls. Administration of a single dose of metformin resulted in an approximately 2-fold increase in AMPK-alpha2 activity ($p<0.05$, n=8).
Conclusion: A single dose of metformin increases AMPK-alpha2 activity and reduces myocardial infarct size 24 hours after administration. Increased AMPK-alpha2 activity may be involved in the mechanisms behind delayed cardioprotection afforded by metformin.

P1557 Connexin43, mitochondria and ischaemic preconditioning

K. Boengler[1], G. Dodoni[2], A. Rodriguez-Sinovas[3], M. Ruiz-Meana[3], F. Di Lisa[2], D. Garcia-Dorado[3], G. Heusch[1], R. Schulz[1]. *[1]Universitätsklinikum Essen, Institut für Pathophysiologie, Essen, Germany; [2]Dipartimento di Chimica Biologica, Universita di Padova, Padova, Italy; [3]Hospital Vall d'Hebron, Servicio de Cardiologica, Barcelona, Spain*

Connexin 43 (Cx43) is causally involved in infarct size reduction by ischemic preconditioning (IP), the underlying mechanism of protection, however, is unknown. In the first part of the present study we analyzed whether Cx43 is localized at mitochondria of cardiomyocytes, and whether such localization is affected by IP. Cx43 was detected by Western blot analysis in mitochondria isolated from mouse, rat, pig and human left ventricular myocardium. The mitochondria were not contaminated with markers of other cell compartments. In pig myocardium subjected to 90 min anterior wall ischemia, no difference in the Cx43 level between mitochondria isolated from the anterior and the control posterior wall of non-preconditioned pig hearts was detected by Western blot (1.1±0.2, normalized to ANT (adenine nucleotide transporter), which is not differentially expressed between mitochondria from non-preconditioned and preconditioned myocardium). However, in preconditioned pig hearts, the Cx43 content in purified mitochondria extracted from the preconditioned anterior wall was 3.4±0.7 fold of that in mitochondria extracted from the control posterior wall (n=13, $p<0.05$). The increase in the mitochondrial Cx43 level occurred rapidly, since the Cx43 protein level was already enhanced with two cycles of 5 min ischemia/reperfusion in isolated rat hearts to 262±63% of baseline.
In the second part of the study, we analyzed the submitochondrial localization of Cx43 and identified mitochondrial proteins interacting with Cx43 in order to elucidate its function at mitochondria. Digitonin-treated pig heart mitochondria – negative for the outer mitochondrial membrane marker protein VDAC (voltage dependent anion channel) – were found positive for both Cx43 and cytochrome c using immunohistochemistry and confocal laser scan microscopy. Furthermore, Western blot analysis on fractionated pig and mouse myocardial mitochondria

demonstrated no signal for Cx43 in the VDAC-positive outer membrane fraction, whereas immunoreactivity for Cx43 as well as the inner mitochondrial membrane protein ANT was detected in the inner mitochondrial membrane fraction. In contrast to VDAC, the translocase of the outer mitochondrial membrane (TOM20) as well as ANT were shown to co-immunoprecipitate with Cx43.
Taken together, these data show that Cx43 is located at the inner membrane of cardiomyocyte mitochondria and that the mitochondrial content of Cx43 is enhanced by IP. The regulation of the mitochondrial Cx43 protein content and its exact function in IP's protection against infarction will have to be defined in further studies.

LIPIDS AND MECHANISMS OF ATHEROGENESIS IN DIABETES

P1558 Increase in HDL-cholesterol produced by rimonabant therapy is associated with large HDL2-like particles: evidence from the RIO-Lipids trial

J.-P. Despres[1], A. Golay[2], L. Sjostrom[3] on behalf of RIO-Lipids study group. [1]*Laval Hospital Research Center, Quebec Heart Institute, Ste-Foy, Canada;* [2]*University Hospital Geneva, Geneva, Switzerland;* [3]*Sahlgrenska University Hospital, Goteborg, Sweden*

Abdominal obesity is associated with reduced HDL-cholesterol levels, a phenomenon accompanied by the presence of small HDL particles and by a preferential reduction in HDL2-cholesterol levels. The selective CB1 antagonist, rimonabant, has been shown to induce significant weight loss, substantial reduction in waist circumference (a measure of abdominal obesity) and a marked increase in HDL-cholesterol in overweight/obese patients treated for one year at a dose of 20 mg/day. Purpose: The present analyses focussed on the RIO-Lipids trial, a study in which a sample of 1036 overweight/obese dyslipidemic patients were randomized to receive a placebo or 5 mg or 20 mg of rimonabant. Efficacy data on body weight, waist circumference, key lipid parameters as well as safety profile have been previously reported.
Methods: The present analysis focuses on several characteristics/correlates of HDL including: HDL particle size measured by 4-30% gradient gel electrophoresis; HDL2-cholesterol and HDL3-cholesterol levels measured by a precipitation technique; apolipoprotein AI measured by nephelometry and cholesterol ester transfer protein (CETP) mass measured by ELISA.
Results: Whereas rimonabant had no effect on CETP mass, the substantial increase in HDL-cholesterol levels produced by rimonabant 20 mg was accompanied with the maintenance of HDL size compared to placebo-treated patients who showed a decrease in the HDL particle size (mean difference:0.53±0.18Å, p=0.004 vs. placebo). Compared to placebo, increases in HDL2-cholesterol and apolipoprotein AI levels trended towards statistical significance (p=0.061 and p=0.074, respectively). Furthermore, changes in HDL-cholesterol levels produced by rimonabant 20 mg were positively correlated with changes in apolipoprotein AI concentrations (r=0.57, p<0.0001). Changes in the measured parameters of HDL (HDL-cholesterol, HDL2-cholesterol, HDL3-cholesterol, apolipoprotein AI and HDL size) were negatively correlated with changes in waist circumference in the rimonabant 20 mg arm (-0.15≤r≤-0.23, p≤0.04). Rimonabant treatment was well tolerated.
Conclusions: Results of RIO-Lipids indicate that weight loss and decrease of abdominal fat produced by rimonabant are not only associated with increased HDL-cholesterol levels but also by the maintenance of large HDL2-like particles. Inhibition of CETP is not involved in the HDL-raising effect of rimonabant whereas apolipoprotein AI levels are increased.

P1559 Rosiglitazone increases the concentration of large, buoyant but not small dense LDL in patients with type 2 diabetes and coronary artery disease

R. Lautamaki[1], T. Ronnemaa[2], K.E.J. Airaksinen[2], A. Leino[3], H. Hiekkanen[4], M. Stewart[5], J. Knuuti[6], P. Nuutila[6]. [1]*University of Turku, Turku PET Centre, Turku, Finland;* [2]*Turku University Central Hospital, Department of Medicine, Turku, Finland;* [3]*Turku University Central Hospital, Department of Clinical Chemistry, Turku, Finland;* [4]*University of Turku, Department of Biostatistics, Turku, Finland;* [5]*GlaxoSmithKline, London, United Kingdom;* [6]*University of Turku, Turku PET Centre, Turku, Finland*

Background: The composition of LDL in patients with type 2 diabetes (T2DM) is characterized by small, dense LDL particles, which are associated with a high risk of myocardial infarction. Some studies suggest that PPARgamma-agonists have beneficial effects on LDL subclass profile in patients with blunted insulin sensitivity.
Aim: The aim of this study was to determine the effect of rosiglitazone (RSG) on LDL subclass profile in T2DM patients with coronary artery disease (CAD).
Methods: We studied 58 patients with T2DM (HbA1c 7.2±0.9%) and ischemic CAD confirmed by stress-rest SPECT and coronary angiography in a randomized, double-blind and placebo-controlled trial. Patients were treated either with RSG 8mg/day (n=29) or placebo (n=29) for 16 weeks. LDL subclass profile and the average LDL particle size were measured with gel electrophoresis before and after the treatment.
Results: RSG improved whole-body glucose uptake from 12.1±5.9 to 17.3±6.9 μmol/kg/min (P<0.0001 vs. baseline and vs. placebo) and decreased HbA1c from 7.2±0.9 to 6.8±0.6% (P=0.0007 vs. baseline, P<0.0001 vs. placebo). Total cholesterol increased from 4.18±0.65 to 4.66±0.85 mmol/L (P=0.001 vs. baseline, P=0.015 vs. placebo) and LDL (including IDL) cholesterol increased from 2.33±0.48 to 2.67±0.61mmol/L (P=0.002 vs. baseline, P=0.050 vs. placebo) in RSG group. From LDL subfractions large, buoyant LDL (>250Å) increased from 1.31±0.36 to 1.46±0.42 mmol/L (P=0.010 vs. baseline, P=0.044 vs. placebo) in RSG group. However, no significant changes occurred in small, dense LDL (0.09 vs. 0.08 mmol/L), in average LDL particle size, or in HDL or triglyceride concentrations.
Conclusion: In patients with T2DM and CAD, RSG treatment increases total and LDL cholesterol concentrations, but not the concentration of small, dense LDL, which is the most critical LDL subfraction with the respect to the risk of myocardial infarction.

P1560 Correlation of decreased adiponectin with increased oxidative stress after a high-fat meal

W.-C. Tsai[1], C.-H. Hsu[1], C.-C. Lin[2], Y.-H. Li[1], L.-J. Lin[1], J.-H. Chen[1]. [1]*National Cheng Kung University Hospital, Department of Internal Medicine, Tainan, Taiwan;* [2]*National Cheng Kung University Hospita, Emergency Medicine, Tainan, Taiwan*

Background: Adiponectin is an adipose-derived plasma protein. Plasma adiponectin levels have been linked to obesity and atherosclerosis. High-fat meal could cause increased oxidative stress and endothelial dysfunction. However, acute effects of high-fat meal on plasma adiponectin level were not fully elucidated. In this study, we investigated the changes of plasma levels of adiponectin and their relationship with oxidative stress after a high-fat meal.
Methods: Forty young healthy men (mean age 22 ± 1 years) were included in this study. They were not obese (body mass index 23.6 ± 1.1 kg/m^2) and without any risk factors. Plasma levels of triglyceride, adiponectin, and glutathione peroxidase (GSH-Px) were measured before and 2 hours after a standard high-fat meal (3677 J, 50 g of fat).
Results: Levels of triglyceride were significantly increased after the high-fat meal (80.3 ± 31.5 vs. 129.4 vs. 49.2 mg/dl, p <0.001). Adiponectin (6.6 ± 2.1 vs. 6.0 ± 2.0 ug/ml, p = 0.002) and GSH-Px (23.6 ± 5.0 vs. 22.4 ± 4.9 ug/ml, p = 0.046) were significantly decreased after the high-fat meal. Degree of adiponectin attenuation was correlated with GSH-Px attenuation (r = 0.460, p = 0.003).
Conclusions: Adiponectin was decreased after a high-fat meal in young healthy men. The attenuation of adiponectin was correlated with increased oxidative stress caused by postprandial hypertriglyceridemia.

P1561 Effects of the exercise training on the LDL metabolism in hypercholesterolemia

E.S. Ficker[1], C.G. Vinagre[2], A.P.M. Chacra[2], V.C. Neves[3], C.E. Negrao[3], M.E.F. Oliveira[2], R.C. Maranhao[2]. [1]*Heart Institute (InCor), Laboratory of Lipid Metabolism, Sao Paulo, Brazil;* [2]*Heart Institute (InCor), Laboratory of Lipid Metabolism, Sao Paulo, Brazil;* [3]*Heart Institute (InCor), Exercise Physiology, Sao Paulo, Brazil*

Background: There is evidence that physical activity have a lower cardiovascular risk due to their higher metabolic fitness. Exercise-training exerts beneficial effects on the lipid profile.
Objective: The purpose of the present study was to evaluate the effects of exercise-training on the metabolism of an lipidic artificial microemulsion with metabolic behavior similar to LDL, in hypercholesterolemic patients.
Methods: six sedentary hypercholesterolemic patients were submitted to a 4 times/week training load, 1 hour/day, for 4 months on bicycle ergometer. All participants underwent a cardiopulmonary exercise test to measure the maximum oxygen consumption (VO2max). The emulsion labeled with 3H-triglycerides (3H-TG-FCR) and 14C-cholesteryl ester (14C-CO-FCR) was injected intravenously. Blood samples were collected at 5 min, 1, 2, 4, 6, 8, 24 hours after injection for the radioactivity determination. The plasma curve decay was performed and the fractional clearance ratio (FCR) was calculated by compartimental analysis. The evaluations were performed before and after the exercise-training protocol.
Results: The FCR of the labeled cholesteryl ester of the emulsion was higher after exercise training, as well as, the plasma HDL cholesterol (table).

Studied parameters pre and post exercise

	Pre-exercise	Post exercise
VO2max (mL/kg/min)	25±2	29±3*
3H-TG-FCR (h-1)	0.0852±0.0223	0.1085±0.0216
14C-CO-FCR (h-1)	0.0458±0.0069	0.0587±0.0076*
Cholesterol: total (mg/dL)	227±28	211±22
LDL	147±13	131±24
HDL	43±10	50±13*
VLDL	30±15	27±11
Triglycerides (mg/dL)	151±63	142±54
Body mass index (kg/m^2)	27±5	28±6

*P<0.05 compared to pre-exercise

Conclusion: Exercise training accelerates the LDL removal from the plasma in

hypercholesterolemic patients, indicated by the higher 14C-CO-FCR. This effect may be one of the mechanisms whereby exercise prevents coronary artery disease.
Technical Support: Master Academy 24 hours

P1562 Lipoprotein(a) in coronary patients with type 2 diabetes is low and not predictive of vascular events

C.H. Saely[1], S. Aczel[1], T. Marte[1], P. Langer[2], F. Schmid[2], L. Koch[2], P. Rein[2], H. Drexel[1]. *[1]Landeskrankenhaus Feldkrich, Department of Medicine and VIVIT, Feldkirch, Austria; [2]VIVIT-Institute, Feldkirch, Austria*

Lipoprotein(a) [Lp(a)] is an important cardiovascular risk factor in the general population. However, prospective data on Lp(a) as a cardiovascular risk factor in patients with type 2 diabetes (T2DM) are scarce and controversial.
Aim: To prospectively investigate the impact of Lp(a) on future vascular events among patients with T2DM as well as among nondiabetic subjects in an angiographically characterized cohort.
Methods: We measured serum levels of Lp(a) in 587 consecutive patients undergoing coronary angiography for the evaluation of coronary artery disease (CAD). Over a median [interquartile range] follow-up period of 4.0 [3.6-4.2] years the incidence of vascular endpoints was recorded.
Results: From the total cohort, 136 patients (23.2%) had T2DM, and 451 patients did not have diabetes. At baseline, Lp(a) was significantly lower in patients with T2DM than in non-diabetic patients (11 [0-30] mg/dl vs. 16 [0-51] mg/dl; p = 0.025). Whereas Lp(a) was strongly and significantly predictive for the presence of CAD at angiography for non-diabetic patients (standardized adjusted HR = 1.437 [1.137-1.815]; p = 0.002), it was not associated with CAD in patients with T2DM (1.335 [0.721-2.469]; p = 0.358). Consistently, in the prospective part of the study Lp(a) proved independently predictive for vascular events among non-diabetic patients (HR = 1.316 [1.094-1.582]; p = 0.004), but not among patients with T2DM (HR = 0.656 [0.380-1.133]; p = 0.130). An interaction term T2DM x Lp(a) was significant (p = 0.023), indicating that Lp(a) was a significantly stronger predictor of vascular events among non-diabetic patients than among patients with T2DM.
Conclusions: Among nondiabetic patients undergoing coronary angiography for the evaluation of CAD, Lp(a) is associated with the presence of CAD at angiography and significantly predictive for future vascular events. However, among coronary patients with T2DM, Lp(a) is low and neither associated with the presence of CAD at angiography nor with the future incidence of vascular events.

P1563 Middle cerebral artery stenosis is a predictor of overall vascular disease mortality in Chinese diabetic subjects

G.N. Thomas[1], M. Schooling[1], B. Tomlinson[2], J.W. Lin[3], W.W.M. Lam[4], V.T.F. Yeung[2], J.C.N. Chan[2], L.K.S. Wong[2]. *[1]University of Hong Kong, Community Medicine Dept., Pokfulam, Hong Kong, China; [2]The Chinese University of Hong Kong, Medicine & Therapeutics Dept., Shatin, Hong Kong, China; [3]Sun Yat-Sen Univ. of Medical Sciences, Neurology Dept., Guangzhou, China; [4]The Chinese University of Hong Kong, Diagnostic Radiology & Organ Imaging, Shatin, Hong Kong, China*

Background: ethnic differences in the prevalence of vascular diseases exist, with higher rates of stroke and diabetic renal disease reported in Chinese compared to Caucasian populations. Similarly, the anatomical distribution of atheromatous cerebrovascular arterial lesions differs between these groups. Stenoses in the middle cerebral artery (MCA) are the most frequently identified lesions leading to cerebrovascular accidents in Chinese subjects.
Objective: to determine if MCA stenoses are predictors of vascular disease mortality in Chinese Type 2 diabetics.
Methods: the mortality status was determined for 1288 Chinese diabetics, who had been previously screened by transcranial Doppler to identify MCA stenosis. The mean follow-up duration was 6.2 years, with 42 deaths related to ICCD-9 coded atherosclerotic vascular disease (stroke, heart or renal disease). A Cox Proportional Hazards Model was used to determine predictors of mortality. Gender, age, body mass index (BMI), systolic blood pressure, duration of diabetes, fasting glucose and triglycerides, smoking status (never/ever) and MCA stenosis (1 or 2 vessel disease) were included in the analysis. All variables met the proportional hazards assumption.
Results: there was a significant trend ($p<0.01$) for increased mortality with the presence of MCA stenoses, with risk increasing from 1 to 2 vessel disease (Hazard ratios 1.79 [95% CI, 0.68-4.71], p=0.23, and 3.30 [95% CI, 1.53-7.11], p=0.002, respectively after adjustment for the risk factors described above). Increasing age ($p<0.001$), smoking ($p<0.05$), and BMI ($p<0.05$) were also significant predictors of mortality, the latter exhibiting a U-shaped relationship.
Conclusion: the presence of MCA stenosis was associated with significantly increased risk of overall vascular disease mortality in these Chinese Type 2 diabetic subjects.

P1564 Type 2 diabetes and coronary artery disease as major determinants of elevated hydroperoxide levels

C. Vassalle, P. Landi, C. Boni, G.C. Zucchelli. *Istituto di Fisiologia del CNR, IFC-CREAS Pisa, Pisa, Italy*

Oxidative stress has a major role in the pathogenesis and development of different chronic and degenerative diseases, including atherosclerosis.
Aim: to investigate whether hydroperoxides levels (as index of oxidative stress) are associated with coronary artery disease (CAD) and the occurrence of different atherogenic risk factors.
Methods: Serum hydroperoxides were measured in 85 patients (18 females, 67 males, age:66±1 years, mean±SEM), who underwent coronary angiography (23 patients without coronary artery atherosclerotic lesions and 62 patients with CAD).
Results: Hydroperoxides were significantly higher in CAD respect to No-CAD patients ($p<0.05$). Moreover, hydroperoxides were significantly higher in patients with combined presence of CAD and dyslipidemia or CAD and type 2 diabetes respect to patients who did not present these determinants (430±23.6 and 323.4±43.9 AU, $p<0.05$; 465.4±356 and 354.2±27.1 AU, $p<0.01$, respectively). In the multivariate analysis, in which hydroperoxide levels above 75th percentile (>482 AU) represented the dependent parameter, the Odds Ratio for CAD resulted 3.1 ($p<0.05$), and increased in patients with both CAD and hypertension, CAD and dyslipidemia or CAD and diabetes.
Conclusion: Occurrence CAD, especially when concomitant with hypertension, dyslipidemia, diabetes, is associated with elevated oxidative stress, suggesting that high hydroperoxide levels might represent new possible predictor and prognostic factors in the clinical setting.

P1565 Ankle-brachial pressure index is important in the diagnosis of coronary artery disease in female patients with diabetes mellitus

Y. Igarashi, T. Chikamori, Y. Usui, S. Hida, H. Tomiyama, H. Tanaka, K. Harafuji, A. Yamashina. *Tokyo Medical University, Department of Internal Medicine II, Tokyo, Japan*

Background: Clinical symptoms of chronic coronary artery disease (CAD) is often atypical in female, particularly in those with diabetes mellitus (DM). Therefore, a simple method to identify a high-risk group among female diabetic patients who is likely to have CAD is of utmost importance in clinical practice.
Methods: Three hundred sixty-one consecutive patients (242 male and 119 female, age 65±11 years) with suspected CAD, excluding those with previous myocardial infarction or coronary intervention, were evaluated by simultaneous brachial and ankle blood pressure measurements and stress myocardial perfusion imaging to obtain ankle-brachial pressure index (ABI) and percent of ischemic segments to total segments (% ischemic myocardium). Of 361 patients, 141 (81 male and 60 female) were diabetics.
Results: Percent ischemic myocardium was similar between 242 male and 119 female patients (5.8±0.4% vs 5.0±0.6%; p=NS), whereas % ischemic myocardium was greater in 141 diabetics than in 220 nondiabetics (7.2±0.6% vs 4.5±0.4%; $p<0.0001$). In 141 diabetic patients, % ischemic myocardium was also similar between male and female (7.5±0.9% vs 6.8±0.9%; p=NS). Applying ABI with a cutoff of 1, female DM patients with ABI <1 showed greater % ischemic myocardium than those with ABI ≥1 (9.6±2.1% vs 5.2±0.8%; p=0.02), whereas no such additional value of ABI was observed in male DM patients (9.2±1.4% vs 6.8±1.1%; p=NS). Furthermore, among 102 diabetic patients who underwent coronary angiography, prevalence of significant CAD was higher in patients with ABI <1 than in those with ABI ≥1 (26/30 vs 41/72; p=0.005).
Conclusions: ABI, a simple index obtained in clinical practice, help better identify a high-risk group of female DM patients who have significant CAD and greater extent and severity of stress-induced myocardial ischemia.

P1566 MAP-kinase/NF-kB-dependent activation and inhibition of PI3-kinase/Nitric Oxide are both involved in pro-atherogenic effects of insulin – a link to the pathogenesis of atherosclerosis in diabetes

R. De Caterina[1], R. Madonna[2], M. Marika[3], A. Pandolfi[4], A. Consoli[4]. *[1]"G. d'Annunzio" University-Chieti, Director, University Cardiology Division, Chieti, Italy; [2]"G. d'Annunzio" University-Chieti, University Cardiology Division, Chieti, Italy; [3]Institute of Clinical Physiology, CNR, Lecce, Italy; [4]"G. d'Annunzio" University-Chieti, Chair of Endocrinology, Chieti, Italy*

Insulin levels are a marker for cardiovascular events, but the link between hyperinsulinemia and atherosclerosis is poorly understood. We previously showed that insulin (I), despite increasing NO production, increases monocyte-endothelial interactions and VCAM-1 expression. We now investigated the co-stimulatory effect of insulin with pro-atherogenic cytokines and investigated signaling pathways involved.
Human umbilical vein endothelial cells were incubated with I (0-24 hours) ± tumor necrosis factor (TNF)-alpha or lipopolysaccharide (LPS), ± the phosphatidylinositol (PI) 3-kinase inhibitor wortmannin (WT), the protein kinase-C inhibitor Ro318220 (Ro), the p38mitogen activated protein (MAP) kinase inhibitor SB203580 (SB), or the extracellular signal-regulated kinase (ERK)-1/2 inhibitor

PD98059 (PD). The expression of VCAM-1, ICAM-1 and E-selectin was assessed by enzyme immunoassays, flow-cytometry and Northern analysis.
At pathophysiological concentrations (10^{-9} - 10^{-7} mol/L), I selectively induced VCAM-1 surface expression and potentiated the effects of TNF and LPS, effects reverted by the proteasome inhibitor lactacystin. Compared with TNF alone, the co-stimulation with I+TNF increased U937 cell adhesion by 2 fold, and markedly induced VCAM-1 mRNA. WT potentiated, while SB, PD or Ro abolished I effect on VCAM-1 expression. I activated NF-kB and potentiated TNF effects (gel shift) and induced a time-dependent phosphorylated ERK1/2 and p38MAPK accumulation, effects potentiated by WT. We then investigated the PI3-kinase pathway activation, involved in the anti-atherogenic, NO-related effects of I. While physiological I concentrations (10^{-11} - 10^{-10} mol/L) increased the pAkt/Akt ratio, higher I concentrations decreased it. The NOS inhibitor L-NAME mimicked the effects of high I in increasing VCAM-1 surface expression, suggesting that stimulation of eNOS only occurs at physiological concentrations of I.
In conclusion: both the inhibition of Akt/eNOS and the direct activation of MAP-kinase/NF-kB contribute to the effects of pathophysiological I concentrations on VCAM-1 expression. These findings potentially explain the paradox of I levels being related directly (and likely causally linked) to atherosclerotic vascular disease despite stimulatory effects of I on the anti-atherogenic NO pathway.

P1567 Activation of receptors for advanced glycation end products (RAGEs) induces cytokine expression in human monocytes

N. Ivanova, D. Walcher, D. Roesch, N. Marx. *University of Ulm, Dept. of Internal Medicine II, Ulm, Germany*

Advanced glycation endproducts (AGEs) are critically involved in vascular dysfunction observed in diabetes mellitus by inducing the expression of pro-inflammatory mediators through activiation of the specific receptors for AGEs (RAGEs) in vascular cells. The regulation of RAGE expression may be an important factor for AGE deleterious consequences, but little is known about such mechanisms in monocytes. The present study investigated whether activation of RAGEs in human monocytes might stimulate the secretion of pro-inflammatory cytokines, which then in turn may increase cellular RAGE expression. Stimulation of freshly isolated monocytes with AGEs or the RAGE activator S100 increased IL-6 as well as TNF-alpha protein secretion in a time- and concentration-dependent manner with a maximal induction after 6 hour treatment with 10μg/mL S100 from 192,287$\pm$52,383pg/ml to 661,126$\pm$211,630pg/ml and from 130,807$\pm$46,531pg/ml to 388,120$\pm$136,092pg/ml, respectively ($p<0.05$). Heat-inactivation of AGEs or S100 abolished this effect. This increase in cytokine protein release was due to an increase in IL-6 and TNF-alpha mRNA expression. In addition, both, IL-6 and TNF-alpha enhanced RAGE protein expression in human monocyte as shown by flow cytometry and western blot analyses. Finally, increasing monocyte RAGE expression by pretreatment with TNF-a enhanced S100-induced IL-6 release. Similar results were obtained, when human monocytes were pretreated with IL-6 before assessment of TNF-alpha release after S100 stimulation. Thus, RAGE activation induces the expression of pro-inflammatory cytokines in human monocytes. In turn, these cytokines enhance monocyte RAGE expression, thus increasing the cells susceptibility towards pro-inflammatory RAGE activators' effects. Such mechanisms may lead to a sustained, self-promoting activation of human monocytes, which may furnish lesion development in diabetic patients.

P1568 Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice

S. Steffens[1], N.R. Veillard[1], G. Pelli[1], F. Burger[1], C. Staub[2], J.L. Frossard[3], C. Arnaud[1], F. Mach[1]. *[1]Foundation for Medical Research, Cardiology Department, Geneva, Switzerland; [2]Legal Medicine, Geneva, Switzerland; [3]Gastroenterology, Geneva, Switzerland*

Atherosclerosis is a chronic inflammatory disease that represents the primary cause of heart disease and stroke. Derivatives of cannabinoids such as delta-9-Tetrahydrocannabinol (THC) modulate immune functions and therefore have a therapeutic potential for the treatment of inflammatory diseases. We tested THC on established atherosclerosis in a murine model. Oral administration of THC (1 mg kg-1 per day) resulted in the significant inhibition of disease progression, as demonstrated by reduced atherosclerotic plaque development within the aortic roots (41.2% reduction versus control group). This effective dose is lower than the dose usually associated with psychotropic effects of THC. Furthermore, we detected CB2 receptor, the main cannabinoid receptor expressed on immune cells, in both human and mouse atherosclerotic plaques. Lymphoid cells isolated from THC-treated mice exhibited diminished proliferation capacity and reduced interferon-gamma secretion, whereas interleukin-10 and transforming growth factor-beta production were not significantly altered. In vitro, THC inhibited macrophage chemotaxis, a crucial step for the development of atherosclerosis. All these effects were completely blocked by a specific CB2 receptor antagonist, and absent when macrophages isolated from CB2 receptor knock-out mice were used. Our data demonstrate that oral treatment with a low dose of THC, through its pleiotropic immunomodulatory effects on lymphoid and myeloid cells, is a potent inhibitor of atherosclerosis progression in the apolipoprotein E knock out mouse model. Thus, THC or cannabinoids with activity at the CB2 receptor may be a valuable target for investigation of their use in treating atherosclerosis.

P1569 Gene polymorphisms influencing the prevalence of myocardial infarction among diabetic and non-diabetic subjects

W.G.M. Relvas[1], M.C. Izar[1], T. Helfenstein[1], A.O. Santos[1], M.I.H. Fonseca[1], S.S.M. Ihara[2], S.W. Han[3], F.A.H. Fonseca[1]. *[1]Federal University of Sao Paulo, Medicine Dept., Sao Paulo, Brazil; [2]Federal University of Sao Paulo, Pathology, Sao Paulo, Brazil; [3]Federal University of Sao Paulo, Biophysics, Sao Paulo, Brazil*

Background: Considering the early development of the macrovascular disease, which precedes hyperglycemia in diabetics, genetic studies should be part of the strategy to identify patients at higher risk of MI. This study was aimed to examine cholesteryl ester transfer protein (CETP), apolipoprotein AI and CIII gene polymorphisms, and to verify whether these genetic determinants are associated with the prevalence of myocardial infarction (MI) or type 2 diabetes.
Methods: The TaqIB restriction fragment length polymorphism (RFLP) in intron I of the CETP gene, the MspI in the third intron of the APOAI gene, and also SstI in the 3' untranslated region of the APOCIII gene were determined using PCR-RFLP. The prevalence of these polymorphisms was compared between diabetic (n=119), and non-diabetic (n=100) middle-aged individuals of both sexes. The groups were controlled for age, sex and prevalence of prior myocardial infarction (MI).
Results: We found a higher prevalence of the B2B2 genotype of the CETP gene among diabetics than that observed in non-diabetics ($p<0.05$), and a lower prevalence of this genotype among patients with previous MI ($p<0.02$). The MspI polymorphisms of APOAI gene showed that M1++ genotype was found mainly in diabetic patients ($p<0.04$). Conversely, the SstI polymorphism of APOCIII gene was not significantly associated with either MI or diabetes.

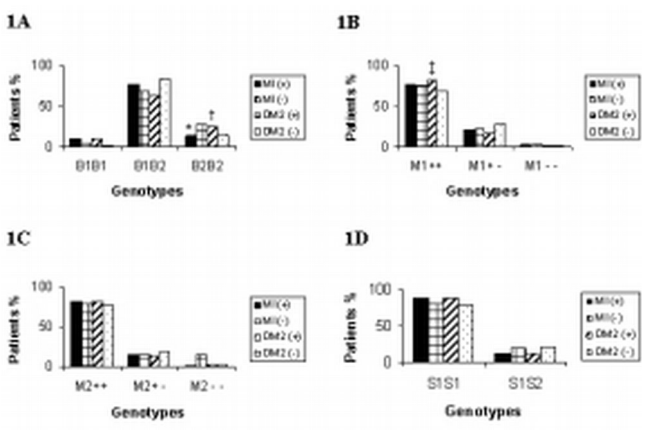


Figure 1

Conclusions: This study revealed the contribution of CETP-TaqIB and Apo AI-MspI polymorphisms in the identification of diabetic individuals. In particular, the former may have an additional role in the primary prevention of coronary disease.

P1570 Prevalence and impact of diabetes mellitus on the complication rate in patients with percutaneous coronary intervention. Results from the ALKK-registry

O. Koeth[1], U. Tebbe[2], B. Gut[1], T. Bonzel[3], R. Zahn[1], J. Senges[1], U. Zeymer[1] on behalf of the ALKK Study Group. *[1]Klinikum Ludwigshafen, Kardiologie, Ludwigshafen, Germany; [2]Klinikum Lippe-Detmold, Kardiologie, Detmold, Germany; [3]Klinikum Fulda, Kardiologie, Fulda, Germany*

Background: Patients with diabetes are at high risk for coronary artery disease and acute coronary events. The aim of this analysis was to evaluate the impact of age on the prevalence of diabetes and the rate of complications in patients undergoing percutaneous coronary intervention (PCI).
Methods: We analysed data from the prospective ALKK-PCI-registry. In 2003

Age (years)	Diabetes n (%)	3-Vessel disease n (%) Diabetes		p-value	Complication: Death, MI, TIA/Stroke n (%) Diabetes		p-value
		yes	no		yes	no	
<50	255 (9%)	63 (25%)	395 (16%)	< 0,001	2 (1%)	38 (2%)	0,36
51-60	780 (16%)	218 (28%)	918 (23%)	< 0,001	10 (1%)	40 (1%)	0,41
61-70	1866 (20%)	695 (38%)	2075 (28%)	< 0,001	29 (2%)	121 (2%)	0,91
71-80	1911 (23%)	803 (43%)	2098 (34%)	< 0,001	68 (4%)	130 (2%)	< 0,001
>80	493 (22%)	241 (49%)	714 (41%)	< 0,01	29 (6%)	55 (3%)	<0.01

27732 conscutive PCIs at 71 hospitals in Germany were included in this registry.
Results: The impact of age on the prevalence of diabetes and the complication rates in patients with and without diabetes is shown in the table.
Summary: The prevalence of diabetes is increasing with age in patients undergoing PCI. Patients with diabetes mellitus have significantly more often diffuse 3-vessel coronary artery disease. In patients over 70 years diabetes is associated with a significant increase of the rate of major complications after PCI.

P1571 Paraoxonase serum activity is increased by aerobic exercise in patients with metabolic syndrome

E. Goldhammer[1], I. Maor[2], A. Tanchilevitch[3], U. Rosenschein[4], G.H. Zaid[3], Y. Biniamini[3]. [1]*Haifa, Israel;* [2]*Bnai-Zion Medical Center, Biochemistry, Haifa, Israel;* [3]*Bnai-Zion Medical Center, Cardiac Rehabilitation Center, Haifa, Israel;* [4]*Bnei-Zion Medical Center, Cardiology Dept., Haifa, Israel*

Background: Human paraoxonase (PON) is an HDL-associated enzyme that is proposed to protect against the oxidation of lipoproteins, moreover, low serum PON activity is considered an independent risk factor for coronary events in men at high risk because of preexisting disease or other CHD risk factors.
Aim: To assess the effects of aerobic exercise training on levels of PON in metabolic syndrome patients participating in an exercise based prevention program.
Material and Methods: 25 patients, age 57.1±6.1yrs, 17 men, and 8 women, with BMI 29.1±2.2 kg/m^2, waist/hip ratio (WHR) 1.15±0.04 s.d., 18 pts with DM type II, 7 pts with impaired fasting glucose (117 mgr%±2.6 s.d.),and Triglicerides 227 mg/dL ± 24 s.d., underwent a 12 week aerobic exercise program, 3 x 45 min sessions/week. PON activity was measured by its arylesterase activity (spectrophotometrically, at 250c, wavelength 270 nm).
Results: PON serum levels increased following exercise training by 20.3%, from 80.7±13.45 to 97.1±14.57 μ/ml, $p<0.01$. Pre and post program PON levels correlated well with WHR, r = 0.75, $p<0.01$ and triglicerides, r =0.79, p =0.014. Multiple regression analysis showed triglicerides and C-reactive protein to be the best independent predictors of change in PON levels with training. Significant correlations were also found with exercise tolerance(in METS), r = 0.91 ($p<0.01$), and peak VO2, r = 0.84 ($p<0.01$). Baseline levels were significantly lower in patients with SBP > 160mmHg, $p<0.001$, and increased by a similar magnitude following exercise program.
Conclusions: Aerobic exercise training increased the anti-oxidative, anti-atherogenic PON in patients with metabolic syndrome. Increased PON levels may be considered one of the mechanisms exercise training improves risk profile in these patients.

P1572 Enhanced baseline activity of mitogen-activated protein kinases and protein kinase B/Akt in monocytes from patients with diabetes mellitus: relation with impaired responsiveness of the VEGFR-1 pathway

V. Tchaikovski[1], J. Waltenberger[2]. [1]*Academic Hospital of Maastricht, Cardiology/CARIM, Maastricht, Netherlands;* [2]*Academic Hospital of Maastricht, Cardiology/CARIM, Maastricht, Netherlands*

Vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) act on endothelial cells and monocytes, two cell types that participate in angiogenesis and arteriogenesis. The chemotactic response of monocytes to VEGF-A is attenuated in diabetic patients as previously shown by our group. This could explain the impaired growth of collaterals in diabetic patients. The aim of the current study was to elucidate VEGF receptor-1-related signal transduction defects that may be responsible for the altered migratory capacity of monocytes in diabetic patients.
Human primary monocytes (Mo) were isolated from peripheral venous blood of diabetic (age 70.8±10.7) and non-diabetic (age 68.5±7.9) individuals using a two-step gradient centrifugation. Mo were stimulated with either VEGF-A or PlGF-1, lysed and further evaluated by Western Blot analysis for assessing the activity of protein kinase B (PKB/Akt) as well as p38 and ERK1/2, two members of the mitogen-activated protein kinase family. For comparison, monocytes were stimulated with N-Formyl-Met-Leu-Phe (fMLP).
In monocytes from non-diabetic individuals, PlGF-1 and VEGF-A (10 ng/mL) significantly stimulated the activation of PKB/Akt (2.0- and 4.1-fold, respectively), p38 (2.2- and 3.2-fold, respectively) and ERK1/2 (2.3- and 2.8-fold, respectively). In contrast, no such ligand-induced activation was detectable in monocytes derived from diabetic patients. However, when we compared the ligand-independent baseline activity of PKB/Akt, p38 and ERK1/2 of non-diabetic and diabetic individuals, a significantly elevated level of activity was found in diabetic individuals (4.1-, 5.5- and 2.8-fold, correspondingly) as compared to non-diabetic subjects. In contrast, fMLP caused a similar activation of PKB/Akt in both diabetic and non-diabetic monocytes (8.4- and 7.4-fold, respectively). Following stimulation with fMLP, the activation of p38 and ERK1/2 was partly attenuated in diabetic monocytes (2.1- versus 6.3-fold in non-diabetic and 3.4- versus 13.6-fold in non-diabetic individuals, respectively).
These data demonstrate a baseline activation of several VEGF-receptor-1-related signaling pathways in monocytes from diabetic individuals. This baseline activation of PKB/Akt, p38 and ERK1/2 may explain the lack of monocyte responsiveness to VEGF-A or PlGF-1 stimulation. These diabetes-associated signal transduction defects provide an explanation for the poor chemotactic response of monocytes to VEGF-A stimulation, and may therefore provide a molecular explanation for the reduced effect of VEGF-A stimulation in diabetic individuals.

P1573 Relationship between platelet CD40 ligand expression and platelet superoxide anion production in hypercholesterolemic patients. Effect of Atorvastatin

V. Sanguigni[1], P. Pignatelli[2], L. Lenti[2], M. Tesauro[3], R. Carnevale[2], S. Di Santo[2], R. Lauro[3], F. Violi[2]. [1]*Roma, Italy;* [2]*University of Rome La Sapienza, Experimental Medicine, Rome, Italy;* [3]*University of Roma Tor Vergata, Internal Medcine, Rome, Italy*

Introduction: Previous studies showed that in hypercholesterolemia platelet CD40 ligand (CD40L), a surface-bound protein with inflammatory and prothrombotic effects, is upregulated. We investigated if in patients with hypercholesterolemia platelet CD40L overexpression may depend on enhanced intraplatelet formation of superoxide anion(O2-) and therefore if atorvastatin could directly affects platelet CD40 ligand expression and O2- production, with a mechanism independent of its cholesterol lowering effect. To explore this issue we undertook an in vitro and in vivo study
Methods: We compared 30 patients with polygenic hypercholesterolemia (16 males, 14 females; mean age, 53.4 years) and 20 sex- and age-matched normocholesterolemic subjects (10 males and 10 females; mean age, 52.6 years).Hypercholesterolemic patients were then randomized to either a diet (American Heart Association step I diet) (N= 15, 8 males, 7 females) or atorvastatin 10 mg/day (N=15, 8 males, 7 females) for three days. Lipid profile, CD40 ligand platelet expression. (by flow cytometric analysis) and O2- production (by chemoluminescence method) were measured at baseline and after 3 days of treatment.
Results: Compared with controls,patients with hypercholesterolemia had enhanced production of O2- ($p>0.001$) and higher platelet expression of CD40L ($p>0.001$). Platelet CD40L significantly correlated with platelet O2- (r=0.77) Both groups (diet and atorvastatin) did not show any changes in lipid profile after 3 days of treatment. In diet group (n=15), no changes in platelet CD40L expression and O2- production was observed. In atorvastatin group (n=15), a significant decrease in platelet CD40L (46.3 ± 14.6 vs 32.2 ± 6.4 AU, $p < 0.001$) and platelet O2- (3.8±0.4 vs 2.3±0.6 SI, $p<0.01$) was observed after three days. Before-after treatment changes between platelet CD40L and platelet O2-. (r=0.66, $p<0.001$) were significantly correlated.
Incubation of platelets with atorvastatin showed a significant decrease (dose-dependent) in platelet CD40L expression and O2- production ($p < 0.005$).
Conclusion: This study provides evidence that in hypercholesterolemia, platelet CD40L overexpression may be mediated by enhanced platelet O2- production. Our data also demonstrated a novel property of atorvastatin, independently of its cholesterol-lowering effect, which consists in a direct antioxidant effect that accounts for reduced platelet production of O2- and in turn platelet CD40L down-regulation.This effect gives further insight in the mechanism through which statins may stabilize aterosclerotic plaque.

CMR: MYOCARDIAL IMAGING WITH GADOLINIUM

P1574 Comparison of right ventricular wall motion anomalies detected by MRI arrhythmogenic right ventricular dysplasia, right ventricular outflow tract tachycardia, Brugada syndrome and normal controls

X. Lyon[1], A. Azarine[2], A. Redheuil[3], E. Mousseaux[2]. [1]*University Hospital, Service of Cardiology, Lausanne, Switzerland;* [2]*HEGP, Department of Radiology, Paris, France;* [3]*HEGP, Department of Cardiology, Paris, France*

Background: Diagnosis of arrhythmogenic right ventricle dysplasia (ARVD) remains a challenge. It is often difficult, in the clinical setting, to distinguish this disease from Brugada syndrome or benign entities as right ventricular outflow tract tachycardia (RVOTT). Presence of wall motion anomalies of the RV are a well known features of ARVD and contributes to the definition of the disease according to the Task Force of the European Society of Cardiology. Absence of morphological anomalies is required to diagnosis RVOTT, but this issue is controversial as several authors had demonstrated the presence of alterations in RV regional kinetic in these patients using magnetic resonance imaging (MRI). Such aberrations were also found in Brugada patients in a single report using electron beam computerized tomography. The aim of this study was to compare RV segmental kinetic in ARVD, RVOTT, Brugada and normal controls.
Methods: A cardiac MRI was performed in 92 patients (ARVD: 34, RVOTT: 28, Brugada: 10, normal: 21). Each RV segment was visualized in two different planes and regional kinetic was classified as 1) normal, 2) minor alterations (hypokinesia, akinesia, mild diastolic bulging) or 3) major alterations (severe diastolic bulging, dyskinesia, aneurysm). Results were compared between groups at the patient level (presence of any anomaly over the RV) as well as for each segment (inflow tract, outflow tract, free wall, anterior and inferior).
Results: Major, but not minor, alterations of RV segmental contractions signifi-

cantly discriminate ARVD from all the other groups with a high specificity (96%) and a mid range sensitivity (76%). Kinetic aberrations were not significantly different in RVOTT, Brugada patients or normal controls. Contractions anomalies were evenly distributed over the RV in each group, in particular an outflow tract predominance was not observed.
Conclusion: This study demonstrates that the presence of major anomalies in RV segmental contractions is highly specific for the presence of ARVD. In contrast to other studies segmental contraction in patient with RVOTT or Brugada syndrome was not different from normal controls. This results emphasize that cine MRI could be a powerful tool for ARVD diagnosis, moreover as it is non invasive it would be of particular interest for screening population at risk as relatives of affected individuals. Finally our observations argue against the hypothesis that RVOTT may represent an early phase of ARVD.

P1575 Myocardial tissue changes in patients with severe pulmonary arterial hypertension

J. Schulz-Menger[1], C.O. Opitz[2], H. Abdel-Aty[3], R. Ewert[4], P. Bock[3], M.G. Friedrich[5]. *[1]Franz-Volhard-Klinik, Cardiology Dept., Berlin, Germany; [2]Cardiology, DRK-Klinikum Westend, Berlin, Germany; [3]Franz-Volhard-Klinik, Charite Campus Buch, Cardiology, Berlin, Germany; [4]Ernst-Moritz-Arndt-Universitaet, Greifswald, Germany; [5]University of Calgary, Department of Cardiac Sciences, Calgary, Canada*

Objectives: Pulmonary arterial hypertension (PAH) leads to pressure overload of the right ventricle (RV) and reduced RV-function, which is associated with unfavorable prognosis. It is well established, that decreased cardiac output is directly related to the clinical severity and prognosis of the disease, yet non-invasive data describing myocardial tissue changes in this setting are lacking.
Hypothesis: We aimed at assessing function and myocardial tissue integrity in PAH patients using cardiovascular magnetic resonance (CMR).
Methods: We investigated 10 patients (6 females, 53±16 years) with primary pulmonary hypertension (PPH, n=7) or PAH (n=3) and were all in NYHA class III (PVR 951±485dyn_sec_cm-5, PAP 47±9mmHg, RAP 7±4 mmHg, CI 2.1±0.5 l/min/m^2, peakVO2 14.8±5.1 ml/kg/min).
Left (LVEF) and right ventricular function (RVEF) and end-diastolic volume (LVEDV-RVEDV) were assessed using steady state free precession sequence using a 1.5 T scanner. Myocardial scarring ("delayed enhancement", DE) was visualized applying a T1-weighted gradient echo sequence covering both ventricles (TR 5.5ms; TE 1.4ms, TI 220-250ms, slice thickness/gap: 10/0 mm) after 0.2 mmol/kg bw of Gd-DTPA.
Results: PAH patients had normal LVEF (65±13%) but reduced RVEF (39±16%, normal values 57±4%) and increased RVEDV (196± 79 ml, index per height 1.2± 0.5 ml/cm). Foci of fibrosis (DE) were detected in the RV (mainly the free wall) in 8/10 patients and in LV in 4 patients
Conclusion: Patients with severe pulmonary arterial hypertension show a high incidence of myocardial fibrosis.

P1576 Evaluation of suspected hypertrophic cardiomyopathy in professional athletes by magnetic resonance imaging

I. Pinto[1], N. Gorayeb[2], M. Batlouni[2], W. Ishikawa[3], A.G.M.R. Souza[2], J.E.M.R. Souza[3], L.C.B. Sousa[3], A.D. Jatene[3]. *[1]São Paulo, Brazil; [2]Inst Dante Pazzanese of Cardiology, Invasive Angiography, São Paulo, Brazil; [3]Hospital do Coração, Cardiac Imaging, São Paulo, Brazil*

Purpose: The adaptations of the athlete's heart to exercise include myocardial hypertrophy and increased contractility, but recently there has been an increased number of sudden deaths in professional athletes due to non-diagnosed hypertrophic cardiomyopathy. Magnetic resonance imaging (MRI) allows proper depiction of cardiac anatomy and function, and could be used to this purpose. The goal of this paper was to evaluate MRI in the evaluation of these patients.
Methods: From August to November 2003 we evaluated 15 asymptomatic professional athletes who were undergoing intense training and activity (Group I), and 15 patients with previously diagnosed hypertrophic cardiomyopathy, but who were asymptomatic or presented minor symptoms at the time of the examination (Group II). All underwent MRI in a 1.5 Tesla scanner, with acquisition of black blood T1 weighed series to evaluate anatomy, gradient-echo sequences (Fiesta ®) to evaluate ventricular function while the regional wall motion was assessed by tagging sequences. Finally, patients received 0.1 mmol/kg of gadolinium in order to try to identify myocardial fibrosis. Results were read by two observers blinded to the clinical diagnosis.
Results: The mean myocardial mass was 158 ± 45 g in Group I and 163 ± 38 g in the Group II (p=0.7). The end diastolic volume was 87 ± 23 ml in Group I and 79 ± 36 ml in Group II (p= 0.4). The Ejection Fraction was 74 ± 8% in Group I and 69 ± 36 ml in Group II (p=0.6). Tagging images were normal in Group I, but in Group II there were abnormal patterns of contraction in the anterior wall of 4 patients and of the lateral wall in 6. Perfusion images were normal in all patients of Group I and there were sub-endocardial perfusion defects in the anterior wall of 8 patients in Group II. Additionally, there was late hyper-enhancement in the myocardium of the anterior wall in 7 patients of Group II.
Conclusion: MRI properly differentiated patients with hypertrohpic cardiomyopathy from athletes, showing abnormalities in the pattern of regional wall motion, along with perfusion defects and small areas of late hyper-enhancement in the patients with diseased cardiac muscle. It may be clinically relevant in the screening of athletes with myocardial disease, who could be at higher-risk of sudden cardiac death.

P1577 Role of magnetic resonance imaging in the assessment of myocardial fibrosis in chronic aortic valve disease

M. Nigri[1], C.E. Rochitte[2], F. Tarasoutchi[2], J.M. Ajl[2], M. Katz[2], G.S. Spina[2], M. Grinberg[2]. *[1]Instituto de Ensino e Pesquisa Albert, Department of Cardiology Albert Einste, São Paulo, Brazil; [2]Institute Heart, Valve, São Paulo, Brazil*

Introduction: severe aortic valve disease can lead to the development of interstitial myocardial fibrosis (MF).This can be detected by myocardial biopsy. Delayed Enhancement Magnetic Resonance Imaging(MRI) technique (MDE) provides the ability of precisely define MF in the myocardial infarction setting and also in other cardiac diseases that course with MF.
Purpose: to evaluate the relationship between MF detected by MRI and by biopsy with rest left ventricular (LV) function in patients (pts) with severe chronic aortic valve disease.
Methods: we evaluated 70 pts, 45 males, mean age 47.6±12.2 years old with severe aortic valve disease. Thirty five pts with predominant stenosis and thirty five with predominant regurgitation. All pts underwent MRI examination. MRI was performed in a 1.5T SIGNA CV/i GE scanner using a gradient echo with an inversion-recovery pre-pulse after injection of 0.2 mmol/kg of gadolinium-DTPA for detection of MF (MDE) and a steady state gradient echo (FIESTA-GEMS) for LV function analysis. Left ventricular ejection fraction (LVEF), end diastolic and systolic volumes were measured by Simpson's rule using MASS analyses software.
Myocardial biopsy(MB) was made during valve replacement surgery in all pts. Biopsy samples were stained by hematoxiline-eosine and Masson's trichrome technique to investigate MF and were qualitatively classified as presence or absence of MF.
Results: MRI detected MF in 44 pts(62.8%) with severe chronic aortic disease. Thirty nine of those (88.6%) were confirmed by MB. MRI sensitivity and specificity compared to biopsy were: 0.84 and 0.80, respectively. LV function differs significantly on those with or without MF defined by MRI.(Table 1).

LVEF vs MRI/MF

MRI/MF	LVEF%	EDV ml	ESV ml
With	46±2	331±28	203±22
Without	65±2	213±24	106±19
P	<0.001	0.003	0.002

MRI-Magnetic resonance imagingMF-myocardial fibrosisLVEF-left ventricular ejection fractionEDV-end diastolic volumESV-end systolic volum

Conclusions: the decrease of left ventricular function in patients with severe chronic aortic valve disease is associated to detectable areas of myocardial fibrosis detected by MRI and by myocardial biopsy. This may contribute to the pathophysiology knowledge of heart failure in this clinical setting.

P1578 Coronary artery and viability evaluation in polyarteritis nodosa, microscopic polyangiitis and Wegener granulomatosis using magnetic resonance imaging

S. Mavrogeni[1], T.C. Karragiorga[2], M.N. Manousakis[2], D.D. Cokkinos[3], M. Douskou[4], H.M. Moutsopoulos[2], D.V. Cokkinos[3]. *[1]Athens, Greece; [2]University of Athens, Dept. Pathophysiology, Athens, Greece; [3]Onassis Cardiac Surgery Center, Athens, Greece; [4]Bioiatriki MRI Unit, Athens, Greece*

Polyarteritis Nodosa (PAN), Microscopic Polyangiitis (MPA) and Wegener Granulomatosis (WG) are forms of necrotizing vasculitis. PAN affects mainly medium-sized vessels. MPA (a PAN-related disorder) involves small to medium-sized vessels, usually with accompanying glomerulonephritis. WG is also a small to medium vessel vasculitis. Coronary arteries can be occasionally affected in all forms. We evaluated the coronary arteries of these patients non-invasively using magnetic resonance angiography (MRA), and performed viability study using contrast enhanced MRI (CE-MRI).
Eleven patients with MPA, 2 with PAN and 5 with WG, without any cardiac symptoms, were studied and compared with 15 age- and sex-matched controls, in whom the absence of stenotic coronary artery disease was proven by X-ray angiography. The maximal diameter of the proximal 1/3 of each coronary vessel was recorded. Ectasia was defined as dilatation of an arterial segment to a diameter at least 1.5 times that of the adjacent normal artery. MRA was performed using a Philips Intera 1.5 T system. Data acquisition was performed with ECG gating in

Table 1

Coronary vessel	MPA+PAN	WG	CONTROLS
LAD	4.67 (1.37)	3.54 (0.30)	2.56 (0.27)
RCA	4.68 (1.00)	3.18 (0.94)	2.43 (0.30)
LCx	4.01 (1.16)	3.14 (0.43)	2.53 (0.23)

Coronary artery diameter(mm) (values as mean(SD))

mid-diastole. All scans were carried out with the patient free breathing. CE-MRI images were acquired 15 minutes after the IV injection of 0.1 mmol/kg Gd-DTPA using an inversion recovery gradient echo pulse sequence.
Coronary artery diameter was found significantly increased in all vasculitis patients compared to controls ($p<0.001$) (Table 1). Criteria for ectasia were fullfiled by MPA+PAN, but not WG patients. The comparison of coronary vessel diameters between MPA+PAN vs WG group had revealed significant difference only for RCA ($p<0.01$). Previous myocardial infarction was documented in 1 patient with MPA.
Coronary ectasia appears a quite common finding in asymptomatic vasculitis patients, while necrosis is rare. Magnetic resonance evaluation is feasible in these forms of vasculitis and may prove of value for treatment guidance.

P1579 Gd-DTPA kinetics and partition coefficient in patients with acute myocardial infarction

C. Klein[1], T. Schmal[2], S.G. Nekolla[3], B. Schnackenburg[4], E. Nagel[2], E. Fleck[2]. *[1]Deutsches Herzzentrum Berlin, Klinik für Innere Medizin/Kardiologie, Berlin, Germany; [2]German Heart Institute Berlin, Cardiology, Berlin, Germany; [3]Klinikum rechts der Isar, Nuklearmedizinische Klinik, Muenchen, Germany; [4]Philips Medical Systems, Hamburg, Germany*

Contrast enhanced magnetic resonance can distinguish between stunned and infarcted myocardium. Aim of the study was to investigate the mechanism of enhancement by determining T1 kinetics of blood, normal, stunned and infarcted (including microvascular obstruction (MVO)) myocardium over time and calculate the partition coefficient (pc).
Methods: 29 patients with acute myocardial infarction (aMI) were examined with a 1.5 T scanner (Intera, Philips, Netherlands) 4±3 days after aMI and invasive revascularisation (TIMI 3). Infarcted, stunned and normal myocardium were defined in the contrast enhanced and cine technique. T1 and pc was calculated (Look-Locker) before and 5 to 40 minutes after 0.2mmol/kg body weight Gd-DTPA for blood and myocardium (pc = delta R1myocardium/delta R1blood).
Results: T1 was significantly ($p<0.0001$) different between normal, stunned and infracted myocardium over the whole period. Significant differences between blood and infarcted myocardium did not exist 20 min after contrast. pc in stunned and infarcted is elevated compared to normal myocardium. Time course of the partition coefficient is shown in fig. 1 (*=$p<0.05$). As there is steady state distribution of Gd-DPTA in normal and stunned myocardium, infarcted areas and especially areas with MVO show an altered pattern suggesting a reduced wash-in and –out kinetic.

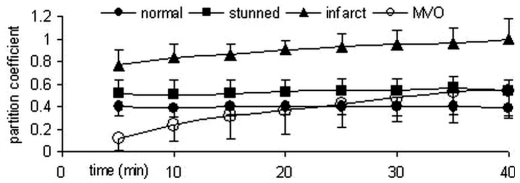


Fig. 1. Partition coefficient over time

Conclusion: in patients with aMI 1) differentiation of infarcted and normal myocardium is possible between 5-40 minutes, 2) stunned exhibits an higher pc than normal myocardium, possibly due to edema and/or partial necrosis and 3) delayed enhancement is mainly due to an increased volume of distribution, but altered wash-in and –out kinetic exists despite complete revascularisation.

ECHOCARDIOGRAPHY, DOPPLER

P1580 Stress echocardiography using 3D multi-plane imaging fastens the procedure without changing wall motion readings

E. Eroglu, J. D'hooge, L. Herbots, F. Rademakers. *University Hospital Gasthuisberg, Department of Cardiology, Leuven, Belgium*

Background: With the introduction of matrix array transducers, the real-time simultaneous acquisition of all standard apical echocardiographic views (2-, 3- and 4-chamber) has become feasible. This might shorten the acquisition and reading of the dobutamine stress echo (DSE) protocol and therefore positively contribute to the clinical use of DSE.
Aim: To test whether 3D multi-plane imaging: 1) is feasible during DSE 2) speeds up the DSE protocol and 3) results in the same segmental wall motion readings.
Methods: 7 consecutive patients with angiographically proven CAD were prospectively enrolled in this study. As a standard stress-echo protocol data were acquired at baseline, during increasing levels of dobutamine infusion and during recovery. At each stage, data were taken with a GE Vivid7-dimensions in the apical 2-, 3- and 4-chamber views using conventional 2D scanning (in three consecutive recordings) and using the new 3D multi-plane imaging approach. The total effective acquisition time for both 2D and 3D-multiplane scanning was measured. All data sets were subsequently scored in random order by a blinded expert reader in terms of wall motion according the guidelines of the ASE. Based on these readings the diagnosis of inducible ischemia was made for each myocardial segment both for the 2D and 3D acquisitions. Differences between the segmental diagnosis based on 2D and 3D data were tested using a McNemar's exact test taking into account the paired character of the measurements. Moreover, differences in acquisition time were tested using a paired student's t-test.
Results: All segments could be interpreted for both imaging strategies. As suggested by McNemar, results are presented in a 2x2 table (table1). No statistical difference (p=0.99) was found between the 2D and 3D readings to detect inducible ischemia. However, a significant reduction in acquisition time ($p<0.05$) was found for the 3D acquisitions (115±77 vs 199±104s).

Table1

	2D ind. ischemia	2D normal
3D ind. ischemia	26	5
3D normal	6	89

Conclusion: 3D multi-plane imaging during DSE was not only shown to be feasible but was also shown to shorten the DSE procedure by about 40% without impact on the interpretation of the exam.

P1581 Safety and predictors of complications with a new accelerated dobutamine stress echocardiography protocol

R. Sanz Ruiz[1], J.A. San Roman[2], J.R. Ortega[3], M. Perez-Paredes[4], M.J. Rollan[5], F. Segura[3], D. Garcia[4], F. Fernandez-Aviles[2]. *[1]Valladolid, Spain; [2]University Hospital, Cardiology (ICICOR), Valladolid, Spain; [3]Hospital Dr. Negrín, Las Palmas, Spain; [4]Hospital Morales Meseguer, Murcia, Spain; [5]Hospital Río Hortega, Valladolid, Spain*

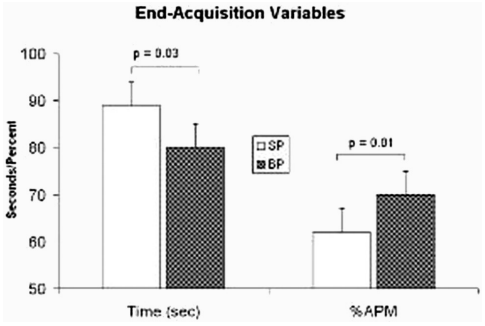
Introduction: A new accelerated DSE protocol used by our group has already demonstrated a diagnostic accuracy similar to the classic protocol and to be time-saving. Its safety profile has not been evaluated. This study sought to document the safety of dobutamine-atropine stress echocardiography (DSE) using a new accelerated dobutamine infusion protocol, to analyze the side effects and complications, and to define their predictors.
Material and Methods: 962 consecutive DSE studies were performed using an incremental protocol from 20 to 40 μg/kg/min in 3-minute stages and followed by atropine if needed, for evaluation of known or suspected coronary artery disease.
Results: 484 patients (51%) had known coronary artery disease (263 previous myocardial infarction, 27%) and 522 (61%) were hypertensive. The baseline ejection fraction was 62,7±9,7 and 308 patients (32%) had baseline WMSI abnormalities. The accelerated protocol could be terminated in 899 patients (93%); 262 of whom (27%) were positive for ischemia. Reasons for prompt termination in the remaining 64 patients were side effects in 17 (2%), arrhythmias in 9 (3 ventricular tachycardia) (0,9%), hypertensive response in 15 (1,6%) and symptomatic hypotension in 8 patients (0,8%). No patient developed heart failure, acute myocardial infarction, ventricular fibrillation or died.
Age > 66 years (OR=0,33, IC 95% 0,18-0,61), baseline SBP > 130 mmHg (OR=9,2, IC 95% 4,44-18,92) and treatment with nitrates (OR=0,39, IC 95% 0,19-0,79) were found in the multivariate analysis to predict hypertensive responses. In the subset of patients with known CAD independent predictors of hypertensive responses were the previous history of hypertension (OR=3,3, IC 95% 1,1-10,6), diabetes mellitus (OR=3,0, IC 95% 1,2-7,8), smoking (OR=3,2, IC 95% 1,2-8,1), treatment with β-blockers (OR=5,1, IC 95% 1,1-23,2), baseline SBP > 130 mmHg (OR=3,8, IC 95% 1,3-10,7) and nitrates (OR=0,2, IC 95% 0,07-0,67). History of hypertension (OR=1,96, IC 95% 1,03-3,79), previous CAD (OR=0,48, IC 95% 0,26-0,87) and baseline heart rate (OR=0,96, IC 95% 0,93-0,99) were confirmed as independent predictors of arrhythmias. In patients with known CAD the only independent predictor of arrhythmias was history of hypertension (OR=3,8, IC 95% 1,05-12,7).
Conclusions: The two-stage accelerated DSE protocol herein described is safe in a low-risk population. We have found a similar incidence of side effects and complications reported on in the literature for the classic protocol.

P1582 Biplane scanning for treadmill stress echocardiography: is image acquisition time reduced in the real world?

S.P. Turner, S. Kapetanakis, E.M. Ho, M.J. Monaghan. *King's College Hospital, Cardiology, London, United Kingdom*

Introduction: Treadmill stress echocardiography is a widely used, well validated technique for the assessment of suspected coronary disease. However, up to 40% of ischemic wall motion abnormalities can resolve before sequential scan plane acquisition is complete, due to the rapid fall in heart rate (HR)/myocardial demand following exertion.
Recently developed matrix transducers allow the simultaneous acquisition of 2 imaging planes from a single precordial position (BP imaging). Reduced post stress BP imaging time has been demonstrated in a small group of healthy young men.
This study investigated the affect of BP imaging on acquisition time and image quality in an unselected group of outpatients referred with chest pain.
Methods: 40 patients were randomly allocated to either BP or single plane (SP)

imaging. The acquisition time and heart rate for apical 4, 2 chamber and parasternal long, short axis planes was recorded. Blinded analysis of the images was performed.
Results: There was no difference between the groups in terms of age, gender, resting heart rate, peak heart rate or heart rate at first image. Total image acquisition time was significantly less for the BP group and end-image heart rate significantly higher (80 ± 4 vs. 89 ± 6 seconds, p=0.03; 70% vs. 62% age predicted maximum HR, p=0.01). In particular BP apical imaging time was 25% less than SP and HR 14% higher (p <0.02 for both). There were non significantly more uninterpretable segments with BP imaging (7 vs. 3, p=0.12)



Time, Age Predicted Maximum HR by Mode

Conclusion: Biplane stress echocardiography, in the clinical setting, reduces scanning time and allows image acquisition at higher heart rates. This may increase sensitivity for detection of reversible ischaemia

P1583 Rapid atrial and ventricular pacing stress echocardiography in coronary artery disease: an alternative technique of stress testing – preliminary results of Polish multicenter study Pol-RAPSE

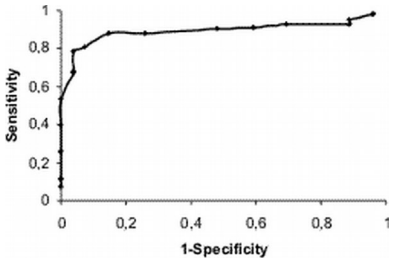
E. Plonska-Gosciniak[1], J.D. Kasprzak[2], T. Rozpara[3], A. Kleinrok[4], A. Gozdzik[5], B. Grzegorzewski[6], Z. Gasior[6], A. Gackowski[7]. *[1]Szczecin, Poland; [2]Medical University, Lodz, Poland; [3]Medical University, Szczecin, Poland; [4]Cardiology, Zamosc, Poland; [5]Medical University, Wroclaw, Poland; [6]Medical University, Katowice, Poland; [7]CM Jagiellonian University, Krakow, Poland*

Aim: The aim of this study was to assess the safety and accuracy of simple, brief echocardiographic stress test protocol based on rapid cardiac pacing in patients (pts) with implanted permanent pacemaker for non-invasive diagnosis of ischemic heart disease (CAD) in pts with and without left ventricular hypertrophy.
Method: we present results of preliminary phase of a national multicenter study Pol-RAPSE (Polish study on Rapid Pacing Stress Echocardiography) with data of 66 pts (mean age 66±10 years, range 46 - 80) with permanent pacemaker (21% VVI, 30% AAI, 49% DDD) qualified for stress echocardiography. Using external programming system heart rate was stepwise increased to 100 beats for 3 minutes and 85% of age-predicted maximal heart rate for 3 minutes using AAI/DDD if feasible and additionally VVI mode. The peak stress was obtained in 57 pts using physiological stimulation of right atrium by AAI and DDD mode and/or in 46 pts by VVI mode. All pts underwent coronary angiography and significant stenosis was defined as ≥50% diameter reduction.
Results: Significant CAD was detected in angiography in 27 (59%) pts (including 1-vessel disease in 11%). Mean duration time of RAPSE examination was 9±3 min. No adverse events were observed. The quality of endocardial border visualization was good in every case. Heart rate at rest and at maximal stimulation was 68±8 and 131±11 per minute (p<0,0001), systolic blood pressure 130±20 and 132±31mmHg (ns), ejection fraction 51±12 and 49±16% (ns), wall motion score index 1,34±0,4 and 1,53±0,5 (p<0,0001) respectively. The feasibility of the test was 97% - only 2 AAI pts (treated with betablockers) failed to reach the target heart rate due to low Wenckebach point. Test specificity was 75%, sensitivity - 77%, accuracy – 75% by AAI and DDD mode and 65%, 69% and 67% respectively by VVI mode (ns). In left ventricular hypertrophy group (n= 40), the EST accuracy was 70% by AAI/DDD mode and 63% by VVI mode (no significant difference vs non-hypertrophy group). In the group with beta blockers therapy (n=42) the accuracy was 77% by AAI/DDD mode and 71% by VVI mode (ns).
Conclusions: RAPSE is a safe, feasible and short lasting examination allowing a good quality of echo image. The method is convenient and efficient for diagnosis of CAD in pts with both AAI/DDD and VVI pacing, including those with left ventricular hypertrophy or beta blockade. Easier interpretation of peak AAI images results in a slight trend towards better accuracy as compared to peak right ventricular pacing.

P1584 Automated peak systolic strain rate increases the accuracy of dobutamine stress echocardiography

C. Bjork Ingul[1], A. Stoylen[1], S.A. Slordahl[1], K. Bjornstad[2], S.A. Aase[1], H. Torp[1], T.H. Marwick[3]. *[1]Norwegian University of Science and Technolog, Trondheim, Norway; [2]St Olav Hospital, Trondheim, Norway; [3]University of Queensland, Brisbane, Australia*

Purpose: Strain rate imaging (SRI) is a promising method for quantification of dobutamine echo (DSE), but segmental measurements are time-consuming. We applied an automated SRI analysis to 137 pts with normal resting function undergoing DSE and coronary angiography and 61 pts at low risk of CAD.
Methods: Automated measurement of peak systolic strain rate (SRs) was obtained by location of a dynamic region of interest in each segment at end-diastole, then tracked throughout the cardiac cycle (GCmat, GE Vingmed, Norway). Longitudinal motion was measured by tissue Doppler and lateral by speckle tracking. SRs was measured by the velocity gradient along the ultrasound beam. Results were compared with wall motion score (WMS) read by a blinded expert. Of 137 pts undergoing DSE and angiography, 84 had CAD (>50% narrowing of at least one major vessel). Pts were randomly divided; group 1 (n=69) established a cutoff for SRs and group 2 (n=68) tested the accuracy of the cutoff.
Results: At peak stress SRs could be analysed in 80% of the segts, and was greater in the normal (n=1727) compared with ischaemic segts (n=177)(-2,6 ± 0,9 1/s vs -0,8 ± 0,2 1/s). In group 1, the area under the ROC curve was 0,90, and the optimal cutoff of peak SRs to distinguish the presence or absence of CAD was -1,3 1/s, giving a sensitivity and specificity of 81% and 89%, respectively (Figure). Use of this cutoff in group 2 gave a sensitivity of 83% and a specificity of 93%. In pts with low probability of CAD, normalcy of SRs using the same cutoff was 82%. Sensitivity of SRs/WMS (p=0,03) for detecting multi vessel disease was 86%/65%, compared with 75%/44% for single vessel disease.



ROC curve

Conclusions: Automated analysis of SRs is feasible for peak dose DSE, and offers an increase in accuracy compared with WMS.

P1585 Ischaemia induced by transoesophageal atrial pacing stress echocardiography predicts mortality

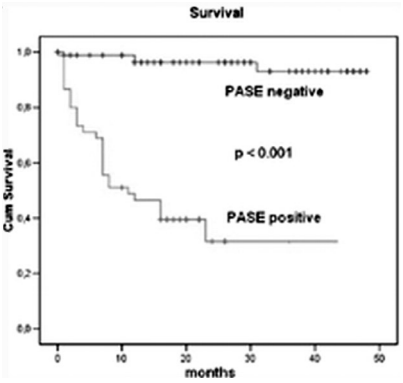
M. Pilati[1], M. Anselmi[2], G. Golia[2], C. Benazzi[2], G. Pesarini[2], C. Vassanelli[2]. *[1]Ospedale Civile Maggiore, Cardiology Department, Verona, Italy; [2]Ospedale Civile Maggiore, Cardiology Department, Verona, Italy*

Objectives: The aim of the present study is to investigate the long-term value of transesophageal atrial pacing in predicting cardiac-related death in patients with known or suspected coronary artery disease.
Background: Exercise, dobutamine and dipyridamole stress-echocardiography are all effective in predicting cardiac death. Transesophageal atrial pacing echocardiography (TAPSE) is a safe alternative to pharmacologic tests, but no information is available about prognosis with TAPSE.
Methods: From January 1988 to September 1997, 857 patients (675 males, 58±9 years) underwent a diagnostic TAPSE test and were followed for a mean of 4.5±3.7 years (median 6 years). The Cox model was used to analyse the association of clinical, resting and TAPSE variables with cardiac death.
Results: TAPSE was abnormal in 281 (32%) patients. There were 46 cardiac-related deaths (5%), 25 among the 281 patients with an abnormal test (8.9%), 21 among the 576 patients with a normal test (3.6%). The multivariable predictors of cardiac death were age, previous revascularization, resting wall motion score index and its change during TAPSE. Abnormal TAPSE significantly increases the value of models predicting cardiac death including clinical and resting Echo-variables. Moreover, cardiac mortality increased progressively with the extent of the induced ischemia.
Conclusions: The TAPSE test is a useful tool in predicting death in patients with known or suspected coronary artery disease, and might be considered an alternative to pharmacologic stressors.

P1586 Prognostic value of noninvasive pacemaker stress echocardiography

E. Pasanisi[1], V. Chubuchny[1], A.C. Borges[1], U. Baldini[1], E. Plonska-Gosciniak[1], U. Startari[1], M. Agrusta[2], E. Picano[3]. *[1]Institute of Clinical Physiology, CNR, Pisa, Italy; [2]Casa di Cura "Montevergine", Mercogliano, Italy; [3]CNR Institute of Clinical Physiology, Pisa, Italy*

Background: Noninvasive pacemaker stress echocardiography (PASE) is simple, rapid, safe and diagnostically efficient option for noninvasive diagnosis of coronary artery disease in the expanding population of patients with permanent pacemakers. There are scarce data regarding association of ischemia on stress imaging techniques with outcome in these patients.
Aim: to assess the prognostic significance of PASE for patients with permanent pacemakers and suspected or known coronary artery disease during prospective follow-up in multicenter, multinational, prospective, observational study.
Methods: 148 patients (98 men, age 69±11 yrs) with permanent pacemakers underwent noninvasive PASE by external programming (10 bpm increment up to evidence of ischemia or target heart rate). All patients were prospectively evaluated during mean follow-up 25±15 months. Both soft and hard end-points were analyzed.
Results: PASE findings were positive for myocardial ischemia in 47 patients (32%) and negative in 101 (68%). During follow-up, there were 5 cardiac-related deaths (3.4% of the total cohort), 3 (2.0%) nonfatal myocardial infarctions and 14 (9.5%) hospital readmissions for unstable angina. 17 patients (11.5%) underwent coronary revascularization (bypass surgery or coronary angioplasty). The overall event-free survival was 34% in the ischemic and 92.1% in the non-ischemic group ($p<0.001$): figure. In a multivariate analysis positive result of stress echocardiography was independently associated with increased risk of end points (hazard ratio=21.9; 95% confidence interval: 7.0 to 68.1; $p<0.001$



Conclusions: myocardial ischemia during PASE is independently associated with increased risk of cardiac events for patients with PM and known or suspected coronary artery disease.

P1587 Value of combination of myocardial contrast echocardiography and dobutamine stress echo in diagnosing coronary disease in patients with left bundle branch block

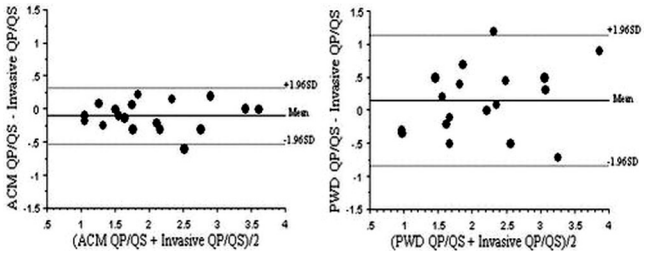
C. Aggeli[1], C. Kokkinakis[2], M. Lolaka[2], G. Roussakis[2], E. Christoforatou[2], A. Maragiannis[2], P. Misovoulos[2], C. Stefanadis[2]. *[1]Athens, Greece; [2]Hippokration Hospital, Cardiology Dept., Athens, Greece*

Septal wall motion abnormalities are frequently observed in patients with left bundle branch block (LBBB).
Aim: To evaluate diagnostic accuracy of the combination of dobutamine stress echo and myocardial contrast echo (MCE) in diagnosing coronary artery disease in patients with LBBB.
Methods: We studied 75 patients (mean age 64±6, 52men) who underwent dobutamine (up to 50μg/kg/min)−atropine stress testing and coronary angiography within one month. The wall motion analysis (WMA) and MCE (using repeated boluses of SonoVue, Bracco) were performed at rest and peak stress. MCE was acquired by low mechanical-index in 3 apical views after acquisition of standard resting and poststress images. Wall motion and MCE components of the study were interpreted sequentially, blinded to other data. The diagnosis of coronary artery disease was based on reversible of wall motion and perfusion abnormalities.
Results: Coronary artery disease was detected in 43 (57%) patients, 39 of them had LAD disease. Left ventricular fractional shortening at rest was 30±6% and ejection fraction was 56±10%. Sensitivity of MCE was higher than that of WMA at maximal stress (91% vs. 65%, $p<0.01$). Specificity was similar for both techniques MCE and WMA (72% vs. 79%, p=NS). Moreover, sensitivity of MCE in diagnosing LAD disease was higher compared to WMA (89% vs. 52%, $p<0.01$), while specificity was similar for both techniques. The combination of MCE and DSE had the best balance for sensitivity and specificity (86% and 78%, respectively).
Conclusion: The combination of dobutamine stress echo and myocardial contrast echocardiography has high diagnostic accuracy in detecting coronary artery disease in patients with left bundle branch block.

P1588 Echocardiographic automated cardiac output measurement of pulmonary output and quantification of intracardiac shunt

N. Mansencal[1], F. Martin[1], J.C. Farcot[1], F. Digne[1], T. Joseph[1], R. Pilliere[1], P. Lacombe[2], O. Dubourg[1]. *[1]Hopital Ambroise Pare, Service de Cardiologie, Boulogne-Billancourt, France; [2]Boulogne, France*

Background: The quantification of intracardiac shunt (ICS) with echocardiographic PW Doppler (PWD) method using pulmonary-to-systemic flow ratio (QP/QS ratio) remains difficult and may induce false quantification of pulmonary output. We sought to validate the recent echocardiographic automated cardiac output measurement (ACM) for the calculation of pulmonary output and the quantification of ICS in adults.
Methods: One hundred and twenty consecutive patients were divided in 1) 40 pts who underwent echocardiographic and invasive explorations (group I) with groups IA (quantification of ICS using ACM, PWD and invasive oximetric methods in 20 pts) and IB (calculation of pulmonary output with ACM, PWD and thermodilution methods in 20 pts); 2) 80 pts underwent calculation of aortic and pulmonary outputs using echocardiographic ACM and PWD methods (group II). All echocardiographic examinations were performed using a Toshiba system equipped with ACM software and a multifrequency transducer.
Results: The feasibility of ACM and conventional PWD methods for the calculation of pulmonary output was respectively 93.3% and 90%. Correlations between ACM and invasive pulmonary output were strong (r^2 =0.92 vs. r^2 =0.80 for PWD). The best correlation and agreement between invasive and echo QP/QS ratio were observed with ACM (r=0.96 vs. r=0.82 for PWD, see Figure). ICS were best-classified with ACM, as compared to PWD (respectively 94% and 72%); sensitivities and specificities for evaluation of significant ICS were 92.3% and 100% with ACM (85% and 40% with PWD).



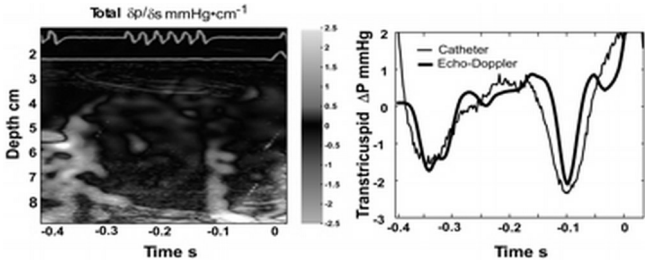
Bland and Altman plots

Conclusions: This study shows that ACM is a reliable and accurate echocardiographic method for calculating pulmonary output and quantifying ICS in adults and may be routinely performed in clinical practice.

P1589 Non-invasive assessment of the transtricuspid right ventricular filling pressure gradient

C. Cortina[1], J. Bermejo Thomas[2], R. Yotti[1], J.C. Antoranz[3], M. Desco[4], J.L. Rojo-Alvarez[5], C. Allue[1], M.A. Garcia-Fernandez[1]. *[1]Hospital General Gregorio Marañon, Lab. of Echocardiography, Madrid, Spain; [2]Madrid, Spain; [3]UNED, Mathematical Physics and Fluids, Madrid, Spain; [4]Hosptial General Gregorio Marañón, Medicina y Cirugía Experimental, Madrid, Spain; [5]Univesidad Carlos III de Madrid, Signal Theory and Comunications, Madrid, Spain*

Background: Due to its low magnitude, the normal transtricuspid right ventricular (RV) filling pressure gradient (DeltaP) remains poorly characterized in vivo. We have recently developed a new method suitable for estimating intracardiac pressure differences by digital post-processing of color Doppler M-mode (CDMM) recordings. The aim of this study was to test the applicability and accuracy of the method to measure the DeltaP across non-restrictive tricuspid valves.
Methods: CDMM images of transtricuspid flow (apical view) and simultaneous high-fidelity pressure signals (RV apex and right atrium) were acquired in 12 closed-chest mini-pigs. Animals were studied at baseline, and after changes in preload (nitroglycerine/volume, n=6; arteriovenous fistula, n=3) and afterload (endotoxin infusion n=3). Images were post-processed using custom-built software that decodes flow velocity, solves Euler's equation, and overlays pressure gradient fields on the greyscale M-mode (left Figure). DeltaPs were calculated by spatial integration between catheter-matched positions in these images (right Figure).
Results: Images suitable for analysis were obtained in all animals. In 526 beats analyzed, the peak-early DeltaP was 1.8±0.7 mmHg. A close agreement between catheter and Doppler measurements was observed for peak early-DeltaP (Rintraclass=0.92, error: 5±16%), peak late (Ric=0.77, error: 2±19%), time-to-peak early (Ric=0.78), and time-to-peak late-DeltaP (Ric=0.90).
Conclusions: For the first time, an accurate measurement of the RV filling force can be obtained by Doppler echocardiography. The precision of this method is as



Figure

least as high as micromanometer catheters. This new tool will provide new insight into the physiology of RV filling.

P1590 Does left ventricular torsion contribute to improve diastolic function after dynamic exercise?

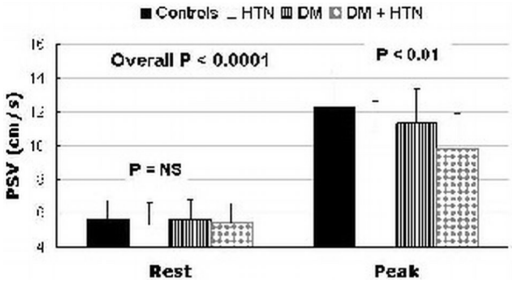
W.-J. Chung, M.-S. Shin, K.S. Kim, E.O. Shim, K.K. Koh, T.H. Ahn, I.S. Choi, E.K. Shin. *Gil Heart Center, Gachon Medical School, Cardiology Division, Incheon, Korea, Republic of*

Purpose: Left ventricular (LV) torsion or twist was believed to store potential energy and to play an important role in generating diastolic suction. And LV torsion was increased after dynamic exercise in normal hearts. But there were few reports about the contribution of increased LV torsion after exercise to the diastolic functional parameters in humans.
Methods: The study group included 98 participants (46 men and 52 women, mean age 44.2±1.6 years) with normal resting LV function and no detectable structural heart disease by baseline echocardiography and exercise treadmill test. Transthoracic echocardiography was performed at rest and immediately after exercise treadmill test. Postexercise image acqusition was completed within 3 minutes. 3 cardiac cycles from each baseline and postexercise were recorded digitally and LV torsion was measured by a novel and simple digitalized method.
Results: Participants showed normal LV systolic function (EF=65.3±0.6%) and normal left atrial volume index (23.4±0.9cc/m^2). Participants exercised for an average of 10 min 47 sec±10 sec and achieved 94.4±1.5% of maximally predicted for age. After dynamic exercise, LV torsion was significantly increased by 39.0%, from 11.4±1.0 to 15.8±1.3 degrees (p=0.001). Also LV end diastolic volume, pulmonary venous atrial flow reversal duration, transmitral E/A ratio and the duration difference between pulmonary venous atrial flow reversal and transmitral A wave were significantly decreased after dynamic exercise (p=0.000, p=0.000, p=0.004 and p=0.049, respectively). And interestingly, changes of LV torsion showed a significant inverse correlation with changes of the duration difference between pulmonary venous atrial flow reversal and transmitral A wave(r=-0.285 and p=0.040). For the novel and simple digitalized measurement method of LV torsion, correlation coefficients of intraobserver and interobserver variations were r=0.91 and r=0.89 respectively (p=0.000 and p=0.001, respectively).
Conclusions: LV torsion contributes to improve diastolic function of LV after exercise. So the change of LV torsion after exercise may provide a useful additional information in assessing the patients with asymptomatic diastolic dysfunction.

P1591 Patients with both diabetes and hypertension have diminished systolic and diastolic functional reserve: results of the myocardial Doppler in diabetes study (MYDID) II

M. Quintana[1], S. Saha[2], S. Govind[2], L.A. Brodin[2]. [1]*Stockholm, Sweden;* [2]*Karolinska University Hospit, Huddinge, Clinical Phyisiology, Stockholm, Sweden*

Background: Left ventricular (LV) diastolic dysfunction is common in patients with type 2 diabetes mellitus (DM) and systemic arterial hypertension (HTN) but without coronary artery disease (CAD). Conflicting results regarding the presence of LV systolic dysfunction in those patients have been reported. We investigated the LV systolic functional reserve in patients with DM, HTN, DM+HTN as compared with healthy controls (C) by means of dobutamine stress Tissue Velocity Echocardiography (TVE).
Methods: 128 subjects without known CAD (59 with DM, 20 with HTN, 27 with DM+HTN, and 22 C), underwent dobutamine stress TVE. Data was obtained on the averaged 4 LV basal segments at rest and during peak stress: longitudinal peak systolic velocity (PSV) and diastolic velocities (E' and A' wave). Data was compared using one-way ANOVA with repeated measures. P<0.05 was considered significant.
Results: The PSV at rest was similar in all groups (P=NS). Likewise, the E'- and A'-wave velocities at rest were similar among all groups (P=NS for both comparisons). From rest to peak stress the PSV increased in all groups but was statistically significant among groups (see figure) and the group with DM+HTN had the lowest increment. The E' wave velocity significantly increased in C, (P>0.001), did not change in DM (P=NS) and decreased in HT (P<0.0001) and HT+DM (P<0.01). The A' wave increased significantly in all groups, but was lowest in DM+HTN as compared with C (P<0.05).



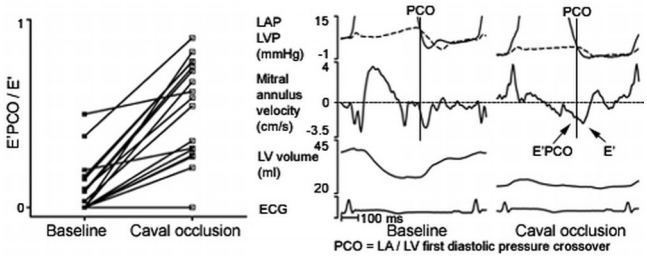
Peak Systolic Velocity

Conclusions: In absence of CAD, patients with DM and HTN had significantly impaired LV systolic functional reserve and LV diastolic dysfunction. The effect of DM and HTN seems to be additive. Dobutamine stress TVE is an excellent method to unmask these markers of diabetes cardiomyopathy.

P1592 Mitral annulus velocity at onset of filling – a marker of diastolic suction

A. Opdahl[1], E.W. Remme[1], T. Helle-Valle[1], T. Edvardsen[1], T. Vartdal[1], E. Pettersen[2], H. Ihlen[2], O.A. Smiseth[2]. [1]*Rikshospitalet University Hospital, Institute for Surgical Research, Oslo, Norway;* [2]*Rikshospitalet University Hospital, Department of Cardiology, Oslo, Norway*

Background: Diastolic suction caused by restoring forces may occur in ventricles that contract below unstressed volume. We hypothesized that restoring forces result in myocardial lengthening prior to onset of mitral flow. The aim of the study was to determine if restoring forces may contribute to early-diastolic mitral annulus velocity (E').
Methods: In 6 anaesthetized dogs left atrial (LA) and LV pressure were recorded by micromanometers. By sonomicrometry we measured LV volume and E' as the time derivate of the LV long-axis. End-systolic volume was reduced by caval occlusion. As a marker of restoring forces we measured annulus velocity at first LAP/LVP crossover (E'PCO), which coincides with onset of mitral filling (Figure). We also calculated E'PCO as a fraction of peak E' (E'PCO/E').
Results: With caval constriction LV end-systolic volume decreased from 29 ± 1 (SEM) to 26 ± 1 ml (p<0.0001) and LV transmural pressure became negative consistent with contraction below unstressed volume. The E'PCO changed from -0.3 ± 0.1 to -1.0 ± 0.2 cm/s (p<0.0001), and E'PCO/E' increased from 0.09 ± 0.03 to 0.47 ± 0.07 (p<0.0001). Peak E' changed from -3.3 ± 0.3 at baseline to -2.1 ± 0.3 cm/s (p=0.0003).



Figure

Conclusions: At reduced end-systolic volume LV lengthening started prior to onset of mitral filling, consistent with diastolic suction due to restoring forces. The E'PCO/E' is proposed as a new non-invasive marker of diastolic suction.

P1593 Right ventricular myocardial acceleration during isovolumic contraction as a prognostic marker in advanced heart failure

U. Conti[1], M. Galderisi[2], S. Banti[1], P. Fontanive[1], F.L. Dini[1], S.M. De Tommasi[1]. [1]*Santa Chiara Hospital, Cardiovascular Diseases Unit 2, Pisa, Italy;* [2]*Federico II University, Clinical and Experimental Medicine, Naples, Italy*

Background: It is well known that a compromised right ventricular (RV) function plays a major role in advanced heart failure (HF). Experimental and clinical studies have shown that myocardial acceleration during isovolumic contraction (IVA) at tissue Doppler (TD) can be an useful index of RV myocardial contractility since it is independent from loading changes. However, to-date no study investigated whether this variable may be useful for prognostic stratification of patients with advanced HF.
Objectives: To ascertain whether the assessment of TD IVA measured at tricuspid annulus may be valuable for predicting prognosis in patients with advanced HF due to left ventricular (LV) systolic dysfunction.
Methods: One-hundred and fifty-five patients diagnosed with advanced HF were

consecutively enrolled. To be selected to participate into the study patients had to have an ejection fraction <35% and a history of HF. A complete echocardiographic and TD study, including RV variables as pulmonary artery systolic pressure, peak systolic tricuspid annular velocity and IVA, was performed in all patients. The RV free wall was imaged and IVA measured at the tricuspid annulus by pulsed wave TD as the ratio between peak isovolumic contraction velocity by its acceleration time. Patients were followed-up for cardiac-related death and hospitalization for worsening HF. The median follow-up was 8 months (range, 1-22).
Results: The study patients had a mean LV ejection fraction of 27±5% and 52% were in NYHA class >2. Fourteen cardiac-related deaths and 26 hospitalizations for worsening HF occurred. At Kaplan-Meier analyses, patients with IVA <3.7 m/sec^{2}exhibited worse survival (p=0.004) and event-free survival (p<0.04). Survival and event free-survival were 88% and 65% in patients with IVA <3.7 m/sec2 compared to 94% and 80%, respectively. At the multivariate Cox analysis, predictors of the combined event were: NYHA class >2 (p=0.0003), ischemic etiology of HF (p=0.007), age >70 years(p=0.03) and IVA <3.7 m/sec^2(p=0.08).
Conclusion: This study demonstrated the usefulness of assessing RV contractile function by IVA in patients with advanced HF. The combination of IVA measurement with clinical evaluation may be valuable to better stratify the risk of patients with advanced HF due to LV systolic dysfunction.

P1594 Relationship between Doppler tissue imaging parameters, serum markers of myocardial fibrosis and ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy

C. Selton-Suty[1], S. Bangratz[2], H. Blangy[2], B. Dousset[3], M. Nippert[2], F. Zannad[2], B. Brembilla-Perrot[2], Y. Juilliere[2]. *[1]C.H.U. Nancy-Brabois, Cardiology Dpt, Nancy, France; [2]Chu Nancy-Brabois, Cardiology Dept., Nancy, France; [3]CHU Nancy, Nancy, France*

Myocardial fibrosis is an adaptative process responsible for side effects in terms of regional myocardial function and ventricular arrhythmias in pts with heart failure.
The aim of our study was to show a link between Doppler tissue imaging (DTI) parameters of myocardial motion and deformation, myocardial fibrosis and occurrence of severe ventricular arrhythmias (VA) in pts with idiopathic dilated cardiomyopathy (DCM) and an implantable cardioverter defibrillator (ICD).
All 18 pts underwent complete echocardiography, measurement of serum markers of collagen activity (synthesis with PINP and PIIINP and degradation with MMP1 and TIMP1) and a count of VA detected by ICD during the last 12 months. Radial motion of anterior septum (AS) and posterior wall (Post) and longitudinal motion of interventricular septum (IVS) were studied by DTI, with measurement of maximal velocities (cm/s) of Sm, Em, and Am waves and of end-systolic strain (e, %).
Mean LVEF was 36±12%, mean myocardial performance index (MPI) was 0.79±0.38, mean BNP value was 111 ± 112 ng/ml. Sustained VA were noted in 5 pts.
Among DTI parameters, Sm IVS was significantly correlated with PIIINP (r=0.504, p=0.04), e Post with MMP1 (r=0.550, p=0.03) and Am SA with MMP1 (r=0.712, p=0.004).
Among standard echographic parameters, 2DLVEF was significantly correlated with MMP1 (r=0.733, p=0.003), E/A ratio and MPI with TIMP1 (respectively r=0.701, p=0.016 et r=0.634, p=0.04)
Comparison of pts with VA to other pts showed a lowering of IVS Em (2.7±1.2 vs 5.2±1.9, p=0.04). There were no significant differences for other DTI parameters, or for serum markers of myocardial fibrosis, apart from a trend toward a higher level of TIMP1 (1357±455 vs 979±196, p=0.07). Among standard echographic parameters, the only difference was the increased value of MPI in patients with VA (1.09±0.38 vs 0.54±0.17, p=0.000).
Thus, this study showed a weak link between DTI parameters and markers of myocardial fibrosis, the most important being between posterior wall end-systolic strain and anterior septal Am wave with MMP1. However, there was a significant relationship between standard echocardiographic parameters of systolic (2DLVEF), diastolic (E/A ratio) and global (MPI) LV function with TIMP1, thereby witnessing the importance of collagen degradation in those high-risk pts.
Furthermore, all those biological and echocardiographic parameters failed to be different according to the degree of severity of rhythmic disturbances, except for MPI which was worse in pts with severe VA.

COMPUTERS IN CARDIOLOGY

P1595 Initial QRS deflection and ventricular repolarisation phase on chest improves localisation of old myocardial infarction

P. Vesterinen[1], H. Hanninen[1], T. Husa[1], P. Korhonen[1], I. Tierala[1], H. Vaananen[2], M. Makijarvi[1], L. Toivonen[1]. *[1]Helsinki University Hospital, Division of Cardiology, Helsinki, Finland; [2]Helsinki University of Technology, Laboratory of Biomedical engineering, Helsinki, Finland*

Conventionally localization of myocardial infarction (MI) by electrocardiographic (ECG) criteria relies on descriptive features of the early QRS complex and the location of the leads with abnormalities.

Aim: We quantitatively analyzed the entire cardiac cycle, registered with body surface potential mapping (BSPM) to improve electrocardiographic localization of MI.
Methods: BSPM, with 120 chest leads, was recorded in 78 patients and 75 healthy controls. All the patients had a single previous MI. Coronary arteriography and cine- or echocardiography was performed to localize MI (30 anterior, 48 inferior). The QRS onset and offset and the end of T wave were automatically determined. Integrals over QRS and STT waves (from J-point to the end of T wave) were analyzed. The QRS integral was divided into temporally equal quartiles. QRSSTT integral was defined as the integral over the entire ventricular electric cycle. Areas under receiver operating characteristic curves (AUC) to distinguish MI patient groups from controls and from each other were determined for the optimal leads (Table).
Results: The 1st and 2nd QRS quartiles and QRSSTT integral were superior to the QRS integral (p=0.02, p=0.02, p=0.05, respectively) in distinguishing between anterior and inferior MI. The 1st QRS was optimal in mid lower back, the 2nd QRS in left upper flank, and QRSTT integral in right lower flank. The STT integral, in right lower flank, was equal to the QRS integral, in left upper flank (p=0.26). All variables separated both MI location groups from the controls.

AUCs for MI detection

AUC of	1st QRS integral	2nd QRS integral	QRSSTT integral	STT integral	QRS integral
Anterior MI	96%	95%	93%	93%	87%
Inferior MI	84%	91%	92%	92%	80%
Anterior vs. Inferior MI	91%	89%	88%	85%	78%

Areas under receiver operating characteristics curves (AUC) for detection of myocardial infarction (MI) in anterior and inferior location

Conclusion: The initial part of the QRS deflection and combining QRS with cardiac repolarization phase appear superior to the whole QRS complex in localization of old MI. Localization of MI can be improved by quantitatively studying the whole electric cardiac cycle on chest areas not covered by standard 12-lead ECG. The process can be automated for clinical purposes.

P1596 Role of the nurse in home telemonitoring of breathing disorders in chronic heart failure patients: the experience of the HHH study

M. Ferrari[1], P. Cereda[2], M. Davanzo[3], M. Maffi[4], F. Bramante[5], M. Ceresa[6], G.D. Pinna[1], F. Cobelli[1]. *[1]Istituto scientifico Montescano, Fondazione "S Maugeri" IRCCS Pavia, Montescano, Italy; [2]Policlinico di Monza, Cardiology, Monza, Italy; [3]Ospedale maggiore TRieste, Cardiology, Trieste, Italy; [4]Policlinico S.Matteo, Cardiology, Pavia, Italy; [5]CNR, Cardiology, Pisa, Italy; [6]Fondazione "S.Maugeri", IRCCS, Cardiology Dept., Montescano, Italy*

Background: alterations of the breathing pattern are very common in patients with chronic heart failure (CHF) and are associated with increased morbidity and poor prognosis. As economical and logistic problems limit the use of standard polysomnography for repeated evaluations over time, intermittent home respiratory telemonitoring (HRT) self-managed by the patient might constitute a potential alternative. In this context, a careful educational program and remote counselling to the patients on the use of HRT would play a critical role in obtaining high compliance and accurate measurements. We assumed that both functions can be efficiently carried out by nurses.
Aim of the study: to evaluate the efficacy of an educational program and remote counselling managed by nurses in a HRT program.
Methods: a novel low-cost, Holter-style 24-hour respiratory recorder, which is suitable to be self- managed by the patient at home and allows transmission (standard telephone line) of acquired data to health care providers is currently under evaluation in the European Community trial HHH (Home or Hospital in Heart Failure, QLG4-CT-2001-02424). All patients enrolled in the study (N=89) were given 1) information on HRT, 2) training program on the use of HRT devices and 3) remote counselling in case of problems in home management of HRT. All these functions were carried out by the nurses involved in the telemonitoring program. Moreover, they also performed all data management procedures required by the study (demographical and clinical data entry into the study databases and process utilities).
Results: in Italy, between July 2002 and July 2004, 635 recordings have been carried out by enrolled patients. Out of them, 561 (88%) were of good signal quality. Every time a recording was scheduled the nurses had a phone contact with the patient to remind it and in 196 occasions, a remote counselling on the use of telemonitoring equipments was necessary. The time spent by nurses for the overall management of HRT was (mean (min-max)): 3 (2.10-4.5) min/patient/day.
Conclusions: the nurse team represents an important and efficient resource in the management and support of a telemonitoring system for intermittent home recording of breathing disorders in CHF patients. These evidences give the nurse team a specific role in teaching knowledge and home-self-management of the disease.

POSTER SESSION 3

MODERATED POSTERS: HEART FAILURE/LV FUNCTION/VALVULAR DISEASE/ PULMONARY CIRCULATION II

P1597 Prosthetic endocarditis: modern surgical options and factors influencing outcome

H. Siniawski, O. Grauhan, M. Musci, A.C. Yankah, H. Lehmkuhl, M. Hofmann, M. Pasic, R. Hetzer. *Deutsches Herzzentrum Berlin, Berlin, Germany*

Background: Mortality in prosthetic active infective endocarditis (AIE) is substantial and infection/reinfection after valve replacement can strongly influence outcome. Selection of the appropriate valve substitute and surgical strategy - early surgery or waiting until antibiotic treatment makes the surgical field aseptic - is controversial. We assessed factors influencing mortality and the infection/reinfection rate.
Patients: Between 01/2000 and 12/2004 1815 patients underwent valve replacement. Among them 237 patients suffering from destructive forms of AIE (prosthetic and native) received either semi-stented Dacron-free antiphlogistically prepared valves and conduits (semi-stented DFV) (163 pts, 9% of all replacements) or homografts (74 pts, 4.1%). We studied 84 (4.52%) patients who subsequently suffered from prosthetic AIE. Mean age was 56±15.7 years; there were 63 men.
Methods: In patients with destructive forms of AIE our strategy was to operate early and to implant cryopreserved homografts or the semi-stented DFV for aortic valve replacement and the semi-stented DFV mitral prosthesis. If possible, tricuspid and mitral valve reconstruction was performed. Mean follow-up was 325±251 days with complete echocardiographic examination performed in all patients. Differences between groups were analyzed using Student's t-test. Multivariate analysis for the whole group was performed to identify independent risk factors.
Results: Eighty out of 84 (97.6%) patients with mechanical (37.3%) or biological (62.7%) (stented or stentless) implants after treatment of non-infective valve diseases suffered from prosthetic AIE. Overall early mortality was 17.01% (14/84). Early infection (<60 days postoperatively) occurred in 9 patients with mortality of 55.6% (5/9) (none had homograft or semi-stented DFV or mitral reconstruction). Late prosthetic AIE appeared at a mean of 6±4 months after implantation. Only 6 of the 237 (2.6%) patients treated with homograft or semi-stented DFV suffered prosthetic infection.
The following predisposing factors for mortality were identified: septic shock (OR 3.44, CI 0.85-13.9) and false diagnosis (unrecognized root abscess with severe damage) in the referring hospital (OR 11.667, CI 3.127-43.522).
Conclusions: Valve surgery with homografts or semi-stented Dacron-free valve prostheses is associated with a low rate of prosthetic infection.
The most potent independent risk factors for death were septic shock and false diagnosis with lengthy antibiotic treatment.

P1598 Clinical features and prognosis of Q fever endocarditis

M. Anguita, J.C. Castillo, M. Delgado, M. Ruiz, D. Mesa, J.M. Arizon, J. Suarez de Lezo, F. Valles. *Hospital Reina Sofia, Servicio de Cardiologia, Cordoba, Spain*

Endocarditis due to Coxiella burnetii has an unusual presentation with a clinical course and outcome not well established. We describe the clinical course and the prognosis of a series of 11 patients with Q fever endocarditis at a single institution over a period of 17 years. Mean age of patients was 40±14 years, 73% (8 patients) were male and 54% were native valve endocarditis (6 patients). The aortic valve was the more frequent site of infection (8 patients). Transtorathic echocardiography showed vegetations in only 36% of cases whereas transesopagheal approach did it in 64%. Mean diameter of vegetation was 9±3 mm. During the active phase 10 patients suffered from severe complications (45% cardiac complications, 45% persistent sepsis, 36% embolisms and 36% neurological complications). Eight patients (73%) underwent surgery during the in hospital phase (18% emergency surgery and 55% elective surgery) and only one patient died. After a follow up of 51±57 months, five patients required surgery but only one died. Most surgical interventions were performed after the first year of the infective episode. In conclusion, Q fever endocarditis is characterised by affecting young people. The clinical course includes a high rate of severe complications thus, surgery during active phase is frequently required. Despite this, prognosis is similar to other types of infective endocarditis.

P1599 Long-term prognosis of infective endocarditis after valvular replacement

L. Perez de Isla, J. Zamorano, F. Florian, C. Almeria, J.L. Rodrigo, V. Serra, L. Mataix, C. Macaya. *Hosp.Clinico San Carlos, Istituto Cardiovasc., Unidad de Imagen Cardiovascular, Madrid, Spain*

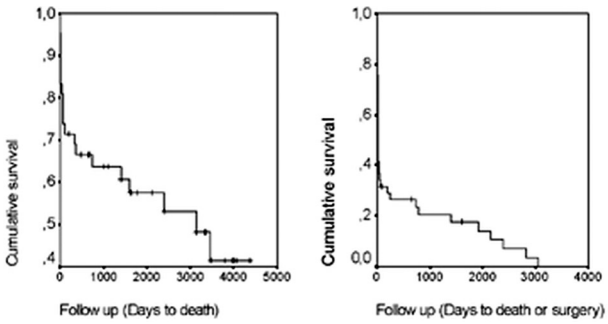
Our aim was to assess the long-term prognosis of patients with infective endocarditis (IE) who underwent valvular replacement during the first admission due to IE and to determine those factors related with a poor long term prognosis.

Methods: 190 consecutive patients with established diagnosis of IE were admitted to our hospital during the inclusion period. Out of them, 51 patients underwent valvular replacement during the in-hospital phase and they were our study population. They were followed during the in-hospital phase and after discharge. The end-point was death due to the IE or to any complication related to it.
Results: Mean age was 58±14 years (41% women). Mean follow-up time was 1522±1466 days. One year mortality was 49% and five years mortality was 75%. One year and five years free of surgery survival were 18% and 8% respectively (See figure). Long-term independent predictors of mortality were the existence of embolic events or shock before the surgery.

Independent predictors of mortality

	RR	95% CI	p
Embolic events	5.36	1.19-24.01	0.018
Shock	24.35	1.72-345.6	0.028

CI = confidence interval. RR = Relative risk.



Survival curves

Conclusions: Long-term prognosis of patients with IE that need valvular replacement is poor due to the high incidence of death and need of a new valvular surgery. Thus, a very close follow up should be done in these patients alter discharge. The existence of embolic events and shock before the surgery are related to a poor long-term outcome.

P1600 Endocarditis on pacemaker leads: an increasing problem

P.L. Massoure[1], V. Le Bouffos[2], M. Berhouet[2], P. Reant[2], S. Lafitte[2], J. Clementy[2], R. Roudaut[2]. *[1]bordeaux, France; [2]bordeaux, France*

Background: Infective endocarditis (IE) on pacemaker (PM) leads are more and more frequent. The management of those IE on PM leads is difficult because the echocardiographic diagnosis is sometimes tricky and the success of treatment is based on the ablation of all the material. Complications are frequent and mortality is significant.
Objective: To study clinical presentation, echocardiographic performance, bacteriological findings, therapy and prognosis of IE on PM leads.
Methods and Results: 60 consecutive patients (48 men, mean age 68,4 years) were admitted in our centre for IE on PM leads between January 1998 and October 2004. The delay between the onset of symptoms (fever 76%, asthenia and wasting 66%, PM exteriorization or local infection 35%) and diagnosis was less than 1 month in 22 cases, between 1 and 3 months in 24 cases, more than 3 months in 14 cases. Delay between the last intervention on PM and symptoms was less than 6 months in 24 cases (10 during the first month). All patients had an inflammatory syndrome.Echocardiography demonstrated one or more vegetation in 89%, which measured less than 15 mm in 28 cases and more than 15 mm in 25 cases. Transthoracic echocardiography (TTE) results were positive in 20%, uncertain in 23%, transesophageal echocardiography (TEE) disclosed vegetations in 87%. Vegetation was located on atrial lead in 24 patients, ventricular lead in 25, both in 4 patients. Infective valvular damage was shown in 4 cases (1 on tricuspid valve, 2 on mitral valves, 1 on mitral+aortic+tricuspid valves). A germ was isolated in 87% (Staphylococcus epidermidis 71%, aureus 20%).
Septic pulmonary embolism complicated IE on PM leads in 27%. Acute renal failure was present in 20%. Surgery (extracorporeal circulation) was performed for 21 patients and percutaneous ablation of material for 36 patients. Antibiotic therapy was given for 6 weeks or more to all patients.
During a mean follow up of 3,5 years, 6 patients died (10%) of IE and 2 of other disease. Only 42 patients needed a permanent stimulation after removal of infected material. Increased mortality is associated with age, diabetes, size and number of vegetations, non ablation of material.
Conclusion: IE on PM leads affect an old population and is essentialy due to staphylococcus. As other kinds of IE, morbidity and mortality are significant. TEE, twice more demonstrative than TTE, shows a vegetation in most cases. Ablation of material must be performed in addition of a 6 weeks antibiotic therapy. Only half patients needed a permanent pacing in this series.

P1601 Prognostic value of troponin T in infective endocarditis

D. Rittoo, F. Greeley, M. Pauriah. *Arrowe Park Hospital, Cardiovascular Unit, Wirral, United Kingdom*

Objective: To determine if Troponin T (TnT) carries an adverse prognosis in patients with acute infective endocarditis.
Method: Twenty eight patients with active infective endocarditis were prospectively studied.Serum TnT was measured at the time of diagnosis and during the course of treatment.Patients received standard care which included serial imaging with transthoracic and transoesophageal echocardiography.Main outcome measures were death, stroke and emergency cardiac surgery.
Result: TnT was $\geq$ 0.10 μg/l in 15 patients (Group A) and $<$ 0.10 μg/l in 13 patients (Group B).
Group A: Median TnT was 0.20 μg/l with a maximum of 1.50 μg/l. Patients characteristics were as follows: age 61$\pm$16 yrs; CRP 121$\pm$73 mg/l; serum creatinine 213$\pm$232 μmol/l. Vegetations were on the aortic valve in 7 patients, mitral valve in 5 patients, aortic valve prosthesis in 1 patient, right atrium in 1 patient and on the aortic and mitral valves in 1 patient. Infective organisms were staphylococcus aureus in 7 patients and streptococcus species in 6 patients. Two patients had negative blood cultures. Seven patients had cardiac failure. Six patients died during admission of whom 5 sustained a stroke. Another patient had a stroke one month after discharge. Two patients required emergency valve surgery.
Group B: Patients characteristics were as follows: age 62$\pm$14 yrs; CRP 129$\pm$95 mg/l;serum creatinine 109$\pm$19 μmol/l. Endocarditis involved the aortic valve in 6 patients, mitral valve in 1 patient, tricuspid valve in 2 patients, aortic valve prosthesis in 2 patients and both mitral and aortic valves in 2 patients.
Infective organisms were staphylococcus aureus in 4 patients, streptococcus species in 4 patients and enterococci in 4 patients. Blood cultures were negative in 1 patient.Four patients had cardiac failure.There were no death or stroke in this group.One patient with TnT of 0.07 μg/l on admission had a subarachnoid haemorrhage due to a ruptured mycotic aneurysm after 4 weeks of treatment with antibiotics.One patient with TnT $<$ 0.03 μg/l required emergency mitral valve surgery because of acute pulmonary oedema secondary to ruptured chordae.
There were no significant differences between the 2 groups with respect to age, CRP, serum creatinine,left ventricular function, presence of cardiac failure, types of infective organisms or severity of valvular dysfunction. However all the deaths and stroke occurred in Group A only (p= 0.007).
Conclusion: Troponin T is frequently elevated in acute infective endocarditis.Patients with TnT $\geq$ 0.10 μg/l are at significantly increased risk of death and stroke.

P1602 Urgent surgery in left-sided infective endocarditis: importance of the indication for surgery in the prognosis

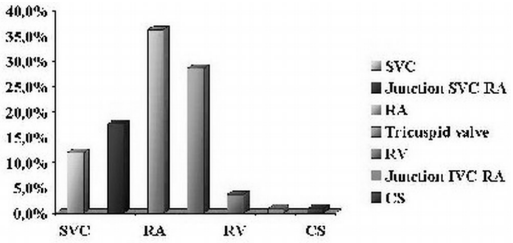
A. Revilla Orodea[1], J.A. San Roman Calvar[1], J. Lopez Diaz[1], I. Vilacosta[2], C. Sarria[3], I. Gomez[1], M. Luaces[2], F. Fernandez-Aviles[1]. *[1]Hospital Clinico Valladolid, Cardiology department, Valladolid, Spain; [2]Hospital Clinico San Carlos, Cardiology department, Madrid, Spain; [3]Hospital la Princesa, Internal medicine department, Madrid, Spain*

Background and objectives: Despite advances in the management of infective endocarditis and a prompt combined medical and surgical approach, the mortality of infective endocarditis remains high. Our aim has been to define the profile of patients with left-sided endocarditis who underwent urgent surgery (defined by surgery before antibiotic treatment was completed) and to analyze prognosis factors of death in these patients.
Patients and methods: Out of a total of 509 patients consecutively diagnosed of endocarditis, we have analyzed the clinical, radiographic, microbiologic, echocardiographic and prognostic variables and the indication for surgery of the 87 patients with left-sided endocarditis who underwent urgent surgery.
Results: Mean age was 56$\pm$14 years (range: 12 to 79). Previous heart disease was present in 59 cases (69%). Transesophageal echocardiography found vegetations in 87% of patients and periannular complications in 37%: 18 abscesses, 14 pseudoaneurysms and 7 fistulae. Clinical symptoms were as follows: fever in 83%, heart failure in 68%, renal failure in 30%, septic shock in 18% and stroke in 15%. Heart failure unresponsive to medical treatment was the main indication for urgent surgery in 57 patients (65%; group A), persistent infection despite adequate antibiotic treatment in 19 patients (22%; B group) and others in 11. A total of 32 patients (37%) died during hospital stay: intraoperative in 8, shock septic in 8, multi-organ failure in 5, ventricular arrhythmia in 3, heart failure in 2 and other causes in 6. The univariate analysis identified 4 variables related to death. The only prognostic factor in the multivariate analysis was persistent infection as the cause for surgery (OR 2.9 IC 95% 1.1-8.1). When groups A and B were compared, we found that patients with persistent infection had more frequently abscesses (32% vs 12%, p 0.08), stroke (16% vs 2%, p 0.046) a higher leucocite count (23424$\pm$10864 vs 16331$\pm$7617, p 0.005) and prosthesis (53% vs 28%, p 0.094).
Conclusions: Patients with left-sided endocarditis and urgent surgery by persistent infection have high mortality rate that may be related with a poor clinical course. Provided the patient needs surgery during the active phase of the disease, heart failure does not impact on the prognosis of these patients.

P1603 Usefulness of intracardiac echography in the diagnosis of endocardial vegetations

C. Bartoli[1], M.G. Bongiorni[1], G. Giannola[2], G. Arena[1], E. Soldati[1], G. Zucchelli[1], A. Di Cori[1], A. Balbarini[1]. *[1]Ospedale di Cisanello, Dipartimento CardioToracico, Pisa, Italy; [2]Ospedale di Cisanello, Dipartimento CardioToracico, Pisa, Italy*

Intracardiac Echography (ICE) is an invasive imaging system useful in many fields of invasive haemodynamic and electrophysiology. ICE provides images of the cardiac structures from a different perspective with respect to the conventional ultrasound, where the transducer is external to the structure of interest.
ICE images typically originate within the structure of interest with a new perspective for evaluating vascular and cardiac structure as well as pathology has developed.
The sensibility of ICE in diagnosing endocardiac vegetations has been proven higher than transesophageal (TEE) and transthoracic (TTE) echocardiography.
Materials and methods: we studied 86 consecutive patients with sepsis and vegetation above leads of an implanted device (pacemaker or defibrillator) that underwent ICE prior to transvenous lead extraction.
We used a 9-French/9-MHz catheter (Ultra ICETM, Boston Scientific Corp., San Josè, CA, USA) connected to the Clearview UltraTM console (Boston Scientific Corp).
Results: ICE allowed clear visualization of vegetations: 13 (12%) inside the superior vena cava (SVC), 19 (17.6%) at the junction between SVC and right atrium (RA), 39 (36.1%) inside the RA, 31 (28.7%) at the level of the tricuspid valve, 4 (3.7%) in the right ventricle, 1 (0.9%) at the junction between inferior vena cava and 1 (0.9%) inside the coronary sinus.
Conclusions: our experience demonstrate the usefulness of ICE in diagnosis of vegetations on pacing and defibrillating leads particularly in sites not visible by TTE and TEE such as inside the superior vena cava and the coronary sinus.



Istogram of sites

ICE is easy, safe and useful during extraction procedures, giving important informations during the procedure and monitoring possible complications.

P1604 Prophylaxis of bacterial endocarditis: have knowledge and acceptance among dentists changed between 1986 and 2004?

C. Piper, R. Geib, D. Horstkotte. *Heart Center NRW, Ruhr Univ Bochum, Department of Cardiology, Bad Oeynhausen, Germany*

Background: Knowlegde, acceptance and application of practice guidelines for prevention of endocarditis among German dentists were evaluated in a longitudinal observation between 1986 and 2004.
Methods: Questionnaires containing 18 questions concerning indication/no indication for endocarditis prophylaxis, for patient and intervention related risks, timing, dosage and choice of antibiotics were answered by 430 randomly selected dentists in 2004. Answers (yes (+) or no (-)) were compared with results of two earlier enquiries using similar (questionnaires adapted to the respective guidelines of the German Dental Association (DGZNK)) in 1986 (n=56) and 1990 (n=78).
Results: (Table 1) Presently, 68% of dentists are familiar with the guidelines. The antibiotics considered for prophylaxis were appropriately reported by 79%, but only 26% used the correct dosage. 61% continued prophylaxis beyond intervention, although guidelines indicated no repeat medication. Younger ($<$ 40 ys) and "less experienced" dentists ($<$ 10 ys in private practice) prescribed endocarditis prophylaxis more often or before interventions not requiring any prophylaxis.

Table 1

Indication	correct*	1986	1990	2004
acquired heart valve disease	+	79%	89%	77%
heart valve replacement	+	89%	91%	97%
MVP + systolic murmur	+	14%	77%	54%
coronary heart disease	–	38%	24%	21%
coronary artery bypasses	–	45%	27%	44%
pacemakers	–	63%	45%	16%
Intervention:				
dental extractions	+	96%	100%	98.8%
peridontal procedures	+	59%	81%	98.6%
further dental procedures	+	n.t.	n.t.	11-49%
cavity filling	–	14%	5%	5%

*correct answer according to the guideline available in 1986, 1990 or 2004: yes(+) or no(-)

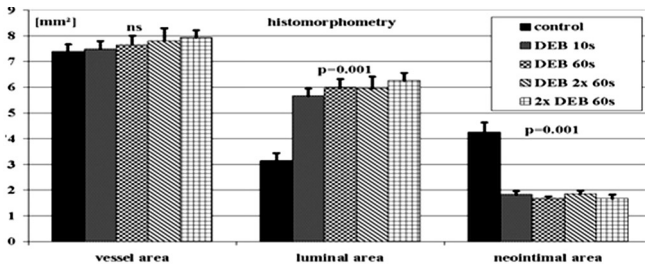
Conclusion: Despite simplified guidelines and considerable effort in education, practical implication of guidelines for endocarditis prophylaxis is still inadequate an has not substantially improved among dentists in Germany during the last 20 ys.

MECHANISMS OF NEOINTIMAL FORMATION

P1605 Paclitaxel-coated balloon catheter: influence of balloon insufflation time and high doses on neointimal formation in the porcine coronary model

B. Scheller[1], U. Speck[2], C. Abramjuk[2], G. Nickenig[1], M. Boehm[1]. *[1]Universitaetsklinikum des Saarlandes, Innere Medizin III, Homburg/Saar, Germany; [2]Radiologie, Charite, Berlin Mitte, Berlin, Germany*

Background: In prior animal trials, we demonstrated a highly significant reduction of neointimal area by paclitaxel-coated angioplasty balloon catheters. During inflation, direct contact with the vessel wall over 60 seconds led to tissue concentrations that were higher but of shorter duration as compared with concentrations reported for paclitaxel-coated stents. The aim of the present study was to investigate the effects of coated balloon inflation times and high doses.
Methods and results: Stents (n=50; diameter 3.0–3.5, length 18 mm) were implanted in LAD and CX coronary arteries of domestic pigs: control (bare stent) and bare stents crimped on paclitaxel-coated balloon catheters (DEB; 5 μg/mm^2) in contact with the vessel wall for 10, 60, and 2 x 60 seconds, or two drug-eluting balloons 60 seconds each.
Quantitative angiography and histomorphometry of the stented arteries asserted statistical equality of the baseline parameters in all groups. After 28 days, paclitaxel-coated balloon catheters significantly reduced the neointimal area by 56 to 61% compared to control.



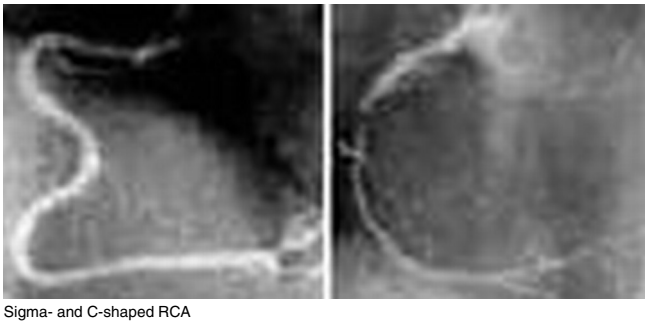
Histomorphometry

Conclusion: Drug-eluting balloons dramatically reduce neointimal formation regardless of balloon inflation times. High doses do not affect the safety and efficacy of this new device in the animal model.

P1606 C-shaped versus Sigma-shaped right coronary artery: an association between morphology and atherosclerotic stenosis

D. Dvir[1], R. Kornowski[2], M. Shechter[1], D. Aravot[3]. *[1]Sheba Medical Center, Cardiology, Ramat-Gan, Israel; [2]Rabin Medical Center, Petach-Tikva, Israel; [3]Carmel Medical Center, Haifa, Israel*

Background: The right coronary artery (RCA) has 2 anatomical morphologies: C and Sigma. The aim of the study was to evaluate whether the C-shape is independently associated with atherosclerosis, and if so, by what pathogenic process.
Methods: Conventional angiographies were evaluated prospectively for atherosclerotic lesions and RCA morphology using quantitative coronary angiography (QCA) software and multivariate analysis was conducted. Afterwards, 3-dimensional angiographies were evaluated prospectively with multi-slice computed tomography (MSCT). The relationship between RCA morphology and systemic markers of atherosclerotic process was examined using biochemical markers and with brachial artery flow-mediated, endothelium-dependent vasodilatation (FMD) and nitroglycerin-mediated vasodilatation (NMD).
Results: The C-shape was highly correlated with atherosclerotic lesions by both QCA measurements (n=120) ($p<0.001$) and MSCT analysis(n=223)($p<0.001$). The calculated relative risk was 4.6 at a follow-up of 5.3±3.7 years (n=29). There were no cases of a morphological change with time. The predictive value of RCA length and morphology for RCA stenosis was high (area under the polygon = 77%). Additionally, FMD (n=49) was significantly greater in patients with Sigma-shaped RCAs than C-shaped RCAs (14.3±4.7% and 9.0±4.2%, respectively; $p<0.04$); there was no such difference in NMD.
Conclusions: Our study is the first to define 2 distinct RCA morphologies which have clinical significance. There is an independent association between C-shaped RCA and atherosclerosis and patients with a C-shape have reduced endothelial function. These findings contribute to the understanding of the pathogenesis of plaque formation and may have several important clinical implications.


Sigma- and C-shaped RCA

P1607 ProvinolsTM, a polyphenolic extract of red wine inhibits in-stent neointimal growth in cholesterol-fed rabbit

M. Elbaz[1], A. Alves[2], R. Andriantsithohaina[2], G. Roul[3]. *[1]Rangueil Hospital, Cardiology Department, Toulouse Cedex 9, France; [2]Rangueil Hospital, Cardiology Department, Toulouse Cedex 9, France; [3]Louis Pasteur University, Pharmacology and Physico-Chemistry, Illkirch, France*

Background and objective: Orally effective drugs in inhibiting neointimal growth after experimental angioplasty is still a big challenge to prevent or reduce restenosis after stenting. Polyphenols have been reported to possess multiple biological activities including antioxydant and antiproliferative properties, generation of nitric oxide from vascular endothelium that leads to vasodilatation and expression of genes protective for the cardiovascular system.
Thus, we investigated, the potential of a polyphenolic extract from red wine, Provinols to decrease neointimal hyperplasia after angioplasty in a high cholesterol-fed rabbit model.
Methods and results: New Zealand white rabbits were fed 1% cholesterol-enriched chow for 8 weeks before iliac balloon-injury and stent placement. After stent implantation, Provinols (20 mg/kg per day) or matching placebo was orally administrated for 4 weeks in a random way. Twenty-eight days after stenting, the arteries were harvested after euthanasia and analyzed for histology assignation. Provinols did not significantly affect blood pressure or plasma cholesterol compared to placebo but it significantly decreased in-stent neointimal growth ($p = 0.0022$), neointimal thickness ($p = 0.0014$), neointimal surface ($p = 0.0004$). Interestingly, Provinols treatment was associated with reduction of arterial fat body deposit ($p < 0.001$) and inflammatory response ($p < 0.001$) to injury.
Conclusions: These results suggest that oral administration of Provinols reduces in-stent neointimal growth, lipid deposition in association with its anti-inflammatory property in iliac arteries from hypercholesterolemic rabbits. These data provide an experimental basis for the beneficial effects of plant-derived polyphenols for the prevention of restenosis associated with stent placement.

P1608 Rapamycin attenuates progenitor cell recruitment after vascular injury in mice

D. Zohlnhoefer[1], T. Nuehrenberg[2], P. Frank[3], I. Haehnel[1], B. Stemmer[2], C. Seyboth[2], S. Seidl[4], A. Schoemig[2]. *[1]Klinikum rechts der Isar, TU München, I.Medizinische Klinik, München, Germany; [2]Deutsches Herzzentrum Muenchen, Klinik fuer Kardiologie, Muenchen, Germany; [3]Klinikum Rechts der Isar TU München, Institut für experimentelle Onkologie, München, Germany; [4]Klinikum Rechts der Isar TU München, Institut für Pathologie, München, Germany*

Background: Restenosis due to neointima is the major limitation after coronary angioplasty and stenting. In several animal studies it has been shown that bone marrow cells contribute to neointimal smooth muscle cell (SMC) content in arterial remodeling after mechanical injury. SDF-1a/CXCR4-interactions play an important role in the recruitment of circulating progenitor cells to the site of vascular injury. Rapamycin reduces neointima formation in patients and animals by combining anti-proliferative and anti-inflammatory properties. However, the effects of rapamycin on the recruitment of progenitor cells in vivo are yet not known. Therefore we investigated neointima formation in a time course study of gene expression using a mouse model of arterial injury.
Methods and Results: 129SvImJ-mice (n=5 per group) underwent wire-injury of the femoral artery. In morphometrical analysis we observed a significant neointima formation 14 days after injury with a mean lumen loss of 32%. Gene expression analysis with cDNA-array technology was performed 3, 7 and 14 days after injury. Out of the analyzed 2352 genes we found 298 differentially expressed genes. Profound changes took place in the expression of genes associated with inflammation (CD14, CD44, IL1b), proliferation (p21, TPO) and adhesion (E-selectin, P-selectin). 3 days after injury we observed an upregulation of genes contributing to progenitor cell recruitment such as SDF-1a and CXCR4. Interestingly, the CXCR3 ligands IP10 and MIG showed an upregulation in neointimal tissue 7 days after injury. It is described that CXCR3/IP10 and -/MIG may be important in adhesion, aggregation and differentiation of progenitor cells. Further-

more, rapamycin treatment reduced not only the expression of progenitor cell-associated-genes such as CXCR4 and CXCR3 on mRNA level but also reduced recruitment of c-Kit positive progenitor cells to the site of vascular injury after 7 days as demonstrated by immunohistochemistry.
Conclusion: Our data indicate an early recruitment of c-Kit+ progenitor cells to the sight of vascular injury via SDF1a/CXCR4, which is reduced by rapamycin. This inhibitory effect of rapamycin on progenitor cell recruitment may explain its high effectiveness in reducing restenosis after stent placement in patients.

P1609 Effect of paclitaxel coated balloons, iopromide paclitaxel, and sirolimus coated stents on neointimal formation in the porcine coronary model

B. Scheller[1], U. Speck[2], C. Abramjuk[2], G. Nickenig[1], M. Boehm[1]. *[1]Universitaetsklinikum des Saarlandes, Innere Medizin III, Homburg/Saar, Germany; [2]Radiologie, Charite, Berlin Mitte, Berlin, Germany*

Background: Drug-eluting stents have shown promising anti-restenotic effects in clinical trials. Their efficacy is believed to depend on the sustained release of antiproliferative drugs. Paclitaxel added to an angiographic contrast medium (CM) and paclitaxel-coated balloon catheters were tested as an alternative option for transferring the drug to the vessel wall.
Methods and results: Paclitaxel was solved in CM or coated on balloons. Adherence to non-inflated balloons was determined after directing the catheter into coronary arteries of pigs. Stents were crimped on paclitaxel coated balloons. 5-6 pigs each received 2 coronary stents applying slight overstretch by using either (a) uncoated balloons, bare stents and plain CM or (b) the same but paclitaxel 200 μM in CM or (c) paclitaxel-coated PTCA balloons 3 $\mu g/mm^2$ with premounted bare stents and plain CM or (d) commercial premounted Cypher stents and plain CM. Restenosis was assessed 4 weeks later by angiography and histomorphometry.
Treatment was successful in all animals. No adverse events were observed which could be assigned to paclitaxel in the CM or balloon coating. Reangiography indicated pronounced restenosis in the control group and least restenosis in the animals which were treated with the coated balloon. Histomorphometry confirmed the efficacy of the 3 routes of drug delivery with the most impressive effect of the coated balloons.

Histomorphometry

	Control	CM + paclitaxel	Coated balloon	Cypher	p
injury score	1.52±0.25	1.56±0.29	1.49±0.22	1.68±0.37	0.513
inflammation score	1.09±0.52	1.10±0.33	1.63±0.85	1.59± 0.54	0.065
vessel area (mm^2)	7.39±0.86	7.26±0.63	7.23±0.68	7.96±1.13	0.213
luminal area (mm^2)	2.25±0.97	2.96±0.96	4.81±0.62	4.15±1.31	0.001
neointimal area (mm^2)	5.14±1.50	4.31±1.00	2.42±0.28	3.81±0.84	0.001
max. neointimal thickness (mm)	0.70±0.34	0.64±0.17	0.20±0.04	0.36±0.13	0.001

Conclusions: Paclitaxel added to CM or coated on PTCA catheters are effective in restenosis inhibition in the porcine coronary overstretch model. Non-stent based drug delivery may avoid some problems due to stent coating and provide additional flexibility in restenosis inhibition.

P1610 The regenerating adult MRL mouse heals the artery without neointima formation

D. De Kleijn[1], J.K. van Keulen[2], B. van Middelaar[2], S.K. Lim[3], M.J. Goumans[2]. *[1]Utrecht University Hospital (G02 523), Lab. of Experimental Cardiology, Utrecht, Netherlands; [2]University Medical Center Utrecht, Experimental Cardiology Lab. (G02 523), Utrecht, Netherlands; [3]Genome Institute, Singapore, Singapore*

Background: The MRL mouse strain is unique in its capacity for regenerative wound healing. The MRL mouse shows closure of ear punches, nearby complete healing of the heart after cryo-injury without scarring and differential matrix metalloprotease (MMP) activity at the wound compared to the non-regenerating C57Bl/6 mouse. Since neointima formation is often considered as arterial scar formation after injury in which MMPs play an important role, we investigated if the arterial response to injury resulting in neointima formation is based on similar underlying processes as ear and heart healing.
Methods: Arterial injury was induced by right carotid ligation in 18 C57Bl/6 and 11 MRL mice. Right carotid (RC) arteries were pressure fixed and harvested at 28 days after ligation. In addition, arteries of 12 MRL mice and 12 C57Bl/6 mouse were pressure fixed at 0 days. Arteries were paraffin embedded, sectioned and stained with Elastin von Gieson and used for morphometry. External Elastic Lamina (EEL) area, media area and intima area were determined using image analysis software. For remodeling, EEL areas were compared between carotids at 28 days after carotid ligation and carotids at 0 days (without right carotid ligation). Data are presented as area (um^2) ± SD.
Results: No difference was found between C57Bl/6 and MRL mice in EEL area before ligation (174653 ± 26440, 173367 ± 35166 resp.) and in EEL area of the unligated left carotid (175024 ± 33373, 171515 ± 22344 resp.) at 28 days. Shrinkage (EEL RC 28 minus EEL RC 0 days) of the ligated right carotid artery tended to be higher in the MRL mouse (35408± 27821) compared to the C57Bl/6 mouse (17819±30637, p=0.06).
Neointima formation was almost absent in the MRL mouse (1192 ± 3172) in contrast to the C57Bl/6 (27635±42134, p=0.003).
Conclusion: The absence of neointima formation in the MRL mouse extends the regenerative capacity of this mouse to the arterial wall and indicates that regeneration of ear and heart share common pathways with neointima formation after arterial injury.

P1611 Instrumental role of the stromal cell derived factor-1/CXCR4 axis in neointimal recruitment of smooth muscle cell progenitors after arterial injury

A. Zernecke[1], A. Schober[1], I. Bot[2], E.A. Liehn[1], P. von Hundelshausen[1], E.A. Biessen[2], C. Weber[1]. *[1]University Hospital Aachen, Molecular Cardiovascular Research, Aachen, Germany; [2]Leiden University, Division of Biopharmaceutics, Leiden, Netherlands*

Background: Bone marrow cells have been shown to contribute to the pathogenesis of vascular remodeling. Recent evidence indicated that the CXC chemokine stromal cell derived factor (SDF)-1alpha, known to be essential for hematopoietic stem cell mobilization and homing, is expressed in smooth muscle cells (SMCs) and participates in neointimal hyperplasia and the recruitment of circulating progenitor cells after arterial injury.
Methods and Results: Here we show that neutralizing SDF-1alpha in apolipoprotein E-deficient (apoE-/-) mice repopulated with LacZ+ bone marrow reduced neointimal plaque area and bone marrow-SMC content 4 weeks after wire-injury of the carotid artery. Similarly, repopulation of apoE-/- mice with bone marrow deficient in the SDF-1alpha recepor CXCR4 diminished wire-induced neointimal hyperplasia and SMC content. One day after denudation of apoE-/- carotid arteries, SDF-1alpha expression was detectable in medial SMCs in the vicinity of apoptotic cells and inhibited by blocking caspase-dependent apoptosis. Accordingly, the upregulation of SDF-1alpha after induction of apoptosis by scratch-injury of medial SMCs in vitro was inhibited by the caspase inhibitor Z-VAD-fmk and mediated by apoptotic bodies. Moreover, luminal SDF-1alpha was detectable in conjunction with surface-bound platelets. The arrest of murine or human peripheral blood progenitor cells in apoE-/- carotid arteries perfused ex vivo one day after injury was inhibited by blocking SDF-1alpha, and their arrest on endothelial extracellular matrix with adherent platelets in vitro was potentiated by SDF-1alpha via CXCR4. The involvement of local SDF-1alpha in neointimal hyperplasia was confirmed by its inhibition after lentiviral transfer of a SDF-1alpha antagonist immediately after injury. Further, we show that SDF-1alpha preferentially mobilized and recruited a subset of c-kit-/lineage-/sca-1+ progenitors for neointimal SMCs expressing platelet-derived growth factor receptor-beta.
Conclusions: Our data reveal a crucial role of the SDF-1alpha/CXCR4 axis for vascular remodeling by recruiting a subset of SMC progenitors in response to apoptosis and in concert with platelets, epitomizing its importance for tissue repair and identifying a prime target to limit lesion development.

P1612 Factor VII activating protease (FSAP) sequesters growth factors and inhibits neointima formation in vivo

D. Sedding[1], J.M. Daniel[2], H. Brunsch[3], R.C. Braun-Dullaeus[4], H. Tillmanns[3], K.T. Preissner[2], S. Kanse[2]. *[1]Universitat Giessen, Abteilung für Molekulare Kardiologie, Giessen, Germany; [2]Giessen University, Biochemistry, Giessen, Germany; [3]Medizinische Klinik I, Abteilung für Molekulare Kardiologie, Giessen, Germany; [4]Dresden University of Technology, Internal Medicine II - Cardiology, Dresden, Germany*

Background: A genetic polymorphism in the plasma serine-protease 'factor VII activating protease' (FSAP) is associated with carotid stenosis, and we previously demonstrated increased FSAP accumulation in atherosclerotic plaques. However, the role of FSAP in vascular lesion formation remains obscure. Here we evaluated the impact of FSAP on growth factor-dependent VSMC proliferation and migration in vitro and neointima formation in vivo.
Methods and Results: Our data indicate that FSAP binds to a number of growth factors, such as platelet-derived growth factor-BB (PDGF-BB), PDGF-AA, transforming growth factorβ, basic fibroblast growth factor and hepatocyte growth factor but not insulin like growth factor-1 or epidermal growth factor. FSAP significantly inhibited the effect of PDGF-BB on Akt and ERK phosphorylation, DNA synthesis and migration of mouse VSMC. To test the effect of FSAP on neointima formation after wire induced injury to the mouse femoral artery, FSAP (10 $\mu g/ml$) was applied topically in a pluronic 127 gel to the denuded arteries. Slow release of FSAP from the gel, presence of FSAP in the vessel wall and functional activity (as shown by increased fibrinogen degradation) could be demonstrated in vitro and in vivo. There was a 75% reduction in neointima formation after 3 weeks in the presence of FSAP compared to vehicle control (neointima/media ratio: 1.05 ± 0.2 vs. 2.7 ± 0.75, n=6, $P<0.01$). In the presence of the serine protease inhibitor, aprotinin, FSAP function was inhibited and the effect of FSAP on neointima formation was reduced. When applied to the contra lateral artery FSAP did not influence neointima formation indicating a local mode of action after release from pluronic 127 gel.
Conclusion: These results suggest that FSAP can sequester, and/or modify growth factors, and inhibits PDGF-mediated proliferation and migration of VSMC as well as neointima formation in vivo. Thereby FSAP acts as a modulator of

neointimal growth and can be used as a pharmacological agent to prevent vascular proliferative disease.

P1613 Pharmacological inhibition and genetic deficiency of tumour necrosis factor-alpha attenuates restenosis development

N.M.M. Pires[1], P.S. Monraats[2], A. Schepers[3], L.S.M. Boesten[4], B.J.M. Van Vlijmen[5], L.M. Havekes[5], P.H.A. Quax[3], J.W. Jukema[2]. *[1]TNO-PG/LUMC, Cardiology Dept., Leiden, Netherlands; [2]Cardiolgy Dept, LUMC, Leiden, Netherlands; [3]TNO-PG/Surgery Dept, LUMC, Leiden, Netherlands; [4]TNO-PG/Dept. Internal Medicine LUMC, Leiden, Netherlands; [5]TNO-PG/Cardiology Dept, LUMC, Leiden, Netherlands*

Purpose: Inflammatory factors are thought to play a regulatory role in restenosis. Tumor necrosis factor-alpha (TNF-alpha), a pleiotropic proinflammatory cytokine, is a key regulator of inflammatory responses. Here we studied the effects of modulating TNF-alpha on the extent of restenosis in a mouse model.
Methods: The involvement of TNF-alpha in restenosis was studied in a mouse model of cuff-induced restenosis. We quantified the changes in vascular TNF-alpha mRNA levels by RT-PCR, in time, after cuff placement around the femoral artery of hypercholesterolemic ApoE*3-Leiden mice. Moreover, the role of TNF-alpha in restenosis development was also assessed in TNF-alpha knockout mice crossbred with ApoE*3-Leiden mice and by local perivascular delivery of thalidomide as a TNF-alpha biosynthesis inhibitor.
Results: TNF-alpha mRNA levels showed a time-dependent upregulation during the restenotic process, peaking at 24h after vascular injury (5,000-fold induction as compared to control healthy vessel). The mRNA levels were elevated up to 7 days after injury. Cuff-induced neointima in TNF-alpha-/-ApoE*3-Leiden mice showed a 66% decrease in intimal thickening as compared to littermate control TNF-alpha+/+ApoE*3-Leiden mice (8.2 ± 5.6 vs. 1.9 ± 1.4 103 μm^2, P=0.016). Furthermore, local perivascular delivery of a TNF-alpha biosynthesis inhibitor, thalidomide, using a drug-eluting polymer cuff also significantly decreased neointima formation by 59% after 14 days (P=0.005), due to a striking decrease in arterial TNF-alpha production as shown by TNF-alpha immunostaining.
Conclusions: TNF-alpha plays a pivotal role in the process of restenosis and critically influences the extent of neointima formation in a mouse model of restenosis. Furthermore sustained local delivery of thalidomide, e.g. via a drug-eluting stent, might be a future strategy to prevent restenosis.

P1614 The role of lectin-like oxidised LDL receptor-1 (LOX-1) in restenotic lesion after angioplasty

H. Eto[1], M. Miyata[2], N. Kume[3], M. Minami[3], S. Hamasaki[2], S. Biro[2], T. Kita[3], C. Tei[1]. *[1]Kagoshima University, Department of Cardiovascular Medicine, Kagoshima, Japan; [2]Kagoshima University, Department of Cardiovascular Medicine, Kagoshima, Japan; [3]Kyoto University, Department of Cardiovascular Medicine, Kyoto, Japan*

Background: LOX-1, a new class of oxidized low density lipoprotein (ox-LDL) receptor, is expressed by intimal smooth muscle cells (SMC) and macrophages in advanced atherosclerotic lesions, as well as vascular endothelial cells covering early atherosclerotic lesions. We reported that LOX-1 mRNA and protein are induced and persistently expressed in neointimal and medial SMC of rabbit aorta for 24 weeks after balloon injury. However, the role of LOX-1 in restenotic lesion after angioplasty remains unknown. On the other hand, the proliferation and migration of SMC cause the neointimal formation after vascular injury. The purpose of this study is to clarify the role of LOX-1 in proliferation of SMC.
Methods: Using human atherectomy specimens of restenotic lesion after percutaneous coronary intervention (PCI), we performed immunohistochemical staining of ox-LDL, LOX-1 and proliferating cell nuclear antigen (PCNA). Furthermore, we performed the cell culture experiments using cultured rabbit SMC, ox-LDL, and a chemical inhibitor of LOX-1; carageenan.
Results: We confirmed that LOX-1 and ox-LDL were expressed in restenotic lesions after PCI by immunohistochemstry. Double immunofluorescence staining revealed a colocalization of LOX-1 and PCNA in restenotic lesions after PCI, suggesting that LOX-1 may be involved in SMC proliferation in restenosis after PCI. Ox-LDL (10 μg/ml) increased the cell number of cultured SMC 3 days after stimulation. The presence of carageenan (250μg/ml) reduced the cell growth stimulation by ox-LDL (10 μg/ml). The cell culture experiments also suggest that LOX-1 may involve in proliferation of SMC stimulated by ox-LDL.
Conclusion: This is the first report which directly demonstrate that LOX-1 may be involved in SMC proliferation and neointimal formation after PCI. LOX-1 might be a molecular target for preventing restenosis after PCI.

P1615 High-dose atorvastatin prevents RESTenosis AfteR complex coronary inTervention. Final results of the RESTART study

F. Imola[1], P.F. Corvo[2], T. Fouad[3], V. Ramazzotti[2], A. Manzoli[1], A. Pappalardo[1], F. Prati[3]. *[1]Ospedale San Giovanni-Addolorata, Cath Lab, Rome, Italy; [2]Aurelia Hospital, Cath Lab, Rome, Italy; [3]Ospedale San Giovanni Addolorata, Cath Lab, Rome, Italy*

Background and objectives: long-term results of bare stenting in complex procedures are affected by an high incidence of restenosis. DES stenting leads to excellent long-term angiographic results but requires long-term antithrombotic treatment to prevent stent thrombosis. We sought to evaluate the efficacy of high-dose atorvastatin for prevention of clinical and angiographic restenosis after complex coronary intervention with stenting.
Methods and results: From November 2003 through February 2004, 91 consecutive patients, at high risk of restenosis, underwent successful stenting (158 stent; 1.7 stent/pts). Patients were eligible if the had one of the following criteria: diabetes mellitus (14.3%); acute myocardial infarction (13.2%); lesion length >15mm (25.0%); lesion in vessels with reference diameter <2.5mm (30.8%); >2 treated lesions (58.2%); graft stenosis (1.1%); side-branch lesion (2.2%). All patients were started on atorvastatin (80 mg/die) on the same day of stenting and continued for at least 9 months.
Five out of 91 patients (5.5%) had clinical restenosis, 4.4% had target vessel revascularization. Angiographic follow-up was performed at mean 8.5 months (7-10 months) in 71 patients (78.0%; 125 stents). Binary angiographic restenosis was observed in 19/71 patients (26.7%) (in-stent restenosis 22.5%; in-segment restenosis 4.2%). Angiographic restenosis was found in 17/125 stents (13.6%). We matched 125 lesions from the present population with a reference group of 600 consecutive lesions treated with stenting at our center in the same period but without high dose statins treatment. 117 lesions were found to match according to the following clinical and angiographic variables: diabetes, acute myocardial infarction, vessel treated, reference diameter, lesion length. Late loss in the atorvastatin group was significantly lower (p=0.0004). See table.

	MLD post	Ref post	%DS post	MLD FU	Ref FU	%DS FU	Late loss
atorvastatin	2.60 (sd 0.42)	2.91 (sd 0.47)	10.3	2.09 (sd 0.57)	2.87 (sd 0.49)	26.6	0.51 (sd 0.54)
control	2.78 (sd 0.45)	2.93 (sd 0.42)	5.41	1.87 (sd 0.80)	2.82 (sd 0.59)	36.0	0.91 (sd 0.67)

MLD = minimal luminal diameterRef = reference vessel diameter%DS = percentage stenosis diameterpost = post stentingFU = follow-up

Conclusions: the RESTART prospective registry showed that 80 mg atorvastatin leads to excellent clinical and angiographic outcome. These results were confirmed in a matched lesion comparison.

P1616 The forkhead transcription factor FoxO1a regulates cell cycle entry of smooth muscle cells and prevents neointima formation

D.G. Sedding[1], K.T. Preissner[2], H. Tillmanns[1], R.C. Braun-Dullaeus[3]. *[1]Giessen University, Internal Medicine/Cardiology, Giessen, Germany; [2]Giessen University, Dept. of Biochemistry, Giessen, Germany; [3]Dresden University of Technology, Internal Medicine/Cardiology, Dresden, Germany*

Background: The forkhead transcription factor FoxO1a represents an important physiological target of phosphatidylinositol-3 kinase (PI3K)/protein kinase B (PKB) signaling and we previously demonstrated that FoxO1a is a key regulator for the cell cycle entry of vascular smooth muscle cells (VSMC) by transactivating the cyclin dependend kinase inhibitor p27Kip1. In the present study we sought to determine if the adenovirus-mediated expression of a transgene encoding a constitutively-active form of FoxO1a (Ad-FoxO1a;AAA) can inhibit VSMC proliferation in vitro and neointima formation in vivo.
Methods and Results: Subconfluent human VSMC were transfected with Ad-FoxO1a;AAA, a mutant in which the three Akt phosphorylation sites have been mutated, or a control vector (Ad-GFP). Immunoblot analysis revealed an increased expression of p27Kip1 and cyclin D1 and a lack of hyperphosphorylated retinoblastoma gene product in FoxO1a transduced cells.
Conclusively, FACS analysis of propidium iodide stained cells indicated a cell cycle arrest in G0/G1 phase. The number of apoptotic cells as determined by TUNEL assay increased significantly as compared to cells transfected with Ad-GFP alone (11.6 ± 2.1 vs. 3.6 ± 0.8; $P < 0.01$). For in vivo studies, the femoral artery of C57BL/6J mice was dilated and adenoviral vectors [5 X 10(8) pfu of Ad-FoxO1a;AAA vs. Ad-GFP] were delivered intraluminally to the denuded segment. 4 days after dilation, immunohistochemical evaluation of GFP expression indicated an efficient transduction of medial cells. The apoptotic rate of medial VSMCs in FoxO1a transduced arteries was significantly increased as determined by TUNEL assay (9.7 ± 2.5 vs. 2.3 ± 0.9; $P < 0.05$). Morphological analysis of femoral arteries 28 days after dilation revealed that the neointima/media ratio was significantly reduced (0.7 ± 0.2 vs. 1.8 ± 0.4; $P < 0.005$).
Conclusion: Overexpression of the constitutively-active form of FoxO1a prevents VSMC cell cycle entry and proliferation by inducing p27Kip1 and cyclin D1 expression and augmenting apoptosis of VSMCs. This combined antiproliferative/pro-

apoptotic effect also prevents neointima formation in vivo. Therefore, local delivery of Ad-FoxO1a;AAA may be a novel approach to prevent vascular proliferative disease.

P1617 Moderate local heating inhibits in-stent neo-intimal hyperplasia without significant increase in thrombosis formation in the rabbit iliac atherosclerotic model

C. Brasselet[1], E. Durand[2], E. Simso[3], E. Lafont[2]. *[1]Hopital Robert Debre, CHU, Departement de Cardiologie, Reims, France; [2]HEGP et INSERM 0016, Department of Cardiology, Paris, France; [3]Boston Scientific, INC, Boston, United States of America*

Background and objectives: We already reported that moderate local heating (50°C) before experimental stenting was associated with 1. a largest minimal luminal diameter related to a lowest in-stent neo-intimal hyperplasia and 2. the lack of increased thrombosis formation as compared with controls. However, severe heating (80°C and more) was associated with a dramatically increase of in-stent thrombosis. The aim of this study was therefore to elucidate the mechanisms involved in this favourable healing.
Material and methods: Sixteen New Zealand white rabbits were treated by stent implantation one month after the induction of atherosclerotic-like lesions. Each artery was randomly assigned to local heating, performed by the PLOSA® balloon (Boston Scientific). Five different temperatures were investigated: control, 50, 60, 80 and 100 C°. We evaluated the cell density and collagen content 6 weeks after angioplasty. This evaluation was completed by day-3 and -15 assessments of cell density and immunostaining with PCNA, TF and CD-31.
Results: Fifty degree heating led to the largest minimal luminal diameter related to the lowest in-stent neo-intimal hyperplasia, without significant increase in thrombosis formation as compared with controls. This was associated with a significant lower collagen content (30.0±12.8% vs. 8.3±4.3%; control vs. 50°C respectively; $p < 0.04$). At day-3 and 15, cell density was significantly lower at 50°C, as compared with control (3115±188 cell/mm^2 vs. 1806±679 cell/mm^2; $p<0.01$ and 4903±697 cell/mm^2 vs. 2235±783 cell/mm^2; $p<0.003$, for days-3 and 15, respectively). This was related to a significant decrease of cell proliferation at day-3 assessed by PCNA immunostaining (77±4 cell/mm^2 vs. 56±12 cell/mm^2; control vs. 50°C; $p<0.02$). Moreover, the high percentage of thrombosis at 80 and 100°C was strongly related to an increase of the expression of TF at day-15 as well as the lack of reendothelialization assessed by CD-31 immunostaining at day-15 (percentage of luminal area CD-31+: 54%; 78%; 73%; 5% and 18%, for control, 50, 60, 80 and 100°C, respectively).
Conclusions: These findings suggest that moderate local heating has a favourable impact on the healing process after angioplasty. It lowers in-stent restenosis via a decrease in both cell density and collagen content, while reendothelialization is preserved loading to a lower amount of in-stent thrombosis.

P1618 Endothelial-monocyte-activating-peptide-II (EMAP-II) contributes to neointima formation: regulation by rapamycin and effects on monocyte recruitment and reendothelialisation

T. Nuehrenberg[1], P. Frank[2], F. Sorge[1], S. Seidl[3], S. Matschurat[4], M.A. Clauss[5], D. Zohlnhoefer[6]. *[1]Deutsches Herzzentrum Muenchen, Klinik fuer Kardiologie, Muenchen, Germany; [2]Klinikum Rechts der Isar TU München, Institut für experimentelle Onkologie, München, Germany; [3]Klinikum Rechts der Isar TU München, Institut für Pathologie, München, Germany; [4]MPI für Herz- und Lungenforschung, Molekulare Zellbiologie, Bad Nauheim, Germany; [5]Indiana Ctr for Vasc.Biology &Medicine, Cellular and Integrative Physiology, Indianapolis, United States of America; [6]Klinikum rechts der Isar, TU München, I.Medizinische Klinik, München, Germany*

Introduction: A major limitation of stent-supported angioplasty is restenosis due to neointima formation. Inflammation is considered to be an important determinant of neointimal growth. EMAP-II, a proinflammatory cytokine with additional pro-apoptotic effects on endothelial cells, plays an important role during the recruitment of monocytes to sites of vessel injury. Rapamycin, combining antiproliferative and anti-inflammatory properties, significantly reduces neointima formation and reduces EMAP-II expression in vitro. Therefore, we investigated the effect of Rapamycin on EMAP-II expression in vivo and on inflammatory reactions governing neointima formation.
Methods and Results: In a mouse model of restenosis (n=6), oral Everolimus, a derivate of Sirolimus, significantly reduced neointima formation and expression of EMAP-II protein. Simultaneous treatment of mice with Everolimus and EMAP-II abrogated the positive effect of Everolimus on lumen loss after vascular injury. Further immunohistochemical analysis for CD3, CD31, CD45 and mac-2 was performed to elucidate the influence of EMAP-II on the cellular composition in the vaso-occlusive tissue. Treatment with Everolimus significantly decreased the infiltration of the vessel wall with monocytes and neutrophils. This effect could almost be abrogated by concomitant administration of EMAP-II. Reendothelialization was assessed by staining against CD31. Mice treated with Everolimus exhibited a significantly higher rate of reendothelialization compared to control whereas EMAP-II co-treatment did significantly decrease the rate of reendothelialization.
Conclusion: These data suggest an important role of EMAP-II in the control of neointima formation. Through inhibition of EMAP-II expression, rapamycin may firstly support an early reendotheliasation and secondly reduce the early recruitment of inflammatory cells to sites of arterial injury. This may further reduce the vascular proliferative response in humans.

P1619 CCR5-but not CCR1-deficiency protects against neointima formation in apolipoprotein E-deficient mice

E.A. Liehn, A. Zernecke, C. Weber. *University Hospital Aachen, Molecular Cardiovascular Research, Aachen, Germany*

The process of neointimal hyperplasia and infiltration in response to injury is regulated by the finely tuned action of pro- and anti-inflammatory cytokines, and involves chemokines, such as RANTES/CCL5. Since the contribution of different RANTES receptors, e.g. CCR1 and CCR5, remains elusive, we analyzed their role in accelerated plaque formation and underlying immune mechanisms by genetic deletion in apolipoprotein E-deficient (apoE-/-) mice. Compared with CCR5+/+ mice, CCR5-/- mice showed a significant reduction in total plaque area four weeks after arterial wire-injury. This was associated with decreased relative content of Mac-2+ macrophages and CD3+ T lymphocytes but an increase in alpha-SMA+ SMCs, reflecting a more stable plaque phenotype. In contrast, the genetic deletion of CCR1 did not affect total plaque area and cellular composition four weeks after wire-injury. Double immunofluorescence staining revealed an intralesional up-regulation of the Th2-associated cytokine interleukin-10 in CCR5-/- versus CCR5+/+ mice, whereas the Th1-cytokine interferon-gamma was increased in plaques of CCR1-/- mice but hardly detectable in control or CCR5-/- mice. These data demonstrate the importance of CCR5 but not CCR1 in lesion development after arterial injury and suggest that the attenuated plaque formation in CCR5-/- mice is due to a shift towards an atheroprotective Th2-type immune response.

P1620 Autologous transplantation of endothelial progenitor cells after stent implantation in the porcine coronary model

K. Walenta[1], B.S. Bruno Scheller[2], M.M. Michael Menger[2], M.B. Michael Bohm[2], G.N. Georg Nickenig[2]. *[1]Innere Medizin III, Unikliniken des Saarlandes, Homburg/Saar, Germany; [2]Innere Medizin III, Unikliniken des Saarlandes, Homburg/Saar, Germany*

Background: Drug-eluting stents (DES) have shown promising anti-restenotic effects in clinical trials. However, delayed endothelialisation is a major drawback of DES. Accelerated reendothelialization could impair neointimal formation. The aim of the present study was to evaluate the influence of intracoronary application of autologous endothelial progenitor cells (EPCs) on neointimal formation in the porcine coronary stent model.
Methods and results: Peripheral blood- derived mononuclear cells (MNCs) from ten healthy pigs were cultured in endothelial basal medium. After four days in culture the adherent cells were removed and resuspended in saline for intracoronary injection. To determine the effect of stem cell transfusion on reendothelialization, EPCs or saline were injected into five pigs after stenting and blockade of the coronary flow for 3 minutes. The intracoronary stents (n=20; diameter 3.0–3.5, length 18 mm) were implanted in LAD and CX coronary arteries of 10 domestic pigs. Treatment was successful in all animals. No adverse events were observed.
Four weeks afterwards these specific coronary regions were investigated histomorphometrically. Histomorphometry of the stented arteries asserted statistic equality of the baseline parameters between the two groups. After four weeks, there was no sig-nificant effect on neointimal formation by the intracoronary EPC application.

Overwiew of the results.

	Control	EPC	p
n	5	5	
vessel area	10.37 ± 0.61 mm^2	10.29 ± 0.76 mm^2	0.813
luminal area	5.46 ± 1.29 mm^2	5.73 ± 1.53 mm^2	0.682
neointimal area	4.92 ± 0.93 mm^2	4.56 ± 1.32 mm^2	0.516
maximal neointimal thickness	1.11 ± 0.25 mm	0.99 ± 0.32 mm	0.370

Conclusions: Our findings show that the concept of a significant reduction of neoin-timal formation by locally applied EPCs after coronary stenting is not supported by the porcine coronary model.

P1621 Effects of imatinib treatment on neointima composition and progenitor cell recruitment

C. Seyboth, P. Frank, T. Nuehrenberg, L. Yuan, D. Zohlnhoefer. *Munich, Germany*

Background: The predominant mechanism of In-Stent-Restenosis is neointima formation. Smooth muscle cells (SMC) represent the main cellular component of the neointima, attracted from the media through chemokines and mitogenes as i.e. PDGF. Current research also indicates a role of circulating c-Kit-positive hematopoetic progenitor cells (HPC) in neointima formation by differentiating into SMCs. Imatinib, the tyrosin kinase inhibitor STI571, is known to

simultaneously inhibit the PDGF receptor kinase and the c-KIT receptor kinase, which plays a role in the proliferation and differentiation of HPC. Here, we investigated the effect of imatinib on neointima formation and molecular mechanisms by comprehensive gene expression analysis in mice.
Methods and Results: Neointima formation was induced in 129 SvImJ mice (n=5) through wire injury to the femoral artery. Animals in the therapeutical group were given 50 and 500 μg of STI 571 i.p. from two days before intervention until euthanasia at 3,7 and 14 days. In cell culture experiments Imatinib reduced the proliferation of SMCs significantly.
Morphometrical analysis did not show significant changes after two weeks. Gene expression analysis with cDNA array technology revealed differential expression of 298 of 2352 genes analyzed. Thereof, 48, 38 and 16 genes were differentially expressed when comparing operation v. 500 μg Imatinib treatment at 3, 7 and 14 days, respectively. Pharmacotherapy initially down regulated genes associated with proliferation (PDGF, TGF-β), stem cell recruitment (CXCR-4, IL-6) and extracellular matrix (MMP 9, MMP14, cathepsin K). However, this effect was not sustained beyond 3 days. Among genes upregulated at seven days we found CXCR-4, c-kit and ALK-1, as confirmed by gene specific PCR. ALK-1 is a downstream effector of TGF-β signalling, acting as an antagonist of ALK-5, which is implicated in the differentiation of HPC into SMCs. Likewise, immunohistochemistry showed a high quantity of c-kit positive cells and low amount of sm-actin positive cells in neointimal tissue from the Imatinib group compared to operation alone.
Conclusion: These data suggest that Imatinib may prevent PDGF-mediated migration of medial smooth muscle cells whereas it does not inhibit HPC recruitment. Upregulation of ALK-1 may have prevented the conversion of HPC into SMCs, thus resulting in an undifferentiated neointima. Therefore, these results further strengthen the role of HPC in restenosis and question the contribution of PDGF in this model of neointima format

P1622 The intracoronarily application of paclitaxel via a new dobbel- ballon catheter prevents in- stent- stenosis in pig

C. Dommke[1], K.K. Haase[1], D. Haghi[1], T. Sueselbeck[1], I. Weinschenk[1], J. Metz[2], M. Borggrefe[1], C. Herdeg[3]. [1]*University Hospital Mannheim, Cardiology Dept., Mannheim, Germany;* [2]*University of Heidelberg, Department of Anatomy and Cell Biology, Heidelberg, Germany;* [3]*University of Tübingen, Department of Cardiology, Tübingen, Germany*

Background: instent-restenosis can be reduced by using paclitaxel eluting stents. Nevertheless local drug application via balloon-catheter can be an alternative technique. It was the aim of this experimental in vivo study to investigate the feasibility and efficacy of a new designed double-balloon-catheter which allows the intracoronary application of paclitaxel.
Methods: 15 bare-metal stents (3,0x13mm) were implanted in the coronary arteries in 8 normal pigs (25±4kg). Directly after implantation 5 stents were treated by paclitaxel application over 2 minutes using the new double-balloon-catheter. Five stents were treated after implantation with NaCl 0,9% only and 5 stents without treatment were used as the control group. Aspirin and clopidogrel were given over 6 weeks to prevent stent-thrombosis. A final angiogram was performed after 6 weeks and the coronaries were cut out after fixation for histology. Morphometric analysis was performed by light microscopy using a computerised morphometry system and restenosis was measured.
Results: in all cases paclitaxel could be applicated sucessfully over the new double-balloon-catheter. All stented arterial segments showed complete endotheliasation. The control group showed 60±6% area instent-stenosis. In stented segments treated with paclitaxel by the double-balloon-catheter area instent-restenosis could be significantly reduced to 17±2% only ($p<0.001$). In the NaCl group the amount of area instent-restenosis was almost the same as in the control group (54±20%).

Group	Degree of stenosis [%]
Stent	60
Stent + Paclitaxel	17
Stent + NaCl	54

Stent/Stent+Paclitaxel: $p<0,001$

Conclusions: in this animal model the local application of paclitaxel was in all stented arteries feasible. Paclitaxel applicated by the new desigend double-balloon-catheter could reduce significantly area instent-restenosis. The arterial segments proximal and distal of the treated stents showed no edge effects.

P1623 p85-PI3K mediates cAMP-dependent ras inhibition and prevents neoinitimal hyperplasia after balloon injury

D. Torella[1], F. Achille[2], G. Tagliamonte[2], A. Leone[2], C. Spaccarotella[2], A. Mongiardo[2], E.V. Avvedimento[3], C. Indolfi[2]. [1]*Federico Ii University, Cardiology Dept., Naples, Italy;* [2]*Cardiology, Medicine, Catanzaro, Italy;* [3]*Federico II University, Molecular Pathology, Naples, Italy*

Purpose: VSMC proliferation and the consequent neointima formation is the main mechanism responsible for restenosis after percutaneous coronary interventions (PCI). cAMP-PKA signaling inhibits while ras activation stimulates VSMC growth in vitro and neointimal hyperplasia after vascular injury. cAMP-PKA phosphorylates p85-PI3K and this is accompanied by preferential association of Ras to PI3K. Aim of the study was to find out the effects of p85PI3K on the interaction of cAMP and Ras in the regulation of VSMC growth in vitro and neointimal formation after experimental balloon angioplasty.
Methods: VSMC were transfected in culture dishes with activated p85 (p85) or dominant negative p85 (p85DN). VSMC proliferation was measured by Brdu incorporation 24 hours after culturing the cells in the presence or absence of c-AMP. Balloon injury of the right carotid was produced in 20 Wistar rats. Straight after the vascular injury, the balloon-dilated arteries were randomly transfected with p85 (n=7), negative mutant p85 (p85DM) (n=7) or green fluorescent protein (GFP, n=6; controls).
Results: cAMP reduced VSMC proliferation compared to not treated cells. Interestingly, transfection of activated p85 decreased VSMC proliferation in the absence of cAMP while cAMP inhibition of VSMC growth was prevented by p85DN. Western blot analysis demonstrated that the formation of the complex Ras and PI3K (inactivating ras function) was markedly stimulated in cells expressing activated p85, while the same complex was greatly reduced in cells expressing p85DN. Conversely, the binding of Ras to Raf1 and the activation of ERK1/2 were significantly inhibited in VSMC expressing activated p85 in the absence of cAMP. Importantly, the in vivo transfection of activated p85-PI3K significantly reduced neointimal formation after balloon injury.
Conclusions: These data indicate that cAMP-PKA-phosphorylated p85-PI3K forms a stable complex with ras proteins, resulting in a selective switch-off of ras effectors. This intracellular molecular change inhibits VSMC proliferation in vitro and neointimal hyperplasia after experimental balloon angioplasty.

OBESITY

P1624 The association of subclinical coronary atherosclerosis with abdominal and total obesity in asymptomatic men

R.D. Santos[1], K. Nasir[2], C.Y. Campbell[2], A. Roguin[2], J.B. Braunstein[2], J.A.M. Carvalho[3], R.S. Blumenthal[2]. [1]*University Sao Paulo, Heart Institute, Sao Paulo, Brazil;* [2]*Johns Hopkins Hospital, Cicarone Prevention Center, Baltimore, United States of America;* [3]*Albert Einstein Hospital, Preventive Medicine Clinic, Sao Paulo, Brazil*

Introduction: this study assessed and compared the association of waist circumference (WC) and body mass index (BMI) with presence and severity of coronary artery calcium (CAC) detected by electron beam tomography in asymptomatic men.
Methods: 451 white men free of known atherosclerosis (ATH) were studied. The subjects were divided into tertiles of WC [first <92.5 cm; second 92.5-100 cm; third ≥101 cm] and BMI [first < = 25.5 kg/m^2; second 25.6-28.4 kg/m^2; third ≥28.5 kg/m^2] respectively. Risk factors fot ATH, plasma lipids, fasting glucose (FBG), as well as cardiorespiratory fitness in metabolic equivalents (METS)were also evaluated. Multiple logistic regressions were employed to assess the independent association of increasing levels of WC and BMI with presence of any CAC. Additionally, ordinal logistic regression was used to assess the relationship of WC and BMI with increasing levels of CAC(calcium scores of 0; 1-9.9; 10-99.9; 99.9-399.9 and ≥400).
Results: the risk of CAC was 2.75 (1.16-6.35) higher among those with WC in the highest tertile compared to men with the lowest (p=0.02). Also, WC correlated with the severity of CAC (table 1). The relationship was found to be independent of BMI, age,lipids, FBG, METS, and ATH risk factors. No significant association of BMI with CAC was found.

Table 1

		1	2	3	p for trend
WC	Model 1	1	1.58 (0.97-2.57)	1.83 (1.15-2.91)	0.01
	Model 2	1	1.51 (0.89-2.53)	1.00 (1.67-2.52)	0.06
	Model 3	1	1.81 (1.03-3.60)	2.22 (1.02-4.61)	0.04
BMI	Model 1	1	1.00 (0.62-1.62)	1.41 (0.88-2.24)	0.14
	Model 2	1	0.89 (0.53-1.47)	1.22 (0.72-2.06)	0.48
	Model 3	1	0.61 (0.33-1.13)	0.70 (0.33-1.5)	0.36

Results of ordinal regression are presented as the OR of being in higher CAC category with increasing tertiles of WC and BMI. Model 1: Age, adjusted;Model 2: Age, smoking status, hypertension, diabetes, total cholesterol, HDL, TG, and METS adjusted; Model 3: Model 2 plus adjustment of BMI or WC

Conclusion: our results consist with the evidence that central obesity compared to BMI, is more strongly related with increased burden of coronary ATH.

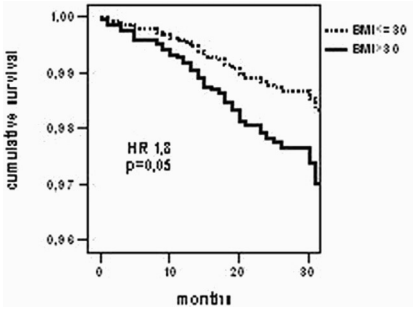
P1625 Obesity is a cardiovascular risk predictor in a high-risk population

W. Reinhard[1], S. Holmer[1], M. Fischer[1], C. Gloeckner[1], A. Baessler[1], H. Schunkert[2], G. Riegger[1], C. Hengstenberg[1]. [1]*University of Regensburg, Internal Medicine II, Regensburg, Germany;* [2]*Internal Medicine II, University of Schleswig-Holstein, Luebeck, Germany*

Obesity (BMI>30) is an independent cardiovascular risk factor still underrepresented in current risk scores and prevention guidelines. We intended to determine the cardiovascular risk associated with obesity in a high risk population of patients with familial accumulation of coronary artery disease (CAD).

Study design: in a prospective cohort study, we examined 2085 previously healthy individuals with a positive family history of myocardial infarction (MI, at least 2 affected family members <60 years, Regensburg MI family study, age>18 years). Individuals with known CAD or diabetes mellitus were excluded. During a 2-year follow-up incidence of cardiac events (MI, revascularisation, cardiac death) was determined.

Results: the prevalence of obesity in our study population was 16.8%. This was consistent with the prevalence of non-related control subjects (17.5%) and with official reports of obesity amongst German middle-aged men (17.6%). The incidence of cardiac events in our study population was 3.1%. In a Cox proportional hazard analysis adjusted for common cardiovascular risk factors, obesity was identified as an independent predictor of cardiac events (hazard ratio (HR) 1.8; p=0.05, see figure). In a second model, HRs for specific events (MI, revascularisation, cardiac death) were calculated. The analyses illustrated that particularly the risk for MI was significantly elevated in obese patients (HR 4.2; p=0.007).



Conclusion: obesity is a strong risk factor for CAD in previously healthy individuals with a positive family history of MI. Specifically, it is associated with a more than 4-fold elevated risk for MI compared to non-obese subjects.

P1626 Metabolic syndrome potentiates the sympathetic abnormalities characterising human obesity

F. Quarti Trevano[1], G. Grassi[1], G. Seravalle[2], R. Dell'Oro[1], F. Scopelliti[1], A. Facchini[1], G. Mancia[1]. [1]*Universita' Milano-Bicocca in, Dipartimento di Medicina, Monza, Italy;* [2]*Istituto Auxologico Italiano, Milan, Italy*

Purpose: Human obesity is characterized by an hyperadrenergic state at which occurrence participates a cluster of pathophysiological factors. The present study has been undertaken with the aim at dissecting the relative contribution of metabolic vs. non-metabolic factors to the sympathetic overactivity characterizing the obese state.

Methods: In 19 obese subjects (O; age:40.6±2.2, body mass index: 31.1±0.9 kg/m^2, mean±SEM) and in 12 age-matched normoweight controls (C; body mass index 23.7±0.4 kg/m^2) we measured, along with cholesterol, triglycerides, insulin, glucose and HOMA index, beat-to-beat arterial blood pressure (BP, Finapres), heart rate (EKG), and efferent postganglionic sympathetic nerve traffic (MSNA, microneurography). Measurements also included a complete overnight polysomnographic study aimed at determining the presence of obstructive sleep apnea (OSA).

Results: Based on metabolic data, O patients were subdivided in 2 groups, one with a normal metabolic profile (OMS-, n=9) and the other one (OMS+, n=10) with elevated plasma cholesterol (221.4±19 mg/dl), plasma triglycerides (199.4±29 mg/dl), HOMA index (4.1±0.5 U) and reduced plasma HDL cholesterol values (44.7±3.9 mg/dl). Thus, according to ATP III criteria, OMS- did not display a metabolic syndrome which was conversely manifest in OMS+. BP values were higher in OMS+ than in OMS- (144.1±3/84.7±2 vs. 134.7±2.6/79.1±2 mmHg, p<0.05) and this was the case also for body mass index (32.4±1.2 vs. 30.6±1 kg/m^2, p=NS). Compared to C, MSNA was significantly higher in OMS- (38.1±2.1 vs. 47.4±2.6 bs/100hb, p<0.05, +23%), a further marked and significant increase being observed in OMS+ (65.6±3.5 bs/100hb, p<0.05, +34% vs. OMS- and +67% vs. C). In this latter group MSNA was greater than in OMS- also when hypertensive patients were excluded. OSA was detected in 4 OMS- and in 8 OMS+, the apnea/hypopnea index, taken as measure of the presence and severity of OSA, being significantly greater in the latter than in the former group (44.4±8 vs. 27.5±6 n°/h, p<0.05).

Conclusions: These data provide the first evidence that a large fraction of the sympathetic activation characterizing the obese state depends on metabolic factors. They also show that 1) in absence of metabolic alterations the increase in body weight only modestly increases MSNA, 2) metabolic syndrome potentiates the sympathetic abnormalities of the obese state and 3) at this potentation participates the presence of OSA and thus the chemoreflex activation.

P1627 The metabolic syndrome can be assessed both continuously and practically with a principal components analysis derived score. The D.E.S.I.R. cohort

T. Hillier[1], A. Rousseau[2], P. Lepinay[3], M. Cailleau[4], M. Novak[5], E. Calliez[6], P. Ducimetiere[2], B. Balkau[2] on behalf of The D.E.S.I.R. Study Group. [1]*Northwest/Hawaii, Kaiser Permanente, Centre for Health Research, Portland, OR, USA;* [2]*INSERM U258, Villejuif cedex, France;* [3]*Centre d'Examens de Santé, Orleans, France;* [4]*IRSA, La Riche, France;* [5]*Centre d'Examens de Santé, Chateauroux, France;* [6]*Centre d'Examens de Santé, Angers, France*

Purpose: The Metabolic Syndrome (MS) is increasingly used to evaluate risk in clinical practice, but is limited by dichotimization of individual parameters, and of the syndrome itself. We develop a simple continuous MS score and evaluate its ability to predict incident diabetes.

Methods: Among 5,024 participants of the D.E.S.I.R. cohort, we defined the MS score by the first principal component of the MS parameters [fasting insulin (I), glucose (G), waist circumference (W), triglycerides (T), HDL cholesterol (HDL), and systolic blood pressure (SBP)]. A second score used the more readily available parameters, G, W, T, and SBP and this simpler score was used to predict incident diabetes among 3,826 participants that had fasting glucose measured at the six-year follow-up exam.

Results: Although the mean MS parameters at baseline differed between men and women, the variance explained and the MS score coefficients were remarkably similar, thus we used a common MS score. Furthermore, the simpler score with G, W, T and SBP was highly correlated with the more complete score (Spearman r=0.94), it explained 50% of the variance among the MS parameters, and the waist circumference had the highest loading (0.59). The MS score was associated with a marked increased risk of incident diabetes per unit SD increase in the score. Results were significant even among subjects without baseline IFG (table).

	Men		Women	
Age adjusted	all	excluding IFG	all	excluding IFG
OR (95% CI)	n=1,858	n=1,628	n=1,968	n=1,895
MS score W,G,SBP,logT	3.7(2.8,4.9)	3.3(2.1-5.2)	6.4(4.3-9.7)	5.2(3.0-9.1)
NCEP MS	2.7(2.2-3.3)	1.9(1.3-2.7)	3.7(2.8-5.0)	2.8(1.8-4.2)

Age adjusted odds ratios (95% CI) for incident diabetes: principal components derived MS score, NCEP MS

Conclusions: Our results, which should be confirmed in other populations, suggest it is possible to evaluate the risk of the MS continuously in a pragmatic fashion with a continuous score from a principal components analysis.

P1628 Fasting plasma glucose predicts traditional cardiovascular risk factors among non-diabetic subjects

M. Leosdottir[1], P.M. Nilsson[2], R. Willenheimer[1], J.-A. Nilsson[2], G. Berglund[2]. [1]*Malmo University Hospital, Department of Cardiology, Malmo, Sweden;* [2]*Malmo University Hospital, Department of Medicine, Malmo, Sweden*

Purpose: According to most international standards fasting plasma glucose (FPG) <6.1 mmol/l is defined as normal. Subjects with impaired fasting glucose (IFG) (6.1-6.9 mmol/l) are known to have increased risk of cardiovascular disease, but it is less well known how the cardiovascular risk factor profile is related to FPG values within the normal range.

The aim of this study was to evaluate the cardiovascular risk factor profile in non-diabetic subjects with normal or borderline FPG values, in a large population-based project in Malmö, Sweden.

Methods: Subjects were identified through an ongoing re-screening of individuals who participated in the Malmö Preventive Project 1974-1992; a population-based study (33,000 adults) designed to identify risk factors for cardiovascular disease. The re-screening started in 2002, with a target population of 25,000 now middle-aged and elderly individuals. All subjects answer a self-administered questionnaire, undergo a physical examination and have blood samples drawn.

In the current analysis, out of the 8151 subjects screened up to the end of 2004, 916 diabetics (11.2%) were excluded. The remaining 7235 subjects (53% men, mean age 72.1±4.0) were divided into deciles according to their FPG values, with IFG subjects forming the 10th decile. We then compared the deciles with regard to systolic (SBP) and diastolic (DBP) blood pressure, body mass index (BMI), waist circumference, blood-lipid profile, smoking and level of exercise.

Results: We observed a statistically significant age-independent increase in SBP and DBP, BMI, waist circumference and LDL/HDL-cholesterol ratios from the 1st

to the 10th decile ($p<0.0001$), with a marked step-up of the risk factors at a FPG level of approximately 5.5 mmol/l (deciles 6-7). Of subjects in deciles 1-5 (FPG 3.6-5.3 mmol/l), 49% had SBP =140 mmHg, compared to 59% in deciles 6-9 (FPG 5.4-6.0 mmol/l), and 65% in decile 10 ($p<0.0001$). Similarly, 58% of subjects in deciles 1-5 were overweight or obese, compared to 71% in deciles 6-9, and 81% in decile 10 ($p<0.0001$). Smokers and individuals with low levels of physical activity were also significantly more common in the upper deciles, although the trend was not as strongly significant as observed with the other risk factors.
Conclusions: Among subjects with normal FPG, cardiovascular risk factor profile worsens considerably with increasing FPG values. Whether cardiovascular risk factor intervention should be recommended for subjects with FPG values in the higher range of currently defined normal values, should be further evaluated.

P1629 Metabolic syndrome and cardiac trophism. Results from the Asklepios Study in 2528 apparently healthy 35-55 year old subjects

E.R. Rietzschel[1], M.L. De Buyzere[1], D. De Bacquer[2], M. Langlois[3], G. De Backer[2], T.C. Gillebert[1] on behalf of the Asklepios Investigators. *[1]University Hospital Ghent, Department of Cardiovascular Diseases, Ghent, Belgium; [2]Ghent University, Department of Public Health, Ghent, Belgium; [3]AZ St-Jan AV Hospital, Department of Clinical Chemistry, Bruges, Belgium*

Background: Recent guidelines identified the metabolic syndrome (MS) as a compound risk factor for cardiovascular disease deserving increased clinical attention. At present limited population data are available on the pathophysiological link between MS and cardiac function and trophism.
Methods: the Asklepios Study is a wide-ranging cross-sectional and longitudinal epidemiological study focusing on the interplay between ageing, cardiovascular haemodynamics and inflammation in preclinical cardiovascular disease. A representative cohort of 2528 apparently healthy 35-55 year old subjects (1302 female; mean age 46±6 years), was sampled from the twinned Belgian communities of Erpe-Mere/Nieuwerkerken. The study included extensive physical and laboratory evaluations. In brief, and focusing on the results submitted, they included: basic clinical data, biochemistry and genotyping, cardiac and vascular echography and doppler (GE/Vingmed Vivid7). All measurements were single site, single observer and single device throughout the study. MS was defined according to recent ADA-amended ATP III criteria (glycemia threshold lowered to 100 mg/dl).
Results: We analyzed the data with respect to the number of MS components present in an individual. We could demonstrate highly significant (all $p<0.01$) and graded effects in function of the number of MS components on left ventricular (LV) mass, and a much smaller effect of LV end-diastolic diameter. As such LV mass increased primarily by concentric remodelling (increasing radius to wall thickness ratio), rather than by primarily increasing cavity dimension. Diastolic function (assessed by mitral inflow, tissue doppler mitral annulus velocities or flow propagation) decreased in a stepwise manner in function of the number of MS components present. To test these effects over and above conventional risk stratification we repeated the analyses after correction for age, gender, systolic blood pressure, cholesterol, smoking, use of antihypertensive or lipid lowering drugs. Effect magnitudes were attenuated after correction, but remained graded and significant for all parameters.
Conclusion: In apparently healthy 35-55 year old subjects, MS is associated with cardiac trophism and a parallel decrease in diastolic function. The cardiac trophism was primarily LV concentric remodelling (increased LV mass and radius to wall thickness ratio). The relation between MS and these abnormalities is graded per additional component of the MS present in an individual, and cannot be explained on the basis of the elevated blood pressure component alone.

PRIMARY PREVENTION

P1630 Predictive value and accuracy of self-reported prevalence of cardiovascular risk factors in 12500 healthy adults

M.T. Lira[1], S. Kunstmann[2], J.C. Molina[2], E. Caballero[1], L. Villarroel[2]. *[1]Santiago, Chile; [2]Santiago, Chile*

Accuracy of self reported (SR) data is crucial as massive populations' surveys are a common method of establishing population's cardiovascular risk factors (CVRF) prevalence. A valid diagnostic test has low percentages of false negatives and false positives.
Objectives: To determine the accuracy of SR values of Blood Pressure (BP), Total Cholesterol (TC) and Blood Sugar (BS) compared with clinical findings and to establish the accuracy and predictive value (PV) of this method.
Method: A questionnaire about their BP, TC and BS was answered by 12,190 healthy adults from the RICAR Project, 6320 women and 5870 men, aged 30-80 y. (mean age 47.6 ± 12 y).Those who knew their parameters (BP n= 2,430, TC n= 1,163 and BS n = 1,556) were asked if they had normal or abnormal values. Using standardized methods we measured Systolic (SBP) and Diastolic Blood Pressure (DBP), Total Cholesterol and 4 hours Post Prandial Blood Sugar (PPBS) and compare them with the referred data. Abnormal values were defined by international guidelines (SBP>140 mmhg, DBP> 90 mmhg, TC>200 mg/dl and PPBS >140 mg/dl). False negatives (FN) and positives (FP),PV and prevalence were determined with a 95% LC.
Results: The educational level was: 12.9% (1,573) elementary, 48.6% (5,924) high school and 38.6% (4,693) technical or professional level.
FN of abnormal values of SBP, DBP, TC and PPBS were 40.9%, 40.7%, 37.7% and 29.9% respectively. FP for the same parameters were 21.3%, 23.4% 30.7 and 10.8% respectively. Positive PV for abnormal SBP, DBP, TC and PPBS were 54.3%, 46.7%, 75.1% and 41.8% respectively. Negative PV for the same parameters were 81.7%, 84.4%, 55.1% and 96.4% respectively.

CVRF Prevalence

CV Risk Factor	True Prevalence (%)	Apparent Prevalence (%)	p value
SBP≥ 140 mm Hg	30	32.6	p<0.01
DBP≥ 90 mm Hg	25.7	32.6	p<0.0001
TC>200 mg/dl	59.8	49.5	p<0.0001
PPBS≥140 mg/dl	10	16.7	p<0.0001

Conclusions: Knowledge of own BP, TC and BS were suboptimal. Negative PV of Self-Reported CVRF were highly precise, except for Total Cholesterol. This method induced a significant difference between true and apparent prevalence CVRF. These results evidence the unreliability of SR data to establish accurate CVRF prevalence in this population.

P1631 Automatic cardiovascular primary prevention intervention uncovers a wide treatment gap, computerised community cardiovascular control (4C-HR)

H. Gilutz[1], Y. Henkin[1], I. Harman-Boehm[2], D.Y. Bonneh[3], E. Paran[4], D. Vardy[3], N. Liebermann[5], A. Porat[6]. *[1]Soroka Medical Center, Cardiology, Beer Sheva, Israel; [2]Soroka MED CTR, Internal med C, Beer sheva, Israel; [3]Ben-Gurion University, Family Medicine Department, Beer Sheva, Israel; [4]Soroka Medical Center, Hypertension Service, Beer Sheva, Israel; [5]Clalit Medical Service, Community Medicine Division, Tel Aviv, Israel; [6]Soroka Med CTR, Internal Med F, Beer Sheva, Israel*

Background: The majority of high-risk patients who need primary prevention measures for cardiovascular disease (CVD) are under-evaluated and under-treated.
Aim: To identify patients at high-risk of developing CVD and recommend appropriate primary prevention measures.
Methods: All patients, aged 35-69y without known CVD from the primary health care clinics of Clalit Health Services in Israel's southern region, were included. Computerized primary care records, hospital registries, laboratory and drug dispensing were used to identify high-risk patients as calculated by the Framingham formula. Cross-referencing laboratory values and drug dispensing automatically corrected over-diagnoses and misdiagnoses. Guidelines for diabetes, hypertension and dyslipidemia were used as thresholds for determining appropriateness of monitoring and treatment, and determining computerized patient-specific recommendations.
Results: Out of 82,106 studied patients, 13,883 (17%) were found to be at high risk for CVD events. High-risk patient's management status is presented in the table. The majority of patients are either under-monitored or under-treated.

Treatment Gap Status

Risk factor	Diabetes	Hypertension	Dyslipidemia
Patients with risk (n)	7,960	7,131	12,972
Missing data (lab or BP)	29%	30%	35%
At target levels	32%	23%	14%
Initiate drug therapy	5%	10%	29%
Drug up titration is required	30%	32%	15%
Consultation recommended	5%	5%	7%

Conclusions: This study demonstrates a significant gap in monitoring and treatment of modifiable risk factors in the primary care setting. Most of the patients did not attain targets levels for risk factor control. These findings serve as a basis for an HMO-wide intervention program using computerized information system of reminders and performance measures.

P1632 Validity of an adaptation of the Framingham cardiovascular risk function: the verifica study

J. Marrugat[1], E. Comin[2], R. Elosua[3], R. Ramos[3], P. Solanas[2], B.H. Nam[4], J. Sala[4], R.B. D'Agostino[4] on behalf of the VERIFICA Investigators. *[1]Institut Municipal d'Investigacio Medica, Unitat de Lipids I Epidemiologia Cardiov., Barcelona, Spain; [2]Institut Català de la Salut, Barcelona, Spain; [3]IMIM, Lipids and Cardiovascular Epidemiology, Barcelona, Spain; [4]Framingham Heart Study and Boston Univ, Boston, USA*

Objective: To assess the accuracy and reliability of the original Framingham coronary risk function and that adapted by the REGICOR (Registre Gironí del Cor) investigators in predicting 5-year coronary heart disease (CHD) event rate in Spain.
Design: Combined prospective and retrospective cohort study.
Setting: 67 primary care centers and a population-based prospective cohort in Spain.

Participants: 5,732 participants aged 35 to 74 years with complete data on initial levels of risk factors and free from CHD at the onset of the study.
Main outcome measures: Comparison of the observed 5-year CHD event rate with the rates predicted by the original and the REGICOR-adapted Framingham risk functions.
Results: Of 5,732 participants, 180 had a coronary event during the 5-year follow-up; Kaplan-Meier rate: 4.0% in men and 1.7% in women. The original Framingham function overestimated 2.6 and 2.8 times this event rate, respectively. The classification of participants with an event (discrimination) by the original Framingham function and by the model that best fitted with the study data was similar in men (area under the ROC curve 0.68 and 0.69, respectively, p=0.273) and better with the best Cox model in women (0.73 and 0.81, respectively, p<0.001). For the four groups of event probability defined by the original Framingham function using 5-year risk cut-points at 5%, 7.5% and 10% (calibration), the findings matched the REGICOR-adapted function's estimate but the goodness of fit differed from the original function's estimate as follows: chi square in men 5.1, p=0.078 and 110.1, p<0.001, respectively; in women 2.7, p=0.256 and 64.3, p<0.001; and in diabetic participants 1.4, p=0.499 and 54.2, p<0.001. More than two thirds of fatal events and 41.0% of all events occurred in the group aged 65 to 74 years.
Conclusion: The original version of the Framingham function applied directly to the Spanish population overestimated the observed rate by a factor > 2.6. However, the Framingham function adapted to local population characteristics accurately and reliably predicted the 5-year CHD event rate for participants aged 35 to 74 years. Adaptation of the Framingham function is a valid alternative to the creation of new functions derived from local cohorts.

P1633 How close is the agreement between the guidelines for the primary prevention of cardiovascular diseases?

R. Darioli[1], J. Perdrix[2], L. Kappenberger[1], J.O. Prior[3]. [1]*CHUV University Hospital, Department of Cardiology, Lausanne, Switzerland;* [2]*Medical Policlinic, Lausanne, Switzerland;* [3]*CHUV University Hospital, Nuclear Medicine, Lausanne, Switzerland*

Background: Current guidelines for the primary prevention of cardiovascular disease (CVD) in clinical practice have emphasized the need to base intervention on assessment of individual global risk rather than on the level of any particular risk factor (RF). In contrast to NCEP/ATP-III guidelines, 3JE-ESC as well as IAS harmonized guidelines (IAS-HG) have included adjustment for European countries at low risk for CVD, such as Switzerland.
Objective: The objective of this study was to compare risk stratification and eligibility for lipid-lowering drug therapy when using these three most recommended guidelines.
Patients and methods: 8829 individuals (41% of women, aged 20-80 yr, mean = 45±12 yr) recruited in the "Lausanne Health Promotion Program" during the 2001-2004 period were analysed to assess their 10-year CV-risk and eligibility for lipid-lowering drug therapy (LLD), using the three sets of guidelines mentioned above. Individuals with history of CVD and/or diabetes mellitus were excluded. The determination of CV-RF was performed with standardized methods.
Results: The prevalence of CV-RF among the participants was 26% for current smoking, 27% for hypertension, 18% for hypercholesterolemia and 12% for obesity. Table 1 presents a comparison of prevalence of CV high-risk patients for each guideline and the corresponding LLD eligibility. The agreement between IAS-HG and NCEP-ATP-III guidelines reached 99% with a higher kappa value (0.79, p< 0.001).

Table 1

Category	3JE-ESC	IAS-HG	NCEP/ATPIII
High-Risk (%)	1.4	0	4
Moderate-Risk (%)	—	29	26
Low-Risk (%)	98.6	71	70
Eligibility to LLD (%)	2.3	11.0	15.8
– Agreement (%)	Reference	90	86
– Kappa Value	Reference	0.22 (p<0.001)	0.20 (p<0.001)

Conclusion: Our analysis demonstrated striking differences among guidelines, with markedly different clinical and economical implications. These results suggest the need to evaluate the additional predictive value of new techniques of atherosclerosis imaging to improve identification of patients requiring more intensive therapy.

P1634 Interleukin 6 predicts atherosclerosis in a low risk population- a link with soluble inter cellular adhesion molecule-1

J. Amar[1], J. Fauvel[2], L. Drouet[3], J.B. Ruidavets[4], B. Perret[2], B. Chamontin[5], H. Boccalon[6], J. Ferrieres[6]. [1]*Hôpital Purpan, Internal Medicine and Hypertension, Toulouse, France;* [2]*INSERM U 563, Service de Biochimie, Toulouse, France;* [3]*Laboratory of Haematology, Hopital Lariboisiere, Paris, France;* [4]*INSERM 558, Epidemiology, Toulouse, France;* [5]*CHU Purpan, Service de Médecine et d'HTA, Toulouse, France;* [6]*CHU, Service de Médecine Vasculaire, Toulouse, France*

Background: Interleukin 6 (IL-6) promotes the expression of inter cellular adhesion molecule-1 (ICAM-1), C reactive protein (CRP) synthesis with potential implications on atherosclerosis progression.
Aim of the study: to analyse in a population based-sample, the relationship between IL-6 and atherosclerotic lesions and the role of ICAM-1 and CRP on this relationship.
Population: Among 1015 subjects, randomly recruited in Haute Garonne a French region at low cardiovascular risk, 948 subjects with complete data for all the measurements, were analyzed. Common carotid intima-media thickness (IMT) and the presence of plaques in the carotid and femoral arteries were assessed by ultrasonography.
Results: IL-6, ICAM-1 and CRP were associated with the number of plaques and IMT. After adjustment for traditional risk factors, IL-6 (p for trend <0.001) and ICAM-1 (p for trend <0.002) were positively associated with the number of plaques but not CRP. Neither IL-6, nor ICAM-1 or CRP were independently associated with IMT. In addition to traditional risk factors, the percentage of the variance of the number of plaques increased significantly (p<0.001) by 2.72% when IL-6 was introduced into the multivariate model. The introduction into the model of ICAM-1 after IL-6 did not increase significantly this percentage.
Conclusion: IL-6 level is associated with stable atherosclerotic lesions independently of traditional risk factors and ICAM-1: the influence of IL-6 on ICAM-1 secretion may play a role in this association. These results highlight the interest of IL-6 in the stratification of cardiovascular risk especially in subjects considered at low or intermediate risk based on traditional risk factors.

P1635 Essential hypertensive patients predisposed to paroxysmal atrial fibrillation exhibit augmented plasma levels NT-proANP

A. Hatziyianni, P. Kyriacou, M. Toutouza, C. Vasiliadi, C. Stefanadis, P. Toutouzas. *Hippokration Hospital, Cardiology Department, Athens, Greece*

Background/Aim: Atrial natriuretic peptide (ANP) is a peptide hormone synthesized in atrial myocytes as a prohormone and stored in secretory granules as a 126 amino acid prohormone. ANP plasma levels have been related to increased atrial pressure and alterations of atrial effective refractory period. The most important stimulus for the release of the ANP into circulation is stretch of the myocyte fibres. We assessed the hypothesis that NT-pro ANP plasma levels may be of prognostic value in hypertensive patients predisposed to AF.
Methods: For this purpose, were measured the N-terminal part proANP (1-98) plasma levels in 50 hypertensive patients with a history of paroxysmal atrial fibrillation (PAF) (group A) and in 30 hypertensive patients without previous history of PAF (group B). In 12 patients from group A, NT-proANP levels were measured during the paroxysm of AF. The patients were also assessed with ambulatory ECG and echocardiography.
Results: There were no differences between the two groups, A and B, regarding the clinical data and demographic data. Patients on group A had increased both left ventricular mass index and left atrial dimension compared to group B (115±27 vs 85±19 gr/m^2 and 3.77±0.3 vs 3.51±0.4 cm, respectively, p <0.05 for both cases), while the left ventricular ejection fraction did not differ (65% vs 67%). The NT-pro ANP plasma levels were significantly higher in group A than group B (3623.87±3186 vs 1945.39±586.88 fmol/ml, p=0.0004). In addition, NT-pro ANP plasma levels were significantly higher during PAF (8155.991±3904.72 fmol/ml, p=0.00204). By applying a multivariate model it was revealed that NT-pro ANP levels were significantly and independently associated with PAF.
Conclusion: NT-pro ANP levels could be a significant and reliable predictive index for the detection of patient prone to the development of PAF in essential hypertensive patients while in sinus rhythm.

WOMEN

P1636 Spectrum of initial ECG findings in women with stress induced (tako-tsubo) cardiomyopathy

S.W. Sharkey[1], E.Z. Grey[2], A.G. Zenovich[1], J.R. Lesser[1], B.J. Maron[1]. [1]*Minneapolis Heart Institute, Minneapolis, United States of America;* [2]*Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, United States of America*

Introduction: Psychological stress can provoke acute reversible left ventricular(LV)dysfunction in women. This clinical entity is often confused with the more common acute coronary syndrome and acute myocardial infarction (MI). We report the presenting ECG findings in women with stress cardiomyopathy. We also report the relationship of initial ECG patterns to the following: time to initial ECG, ejection fraction, and elevated admission troponin.
Methods: Forty-one consecutive females met our inclusion criteria for stress cardiomyopathy: 1) symptoms of acute myocardial ischemia; 2) major LV wall motion abnormality with apical ballooning in the absence of significant coronary disease. The average age was 66.9 ± 12.3 (32-91) years.
Results: Admission ECG findings are summarized in Table 1. Also, precordial Q waves or poor R wave progression were present in 26(65%)of patients. All patients showed evolution of T wave inversion usually in both precordial and limb leads by hospital discharge or at 1-month follow-up. Improvement in R wave

voltage by discharge was common. Ejection fraction improved to normal(> or = 50%)usually within 30 days in all patients.
Inter-group comparison (ANOVA) showed that neither EF, age, symptom-to-ECG,nor elevated admission troponin significantly correlated with the ECG findings.

Table 1. Spectrum of ECG changes and relationship to EF, time-to-ECG #1, and elevated initial troponin

	Anterior MI (acute)	Anterior ME (age undetermined)	Diffuse T-wave inversion	Other	p-value
Patients	20(49%)	11(27%)	5(12%)	5(12%)	
Ejection Fraction	26.5%±7.3 (15%-40%)	30.5%±10.4 (20%-45%)	34%±12.5% (15%-45%)	34%±6.5% (30%-45%)	0.19
Time to ECG (hours)	13.0±18.9 (0.5-72)	3.5±3.2 (1-10)	12.2±13.9 (1.5-39)	4.8±2.8 (0.5-8)	0.33
Troponin # 1elevated	19 (95%)	10(91%)	3(60%	5(100%)	NS

Conclusions: Substantial variation exists in the initial ECG patterns in patients with stress cardiomyopathy. Electrocardiograms consistent with anterior MI (acute or age indeterminate) were present in 76%. A substantial minority (24%) had a nondiagnostic ECG creating ambiguity in the emergency room diagnosis of stress cardiomyopathy. In patients with stress cardiomyopathy, marked LV dysfunction is frequent irrespective of the initial ECG findings. Complete recovery of LV ejection fraction occurs despite the common occurrence of precordial Q waves or poor R wave progression.

P1637 Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and neurohormonal assessment

M. Feola[1], F. Albrile[2], A. Francini[3], A. Biggi[3], O. Garrone[4], M. Occelli[4], M. Merlano[4], E. Uslenghi[1]. [1]*Hospital Santa Croce-Carle, Dept of Cardiovascular Diseases, Cuneo, Italy;* [2]*Hospital Santa Croce-Carle, Laboratory Departement, Cuneo, Italy;* [3]*Hospital Santa Croce-Carle, Nuclear Medicine, Cuneo, Italy;* [4]*Hospital santa Croce-Carle, Oncology Division, Cuneo, Italy*

The incidence of congestive heart failure (CHF) after anthracycline chemotherapy in patients affected by breast carcinoma varied from 2% to 26% according to the dosage of the drug. The incidence of asymptomatic left ventricular dysfunction is certainly higher and the cytotoxic damage could be revealed early. The aims of this study were: a) to evaluate the early modification of left ventricular ejection fraction (LVEF) obtained with multiple gated radionuclide ventriculography after the first 6 cycles of chemotherapy and b) to analyse the effects of chemotherapy on troponin I and neurohormonal assessment.
Methods: Patients with early breast cancer that underwent surgical treatment followed by chemotherapy were enrolled. The chemotherapy consisted in a single bolus infusion of epirubicin 90 mg/mq, cyclophosphamide 600 mg/mq, fluorouracil 600 mg/mq repeated every three weeks for 6 cycles. The presence of coronary artery disease, valvular disease, left ventricular dysfunction (LVEF<50%), liver disease or renal failure were considered exclusion criteria. All patients underwent clinical assessment, radionuclide ventriculography, troponin I, brain natriuretic peptide (BNP), endothelin 1 (E1), Bigendothelin1 (BigE1) and rest aldosteron at baseline and within 1 month after the last chemotherapy cycle. LVEF was performed by radionuclide ventriculography using multigated ECG triggered sampling with at least 32 frames each RR interval.
Results: 40 pts (38 females, age 56.3±11.2 ys) were included; 12 (30%) were hypertensive. At follow-up one subject developed overt CHF. A significant reduction LVEF was demonstrated at radionuclide ventriculography (62.4±5.8% vs 58.6±7.8%, p=0.003). The BNP plasma level increased (from 35.5±44.7 pg/ml to 66.6±102.7 pg/ml, p=0.006) so as the level of troponin I (from 0.01±0.01 ng/ml to 0.05±0.04 ng/ml, p=0.0001); the plasma level of aldosteron at rest reduced (from 97.7±55.5 pg/ml to 74.3±37.4 pg/ml, p=0.02). No significant differences were obtained in the dosage of E1 (from 0.5±0.5 fmol/ml to 0.24±0.3 fmol/ml, p=0.16) and BigE1 (from 1.7±1.9 fmol/ml to 1.8±1 fmol/ml, p=0.8).
Conclusions: Radionuclide ventriculography revealed early reduction of LVEF after anthracycline chemotherapy. BNP and troponin I might be considered promising tests for early detection of induced cardiotoxicity.

P1638 Aortic pulse pressure and aortic pulsatility are associated with the angiographic coronary artery disease in women

Y. Guray[1], U. Guray[2], H. Altay[1], S. Cay[1], M.B. Yilmaz[1], H. Kisacik[1], S. Korkmaz[1]. [1]*Yuksek Ihtisas Hospital, Cardiology, Ankara, Turkey;* [2]*Ankara, Turkey*

Background: Studies indicated that both aortic pulse pressure (PP) and aortic pulsatility are independently associated with the angiographic coronary artery disease (CAD). However, most of these studies included a majority of male subjects, and women were underrepresented.
Objective: We investigated the relation of aortic PP and aortic pulsatility derived from invasively measured ascending aortic pressure waveform and presence of angiographic CAD (>50% diameter stenosis) in women undergoing diagnostic coronary angiography.
Methods and Results: From September 2003 to April 2004, 262 female subjects (mean age 61±10 years; minimum 33 years - maximum 79 years) without hemodynamically significant valve disease undergoing first cardiac catheterization were consecutively included in the study. Systolic, diastolic, and mean pressure waveforms of the ascending aorta were measured during cardiac catheterization with a fluid-filled system. Aortic pulsatility was estimated as the ratio of aortic PP to mean pressure. Angiographic CAD was detected in 175 (67%) patients. The mean age of patients with CAD was higher and patients with CAD had more often diabetes mellitus as compared with those without CAD. There were no significant differences between two groups with respect to presence of hypertension, history of current smoking and body mass index. Although levels of serum total cholesterol and high density lipoprotein (HDL) cholesterol were comparable, serum levels of triglycerides and ratio of total cholesterol to HDL-cholesterol were significantly higher in patients with CAD as compared with those without CAD. In multiple-adjusted logistic regression, both aortic PP and aortic pulsatility were independently associated with the presence of CAD (for 10 mmHg increase in PP: odds ratio [OR] =1.3, 95% confidence interval [CI] =1.1-1.76; for 0.1 increase in aortic pulsatility: OR=1.8, 95% CI=1.3-2.4). When patients were divided into tertiles according to the level of aortic pulsatility, it was noted that multiple-adjusted OR of presence CAD was 2.2 (95% CI=1.1-4.4) for the middle tertile of the aortic pulsatility level and 5.9 (95% CI=2.7-12.8) for the highest tertile of the aortic pulsatility level as compared to the lowest tertile.
Conclusion: In female subjects referred to coronary angiography, ascending aorta PP and aortic pulsatility are significantly associated with the presence of angiographic CAD and these associations are independent of age and other cardiovascular risk factors.

P1639 Influence of sex and age on long-term survival in systematic off-pump coronary artery bypass surgery

I. El-Hamamsy, P. Demers, D. Bouchard, M. Pellerin, R. Cartier. *Montreal Heart Institute, Department of Surgery, Montreal, Canada*

Background: Off-pump coronary artery bypass surgery (OPCAB) is used alternatively to conventional "on-pump" approach for coronary artery revascularization. Sex and age have been shown to adversely affect operative mortality risk as well as long-term survival.
Aims of the study: To evaluate the effect of age and sex on long-term mortality following OPCAB surgery.
Methods: We have prospectively followed up 900 consecutive and systematic OPCAB patients operated between September 1996 and April 2003 representing 98% of all coronary revascularizations during the same time frame. Follow-up was complete in 99% of the cohort.
Results: Average age was 64±10 years, there were 198 women (21%) and 702 men (79%), 73% had triple vessel disease, in 69% surgical indication was unstable angina and 5.3% were operated in emergency. On average 3.2 grafts/patient were performed. Women were older, 68+10 vs 63+10 years (p<0.0001). Operative mortality was 1.1%, 0.9% in men and 2% in women (p=ns). By logistic regression analysis, peripheral vascular disease (OR: 14.2, p=0.02), and CKMB (OR: 1.01, p=0.06) were the main risk factors for operative mortality. Eight-year survival was 84±2.9% for men and 69.3±7.8% for women, (p=0.004). By Cox regression analysis, age (OR: 1.07, p<0.001), incomplete revascularization (OR: 3.54, p<0.001), peripheral vascular disease (OR: 1.67, p=0.05), and diabetes (OR: 1.75, p=0.03) were significant predictors of long-term mortality. When revascularization was performed before 65 years of age, sex was identified as an adverse risk factor on survival (OR: 7.7; p=0.006) but not after (OR: 0.9; p=0.8).
Conclusion: In this series of systematic OPCAB surgery, sex was shown to adversely affect long-term survival mainly in younger patients.

P1640 The metabolic syndrome is independently predictive for vascular events in women undergoing coronary angiography

C.H. Saely[1], S. Aczel[1], T. Marte[1], P. Langer[2], G. Hoefle[3], H. Drexel[1]. [1]*Landeskrankenhaus Feldkrich, Department of Medicine and VIVIT, Feldkirch, Austria;* [2]*VIVIT-Institute, Feldkirch, Austria;* [3]*LKH-Feldkirch, Innere Medizin, Feldkirch, Austria*

Objective: To evaluate the association of the metabolic syndrome (MS) with coronary artery disease (CAD) as well as the impact of the MS on future vascular events in women undergoing coronary angiography.
Methods: We enrolled 241 consecutive women undergoing coronary angiography for the evaluation of established or suspected CAD. According to ATP III criteria, we defined the MS as the presence of any three of: waist circumference >88 cm, triglycerides ≥150 mg/dl, HDL cholesterol <50 mg/dl, blood pressure ≥130/85 mmHg, or fasting glucose ≥110 mg/dl.
Results: From the total cohort of 241 women, 84 women (34.9%) had the metabolic syndrome. After adjustment for age, smoking, body mass index, LDL cholesterol, and use of aspirin, of antihypertensive drugs and of lipid-lowering drugs, the MS was associated with an increased risk of significant coronary stenoses ≥50% (OR = 2.15 [1.12-4.11]; p = 0.021). Prospectively, in Cox regression analyses adjusting for the covariates given above as well as for the presence of significant coronary stenoses at baseline, the MS significantly predicted vascular events (n = 19) during a follow-up period of 2.2 ± 0.5 years (OR = 5.52 [1.34-

22.47]; p = 0.017). Women with the MS exhibited a significantly higher HOMA index of insulin resistance than those without the MS (p <0.001). After additional adjustment for HOMA insulin resistance the MS remained significantly associated with the presence of significant coronary stenoses and significantly predictive for the incidence of vascular events.
Conclusions: Among women undergoing coronary angiography, the MS is associated with angiographic CAD and is independently predictive for future cardiovascular events. Insulin resistance does not explain the full amount of risk inferred by the MS.

P1641 Do we understand sudden cardiac death and the benefits of implantable cardioverter-defibrillator therapy in women?

N. Thiessen[1], E. Grey[1], K. Menssen[2], L. Kallinen[1], R. Hauser[2]. *[1]Minneapolis Heart Institute Foundation, Cardiology, Minneapolis, United States of America; [2]Minneapolis Heart Institute Foundation, Cardiology, Minneapolis, United States of America*

Purpose: Gender may affect the clinical characteristics and influence the outcomes of patients (pts) who receive ICD therapy. This study compared women and men ICD pts for underlying heart disease, systolic function, electrical therapy (shocks or antitachycardia pacing), and survival (S%).
Methods: Actuarial S% were calculated by the Kaplan-Meier method for 1,280 pts who underwent ICD implantation at our center between 1987 and 2004. Left ventricular ejection fraction (EF) was measured by echocardiography or ventriculography. The number of pts who received electrical therapy(Rx) was reliably assessed for 792 pts implanted after 1997.
Results: Average age at implant was 59±17 yrs for 288 women compared to 64±16 yrs for 991 men (p<.0001). EF was 0.40±0.20 for women and 0.32±0.15 for men (p<.0001). Underlying heart diseases (coronary artery disease (CAD), ischemic (ICM), non-ischemic (NICM) and hypertrophic (HCM) cardiomyopathy, hypertensive (HHD), valvular (VHD), hereditary disorders (HER), and no structural disease (NOS), for women compared to men are shown in the table. Overall S% for women vs men were: 3 yrs- 87±2 vs 84±1; 5 yrs- 79±3 vs 73±2; 10 yrs- 47±5 vs 41±3, 15 yrs- 37±8 vs 25±4 (p=0.083). No significant differences in S% were found between women and men for ICM (p=0.535) or NICM (p=0.416). More men received electrical Rx (203/598; 34%) than women (53/178; 30%) (p=.045).

Heart Disease in Women and Men

	#	CAD	ICM	NICM	HCM	HHD	HER	VHD	NOS
Women	289	160(55)	110(38)	48(17)	28(10)	62(21)	12(4)	27(9)	5(1)
Men	991	780(79)	641(65)	115(12)	51(5)	73(7)	9(1)	44(4)	22(2)
P Value		<.0001	<.0001	0.025	0.005	<.0001	<.0001	.001	.375

Number(%)

Conclusions: In our experience, women who received ICDs were younger, had better systolic function, and fewer received electrical Rx. However, survival after ICD implantation was not significantly different for women compared to men. These observations, including significant gender differences in underlying heart disease, suggest that sudden cardiac death and the benefits of ICD therapy may be different in women than men. These results should prompt prospective multicenter studies.

P1642 Undertreatment of women with atherothrombosis: results from the worldwide REACH registry

P.G. Steg[1], D.L. Bhatt[2], M.T.B. Abola[3], I. Baumgartner[4], E.M. Ohman[5], J. Rother[6], S. Uchiyama[7], P.W.F. Wilson[8] on behalf of the REACH Registry Investigators. *[1]Hopital Bichat-Cl.Bernard, Service de Cardiologie, Paris Cedex 18, France; [2]Cleveland Clinic Foundation, Department of Cardiovascular Medicine, Cleveland, United States of America; [3]Philippine Heart Center, Section of Peripheral Vascular Disease, Quezon City, Philippines; [4]University Hospital, Division of Angiology, Bern, Switzerland; [5]University of North Carolina, Division of Cardiology, Chapel Hill, United States of America; [6]Universitäts-Klinikum, Neurologie, Hamburg, Germany; [7]Tokyo Women's Medical University, School of Medicine, Tokyo, Japan; [8]Medical University of South Carolina, Endocrin., Diabetes, Medical Genetics, Charleston, United States of America*

Background: atherothrombosis is a significant health problem and leading cause of mortality worldwide, but its specific impact in women may not be well understood.
Aims: to study risk factor distribution, clinical presentation, and treatment of atherothrombosis by gender in the REACH (REduction of Atherothrombosis for Continued Health) Registry.
Methods: the REACH Registry is an international, prospective, observational registry of outpatients with multiple risk factors for atherothrombotic events or with symptomatic atherothrombosis (documented coronary artery, cerebrovascular or peripheral arterial disease). Between December 2003 and July 2004, 63,857 patients were enrolled in 5,182 sites in 43 countries worldwide.
Results: See table.
Conclusion: women with atherothrombosis have a higher overall risk profile than men but differ substantially in the achievement of prevention goals. Revascularization procedures and evidence-based medical therapies are used less often in women. Physicians should be aware of these differences and specifically target women for more active prevention and treatment.

REACH Registry baseline characteristics

	Men (N=39,581)	Women (N=23,082)	P
Age (mean)	67.2	70.4	<0.0001
Diabetes (%)	42.6	47.7	<0.0001
Hypertension (%)	79.7	88.1	<0.0001
Systolic BP (mmHg)	136.4	140.5	<0.0001
Cholesterol (mg/dL)	186.9	202.3	<0.0001
Triglycerides (mg/dL)	161.8	165.9	<0.0001
Non-achievement of goals			
BP ≥140 or > =90 (%)	47.6	53.3	<0.0001
Cholesterol >200 mg/dL (%)	34.2	47.3	<0.0001
Current smoking (%)	16.9	11.9	<0.0001
BMI ≥30	30.1	36.1	<0.0001
Utilization of treatment			
Any antiplatelet therapy (%)	81.4	74.7	<0.0001
Any statin therapy (%)	72.6	69.2	<0.0001
Hx of PCI or CABG among CAD patients [n=36,029] (%)	42.3	34.9	<0.0001
Hx of PAD surgery amongst PAD patients [n=11,041] (%)	40.1	33.1	<0.0001

P1643 Impact of female gender on the outcome of patients with left main coronary artery disease: a single center experience

T. Katircibasi[1], M. Baltali[2], T. Kocum[1], H.T. Kiziltan[3], T. Erol[1], H. Atalay[3], S. Demircan[1], H. Muderrisoglu[4]. *[1]Baskent University, Adana, Cardiology, Adana, Turkey; [2]Adana, Turkey; [3]Baskent University, Adana, Cardiovascular Surgery, Adana, Turkey; [4]Cardiology, Baskent University, Ankara, Turkey*

The aim of our study is to evaluate baseline clinical-angiographic characteristics, in-hospital and long-term outcome among patients with left main coronary artery (LMCA) disease with respect to gender.
Methods: Clinical-angiographic characteristics, in-hospital mortality and long-term outcome over a mean period of 25.1±16 months were studied among 199 patients with LMCA disease (49 women, mean age 63.8±8 and 150 men, mean age 62.7±8). A subgroup analysis was performed in 140 patients (32 women, mean age 62.3±8 and 108 men, 61.9±8) undergoing CABG surgery.
Results: There was no difference between two genders with regard to age and clinical presentation. Women with LMCA disease had higher rates of hypertension (75.7% versus 53.3%, p=0.007), but were less frequently smokers (28.6% vs 69.3%, p<0.001). Truncal LMCA lesions were less frequently seen among women (28.6% vs 48.7%, p=0.02). Univariate analysis revealed a higher rate of in-hospital mortality among women (12% vs 3%, p=0.03), but Cox regression analysis did not reveal any significant impact of female gender on in-hospital mortality. There was no significant impact of female gender on long-term mortality. In the subgroup analysis of surgically treated patients, no difference was found between two genders with regard to age and clinical presentation. Coronary angiography revealed more frequent ostial LMCA lesion morphology among women (22.0% vs 7.4%, p=0.04). There were 10 deaths (7.1%) at the end of follow-up. The overall mortality was higher among women in the surgically treated group (5 women,15.6% vs 5 men, 4.6%, p=0.049). Early postoperative mortality was also higher among women as compared with men (4 women, 12.5% vs 1 man, 0.9%; p=0.01), but late mortality did not differ between two genders. Cox regression analysis revealed that the independent predictors of increased total mortality are female gender (OR 8.34, 95% CI 1.79-38 .76, p=0.007), low LVEF (OR 0.93, 95% CI 0.87-0.99, p=0.03), advanced age (OR 1.12 95% CI 1.02-1.23, p=0.014), and degree of LMCA stenosis (OR 1.068, 95%CI 1.005-1.135, p=0.03). The same analysis revealed female gender as the only independent predictor of early postoperative mortality (OR 13.18 95%CI 1.444-120.343, p=0.02) and advanced age as the only independent predictor of late mortality (OR 1.374 95%CI 1.106-1.707, p=0.004).
Conclusion: Our study revealed that female gender is an independent predictor of long term mortality among patients with surgically treated LMCA disease. This finding is probably due to a higher rate of death seen during early postoperative period.

P1644 Sex differences in presentation with persistent total occlusion after acute MI: a report from the occluded artery trial (OAT)

K. Ramanathan[1], D. Atchison[2], S. Abramsky[3], A. Mon[4], A.M. Tunesi[5], S.A. Forman[6], J.S. Hochman[3], H. Reynolds[3]. *[1]Cardiovascular Clinical Research Center, New York, United States of America; [2]Toronto General Hospital, Department of Cardiology, Toronto, Canada; [3]New York University School of Medicine, Cardiovascular Clinical Research Cente, New York, United States of America; [4]Mount Sinai Medical Center, Cardiology, Miami Beach, United States of America; [5]Royal Perth Hospital, Cardiology, Perth, Australia; [6]Maryland Medical Research Institute, Baltimore, United States of America*

Background: In patients with acute myocardial infarction (AMI), sex differences

in risk factors, pre-hospital delay and time to treatment may influence in-hospital care, enrollment in clinical trials and clinical outcomes. It is not known whether sex differences exist in the clinical profile of patients with likelihood of persistent total occlusion of the infarct-related artery (IRA) in the subacute phase of AMI.
Methods: Analysis by sex of baseline clinical and core lab angiographic data from the initial (n=1970), consecutive patients enrolled in the Occluded Artery Trial (OAT). OAT enrolled patients by protocol are asymptomatic after AMI (3-28 days) and have total occlusion (TIMI 0-1 flow) of the IRA. The OAT screening log and registry were also reviewed.
Results: Women comprise 22% of patients enrolled to date. Women were older (64±11 vs. 57±11y), had a higher prevalence of diabetes (30 vs. 18%), hypertension (64 vs. 44%) and history of heart failure (4 vs. 2%) with less frequent prior MI (8 vs. 13%) and current smoking (26 vs. 43%, $p<0.01$ for all). Use of fibrinolytic therapy and time from MI symptom onset to angiography were similar. The majority of patients had TIMI 0 flow in the IRA; however, TIMI 1 flow was more common in women (19 vs. 14%, p= 0.04). The maximum collateral flow grade to the IRA was similar for both sexes. The distribution of the infarct-related artery differed between the sexes with more LAD (42 vs. 34%) and fewer RCA (44 vs. 50%) amongst women (p=0.02). Mean peak creatine kinase was lower in women (1152 vs. 1400 U/L, $p < 0.01$). The mean left ventricular ejection fraction (LVEF) for women and men were similar (48 vs. 49%) however, more women had a mean LVEF<30% (11 vs. 5%, $p<0.001$) Women comprise 23% of patients in the OAT Registry (non-enrolled OAT eligible patients, n=314), and 30% in the OAT screening log (all post-MI pts during 1-month, n=1966), $p<0.01$ for comparison of log with enrolled patients.
Conclusions: The sex distribution of patients enrolled in OAT suggests that there are differences in the likelihood of and presentation with persistent IRA occlusion in the subacute phase of AMI. The percentage of women in OAT is consistent with the concurrent OAT registry. Further investigation may identify sex differences in pathophysiology, which may account for the lower numbers of women with occluded IRA in a clinically stable condition post-MI.

P1645 The effects of exercise capacity, sedentary lifestyle on haemostasis among middle-aged women with CHD

E. Nagy, F. Al-Khalili, I. Janszky, M. Eriksson-Berg, K. Schenck-Gustafsson. *Stockholm, Sweden*

Background: The relationship between physical fitness and hemostasis has been poorly documented especially among women.
Material and method: The Stockholm Female Coronary Risk Study included females aged < 65 years, resident in the greater Stockholm area, that were recently hospitalized for an acute coronary event between February 1991 and February 1994. A total of 292 female patients were included. Extensive clinical screening including exercise testing and blood tests were performed 3 – 6 months after the coronary event. Physical inactivity was assessed according to the shortened version of the WHO questionnaire.
Result: After controlling for the potential con-founders physical inactive patients had significantly higher values of Von Willebrand factor ($p< 0,01$) and Factor VII antigen ($p< 0,02$) when compared to physically active patients. Fibrinogen levels showed a trend toward higher levels in the physically inactive patients ($p< 0,07$). Exercise capacity according to the results of bicycle-ECG showed an independent inverse relation to fibrinogen ($p< 0,03$) and PAI-1 ($p< 0,03$) plasma levels.
Conclusion: We found that physically inactive female CHD patients have a procoagulant bloodprofile. Plasma levels of Factor VII, von Willebrand, factor PAI-1 and Fibrinogen showed a statistically significant and independent relation to physical activity in middle aged women recently hospitalised for an acute coronary syndrome.

P1646 Agonistic autoantibodies against beta1-adrenergic receptor in serum of patients with peripartum cardiomyopathy

G. Wallukat[1], A. Damasceno[2], O. Foerster[3], C. Wegner[1], T. Christ[4], S. Bartel[1], G. Arif[3], K. Sliwa[3]. *[1]Max-Delbruck-Centrum f. Molek. Med., Berlin, Germany; [2]Eduardo Mondlane University, FacMed, Maputo, Mozambique; [3]University of the Witwatersrand, Chris Hani Baragwanath Hospital, Johannisburg, South Africa; [4]Technical University, Physiology, Dresden, Germany*

Introduction: Peripartum cardiomyopathy (PPCM) is a pregnancy associated disorder occurring between 1 month antepartum and 5 months postpartum. PPCM occurs 1:15,000 in Western Europe, but has an incidence of 1:1000 in South Africa. The etiology of PPCM is unknown. Autoantibodies (AAB) against the β1-adrenergic receptor (β1-AR) were recently shown to contribute to the development of dilated cardiomyopathy. We investigated the role of β1-AR AAB in the pathogenesis of PPCM.
Methods: We analyzed the activity of AAB against the β1-AR receptor in serum of PPCM patients from South Africa (SA, n=13), Mozambique (M, n=12) and Germany (G, n=1). Samples were analyzed at time of first presentation with the diagnosis of PPCM, after 3 months (M) and after 6 months (SA, M) of treatment. Patients received standard medical therapy for heart failure. The AAB were identified with a bioassay using cultured spontaneously beating neonatal rat cardiomyocytes. These cells respond to a β-adrenergic stimulation with an increase in beating rate.
Results: Analysis at baseline revealed the presence of agonist-like AAB (6.05±1.01 LU)
directed against β1-AR in the serum of all PPCM patients, but not in the serum of healthy controls. The agonistic effect was dose-dependent and inhibited by β1-AR antagonists. The effect was also neutralized by peptides corresponding to the second extracellular loops of the human β1-AR. The AAB recognized the RAESDE and DEARRCY epitopes on the second extracellular loop of the β1-AR and are immunoglobulins of the IgG2 and IgG3 subclasses. After 6 months (M, SA) a significant reduction ($p<0.0001$) of AAB activity was observed (2.46±1.41 LU). This diminution was accompanied - with the exception of two patients - with an improvement of cardiac function and NYHA functional class from IV or III to II or I. PPCM AAB caused a long-lasting agonistic effect without desensitizing the β1-AR. In the presence of AAB desensitisation of the β1-AR was even prevented after co-incubation with the β-adrenergic agonist isoprenaline. The β1-AR AAB of PPCM patients induce apoptosis in neonatal cultured rat heart cells via the CaM-Kinase und increase the Ca^{2+} current of the L-type Ca^{2+} channel of isolated human cardiomyocytes.
Conclusion: 1. Agonistic β1-AR AAB seem to play a role in the pathogenesis of PPCM. 2. Agonistic β1-AR AAB did not desensitize the β1-AR in PPCM patients. 3. β1-AR AAB were inhibited by β1-AR antagonists in this model, offering an explanation for the clinical benefit that PPCM patients experience on β-blocker therapy.

P1647 Comparison of endothelial functions with flow mediated dilatation in women with and without preeclampsia

N. Baris[1], M. Gol[2], A.Y. Goktay[3], C. Karas[2], C. Altay[3], B. Akdeniz[1], S. Guneri[1], N. Demir[2]. *[1]Dokuz Eylul University, Cardiology, Izmir, Turkey; [2]Dokuz Eylul University, Obstetrics and Gynecology, Izmir, Turkey; [3]Dokuz Eylul University, Radiology, Izmir, Turkey*

Background: Preeclampsia is characterized with hypertension and proteinuria during pregnancy. It was reported that women who experience preeclampsia are at a greater risk of atherosclerosis later in life compared with women who had normal pregnancies. The aim of the present study was to compare endothelial functions with flow mediated dilatation (FMD) method in women who had preeclampsia and normal pregnancy.
Methods: Ten women with the history of preeclampsia (mean age: 30.1±4.8) and 10 women who had normal pregnancy (mean age: 28.1±3.2) were enrolled in the study. Women who had risk factors for atherosclerosis such as smoking, hypertension, diabetes, hyperlipidemia, history of family, and history of vasoactive drug use were not included in the study. All women were examined with FMD and nitrate mediated dilatation(NMD) at least after 6 months of delivery. Consumption of caffeine was prohibited before examination. FMD and NMD were performed according to definition in previous studies. All examinations were performed at the follicular phase of menstrual cycle.
Results: Two groups were comparable for age (p=0,285). The percentage of FMD decreased significantly in the preeclamptic group compared to healthy controls. However, there was no significant difference in the percentage of NMD between the groups (Table).

Table 1. Comparison of endothelial functions in women with and without preeclampsia

	Preeclampsia (n=10)	Control (n=10)	p
FMD (%)	7,2±3,6	12,0±5,7	0,04
NMD (%)	16,9±8,6	19,5±11,9	0,586

Conclusion: Women with a history of preeclampsia have impaired endothelial functions compared to women with a previously healthy pregnancy. This may indicate increased risk of atherosclerosis in the following years of women who had a previous pregnancy with preeclampsia.

P1648 Endothelial dysfunction is present one year after a preeclamtic pregnancy

R. Rafik Hamad[1], M.J. Eriksson[2], A. Silveira[3], A. Hamsten[3], K. Bremme[1]. *[1]Karolinska University Hospital, Obstetrics and Gynecology, Stockholm, Sweden; [2]Klin fys, Dept. of Clinical Physiology, Stockholm, Sweden; [3]Karolinska Institute, Gustaf V Research Institute, Stockholm, Sweden*

Objective: Preeclamptic toxemia (PET) is associated with increased risk of cardiovascular disease in women later in life. We therefore hypothesised that women with a history of PET might have abnormal levels of markers of endothelial dysfunction or inflammation, reflecting either predisposition to preeclampsia or changes induced by the preeclamptic process.
Methods: 18 women with a history of PET and 17 age-matched healthy controls were investigated one year after delivery. All subjects underwent non-invasive ultrasound examination of the brachial artery for evaluation of flow-mediated vasodilatation (FMD), 24-hour blood pressure measurement (ABPM), and examination of blood lipoproteins, metabolic and haemostatic factors.
Results: Women with history of PET had lower FMD 2.5±3.0% compared to

10.3±2.0%, p<0.0001. APBM showed higher systolic, diastolic and mean arterial blood pressure during daytime in PET group 123±9 mmHg, 81±6 mmHg, 95±6 mmHg than in CTR 116±9 mmHg, 76±7 mmHg, 90±7 mmHg (p=0.02, p=0.03, p=0.03). Higher fasting glucose and insulin levels, 4.6(4.4-4.8) mmol/L, 46±20 pmol/L were found in PET compared to 4.4(4.3-4.6) mmol/L, 30±10 pmol/L in CTR (p<0.05, p<0.01). No significant differences were found in other metabolic, blood lipoproteins and haemostatic factors. In the PET group FMD measured one year after pregnancy correlated inversely with the maximal systolic blood pressure measured during index pregnancy (r = -0.470, p=0.049). FMD correlated significantly with gestational age and birth weight when PET and CTR groups were analysed together, r = 0.665, p<0,0001 and r = 0.746, p<0.0001.
Conclusion: Women with a previous history of PET, one year after index delivery, are at increased risk for developing cardiovascular disease because of endothelial dysfunction, higher blood pressure, and higher fasting insulin and glucose.

P1649 Statins reduce total and cardiovascular mortality in patients that underwent coronary artery bypass grafting surgery (CABG) despite their hypolipidemic effect

A. Papathanasiou, I. Toumpoulis, K. Pappas, I. Leontaridis, C. Katsouras, L. Mihalis, K. Kalantzi, J. Goudevenos. *University Hospital of Ioannina, Cardiology Division, Ioannina, Greece*

Purpose: It is known that statin therapy reduces mortality in patients with coronary artery disease. The aim of our study was to assess the association between statin therapy and mortality among patients that underwent CABG.
Methods: This was an observational study from Northwestern Greece. All 1870 dyslipidemic consecutive patients (1657 men, 212 women, mean age 58.7±9.6 years) from this region, who underwent a first CABG between 1986 and 2002, survived the first month and visited our outpatient clinic for scheduled examination within 6 months after the procedure, were enrolled in the study. All classical risk factors at the time of the surgery as well as administration of aspirin, ACEi, beta-blockers and statins after the procedure, during follow-up, were recorded. We used Cox proportional hazard analysis to calculate adjusted hazard ratios (HR) for patients receiving or not statin therapy and adjusted Kaplan-Meier survival curves were constructed for the 2 study groups.
Results: During a total of 9,345 patient-years follow up (median follow up 5,2 years, range 2-16 years), only 40% of patients were receiving statin therapy and in 50% of these total (TC) and LDL cholesterol target goal were achieved (TC <190 mg/dl, LDL-C <100 mg/dl). In addition, 222 deaths occurred. Of these 179 (80.6%) were due to cardiovascular causes. Futhermore, 467 MACE (non fatal NSTEMI, STEMI, ischemic stroke and a new revascularization procedure) recorded. In multivariate Cox regression analysis and after adjustment for all risk factors, age and use of aspirin, ACEi and b-blockers, the hazard ratio of total and cardiovascular mortality for patients receiving statin therapy was 0.478 (0.280-0.817 95%CI, p=0.007) and 0.429 (0.230-0.797 95%CI, p=0.007) respectively. Patients' levels of TC and LDL cholesterol showed no effect on long-term total and cardiovascular mortality (hazard ratios were 0.765, 0.464-1.263, 95%CI, p=0.295 and 0.802, 0.457-1.407, 95%CI, p=0.441 respectively). Finally neither statin administration, nor lipid profile during follow-up, altered hazard ratios for MACE (0.972 0.754-1.252 95%CI, p=0.825 and 1.063 0.865-1.306 95%CI, p=0.559 respectively). The estimated 16-year Kaplan Meier survival curves from total and cardiovascular causes, for the 2 study groups are diverged at 2-3 years and continued to diverge throughout the entire follow-up period.
Conclusions: In patients that underwent CABG, statin administration results in above 50% reduction of total and cardiovascular mortality. This reduction seems to not be correlated with their hypolipidemic effect.

P1650 Why is the hospital mortality of acute myocardial infarction higher in women than in men?

I. Durand-Zaleski[1], B.D. Dormont[2], C.M. Milcent[3], P.G. Steg[4]. *[1]French National Health Autority, Guidelines, Saint Denis La Plaine, France; [2]Thema UPX-Nanterre, Economics, Nanterre, France; [3]CNRS- PSE, Health Economics, paris, France; [4]Xavier Bichat Hospital, AP-HP, Cardiology, Paris, France*

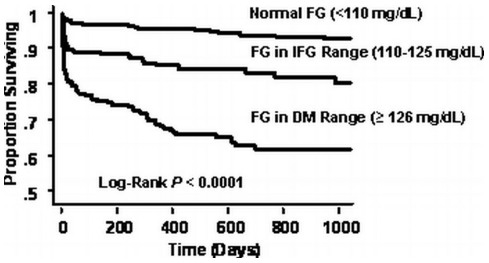
Background: The short-term mortality of acute myocardial infarction (AMI) is higher in women compared to men. Previous studies have found gender differences in the use of revascularization procedures and suggested these account for the gender differences in survival.
Objectives: to compare in-hospital gender-specific mortality for French patients hospitalized for an AMI (defined by ICD discharge diagnosis) and to identify predictors of treatment patterns and outcomes.
Methods: data were drawn from a comprehensive prospective nationwide payment database of all French hospitals in 1997 Demographic data, comorbidities, procedures and outcomes were recorded for each admission. Hospital characteristics (ownership, type, volume) were also studied. The outcome measure was in-hospital mortality. Logistic regression was performed to test whether the gender-specific mortality differed according to age, co-morbidities, use of procedures and hospital characteristics.
Results: A total of 44,260 AMI hospital stays were studied of which 69% were men and 31% women. Women were older (76 vs 65 years, p=p<10-3). In-hospital mortality was also higher for women (15% vs 7%, p=p<10-3). The use of procedures (coronary angiography and PCI) was higher in men than in women (43 vs 26%, 22 vs 12% respectively, p< 0.p<10-3 for both). Age-adjusted mortality was consistently higher in women for all age categories (p<10-3), except above 85 years, and remained higher after adjustment for comorbidities. Higher rates of revascularization procedures independently predicted reduced mortality (OR=0.4 for PCI). Thus, lower use of revascularization procedures in women accounts for some of their "excess" age-adjusted mortality compared to men. However, the "protective effect" was more marked for men than for women, at least in women below age 75. While men were more frequently admitted to for-profit centers or tertiary care centers than women, hospital characteristics did not account for the differences in mortality.
Conclusion: Our results confirm that, in France in 1997, the age-adjusted mortality of hospitalized AMI was higher in women than in men. This excess mortality is not entirely explained by differences in comorbidities, hospital characteristics or use of procedures during the index hospital stay. In fact, the somewhat reduced protection afforded by procedures in women compared to men suggest that biological gender differences may impact mortality and the effectiveness of procedures in this context.

RISK ASSESSMENT DIABETES/CAD

P1651 Fasting glucose is a powerful independent risk factor for long-term mortality in patients with acute myocardial infarction. A prospective study

M. Suleiman, H. Hammerman, M. Kapeliovich, Y. Agmon, M. Boulos, R. Beyar, W. Markiewicz, D. Aronson. *RAMBAM Medical Center, Cardiology Dept., Haifa, Israel*

Introduction: Stress hyperglycemia in patients (pts) with acute myocardial infarction (MI) has been associated with increased mortality. The majority of studies looked at the relationship between admission glucose and outcome, while the added prognostic importance of fasting glucose (FG) has not been prospectively explored. We studied whether an abnormal FG assessed early after an MI, is related to long-term prognosis.
Methods: We prospectively studied the relationship between FG and long-term mortality in 785 nondiabetic patients (pts) presenting with acute MI. FG was obtained >8 hours fast within 24 hours from admission. The pts were categorized into 3 groups: 1) FG in the normal range (<110 mg/dL), 2) impaired fasting glucose (IFG; 110-125 mg/dL), and 3) FG in the diabetes range (DM; ≥126 mg/dL). Cox proportional hazards analyses were performed to determine the relation between categories of FG and mortality adjusting for age, sex, baseline creatinine, hypertension, smoking, Killip class on admission, systolic blood pressure and heart rate on admission, anterior infarction, previous MI and reperfusion therapy.
Results: The median follow up was 23 months (range 6 to 42 months). Mortality rates were 6.2%, 17.0% and 36.6% in pts with normal FG, IFG, and FG in the DM range, respectively. Kaplan-Meier survival curves for the 3 study groups are shown in the Figure. Compared to normal FG, the adjusted RR for mortality was 2.7 in pts with FG in the IFG range (95% CI 1.5-4.6, P = 0.0005) and 4.5 in pts with FG in the DM range (95% CI 2.8-7.3, P < 0.0001).



Kaplan-Meier Survival Curve

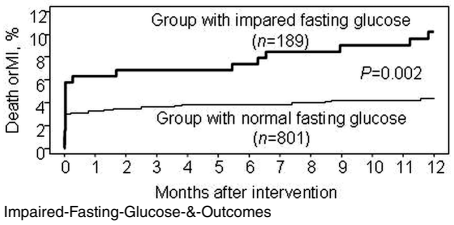
Conclusion: FG on admission is a powerful indicator of long-term prognosis in nondiabetic pts with acute MI. The risk for mortality increases markedly even with mild elevations of FG.

P1652 Prognostic value of impaired fasting glucose for the outcomes of patients with stable angina treated with percutaneous coronary interventions

A. Dibra[1], G. Ndrepepa[2], J. Mehilli[2], H. Bollwein[3], J. Hausleiter[2], J. Pache[2], A. Schoemig[2], A. Kastrati[2]. *[1]Deutsches Herzzentrum, Adult Cardiology, Munich, Germany; [2]Deutsches Herzzentrum, Adult Cardiology, Munich, Germany; [3]1. Medizinische Klinik rechts der Isar, Cariology, Munich, Germany*

Objective: To study the prognostic value of impaired fasting glucose (IFG) in the range 100-109 mg/dl, for patients with stable angina treated with percuataneous coronary interventions (PCI).

Background: IFG, a pre-diabetes category which defines the zone between the lower limit of diabetic fasting glucose and the upper limit of normal fasting glucose (NFG), is considered an important risk marker for cardiovascular disease. Previous studies, based on the first definition of the American Diabetes Association for IFG (fasting glucose 110-125 mg/dl), have reported worse outcomes among patients with IFG as compared with patients with NFG. There is no evidence on the prognostic value of the newly defined IFG range (fasting glucose 100-109 mg/dl) relative to the outcomes of patients with coronary artery disease undergoing PCI.
Methods: We studied a series of 990 consecutive patients who underwent PCI for stable angina. Two groups were defined according to fasting plasma glucose levels: IFG group (fasting glucose 100-109 mg/dl; 189 patients) and NFG group (fasting glucose <100 mg/dl; 801 patients). The primary endpoint of the study was the composite of death or myocardial infarction (MI) at one-year follow-up.
Results: One-year cumulative rate of death or MI was 10.3% in the IFG group and 4.4% in the NFG group (P=0.002). In the multivariate model, impaired fasting glucose was an independent predictor of the occurrence of death or MI: adjusted hazard ratio, 2.30 [95% confidence interval, 1.30-4.07], P=0.004.



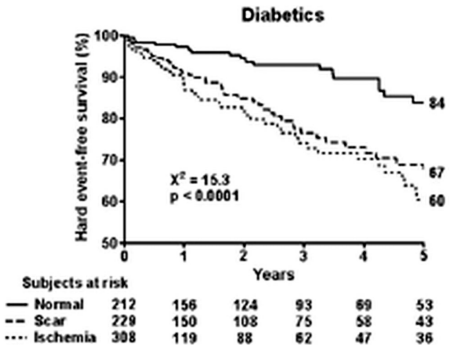
Impaired-Fasting-Glucose-&-Outcomes

Conclusions: The presence of IFG in the range of 100-109 mg/dl among patients with stable angina who undergo percutaneous coronary interventions may identify a patient subset with an increased risk of death or MI.

P1653 Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease

L. Cortigiani[1], R. Bigi[2], R. Sicari[3], P. Landi[3], F. Bovenzi[2], E. Picano[4]. *[1]Ospedale C. di Marte, Cardiologia, Lucca, Italy; [2]University School of Medicine, Cardiology Unit, Milan, Italy; [3]Institute of Clinical Physiology, CNR, Pisa, Italy; [4]CNR Institute of Clinical Physiology, Pisa, Italy*

Background: although stress echocardiography is a useful tool for risk stratification of diabetic patients, it has not been established whether it retains the same prognostic information in diabetics as compared to nondiabetics.
Aim: to compare the prognostic value of pharmacological stress echocardiography in patients with and without diabetes mellitus and known or suspected coronary artery disease.
Methods: 5456 patients (749 diabetics) undergoing dipyridamole (n=3306) or dobutamine (n=2150) stress echocardiography at two different institutions were prospectively followed-up for the occurrence of hard events (death and/or nonfatal myocardial infarction).
Results: During a median time of 31 months, 411 (7.5%) deaths and 236 (4.3%) nonfatal infarctions were observed. One hundred thirty-two events occurred in diabetics and 515 in nondiabetic (18% vs 11%; p<0.0001). Moreover, 1607 (29%) patients underwent coronary revascularization and were censored. Ischemia at stress echo, resting wall motion score index, and age were independent predictors of death and hard events in both diabetic and nondiabetic patients. Compared to a normal test, ischemia and scar test patterns were associated to significantly lower age-corrected 5-year hard event-free survival both in diabetic (figure) and in nondiabetic patients. However, a normal test was associated with greater than 2-fold annual event rate in diabetics as compared to nondiabetics either younger (2.6 vs 1.0%) or older (5.5 vs 2.2%) than 65 years.



Conclusions: Stress echocardiography is equally effective in risk stratifying diabetic and nondiabetic patients independently of age. However, the normal test result predicts a less favourable outcome in diabetics than in nondiabetics.

P1654 Hypoglycemia during hospitalisation – important risk marker of mortality in diabetic patients with acute coronary events

A. Svensson[1], D.K. McGuire[2], P. Abrahamsson[1], M. Dellborg[1]. *[1]Sahlgrenska University Hospital/Ostra, Clinical Experimental Research Laboratory, Gothenburg, Sweden; [2]University of Texas-Southwestern, Donald W Reynolds Cardiovasc. Clin Res, Dallas, United States of America*

Background: Diabetes mellitus is associated with an increased mortality for patients with coronary artery disease, and hyperglycemia at the time of presentation and during the hospital course for acute coronary syndrome (ACS) events independently predicts adverse outcomes. Whether hypoglycemia documented during hospitalization is similarly predictive remains unclear.
Methods: The study objective was to investigate whether an independent association exists between hypoglycemia during hospitalization and long-term survival in a cohort of 713 consecutive DM patients with an ACS event treated at a single center 1988-1998. The primary study endpoint was 2-year mortality collected from the Swedish cause-specific mortality register. Patients were categorized based on the lowest blood glucose measurement recorded during hospitalization into three groups: low (i.e hypoglycemic; < 3.0 mmol/L; n=44); intermediate (3.1 to 6.5 mmol/L; n=364); and high (i.e persistently hyperglycemic; > 6.6 mmol/L; n=276). Multivariable Cox proportional hazard modeling was used to analyze the association between admission glucose measurements, lowest recorded glucose measurements, and clinical outcomes, adjusted for known risk factors.
Results: Mean age was 70.1 ± 10 yrs with 38% female. Mean (SD) lowest blood glucose was 6.5 ± 3.1 mmol/L. Compared with the intermediate group, both the hypoglycemic and the persistently hyperglycemic groups had significantly higher adjusted 2-year mortality risk (table).

Lowest blood glucose, during hospital stay	Unadjusted (a) Hazard Ratio (95% CI)	Adjusted (a,b) Hazard Ratio (95% CI)
Hypoglycemic	1.77 (1.09-2.86)	1.93 (1.18-3.17)
Persistently hyperglycemic	1.60 (1.22-2.11)	1.48 (1.09-1.99)

a) Cox proportional hazard model, with reference group = "intermediate" (lowest glucose 3.1 to 6.5 mmol/L); b) adjusted for age, sex, DM duration, ACS type, creatinine, on-arrival glucose, year of study entry, hypercholesterolemia, hypertension, peripheral vascular disease, smoking status, prior MI, prior CHF, prior coronary revascularization, and b-blocker use at discharge.

Conclusion: Among patients with DM admitted for an acute coronary event, a U-shaped relationship exists between lowest documented blood glucose and 2-year all cause mortality, with both documented hypoglycemia and persistent hyperglycemia independent predictors of risk for 2-year mortality.

P1655 Admission blood HbA1c levels in acute myocardial infarction patients: association with coronary risk factors, myocardial perfusion abnormalities and angiographic morphology on 4-week follow-up

M. Cakmak[1], A. Emre[2], N. Cakmak[2], S. Cetemen[2], D. Oz[2], U. Filizcan[2], U. Gurkan[2], B. Ersek[2]. *[1]Üsküdar, Turkey; [2]siyami ersek hospital, cardiology, Istanbul, Turkey*

Background: Admission blood glucose level is a prognostic factor after myocardial infarction (MI) in patients with and without diabetes. We examined the relation of admission blood HBA1c to myocardial perfusion and coronary morphology at 4-week follow-up.
Methods: Blood specimen was obtained for HbA1c measurement from 100 patients (29 female, 71 male patients, mean age 60±10 years) within 6 hours of admission of MI. All patients underwent coronary angiography and exercise thallium scintigraphy 4 weeks after the acute episode. SPECT images were interpreted using 20 segments with a 5-point scale (0=normal, 4=no uptake). Total perfusion (TPS) and ischemic scores (TIS) were derived by adding the score of all segments.
Results: Mean admission glucose and HBA1c levels were 230±74 mg/dl and 8.4±1.3 mg/dl, respectively. Those with >3 coronary risk factors had higher HBA1c levels (9.1±1.6 vs 7.7±1.7, p=0.02). Blood HbA1c levels did not show statistically significant correlation either with TPS or TIS (r=0.48, r=0.38,p=NS) in the study group as a whole. However, a relatively strong correlation was observed between HbA1c levels and TPS in patients with hypercholesterolemia (HCL) (r=0.61, p<0.01). HbA1c levels were also related to TIS in the HCL group (r=0.53,p<0.05).Stepwise multiple regression analysis showed that HbA1c was a strong determinant of perfusion in patients with HCL only (β=0.52, p=0.01). HbA1c was not related to the angiographic extent of CAD as defined by the number of vessels involved.
Conclusion: In AMI patients with hypercholesterolemia, admission HbA1c levels are associated with a greater degree of perfusion abnormalities but not with the angiographic extent of CAD.

P1656 Contemporary prognosis of angina: multi-centre outcome analysis of 8762 patients attending rapid access chest pain clinics

N. Sekhri[1], G. Feder[2], C. Junghans[3], H. Hemingway[3], S.C. Cotter[2], A.D. Timmis[4]. *[1]Newham General Hospital, Dept Cardiology, London, United Kingdom; [2]Royal Hospitals Trust, Department of General Practice, London, United Kingdom; [3]University College, Dept Epidemiology and Public Health, London, United Kingdom; [4]London Chest Hospital, Dept. of Cardiology, London, United Kingdom*

Background: Rapid chest pain assessment is now a priority in many countries, based on the assumption that it successfully identifies those with angina whose risk of adverse events is increased. This assumption is unproven, and the prognosis of angina in this group of patients is unknown.
Methods: Multi-centre cohort study of 8762 first time attendees at rapid access chest pain clinics with undiagnosed chest pain. Patients known to have coronary disease (previous ACS, revascularization or diagnostic angiography) were excluded. Median (IQR) follow-up was for 2.57 (1.96-4.15) years.
Results: Angina was diagnosed in 27% of the cohort. These patients were older and more frequently male and white than patients diagnosed with noncardiac chest pain. In angina, adjusted hazard ratios for CHD death and non-fatal MI were 1.87 (1.13-3.10), rising to 4.69 (3.34-6.59) for hospital admission with unstable angina. Standardised mortality ratios (SMRs (95% CI)) for coronary death in patients with angina were significantly increased in both men (203 (151-255)) and women (218 (136-301)), particularly those aged <65 years (354 (203-506) and 476 (146-806)). However, SMRs for non-cardiac causes of death (cancer, COPD) were lower than the general population, indicating "selection by fitness" of patients referred for rapid chest pain assessment. The heightened risk for patients diagnosed with angina was reflected in an annualised cardiovascular mortality rate of 1.6%, similar to the "high-risk" HOPE population (1.6%) but higher than the "low risk" EUROPA (0.9%), ACTION (1%), and PEACE (0.8%) populations.
Conclusion: This study has provided the most contemporary estimate available of the prognosis of incident angina in the community. Despite the conservative nature of the estimate – based on the selection by fitness we identified – those patients diagnosed with angina were at high cardiovascular risk compared with the general population and the participants in recent clinical trials. The findings have confirmed the importance of rapid chest pain assessment for identifying patients at increased risk.

P1657 Can patients presenting with chest pain in primary care be successfully triaged without hospital admission?

C.L. Murphy[1], T. Stanton[1], S.K. Glen[1], J. Spratt[1], J.J.V. McMurray[2], A.B. Bridges[1]. *[1]Stirling Royal Infirmary, Dept of Cardiology, Stirling, United Kingdom; [2]Western Infirmary Glasgow, Dept of Cardiology, Glasgow, United Kingdom*

Primary care practitioners(PCPs)find triage of chest pain difficult.This leads to unnecessary admissions with non-coronary chest pain or low-risk coronary heart disease(CHD). Conversely,high-risk CHD may not be recognised and essential preventive and therapeutic interventions delayed.One solution is the provision of a Rapid Access Chest Pain Clinic(RACPC), where patients are seen at short-notice for assessment and an exercise tolerance test(ETT–full Bruce protocol).
Purpose: a measure of the success of such a clinic is whether patients identified as at low risk have a good long-term prognosis.We describe the outcomes of a RACPC run for 5 years by PCPs within a hospital Cardiology department.
Methods: this analysis describes all patients seen between April 1999-April 2004. Patients were categorised into 5 groups according to their ETT result,and a sixth group consisted of those deemed unsuitable to undergo an ETT.
Categories: 1)"Negative ETT"ie.target heart rate(HR)and predicted exercise duration(PED)achieved,with no cardiac symptoms(CS)or ECG abnormalities. 2)"Positive ETT-not requiring admission"ie.CS or ischaemic ECG changes;managed >6 minutes.3)as 2 but managed <6 minutes.4)"Positive ETT–requiring admission" ie.ischaemic ECG changes <3 mins or life threatening arrhythmia at any stage. 5)"Inconclusive"ie.unable to achieve target HR or PED due to poor mobility/effort,but no ischaemic ECG changes or CS.6)"Unsuitable for ETT" ie new diagnosis of aortic stenosis/arrhythmia.
Results: of 4692 patients referred, 4219(90%)had an ETT.Patient outcomes are shown in the table.

Table Of results

Category	No. of patients	Death No. (%)	Myocardial Infarction No. (%)
-ve ETT.	2788	28(1.0)	20(0.7)
+ve ETT at >6mins.Not requiring admission.	288	5(1.7)	2(0.7)
+ve ETT at <6mins. Not requiring admission.	529	15(2.8)	12(2.3)
+ve ETT requiring hospital admission.	109	9(8.3)	26(23.9)
Inconclusive ETT.	505	12(2.4)	7(1.4)
Unsuitable for ETT.	473	26(5.5)	15(3.2)

Conclusions: this long-term follow up of a large cohort of patients referred to a RACPC shows that this model effectively triages patients with chest pain in primary care, appropriately and safely reassuring the majority of whom,do not have high risk CHD or need hospital admission.

P1658 Complement component C5a predicts future cardiovascular events in patients with advanced atherosclerosis

W.S. Speidl[1], M. Exner[2], J. Amighi[1], O. Wagner[2], E. Minar[1], K. Huber[3], J. Wojta[1], M. Schillinger[1]. *[1]Medical University of Vienna, Department of Internal Medicine II, Vienna, Austria; [2]Medical University of Vienna, Department of Laboratory Medicine, Vienna, Austria; [3]Wilhelminenspital, 3rd Medical Department, Vienna, Austria*

Background: Activation of complement may occur in atherosclerotic lesions and the complement component C5a exerts strong chemotactic and proinflammatory effects. Whether plasma levels of C5a may predict risk in patients with advanced atherosclerosis is not known.
Methods: We studied 173 patients with symptomatic peripheral artery disease (median age 72, 82 male). Cardiovascular risk profile, levels of complement factor C5a and other inflammatory parameters (high sensitivity CRP [hs-CRP], serum amyloid A [SAA], fibrinogen) were obtained at baseline, and patients were followed for median 22 months (interquartile range 13 to 27) for the occurrence of major adverse cardiovascular events (MACE: myocardial infarction, percutaneous coronary interventions, coronary artery bypass graft, carotid revascularization, stroke, and death).
Results: We observed 65 MACE in 49 patients (28%). Cumulative event-free survival rates at 6, 12, and 24 months were 93%, 85%, and 71%, respectively. Adjusted hazard ratios for the occurrence of MACE according to increasing quartiles of C5a were 1.93 (p=0.20), 2.53 (p=0.050) and 2.88 (p=0.023), respectively, as compared to the lowest quartile, irrespective of the level of other unspecific inflammatory parameters.
Conclusion: Complement activation, indicated by elevation of C5a, seems to contribute to the cardiovascular risk of patients with advanced atherosclerosis. Determination of C5a may add to the predictive value of other inflammatory parameters.

P1659 High sensitivity C-reactive protein and its G/C genetic polymorphism in patients with angina pectoris

H. Mohamed Fereig Hamed, S. Abd El-Shafee, W. Radwan. *Cairo, Egypt*

The role of bacterial and non-bacterial inflammation in the pathogenesis of unstable angina has been lately a subject of increasing interest. Indirect evidence for inflammation in disturbed athermanous plaques has been suggested by elevated levels of various inflammatory markers like high sensitivity C-reactive protein (hs-CRP). The purpose of this study is to assess the relation of hs-CRP level to the number of coronary vessels affected, and to detect which of its genotypes is associated with more extensive coronary artery disease (CAD) in patients with angina pectoris.
Methods: we studied 80 patients (pts) with angina pectoris, 39 pts with stable angina (SA) and 41 pts with unstable angina (UA). Twenty healthy normal (NL) subjects served as a control group. Diagnostic coronary angiography was performed to confirm the presence of CAD in all ischemic pts and to determine the extent of CAD expressed in terms of number of vessels affected. Mean values of hs-CRP were measured in all study cases. The polymerase chain reaction (PCR) technique was applied to assess hs-CRP genotype in 66 of the ischemic pts and 15 of NL group.
Results: The value of hs-CRP was significantly higher in pts with UA compared to those with SA (1.7 ± 0.47 versus 0.6 ± 0.1 mg/dl ($p<0.05$), and also compared to NL subjects in whom the hs-CRP was 0.3 ± 0.07 mg/dl ($p<0.05$). The difference in hs-CRP between pts with SA and NL subjects was not significant. Correlated with extent of CAD, hs-CRP level was higher with more number of vessel affected in both pts with SA and UA. Subdivided according to CRP genotype pattern, the mutant polymorphic GC pattern was shown in only 7 pts (5 UA & 2 SA). The rest of pts and all NL subjects had GG pattern. The mean value of hs-CRP was significantly higher in GC carriers compared to GG carriers (1.15 ± 1.09 versus 0.43 ± 0.37 $p< 0.001$). The GC polymorphic genotype level was significantly associated with multivessel disease compared with GG genotype ($p = 0.001$).
Conclusion: The level of hs-CRP increases with the increase in the extent of CAD especially in UA patients. GC genotype is associated with more extensive CAD than the GG genotype, highlighting a subset of pts necessitating more aggressive therapy or more urgent intervention.

P1660 Circulating intercellular adhesion molecule-1, vascular cell adhesion molecule-1,E-selectin ,P-selectin, TNFa, VEGF, IL-6 in patients with coronary artery disease at rest and after a treadmil test

K. Tsoutsoumanou, G. Apostolakis, A. Sfiridaki, A. Dermitzakis, A. Koziri, L. Ploumidis, M. Grigoraki, K. Meidanis. *General Hospital Venizeleio, Cardiology Clinic, Herakleion, Greece*

Background: It has been shown that endothelial cell adhesion molecules play an important role in the development of coronary atherosclerosis and inflammatory disease.
Purpose: We sought to test whether soluble vascular cell adhesion molecules (VCAM-1), intercellular adhesion molecule (ICAM-1), cytokines (IL-6, TNFa) and

selectins (P-selectin, E-selectin) are increased in patients with documented coronary artery disease and to assess whether these markers of inflammation increased after exercise.
Methods: Plasma levels of the soluble endothelial adhesion molecules ICAM-1,VCAM-1,E-selectin,P-selectin,TNFa,VEGF,IL-6 were measured in venous blood samples taken before and 7 min after the treadmill test. The study groups consisted of 73 patients (mean age 56.5±12.7 years) : 24 patients with coronary artery disease (group A),33 patients with coronary risk factors (group B),and 16 healthy persons (control group C).
Results: Patients with CAD and in patients with risk factors for CAD pre and post exersice concentrations of ICAM were significally higher in comparison with control group. The patients with CAD had lower ($p<0.05$) circulating levels of VEGF pre and post exersice compared with healthy persons. However these was no difference in the levels of VCAM-I, E-selectin,P-selectin,TNFa,and IL-6 between the patients with CAD or with coronary risk factors and normal control subjects (table).

pre Treadmil test	VCAM-1	ICAM-1	E-Selectin	P-Selectin	TNF-a	VEGF	IL-6
Pre Treadmil test							
A. CAD	690,71	261.07	39.19	141.42	8.42	270	4.60
n=24	±215.31	±105.19	±17.86	±48.01	±0.99	±152.41	±1.87
	p<0,26	p<0.08	p<0.39	p<0.34	p<0.04	p<0.04	p<0.11
B. Risk patients	768.60	276.73	70.88	170	8,661	397.82	3.7
n=33	±248.52	±105.4	±90.88	±74.84	±1.54	±226.21	±0.71
	p<0.46	p<0.03	p<0.21	p<0.13	p<0.31	p<0.29	p<0.41
C. Control	758	190.16	37.03	131.66	8.3	460	2.63
n=16	±205.47	±332.24	±12.76	±12.17	±0.98	±342.92	±2.54
Post Treadmil test							
A. CAD	758.71	265.14	39.19	141.42	8.42	270	4.60
n=24	±361.33	±110.87	±16.19	±91.36	±1.73	±176.80	±1.13
	p<0.20	p<0.04	p<0.34	p<0.32	p<0.32	p<0.03	p<0.08
B. Risk patients	807.86	282.76	58.06	168.04	9.53	413.26	5.66
n=33	±356.73	±97.56	±	±65.13	±2.21	±235.11	±7.34
	p<0.18	p<0.008	p<0.14	p<0.26	p<0.29	p<0.19	p<0.22
C. Control	726.25	187.33	36.42	158	9.2	498.33	3.37
n=16	±146.86	±61.61	±16.07	±65.95	±2.87	±330.55	±0.20

Conclusion: These results confirm that soluble markers of endothelial injury are uniformly increased in patients with documented CAD as compared to those with coronary risk factors and healthy controls. High levels of ICAM-I and, low levels of VEGF could indentify endothelial injury in such patients.

P1661 Relationship between plasma levels of soluble receptor for advanced glycation end products (sRAGE) and coronary artery disease

C. Falcone[1], E. Emanuele[2], A. D'Angelo[3], P. Buzzi[4], M. Calcagnino[4], C. Belvito[4], A. Repetto[5], D. Geroldi[2]. *[1]IRCCS Policlinico S.Matteo, University of Pav, Cardiology Department, Pavia, Italy; [2]University Hospital, Interdipartimental Center for Research, Pavia, Italy; [3]IRCCS, Policlinico S.Matteo, Dep. Internal Medicine, Pavia, Italy; [4]Pol S Matteo IRCCS/University of Pavia, Cardiology, Pavia, Italy; [5]Policlinico San Matteo, Cardiology, Pavia, Italy*

The receptor for advanced glycation end products (RAGE) is a cell surface receptor whose signalling pathway has been implicated in atherogenesis. RAGE has an endogenous secretory receptor form, called soluble RAGE (sRAGE), that could exert antiatherogenic effects by acting as a decoy. We sought to determine whether a decreased plasma level of sRAGE could be independently associated with the prevalence of coronary artery disease (CAD) in nondiabetic men.
Methods: Plasma concentrations of sRAGE were determined in 328 nondiabetic male patients with angiographically proved CAD and in 328 age-matched healthy controls. Plasma sRAGE levels were measeured by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit.
Results: The concentration of sRAGE in plasma was significantly lower ($P<0.0001$) in CAD cases [median (interquartile range): 966 (658-1372) pg/mL] than in control subjects [1335 (936-1495) pg/mL]. In the first quartile (plasma sRAGE level <776 pg/mL), the number of CAD patients was 2.64-fold higher that of the control subjects ($P<0.0001$). On the other hand, the number of CAD patients in the fourth quartile (plasma sRAGE level >1647 pg/mL) was near three times lower than the control subjects ($P<0.0001$). In logistic regression analysis, the multivariate-adjusted odds ratio for the presence of CAD was 6.719 (95% CI, 3.773 to 11.964, $P<0.0001$) when the lowest quartile of the sRAGE level was compared with the highest quartile.
Conclusions: Our findings indicate that low levels of sRAGE in plasma are independently associated with the presence of CAD in nondiabetic men and suggest that sRAGE is one of the clinically important molecules associated with atherosclerosis.

P1662 Toll-like receptor 4 expression on peripheral blood monocytes predicts the risk of coronary artery disease in patients with low C-reactive protein

R. Shiraki, N. Inoue, K. Otsui, T. Honjo, T. Takahashi, S. Kawashima, M. Yokoyama. *Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Kobe, Japan*

Purpose: Toll-like receptors (TLRs) are pathogen-associated protein recognition molecules, that have important roles in the pathogenesis of atherosclerosis. On the other hand, C-reactive protein (CRP) is an independent coronary risk factor, and subjects with serum high-sensitivity CRP (hsCRP) levels under 1mg/L are defined as a low risk group. Cardiovascular events do occur, however, even in subjects with low hsCRP levels. In the present study, we investigated whether TLR4 expression on human peripheral blood monocytes (PBMCs) and serum hsCRP levels predict the occurrence of coronary artery disease (CAD).
Methods: Blood samples were isolated from 80 CAD patients and 80 non-CAD subjects (control group). The serum levels of hsCRP and the TLR4 expression level on PBMCs were quantitatively investigated by enzyme-linked immunosorbent assay and flow cytometry, respectively. To evaluate the TLR4 expression on PBMCs, mean fluorescent intensity (MFI) was determined and the ratio of TLR4 MFI to negative control MFI was calculated.
Results: Serum hsCRP in the CAD patients was higher than in the control group. There were, however, 41 patients with serum hsCRP levels under 1mg/L among the CAD patients. Among the subjects with low serum hsCRP, the TLR4 expression on PBMCs was higher in CAD patients than in the control group (1.32 [1.13-1.71] vs 1.20 [1.08-1.35]; the ratio of TLR4 MFI to negative control MFI, $p<0.05$, after adjustment for other coronary risk factors). Moreover, CAD occurred in subjects with a higher TLR4 expression level on PBMCs more often than in subjects with a lower expression level. The odds ratio of the TLR4 expression level on PBMCs for the CAD group compared to the control group was 10.7 in the total population and 29.2 in the low-hsCRP subjects.
Conclusions: Even in subjects with low serum hsCRP, the TLR4 expression level on PBMCs in the CAD group was significantly higher than that in the control group. Thus, the combined measurement of serum hsCRP and the TLR4 expression on PBMCs, especially among low-hsCRP subjects, might predict coronary risk more precisely than hsCRP alone.

P1663 Angiotensin converting enzyme inhbitors modify vascular endothelial growth factor expression and circulating levels in patients with stable coronary artery disease

M.E. Marketou[1], D. Panutsopulos[2], E.A. Zacharis[1], G.E. Kochiadakis[1], D. Arfanakis[1], D.A. Spandidos[1], P.E. Vardas[3]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University, Laboratory of Virology, Heraklion, Greece; [3]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: The renin-angiotensin system has been implicated in the development and progression of atherosclerosis. Vascular endothelial growth factor (VEGF) is a key component in both inflammatory angiogenesis and atherosclerotic plaque progression. We investigated the effect of perindopril – a long-acting angiotensin converting enzyme inhibitor (ACE-i) - on the circulating protein levels and the expression of VEGF mRNA in patients with stable coronary artery disease (CAD).
Methods: Twenty patients (14 male, aged 68 ± 9 years) with stable angina lasting > 6 months and without clinical evidence of heart failure or uncontrolled hypertension were randomly assigned to receive treatment with either 4 mg perindopril (n= 10) or placebo (n= 10). Blood samples were taken before and 3 months after therapy initiation. Mononuclear cells were isolated using anti-CD14+ antibodies and mRNAs were estimated by real-time quantitative reverse transcriptase-PCR (TaqMan). VEGF serum levels were determined each time by ELISA.
Results: There were no significant baseline differences in mononuclear VEGF expression and serum levels between the two groups (p=NS, for both). Treatment with perindopril significantly reduced VEGF mRNA and serum levels. (see Table 1).

Table 1

	Perindopril		Placebo	
	Baseline	3 months	Baseline	3 months
mRNA VEGF (unitless)	8.3 ± 2.2	6.1 ± 3.2*	7.2 ± 4.3	7.4 ± 5.1
VEGF serum levels (pg/ml)	279 ± 102	194 ± 82*	354 ± 126	368 ± 158

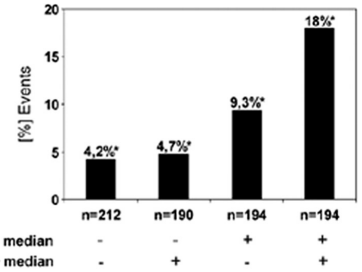
*: $p< 0.05$ compared to baseline values

Conclusions: Treatment with perindopril results in a significant attenuation in VEGF expression and circulating levels in patients with stable CAD. Our findings may afford a better understanding of the anti-atherogenic effects of ACE-i.

P1664 Complementary prognostic role of coronary angiography score and C-reactive protein levels in patients with stable coronary artery disease

R. Arroyo-Espliguero[1], P. Avanzas Fernandez[2], J. Quiles[3], J.C. Kaski[4]. *[1]Hospital de Guadalajara, Division of Cardiology, Guadalajara, Spain; [2]Hospital Central de Asturias, Division of Invasive Cardiology, Oviedo, Spain; [3]Hospital de San Juan, Cardiology, Alicante, Spain; [4]Coronary Artery Disease Research Unit, London, United Kingdom*

Background and aims: Most coronary occlusions resulting in acute events occur at the site of non severe stenoses. We assessed the prognostic value of non obstructive coronary artery stenoses and C-reactive protein (CRP) levels in patients with chronic stable angina (CSA).
Material and Methods: We studied 790 consecutive patients with CSA undergoing coronary angiography. The composite endpoint of acute myocardial infarction, unstable angina and cardiac death was assessed at one year follow-up. CRP measurements were performed at study entry. Severity and extent of CAD were assessed according to the Sullivan method.
Results: During the follow up period, 71 patients (9%) had at least one of the events comprised in the combined study end-point. Patients who suffered adverse events had a significantly higher vessel score (2.0[1.0-3.0] vs. 1.0[0.0-2.0], P<0.001), extension score (23.5 [17.0-34.5] vs. 16.0 [6.0-27.0], P<0.001) and CRP levels (mg/L) (3.0[1.8-7.2] vs. 2.3 [1.1-4.7], P=0.001) compared to patients without events. After adjustment using logisitc regression, extent score (OR 4.4 [2.3-8.4] CI 95%; P<0.001) and CRP levels (OR 1.8 [1.1-3.0] CI 95%; P=0.04) remained the independent predictors of the combined end-point. Figure 1 shows significant differences in percentages of events among patients classified according to the medians of extent score (17%) and CRP levels (2.4 mg/L).



Figure

Conclusion: Angiographic extent of CAD and CRP levels predict adverse events in patients with CSA, regardless of the number of severe flow-limiting coronary artery stenoses. Our results indicate that CRP levels and disease extent score, a measure of the diffuse coronary artery atheromatous burden, are both independent and additive predictors of cardiovascular risk in angina patients.

P1665 Circulating thrombomodulin in ischaemic heart disease. Correlation with the extent and severity of coronary atherosclerosis

A. El Naggar[1], A. Rizk[2] on behalf of CCC. *[1]Cairo University Hospitals, Critical Care Department, Cairo, Egypt; [2]Cairo University Hospital, Critical Care Dept., Cairo, Egypt*

Abnormal endothelial physiology has been implicated both in early atherogenesis and later, in the control of dynamic plaque behavior.The biologic link between endothelial damage and atherosclerosis may be related to decreased arterial bioavailability of NO,which may predispose to leucocyte and platelet adhesion, vasoconstriction and smooth muscle cell proliferation.
Substances released by the endothelium include prostacyclin,NO, endothelin, VWF & thrombomodulin TM, etc.Thrombomodulin is an integral membrane glyco protein that can change the function of thrombin,to an anticoag-ulant through activation of the protein C which, in the presence of protein S inactivates fVIIIa and fVa, &thereby inhibits further formation of thrombin. Soluble TM is thought to indicate endothelial-cell damage.A positive relation between the conc of soluble TM & the risk of atherosclerotic disease is widely assumed.
Aim of the study is to assess the diagnostic role of circulating TM as a marker of the extent & severity of CAD,we studied 150 pts with IHD,(118M,32F) with a mean age of (53.4 + 8.3),together with 20 nonischemic pts who were catheterized prior to valve replacement(13M,7F} a mean age of(58.4+ 4.5)) serving as controls.Out of 150 ischemic pts,77 had anginal pain& 73 had AMI.
Following clinical evaluation,12leads ECG,chest X ray, all pts were subjected to routine lab and coronary angio to assess the extent&severity of the senotic lesions using Gensini scoring system.All pts had TM levels, measured in arte rial samples withdrawn from coronary artery during catheter procedure using ELISA.Compared to controls,ischemic pts exhibited significantly higher levels of plasma TM (42.5+ 15.4 vs 2.8+ 0.8, p < 0.0000), with progressively higher levels of plasma TM from anginal Gp than AMI Gp (35.7+11.3) vs 49.6+16.1 with p< 0.000001).TM correlated significantly with the severity of coronary artery pathology,expressed as Gensini score with p<0.000 for angina Gp & p<0.000 for AMI Gp. Again, both Gps exhibited significant correlation between TM level and the number of diseased vessels with p<0.000 for both Gps.In conclusion: TM,an endothelial glycoprotein resulting from the damage to vascular endothelium by the atheromatous process,showed significant correlation with the extent and severity of CAD (expressed by Gensini score system).The higher TM level in AMI Gp compared to AP Gp points to the more significant endothelial damage in the former compared to the latter that stresses the importance of TM as a mole cular marker of endothelial dysfunction in Acute Ischemic Syndromes.

P1666 Abnormalities in T wave morphology is associated with disease severity in patients with coronary artery disease

Y. Gang[1], K. Hnatkova[2], A. Ghuran[2], S. Jones[3], A.J. Camm[2], M. Malik[2]. *[1]St. George's Hospital Medical School, Cardiac and Vascular Sciences, London, United Kingdom; [2]St. George's Hospital Medical School, Cardiac and Vascular Sciences, London, United Kingdom; [3]St. George's Hospital, London, United Kingdom*

Background: T wave morphology (TWM) descriptor, especially the 3D QRS-T angle, is a powerful risk stratifier in patients (pts) after myocardial infarction (MI). Data on TWM analysis in pts with coronary artery disease (CAD) without MI are scanty, and the relation of left ventricular function (LVF) to TWM has not been fully investigated.
Methods: Digital 12-lead ECGs were recorded from 192 pts with angiographically documented CAD, including 103 pts with stable angina (SA), 68 post MI pts (MI) and 21 pts with both MI and ventricular tachycardia or fibrillation (VT). TWM analysis was performed from 12-lead ECGs in a fully automatic manner using custom developed software. Three TWM descriptors (T wave complexity ratio, CR; TWM dispersion, TMD; the 3D angle between QRS complex and T wave vectors, i.e. total cosine R-to-T, TCRT) were derived from each ECG.
Results: Significant differences were found in CR (p=0.006), TMD (p=0.000) and TCRT among normal control (NC), SA, MI and VT (corresponding TCRT 0.53±0.04, 0.33±0.06, 0.10±0.07, -0.20±0.15, p=0.000); between NC and other 3 groups, and between SA and MI or VT (p<0.05 for all). TMD was significantly greater in VT compared to MI (p<0.05). When all pts with impaired LVF were excluded, similar results were found in CR and TMD (table). VT and MI showed significantly greater TMD compared to SA (p<0.05). Weak correlation between CR, TMD, TCRT and age were found (r=0.23, 0.24 and –0.19, respectively, p<0.05). No correlation was found between number of diseased vessels and any TWM indices. There was weak correlation between LV function and these indices (r=-0.32 – 0.47). There were no differences in any indices between pts on and not on beta-blockers.

Comparison of TWM measurements

mean (se)	Group	NC	SA	MI	VT
CR	impLVF	0.143 (0.007)	0.164 (0.010)	0.199 (0.013)	0.266 (0.037)
	norLVF	0.143 (0.007)	0.148 (0.008)	0.189 (0.019)	0.321 (0.094)
TMD	impLVF	11.48 (0.74)	22.60 (2.30)	41.82 (3.62)	56.94 (5.78)
	norLVF	11.48 (0.74)	18.61 (2.13)	35.70 (5.11)	60.53 (15.63)

impLVF=pts with impaired left ventricular function; norLVF=pts with normal left ventricular function

Conclusions: TWM abnormalities are associated with poorer myocardial preservation and arrhythmic substrate. TWM analysis can provide important information for assessment of clinical outcome in CAD.

P1667 Influence of the Renin Angiotensin System genes polymorphism and its associations in the risk of early coronary artery disease

R. Palma dos Reis[1], A.I. Freitas[1], S. Freitas[1], A.C. Sousa[1], S. Gomes[1], A. Almada Cardoso[1], A. Brehm[1], M. Mendonca[2]. *[1]Hospital Central Funchal, Cardiology, Funchal, Portugal; [2]Hospital Central Funchal, Cardiology dept, Funchal, Portugal*

Introduction: The family history of coronary artery disease (CAD) especially if it occurs at young age is a potent risk factor for its occurrence. The identification of the existing genetic polymorphism in these patients, will allow to correlate target genes with the early start of CAD.
Aims: We intend to evaluate the influence of the the Renin Angiotensin System (RAS) Genes polymorphism and Its associations, in the risk of early CAD.
Materials and Methods: We performed a case/control study, involving a total population of 201 individuals, all under the age of 50 years (100 coronary and 100 controls) without significant differences concerning age and sex). The coronary patients with mean age of 44.2±4.0 had a history of myocardial infarction or coronary artery disease with obstruction of more than 75% of one of the main coronary vessels proved by coronarioangiography and the 100 controls with mean age of 43.1±4.2 were randomly selected from the electoral rolls. We evaluated the cases and controls for the gene polymorphism of the RAS: converting angiotensin enzyme: ACE I/D and ACE A11860G (ACE8 A/G), angiotensinogen (AGT 174T/M e AGT 235 M/T), receptor 1 of the angiotensin II (ATIR A/C) and the association ACE DD + ATIR CC, ACE DD + AGT 235 TT and ACE DD + ACE 8 GG). The evaluation of each polymorphism was done and the respective odds ratio was calculated, as well as the 95% confidence intervals, in the cases and controls

Results: The variant DD of the ACE I/D is significantly higher in the patients with an odds ratio of 2.85 (1.49-5.50) p<0.0001, the variant GG of ACE 8 A/G was also significantly higher in the patients with an odds ratio of 2.72 (1.40-5.34) p=0.002. The association of ACE DD + ACE 8 GG, was also significant p=0.002, odds ratio 2.73 (1.37-5.45).

ACE Polymorphisms and early CAD Risck

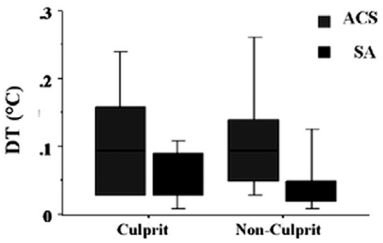
Polymorphism	Case (n=100)	Control (n=100)	Significant (P value)	Odds Ratio (Significant Interval)
ACE DD	46 (46.0%)	23 (23.0%)	p<0.0001	2.85 (1.49-5.50)
ACE 8 GG	42 (42.0%)	21 (21.0%)	p=0.002	2.72 (1.40-5.34)
ACE DD + ACE 8 GG	39 (39.0%)	19 (19.0%)	p=0.002	2.73 (1.37-5.45)

Conclusions: In the present study the ACE DD and the ACE 8 GG genotype, constitute risk factors of early CAD, and can helps us to decode the family tendency of early DAC Their presence can justify an intensive primary prevention of the other changeable risk factors, in this patients.

P1668 Widespread thermal heterogeneity of culprit and non-culprit de novo atheromatic lesions

M. Drakopoulou, K. Toutouzas, I. Mitropoulos, E. Tsiamis, M. Vavuranakis, A. Androulakis, D. Tousoulis, C. Stefanadis. *Ippokration Hospital, Dept of Cardiology, Athens, Greece*

Background: Several studies demonstrate that vulnerable plaques are multiple due to widespread inflammation. Others support that are limited to the culprit lesion (CL). Coronary thermography detects inflammatory status locally. We investigated whether: 1)thermal heterogeneity in non-culprit lesions (NCL), and 2) there is a correlation of heat production between CL and NCL.
Method: We included patients (pts) suffering from stable angina (SA) or acute coronary syndromes (ACS). All patients should have at least two angiographically significant lesions at different vessels. CLs should be identified in all patients by a combination of ECG, wall motion abnormalities, scintigraphic perfusion defects, and/or coronary angiogram. Pts with chronic total occlusions and multiple significant lesions at the culprit vessel were excluded. We measured at each lesion the temperature difference (DT) between the atherosclerotic plaque and the proximal vessel wall temperature using a thermography catheter (Medispes, Switzerland).
Results: We studied 42 consecutive patients: 23 with SA and 19 with ACS. The majority was under statin treatment (69%). Stenosis (%) was greater in the CLs compared to the NCLs (73.55±14.76% vs 66.42±11.96%, p=0.06). DT was similar in CLs and NCLs (0.09±0.10°C vs 0.08±0.10°C, p=0.86). An increase in DT by type of syndrome was observed in both CLs and NCLs (CL; SA: 0.06±0.04, ACS: 0.10±0.07°C p=0.03, vs NCLs; SA: 0.05±0.06 vs ACS: 0.13±0.14°C, p=0.01).



DT-CL-NCL by Syndrome

Conclusion: Intermediate NCLs have thermal heterogeneity, which is increased in patients with ACS. The present study supports that there is widespread thermal heterogeneity supporting the concept of global coronary instability.

EXERCISE TESTING

P1669 Cardiac peptides during exercise in patients with valvular heart disease

D. Pop, D. Zdrenghea, M. Ilea, M. Giurgea, A. Olteanu, G. Bodisz. *The Rehabilitaiton Hospital, Dept. of Cardiology, Cluj Napoca, Romania*

Introduction: Cardiac peptides are increased at rest in patients with valvular heart disease function of NYHA class, but their values during exercise were not studied until now.
Method: We studied 37 patients, 21 males and 16 females, aged 47±30 years, with rheumatic or degenerative valvular disease -mitral, aortic or combined. The diagnosis was established on clinical and echo-Doppler basis. Atrial fibrillation was detected in 30% of the patients. All patients performed a symptom limited exercise stress testing on cycloergometer. At rest and at peak effort, using ELISA method, plasmatic value of Nt-proBNP (nv<250 fmol/ml) and Nt-proANP (nv<1950 fmol/ml) were determined.
Results: Both Nt-proBNP (597±432fmol/ml) and Nt-proANP (3800±3500 fmol/ml) were increased at rest, even in patients without overt congestive heart failure. During exercise both cardiac peptides increased (Nt-proBNP-761±450 fmol/ml, p<0,05; Nt-proANP-3954±3429 fmol/ml, p>0,05), but less than it was reported in congestive heart failure patients; probably because the maximum effort level was small (52.3±37 watts). The insignificant increase of Nt-proANP could be related to already much increased rest values, partially because of atrial fibrillation. The values of cardiac peptides were significantly increased in III NYHA class in comparison with II NYHA class patients, both at rest (Nt-proBNP-420±350fmol/ml II NYHA; 680±529fmol/ml III NYHA; Nt-proANP-2600±2100fmol/ml II NYHA; 4280±3501 fmol/ml III NYHA) and at peak exercise (Nt-proBNP-602±535fmol/ml II NYHA; 840±721fmol/ml III NYHA; Nt-proANP-3300±2942fmol/ml II NYHA; 4700±3421 fmol/ml III NYHA).
Conclusion: Cardiac peptides are increased at rest, in valvular heart disease patients and even more increased during exercise, but less than in congestive heart failure patients, probably in relationship with already important haemodynamic disturbances at rest.

P1670 Valve resistance is a strong physiological severity index in patients with mitral stenosis

C. Izgi[1], N. Ozdemir[2], C. Cevik[2], O. Ozveren[2], T. Akgun[2], C. Kaymaz[2], M. Ozkan[2]. *[1]Istanbul, Turkey; [2]istanbul, Turkey*

Background: Severity of mitral stenosis (MS) is conventionally assessed by means of valve area and mean diastolic gradient. However ability of these stenosis indices to predict the hemodynamic burden of MS, which is the degree of pulmonary artery hypertension, is limited. Valve resistance (VR) is the physiological rather than anatomical expression of stenosis since it incorporates both pressure and flow data. Since in patients with aortic stenosis hemodynamic burden on the left ventricle has been shown to be closely related to aortic VR but not to valve area, we hypothesized that mitral VR may be an important determinant of pulmonary artery pressure (PAP) and exercise capacity in patients with MS.
Objectives: This study assessed the relation between the echocardiographic paremeters of stenosis severity, in particular mitral VR and the resting and stress PAP and exercise capacity in patients with MS.
Methods: Twenty patients with pure MS were included in the study. Mitral valve area, mean diastolic mitral gradient, VR, net atrioventricular compliance and left atrial diameter were derived from resting Doppler echocardiographic examination as possible determinants of resting and stress PAP. PAP was measured by Doppler echocardiography at rest and during dobutamine induced stress. Patients completed a symptom limited exercise test to determine exercise capacity. Determinants of resting and stress PAP and exercise capacity were analysed by correlation and regression analysis.
Results: Systolic PAP increased significantly from 39 ± 9 at rest to 60 ± 18 mmHg during dobutamine induced stress. VR was the most closely correlated stenosis indicator with the resting and stress PAP (r=0,80, p<0,001 and r=0,93, p<0,001 respectively) and it was an independent predictor for both with multivariate stepwise regression. Exercise capacity was mostly and equally correlated with stress PAP (r= -0,62, p=0,004) and VR (r=-0,62, p=0,004). Multivariate analysis revealed stress PAP as the only significant independent predictor of exercise capacity.
Conclusions: In patients with MS valve resistance is the strongest and the independent predictor of both resting and stress PAP and by this aspect it is superior to valve area and mean gradient in the expression of stenosis severity. While the only independent predictor of exercise capacity is stress PAP in patients with MS; the resting parameter valve resistance is equally correlated to exercise capacity with stress PAP. These results underline the importance of valve resistance as a severity index in patients with MS.

P1671 Determinants of exercise-induced changes in mitral regurgitation in patients with mitral valve prolapse

V. Giga, M. Ostojic, B. Vujisic-Tesic, A. Djordjevic-Dikic, J. Stepanovic, B. Beleslin, I. Nedeljkovic, M. Nedeljkovic. *Institute for Cardiovascular Diseases, Belgrade, Serbia and Montenegro*

Background: Mitral regurgitation (MR) decreases with exercise in majority of patients with mitral valve prolapse (MVP). However, the determinants of exercise-induced changes in this group of patients are not firmly established.
Aim: The aim of our study was to assess determinants of exercise-induced changes in mitral regurgitation (MR) in patients with mitral valve prolpse (MVP) and preserved left ventricular function (LV).
Method: Our study group comprised of 46 patinets (28 males, 18 female, 54±8 years) with mitral regurgitation due to MVP in sinus rhythm with an ejection fraction > 60%. All the patients underwent stressechocardiography testing on treadmill using Bruce protocol. Regurgitant volume (RVOL), using PISA method, as well as LV ejection fraction (EF), end-diastolic and end-systolic volume index (EDVI, ESVI) and mitral annulus dimension were measured at rest and immediately after exercise. Exercise-induced changes in echocardiographic features with exercise were expressed as absolute differences between exercise and resting values (delta value). Patients with electrocardiographic or echocardiographic evidence of ischemia were not included in the study.
Results: It was possible to assess RVOL using PISA method in 41/46 pts (feasibility 89%). MR decreased in 31/41 (76%) pts with exercise, whereas increase

in MR was observed in 10 patients (24%). Exercise-induced changes in RVOL were not related to the severity of mitral regurgitation at rest (RVOL rest) (r = 0.059, p =0.754). Exercise-induced changes in RVOL were not related to resting echocardiographic features (EDVI,r = - 0.052, p=0.781; ESVI, r = 0.024, p=0.898; EF r = -0.019, p=0.919), except to mitral annulus diameter at rest (r = 0.519, p = 0.003). In univariate analysis exercise-induced changes in RVOL correlated best with changes in EF (r= -0.890, p= 0.0001), ESVI (r = 0.848, p = 0.0001) and in mitral annulus diameter (r=0. 0.859, p=0.0001). However, multiple linear regression, revealed exercise-induced changes in EF (p= 0.001) and in mitral annulus dimension (p=0.034) as the only independent predictors of changes in mitral regurgitation (generalized r^2 =0.78).
Conclusion: Exercise-induced chages in mitral regurgitation in this group of patients with mitral valve prolapse and preserved left ventricular function were independently related to exercise induced changes in ejection fraction and in mitral annulus diameter, and not to echocardiographic features at rest.

P1672 Dynamic left ventricular dyssynchrony contributes to exercise symptoms and dynamic mitral regurgitation in heart failure patients: a quantitative exercise Doppler echocardiographic study

P.L. Lancellotti[1], F. Lebois[2], G. Van Camp[3], B. Cosyns[4], L.A. Pierard[2]. *[1]CHU Sart Tilman, Service de Cardiologie, Bâtiment B 35, Liège, Belgium; [2]University Hospital, Cardiology Dept., Liège, Belgium; [3]AZ VUB, Cardiology, Brussels, Belgium; [4]CHIREC, Cardiology, Braine l'Alleud, Belgium*

Background: In heart failure patients, exercise-induced increases in mitral regurgitation (MR) severity contributes to limitation of exercise capacity and conveys a poor prognosis. The role of dynamic left ventricular (LV) dyssynchrony – intermittent changes in LV synchronicity during exercise – as a determinant of dynamic MR has never been investigated.
Methods: Thirty-five consecutive patients with chronic ischaemic LV dysfunction underwent measurement of effective regurgitant orifice (ERO) and of LV synchronicity at rest and during semi-supine exercise test.
Results: During exercise, the degree of LV dyssynchrony - the difference, among the 6 LV walls, between the longest and the shortest times to peak myocardial sustained systolic velocity - increased by at least 10 ms (range: 10 to140 ms) in 16 patients, remained stable in 4 and decreased by at least 10 ms (range: -10 to -70 ms) in the remaining 15. With multivariate analysis, an increase in LV dyssynchrony and in systolic tenting area emerged as determinants of exercise-induced changes in ERO (r^2 =0.67, p=0.00001). Changes in LV dyssynchrony were also associated with changes in systolic tenting area (r=0.52, p=0.0013). Changes in ERO and in LV dyssynchrony at exercise correlated with changes in stroke volume (r^2 =0.71, p=0.0008). With multivariate regression analysis, larger increases in ERO (p=0.022) and in LV dyssynchrony (p=0.045) independently predicted the occurrence of exercise-induced dyspnea.
Conclusions: In heart failure patients, dynamic LV dyssynchrony contributes to exercise-induced increases in the severity of MR and hence limitation of stroke volume adaptation and exertional dyspnea.

P1673 Ebstein anomaly: cardiopulmonary exercise test in the evaluation of exercise capacity and degree of echocardiographic index of progression of this malformation

O. Trojnarska[1], A. Gwizdala[2], A. Siniawski[2], Z. Oko-Sarnowska[3], R. Ochotny[2]. *[1]Inst. of Cardiology, Poznan Medical Academy, First Department of Cardiology, Poznan, Poland; [2]University of Medical Sciences, Cardiology, Poznan, Poland; [3]University of Medical Sciences, Clinical Farmacology, Poznan, Poland*

Introduction: Ebstein anomaly is characterized by displacement of part of tricuspid ring in the direction of apex of the heart and inappropriate attachment of valvular cusps resulting in significant decrease in right ventricular function and tricuspid regurgitation.
Aim of the Study: was estimation of physical capacity measured with spiroergometry in adult patients with Ebstein syndrome and its possible correlation with echocardiographic index of anatomical progression of the malformation.
Material and Method: Twenty patients were studied aged 24 to 63 years (mean 40,3 years). Control group consisted of 19 healthy persons aged 22 to 61 years (mean 39,9). Echocardiographic examination: Index of progression of Ebstein's (EGE) malformation was calculated- quotient of right ventricular area and atrialized right ventricle and sum of right and left ventricular area and left atrium. Fallowing degrees of progression of the malformation (EGE) were set: I<0,5, II:0,5-0,9, III:1,0-1,49, IV>1,5. Maximal physical effort was measured on moving track according to modified Bruce's protocol, resting spirometry measured FVC, VE, FEV1 and peak VO2. VE/VCO2 slope index was analyzed.
Results: Following parameters in the studied gropu were decreased compared to control group: VO2 max- 21,9±5,4 ml/kg/min vs 33,6±8,3 p=0,00001, peak VO2 w l/min: 1,7±0,6 vs 2,5±0,9 p= 0,002, maximal heart rate at the peak of exercise-HR max 158,0±18,9 beats per minute vs 177,7±15,4 p=0,001, systolic pressure at peak of exercise 145,7±14,4 mmHg vs. 171,1±23,3 p=0,0003, VE- 71,3±17,0 l/min vs. 93,8±37,1 p=0,02, VE/VCO2 slope, was higher than in control group (40,1±8,1 vs. 26,9±3,6) (p=0,00001). In 75% of studied patients exceeded 34.
Parameters of pulmonary function - FVC 4,5 ±1,0 vs 4,6±1,1 l. FEV1-3,5±0,6 vs. 3,6±0,9 l, did not differ between groups. Number of patients in each EGE group: I-0, II-9, III-6, IV-5 patients. VO2 (ml/kg/min) in group II 24,5±3,9 were higher than in III 17,2±5,2 p=0,007 and IV 22,9±4,7 p=0,05. HR max- in group II 169,1±12,5 bpm was higher than in IV 146,6±20,5 p=0,03 and III: 150,8±19,0 p=0,05).
Conclusions: 1. Physical capacity among adult patients with Ebstein syndrome in significantly decreased.
2. Physical capacity in this group decreases with degree of echocardiographic progression of the malformation.

P1674 Functional capacity and NT-proBNP are closely related to right ventricular pressure/volume overload in corrected tetralogy of Fallot

C. Passino, L. Ait-Ali, M. Fontana, C. Prontera, M. Emdin, P. Festa. *National Research Council, Institute of Clinical Physiology, Pisa, Italy*

Cardiac natriuretic hormones (in particular BNP) play a key role in volume homeostasis and their plasma level are a sensitive and specific marker of cardiac dysfunction. Peak oxygen consumption (VO2), by cardiopulmonary exercise testing (CPX), is a marker of functional capacity and holds an established prognostic power in cardiac patients.
In patients with right ventricular pressure and/or volume overload caused by surgical right outflow tract reconstruction, an early detection of right ventricle dysfunction is critical in order to prevent irreversible right ventricular (RV) failure. Magnetic resonance imaging (MRI) is an accurate method to assess RV volume and performance. Aim of our study was to evaluate functional capacity and NT-proBNP (the amino-terminal inactive peptide derived from the cleavage of the prohormone proBNP) plasma levels and their relation to MRI findings in patients after surgical correction of tetralogy of Fallot.
Forty-one stable patients (22 males, age 19±1 years, mean±SEM) with surgically corrected tetralogy of Fallot, underwent a MRI study (for RV function and pulmonary regurgitation quantification), NT-proBNP plasma assay, echocardiogram and CPX. Twelve age/sex matched healthy volunteers underwent NT-proBNP plasma assay and CPX and served as control group.
NT-proBNP plasma concentration was elevated in patients as compared to controls (169±24 vs 42±6 pg/ml, p<0.01). Maximal workload was, on average, lower in patients than in controls (94±5 vs 147±20 W, p<0.01), as well as peak VO2 (1.6±0.3 vs 0.95 L/min) and peak VO2/kg (19.4 vs 31.6 ml/min/kg, p<.001). In patients, peak VO2/kg and NT-proBNP showed a significant negative correlation (R=0.57, p<0.001). Moreover, peak VO2/kg correlated with RV end-systolic and end-diastolic volume (R=0.55 and R=0.47, respectively, both p<0.001) and with the severity of pulmonary regurgitation (R=0.40, P=0.02). NT-proBNP showed a significant correlation with RV end-systolic and end-diastolic volume (R=0.44, p<0.01 and R=0.36, p=0.02, respectively) and with estimated RV systolic pressure (R=0.35, p=0.03).
These results show a clear linkage between RV function and cardiac natriuretic expression and functional capacity, suggesting that either NT-proBNP plasma assay and CPX are useful complementary tools for an optimal management of patients after surgery for correction of tetralogy of Fallot.

P1675 Exercise induced hypertension is not related with a residual gradient after correction of coarctation of the aorta

J. Ferreira Santos[1], A. Teixeira[2], R. Anjos[2], M. Mendes[3], F. Ferreira[2], F. Maymone Martins[2]. *[1]Sao Bernardo Hospital, Cardiology, Setubal, Portugal; [2]Santa Cruz Hospital, Pediatric Cardiology, Carnaxide, Portugal; [3]São Bernardo Hospital, Cardiology Department, Setúbal, Portugal*

Background: Patients (pts) with corrected coarctation of the aorta (CoA) frequently have exercise induced hypertension, which mechanism is not entirely clarified.
Aim: To explore the relation between exercise induced hypertension and the gradient in the thoracic aorta before and at peak exercise in pts with corrected CoA.
Methods: In 26 pts (medium age 30±10 years) with successfully corrected CoA (surgery, angioplasty or stent), a treadmill stress test was performed to evaluate the arterial pressure response to exercise. The residual gradient on the site of the CoA correction was assessed before and immediately after exercise (1st, 3th and 5th minute). The arm-leg blood pressure gradient (arm-leg PG) and the Doppler corrected gradient (Doppler PG) – determined on the continuous wave Doppler flow signal in the descendent thoracic aorta - were used for assessing the gradient. Exercise induced hypertension (exercise-HT) was defined as a peak systolic arterial pressure greater or equal to 250 mmHg or diastolic arterial pressure greater or equal to 120 mmHg. Pts were divided in two groups based on the presence of exercise-HT and compared between them.
Results: In nine pts there was exercise induced hypertension. These pts had higher systolic and diastolic arterial pressures pre-exercise (table). Groups did not differ in age, type of anti-hypertensive therapeutic, time since last correction of CoA and prior history of re-coartaction. There were no differences in the PG arm-leg and PG-Doppler before and after exercise (table).

Comparison between groups

	With exercise-HT (n=9)	Without exercise-HT (n=16)	p
Rest Systolic Arterial Pressure	172 ± 21	141 ± 19	0.001
Rest Diastolic Arterial Pressure	95 ± 13	81 ± 8	0.002
Rest arm-leg PG	0 (0-6.5)*	0 (0-11.5)*	1.000
1 min pos-exercise arm-leg PG	35.9 ± 20.9	38.5 ± 22.9	0.780
Rest Doppler PG	17.5 ± 8.4	16.5 ± 8.7	0.778
1 min pos-exercise Doppler PG	29.9 ± 14.9	37.2 ± 21.9	0.387

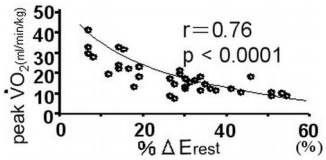
Values in mmHg; *Median and inter-quartil interval

Conclusion: Exercise-HT is present in about one third of pts with treated CoA and it is not mediated by an increased gradient in the zone of correction assessed at baseline and after exercise. Hypertension at rest seems to be related to exercise-HT reinforcing the need to a better arterial pressure control.

P1676 Evaluation of exercise tolerance by dynamic minimal exercise stress echocardiography in patients with congestive heart failure

T. Yuasa, Y. Otsuji, T. Uemura, Y. Bo, K. Nakashiki, E. Kuwahara, A. Kisanuki, C. Tei. *Kagoshima University Hospital, First Department of Internal Medicine, Kagoshima, Japan*

Background: Similarly elevated left atrial (LA) pressure at each patients' maximal exercise between patients with poor and relatively preserved exercise tolerance by congestive heart failure (CHF) suggest that LA pressure increase greater by same degree of exercise in patients with poor exercise tolerance. We hypothesized that increase in the transmitral E velocity by Doppler echo, expressing the increase in the left atrial pressure, even by mild exercise can potentially be related to patients' exercise tolerance in patients with CHF.
Methods: Subjects consisted of 30 patients with grade 2 to 3 CHF and 6 controls. Peak VO2 was measured conventionally by analyzing their expirated gas during multiple step ergometer exercise. By minimal exercise stress echo with 10W exercise by ergometer, mitral flow and its change to baseline was evaluated by pulsed Doppler echo [E velocity, delta E, %delta E, E deceleration time (DcT), delta DcT, %delta DcT.] Results: 1) Erest and DcTrest were not significantly correlated with peak VO2. 2) In contrast, %delta E as well as %delta DcT had good and significant correlations with peak VO2 (r=0.76 and r=0.66, p<0.001).



Peak VO2 vs. %delta E

Conclusion: Dynamic minimal exercise stress echo allows practical prediction of exercise tolerance in patients with congestive heart failure.

P1677 Correlation between enhanced ventilatory response to exercise, pulmonary hypertension and severe diastolic dysfunction in patients with chronic heart failure

A.B. Scardovi[1], C. Coletta[1], N. Aspromonte[1], T. Infusino[1], S. Perna[1], P. D'Errigo[2], F. Seccareccia[2], V. Ceci[1]. *[1]S. Spirito Hospital, Rome, Cardiology, Rome, Italy; [2]Istituto Superiore di Sanità, Rome, Italy*

The aim of this study was to evaluate if there is a correlation between enhanced ventilatory response to exercise (EVR), determined during cardiopulmonary exercise test, and pulmonary arterial hypertension (PH) and left ventricular diastolic dysfunction (DD), measured by Doppler echocardiography, in chronic heart failure patients with left ventricular ejection fraction (LVEF) < 45%.
Methods: One hundred and twenty consecutive outpatients were considered (age: 62 ± 12; female: 28%; beta-blocker therapy: 56%; ischemic 52%; NHYA class I: 8%; II: 60%; III: 32%; mean LVEF 34 ± 9%). The EVR was assessed as ventilation and carbon dioxide production ratio (VE/VCO2) slope > 35. Doppler echocardiography selected parameters were transmitral peak E (E) and A wave (A) velocity (cm/sec), E/A ratio and E velocity deceleration time (msec, EDT). DD was defined as E/A ratio > 1 and EDT < 140 msec, PH as right ventricular - atrium gradient > 30 mmHg.
Results: Mean pulmonary systolic pressure was 47 + 15 mmHg. Fifty-four out of 120 patients had EVR (45%) (VE/VCO2 slope mean value 35.59 ± 8.28). Mean TDE and E/A values were 180 ± 60, 1.8 ± 1.2 respectively. A significant reverse correlation between VE/VCO2 slope and EDT
(r = - 0.320; p <0.01) was detected. Furthermore we found a significant direct correlation between pulmonary systolic pressure and VE/VCO2 slope (r = 0.511; p < 0.01) and between E/A and VE/VCO2 slope (r= 0.350; p< 0.01). Thirty out of 44 pts with DD (68%) had EVR.
Conclusions: DD and PH, measured by Doppler echocardiography, seems to be a reliable marker of EVR at cardiopulmonary exercise test. Moreover, they represent an easily-available and low-cost first-step approach for the prediction of outcome in CHF patients with inability to exercise.

P1678 Effects of exercise training on neurohormal activation and left ventricular systolic and diastolic function in patients with heart failure

L. Boncompagni, A. Sabini, S. Baldassarre, S. Bartolucci, M. Paggini, L. Bolognese. *San Donato Hospital (USL 8), Division of Cardiology, Arezzo, Italy*

Background: Brain natriuretic peptide (BNP) is elevated in chronic heart failure (HF) and correlates with a restrictive filling pattern. However, no data are available on the effects of exercise training, an effective method of treatment of HF, on neurohormal activation and left ventricular (LV) systolic and diastolic function in this setting.
Methods: Forty-seven patients (35 males, age 63.7±4.3) with moderate to severe HF (NYHA class II-III) entered into a training program and were prospectively evaluated. All patients underwent comprehensive echocardiography and cardiopulmonary exercise test and plasma BNP determination at baseline and after 6 months. LV ejection fraction (EF), LV endsystolic (LVESV) and enddiastolic (LVEDV) volumes and, deceleration time (DT) were serially evaluated.
Results: Exercise training over a period of six months resulted in an improvement of functional status on average by 1 NYHA class. Moreover, peak VO2, increased and VE/VCO2 slope decreased (17.6 ml/kg/min±0.73 before and 18.76±0.98 after training; p< 0.0001; 34.07±1.54 before and 30.85±1.23 after training: p< 0.0001, respectively). A significant reduction in BNP levels (from 199.7±41.74 to 127.1±31.76 p< 0.0001) and LVEDV (from 172.7±14.4 ml to 165.8±12.8 ml; p< 0.007) was observed from baseline to 6-months, as well as an increase in LVEF (from 32.1±2.02 to 36.2±2.02, p< 0.0001) and DT (from 174.9±10.3 to 190.8±6.7; p< 0.0001). Multiple regression analysis showed a significant direct correlation between delta BNP levels and VE/VCO2 before training (p= 0.02) and delta 6-month VE/VCO2 (p= 0.02). An inverse correlation was found between delta BNP levels and baseline peak VO2 (p= 0.01), LVEF (p= 0.01), and DT (p=0.02).
Conclusions: Long-term exercise training is associated with an enhanced physical work capacity, an improvement in LVEF and LVEDV and a significant reduction in BNP levels and DT. BNP levels are clearly associated with exercise capacity and systolic and diastolic LV function in chronic HF.

P1679 Aortic biophysical properties influence exercise tolerance in patients with non-ischaemic dilated cardiomyopathy

A.P. Patrianakos[1], F.I. Parthenakis[1], D. Karakitsos[2], E.A. Zacharis[1], M. Saatsaki[1], N.C. Klapsinos[1], E. Nyktari[1], P.E. Vardas[3]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Nephrology Dept., Heraklion, Greece; [3]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: Aortic (AO) wall stiffness modulates left ventricular (LV) function and aortal functional alteration has been documented in heart failure.
Using a novel echocardiographic method we evaluated the relationship of the proximal aorta biophysical properties with the exercise capacity in patients with non-ischemic dilated cardiomyopathy (NIDC) and mild to moderate heart failure (NYHA II-III).
Methods: We studied 30 clinically stable patients, 54.2 ±11.2 years, with angiographically proven NIDC in sinus rhythm and a left ventricular ejection fraction 34.8±12.7% and 30 age-matched controls. The proximal ascending AO diameter in systole(s) and diastole (d) was measured by M-mode echocardiography. We evaluated the biophysical properties of AO in the region of AO arch by measuring the distance between ascending and descending AO from the suprasternal view with 2D-ultrasound and the AO flow wave transit time (T) which was measured with pulsed-wave Doppler signal to travel in this region. Systolic (SBP) and diastolic (DBP) blood pressure was simultaneous calculated. The aortic pulse wave velocity (PWV) = AO distance/T, pressure strain elastic modulus (PSEM) = (SBP-DBP)/[(AOs - AOd))/AOd] and b-index = ln (SBP/DBP)/[(AOs - AOd)/AOd] were calculated. A cardiopulmonary exercise test was performed on all pts. Exercise duration and maximal Oxygen consumption (MVO2), as well as the predicted MVO2, based on age and body mass index,were calculated.
Results: Patients showed increased PWV (4.6±1.55 vs 3.05±1.5 m/sec; p=0.01), PSEM (657±321 vs 412±136 mmHg; p<0.001) and b-index (6.3±2.7 vs 4.4±1.2; p<0.001) compared to controls. The PWV was correlated with NYHA class (r=0.32, p =0.03), PSEM (r=0.47, p<0.001) and b-index (r=0.46, p<0.001) but not with BP or other echocardiographic parameters. A significant correlation was also found between the predicted maximal VO2 and PSEM (r= -0.33, p=0.03), PWV(r=-0.43,p=0.01) and b-index (r=-0.36, p=0.03). Multivariate regression analysis revealed that the aortic PWV was independently associated with the predicting MVO2.
Conclusions: The increased AO stiffness independently affects exercise capacity in NIDC patients. The AO biophysical properties thus evaluated seem to be clinically important and could become an additional therapeutic target in those patients.

P1680 Comparison of haemodynamic indicators of cardiac pumping capacity in the long-term prognostic assessment of patients with chronic heart failure

S.G. Williams[1], M. Jackson[2], D. Barker[3], D.J. Wright[2], A. Patwala[2], L.B. Tan[3]. *[1]Wirral, United Kingdom; [2]Cardiothoracic Centre, Liverpool, United Kingdom; [3]University of Leeds, Unit of Molecular Vascular Medicine, Leeds, United Kingdom*

Objectives: A previous report confirmed the prognostic value of peak cardiac power output (CPO) in patients with chronic heart failure (CHF). This study assessed the prognostic value of various indicators of cardiac pump function including cardiac output reserve and the newer surrogate marker, peak circulatory power in this group of patients with chronic CHF over a longer period of follow-up.
Methods: Two hundred and nineteen unselected, consecutive patients with CHF (166 men, mean [±SD] age of 56±13 years) who underwent maximal symptom limited cardiopulmonary treadmill exercise testing with non-invasive estimation of cardiac output using carbon dioxide re-breathing techniques, were followed-up for a median period of 8.6±1.0 years in survivors. CPO was calculated from the product of cardiac output and mean blood pressure (MAP) and cardiac output reserve was estimated by subtracting resting from peak exercise CO. Circulatory power was calculated from the product of peak oxygen consumption (VO2) and MAP. Univariate analyses were performed on continuous variables using the Wilcoxon rank sum test and chi-squared tests for categorical data. Significant multivariate predictors of death were sought by the Cox proportional hazards model.
Results: All cause mortality was 36% (78 deaths). Multivariate analysis identified cardiac output reserve to be the only independent predictive of outcome in this population, with a hazard ratio (95% CI) of 0.682 (0.612-0.757, P<0.001) for each l/min reduction in cardiac output reserve. Peak VO2, peak circulatory power and peak CPO, although significant on univariate testing, did not contribute significantly to the identification of patients who died above the information provided by cardiac output reserve on multivariate testing. Survival at 10 years in patients with a good (>8.1 l/min), moderate (=5.8 - <8.1 l/min) or poor (=5.8 l/min) cardiac output reserve was 89%, 63% and 36.1% respectively (P<0.001).
Conclusion: Cardiac output reserve, measured non-invasively by cardiopulmonary exercise testing, has superior prognostic power to other haemodynamic variables (including peak VO2, circulatory power and CPO) and is the sole independent predictor of long-term survival in a group of 219 consecutive ambulatory patients with CHF.

P1681 Patients with peripheral vascular disease elicit elevated upper-limb pulse wave velocity at rest and during acute exercise stress

M.A. Conway[1], W.F. Alves[2], K.F. Reid[1]. *[1]St Luke's Hospital, Department of Cardiology, Kilkenny, Ireland; [2]Clinica San Lorenzo, Angiologia e Cirurgia Vascular, Fortaleza, Brazil*

Introduction: Stiffening or arteriosclerosis of the arterial wall can be assessed non-invasively by measurement of pulse wave velocity (PWV). Little is known about the PWV of the upper-limb in patients with peripheral vascular disease (PVD), therefore, we examined carotid-radial PWV at rest and during a single bout of isometric handgrip exercise (ISOMEX) in PVD patients and compared them to healthy subjects.
Methods: Dominant-arm PWV and non-invasive haemodynamics (BP & HR) were examined in 10 PVD patients (age (mean ± SD) 63.8 ± 9.4 yrs, BMI 25.1 ± 2.4 kg/m^2) versus 10 healthy controls (age 62.3 ± 11.2 yrs, BMI 27 ± 3.7 kg/m^2) at rest, during and into recovery from 3-minutes of supine sub-maximal ISOMEX (30% MVC) of the non-dominant arm.
Results: PVD patients had significantly higher resting PWV (9.52 ± 1 m/sec) compared to controls (8.37 ± 0.8 m/sec) (P = 0.01). ISOMEX PWV was significantly greater in PVD patients (10.88 ± 1.2 Vs 9.17 ± 0.9 m/sec, P = 0.002), as was the PWV measured post-exercise (9.82 ± 1.5 Vs 8.62 ± 1.1 m/sec, P = 0.03). The actual PWV increase induced by ISOMEX was also larger in the PVD patients (P < 0.05).
Conclusions: Vascular stiffness of the upper limb is increased in PVD patients. The ISOMEX PWV stress test elicits marked changes of PWV in this disorder, as a result of amplified efferent sympathetic nervous outflow. Such a test may be valuable for further characterising PVD patients and evaluating the effects of therapy on sclerotic alterations of the arterial wall.

P1682 Comparison of effects of movement and work load on ergoreceptor reflex

A. Hager[1], W. Koch[2], H. Stenzel[3], J. Hess[4], J. Schöber[3]. *[1]Deutsches Herzzentrum München, Kinderkardiologie, München, Germany; [2]Klinik für Kinder und Jugendliche, Pforzheim, Germany; [3]Kinderklinik 3. Orden, München, Germany; [4]Deutsches Herzzentrum München, Kinderkardiologie Abt., München, Germany*

Objective: Increased ergoreceptor function causes dyspnoea and a reduced exercise capacity in patients with heart failure. To study ergoreceptor reflex, investigations have often been performed in patients with central hypoventilation syndrome. They lack ventilatory chemosensitivity and depend solely on ergoreceptor function. A substantial increase of respiration has been reported in these patients for passive movement while sleeping and active movement on a treadmill. The aim of the study was to investigate ventilatory response to increasing work load but constant movement.
Patients and Methods: Twenty patients (12.4 ± 4.0 years, 8 female) and 17 healthy volunteers (14.7 ± 4.0 years, 13 female) performed a symptom-limited cardiopulmonary exercise test on a bicycle. Patients were asked to keep pedaling at a constant rate of about 60 revolutions per minute throughout the wholetest. In patients with a diaphragmatic pacer this pacer was turned off for the test. Values were compared between patients and controls by a two-sided t-test.
Results: Patients could adequately exercise and showed normal peak oxygen uptake (35.7 ± 11.4 versus 38.1 ± 9.4 ml/kg/min, p=0.496). Minute ventilation rose in both group similarly from rest to cycling with 0.5 Watt/kg (effect of movement), from 0.5 Watt/kg to the anaerobic threshold (effect of workload), and - but in patients less prominent - from anaerobic threshold to peak exercise (effect of workload and lactate). Ventilatory efficiency expressed as VE-VCO2 slope did not differ.
Conclusions: Ergoreceptors are sensitive both to movement and to work load. They are responsible for most of the respiratory drive up to the anaerobic threshold.

P1683 The role of exercise on platelet aggregation in patients with stable coronary artery disease: exercise induces aspirin resistant platelet activation

B. Pamukcu, H. Oflaz, R.D. Acar, S. Umman, N. Koylan, B. Umman, Y. Nisanci. *Istanbul, Turkey*

Objectives: The aim of our study was to determine the relation between exercise stress test and aspirin resistance in patients with stable coronary artery disease.
Background: Clinically aspirin resistance is defined as having thrombotic and embolic cardiovascular events despite regular aspirin therapy.
Methods: We studied platelet functions of 62 patients with stable coronary artery disease by Platelet Function Analyzer (PFA-100, Dade Behring, Germany) at rest and after exertion (in the first minute of the recovery period) with collagen and/or epinephrine (Col/Epi) and collagen and/or ADP cartridges. Closure time (CT) < 193 seconds was defined as aspirin resistance with Col/Epi cartridges of PFA-100. Symptom limited treadmill stress test (protocol of Bruce) was performed with Oxford Streslink TD-1 system.
Results: 8 (12.9%) patients were aspirin resistant by PFA-100 (CT<186s despite regular aspirin therapy) at rest. At the first minute of the recovery period of exercise stress test 14 (22.5%) patients were aspirin resistant by PFA-100. CTs with Col/ADP were respectively 89±6 s (83-100s) and 89±5 s (82-104s) at rest and after exercise (p=0.107). 20.3% (11/54) of patients known as in vitro aspirin sensitives at rest had shorter CTs and 11.1% (6/54) had aspirin resistance after exercise (p=0.004).

Aspirin Resistance* by PFA-100

Variable	Basal (n=62)	In the first minute of recovery (n=62)	p
Aspirin Resistance	8 (12.9%)	14 (22.5%)	.004
CT with COL/ADP (s)	89 (SD:6)	89 (SD:5)	.107

Values are mean ± SD or n(%), * CT < 193s with Col/Epi cartridges of PFA-100.

Conclusion: We conclude that 11.1% of in vitro aspirin sensitive subjects at rest had aspirin resistance after exercise by PFA-100. In some individuals, exercise induced platelet activation is aspirin insensitive at usual antiplatelet doses. We need further clinical trials to optimize antiplatelet therapy in patients with coronary artery disease.

P1684 Influence of age and gender on heart rate recovery after exercise in healthy individuals was more important than indices of 24-hour heart rate variability

E.Y. Chuang[1], I. Antelmi[1], M.R.D.O. Latorre[2], C.J. Grupi[1], A.T. Yamada[1], F. Araujo[1], Mansur[1]. *[1]Heart Institute (incor) Hc Fmusp, Clinical Division, São Paulo, Brazil; [2]School of Public Health, Epidemiology, Sao Paulo, Brazil*

The decrease in heart rate recovery after treadmill electrocardiographic exercise stress test was associated with higher mortality in clinical series. Heart rate recovery after exercise is also modulated by the autonomic nervous system that may be evaluated by heart rate variability indices on 24-hour ambulatory electrocardiographic monitoring. Higher recovery rate is an expression of faster parasympathetic reactivation and sympathetic tonus withdrawal. We performed this study to test the hypothesis that a difference in the heart rate recovery after treadmill electrocardiographic exercise stress test in healthy individuals might be associated with indices of heart rate variability on 24-hour ambulatory electrocardiographic monitoring.
Methods: 485 asymptomatic individuals aged 40.4 ± 12.1 years, 204 men (42.1%) and 281 women (57.9%) without any evidence of heart disease after careful clinical and laboratory examination were submitted to treadmill electrocardiographic exercise stress test and 24-hour ambulatory electrocardiographic monitoring.Heart rate variability was studied on time as well as on frequency domain. Heart rate recovery was recorded once every minute up to 5 minutes after exercise. Statistical analysis was performed with Pearson correlation and ANOVA.

Results: Higher recovery rate after exercise was associated with lower age (R 0.19-0.35, p<0.001) and female sex in the first (4±1.1 beats; p=0.001), second (5.7±1.2 beats; p<0.01) and third minute (4.1±1.1 beats; p<0.001) after exercise. There was a significant correlation between heart rate recovery and heart rate variability indices SDNN, SDANN, SDNNi, rMSSD, pNN50, VLF, LF, HF at 3rd. and 4th minutes of recovery. No correlation with any index were obtained at first, second and fifth minute but VLF at 2nd to 5th minute (R 0.1; p<0.05). However, after controlling for age statistical significance at 3rd minute with all heart rate variability indices, and at 4th minute with rMSSD, pNN50%, LF and HF was lost; the indices SDNN, SDNNi and VLF lost also correlation power at 3rd and 4th minute after exercise. Analysis of the correlation between heart rate recovery and indices of heart rate variability by gender and controlling by age revealed no significant correlation.
Conclusions: Age and gender influence over heart rate recovery in healthy individuals after treadmill electrocardiographic exercise stress test was more important than autonomic influence as evaluated by the indices of heart rate variability in 24-hour ambulatory electrocardiographic monitoring.

P1685 Can autonomic dysfunction be identified by exercise stress test in patients with familial amyloidotic polyneuropathy?

M.C. Azevedo Coutinho[1], M.J. Correia[2], I. Conceicao[3], M.G. Varela[2], P. Marques[2], A. Bernardes[2], A. Silva[2], J.A. Correia da Cunha[2]. *[1]Lisboa, Portugal; [2]Santa Maria Hospital, Cardiology, Lisbon, Portugal; [3]Santa Maria Hospital, Neurology, Lisbon, Portugal*

Background: Familial amyloidotic polyneuropathy (FAP) type I is a hereditary form of amyloidosis characterized by progressive autonomic nervous system dysfunction. Impaired heart rate (HR) response to exercise measured by chronotropic index (CI) and abnormal heart rate recovery (HRR) are reflective of autonomic abnormalities during and after exercise. We sought to determine whether CI and HRR were altered in FAP patients and if they correlated with heart rate variability (HRV) analysis.
Methods: 24 patients with TTRVal30Met mutation (13 male, mean age=39.2±13.4 yrs) and 24 age-matched control subjects underwent symptom-limited exercise stress test. CI was calculated as: (peak HR-rest HR)/(220-age-rest HR), with a value <0.8 being low. HRR was defined as peak HR-HR at 1-minute post peak exercise. HRR ≤22 bpm was considered abnormal. FAP patients also underwent 24-hour Holter monitoring in order to assess HRV analysis.
Results: exercise variables are shown in table. CI was low in 67% of the FAP patients and in 4% of the normal subjects (p<0.0001). HRR was abnormal in 58% of the patients and 8% of the control group (p=0.0008). Significant correlations were found between HRR and SDNN (r=0.48, p=0.02), total power (r=0.58, p=0.003), LF (r=0.57, p=0.003) and HF (r=0.57, p=0.003), but not between CI and any HRV parameter.

Exercise stress variables

	FAP patients (n=24)	Normal subjects (n=24)	P value
Rest HR (bpm)	94±14	81±9	0.0005
Peak HR (bpm)	152±23	174±14	0.0002
HR at 1st min post exercise (bpm)	130±20	136±17	ns
Exercise duration (sec)	552±137	679±116	0.001
CI	0.7±0.2	0.9±0.1	<0.0001
HRR (bpm)	21±12	38±13	<0.0001

Conclusions: in FAP patients, exercise stress test can demonstrate autonomic dysfunction early in the course of the disease. HRR, which is a simple measurement that is related to HRV, should aid in providing prognostic information.

P1686 Prognostic value of exercise testing in patients with hypertrophic cardiomyopathy

G. Brion, R. Peidro, A. Angelino, T. Zalazar, J. Kriskovich, H. Casabe, A. Fernandez. *Fundacion Favaloro, Rehabilitation CU, Buenos Aires, Argentina*

Aims: 1) to determine the prognostic value of ET in patients with hypertrophic cadiomyopathy (HC) 2) evaluate security of the test.
Method and results: 148 maximum symptom-limited treadmill ET with Bruce protocol was performed in 111 consecutive patients, aged 44.2 ± 19.5, 77 (69%) male. Abnormal systolic blood pressure response (ASBPR) was defined as an increase in the systolic blood pressure < 20 mmHg from rest to peak exercise or a fall > 10 mmHg. There was no registered complication related to the ET. During the follow up period (mean 45 ± 36 months) there was 19 events: 6 sudden death, 7 implantation of cardioverter-defibrillator, 4 refractory heart failure that needed an invasive procedure: 2 pacemakers for resynchronisation and 2 surgical septal myectomy. In the event group 17 (89.5%) patients had ASBPR versus 14 (16%) in the group without event (p<0.0001). ASBPR had a sensitivity of 89%, specificity of 84%, positive predictive value of 55% and negative predictive value of 97% for the prediction of event.
Conclusions: 1) Abnormal SBP response is a strong predictor of event in patients with HC; its high negative predictive accuracy makes it a valuable screening test for identification of low-risk patients. 2) ET is safe in HC patients.

Abstract P1686 – Table 1

	Group with end point (n=19)	Group without end point (n=88)	OR	CI 95%	p
Male, n (%)	13 (68%)	65 (74%)			NS
Age (yeas)	44±20	46±17			NS
Familiary history of SD	8 (42%)	9 (10%)	6.3	2 - 20	0.001
Familiary history of HC	7 (37%)	11 (12%)	4	1.3 - 12.5	0.01
Left ventricular wall thickness (mm)	19.3±4.7	22.8±8.1			0.03
Abnormal SBP response	17 (89.5%)	14 (16%)	45	9.3 - 216.5	< 0.001
Symptoms	8 (42%)	17 (19%)	3	1.05 - 8.7	0.03
Ventricular arrhythmia	8 (42%)	32 (36%)			NS
Changes in ST segment	6 (32%)	28 (32%)			NS
Maximum SBP (mmHg)	134±29	166±28			< 0.001
Maximun SBP<152 mmHg	16 (84%)	27 (31%)	12	3.2 - 44.8	< 0.001
Maximun SBP x HR	19705±7147	25985±6248			< 0.001
Maximum SBP x HR<21000	14 (74%)	21 (24%)	8.9	2.8 - 27.7	< 0.001
METS	9.1±2.8	11.2±4.3			0.04

P1687 The oxygen uptake efficiency slope improves after heart transplantation and predicts post-transplant maximal exercise capacity

C. Van Laethem[1], S. Verstreken[2], J. Bartunek[2], M. Goethals[2], F. Wellens[2], M. Walravens[2], M. Vanderheyden[2]. *[1]OLV hospital, Cardiovascular Research Centre, Aalst, Belgium; [2]OLV hospital, Cardiovascular Research Centre, Aalst, Belgium*

Background: The Oxygen Uptake Efficiency Slope (OUES), expressed as slope VO2/logVE, is a new effort-independent exercise variable, used in the evaluation of adult CHF patients. Whether heart transplantation influences this parameter remains undetermined.
Purpose: To evaluate the characteristics of OUES in heart transplantation(Tx) pts and to investigate its potential to predict functional recovery following Tx.
Methods: 30 Tx patients (25 men, age at HTX: 60 ± 9years, post-Tx LVEF 56 ± 14%) performed a maximal cardiopulmonary exercise (CPX) test (RER =1.1) before and 14 ± 4 months following Tx.
Results: After Tx, peakVO2 (13,1± 3,7 vs 17,0 ± 3,3 ml/kg.min), peak VE (46,0 ± 13,6 vs 59,2 ± 11,6), peak VE/VCO2 (40,9 ± 8,5 vs 36,5 ± 5,4), VE/VCO2-slope (40,7 ± 10,5 vs 34,2 ± 5,9), OUES (1157 ± 453 vs 1482 ± 457) and OUES/kg (15,9 ± 5,0 vs 19,8 ± 4,7) improved significantly (all P<0.05), whereas BMI, anaerobic threshold (VAT) and pulmonary diffusion capacity did not change. Following Tx a significant correlation was noted between OUES and peakVO2 (r = 0,660, P<0,001, see fig.1). In addition, the pre-Tx OUES/kg correlated best to post-Tx peakVO2 (r = 518, p=.04), compared to other pre-Tx parameters such as age, LVEF, BMI, peakVO2, VAT and VE/VCO2-slope.

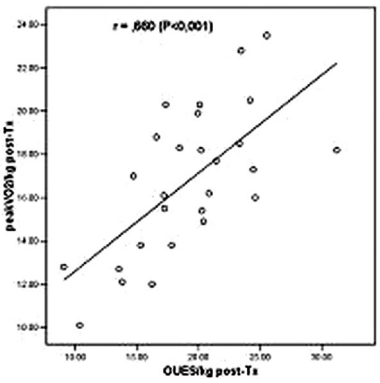


Figure 1

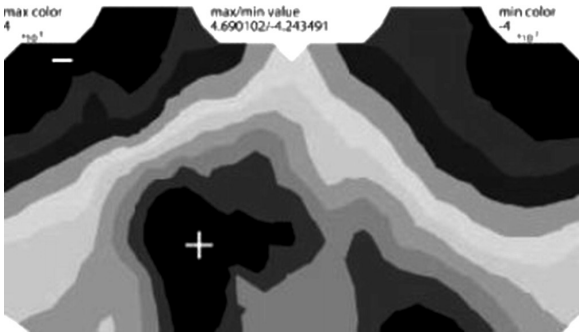
Conclusion: In Tx recipients, a significant correlation is noted between OUES and peakVO2 which makes this index suitable as possible surrogate for peakVO2 for pts performing submaximal CPX tests. The OUES improves significantly during the first years after Tx. In addition, the pre-Tx normalized OUES for body weight might have the potential to predict the maximal exercise capacity after Tx.

P1688 Identification of the optimal sites to detect exercise-induced myocardial ischaemia by ST/HR area loop

H. Hanninen[1], M. Timoharju[2], H. Vaananen[2], M. Makijarvi[2], T. Katila[2], L. Toivonen[3]. *[1]Helsinki University Central Hospital, Division of Cardiology, Cardiovascular Lab, Helsinki, Finland; [2]Helsinki University of Technology, Helsinki, Finland; [3]Helsinki University Central Hospital, Division of Cardiology, Helsinki, Finland*

Background: Relating ST-amplitude and heart rate by calculating ST/HR loop area improves the performance of exercise testing in detection of coronary artery disease (CAD). We applied body surface potential mapping to identify the optimal sites of ST/HR loop area to detect exercise-induced ischemia.
Methods: We studied 39 patients with CAD and 20 controls with 123-lead exercise-BSPM. The patients were selected to have stenoses in different vessels

to represent CAD in general (15 left anterior descending, 12 on left circumflex, and 12 right coronary artery stenoses). In each lead, the ST/HR loop area was calculated as the difference between the exercise and recovery ST/HR integral (mV*beats per minute, mVbpm). T-test was applied to identify the optimal sites to separate the groups.
Results: The largest ST/HR loop area in CAD group was over left anterior chest near standard lead V4 (CAD 2.10 ± 3.00 mVbpm vs. controls 0.03 ± 2.21 mVbpm, $p < 0.01$). The optimal site to separate groups, however, was over the left inferior chest at midaxillary line (CAD 0.76 ± 1.72 mVbpm vs. controls –1.78 ± 2.44 mVbpm, $p< 0.001$). The area under receiver operating characteristic curve for the optimal lead was 83% whereas for lead V4 it was 73%. The ST/HR loop area was positive in CAD whereas it was negative in controls over the anterior chest.



T-value map of the ST/HR area loop

Conclusions: The performance of ST/HR loop area can be improved by using optimal recording locations over chest in exercise stress test. These lay outside the standard 12-lead ECG sites, implying that in exercise stress testing lead locations could be modified

P1689 Diagnostic value of high frequency mid qrs analysis in the detection of exercise induced ischaemia

H. Silber[1], T. Sharir[2]. *[1]Meir General Hospital, Heart Institute, Kfar Saba, Israel; [2]Maacabi Healthcare Services, Procardia, Tel-Aviv, Israel*

Exercise induced myocardial ischemia is commonly detected by repolarization changes. Ischemia changes in depolarization are more difficult to detect, being hidden in the high amplitude QRS complex. A novel technology (HyperQ™ system, BSP) analyzes low-amplitude, high-frequency (150 - 250 Hz) components of the QRS. Diagnostic efficacy of this technology in detecting exercise-induced ischemia was assessed in population referred to myocardial perfusion imaging (MPI).
A total of 936 consecutive patients (643 males) underwent exercise MPI, using Tl-201 or Tc-99 sestamibi SPECT. Perfusion images were visually scored, using 5 points, 20 segment left ventricle model. Ischemia was defined as summed difference score ≥3. The HyperQ system was used for high-resolution 12-lead ECG recording and analysis of mid-QRS high-frequency (HF) components through the exercise test. The root-mean-square (RMS) values of the HF QRS signal were computed for the 12 leads at several predetermined points along the test.
MPI detected stress-induced ischemia in 82 subjects (8.8%). Statistically significant differences between the ischemic and non-ischemic subjects were detected by the HyperQ system, dominantly in V2-V4 leads. Ischemic patients demonstrated higher HF QRS resting values and steeper descending slope towards peak exercise, compared with non-ischemic patients (Figure 1).Evaluation of HF QRS parameters using multivariate logistic regression analysis revealed rest RMS values of HF QRS at V1, and peak-to-rest RMS difference values at V2 as independent predictors ($p < 0.05$) of ischemic MPI.
Stress-induced ischemia could be detected using high-frequency mid-QRS analysis, offering an improved noninvasive tool for the detection of ischemic heart disease.

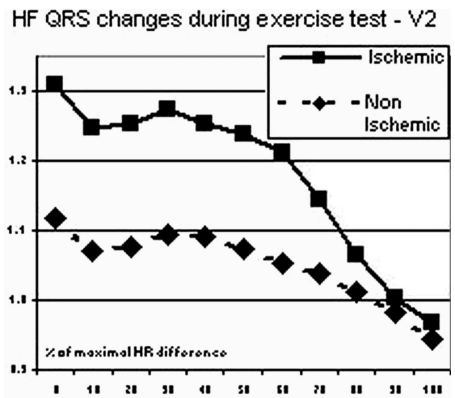


Figure 1

INFLAMMATORY MARKERS/ BIOCHEMICHAL SUBSTANCES

P1690 Tissue inhibitor of metalloproteinase (TIMP-1) is a predictor of recurrent cardiovascular events in the LIPID study

P. Nestel[1], S. Blankenberg[2], R.J. Simes[3], A. Kirby[4], A. Tonkin[5]. *[1]Baker Heart Research Institute, Melbourne, Australia; [2]Johannes Gutenberg University, Mainz, Germany; [3]University of Sydney, NHMRC Clinical Trials Centre, Camperdown, Australia; [4]University of Sydney, NHMRC Clinical Trials Centre, Camperdown, Australia; [5]Monash University, Epidemiology and Preventive Medicine, Melbourne, Australia*

In acute coronary syndromes (ACS) plaque rupture is induced by collagenase activity of matrix metalloproteinases (MMPs) that exceeds inhibition by TIMP. Both MMPs and TIMP-1 appear in increased concentration in the circulation after ACS. Since MMPs have been found to be predictive of future cardiovascular (CV) events we have evaluated the predictive strength of circulating TIMP-1 in a retrospective nested case-control study within the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.
Methods: 250 pairs of matched subjects, half of whom had suffered a recurrent CV event over 2.5 years following the blood sample vs 250 who remained free of further events during the same period of follow-up as their matched case were selected randomly. Using an ELISA method we measured plasma free TIMP-1 plus TIMP-1/MMP complexes (including TIMP-1/MMP-9). Relationships between TIMP-1 and CV events were adjusted for a previously published multiple risk score, treatment allocation and hsCRP levels and tested in a multivariate conditional logistic regression model. TIMP-1 levels were also examined as quartiles.
Results: Plasma TIMP-1 was significantly higher among cases than controls (806 [704-931] vs 736 [647-842] pg/ml; $P<0.001$). The relative risk of recurrent CV events increased across TIMP-1 quartiles (<672 through >889 pg/ml; P for trend<0.001); RR was 2.8 for subjects in highest vs lowest quartile. RR due to TIMP-1 was independent of multiple risk score and of hsCRP.
Conclusion: Plasma TIMP-1, a novel biomarker that probably reflects concomitant rise in circulating MMPs, was found to be highly predictive of recurrent CV outcomes (CV death, non-fatal myocardial infarction, stroke).

P1691 Amino-terminal pro-B-type natriuretic peptide (NT-proBNP): a risk factor for most seasons

D.J. Campbell[1], M. Woodward[2], J. Chalmers[2], S. Colman[2], A.J. Jenkins[3], B. Neal[2], A. Patel[2], S. MacMahon[2]. *[1]St. Vincent's Inst. of Med. Research, Molecular Cardiology, Fitzroy, Australia; [2]The George Inst for Internat Health, Camperdown, Australia; [3]St. Vincent's Hospital, Medicine, University of Melbourne, Fitzroy, Australia*

We investigated whether NT-proBNP and other plasma markers predict risk of congestive heart failure (CHF), myocardial infarction (MI), ischaemic stroke (IS) and intracerebral haemorrhage (ICH). We performed four nested case-control studies of the 6105 participants of the PROGRESS study, a multicentre, randomised, double-blind, placebo-controlled study of a perindopril-based blood pressure lowering regimen among individuals with previous stroke or TIA. All participants had blood taken on enrolment, and mean follow-up was 3.9 years. Participants who developed CHF (n=258), MI (n=206), IS (n=252) and ICH (n=41) were matched to 1-3 control subjects. Matching criteria were age, gender, qualifying event, geographic region, and randomised therapy. Odds ratios (95% confidence interval) are quoted for subjects in the highest, as compared with the lowest, quarter of each marker. NT-proBNP and CRP predicted CHF; odds ratio 4.5 (2.7-7.5) for NT-proBNP and 2.9 (1.9-4.7) for CRP, and each remained a predictor of CHF after adjustment for other predictors. NT-proBNP, CRP and renin predicted MI; odds ratio 2.2 (1.3-3.6) for NT-proBNP, 2.2 (1.3-3.6) for CRP, and 1.7 (1.1-2.8) for renin. NT-proBNP and renin, but not CRP, remained predictors of MI after adjustment for other predictors. NT-proBNP and soluble vascular cell adhesion molecule 1 (sVCAM-1) predicted IS; odds ratio 1.9 (1.2-3.0) for NT-proBNP and 2.3 (1.5-3.8) for sVCAM-1, and each remained a predictor of IS after adjustment for other predictors. None of these plasma markers predicted ICH. We conclude that NT-proBNP assists identification of individuals at risk of CHF, MI, and IS, but not ICH, following stroke or TIA.

P1692 Elevated serum concentrations of interleukin-18 do not predict incident coronary events in middle-aged men and women: results from the Monica/Kora Augsburg cohort study, 1984-2002

W. Koenig[1], J. Baumert[2], B. Thorand[2], L. Chambless[3], H. Loewel[2], C. Meisinger[2], H. Kolb[4], C. Herder[4]. *[1]University of Ulm Medical Center, Department of Internal Medicine II, Ulm, Germany; [2]Institute of Epidemiology, GSF Research Center, Neuherberg, Germany; [3]University of North Carolina, Department of Biostatistics, Chapel Hill, United States of America; [4]University of Düsseldorf, German Diabetes Research Institute, Düsseldorf, Germany*

Purpose: Interleukin (IL) 18, a pleiotropic cytokine plays a central role in the inflammatory cascade. It has been detected in atherosclerotic plaque and an IL-18 inhibiting protein was shown to reduce atherosclerosis in animal experiments. However, epidemiologic data relating systemic concentrations to risk of coronary heart disease (CHD) are sparse and controversial. Therefore, we prospectively investigated whether increased serum concentrations of IL-18 are associated with an increased risk of incident CHD.
Methods: A case-cohort study was conducted in initially healthy, middle-aged men and women based on data from the MONICA/KORA Augsburg studies collected between 1984 and 2002 (mean follow-up time 10.3 years). Concentrations of IL-18 were measured in stored serum samples of 384 case subjects (296 men and 88 women) with incident CHD (non-fatal and fatal myocardial infarction and coronary death) and 1979 non-case subjects (1008 men and 971 women).
Results: Median concentrations of IL-18 were 181.4 pg/mL (inter quartile range, IQR 118.3 – 260.3) in non-cases and 194.1 pg/mL (128.6-279.2) in cases for men and 167.5 pg/mL (IQR 116.0 – 235.9) and 173.5 pg/mL (IQR 131.3 – 250.0) for women, respectively. In crude and in age and survey adjusted analyses, there was a statistically significant association between increased concentrations of IL-18 and incident CHD in men (hazard ratios (HRs) and 95% confidence intervals (CIs) comparing tertile extremes were 1.42, 95% CI, 1.06-1.90 and 1.45, 95% CI, 1.07-1.95 respectively), whereas no significant association was seen in women (HR 1.54, 95% CI, 0.92-2.57 and HR 1.45, 95% CI, 0.87-2.44, respectively). In multivariable analyses, accounting for age, survey, body mass index, smoking, physical activity, alcohol consumption, systolic blood pressure, total cholesterol/HDL ratio, and family history of CHD, this association was attenuated and no longer statistically significant in men (HR 1.22 (0.90-1.67) and remained non-significant in women (HR 1.20, 95%CI, 0.69-2.10).
Conclusions: Elevated serum concentrations of IL-18 are not independently associated with an increased risk of CHD in men and women of this large population-based case-cohort study.

P1693 Lipoprotein-associated phospolipase A2 plasma concentrations predict cardiovascular events in patients with coronary heart disease

W. Koenig[1], D. Twardella[2], H. Brenner[2], D. Rothenbacher[2]. *[1]University of Ulm Medical Center, Department of Internal Medicine II, Ulm, Germany; [2]German Centre for Research on Ageing, Department of Epidemiology, Heidelberg, Germany*

Purpose: Lipoprotein-associated phospolipase A2 (Lp-PLA2), an enzyme mainly produced by monocytes/macrophages and circulating primarily bound to LDL cholesterol, generates potent proinflammatory products and has been reported to predict cardiovascular events in initially healthy subjects. We sought to evaluate whether Lp-PLA2 is also associated with prognosis in a large cohort of patients with clinically overt coronary heart disease (CHD).
Methods: Plasma concentrations of Lp-PLA2 were determined by ELISA (Diadexus Inc, South San Francisco, CA, USA) at baseline in a cohort of 1031 patients aged 30-70 years with CHD participating in an in-patient rehabilitation program after an acute coronary syndrome All patients were followed for a mean of 33.5 months and a combined endpoint (N= 71, 6.9%; fatal and non-fatal myocardial infarction (MI) and stroke) was used as the outcome variable. The Cox proportional hazards model was used to determine the prognostic value of Lp-PLA2.
Results: Baseline levels of Lp-PLA2 were higher in subjects who experienced an event compared to event free-subjects (279.6 $\pm$ 74.3 vs. 266.8 $\pm$ 84.1 ng/mL). Lp-PLA2 was positively correlated with age (r=0.08, p=0.01), C-reactive protein (CRP) (r=0.18, $p<0.0001$), LDL cholesterol (r=0.40, $p<0.0001$), negatively with HDL cholesterol (r=-0.14, $p<0.0001$), but only marginally with body mass index (BMI) (r=-0.06, p=0.06). In a multivariate model, Lp-PLA2 was associated with an increased rate of future cardiovascular events. After controlling for age, gender, BMI, smoking, social class, history of MI and diabetes mellitus (DM), severity of CHD, HDL-cholesterol, treatment with lipid-lowering drugs and CRP, the hazard ratio (HR) was 2.77 (95% confidence interval (CI) 1.44-5.35) and 2.79 (95% CI 1.40-5.55) when the second and top tertile were compared to the bottom tertile. After additional adjustment for LDL, the HRs were moderately attenuated, 2.40 (95% CI, 1.23-4.70) and 2.05 (95% CI, 0.98-4.27), respectively. Further inclusion of cystatin C, and N-terminal proBNP in the model did not appreciably affect the results.
Conclusions: Elevated levels of Lp-PLA2 appear to be predictive of future coronary events in patients with manifest CHD independent of a variety of potential risk factors including markers of inflammation, renal function, and hemodynamic stress.

P1694 Prognostic value of N-terminal pro-B Natriuretic Peptide levels: prospective cohort study in patients with stable coronary heart disease

D. Rothenbacher[1], W. Koenig[2], H. Brenner[1]. *[1]German Centre for Research on Ageing, Deptment of Epidemiology, Heidelberg, Germany; [2]University of Ulm Medical Center, Department of Internal Medicine II, Ulm, Germany*

Purpose: It has been suggested that B-type natriuretic peptide (BNP) and the amino-terminal (NT)-proBNP may be associated with cardiac processes other than ventricular dysfunction. However, the prognostic value in patients with stable coronary heart disease (CHD) is yet unclear. In this study we investigated the potential relevance of NT-proBNP in the prediction of secondary cardiovascular events in a large cohort of patients with stable CHD.
Methods: 1033 patients aged 30-70 years were examined several weeks after myocardial infarction (MI) or coronary artery revascularization. NT-proBNP was measured from fasting serum samples (Elecsys, Roche Diagnostics, Mannheim, Germany). The outcome variable were fatal and non-fatal cardiovascular disease (CVD)-events.
Results: During a mean follow-up of 33 months 71 patients (6.9%) experienced a secondary CVD-event. Increased NT-proBNP levels were strongly and independently associated with secondary CVD events (p=0.0004). Patients in the top quartile of the NT-proBNP distribution at baseline had a hazard ratio (HR) of 2.73 (95% confidence interval (CI) 1.26-5.91) for subsequent secondary CVD-events compared to those in the bottom quartile, even after controlling for a large variety of potential confounders including markers of inflammation and renal insufficiency. Results were similar if the population was restricted to patients with no or only minor impairment of the left ventricular function.
Conclusions: These data are in support of the prognostic value of NT-proBNP among patients with stable CHD and suggest that NT-proBNP is a useful marker which may provide complementary information to the established risk determinants.

P1695 Family history, plasma homocysteine, and age at onset of symptoms of myocardial ischaemia in patients with different methylenetetrahydrofolate reductase genotypes

A. Mager[1], N. Koren-Morag[2], D. Hasdai[3], D. Harell[4], N. Magal[5], A. Battler[3], M. Shohat[5]. *[1]Rabin Medical Center, Beilinson Campus, Cardiology, Petah-Tikva, Israel; [2]Tel-Aviv University, Sackler Faculty of Medicine, Tel-Aviv, Israel; [3]Rabin Medical Center-Beilinson Campus, Cardiology, Petah Tikva, Israel; [4]Rabin Medical Center, Biochemistry Laboratory, Petah-Tikva, Israel; [5]Rabin Medical Center-Beilinson Campus, Medical Genetics and FMRC, Petah-Tikva, Israel*

Elevated fasting plasma homocysteine (tHcy) level is associated with early onset of coronary artery disease (CAD), particularly in homozygotes for the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene. Family history is a predictor of increased plasma homocysteine and may be involved in early-onset CAD. This study examined the relationships among family history, plasma tHcy and age at onset of CAD, and the role of the MTHFR genotype in this context.
Methods and results: We screened 284 patients with first CAD symptoms at age <65 years for fasting tHcy level and the C677T mutation. On multiple regression analysis, tHcy, family history, male gender and smoking were independently associated with age at onset of CAD. However, separate analysis of patients with (n=57) and without (n=209) the MTHFR 677 T/T (homozygous mutant) genotype showed that tHcy and family history predicted earlier onset of CAD only in T/T homozygotes, and male gender and smoking-only in patients with non-T/T genotypes. Family history in T/T homozygotes was associated with higher tHcy levels (p=0.008) and a stronger association between tHcy and age at onset of CAD (r=-0.57, $p<0.01$ in T/T homozygotes with vs. r=0.11, p=0.6 in T/T homozygotes without family history). These associations were not observed in patients with non-T/T genotypes.
Conclusions: The MTHFR genotype modifies the effects of family history, tHcy and other risk factors on age at onset of CAD. Family history is associated with earlier onset of CAD, higher tHcy levels and a stronger association between tHcy and age at CAD onset in T/T homozygotes.

P1696 Homocysteine and its relation to cotinine as a marker of passive smoke exposure among nonsmokers in NHANES III

H.Y. Kim[1], D.D. Sin[2], J.Y. Kim[3]. *[1]The Catholic University of Korea, Cardiology Department, Seoul, Korea, Republic of; [2]University of British Columbia, Vancouver, Canada; [3]The Catholic University of Korea, Cardiology Department, Seoul, Korea, Republic of*

Background: smoking is known to be associated with an increased plasma homocysteine level. Both are associated with an increased risk of cardiovascular disease. However, little information is available on the effect of passive smoking on the level of homocysteine in nonsmokers.
Method: we analysed data from self-reported non-smokers, >40 years of age, of

the Third National Health and Nutrition Examination Survey (n=6526). We quantified passive nicotine exposure by dividing non-smokers into quartiles based on serum cotinine values. We used multiple linear and logistic regression models to determine the independent relationship between serum cotinine and levels of homocysteine, vitamin B12 and folate expression. Elevated homocysteine levels were defined as >80th percentile. Reduced folate or vitamin B12 levels were defined as <20th percentile of their variable.

Results: the prevalence of hyperhomocysteinemia significantly increased from 19.6% in the lowest cotinine quartiles to 23.4% in the highest cotinine quartile. After adjustments for age, sex, body mass index, and race, the elevated levels of cotinine were related to elevated levels of homocysteine and reduced levels of folate (Table). No association was detected between cotinine and vitamin B12.

Relative odds across cotinine quartiles

	Q2	Q3	Q4	P for trend
Folate	1.20 (0.74-1.96)	1.89 (1.20-2.99)*	1.86 (1.44-3.61)*	<0.0001
Vitamin B12	1.10 (0.74-1.62)	1.32 (0.89-1.96)	1.18 (0.79-1.76)	0.293
Homocysteine	0.98 (0.65-1.48)	1.44 (0.96-2.16)	1.97 (1.32-2.92)*	<0.0001

expressed as odds ratio(95% confidence interval)*P<0.05 compared with quartile 1(Q1)

Conclusion: these findings suggest that even among nonsmokers, elevated serum cotinine as a marker of passive smoke exposure is independently associated with an elevated homocysteine level.

P1697 Interleukin (IL)-18 and risk of coronary events: lack of association in a prospective nested case-control study from southern Germany

N. Khuseyinova[1], J. Baumert[2], C. Meisinger[2], H. Loewel[2], W. Koenig[1]. [1]*University of Ulm Medical Center, Department of Internal Medicine II, Ulm, Germany;* [2]*National Research Center for Health, Institute of Epidemiology, Neuherberg, Germany*

Purpose: Cytokine-mediated inflammation accompanies atherosclerosis from its initiation to the occurrence of clinical endpoints. Recently, IL18 has been suggested to play a central role in the inflammatory cascade. IL18 possesses the abilities to induce expression of matrixmetalloproteases and INF-gamma, that characterize them as a potent mediator of atherosclerotic plaque destabilization and vulnerability. IL18 has been reported to predict cardiovascular events in patients with clinically overt coronary heart disease (CHD). However, data in initially healthy subjects are scarce and controversial.

Methods: We measured plasma concentrations of IL18 by ELISA (MBL, Nagoya, Japan) and C-reactive protein (CRP) by a high-sensitivity immunoradiometric assay at baseline in a nested case-control study comprising 81 men, aged 45-74 with incident CHD and 238 age-matched controls with a mean follow-up time of 5.6 years (SD 2.5). Subjects came from two population-based MONICA/KORA Augsburg surveys conducted in the years 1989/90 and 1994/95. A combined endpoint of fatal and non-fatal myocardial infarction (MI) and sudden cardiac death was used as the outcome variable. Cox PH regression was performed to assess the relative risks (hazard ratios (HR)) for IL18 and CRP.

Results: Baseline levels of IL18 were slightly higher in subjects who experienced an event compared to event-free subjects (241.0 vs 218.5 pg/mL; p=0.14), but clearly elevated for CRP (2.9 vs 1.7 mg/L, p<0.001). IL18 (log-transformed) correlated positively with TC/HDL ratio and CRP in controls, with oxLDL in cases and negatively with HDL in both study groups. After adjustment for traditional cardiovascular risk factors, TC/HDL ratio and CRP, the relative risk of future coronary events comparing the top tertile of the IL-18 distribution to the bottom tertile was 1.47 (95% confidence interval (CI), 0.82-2.63; p=0.35). However, in this population increased CRP (T3 vs T1) was a strong and independent predictor of future CHD events, even after multivariable adjustment, including IL18 (HR 2.8; 95% CI, 1.47-5.34, p=0.007).

Conclusions: In contrast to CRP, plasma concentrations of IL18 were not statistically significantly associated with future coronary events in apparently healthy men from an area with moderate absolute risk of CHD. This study therefore suggests that IL18 may only serve as a marker of future cardiovascular events in men with manifest CHD and/or in areas of high absolute risk of CHD. Further studies are warranted to establish the role of IL18 in the prediction of CHD risk.

P1698 Family history, plasma homocysteine, and age at onset of symptoms of myocardial ischaemia in patients with different methylenetetrahydrofolate reductase genotypes

A. Mager[1], N. Koren-Morag[2], M. Shohat[3], D. Harell[4], A. Battler[5]. [1]*Rabin Medical Center, Beilinson Campus, Cardiology, Petah-Tikva, Israel;* [2]*Tel-Aviv University, Sackler Faculty of Medicine, Tel-Aviv, Israel;* [3]*Rabin Medical Center-Beilinson Campus, Medical Genetics and FMRC, Petah-Tikva, Israel;* [4]*Rabin Medical Center, Biochemistry Laboratory, Petah-Tikva, Israel;* [5]*Rabin Medical Center, Cardiology, Petah-Tikva, Israel*

Elevated fasting plasma homocysteine (tHcy) level is associated with early onset of coronary artery disease (CAD), particularly in homozygotes for the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene. Family history is a predictor of increased plasma homocysteine and may be involved in early-onset CAD. This study examined the relationships among family history, plasma tHcy and age at onset of CAD, and the role of the MTHFR genotype in this context.

Methods and results: We screened 284 patients with first CAD symptoms at age <65 years for fasting tHcy level and the C677T mutation. On multiple regression analysis, tHcy, family history, male gender and smoking were independently associated with age at onset of CAD. However, separate analysis of patients with (n=57) and without (n=209) the MTHFR 677 T/T (homozygous mutant) genotype showed that tHcy and family history predicted earlier onset of CAD only in T/T homozygotes, and male gender and smoking-only in patients with non-T/T genotypes. Family history in T/T homozygotes was associated with higher tHcy levels (p=0.008) and a stronger association between tHcy and age at onset of CAD (r=-0.57, p<0.01 in T/T homozygotes with vs. r=0.11, p=0.6 in T/T homozygotes without family history). These associations were not observed in patients with non-T/T genotypes.

Conclusions: The MTHFR genotype modifies the effects of family history, tHcy and other risk factors on age at onset of CAD. Family history is associated with earlier onset of CAD, higher tHcy levels and a stronger association between tHcy and age at CAD onset in T/T homozygotes.

ENDOTHELIAL FUNCTION

P1699 Improved endothelial function by dual endothelin receptor blockade in individuals with insulin resistance

A. Shemyakin[1], F. Bohm[1], S. Efendic[2], P. Bavenholm[2], J. Pernow[1]. [1]*Karolinska University Hospital, Solna, Department of Cardiology, Stockholm, Sweden;* [2]*Karolinska Institute, Department of Molecular Medicine, Stockholm, Sweden*

Objective: Insulin resistance, which is a major cardiovascular risk factor, is associated with endothelial dysfunction and enhanced production of endothelin-1 (ET-1). The study objective was to test whether selective ETA or dual ETA/ETB receptor antagonism improves endothelium-dependent vasodilatation (EDV) in insulin resistant individuals.

Methods: Insulin sensitivity was assessed by hyperinsulinaemic-euglycaemic clamp in 16 subjects without any history of cardiovascular disease. The subjects were divided into an insulin sensitive (n=7) and an insulin resistant group (n=9). Forearm blood flow (FBF) was measured using venous occlusion plethysmography. EDV and endothelium-independent vasodilatation (EIDV) were determined by intra-arterial administration of acetylcholine and sodium nitroprusside, respectively, before and following a 60 min infusion of the ETA receptor antagonist BQ123 (10 nmol/min) alone or in combination with the ETB receptor antagonist BQ788 (5 nmol/min).

Results: The insulin-sensitivity value (M-value) was 4.9+0.5 (mg/kg/min) in the insulin resistant group compared to 14.8+1.3 in the insulin sensitive group (P<0.001). Intra-arterial infusion of BQ123 did not significantly influence EDV or EIDV in either group. Combined administration of BQ123 and BQ788 enhanced EDV in insulin resistant subjects (P<0.01; Fig. 1) but not in the insulin sensitive group. Combined ETA/ETB receptor antagonism improved EIDV in the insulin resistant group (P<0.001).

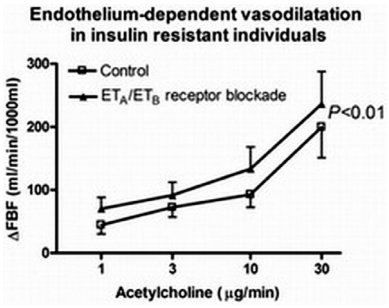


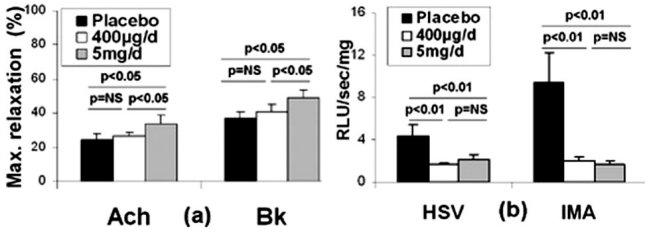
Figure 1

Conclusions: The present study suggests that dual ETA/ETB receptor blockade improves endothelial and smooth muscle cell function in patients with insulin resistance. This indicates that ET-1 is involved in vascular dysfunction in individuals with insulin resistance.

P1700 Chronic treatment with folic acid improves endothelial function and decreases superoxide production in human vessels. A double blind placebo control study

C. Shirodaria[1], C. Antoniades[1], J. Lee[1], J. Khoo[1], R. Pillai[2], C. Ratnatunga[2], S. Neubauer[1], K.M. Channon[1]. *[1]University of Oxford, Cardiovascular Medicine, Oxford, United Kingdom; [2]John Radcliffe Hospital, Cardiothoracic Surgery, Oxford, United Kingdom*

Folic acid improves endothelial function, partly by lowering homocysteine levels, but its direct effects on vascular function in atherosclerosis remain unclear.
Aim: We evaluated the effect of chronic treatment with folic acid on endothelial function and superoxide production in human saphenous veins (HSV) and internal mammary arteries (IMA) of patients undergoing coronary bypass surgery (CABG).
Methods: In this double-blind placebo controlled study, 21 patients with CAD were randomised to receive folic acid 5mg/d, folic acid 400μg/d or placebo (n=7 in each group) for 6 weeks before CABG. Blood samples were received at baseline and one day before CABG. Vasomotor responses to acetylcholine (ACh) and bradykinin (BK) were evaluated in HSV segments harvested during the operation. Basal and NADPH-mediated superoxide production was measured (with 5 μM lucigenin chemiluminescence) in paired samples of both HSV and IMA.
Results: Homocysteine levels were decreased in patients treated with 5 mg/d or 400μg/d folic acid, but not in the placebo-treated group. Patients treated with 5mg/d had better vasomotor responses to ACh and BK compared to those treated with 400μg/d or placebo ($p<0.05$ for both, Figure a). Both basal and NADPH oxidase-derived superoxide were lower in patients treated with folic acid (5mg/d or 400μg/d) compared to placebo, in both HSV and IMA ($p<0.01$ for both, Figure b).



Figure

Conclusions: Folic acid improved endothelial function independently from the decrease in homocysteine levels. However, vascular superoxide production was decreased both in patients treated with low- and high- doses of folic acid. These findings suggest that chronic treatment with folic acid may improve vascular function, in a mechanism not strictly dependent on homocysteine lowering.

P1701 Oral treatment with tetrahydrobiopterin reverses endothelial dysfunction and oxidative stress in hypercholesterolemia

D. Hurlimann[1], G. Noll[1], R. Chenevard[1], M. Eto[1], F. Enseleit[1], N. Blau[2], T.F. Luscher[1], F. Cosentino[3]. *[1]University Hospital, Cardiology, Zurich, Switzerland; [2]Children's Hospital, Clinical Chemistry and Biochemistry, Zürich, Switzerland; [3]"La Sapienza" University, 2nd Faculty of Medicine, Rome, Italy*

Introduction: Reduced availability of tetrahydrobiopterin (BH4), an essential cofactor of nitric oxide synthase, causes both decreased NO production and increased reactive oxygen species (ROS) formation. Several studies have shown that supplementation of BH4 improves impaired endothelial dysfunction under various pathological states. However, no data are currently available concerning the effect of chronic BH4 supplementation in humans. This study was designed to evaluate the effect of oral BH4 on endothelial function and oxidative stress in hypercholesterolemic patients.
Methods: Twenty-two subjects with LDL>4.5mmol/L and no signs of macrovascular disease, were randomized in a double-blind fashion to 4-week treatment with BH4 (400mg bid) or placebo. Forearm venous occlusion plethysmography and intra-arterial infusion of acetylcholine (ACH) and sodium nitroprusside (SNP) were used to assess endothelium-dependent and –independent vasodilation at baseline and after 4 weeks of treatment. Furthermore, 8-epi-prostaglandin F2a and BH4 plasma levels were measured. An age-matched group of healthy volunteers served as control.
Results: A significant increase of BH4 levels was observed after oral supplementation (42±26 vs 4.9±2.3 nmol/l at baseline, $P<0.05$), whereas no changes occurred in the placebo group. The vasodilatory response to ACH, but not to SNP, was significantly reduced in hypercholesterolemic subjects compared with controls (1519±550 vs 2029±550 expressed as area under the curve in arbitrary units, $P<0.05$). Treatment with BH4 restored endothelium-dependent, NO-mediated vasodilation (1473±512 vs 2116±758 arbitrary units, at baseline and after 4-week treatment, respectively, $P<0.05$), but had no effect upon SNP-induced vasodilation. An in vivo marker of ROS formation 8-epi-prostaglandin F2a was significantly reduced only in the BH4 treatment group (- 0.4±0.2 vs. 0.1±0.1 ng/mL, changes after BH4 and placebo respectively, $P<0.05$).
Conclusion: This study shows for the first time that endothelial dysfunction and oxidative stress can be reversed by chronic treatment with BH4. Our findings underscore the relevance of BH4 for NO synthesis in vivo in humans, but also provide support into a new therapeutic approach to prevent initiation and progression of cardiovascular disease in hypercholesterolemia.

P1702 The structural sphingosine 1-phosphate analog and immunosuppressant FTY720 induces eNOS-dependent arterial vasodilation via the lysophospholipid receptor S1P3

P. Keul[1], M. Toelle[2], V. Brinkmann[3], J. Jankowski[2], J. Chun[4], W. Zidek[2], M. van der Giet[2], B. Levkau[1]. *[1]University Hospital Essen, Institute of Pathophysiology, Essen, Germany; [2]Med. Klinik IV, Charite – Campus Benjamin Franklin, Berlin, Germany; [3]Transplantation and Immunology, Novartis Inst. for BioMedical Research, Basel, Switzerland; [4]The Scribbs Research Institute, Molecular Biology, La Jolla, California, United States of America*

We have previously identified the bioactive lysophospholipid sphingosine 1-phosphate (S1P) contained in High-density lipoproteins (HDL) as responsible for a major part of the vasodilatory effect of HDL in vitro and in vivo (J Clin Invest., 2004). This effect is mediated by eNOS activation via the endothelial S1P3, a G protein-coupled receptor from the lysophospholipid receptor (S1P1-5) family. In the present study, we investigated the vasoactive effects of the novel pharmacological S1P structural analog FTY720, a potent immunosuppressive agent currenty in Phase III clinical trials for kidney graft rejection.
We show that FTY720 potently induced endothelium-dependent arterial vasodilation in phenylephrine precontracted mouse aortae. Vasodilation did not occur in arteries from eNOS-deficient mice, implicating an effect dependent on activation of the eNOS/NO pathway. Accordingly, FTY720 induced NO release, enzymatic eNOS activation and Akt-dependent Ser1177-phosphorylation. For biological efficacy, FTY720 required endogenous phosphorylation, since addition of the sphingosine kinase antagonist N',N-dimethylsphingosine (DMS) prevented activation of eNOS in vitro and inhibited vasodilation in isolated arteries. The endothelial phosphorylation of FTY720 was extremely rapid with an almost complete conversion to the phosphorylated form (FTY720-P) already after 2 minutes as determined by mass spectrometry of supernatants of cultured endothelial cells and whole aortae. Finally, we identified the lysophospholipid receptor S1P3 as the S1P receptor responsible for arterial vasodilation by FTY720, as the effect was completely abolished in arteries from S1P3-deficient mice.
Endothelial integrity, especially the expression of protective vasoactive agents such as NO may be a key factor in the sensitivity of transplanted organs to transplantation-mediated injury. Interestingly, FTY720 has been shown to effectively prevent graft artherosclerosis and chronic allograft rejection in models of cardiac transplantation, where accelerated atherosclerosis takes place. Thus, FTY720 is the first immunomodulator for the prevention of organ graft rejection in clinical development that may protect endothelial integrity through stimulation of NO production, and may thus display beneficial activities on transplant survival and graft atherosclerosis beyond classical T cell immunosuppression.

P1703 Low-grade inflammation and microalbuminuria in male essential hypertensive subjects: relationships of urinary albumin excretion with C-reactive protein, interleukin-18 and soluble CD 40 ligand

C. Tsioufis, K. Dimitriadis, M. Toutouza, E. Taxiarchou, G. Chartzoulakis, P. Stougiannos, C. Stefanadis, I. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: Subclinical inflammatory processes are related to atherosclerosis progression and adverse cardiovascular outcome. In this study, we examined whether urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR), is correlated with high sensitivity C-reactive protein (hs-CRP), interleukin (IL)-18 and soluble CD40 ligand (sCD40L), in hypertensive subjects.
Methods: The study population consisted of 108 newly diagnosed untreated non-diabetic male patients with stage I to II essential hypertension [aged 44 years, office blood pressure (BP)=148/95 mmHg]. According to ACR values determined as the mean of two non-consecutive spot urine samples, participants were divided into two groups: microalbuminurics (n=28) (mean ACR=30-300 mg/g) and normoalbuminurics (n=80)(mean ACR<30 mg/g). Moreover, venous blood samples were drawn for estimation of lipid profile, IL-18, sCD40L and hs-CRP levels, according to established techniques.
Results: Microalbuminurics compared to normoalbuminurics were older (50±8 vs 42±5 years, $p<0.05$), had greater BMI (27.51±1.6 vs 24.1±3 kg/m^2, $p<0.05$), longer duration of essential hypertension (1.6±0.2 vs 0.6±0.4 years, $p<0.05$), higher office systolic BP values (153±10 vs 146±8 mmHg, $p<0.05$), greater left ventricular mass index and relative wall thickness (114±15 vs 100±18 gr/m^2 and 0.44±0.06 vs 0.39±0.03, respectively; $p<0.05$ for both cases). Microalbuminurics compared to normoalbuminuric hypertensives, had greater hs-CRP (2.55±1.18 vs 1.45±0.52 mg/l, $p<0.05$), whereas these two groups did not differ regarding IL-18 and sCD40L values (p=NS, for both cases). Analysis of covariance revealed that hs-CRP values were significantly different between the two groups after adjustment for age, sex, BMI, left ventricular mass index and office systolic/diastolic BP ($p<0.05$). Moreover, in the entire population ACR exhibited a

positive correlation with hs-CRP (r=0.603, p<0.0001), whereas there was no association with both IL-18 and sCD40L (p=NS for both cases). When multiple linear regression analysis was performed, it was revealed that age, BMI, office systolic BP and hs-CRP levels were significant independent predictors of the ACR (p<0.05).
Conclusions: In newly diagnosed essential hypertension, microalbuminuria is accompanied by elevated hs-CRP levels, but not by augmented IL-18 and sCD40L concentrations, suggesting activation of different inflammatory pathways in the progression of renal and cardiovascular atherosclerotic disease. The pathophysiological mechanisms of the abovementioned associations remain to be further elucidated in future studies.

P1704 Neuregulin-1 in endothelium-cardiomyocyte cross-talk

K. Lemmens, F.M. Segers, W. De Keulenaer. *University of Antwerp, Physiology dpt, Antwerp, Belgium*

Introduction: Neuregulin-1 (NRG-1) is a cardio-active growth factor. Recombinant NRG-1 regulates survival, growth and contractility of cardiomyocytes in vitro. Experimental impairment of NRG-1/ErbB signaling results in cardiomyopathy in vivo. The role of NRG-1 in chronic heart failure is incompletely understood.
Hypothesis: We hypothesized that NRG-1 is a paracrine factor synthesized and controlled by cardiac endothelial cells in conditions of "stress", mediating "protective effects" on adjacent cardiomyocytes.
Results: 1. Immunohistochemical staining of rat tissues showed intense NRG-1 expression in cardiac endothelial cells of the endocardium and of the cardiac micro-vasculature (CMVE). NRG-1 staining was absent in vascular endothelium of larger coronary arteries and veins and in aorta. 2. In rat CMVE in culture, NRG-1 mRNA and protein expression was induced by endothelin-1 (max 11.8 ± 6.7 fold, p=0.01) and by 5% cyclic stretch (max 3.5 ± 0.4, p=0.04), but downregulated by angiotensin II (max 11.6 ± 5.4 fold, p=0.03) and phenylephrine (max 2.4 ± 0.5 fold, p=0.02).
3. Culture medium conditioned by rat CMVE, as well as co-culture with CMVE induced phosphorylation and cleavage activation of the ErbB2 receptor of neonatal rat cardiomyocytes (NRCM). Pre-treating NRCM with anti-ErbB2 antibody inhibited cleavage activation.
4. Culture medium conditioned by rat CMVE, as well as co-culture with CMVE induced hypertrophy of NRCM (increase of cell surface area and enhanced BNP mRNA expression). Pre-treating NRCM with anti-ErbB2 antibody abolished these effects.
5. Culture medium conditioned by rat CMVE, as well as co-culture with CMVE protected against daunorubicin-induced cardiomyocyte apoptosis (assessed with TUNEL assay and annexin staining). Pre-treating NRCM with anti-ErbB2 antibody abolished these effects.
Conclusion: NRG-1 is an endothelial factor involved in paracrine endothelium-cardiomyocyte cross-talk. Various neurohormones and mechanical strain have variable effects on endothelial synthesis of NRG-1.

P1705 Effects of mechanical stretch and oxidant stress on vascular endothelial growth factor-mediated PKB/Akt expression in HUVEC

B. Kou, M. Vatish, D.R.J. Singer. *Warwick University Medical School, Clinical Sciences Research Institute, Coventry, United Kingdom*

Background: Reduced capillary density (rarefaction) occurs with cardiovascular risk factors as well in established cardiovascular disease. VEGF is a key player in endothelial cell proliferation and angiogenesis, with PKB/Akt a critical signalling pathway. Both mechanical and oxidant stress are major factors implicated in development of endothelial dysfunction in other settings. We therefore investigated effects of mechanical and oxidant stress on VEGF-mediated PKB/Akt expression in human endothelial cells (HUVEC).
Methods: We grew primary cultures of endothelial cells obtained from human umbilical cords obtained following elective Caesarean Section, with written informed consent and local ethics committee approval. PKB/Akt expression was studied by semi-quantitative Western blot analysis. Effects of incubation with VEGF 10-100ng/ml were studied from 6h-96h. For mechanical stress, we applied 1Hz continuous action (Flexercell). Oxidant stress was induced by the xanthine 250mM/XOD(20-80U/ml) system. The SOD-mimetic Tiron (0.1-10U/ml) was used to assess effects of superoxide on basal and stimulated PKB/Akt expression. Results are mean±SEM for data in triplicate, with analysis by ANOVA.
Results: There were biphasic effects of HUVEC stretch, with 63±3% inhibition of PKB/Akt expression at 6h (p<0.01), return to basal expression at 12-24h and increase by 70±9% after 72h stretch (p<0.001). Basal PKB/Akt expression decreased by 62±8% after 24hr with xanthine/XOD/80U/ml (P<0.05 vs. baseline). The SOD-mimetic Tiron caused dose and time-dependent increases in PKB/Akt expression (P<0.05 vs. basal), maximal at 4.2±0.2 times basal with Tiron 5.0mM for 24h. VEGF induced dose-dependent stimulation of PKB/Akt expression, maximal 5.1±0.4 fold after 48hr incubation with VEGF 30ng/ml [P<0.05 vs. basal values]. Cell stretch enhanced VEGF-stimulated PKB/Akt expression by ca. 40% (max: 48hr: VEGF 30ng/ml alone 5.1±0.4 fold basal; VEGF + stretch 7.3±0.7 fold: P<0.01 vs. VEGF alone). Xanthine/XOD caused dose-dependent inhibition of PKB/Akt expression by VEGF 30ng/ml, maximally 25% reduced by XOD 80U/ml. Tiron fully reversed inhibition by xanthine/XOD of basal and VEGF-stimulated PKB/Akt expression (P<0.05).
Conclusion: Our studies showed significant potentiation by mechanical stretch of VEGF-mediated PKB/Akt signalling in human endothelial cells. Our findings also show that oxidant stress can suppress VEGF-mediated PKB/Akt signalling, with superoxide implicated in the inhibitory mechanism. These results suggest potential mechanisms for altered capillary density in cardiovascular disease.

P1706 Effect of influenza vaccine on endothelial function in patients with type 2 diabetes

R.G. Bogle, L. Sasikethan, J. Jean-Marie, J.S. Kooner. *Ealing Hospital NHS Trust, Department of Cardiology, Middlesex, United Kingdom*

Influenza infection is associated with increased risk of myocardial infarction and stroke. Potential mechanisms include inflammatory cytokines, endothelial dysfunction and alteration in coagulant activity (1). The aim of the present study was to examine whether simulated influenza infection using split, inactivated influenza virus could provoke endothelial dysfunction.
Endothelial-function was assessed in 12 type 2 diabetics by measurement of flow-mediated dilatation (FMD) of the brachial artery by high resolution ultrasound as described previously (2). Endothelium-independent vasodilatation was assessed by measurement of glyceryl trinitrate (200mcg, s.l) induced dilation of the brachial artery. Each subject was randomized (double-blinded) to either influenza vaccine (Fluvarix, 2003/2004) or placebo (0.9% saline, 0.5ml) by deep i.m. injection. FMD and GTN induced dilatation were measured in the brachial artery 24h and 1 week later. Venous blood was drawn before each assessment. Results were analysed by one-way analysis of variance and Dunnett's test with p<0.05 considered significant.
There was no significant effect of placebo or influenza vaccination on baseline brachial artery diameter and no alteration of FMD in subjects randomized to placebo: baseline FMD: 7.8±4.6%, 24h: 5.5±3.4%, 1 week: 6.6±4.0% (n=6). In contrast endothelium-dependent FMD was significantly reduced from 8.6±6.4% to 3.8±3.2% (P<0.05, n=6) 24h after influenza vaccination returning towards baseline 1 week later (5.9±3.1% P<0.05). GTN-induced, endothelium-independent, dilatation was not significantly affected by placebo or influenza vaccine. Similarly there was no effect of influenza vaccine or placebo on plasma levels of high-density lipoporotein, or erythrocyte sedimentation rate, white cell count or fibrinogen. These results demonstrate that a single challenge with split inactivated influenza virus results in a transient impairment of endothelium-dependent but not endothelium-independent dilatation without alteration in clinical markers of infection or inflammation. These results indicate that FMD is a sensitive method for examination of mild inflammatory stimuli on endothelial function and raise the possibility that influenza infection impairs endothelial function thereby promoting atherosclerosis and the risk of an acute coronary syndrome.
1. Madjid M et al. (2003). Circulation. 108:2730-6.
2. Chambers JC et al. (1999). Circulation 99:1156-60.

P1707 Kinetics and viability of circulating endothelial cells in patients with acute ST-elevation myocardial infarction and percutaneous coronary intervention

K. Vargova, E. Toth-Zsamboki, J. Bencze, I. Hizoh, G. Kerecsen, E. Csoti, R.G. Kiss, I. Preda. *SE-Hungarian Academy of Sciences, Cardiovascular Research Group, Budapest, Hungary*

In patients with coronary artery disease, endothelial dysfunction has been demonstrated. Circulating endothelial cell (CEC) count can serve as a useful marker of endothelial injury in various pathological conditions.
The aim of our study was to assess the kinetics and viability of CECs in patients with acute ST-segment elevation myocardial infarction (STEMI) and subsequent percutaneous coronary intervention (PCI).
CECs were isolated from whole blood (anti-CD-146, magnetic beads) of patients suffering from cardiovascular diseases. Endothelial origin of the CECs was confirmed by von Willebrand factor (vWF) staining. Second, CEC count(only CECs with 30-50 μm in diameter) and viability was determined in 14 patients with acute myocardial infarction (STEMI) and 12 with stable angina (SA) before and immediately after PCI, 24 hours and 72 hours later with acridineorange-propidiumiodide (AO-PI)staining.
In stable angina group (SA), the number of CECs before PCI was significantly higher (M(median): 3,25/ml; IQR (interquartile range): 1,3-10,5/ml) compared to healthy controls (M: 0,85/ml; IQR: 0,5-1,8/ml, p= 0,034). On the first day after PCI, CEC count rose (M: 8,22/1ml; IQR: 4,0-12,0/ml); on the third day after PCI decrease of CECs was detected (M: 3,75/ml; IQR: 1,33-6,0/ml).
In STEMI, the level of CECs determined before PCI was significantly higher (M: 9,1/ml; IQR: 4,75-19,0, p=0,008) compared to SA group. The CEC count rose after PCI (M: 12,0/ml; IQR: 6,5-23,0/ml) and peaked (M: 18,0/ml; IQR: 6,5-53,0/ml, p=0,043) 24 hours after coronary intervention. Comparing to baseline, the number of CECs in 72 hour samples was lower (M: 5,01/ml; IQR: 1,25-34,0/ml).
In STEMI group,majority of CECs isolated pre-, post-, 24 hours and 72 hours after PCI were viable (mean:88,5%, 86,6%, 85,3%,80,2%, respectively). In SA group, the number of viable CECs isolated pre- and 24 hours after PCI was very similar

to those in STEMI(mean: 85,3%, 88,4%). 72 hours after PCI decrease of viable CECs (56,2%) was detected.
In conclusion, we have confirmed elevated CEC count in STEMI and SA patients; PCI leads to further explicit damage and shedding of the vascular endothelium. Notably, endothelial injury was more prominent in the STEMI group, indicating that CEC count might reflect the cardiovascular risk. Unexpectedly, CEC count peaked 24 hours after PCI, indicating continuous detaching of endothelial cells from the subendothelial matrix. Pathomechanism of the late PCI-dependent CEC count elevation in STEMI patients deserves further investigation.

P1708 Time-course of acute myocardial infarction-dependent peripheral mobilisation of endothelial progenitor cells

P. Fabbi[1], V. Manca[2], I. Rocco[3], S. Garibaldi[2], G. Ghigliotti[2], P. Spallarossa[2], C. Brunelli[2], A. Barsotti[2]. [1]*University of Genoa, Dept. of Internal Medicine, Cardiology, Genoa, Italy;* [2]*University of Genova, Dept of Internal Medicine, Cardiology, Genova, Italy;* [3]*Emato-oncology, Department of Internal Medicine, Genoa, Italy*

Purpose: it has been demonstrated that circulating endothelial progenitor cells which originate by haematopoietic stem cells (EPCs) differentiate into mature endothelial cells, and may contribute to re-endothelialisation and neovascularisation at sites of injured tissue. Initially, EPCs in the bone marrow or immediately after their migration into the systemic circulation bear a specific cluster of surface markers (CD133, CD34, VEGFR-2) that is gradually lost at later times when these cells start to differentiate into mature endothelial cells. These "mature" EPCs lose CD133 and express Ve-cadherin, von Willebrand factor and other surface markers. Recent studies in humans demonstrated also that haematic mobilisation of CD34+ stem cells occurs during an acute ischaemic event. Our study was undertaken to establish time-intervals associated to recruitment of and type of recruited EPCs after heart ischaemia associated to acute myocardial infarction (AMI) in patients without comorbidities (diabetes mellitus, chronic renal failure, age $>$ 75) associated to an increased risk for early events after a non fatal AMI.
Methods: peripheral blood (50cc) was collected from 11 patients with ST-elevation AMI (STEMI)at: 3,7,15, 28 days after AMI. Haematic mobilisation of precursors has been identified with the expression of CD34 surface marker Maturation stage of EPCs has been verified through identification of CD133 and VEGFR2 subpopulations. Mononuclear cells fraction (CD34) has been separated by means of density gradient centrifugation (Ficoll Hipaque). After the passage on a magnetic column, CD34+ cells labelled with antibody conjugated microbeads have been purified from the positive fraction (MACS; Miltenyi Biotech). CD34+(Ab-FITC) cells and the two subpopulations: CD133 $\pm$ and VEGFR-2 $\pm$ (Ab-FITC e Ab-PE) have been identified with cytofluorimetric analysis.
Results: in our patients a peak of CD34+ cells is consistently observed at day 7 after AMI (per cent increase vs baseline:48$\pm$0.2%); at the same interval, the CD133-/VEGFR+ subpopulation is increased vs baseline of a mean 40.2$\pm$1.03%.
Conclusions: in our patients with STEMI, an increase of committed EPCs derived by bone marrow is demonstrated 7 days after the acute cardiac event. This interval may be selected to evaluate whether a difference in number and type of circulating progenitors of hematopoietic cells exists between patients with STEMI with or patients with STEMI without severe clinical conditions which are associated to different prognosis.

P1709 Endothelial progenitor cell function in hypoxic pulmonary hypertension

G. Marsboom[1], P. Pokreisz[1], P. Vermeersch[1], M. Pellens[1], H. Gillijns[1], D. Collen[1], S. Janssens[2]. [1]*University of Leuven, CTG (VIB-3), Leuven, Belgium;* [2]*University of Leuven, Department of Cardiology, Leuven, Belgium*

Introduction: Functional impairment of Endothelial Progenitor Cells (EPCs) is a hallmark of atherosclerotic disease, but remains largely unstudied in pulmonary hypertension. Therefore, we examined the number and adhesive properties of circulating EPCs isolated from normoxic and chronically hypoxic mice and compared their phenotype and capacity to incorporate into vascular networks.
Methods: Nine to 11 weeks old C57BL/6 mice were kept for 3 weeks in normoxia or chronic hypoxia (FiO2 10%). Thereafter, spleen-derived mononuclear cells were cultured on fibronectin-coated dishes in EBM-2 medium. After 7 days, cells were characterized as EPCs by the uptake of acetylated LDL and BS-1 lectin binding. Flow cytometry was done on a FACSCalibur, with at least 8000 events recorded. Adhesive properties were assessed on fibronectin-coated and BSA-blocked dishes and incorporation into a vascular network was studied by coplating EPCs and HUVECs on matrigel.
Results: The number of circulating EPCs in mice exposed to chronic hypoxia was significantly increased as 1.47$\pm$0.22% of spleen-derived mononuclear cells in the hypoxic animals vs. 1.08$\pm$0.25% in normoxic animals develop an EPC phenotype after 7 days of in vitro culture. The total number of EPCs residing in the spleen was also greater after 3 weeks hypoxia then after normoxia (11.8 $\pm$ 1.8 x10E5 versus 8.1$\pm$1.5 x10E5 respectively, n=7, P = 0.04). Flow cytometry revealed a 10$\pm$2.% decrease in VEGFR-2 expression in EPCs from chronically hypoxic mice compared to normoxic mice (n=4, P = 0.03). Adhesion to immobilized fibronectin of EPCs derived from chronically hypoxic mice was significantly lower compared to EPCs derived from normoxic mice (26$\pm$7% decrease, n=7, P = 0.03). Finally, incorporation of EPCs from chronically hypoxic mice into a vascular network was decreased by 22$\pm$6% (n=3, P = 0.07).
Conclusion: Chronic hypoxia increases the number of circulating EPCs, but reduces their differentiation potential (decreased expression of VEGFR-2) resulting in a functional impairment (decreased adhesion to fibronectin and incorporation into a vascular network). Chronic hypoxia is associated with a maladaptive EPC phenotype which may hinder their repair capacity in pulmonary vascular disease.

P1710 Circulating endothelial microparticles impair vascular function in end stage renal failure patients

N. Amabile[1], A. Guerin[2], Z. Mallat[1], A. Leroyer[1], J. Boddaert[1], A. Tedgui[1], G. London[2], C.M. Boulanger[1]. [1]*INSERM U541, Paris, France;* [2]*CH Manhes, Department of Nephrology, Fleury Merogis, France*

Background: Endothelial dysfunction and arterial stiffness are major determinants of the cardiovascular risk in patients with end-stage renal failure (ESRF). Microparticles (MPs) are membrane fragments shed from damaged or activated cells that have various biological effects. We hypothesized that circulating MPs not only correlate with, but also contribute to arterial disease in ESRF patients.
Methods: Arterial stiffness parameters [aortic pulse wave velocity (PWV), carotid intima/media thickness (CIMT), carotid pulse pressure (PP) and carotid incremental modulus of elasticity (Einc)] were evaluated by ultrasonographic methods in 46 ESRF patients (63 $\pm$8 yr). Brachial artery (BA) vasodilatation was assessed by echography by the changes in artery diameter before and after the application of a 44°C thermocontrolled waterbath (flow induced vasodilatation) and sublingual application of glycerine trinitrate (TNT-induced dilatation).
Circulating MPs origin and numbers were characterized on poor platelet plasma withdrawn prior to hemodialysis, using cytofluorometric analysis. MPs pellets and supernatant were isolated from patients' blood by centrifugation. Rat aortic rings were incubated for 24 hours with either pellets (MP group) or supernatant (control group). NO-mediated relaxations and cyclic GMP production, a biochemical index of NO release, were then evaluated in the two groups.
Results: Circulating levels of both PMP (CD31+/CD41+ MPs) and EMP (CD31+/CD41- MPs) were increased in ESRF patients when compared to healthy controls ($p<0.001$). EMP levels highly correlated with the loss of the brachial artery flow-mediated dilatation (r =-0.543; p =0.004) whereas this relation was not found for PMP levels (r =0.056, p =0.789). Furthermore, a strong relationship was found between circulating EMP levels and PWV (r = 0,613; $p<0,0001$), Einc (r =0.535; p=0.0002) and PP (r =0.483, p =0.001) but not with CIMT (r =0.178, p=NS). No relation was established between circulating PMP levels and any of these arterial stiffness parameters. Exposure of rat aortas to plasma MP from ESRF patients impaired endothelium-dependent relaxations to acetylcholine and cyclic GMP generation compared to control group. Again, endothelial dysfunction correlated with EMP (r =0.891; p =0.003), but not PMP concentrations in the incubation medium.
Conclusion: Although both EMP and PMP levels are increased in ESRF patients, our results identify circulating endothelial microparticles as a major determinant of endothelial dysfunction and arterial stiffness in these subjects

P1711 Real-time measurement of NO concentration in coronary sinus by a newly developed catheter-type NO sensor

Y. Neishi[1], S. Mochizuki[2], M. Goto[2], T. Kume[1], S. Renan[1], T. Kawamoto[1], T. Akasaka[1], K. Yoshida[1]. [1]*Kawasaki Medical, Cardiology Dept., Kurashiki, Japan;* [2]*Kawasaki Medical School, Medical Engineering, Kurashiki, Japan*

Background: Recently, it has become apparent that biologically active endothelium-derived nitric oxide (NO) can be detected in the blood stream. In the coronary circulation, NO has been considered to play crucial roles in health and diseases. Thus, to evaluate NO concentration in the coronary circulation, we have developed a catheter-type NO sensor applicable to the coronary sinus in vivo.
Methods: A NO sensor (Innovative Instruments, Inc.) mounted in 4-Fr catheter with a soft tip for protection of vascular wall was placed in the coronary sinus through a 7-Fr JR catheter from the right jugular vein of anesthetized dogs (n=7). Coronary flow velocity was measured by a Doppler flowire (Volcano). Acetylcholine (ACh, 0.4 and 1.0 μg/kg) and NG-methyl-L-arginine (L-NAME, 10 μg/kg/min for 20min) were infused into the left coronary artery to stimulate and inhibit NO production, respectively.
Results: NO concentration was successfully measured by the NO sensor in all dogs studied. ACh increased coronary flow velocity immediately accompanied by an increase in NO concentration in the coronary sinus in a dose-dependent manner (6.8$\pm$2.1 nM and 8.2$\pm$2.5 nM, p=0.05). L-NAME decreased basal NO concentration by 3.1$\pm$0.8 nM and suppressed the NO synthesis by ACh (1.9$\pm$0.6 nM, p=0.03 and 2.8$\pm$0.8 nM, p=0.05 vs before L-NAME).
Conclusion: NO concentration can be measured in the coronary sinus by a newly developed catheter-type NO sensor. This catheter-type NO sensor is useful and safe to evaluate endothelium-derived NO in the coronary circulation.

P1712 The multidrug resistance protein 1 (MRP1) modulates vascular function and atherogenesis

C. Mueller[1], J. Widder[2], T. Czech[3], C.H. Chen[3], D.G. Harrison[2], G. Nickenig[3]. *[1]Univ. -Kliniken des Saarlandes, Innere Med. III - Kardiologische, Homburg, Germany; [2]Emory University, Cardiology, Atlanta, United States of America; [3]Universitätskliniken des Saarlandes, Innere Medizin III Kardiologie, Homburg/Saar, Germany*

Oxidative stress has been connected with endothelial dysfunction, apoptosis and plaque development in the vasculature. One of the major cellular oxidant defense systems against reactive oxygen species (ROS) involves the redox couple of reduced and oxidized glutathione (GSH/GSSG). It has been shown that ROS exposure caused by oscillatory shear decreases the intracellular GSH levels in endothelial cells (HAECs) and this due to an active transport of GSSG by the multidrug resistance protein 1 (MRP1). MRP1 is one of nine currently known MRP proteins. Inhibition of MRP1 by MK571, a specific pharmacologic inhibitor, or downregulation by siRNA both efficiently prevented this export in HAECs. The aim of this study was to investigate the role of MRP1 as a modulator of atherogenesis and endothelial dysfunction

Vascular smooth muscle cells were stimulated with Angiotensin II (10-6) and expression of MRP1 was analysed by western blot. MRP1 was not only expressed in VSMC but also upregulated in a dose dependent manner indicating an important role in the setting of cellular oxidative stress management. DCF fluorescence measurements revealed that pharmacologic inhibition of MRP1 as well as downregulation by specific siRNA resulted in a significantly reduced rate of ROS production. Furthermore the rate of apoptosis, measured via caspase 3 activity, was significantly diminished. To investigate the relevance of these findings in vivo two groups of ApoE-/-mice (n=6/group), an animal model of rapid atherosclerotic lesion development, received Western diet for 5 weeks. Additionally one group was treated with MK 571. Blocking of MRP1 resulted in a reduction of atherosclerotic plaques area by 50%. Furthermore the endothelium dependent vasorelaxation was measured and showed a significantly less impaired endothelial function in mice treated with MK 571.

Our results indicate a strong connection between MRP1, vascular function and atherogenesis. MRP1 may provide a potentially new therapeutic target for the treatment of endothelial dysfunction and atherosclerosis.

P1713 Osteoprotegerin (OPG): a protective role of endothelium against arterial calcification

C. Cola[1], R. Mango[1], F. Clementi[1], G.B. Forleo[1], C. Postorino[1], G. Novelli[2], J.L. Mehta[3], F. Romeo[1]. *[1]University of "Tor Vergata", Cardiology, Rome, Italy; [2]University of "Tor Vergata", Genetic, Rome, Italy; [3]University of Arkansas, Cardiology, Little Rock, United States of America*

Background and Objectives: Arterial calcification is a complex and well regulated process shearing features with bone formation. To investigate the role of endothelial cells in this process we monitored the expression of two bone-associated proteins: osteopontin (OPN) and osteoprotegerin (OPG). OPN is a secreted integrin-binding protein, inhibitor of vascular smooth muscle cells calcification, and chemoattractant/activator of inflammatory cells. Osteoprotegerin (OPG), a member of the TNF receptor family, represents a protective factor for the vascular system: it inhibits arterial calcification and modulates inflammation. OPG -/- mice exhibit severe osteoporosis and vascular calcification. Moreover OPG serum levels in humans are associated with the severity of Coronary Artery Disease (CAD).

Methods and Results: Human coronary artery endothelial cells (HCAECs) were treated with ischemia (Nitrogen 95%, Carbon Dioxide 5%), for 2, 8 and 24 hours. Total RNA was extracted and reverse-transcribed, and expression of OPN and OPG quantified by real-time PCR.

OPN was expressed at very low levels in controls and treated cells; OPG expression exhibited a significant increase at 2 hr (p=0.04) and a further increase at 8 hr (p=0.002). This increase was no longer seen at 24 hours treatment.

Conclusion: While the pro-inflammatory OPN is expressed at very low level by endothelial cells, OPG, protective against calcification and anti-inflammatory is over-expressed in condition of ischemia. The endothelium, when exposed to atherosclerotic stimuli, regulates the process of arterial calcification by enhancing the expression of the inhibitory and protective OPG in a time dependent manner.

P1714 Effects of irbesartan and perindopril on endothelial function and inflammatory process in patients with stable angina pectoris: evidence for anti-inflammatory properties

P. Kourtallaris[1], D. Tousoulis[2], C. Antoniades[1], C. Vlachopoulos[1], G. Vyssoulis[1], G. Latsios[1], C. Pitsavos[1], C. Stefanadis[1]. *[1]Athens University Medical School, Cardiology Department, Athens, Greece; [2]Athens, Greece*

Endothelial dysfunction plays an important role in the pathogenesis of atherosclerosis. C-reactive protein (CRP) and fibrinogen (fibr), markers of acute phase response, are increased in coronary atherosclerosis (CAD). The effect of ACE-I and AngII inhibitors on endothelial function and inflammation are unclear.

Aim: We compared the effect of irbesartan or perindopril on endothelial function and levels of CRP and Fib in patients with CAD and stable angina.

Methods: In this study 60 patients with CAD and stable angina were enrolled. Twenty patients received irbesartan (75 mg/day), 20 received perindopril (2 mg/day) and 20 received no treatment for 4 weeks. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography at baseline and after treatment. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from baseline to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration respectively.

Results: No significant difference was observed in EDD and EID at baseline, between groups. EDD was improved in both perindopril and irbesartan-treated groups (from 40.6±3.9 and 35.7±4.1 to 64.3±5.4 and 65.3±6.8% respectively, $p<0.01$ for both), while remained unaffected in controls (from 38.4±3.5 to 36.8±3.1% respectively, p=NS). EID remained unchanged in all groups. CRP serum level was decreased in irbesartan group (from 4.45±0.59 to 2.88±0.65 ng/ml, $p<0.05$), while remained unaffected in perindopril and control group (from 4.59±2.45 and 8.34±2.5 to 3.81±0.99 and 7.27±5.2 ng/ml, p=NS). Fib levels were decreased in irbesartan group (from 324± 17 to 291±25 ng/ml, $p<0.05$) but not in perindopril and control groups (from 332±18 and 359±27 to 305±18 and 318±25 ng/ml respectively, p=NS for both).

Conclusions: Both irbesartan and perindopril, improve endothelial function in patients with CAD and stable angina. However, irbesartan but not perindopril affects inflammatory process by decreasing serum levels of CRP and fibrinogen. These findings indicate that this angiotensin II receptor antagonists beyond its effects on endothelial function, may also affects inflammatory process in patients with stable angina.

P1715 Adiponectin is associated with coronary endothelial function independent of insulin resistance in non-diabetic patients

H. Okui, S. Hamasaki, T. Kataoka, M. Ogawa, K. Saihara, E. Mizoguchi, S. Minagoe, C. Tei. *Kagoshima University, Department of Cardiovascular, Respiratory and, Kagoshima, Japan*

Background: The American Heart Association (AHA) has recently determined obesity as a modifiable risk factor for coronary artery disease. Vascular endothelial dysfunction has been demonstrated in overweight or obese patients with insulin resistance. A newly discovered adipose-specific molecule, adiponectin, was shown to be decreased in obese patients, as in patients with coronary artery disease. Therefore, the present study investigated the association of adiponectin and insulin resistance with coronary endothelial function.

Methods: A total of 25 consecutive non-diabetic patients with normal coronary arteries at angiography were enrolled in this study. Coronary vascular reactivity was evaluated by intracoronary administration of acetylcholine (Ach) using a Doppler guidewire. The level of fasting immunoreactive insulin, fasting plasma glucose, and the plasma adiponectin concentrations were measured in each subject. Homeostasis model assessment (HOMA-R) was used as an indicator of insulin resistance.

Results: Plasma log adiponectin concentration had positive correlations with the percent change in coronary blood flow (CBF) and coronary artery diameter (CAD) induced by acetylcholine ($r=0.72$, $p<0.0001$; $r=0.75$, $p<0.0001$, respectively). HOMA-R negatively correlated with the percent change in CBF and CAD induced by Ach ($r=-0.70$, $p<0.0001$; $r=-0.83$, $p<0.0001$, respectively). In a multiple linear regression analysis, log adiponectin and HOMA-R were independent predictors of the percent change in CBF and CAD induced by Ach ($p<0.05$).

Conclusions: Serum adiponectin concentration appears to be highly associated with coronary endothelial function. This association seems to be independent of its link with insulin resistance.

P1716 The degree of endothelial cell apoptosis determines coronary endothelial function in patients with coronary artery disease

N. Werner[1], S. Wassmann[2], P. Ahlers[2], S. Kosiol[2], T. Schiegl[2], G. Nickenig[2]. *[1]Saarbrücken, Germany; [2]Universitätskliniken des Saarlandes, Innere Medizin III, Homburg-Saar, Germany*

Background: Endothelial dysfunction predicts morbidity and mortality in patients at cardiovascular risk. Endothelial function may be decisively influenced by the degree of endothelial cell apoptosis. Endothelial microparticles are small membrane vesicles which are directly shed from mature endothelial cells during apoptosis. Endothelial microparticles have been shown to be elevated in conditions of endothelial cell damage, e.g. in patients with thrombotic thrombocytopenic purpura and preeclampsia but also in acute coronary syndromes, diabetes, hypertension, and hypertriglyceridemia. However, it is unknown whether the increased numbers of EMP in patients with cardiovascular risk factors are an independent risk marker in cardiovascular disease.

Methods and Results: To test this hypothesis in humans, endothelial function was invasively assessed in 50 patients with coronary heart disease by quantitative coronary angiography during intracoronary acetylcholine infusion. Flow cytometry was used to assess endothelial cell apoptosis by quantification of circulating endothelial apoptotic microparticles in peripheral blood. Increased endothelial apoptotic microparticle counts positively correlated with impairment of coronary endothelial function. Multivariate analysis revealed that increased endothelial mi-

croparticle counts predict severe endothelial dysfunction independent of classical risk factors such as hypertension, hypercholesterolemia, smoking, diabetes, age, or sex.
Conclusions: In patients with coronary heart disease, endothelial function closely relies on the degree of endothelial cell apoptosis which is readily measurable by circulating endothelial apoptotic microparticles. These findings possibly provide new options for risk assessment and may have implications for future treatment strategies of coronary heart disease.

P1717 NO production by angiotensin II in endothelial cells is modulated by two different subcellular pools of superoxide anions

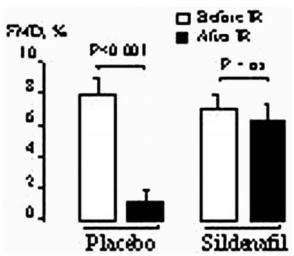
I. Lobysheva[1], B. Gallez[2], C. Dessy[1], O. Feron[1], J.L. Balligand[1]. *[1]Universite Louvain (UCL), Dept. of Medicine, Pharmacology Unit, Brussels, Belgium; [2]Université catholique de Louvain, MR unit, School of Pharmacy, Brussels, Belgium*

Generation of superoxide anions under pathologic conditions accelerates endothelial dysfunction. Angiotensin II (Ang II), a vasoconstrictor agent, is a potent activator of the vascular NAD(P)H oxidase leading to increased production of superoxide anions (O2-.), but can also stimulate NO formation in endothelial cells. The functional significance of the concurrent production of these two radicals, in particular with regard to the subcellular compartment where they are produced, however, is unclear. We directly measured the production of NO and O2-. in bovine aortic endothelial cells (BAEC) treated with Ang II using EPR spin-trapping (with [Fe(II)(DETC)2] and DMPO, respectively) and examined its modulation by anti-oxidants with different subcellular distributions. Ang II increased NO and O2-. to 158±12% and 219±5% of levels in unstimulated cells; the former was inhibited by L-NAME (to 89±10%) and the latter by apocynin, a NAD(P)H oxidase inhibitor (to 68±23% of control; $P<0.05$ for both; n=3 different experiments). Of note, the NO signal was also abrogated by apocynin (to 67±10%; $P<0.05$), suggesting the implication of ROS production by NADPH oxidase in the activation of eNOS. Conversely, the O2-. signal was inhibited by L-NAME (to 47±10%; $P<0.05$; n=3), suggesting superoxide production by uncoupled eNOS in response to AngII. Both signals were also blunted by the PI3K inhibitor, LY294002, (to 74±14%; $P<0.05$) suggesting the implication of this kinase in the coupling of AngII to eNOS and O2-. production. The relatively hydrophobic and membrane-restricted antioxidants, PEG-SOD, MnTBAP or alpha-tocopherol increased the NO signal with AngII at the membrane (to 156±14% of levels without antioxidants; $P<0.05$). Conversely, the hydrophilic and cell diffusible N-acetyl-cysteine (NAC) and Trolox inhibited the NO signal with AngII (to 21±7 and 88±5%; $P<0.05$), pointing out to the inhibition, by these antioxidants, of an intracellular pool of O2-. critical for eNOS activation by AngII. NAC and Trolox had no effect on the NO signal with the receptor-independent calcium ionophore, A23187.
We conclude that NAD(P)H oxidase-derived superoxide anions mediate the stimulatory effect of Ang II on the endothelial NO formation in a PI3-kinase-dependent manner. The differential effect of membrane-restricted versus intracellular antioxidants on the NO signal suggests that two fluxes of ROS differentially modulate NO formation by AngII in endothelial cells.

P1718 Endothelial protective effect of phosphodiesterase V inhibition in the setting of ischaemia and reperfusion. A human in vivo study

T. Gori[1], S. Sicuro[1], S. Dragoni[1], G. Di Stolfo[1], G. Donati[1], C. Pierli[2], S. Forconi[1], J.D. Parker[3]. *[1]Ospedale Le Scotte, Internal Cardiovascular Geriatric Medicine, Siena, Italy; [2]Osp Le Scotte, U.O Emodinamica, Siena, Italy; [3]Mount Sinai Hospital, Cardiology/suite 1609, Toronto, Canada*

Background: Animal studies have demonstrated that administration of sildenafil can limit myocardial damage induced by prolonged ischaemia, an effect that appears to be mediated by opening of ATP-sensitive potassium (K-ATP) channels. No study has investigated whether sildenafil can also prevent the impairment in endothelium-dependent vasodilatation induced by ischaemia-reperfusion (IR) in humans.
Methods and Results: in a double-blind, placebo-controlled, cross-over design, 10 healthy male volunteers (age 25-45 years) were randomized to oral sildenafil (50 mg) or placebo. Two hours later, endothelium-dependent, flow-mediated dilatation (FMD) of the radial artery was measured before and after IR (15 minutes of ischemia at the level of the brachial artery followed by 15 minutes of reperfusion). Seven days later, subjects received the other treatment (i.e., placebo or sildenafil) and underwent the same protocol. Pre-IR radial artery diameter and FMD, as well as baseline radial artery diameter after IR, were similar between visits (P=ns). After placebo administration, IR significantly blunted FMD (before IR: 7.9±1.1%; after IR: 1.2±0.7%, $P<0.01$). Importantly, Sildenafil limited this impairment in endothelium-dependent vasodilatation (before IR: 7.0±0.9%; after IR: 6.2±1.1%, P=ns; $P<0.01$ compared to placebo). In a separate protocol, this protective effect was completely prevented by prior administration of the sulfonylurea glibenclamide (glyburide, 5 mg), a blocker of K-ATP channels (n=7; FMD before IR: 10.3±1.5%; after IR: 1.3±1.4%, $P<0.05$).
Conclusions: in humans, oral sildenafil induces potent protection against IR-induced endothelial dysfunction through opening of K-ATP channels. Further studies are needed to test the potential clinical implications of this finding.



P1719 Accumulation of extracellular ATP protects against acute endothelial reperfusion injury

D. Guenduez[1], F.V. Haertel[2], M. Aslam[2], H.M. Piper[2], T. Noll[2]. *[1]Justus-Liebig-University, Physiologisches Institut, Giessen, Germany; [2]Justus-Liebig-University, Physiologisches Institut, Giessen, Germany*

During reperfusion endothelial barrier failure causes a harmful edema formation and thus disturbs cardiac recovery. This barrier failure is due to an activation of the endothelial contractile machinery causing cell retraction and formation of interendothelial gaps. Recently, we showed that extracellular ATP inactivates the contractile machinery and stabilizes the endothelial barrier.
Aim: Here we studied whether extracellular ATP can protect the endothelial barrier against an imminent reperfusion-induced failure. Since ATP is released spontaneously from EC under different (patho)physiological conditions, we further analyzed, whether inhibition of ATP degradation can enhance this protective effect.
Methods: In cultured microvascular coronary endothelial cells (CEC) ATP release (bioluminescence assay), activation of contractile machinery (myosin light chain phosphorylation), and intercellular gap formation (GF, video imaging system) were measured. In isolated perfused rat hearts myocardial water content (MWC) was determined.
Results: Reperfusion of CEC lead to a slight accumulation of extracellular ATP, an activation of the contractile machinery, and therefore formation of GF. Whereas, reperfusion in presence of ARL 67156 alone, a specific inhibitor of ectonucleotidases (CD39), strongly enhanced accumulation of extracellular ATP, abolished reperfusion-induced activation of the contractile machinery and reduced GF, significantly. Reperfusion in presence of exogenously added ATP plus ARL caused an additional reduction of the both aforementioned effects. In contrast, rise in ATP degradation by apyrase, a soluble CD39, or adenosine provoked an increase in GF, which could completely be inhibited by 8-phenyltheophilline (8-PT), an adenosine receptor antagonist. In Langendorff-perfused rat hearts reperfusion-induced increase in MWC was significantly reduced, when ARL plus ATP were added to the reperfusion medium, whereas an increase in MWC could be blocked by 8-PT under conditions favoring ATP degradation.
Conclusion: Extracellular ATP either released from cells or exogenously applied, protects against acute endothelial reperfusion injury in coronary endothelial cells and in an intact coronary vascular system. However, when ATP is degraded, its barrier stabilizing effect is overruled by the permeabilizing effect of adenosine. Manoeuvres preventing ATP degradation or antagonizing adenosine receptors interactions preserve the stabilizing effect. These findings may open new therapeutic options for protection against acute coronary reperfusion injury.

P1720 Evaluation of endothelial dysfunction in patients affected by ulcerative colitis

C. Di Campli, A. Papa, A. Armuzzi, M.A. Zocco, P. Tondi, R. Flore, A. Gasbarrini, A. Santoliquido. *A. Gemelli University Hospital, Internal Medicine, Roma, Italy*

Background and aims: inflammatory bowel diseases are characterized by disorders of immunity, thrombosis of large vessels, and microthrombosis of mucosal vessels. In particular, human intestinal microvessels from chronically inflamed IBD (inflammatory bowel diseases) show microvascular endothelial dysfunction, characterized by loss of NO-dependent dilation that may contribute to reduced perfusion, poor wound healing, and maintenance of chronic inflammation.
We aimed to assess the systemic endothelial function and soluble adhesion molecules in patients with UC (ulcerative colitis).
Materials and methods: 18 patients affected by UC were consecutively enrolled. The disease activity was evaluated by CAI score. The endothelial dysfunction at the brachial artery was performed according to the standard protocol. The FMD (flow-mediated dilation) was expressed as percent change in diameter after reactive hyperemia relative to the baseline value. The serum levels of sE-Selectin, sVCAM, and sICAM and VEGF were measured by ELISA. A group of 15 healthy subjects matched by sex and age were enrolled as control group.
Results: the mean FMD in patients with UC was significantly reduced compared to FMD of healthy controls (7.1 ± 5.54 vs 15.7 ± 9.1; $p<0.004$). Endothelial independent vasodilation was similar between the two groups (20.0 ± 5.2 vs 18.57 ± 7.4, NS). There was no significant difference in serum levels of VEGF, ICAM1

and VICAM between the two groups. The serum levels of sE-Selectin were significantly lower in patients with UC compared to controls. Dividing the patients into two groups, with a CAI score cut off value > 150, we have observed a direct correlation between activity disease and endothelial dysfunction, with a significant difference of endothelial dysfunction between the two groups ($p < 0.01$).
Conclusions: As demonstrated in other inflammatory chronic diseases, endothelial dysfunction could be an independent risk factor for cardiovascular disease. This is the first report of systemic endothelial dysfunction in patients affected by UC. Further prospective studies are needed to demonstrate if endothelial dysfunction in these patients could somehow influence the prognosis of UC.

P1721 Beta-receptor antagonists inhibit C-reactive protein-mediated activation of human coronary artery endothelial cells

G. Sauter[1], U. Kreutzer[2], T. Risler[2], S.C. Wolf[2], B.R. Brehm[3].
[1]University of Tuebingen, Internal Medicine IV, Tuebingen, Germany; [2]University of Tuebingen, Internal Medicine IV, Tuebingen, Germany; [3]University of Tuebingen, Hertie-Institute, Tuebingen, Germany

Background: C-reactive protein (CRP) is an important risk factor for cardiovascular disease. However, recent data suggest that CRP is not only a nonspecific marker of inflammation but directly promotes the development of atherosclerotic lesions. In endothelial cells, CRP induces the expression of inflammatory cytokines and adhesion molecules.
Objective: In the present study, we examined the effect of beta-receptor antagonism on CRP-induced upregulation of interleukin (IL) -6 and -8, monocyte chemoattractant protein 1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) in human coronary artery endothelial cells (EC).
Methods and Results: EC were incubated with metoprolol, carvedilol or nebivolol (10-5 mol/l) for 72 hours. Then, human recombinant CRP (25 μg/ml) was added for 8 hours. mRNA-expression of IL-6 and –8, MCP-1, VCAM-1 and ICAM-1 was determined by real-time RT-PCR.
CRP significantly increased the expression of IL-6 (+1473%), IL-8 (+1545%), MCP-1 (+4644%), VCAM-1 (+878%) and ICAM-1 (+2775%) mRNA. Preincubation with nebivolol attenuated the increase in the expression of IL-6 (32,16%), IL-8 (18,51%), MCP-1 (10,64%), VCAM-1 (24,35%), and ICAM 1 (29,79%) mRNA. Carvedilol also inhibited the effect of CRP on the induction of IL-6 (31,31%), IL-8 (13,93%), MCP-1 (5,60%), VCAM-1 (14,73%) and ICAM-1 (6,57%) mRNA. Pretreatment with metoprolol only reduced CRP-mediated IL-8-upregulation (41,19%).
The secretion of MCP-1 as assessed by ELISA was reduced after 72 hours of incubation with nebivolol or carvedilol. CRP stimulated MCP-1 production in control cells. Metoprolol did not inhibit CRP-mediated MCP-1 secretion.
Conclusion: These data demonstrate, that beta-receptor blockers can attenuate the CRP-mediated upregulation of proinflammatory genes in human coronary artery endothelial cells. This might be one of the mechanisms underlying the positive effects of beta-blocker therapy on morbidity and mortality in patients with coronary artery disease.

P1722 Enhanced expression of TLR4 in smooth muscle cells in human atherosclerotic coronary arteries – role of inflammatory cytokines

K. Otsui, N. Inoue, R. Shiraki, T. Honjo, M. Takahashi, S. Kawashima, M. Yokoyama. *Kobe University Graduate School of Medicine, Division of Cardiovascular and Respiratory Me, Kobe-city, Japan*

Toll-like receptors (TLRs) play a crucial role in innate immunity as the first defense system against microbial infection. So far, ten TLRs have been identified. TLR1, TLR2 and TLR4 are expressed in atherosclerotic vessels. Particularly, it is reported that exogenous as well as endogenous ligands for TLR4 are expressed during arterial injury. However, the expressional pattern of TLRs in human coronary arteries of patients with coronary artery disease (CAD) and their regulatory mechanisms are still unknown.
In the present study, we investigated the expressional patterns of TLR4 in coronary specimens obtained from CAD patients (stable angina; n=10, unstable angina; n=11) by directional coronary atherectomy or autopsy cases (n=6). In atherosclerotic coronary arteries, the immunoreactivity of TLR4 was co-localized with almost infiltrating inflammatory cells, suggesting that TLR4 expression is closely associated with vascular inflammation. Vascular smooth muscle cells (VSMCs) in atherosclerotic coronary arteries intensely expressed TLR4 even in the regions where few inflammatory cells existed. In contrast, TLR4 expression was barely detected in VSMCs of non-atherosclerotic coronary arteries. These findings suggest that VSMCs in atherosclerotic coronary arteries are likely activated to express TLR4. Furthermore, the stimulation with angiotensin II increased the expression of TLR4 mRNA in cultured VSMCs. Thus, pro-inflammatory cytokines produced in the active inflammatory lesions might contribute to the enhanced expression of TLR4 in VSMCs of atherosclerotic arteries.

P1723 Homocysteine stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-kb activation induced by intracellular oxidative stress: protective role by natural antioxidants

M.A. Carluccio[1], M.A. Ancora[1], M. Massaro[1], M. Carluccio[2], C. Storelli[3], A. Distante[1], R. De Caterina[4]. *[1]Institute of Clinical Physiology, CNR, Lecce, Italy; [2]CNR Institute of Clinical Physiology, Laboratory for Thromb & Vasc Research, S.Cataldo - Pisa, Italy; [3]University of Lecce, Department of Biology, Lecce, Italy; [4]"G. d'Annunzio" University-Chieti, Director, University Cardiology Division, Chieti, Italy*

Hyperhomocysteinemia is a risk factor for cardiovascular disease. Since monocyte adhesion to the endothelium is a crucial event in atherogenesis and vascular cell adhesion molecule(VCAM)-1 is an important mediator of such interactions, we evaluated the effects of homocysteine (Hcy) on endothelial VCAM-1 expression, and explored mechanisms involved.
Human umbilical vein endothelial cells were stimulated with Hcy or cysteine for 20 hours. Hcy, but not cysteine, at 100 μmol/L (a concentration of moderate-to-severe hyperhomocysteinemia), induced VCAM-1 protein and mRNA (2.4 ± 0.3 folds vs control, $p<0.05$; and 1.9 ± 0.2 folds vs control, $p<0.05$ at enzyme immuno assay and Northern analysis respectively), but not ICAM-1 or E-selectin. Hcy-stimulated VCAM-1 expression was significantly reduced by the proteasome inhibitor lactacystin, suggesting the involvement of the nuclear factor(NF)-kB pathway. Indeed, Hcy activated NF-kB at EMSA, induced the nuclear translocation of the p65 NF-kB subunit at Western and immunofluorescence analyses, and increased the phosphorylation and subsequent degradation of the inhibitor(I)-kBa. Since I-kB phosphorylation is a redox-sensitive process, we assessed the effect of antioxidants on Hcy-stimulated VCAM-1 expression. Natural antioxidants such as resveratrol and hydroxytyrosol at 25 μmol/L, as well as 10 μmol/L pyrrolidinedithiocarbamate and 10 mmol/L N-acetyl cysteine all inhibited VCAM-1 expression by about 40 ± 5% vs control. The overproduction of intracellular reactive oxygen species (ROS) by Hcy was confirmed by the 2',7'-dichlorofluorescein diacetate method. Here Hcy induced a 35 ± 4% increase in intracellular ROS at flow cytometry. 10 μmol/L apocynin and diphenyleneiodonium, both NADPH oxidase inhibitors, reduced Hcy-stimulated VCAM-1 expression by 40 ± 7%, suggesting NADPH oxidase stimulation as a source of ROS production by Hcy.
In conclusion: Pathophysiologically relevant Hcy concentrations induce endothelial VCAM-1 expression activating the NF-kB signaling pathway. This effect is largely determined by an induction of NADPH oxidase activity. Natural antioxidants may counterbalance Hcy effects on endothelial activation.

P1724 Vascular endothelial growth factor-dependent leucocyte adhesion to endothelial cells involves Ca(2+)- and ROS-induced upregulation of VCAM-1 and ICAM-1

C.A. Schaefer[1], M.B. Schaefer[2], F. Renner[3], A.K. Most[4], M. Hartmann[4], K. Mayer[2], A. Erdogan[4], C.R.W. Kuhlmann[4]. *[1]Giessen, Germany; [2]Justus-Liebig-University of Giessen, Lung Center, Giessen, Germany; [3]Justus-Liebig-University of Giessen, Dept. of Nephrology, Giessen, Germany; [4]Justus-Liebig-University of Giessen, Dept. of Cardiology and Angiology, Giessen, Germany*

Vascular endothelial growth factor (VEGF) is a pluripotent activator of endothelial cells including signaling cascades of vascular inflammation. In the present study we examined whether the VEGF-induced increase of Ca(2+) and ROS is involved in the adhesion of leucocytes to endothelial cells. The adhesion of [^{3}H]-labeled monocytotic U937 cells to endothelial cells derived from human umbilical cord veins (HUVEC) was significantly increased if HUVEC were incubated with VEGF (30 ng/ml; 304.9±14.3% of control, $p<0.05$, n=12). This VEGF-induced effect was significantly reduced by the addition of the Ca(2+) chelator BAPTA (10 μmol/l) or the NAD(P)H-oxidase inhibitor diphenyleniodonium (DPI; 5 μmol/l). In detail, the adhesion was (in % of control) 159.6±13.1 (VEGF+BAPTA), 98.9±7.1 (BAPTA), 119.2±9.8 (VEGF+DPI), 88.7±14.9 (DPI) ($p<0.05$ vs. VEGF, n=12). The expression of the adhesion molecules ICAM-1 and VCAM-1 was examined using fluorescence activated cell sorting. Incubation of HUVEC with VEGF (30 ng/ml) resulted in a significant increase of ICAM-1 (307.5±33.2% of control) and VCAM (216.1±52.7% of control). Again, the effect of VEGF was significantly reduced by the addition of BAPTA, or DPI ($p<0.05$, n=4).
In conclusion the data of the present study demonstrate an important role of Ca(2+) and ROS in VEGF-induced endothelial inflammatory signaling.

P1725 MHC class II is highly expressed in endothelium and vasa vasorum of internal mammary arteries of patients with acute coronary syndromes suggesting a widespread vascular inflammation

C. Foglieni[1], F. Maisano[2], L. LiVolsi[1], A. Castiglioni[2], A. Giazzon[1], G. Ruotolo[1], A. Maseri[1], A.E. Becker[3]. *[1]San Raffaele Scientific Institute, Cardiothoracic and Vascular Department, Milano, Italy; [2]HSR, Division of Cardiac Surgery, Milano, Italy; [3]San Raffaele Scientific Institute, Milano, Italy*

Background: Recurrent acute coronary syndromes (ACS) are often characterized by multiple unstable coronary plaques, complex carotid plaques, and ele-

vated circulating levels of activated leukocytes and soluble inflammatory markers. Although resistant to atherosclerosis, internal mammary arteries (IMA) are exposed to circulating inflammatory stimuli.
Aim: to assess the inflammatory activation of IMA in paradigmatic patients (pts) with ACS or chronic stable angina (CSA).
Methods: We studied 22 pts undergoing coronary surgery: 8 ACS and 14 CSA. Clinical data: demographics, medical history, and risk factors (hs-CRP, IL-6, lipids, insulin and glucose levels) were obtained. IMA were sampled during surgery. The absence of morphological alterations was assessed with Hematoxylin/Eosin and Movat. CD31, E-selectin, CD106, MHC class I, MHC class II, CD54, iNOS, tissue factor, and TLR-4 expression intensity (+++ bright, ++ good, + visible, ± weak) was analyzed by confocal microscopy on serial sections.
Results: MHC class II was significantly more expressed by endothelium (END) of IMA lumen and vasa vasorum of ACS compared to CSA pts. An intensity > ++ was found in 50% ACS, but only in 7% of CSA pts lumina, and in 75% ACS but 21% CSA vasa vasorum. Smaller differences between the two groups were also found in luminal END for TLR-4 and E-selectin (evident in 25% and 62% of ACS, undetectable in 100% and 86% of CSA pts, respectively).
Conclusions: The expression of MHC class II and, to a lesser extent, TLR-4 and E-selectin on END of the IMA lumen and vasa vasorum is compatible with a widespread endothelial inflammatory activation in ACS pts.

P1726 Monocyte toll-like receptor 2 stimulation leads to increased firm adhesion to endothelial cells under flow conditions and increased migratory capacities

M.M. Oude Nijhuis[1], G. Pasterkamp[2], N.I. Sluis[2], U. Zahringer[3], D.P.V. de Kleijn[2], J.D. Laman[4], L.H. Ulfman[5]. [1]*University Medical Center Utrecht, Experimental Cardiology Dept., Utrecht, Netherlands;* [2]*University Medical Center Utrecht, Experimental Cardiology, Utrecht, Netherlands;* [3]*Center for Medicine and Biosciences, Department of Immunochemistry, Borstel, Germany;* [4]*Erasmus MC, Department of Immunology, Rotterdam, Netherlands;* [5]*University Medical Center Utrecht, Department of Pulmonary Diseases, Utrecht, Netherlands*

Background: In mice models, Toll-like receptor 2 (TLR2) ligation stimulates atherosclerotic plaque and intima formation. In addition, the TLR2 ligand peptidoglycan (PGN) is observed in macrophages of unstable atherosclerotic lesions. Monocytes play an important role in the initiation and progression of atherosclerosis. We determined the effect of TLR2 ligation on I) adhesion molecule expression by flow cytometry, II) monocyte adhesion to endothelial cells under flow conditions, III) monocyte binding to ICAM-1 coated beads and IV) monocyte migration using a Boyden chamber assay.
Results: Stimulation with two TLR2 ligands, purified Staphylococcus aureus PGN and synthetic Pam3Cys-SK4, significantly increased the expression of beta2-integrins (CD11b/CD18), whereas L-selectin (CD62L) expression was decreased compared to non-stimulated cells. Furthermore, total adhesion (=rolling and firm adhesion) of the TLR2-stimulated monocytes to L-cells, constitutively expressing ICAM-1 and E-selectin, was decreased (shear stresses 0.8-1.6 dyn/cm^2). This was most likely due to the L-selectin shedding, since monocyte incubation with a blocking L-selectin antibody resulted in a comparable number of adherent monocytes as TLR2-stimulated cells. Interestingly, TLR2 ligation resulted in an increased percentage firmly adherent monocytes under flow conditions (PGN: 92±3%, and Pam3Cys-SK4: 96±1% versus control: 52±7%, $p<0.001$ and p=0.004, respectively) and also to a beta2-integrin dependent increase in binding to ICAM-1 coated beads (PGN: 38±6%, and Pam3Cys-SK4: 37±3% versus control: 18±3%, p=0.02 and p=0.01, respectively). The polarized phenotype of TLR2-ligated monocytes on L-cells was confirmed in migration assays showing that these cells are primed for an increased migration towards the chemoattractant C5a (PGN: 45±5 μm and Pam3Cys-SK4: 61±9 μm versus control: 24±3 μm, p=0.01 and p=0.02, respectively).
Conclusion: This study demonstrates that TLR2 ligation results in an increase in adhesive and migratory capacities of monocytes. These results suggest a pathway by which TLR2 ligation promotes atherosclerotic disease in vivo.

P1727 Pro/anti-inflammatory T-lymphocytes interplay in familial hypercholesterolemia is modulated by plasma cholesterol

M. Puntoni[1], F. Bigazzi[1], S. Lusso[2], D. Chimenti[2], F. Minichilli[3], P. Migliorini[2], T. Sampietro[4], A. Bionda[2]. [1]*Institute of Clinical Physiology, Dyslipidemias & atherosclerosis, Pisa, Italy;* [2]*University of Pisa, Department of Internal Medicine, Pisa, Italy;* [3]*CNR Institute of Clinical Physiology, Pisa, Italy;* [4]*Institute of Clinical Physiology, Dyslipidemias & atherosclerosis, Pisa, Italy*

Objective: The inflammatory/immune system involvement in the atherogenic process is fairly described in experimental models, poorly in humans. Assuming that high cholesterol levels (Chol) trigger inflammatory/immune responses, we examined the activities of cells regulating inflammation and expression of Major Histocompatibility Complexes (MHC) concurrent with changes of Chol in FH patients undergoing LDL apheresis, a model where a selective lowering of CH, naturally rebounding to baseline conditions, allows multiple observations in controlled conditions.
Methods: Seven heterozygous and one homozygous FH subjects were studied before, at the end, 2, 4, 7 days after dextransulfate apheresis. Treating 9-10 plasma liters, Chol, LDL-Chol, apoB, triglycerides levels were reduced by 74%, 82%, 79%, 56%, respectively. CD3+, CD20+, CD8+, CD4+, CD16+, CD56+ and CD14+ cells isolated from peripheral blood by Ficoll-Hypaque, marked by FITC, PE, TC-conjugated specific antibodies (including anti MHC-I/II, and anti CD40L) were cytometrically determined. The extracts of fixed, permeabilized T cells and monocytes were incubated with antibodies to INF-gamma, IL2, IL6, IL10 and IL4 cytokines.
Results: Correlation between Chol and lympho-monocytes were observed with multiple regression analyses. Hypercholesterolemia has higher CD8+ (p=0.013), MHC-I (p=0.018) and MHC-II (p=0.008) and INF-gamma expression as compared to the one determined in the four steps of observations where Chol levels were 62.2±5.04 mg/dl, soon after apheresis, and 251.7±15.10 mg/dl at day 7; at these times a lower presence of CD4+ (p=0.015) cells and IL4 was found.
Conclusions: Chol levels show modulation of immunocompetent cells interplay.

P1728 Endothelial function in subcutaneous small arteries of hypertensive patients does not predict cardiovascular events

E. Porteri[1], D. Rizzoni[2], C. De Ciuceis[1], G.E.M. Boari[1], F. Zani[1], M. Miclini[1], G.A.M. Tiberio[1], E. Agabiti Rosei[1]. [1]*University of Brescia, Dept. of Medical and Surgical Sciences, Brescia, Italy;* [2]*Brescia, Italy*

Objective: Endothelial dysfunction in the coronary circulation or in the brachial artery is associated to a greater incidence of cardiovascular events. No data are presently available about the possible prognostic role of endothelial dysfunction in human small resistance arteries.
Design and Methods: Ninety subjects were included in the present study. They were 10 normotensive subjects, 36 patients with essential hypertension, 10 patients with pheochromocytoma, 11 patients with primary aldosteronism, 10 patients with renovascular hypertension, and 13 normotensive patients with non-insulin dependent diabetes mellitus (NIDDM). All subjects were submitted to a biopsy of subcutaneous fat from the gluteal or the anterior abdominal region. Small resistance arteries were dissected and mounted on an isometric myograph, and the concentration-response curves to acetylcholine (ACH, from 10^{-9} 10^{-5} Mol/L) (endothelium-dependent vasodilatation) and sodium nitroprusside (from 10^{-9} to 10^{-5} Mol/L) (endothelium-independent vasodilatation) after precontraction of the vessels with norepinephrine 10^{-5} Mol/L were evaluated. The subjects were re-evaluated (by clinical visits or telephonic interviews) after an average follow-up time of 5.6 years (2.6-10.7).
Results: Twenty-nine subjects had a documented fatal or non fatal cardiovascular (CV) event (5.87 events % per year). The endothelium-dependent vasodilatation in the subcutaneous small arteries was similar in subjects with or without CV events (see table). Also endothelium-independent vasodilatation to sodium nitroprusside was similar in the two groups (-72.0±20.6% vs -76.4±17.8%).

	ACH 10^{-9} M	ACH 10^{-8} M	ACH 10^{-7} M	ACH 10^{-6} M	ACH 10^{-5} M
CV events	-12.4±14.8	-20.8±15.6	-33.7±17.5	-49.5±20.0	-60.5±18.9
No CV events	-15.3±20.0	-28.0±24.2	-40.0±25.9	-52.4±26.4	-62.2±25.9

Conclusions: Our results indicate that endothelial dysfunction in the microcirculation does not predict cardiovascular events. The prognostic role of endothelail dysfunction in human small arteries of patients at low-medium risk should be further investigated.

CLINICAL EL.; VENTRICULAR TACHYCARDIA

P1729 Diagnostic management of patients with unexplained palpitations: prolonged monitoring versus conventional strategy

F. Giada[1], A. Raviele[1], M. Gulizia[2], M. Francese[2], M. Brignole[3], C. Menozzi[4], L. Santangelo[5], M. Santomauro[6] on behalf of the RUP study investigators. [1]*Umberto I Hospital, Cardiovascular Department, Mestre, Italy;* [2]*S.Luigi-S.Currò Hospital, Cardiology Department, Catania, Italy;* [3]*Riuniti Hospital, Cardiology Department, Lavagna (GE), Italy;* [4]*S.Maria Nuova Hospital, Cardiology Department, Reggio Emilia, Italy;* [5]*2° Policlinico Hospital, Cardiology Department, Napoli, Italy;* [6]*Federico II Hospital, Cardiology Department, Napoli, Italy*

Background: The diagnostic management of patients (pts) with palpitations of unexplained origin after negative initial clinical assessment (including ECG, echocardiogram, 24 hour Holter monitoring, and blood chemistry examinations) is often difficult. The aim of this study, a multicentre, prospective, randomized trial, was to compare in these pts the diagnostic yield of conventional diagnostic strategy (CDS) with that of prolonged monitoring using an implantable loop recorder (ILR).
Methods: We studied 49 consecutive pts (aged 53±16 yrs, 33 females) without or with only mild heart disease, and with clinically significant, relatively frequent (1 episode per month), sustained (>1 minute) unexplained palpitations. Enrolled pts were randomized either to CDS (n=24) or to ILR (Reveal Plus, Medtronic)

implantation (n=25). CDS included a 4 to 6 week period of monitoring with external recorder followed by electrophysiological study (EPS). Pts randomized to ILR implantation were monitored for at least 1 year.
Results: Baseline clinical characteristics did not differ between groups. In the CDS group a diagnosis was obtained in 5 pts (atrial fibrillation 1 case, supraventricular tachycardia 4 cases), and 1 pt was lost to follow-up. In the ILR group a diagnosis was obtained in 14 pts (supraventricular tachycardia 3 cases, sinus tachycardia 3 cases, atrial fibrillation 5 cases, atrial flutter 2 cases, 2nd degree AV block 1 case), palpitations did not recur in 4 pts, and 7 pts are still in follow-up. Thus, the diagnostic yield of ILR was higher respect to CDS (56% vs21%, p=0.01). Nine of 19 pts with negative CDS underwent ILR implantation. During follow-up a diagnosis was obtained in 6 pts (supraventricular tachycardia 1 case, sinus tachycardia in 4 cases, complete paroxysmal AV block 1 case), symptoms did not recur in 2 pts, and 1 pt is still in follow-up. No significant adverse event was observed during the study.
Conclusions: A prolonged monitoring strategy with ILR may be a safe and more effective alternative diagnostic approach to conventional testing in the management of unexplained palpitations in pts without or with only mild heart disease. ILR implantation allows to obtain a diagnosis in most of the pts with negative CDS.

P1730 Prediction of total heart block after transcoronary ablation of septal hypertrophy: results of electrophysilogic investigation in 140 HOCM-patients

T. Lawrenz, F. Lieder, M. Bartelsmeier-Schmale, C. Leuner, G. Beer, C. Stellbrink, H. Kuhn. *Bielefeld Hospital, Department of Cardiology, Bielefeld, Germany*

Background: Transcoronary alcoholablation of septal hypertrophy (TASH) is accepted as a therapeutic catheter-based option in the treatment of pts with hypertrophic obstructive cardiomyopathy. However, the in-hospital sudden unexpected total heart block after an uncomplicated intervention remains one of the most frequently observed complication with the potential of lethal outcome. In the present study we analysed electrophysiological (EP) changes during TASH by performing simultaneously intracardiac investigation during the procedure and correlated the parameters with the occurrence of total heart block.
Methods: Surface ECG- and intracardiac EP-parameters were assessed at baseline and after TASH in all pts (PQ-interval, QRS-interval, AV-nodal function assessed by antegrade and retrograde incremental pacing, AH-interval, HV-interval). Continuous telemetric monitoring was performed up to day 8 after TASH to identify pts with sudden total heart block.
Results: TASH was performed successfully in 136 of the 140 HOCM pts (age: 57.0 $\pm$ 14.6 y., alcohol dosis: 0.93 $\pm$ 0.38 ml of ethanol). Sudden unexpected total heart blocks occurred in 10 pts (7.2%) after TASH (day 1 - 4 after TASH, average 31.6 $\pm$ 39.6 h. after TASH). Pts with sudden unexpected total heart block and pts without total heart block did not differ significantly regarding the ECG- and EP-parameters except the retrograde AV-nodal function: after TASH the retrograde AV-nodal conduction was existent in 35% of the pts without total heart block and in 0% of the pts with sudden unexcepted total heart block (p = 0.001). None of the pts with unimpaired retrograde AV-nodal conduction after TASH developed a total heart block during follow-up. There were no significant differences in both groups regarding other parameters (age, amount of ethanol, intraventricular gradients, temporary intraprocedural total heart blocks).
Conclusion: Pts with a retrograde AV-nodal conduction disorder after TASH appear to be at higher risk of sudden unexpected total heart block. Careful telemetric monitoring should be performed in those pts. In addition in pts who are at high risk of total heart block the duration of prophylactic temorary pacemaker treatment should be prolonged up to day 4 after TASH.

P1731 Revascularisation and inducibility of malignant ventricular arrhythmias in patients with coronary artery disease who survived life threatening ventricular arrhythmia

M. Skvarilova[1], A. Bulava[2], M. Fiala[3], J. Lukl[4]. *[1]General University Hospital, IInd Dep. of Cardiology and Angiology, Prague, Czech Republic; [2]University Hospital Olomouc, I. Department of Internal Medicine, Olomouc, Czech Republic; [3]Cardio-center Trinec, Trinec, Czech Republic; [4]University Hospital, I. Department of Internal Medicine, Olomouc, Czech Republic*

Background: Pts with coronary artery disease (CAD), who survived malignant ventricular arrhythmia (VA), are susceptible to sudden cardiac death. Implantable cardioverter defibrillator (ICD) is a modality of treatment, but its cost is considerably high. Revascularization is generally a prerequisite to the implant and programmed ventricular stimulation (PVS) has been used in risk stratification.
Goal: To assess whether PVS enables better risk stratifications in survivors of malignant VA with CAD and evaluate the influence of revascularization on induction of VA during PVS.
Methods: 54 pts (mean age 65 years, 74% males) with documented malignant VA underwent baseline PVS (protocol consisting of 1, 2, and 3 extrastimuli delivered to sinus rhythm, and during drives of 120 bpm and 140 bpm, respectively, including burst pacing - both from RV apex and RV outflow tract). The same protocol was applied after revascularization (PCI or CABG or both). All patients taking class Ic or III antiarrhythmic drugs were excluded. Pts were divided according to the type of arrhythmia induced during baseline PVS: Group I (those with induced ventricular fibrillation (VFib) and/or polymorphic ventricular tachycardia (pVT)) and group II (those with induced monomorphic ventricular tachycardia (mVT)). Type of arrhythmias and other parameters were evaluated after revascularization and during mean 36 months of follow-up.
Results: The same type of arrhythmia (i.e. VFib or pVT) after revascularization was induced in 47% of pts in group I, whereas in group II, identical arrhythmia (i.e. mVT) after revascularization was induced in a significantly higher proportion of pts - in 85%, p=0.004. Completeness of revascularization positively influenced the inducibility of VA (p=0.008), but not the type of revascularization (PCI vs. CABG). ICD discharge during follow up was detected in only 20% of pts in group I, whilst in 52% of pts in group II (p=0.001). In a multivariate analysis, presence of ICD therapy during follow up was significantly influenced by the QRS width (p=0.01).
Conclusions: Revascularization is less capable of influencing arrhythmogenic substrate in pts with monomorphic ventricular tachycardias than in pts with polymorphic ventricular arrhythmias or ventricular fibrillation. Pts with monomorphic ventricular tachycardias are more likely to have an ICD discharge especially when they have wide QRS.

P1732 Evaluation of alternative methods used for entrainment mapping

P. Derejko[1], L.J. Szumowski[1], P. Sanders[2], E. Szufladowicz[1], P. Urbanek[1], R. Bodalski[1], M. Haissaguerre[2], F. Walczak[1]. *[1]Institute of Cardiology, Klinika Zaburzen Rytmu Serca, Warsaw, Poland; [2]Hôpital Cardiologique du Haut-Lévêque, Bordeaux-Pessac, France*

Measuring the post pacing interval (PPI) and correcting for tachycardia cycle length (TCL) is a useful entrainment response (ER) in the mapping and ablation of re-entrant arrhythmias. Infrequently this is impossible to assess due to electrical noise. To overcome this, two alternative methods for assessment of ER have been described: the N+1 difference (N+1 diff) and PPIR method. PPI-TCL difference correlates very well with ER assessed by the new methods but the agreement with PPI-TCL was established only in relation to PPIR method. Moreover it is not known which of these methods is superior in assessment of ER.
Methods: We analyzed 50 episodes of ER in 10 patients (pts) undergoing RF ablation of re-entrant arrhythmias (5 pts VT; 5 pts AFL). Each time ER was estimated by PPI-TCL as well as by both alternative methods. For N+1 diff ER was calculated according to the formula ER (N+1 diff) =(S-Egn+1)-(Ln+2-Egn+3); where S-Egn+1 is the interval from the last stimulus (S) that resets tachycardia (T) to a reference electrogram (Eg) during the second beat after S; Ln+2-Egn+3 is the interval from the local activation (L) at the pacing site during second beat after S to Eg during the third beat after S.
In PPIR method ER was calculated according to the formula: ER PPIR=(PD-TD)+(PPIR-TCL) where PD and TD are latencies between S and L at the pacing site referenced to the remote Eg and PPIR is the PPI recorded at the remote electrode. Places with ER $\leq$ 30 ms were considered to be 'in circuit'. Agreement between methods was assessed by means of Bland-Altman test, kappa coefficient (k) and correlation coefficient (r).
Results: Agreement between PPI-TCL and alternative methods was very good. For the N+1 diff systematic error (SysEr) was 0.04$\pm$11.1 ms; r=0.99 ($p<0.001$); k=0.91 (95% confidence interval (CI) ranged from 0.79 to 1). For PPIR method SysEr was 1.53$\pm$12.6 ms; r=0.985 ($p<0.001$); k=0.95 (95% CI ranged from 0.86 to 1). Agreement between both alternative methods was also very high: SysEr=-1.47$\pm$11.2 ms; r=0.987 ($p<0.001$); k=0.97 (95% CI - from 0.88 to 1).
Conclusion: Each of alternative methods may be used for evaluation of ER when PPI-TCL cannot be assessed directly. Results obtained by both alternative methods are comparable.

P1733 Idiopathic fascicular tachycardia: new insights in the electrophysiologic mechanism

R. Fagundes[1], M.L.A. Fagundes[2], L.B. Arantes[2], R.L. Fagundes[2], F.C.A. Fagundes[2], R.M. Sa[2], M. Mantica[3], C. Tondo[3]. *[1]St Ambrogios Clinic, Arrhythmia Unit, Milano, Italy; [2]INCL, INCL, Rio de Janeiro, Brazil; [3]St Ambrogios Clinic, Arrrythimia, milano, Italy*

Background: Idiopathic fascicular ventricular tachycardia (FVT) is a rare cardiac arrhythmia with specific electrophysiologic patterns. The arrhythmogenic mechanism and the circuit are still unclear.
Aim of the study: Evaluate the electrophysiologic characteristics of the circuit of FVT.
Methods: This retrospective study included 40 patients (pts) with ventricular tachycardia (VT), 20 pts (mean age 33$\pm$18 yrs) with FVT and 20 (mean age 69$\pm$12) with myocardium ventricular tachycardia (MVT) referred to our institutions for catheter ablation.Two catheters were positioned, in the apex of the right ventricle and at His bundle region. A 8 F radiofrequency ablation catheter was introduced in the left ventricle for mapping and ablation.
Results: During VT, QRS duration and VH intervals resulted shorter in FVT pts as compared to MVT pts (125 $\pm$14 ms vs 153$\pm$34 ms, $p<0.05$; and 29$\pm$13 ms vs 183$\pm$45 ms, $p<0.05$, respectively). In sinus rhythm, in pts with FVT, the HV interval was greater as compared to the group control of 20 patients with MVT(51,6 +9,6 ms vs 38 +12,8ms, $p<0.05$).

During VT in the FVT group the right ventricle potential was earlier than retrograde His by 15 ms in 6 pts (26%). In 5 pts (25%) with FVT, concealed entrainment was demonstrated. Furthermore, in these pts a fascicular potential (POT) guiding ablation in the postero septal region of the left ventricle was also recorded with a broad timing variation in relation to ventricular myocardium activation (21±13 ms).
Conclusions: 1) The very short VH during FVT is due to the tachycardia circuit involving the specialized system and thus, explains the narrow QRS.
2) During FVT, the earlier right ventricular activation than His bundle may be due to penetration through the mid-interventricular septum. This would constitute a macroreentry with rapid anterograde transseptal conduction faster than the retrograde His activation.The prolongation of HV interval is an evidence of a participation of ventricular conduction system in the tachycardia circuit. The concealed entrainment is an electrophysiologic finding to prove a reentry in the FVT. The POT would mark the exit point of the activation of the conduction system and its entrance in the ventricular myocardium with a broad timing variation thus, supporting the hypothesis of a macroreentry circuit.

P1734 Surgical ablation for ventricular tachycardia after myocardial infarction guided by preoperative electroanatomical mapping

J. Kautzner[1], J. Bytesnik[1], R. Cihak[1], P. Peichl[1], J. Pirk[2]. [1]*Institute Clin & Experimental Medicine (IKEM), Department of Cardiology, Prague, Czech Republic;* [2]*Institute Clin & Experimental Medicine, Department of Cardiovascular Surgery, Prague, Czech Republic*

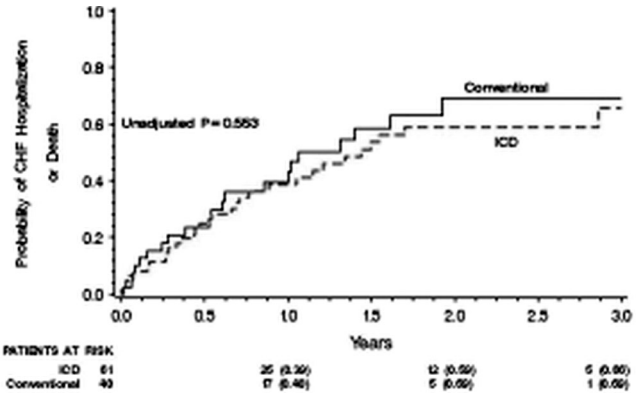
Introduction: Surgical ablation of an arrhythmogenic substrate offers potential cure of ventricular tachycardias (VTs) in patients after myocardial infarction (MI), especially when associated with myocardial revascularization. The aim of this study is to describe early experience with a novel approach of guiding surgical ablation by preoperative electroanatomical mapping.
Methods: The study population consisted of 23 patients (2 women, mean age 65 ± 9 years) with previous Q-wave MI and at least one documented episode of sustained, monomorphic VT, occurring more than one month after the index MI. Left ventricular ejection fraction was 32 ± 10%. All but three patients had clinical indication for concomitant coronary bypass surgery, and underwent preoperative programmed ventricular stimulation and detailed electroanatomical mapping of the left ventricle (CARTO, Biosense-Webster) in sinus rhythm. Pacing from the mapping catheter was used to determine zones of slow conduction (stimulus-to-QRS interval > 40 ms) and/or dense scar (no capture at > 10 mA), and exits for inducible VTs. Exits were subsequently marked by applications of radiofrequency current and these were used as landmarks during surgery. All surviving patients were restudied within one to two weeks after surgery using identical programmed electrical stimulation protocol.
Results: Two (8.7%) patients died within the perioperative period (30-days). In the remaining cohort, clinical VT was not inducible in none of the patients. VT of different morphology was induced in 5 subjects (23.8%) and they were implanted with an implantable cardioverter-defibrillator. During the mean follow-up of 18±10months, no patient died of sudden cardiac death and no sustained VT episode was documented.
Conclusions: Surgical ablation of an arrhythmogenic substrate guided by preoperative electroanatomical mapping and associated with myocardial revascularization appears to be both safe and efficacious procedure that prevents VT recurrences in post-MI patients.

ICD THERAPY

P1735 ICD therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation

W. Zareba[1], J.S. Steinberg[2], S. McNitt[3], A.J. Moss[3]. [1]*University of Rochester, Heart Research Dept, Rochester, United States of America;* [2]*St-Luke-Roosevelt Hosp., Cardiology, New York, United States of America;* [3]*University of Rochester, Heart Research - Cardiology, Rochester, United States of America*

Background: Atrial fibrillation (AF) was found as baseline rhythm at enrollment in 102 (8%) MADIT II patients. This analysis aimed to determine the effectiveness of ICD therapy in MADIT II patients with AF as well as to identify their risk of combined endpoint consisting of hospitalization of CHF or death, usual endpoint for resynchronization therapy that could be considered in decompensated AF patients.
Methods and Results: In comparison to 1,007 patients in sinus rhythm, AF patients were older, were less frequently females, had wider QRS complex, higher BUN and creatinine levels ($p<0.05$ for all parameters). Ejection fraction was not different between groups; NYHA was non-significantly higher in AF patients. AF patients were treated more frequently with digitalis and diuretics, but less frequently with lipid lowering therapy than sinus rhythm patients.
ICD therapy was effective in reducing mortality in AF patients from 39% 2-year mortality in 41 conventionally treated patients to 22% 2-year mortality in 61 ICD-treated patients (p=0.074 from Kaplan-Meier curves; hazard ratio = 0.51; p=0.079). However, combined endpoint of hospitalization for CHF or death was observed at 2 years in 69% of conventionally treated patients and in 59% of ICD treated patients (NS). The high incidence of CHF hospitalization in both groups indicates need for more aggressive heart failure management with a possibility of resynchronization therapy, atrial fibrillation ablation, or AV node ablation combined with resynchronization therapy.



CHF Hospitalization or Death in AF Pts

Conclusions: Although MADIT II patients with atrial fibrillation benefit from ICD therapy, there is a need for more aggressive treatment decreasing the risk of heart failure in patients with atrial fibrillation.

P1736 Long-term effects of the implanted cardioverter defibrillator on quality of life

D.L. Carroll[1], G.A. Hamilton[2], B. Kenney[1]. [1]*Massachusetts General Hospital, Boston, United States of America;* [2]*Rikshospitalet, Oslo, Norway*

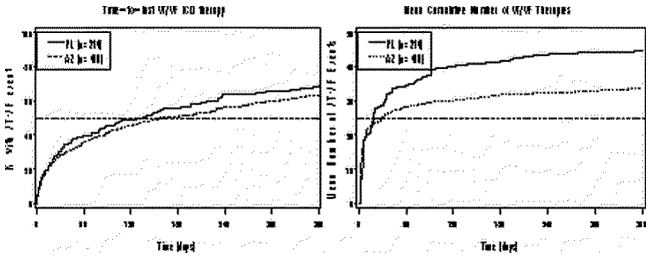
Living with an implanted cardioverter defibrillator (ICD) has known survival benefits but little is known about the effects of this device on quality of life over time in ICD recipients. Therefore the purpose of this study was to investigate changes in perceptions of quality of life, health status, and psychological status in ICD recipients during the first 4 years after ICD implantation.
Seventy subjects, 51 males and 19 females with a mean age 64 years, range 21 to 84 years, completed the study questionnaires; MOS short form (SF-36), Ferrans and Powers Quality of Life Index (QLI), and the Profile of Moods States (POMS) at implantation, 6 months, and 1, 2, 3, and 4 years after ICD implantation either by personal interview or over the telephone with the investigators. During the four years of follow-up, 10 subjects (14%) died and 19 subjects (27%) were lost to follow-up or withdrew from the study.
There were significant changes over time in the physical (PCS) and mental (MCS) health composite summary scores of the SF-36 with MCS improving (F= 2.95; $p<0.02$) and PCS worsening (F=3.69; $P<0.008$) over the four years. The health transition score of the SF-36 was significantly higher at 4 years when compared to implantation (F=8.28; $p<0.008$). Negative psychological moods; anger, confusion, fatigue, depression, and anxiety, were significantly lower over time. The total psychological distress score of the POMS was also significantly lower over time (F=10.21; $p<0.001$). In addition, there was an increase in perceived vigor on the POMS over time (F=3.53; $p<0.004$). There were no significant differences in the health/functioning, psycho-spiritual, family, and socio-economic domains or total quality of life scores from the QLI over time.
This study provides the first set of data that the mental health of ICD recipients improves over time indicating a psychological adjustment to living with an ICD. The PCS score demonstrated a decline in physical functioning over the 4 years. There are few cardiac rehabilitation programs designated for ICD recipients. The declining PCS indicates a need to evaluate a comprehensive rehabilitative approach and to initiate assessments on the effect of strength training and activity progression in ICD recipients in a supervised environment.

P1737 Analysis of all recurrent events is superior to the time-to-first event in assessment of drug therapy to prevent ICD therapies

P. Dorian[1], H.R. Al-khalidi[2], S.H. Hohnloser[3], J.M. Brum[4], D.S. Tatla[4], M. van der Laan[5], C.M. Pratt[6]. [1]*St Michael's Hospital, Division of Cardiology, Toronto, Canada;* [2]*Procter & Gamble, Biostatistics Dept, Mason, United States of America;* [3]*J.W. Goethe-University, Department of Cardiology, Frankfurt, Germany;* [4]*Procter & Gamble Company, Mason, United States of America;* [5]*Procter & Gamble Pharmaceuticals, Egham, United Kingdom;* [6]*The Methodist DeBakey Heart Center, DEpartment of Medicine, Houston, United States of America*

Background: "Time to first event" (TFE) is often used as the primary endpoint in assessing the efficacy of antiarrhythmic therapies. This analysis assumes TFE has the same distribution as inter-event intervals (IEI). We hypothesized that time

intervals between VT/VF events in ICD patients would be clustered and appropriatley analyzed by "counting" all IEI. We analyzed the effects of azimilide (AZ) on VT/VF recurrence in a blinded, placebo (PL) controlled randomized study in ICD recipients.
Methods: A total of 633 patients with ICDs received either PL (n=214), or AZ (n=419). Treatment was for one year, regardless of recurrences. Therapies for VT/VF events were adjudicated by a blinded Events Committee. The Andersen-Gill (AG) mean intensity model (a semi-parametric model which does not assume that IEI follow an exponential distribution) was used to analyze all IEI, and Cox's model and log-rank statistic was used to analyze TFE.
Results: Baseline demographics were similar in AZ and PL with respect to age PL (62 ± 12 years) vs AZ (63 ± 12), NYHA Class III PL (9%) vs AZ (11%), history of MI PL (66%) vs AZ (63%) and ejection fraction PL (33.6%) vs AZ (34.7%). Intent to treat analysis using AG model showed AZ significantly reduced recurrence of all VT/VF events (hazard ratio (HR) = 0.55, 95% CI 0.32-0.94; p=0.03). However, when only the 1st event is considered, AZ did not significantly prolong the TFE (HR = 0.87, 95% CI 0.71-1.10; log-rank p=0.20). Events were highly clustered, with > 50% of IEI less than 1 day, verifying the assumption of non-exponential distribution of IEI (p=0.0001).



Figure

Conclusion: Analyzing total VT/VF arrhythmia burden using all recurrent events is more appropriate than utilizing only the first VT/VF arrhythmic event in evaluating drug therapy.

P1738 MADIT II indication in clinical practice: two years experience from the Search-MI registry

A. Proclemer[1], M. Santini[2], G. Boriani[3], M. Lunati[4], W. Rauhe[5], G. Botto[6], J. Comisso[7], E. Santi[7] on behalf of the Search-MI registry investigators. *[1]S.M. della Misericordia Hospital, Cardiology, Udine, Italy; [2]S. Filippo Neri Hospital, Cardiology, Rome, Italy; [3]S. Orsola Hospital, Cardiology, Bologna, Italy; [4]Niguarda Hospital, Cardiology, Milan, Italy; [5]S. Maurizio Hospital, Cardiology, Bolzano, Italy; [6]S. Anna, Cardiology, Como, Italy; [7]MEDTRONIC, CRM, Roma, Italy*

The MADIT II (MII) study demonstrated that patient (pts) with LVEF≤30% after MI, had a significant reduction in all cause death, if assigned to ICD therapy. In July 2002 the prospective European Registry Search-MI (SMI) was started with the purpose to follow patients in clinical practice, treated with ICD on the base of MII indication. The results of two and a half years activity are reported hereby.
Methods: In 48 Italian centers 444 pts with MII indication were enrolled after implant of an ICD (VVIR 53%, DDDR 26% or CRT 21%).
Results: The baseline characteristics compared with MII population are reported in the table. The average follow-up (fu) was 11 months and 38/303 (12.5%) pts with fu had appropriate device intervention, 23 pts (7.6%) were treated with at least a shock and 24 pts (7.9%) with ATP. One year total mortality regarded 16 patients (5.7%): 4 not cardiac, 2 not classified, 10 cardiac (6 not sudden, 4 sudden but 2 not arrhythmic). Mortality was not significantly different considering pts groups implanted with CRT, VVIR and DDDR devices.

Comparison MADIT II-Search-MI

Characteristics (%)	MADIT II	Search-MI
NYHA class I	35	8
NYHA class II	35	44
NYHA class III/IV	30	47
Hypertension	53	41
Diabetes	33	26
CABG	45	33
PCI	58	41
AF	9	23
LBBB	19	28
Amiodarone	13	29
Statins	67	42
LVEF	23	26

p<0.01

Conclusion: SMI pts compared to MII were more affected by AF and LBBB (CRT pts) and less by diabetes and hypertension; a smaller number of pts had undergone CABG and PCI. Higher intake of Amiodarone and lower intake of Statins were also documented. Mortality of SMI pts seems to be comparable to the ICD arm of MII study also in terms of classification.

P1739 Internal defibrillation is not impaired by a ventricular support system

J. Smid[1], O.M. Frass[1], H.U. Schildhaus[2], J. Mittag[1], R. Schneider[1], J.C. Geller[3], H.U. Klein[1], S. Reek[4]. *[1]Univ. Hospitals Magdeburg, Cardiology Dept., Magdeburg, Germany; [2]Univ. Hospitals, Pathology, Magdeburg, Germany; [3]Zentralklinik, Cardiology, Bad Berka, Germany; [4]Univ.-Klinikum Magdeburg, Klinik f.Kardiol., Angiol. & Pneumologie, Magdeburg, Germany*

The Paracor Ventricular Support System (PVSS) is intended for non-pharmacologic treatment of congestive heart failure via passive restraint. The PVSS is made of Nitinol wire coated with silicone tubing. The PVSS is delivered through a sub-xiphoid or thoracotomy incision onto the epicardial surface surrounding both ventricles. Since many patients with CHF will also benefit from implantable cardioverter-defibrillator (ICD) therapy, a combined use of PVSS and an ICD may be desirable. The metallic restraint, however, may impair internal defibrillation as it has been observed with abandonned epicardial defibrillation patch electrodes.
To evaluate the effect of the PVSS on internal defibrillation of induced ventricular fibrillation, six pigs (41.2±2.6 kg) were studied under general anesthesia. The PVSS was placed using the Paracor delivery system through a mini-thoracotomy. A defibrillation electrode (Endotak Reliance, 0149, Guidant) was positioned via the left jugular vein and connected to an external defibrillator (Ventak ECD, CPI). Defibrillation threshold (DFT) testing after 10 sec of induced VF was performed with (PVSS+) and without (PVSS-) the PVSS in a randomized order. R-wave amplitude (R), pacing threshold (PT), impedance of pacing (P-Imp) and defibrillation (D-Imp) electrodes and DFT were not different between groups (Table).

Electrophysiologic parameters

	PVSS-	PVSS+	p
R (mV)	5.6±2.5	8.1±5.2	NS
PT (V)	0.7±0.4	1.0±1.2	NS
P-Imp (Ohm)	915±157	805±189	NS
D-Imp (Ohm)	48.2±5.8	49.0±5.0	NS
DFT (J)	22.5±10.2	22.8±10.6	NS
DFT (V)	509±129	519±130	NS

The PVSS does not impair internal defibrillation of ventricular fibrillation acutely. Therefore combined use of the PVSS and an ICD in patients with heart failure seems to be feasible and warrants further evaluation.

P1740 Initial experience with home monitoring in ICD-patients

O. Ritter[1], W. Bauer[2]. *[1]University of Wuerzburg, Cardiology Dept., Wurzburg, Germany; [2]University of Wuerzburg, Department of Cardiac Surgery, Wuerzburg, Germany*

Background: Implantable cardioverter defibrillators (ICD) are an effective therapy in the treatment of life-threatening arrhythmias. The expanding indications for primary and secondary prevention and the increasing complexity of the devices result in time-consuming follow-up visits. The concept of home monitoring has been already demonstrated for pacemaker patients. Here we report on our intial results with ICD-patients.
Methods: 78 consecutive patients who received an ICD with home monitoring technology were followed-up for frequency of VT or VF and for lead impedance, battery voltage, ineffective shocks and software problems.
Results: From the 77 patients with home monitoring ventricular tachycardia (VT) was reported in 13 patients. Ventricular fibrillation (VF) was detected in 17 patients with the number of VF episodes ranging from 1 to 8. In the 29 patients with dual chamber ICD, there were 5 patients with reported supraventricular tachycardias. Also in 5 patients a maximum 31 Joule shock was ineffective to terminate tachcardia at least one time. Shock impedance was reported to be conspicuous in 7 cases. We were able to distinguish between low and high risk patients with the possibility to have less frequent follow-up's in low risk patients. Nevertheless, patients have close monitoring of their device via home monitoring technology.
Conclusion: Currently there are two major advantages of home monitoring. On the clinicians side there is the possibility to select patients at low risk and assign those patients to a group with longer follow-up visits, e.g.one time a year. This will reduce the rush on ICD outpatient clinics. On the patients side there is a maxiumum of safty as the indispensable data like battery status, lead impedance and number of events are updated every day.

P1741 Management of lead failure in patients with implantable cardioverter defibrillators (ICD)

J. Eckstein[1], M. Zabel[2], D. Kalusche[3], P. Ammann[1], B. Schaer[1], S. Osswald[1], C. Sticherling[1]. *[1]University Hospital, Cardiology Dept., Basel, Switzerland; [2]University Hospital Benjamin Franklin, Cardiology, Berlin, Germany; [3]Herzzentrum Bad Krozingen, Elektrophysiologie, Bad Krozingen, Germany*

Background: ICD-lead failure such as lead fracture, insulation defect, loss of sensing or oversensing may occur in pts with implanted ICD Systems and account for ICD malfunction with deleterious consequences. As the number of ICD

implantations and the lifetime of chronically implanted leads grow, there will be a higher prevalence of lead related problems. The aim of this retrospective study was a) to determine the incidence of clinically relevant ICD-lead problems, b) to elicit the main causes of these problems, and c) to evaluate the feasibility and safety of solving the problem by the additional implantation of a pace/sense (P/S) electrode.
Methods: 1657 patients implanted with an ICD system at 3 European centers between May 1995 and January 2004 were followed up for 60±31 months. Patients with ICD-lead related problems were identified and classified as to the kind of complication, the longevity of the implanted lead and how the problem was approached. These patients were then followed up for 33±31 months and the efficacy of the therapeutic approach was evaluated.
Results: The incidence of ICD-lead related problems was 2.2% (37 pts). The cause of dysfunction was insulation defect in 8 cases (22%) (all silicone coated), lead fracture in 8 cases (22%), R-wave reduction in 3 (8%), and oversensing in 5 pts (14%). In 21 pts (57%) lead dysfunction resulted in inappropriate ICD therapies. The mean time from implantation of the ICD-lead to failure was 23±17 months. Therapy consisted of placement of an additional P/S electrode in 20 cases (54%) and replacement of the defibrillation-lead in 17 cases (46%). No adverse events occurred. Mean follow up was 33±31 months. Two pts (5%) required a second intervention due to non-lead related problems (left ventricular position, noise through contact with former lead). In the remaining pts no further problems occurred.
Conclusion: ICD-lead failure is a common clinical problem and occurs in approximately 2% of the growing ICD population. If it is possible to prove the integrity of the high voltage portion of the ICD lead, these problems can be solved by simply adding an additional P/S lead. Otherwise the implantation of a new ICD-lead is required. These approaches were safe and mended all problems in our population.

P1742 Sub-cutaneous electrical defibrillation in canines

R. Cappato[1], G. Bardy[2]. [1]*Istituto Policlinico San Donato, Arrhythmia and EP Center, San Donato, Italy;* [2]*University of Washington, Department of Cardiology, Seattle WA, United States of America*

Background: We tested the efficacy of electrical defibrillation using a subcutaneous (S)-only electrode approach.
Methods: In 9 dogs (weight 28 ± 3 kg), an initial 8 cm long horizontal incision was created in the 4th to 6th intercostal space along the anterior axillary line. Two pockets were created for placement of a first S electrode (EL) with its leading edge in close proximity to the left edge of the sternum (ST) and a second S electrode at the site of incision along the lateral axillary line (L), such that the two ELs would lay 15±2 cm apart along the same horizontal line. ELs with active surface areas of 5, 10 and 20 cm^2 or with 8 cm-long rod were subsequently positioned in the two pockets and tested for DFT according to different combinations (Table). A custom high output biphasic waveform generator (Cameron Health, Inc.) was connected to the S ELs to conduct S DFT testing following 10 sec-long intervals of VF induced with AC through an endocardial RVA catheter.
Results: Using a step-down skip method for the different configurations, 64 DFT tests with 7 EL configurations were performed. All EL configurations successfully terminated VF. The DFT (delivered energy) in the different EL configurations is summarized in table 1.

Table 1

ST/L E (cm^2)	20/5	20/10	20/20	10/5	5/5	5/20	rod 8/20
Mean DFT (J) ± SD	65.3 ± 8.9	38.2 ± 16.1	13.8 ± 3.7	30.6 ± 8.8	48.9 ± 26.6	58.7 ± 21.4	39.9 ± 8.6

Conclusion: All investigated S defibrillation configurations proved effective within a range of energies between 10 and 75 J delivered from two ELs lying 15 cm apart in the left hemithorax space. These observations open the way for the development of an S-only implantable defibrillator for human use.

P1743 Left ventricular impairment as a risk factor for implantable cardioverter-defibrillator shocks in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia

J.M. Rubio[1], P.P. Perez[1], A. Hernandez-Madrid[2], J.A. Cabrera[3], B. Ibanez[1], P. Ramirez[1], C. Moro[2], J. Farre[1]. [1]*Fundación Jiménez Díaz, Cardiology, Madrid, Spain;* [2]*Hospital Ramon y Cajal, Cardiology, Madrid, Spain;* [3]*Fundacion Jimenez Diaz, Cardiology, Madrid, Spain*

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is a myocardial disease associated with ventricular tachyarrhythmias (VT) and sudden death. As the disease progress, right and left ventricular impairment is more evident, probably indicating a greater risk for developing VT and heart failure.
Methods: We have analyzed the outcome of 26 Pts with ARVC (48±15 years; 77% male) treated with an Implantable Cardioverter-defibrillator (ICD). The indications for an ICD were: 1) Documented, poor tolerated VT (16 Pts), 2) Syncope and inducible VT (7 Pts), 3) Aborted sudden death (3 Pts). All of them met the International Task Force criteria. All the systems were implanted transvenously. Left ventricular ejection fraction (LVEF) was calculated by LV angiography. Mean LVEF was 54±12% (range 30-70). Eight Pts presented signs of LV impairment, (defined as a LVEF < 50%), four between 50% and 35% and four <35%. All of them were on different antiarrhythmic drugs. We have compared the ARVC Pts with 225 Pts (64 ± 10 years; 89% male; mean LVEF 32 ± 12%) with coronary artery disease (CAD) and an ICD.
Results: Mean follow-up was 72±43 months. The sensed R-wave at implant was 9?3mV (14±5mV in CAD group; $p<0.001$). During follow-up, 18 Pts (69%) in the ARVC group had ICD shocks (86% appropriate), an incidence significantly higher than in CAD Pts (55%; $p < 0.01$). Time to first shock after implant in ARVC group was 12±12 months (12 ± 16 months in CAD group). 10/18 ARVC Pts (55%) with preserved LVEF had ICD shocks, but 8/8 (100%) Pts with LV impairment had ICD shocks (all of them appropriate; $p<0.03$).
Conclusions: Patients with ARVC have a significantly higher arrhythmia recurrence rate that requires appropriate ICD shocks than Pts with CAD. Moreover, the incidence of appropriate ICD shocks is significantly greater in Pts with ARVC and LV impairment, probably indicating a higher risk for VT recurrence in advanced forms of the disease.

P1744 Discriminant analysis of the results of RV cineangiography in patients with ARVC

Y.Y. Dumpis[1], S.M. Yashin[1], A.B. Vaynshteyn[2]. [1]*Saint-Petersburg State Medical University, Faculty surgery, Saint-Petersburg, Russian Federation;* [2]*Saint-Petersburg State Medical University, Faculty Surgery, Saint-Petersburg, Russian Federation*

Aim of study: To create a score system for evaluation of right ventricle cineangiography with purpose to diagnose arrhythmogenic right ventricle cardiomyopathy (ARVC/D).
Methods: Right ventricle (RV) cineangiography (CL: Multistar D + Polytron 1000, Siemens; Views: RAO300, Ant-Post, LAO300,left lateral; Injection: Omnipaque-350, 14-15ml/s, vol. per view =30ml; Analisys: original three-dimensional method of calculation of EDV(ml/m^2) and EF(%) for inlet of RV and RVOT separately and for entire RV using Ant-post. and Left lateral views) was performed in 82 pts (mean age 39,62±14,39, male=32, female=55) with sustained ventricular tachyarrhythmias with purpose to evaluate morphology and haemodynamics of RV. All pts were carefully evaluated for presence of ARVC/D using Task Force Criteria (McKenna, 1994). After that all pts were divided into two groups: I group - 55 pts with idiopathic VA, II group - 27 pts, in whom ARVC/D was proven using "Criteria for diagnosis of ARVC/D". Men were dominant in group II n=16(59,25%), difference in age between groups was insignificant. Complex graduated table of cineangiographic signs of ARVC/D using evaluation of global and regional dilatation, global and regional EF%, presence of abnormal local dilatations, its location and kinetics, pathological fissuration of myocardium of RV was created bases on approved cineangiographic signs of ARVC/D. All angiograms were then evaluated using this table. Statistical analysis of results was undertaken with purpose to identify most specific cineangiographic signs of ARVC/D and create score system of evaluation of RV angiograms. Forward stepwise discriminant function analysis with classification functions computation was perfomed.
Results: Highly significant ($p<0,0001$) discriminant function with Wilks' Lambda = 0.30278 including 5 most discriminatory powerful factors was set. Diskynetic aneurysms in inlet RV (partial lambda =0,8597), RVOT (partial lambda =0,7133), in apex of RV (partial lambda =0,9512), pathologic fissuration of myocardium of RV (partial lambda =0,8183) and regional dilatation of inlet RV (partial lambda =0,9394) were found to be most specific cineangiographic findings in ARVC/D. Score system of analysis of RVA using classification functions was established. Posterior classification matrix revealed 93,9 percent of correctly predicted classifications.

P1745 Single, 15J test shock during ICD implantation

M. Wasniewski, P. Mitkowski, A. Baszko, R. Ochotny, A. Cieslinski. *Ist Department of Cardiology, Poznan, Poland*

An important part of ICD implantation procedure is to demonstrate that device can recognise ventricular fibrillation and successfully defibrillate it with safety margin of energy. Currently there is a tendency to simplify and shorten procedure; therefore precise estimation of defibrillation threshold is usually replaced by two or three shocks with energy 15 to 20J.
The aim of the study was to verify usefulness of single 15J shock during implantation procedure.
The study group consisted of 137 patients (age: 57 ± 18), mean EF (42 ± 10%). Dual chamber device received 42 patients, dual coil electrode 39, coronary artery disease was etiology in majority of patients - 99, idiopathic VF - 15, hyperthrophic cardiomyopathy - 4, dilated cardiomyopathy - 8, congenital heart defects - 5, long QT syndrome - 3, arrhythmogenic right ventricular dysplasia - 3 patients.
Single 15J test shock was successful in 111 patients (81%). Predischarge ICD testing was performed 5 ± 1 days after implantation. Subgroup with successful first 15J shock was tested 15J shock again with 104/111 successes (94%); 20J shock was effective in all remaining 7 patients.
Patients with ineffective first 15J shock (26/137) were successfully defibrillated with 20J energy with exception of 2 that required 24J shock. These values were confirmed during predischarge testing and 2 patients required ICD with maximum defibrillation energy of 34J. There was no single parameter that could predict

results of 15J test shock (age, ejection fraction, type of electrode or ICD, etiology or electrical parameters during implantation).
Conclusion: 15J test shock is effective in majority of patients during implantation as well as predischarge testing. All patients with successful 15J shock during implantation had defibrillation threshold equal or below 20J during predischarge testing.

P1746 The growing clinical and economic burden of implantable cardioverter defibrillators: comparison of patient longevity and the service life of ICD pulse generators

R. Hauser, K. Menssen, L. Kallinen. *Minneapolis Heart Institute Foundation, Cardiology, Minneapolis, United States of America*

Purpose: The safe and cost-beneficial application of implantable cardioverter-defibrillator (ICD) therapy depends, in part, on the longevity of the patient population and the service life of ICD pulse generators. Accordingly, we assessed the survival of patients undergoing ICD implantation and compared it to the service life of their ICD pulse generators (PG).
Methods: Kaplan-Meier actuarial survivals (S) were calculated for patients and PGs that were implanted and followed at our institution since 1994. The PGs included single chamber (SC), dual chamber (DC), and cardiac resynchronization (CRT) models. PG service life was defined as the interval between implant and failure due to battery depletion as signified by the elective replacement indicator or a malfunction caused by an electronic or housing defect. The log rank test was used to compare groups.
Results: The 1,029 patients had ischemic heart disease (73%), non-ischemic cardiomyopathy (13%), hypertrophic cardiomyopathy (5%), and other cardiac conditions; indications for implant included VT/VF (81%) and primary prevention (19%). The survivals of patients and PGs are shown in the table; the difference between groups was significant ($p<.001$). The proportions of PG failures due to battery depletion were SC-85% (198/232), DC-90% (109/121), and CRT-40% (2/5); p=0.25 for SC vs DC. Compared to 2001-2002, ICD implants during 2003-2004 increased 76% from 345 to 609; in 2004, 33% of implants were DC and 44% were CRT devices. PG costs alone increased from $2.6 million in 2001 to $7 million in 2004.

Survival of Patients and PGs (±SE)

	No.	3 yrs	5yrs	6yrs	7yrs	10yrs
Patients	1,029	87(1)	76(2)	70(2)	63(3)	54(4)
SC	706	91(1)	50(3)	37(3)	6(3)	
DC	631	94(1)	27(4)	14(4)		
CRT	192	92(5)				

p<.001

Conclusions: The disparity between patient longevity and the service life of ICD PGs is growing as more implants are DC and CRT devices. Unless PG service life improves substantially, patients will undergo more frequent replacement procedures and ICD costs will continue to increase at a disturbing rate. As indications expand, longer-lived ICD PG batteries will be needed if this therapy is to be cost-beneficial.

P1747 Cost-benefit analysis of preventing sudden cardiac deaths with an implantable cardioverter defibrillator (ICD) vs. amiodarone

H.B. Deniz[1], A.J. Ward[1], J.A. O'Brien[1], J.L. Ehreth[2], F. Malik[2], J. Caro[3]. *[1]Caro Research, Concord, MA, United States of America; [2]Medtronic Europe Sarl, Western Europe & Emerging Markets, Tolochenaz, Switzerland; [3]Caro-Research Institute, Concord, United States of America*

Purpose: To estimate the long-term health and economic impact of primary prevention of sudden cardiac deaths with an ICD vs. amiodarone in the UK. Recently, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) confirmed the efficacy of ICD's in both ischemic and non-ischemic patients with left ventricular dysfunction: all-cause mortality was decreased 23% versus placebo. However, SCD-HeFT showed no significant reduction in mortality among those receiving amiodarone compared to the placebo.
Methods: A discrete event simulation of a patient's course after implantation of an ICD or receiving amiodarone treatment, both in addition to optimal other medication (beta blocker, diuretic, statin, ACE inhibitor), was developed. Model parameters and risk functions were developed and derived mainly from SCD-HeFT results. Rates of life-threatening arrhythmia and other deaths are assumed identical for each treatment. When an arrhythmia occurs, case-fatality rate and probability of hospitalization are applied depending on the treatment. For ICDs, device/lead related complications may arise and lead to a re-operation or revision of the implant. For amiodarone, patients may suffer drug toxicity resulting in hospitalization. The economic value UK society places on a life (GBP £1,445,000, €2,096,377) is based on a willingness-to-pay approach used by the Department of Transport, UK. Costs for resource utilization were based on NHS reference costs, other published literature and Medtronic Ltd. Costs are reported in 2004 GBP, discounted at 3.5%. 100 replications of 1,000 patient pairs were run. Sensitivity analyses were performed for key input parameters.
Results: Over 5 years, the rate of death due to a sudden cardiac event dropped from 18.5% of the 1,000 patients receiving amiodarone to 10.8% in those with an ICD; while death due to other causes was unchanged. When the value of life was taken into account, the cost benefit ratio was found to be 0.17 that is only £0.17 has to be invested for every £1 of benefit gained by society. Sensitivity analyses showed ICD is worthwhile to implant whenever a human life is valued at least £247,086 (€358,467).
Conclusion: Although ICDs increase immediate costs, the investment in this treatment is worthwhile given the values British and other industrialized societies place on human life.

P1748 Comparison of mortality and arrhythmogenic morbidity between single chamber and dual chamber implantable cardioverter defibrillators – results of a prospective randomised trial

C. Kolb[1], I. Deisenhofer[2], P. Barthel[2], S. Schmieder[2], B. Zrenner[2], M.R. Karch[2], C. Schmitt[2]. *[1]Muenchen, Germany; [2]Deutsches Herzzentrum München, München, Germany*

Background: In patients who need an implantable cardioverter defibrillator (ICD) a dual chamber device is indicated in the case of concomitant significant sinus nodal disease or atrioventricular block. It is unknown whether patients who do not present with a standard indication for dual chamber antibradycardia pacing at the time of ICD implantation benefit from atrioventricular synchronised pacing in the long run.
Methods: One hundred patients (age 60±12 years, 11 female) with indication for the implantation of a cardioverter defibrillator and with no antibradycardia pacing indication were randomly assigned to either receive a dual chamber ICD (n=52) or a single chamber ICD (n=48). Patients were regularly followed up for a mean of 52±14 months and evaluated for mortality and arrhythmogenic morbidity.
Results: All-cause mortality (21% for single chamber and 31% for dual chamber ICD recipients) and cardiovascular mortality (13% in the single chamber group versus 21% in the dual chamber group) was not influenced by the ICD types. Differences in the ventricular tachyarrhythmia load were not different in both groups. Patients with a single chamber ICD had 23±74 episodes of ventricular tachyarrhythmias and received 1.5±2.7 cardioversions or defibrillations during follow-up compared to 54±134 episodes of ventricular tachyarrhythmias and 14±49 cardioversions or defibrillation for patients of the dual chamber ICD group. Antibradycardia pacing indication remained absent in all but three patients during follow-up.
Conclusion: In patients who require an implantable cardioverter defibrillator and who have no conventional indication for dual chamber pacing, dual chamber ICD compared to single chamber ICD have no advantage in a long-term follow-up concerning mortality and arrhythmogenic morbidity.

P1749 Simultaneous abdominal compression CPR improves clinical outcomes of resuscitation: results of a 3-year clinical study

T.K. Petelenz[1], T.J. Petelenz[2], P. Chrusciel[3], J. Wolkowski[4]. *[1]Silesian University Medical School, Cardiology Foundation, Katowice-Ochojec, Poland; [2]University of Utah, Department of Bioengineering, Salt Lake City, United States of America; [3]City Hospital, Cardiology Department, Nowy Targ, Poland; [4]City Hospital, Cardiology Department, Dabrowa Gornicza, Poland*

Chest compression cardiopulmonary resuscitation (STD-CPR) is a resuscitative procedure of choice in Sudden Cardiac Arrest (SCA). It is, however, only 5-10% effective, due mainly to insufficient arterial pressure generated by chest compressions. Especially under out-of hospital conditions, complications result from excessive forces, and from frequently prolonged brain ischemia. Based on hemodynamic studies that demonstrate low efficacy of chest compressions in generating sufficient arterial pressure, a modified CPR procedure using simultaneous abdominal compressions (SAC-CPR) was proposed. With SAC-CPR, we have demonstrated, in a small number of patients, a 100% increase in survival rate in victims of SCA treated with SAC-CPR as opposed to the treatment using STD-CPR.
Aim of the study: The objective of the study was to compare safety and efficacy of the SAC-CPR method with the results of STD-CPR procedure.
Methods: In a prospective 3-year trial (2002-2004), unconscious SCA victims (125 patients, 72±11yrs) were treated using the SAC-CPR method and the clinical outcomes were compared with the retrospective 2-year (2000-2001, 138 patient, 69±12yrs) STD-CPR records in the same hospitals. Return of spontaneous circulation (ROSC) and consciousness were classified as "success".
Results: (Table 1) The SAC-CPR method resulted in statistically significant ($p<0.01$) improvement in patient outcomes as compared to the STD-CPR: overall survival in the SAC-CPR group reached 35% vs. 16% in the STD-CPR group, independent of SCA mechanism (VF or asystole). Incidence of complications was lower in the SAC-CPR group and no adverse effects related to abdominal compressions were observed.
Conclusions: Results indicate that modified SAC-CPR method significantly improves survival in patients with SCA of cardiogenic origin, and is a safe and effective enhancement of the STD-CPR method. Multicenter clinical studies to

Table 1. Summary of the study

Method	Total	SCA Mechanism VF	SCA Mechanism ASY	Success VF	Success ASY	Success Total	Success Total %
STD-CPR	138	112 (81%)	26 (19%)	19 (17%)	3 (12%)	22	16%
SAC-CPR	125	78 (62%)	47 (38%)	27 (35%)	17 (36%)	44	35%

(VF – Ventricular Fibrillation, ASY – asystole or block)

establish safety limits under in- and out-of-hospital conditions, and widespread educational efforts are needed to introduce SAC-CPR into clinical practice.

P1750 Results of the European and Canadian safety and performance studies for the smallest passive and active fixation quadripolar defibrillator leads

B. Kuepper[1], P. Della Bella[2], D. Schmitz[3], M. Workel[4], J. Janssen[5], H. Heuer[3]. *[1]Schüchtermann Klinik, Bad Rothenfelde, Germany; [2]Centro Cardiologico Monzino, Milan, Italy; [3]St. - Johannes Hospital, Dortmund, Germany; [4]Medtronic Bakken Research Center, Maastricht, Netherlands; [5]Medtronic Bakken Research Center, Maastricht, Netherlands*

Background: The new Sprint Fidelis™ defibrillator leads, model 6948 (tines) and 6949 (screw-in), are 6.6 Fr, isodiametric, quadripolar, steroid eluting leads, which pass through a 7 Fr introducer. Both leads were evaluated on safety, handling and electrical performance in seperate studies.
Methods: Two prospective, non-randomized, historically controlled, multi-center studies in Europe (80 pts) and Canada (80 pts) evaluated the acute and near-term chronic performance of the 6948 and 6949 leads, respectively, in patients with a Class I or II ICD indication. The safety objective was to demonstrate equivalence of the lead-related adverse event (LRAE) free rate at one month to comparable models 6944 (LRAE free rate=95.2%) and 6943 (LRAE free rate=94.7%) respectively. Equivalence was demonstrated if the lower limit of the one-sided 95% confidence bound for the LRAE free rate at one month was at least 83% (6948 lead) or 82.7% (6949 lead). Defibrillation Threshold (DFT) was measured at implant using the Binary Search Protocol. Electrical data were measured at implant and at one-month.
Results: Seventy-five out of 80 pts with a 6948 lead (93.8%) remained free of LRAEs. The 95% lower confidence bound was 87.3%. Seventy-four out of 79 pts with a 6949 lead (93.7%) remained free of LRAEs. The 95% lower confidence bound was 87.2%. Thus, equivalence of the 6948 and 6949 models to comparable models was achieved. The overall ease of lead handling was rated good to excellent by all physicians.

Electrical measurements

Electrical values (Mean ± SD)	Implant 6948	Implant 6949	1-month 6948	1-month 6949
R-wave (mV)	8.7 ± 3.4 (n=78)	8.9 ± 3.2 (n=74)	10.5 ± 3.8 (n=76)	10.9 ± 4.6 (n=70)
PWT at 1.0 V (ms)	0.17 ± 0.13 (n=79)	0.25 ± 0.19 (n=73)	0.19 ± 0.16 (n=74)	0.26 ± 0.11 (n=69)
DFT (J) (mean)	8.1 (n=63)	7.9 (n=65)	NA	NA
Pacing impedance (Ohm)	747 ± 124 (n=78)	644 ± 127 (n=79)	693 ± 125 (n=77)	541 ± 95 (n=70)
Defibrillation impedance (Ohm) (GEM devices)	15.6 ± 2.6 (n=28)	NA	19.4 ± 1.9 (n=28)	NA
Defibrillation impedance (Ohm) (Marquis devices)	43.6 ± 5.9 (n=50)	42.4 ± 6.4 (n=79)	46.2 ± 5.4 (n=49)	46.0 ± 5.5 (n=70)

NA=not applicable

Conclusions: These multi-center studies confirm that the downsized diameter defibrillator leads perform equivalent to other market released leads, with low LRAE rates and low DFTs, while providing the advantage of smaller introducer size and reduced cross-sectional venous obstruction.

P1751 Electro-anatomic substrate modification results in prevention and reduction of ICD shocks in patients with drug refractory recurrent postinfarction unstable ventricular tachycardias

A. Elvan, M. Sadreddini, P.P.H.M. Delnoy, W.P. Beukema, A.R. Ramdat Misier. *Isala Klinieken, Ioc Weezenlanden, Cardiology, Zwolle, Netherlands*

Background: the primary purpose of this study was the assessment of recurrences of unstable ventricular tachycardia (VT) in patients who were treated with Carto-guided electro-anatomic substrate modification plus amiodarone, the best available antiarrhythmic drug, compared to patientswho underwent only substrate modification.
Methods: the study population consisted of 34 consecutive patients (32 male), age 67±9.3 years, who underwent ICD implantation after the index episode of unstable VT. 7 patients had an old anterior infarction, 12 inferior and 15 inferoposterolateral infarction. LV ejection fraction was 32±11%. Preablation, these patients experienced recurrences of unstable VT with ICD interventions (mean 2.6±4.2, range 1-23 ICD shocks). 9 patients were treated with the combined approach of Carto-guided substrate modification and amiodarone after the first recurrence of unstable VT (group A). 25 patients were treated with only substrate modification (group B). Scar mapping was performed: scar was defined as the presence of potentials with an amplitude of <0.5 mV. Linear lesions were placed in sinus rhythm after the substrate mapping was completed. The endpoint of the ablation was the noninducibility of VT (success) or lack of adequate sites and/or ineffective lesions (failure). In case of noninducibility, the ablation strategy was based on the anatomy of the substrate.
Results: we performed 41 procedures in 34 patients, i.e. 6 redo procedures. After the first ablation procedure, 7/9 patients were noninducible (group A) whereas in group B 23/25 patients were noninducible. After the redo ablation procedure, 5/6 patients were noninducible. One patient on amiodarone underwent a re-redo procedure and was noninducible after this procedure. At the latest follow-up (follow-up duration 14.3±6.2 months) 4 patients had recurrences of VT without ICD intervention, one patient in group A experienced an ICD shock due to VF.
Conclusions: suppression of the arrhythmogenic foci using amiodarone provides unsatisfactory results. RF ablation of the arrhythmogenic substrate reduces or prevents recurrences of drug refractory VT.

P1752 Re-used of defibrillators – a safe alternative?

S. Pescariu[1], B. Dodinot[2], D. Lighezan[3], D. Cozma[3], D. Brie[3], A. Ionac[3], S.I. Dragulescu[3]. *[1]Timisoara, Romania; [2]Stimubank, Nancy, France; [3]Institute of Cardiovascular Diseases, Cardiology, Timisoara, Romania*

Aim: The aim of the study was to prove the safety of the re-used implantable cardioverter defibrillators (ICD) in an area with poor health care services.
Methods: Between 31.10.2000 and 31.10.2004 we received 23 explanted implantable cardioverter defibrillators (ICD), provided from "Stimubank" Nancy, France: 18 VVIR, 4 DDDR, 1 biventricular. The criteria for re-using were: no sign of damage at examination and a remaining longevity more than 70% proved at interrogation of ICD, analyzing the programmed braycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and the frequency of high voltage capacitor charging. After the re-sterilization, only 17 ICD's could be interrogated. It must be pointed out that Stimubank eliminated more than 20 devices presenting battery depletion due to multiple shocks, generally occurring after explantation, when the devices were not desactivated.
Seventeen patients (mean age 53,6±23 years) with class I indication for ICD were implanted (after the information and written consent regarding the implant of a re-used device) with re-used ICD's: 14 VVIR, 2 DDDR, 1 biventricular. All the implanted leads were new.
Results: The follow-up was 27±10 months. Two patients with end stage cardiac heart failure died. There were no infections and no malfunctions of the ICD's. There was no early replacement due to battery depletion, excepting one patient with multiples capacitors charges.
Conclusion: The implantation of re-used ICD's can be performed without increased risk to patients provided with a proper routine for technical control and sterilization. This is a life saving solution in areas with poor health care services but with correct knowledge of medical procedures for implantation and follow-up. Immediate post-explantation desactivation of the ICD seems mandatory to prevent premature battery depletion.

P1753 Prevalence of sleep apnoea in patients with implantable cardioverter defibrillator

L. Luethje[1], T. Raupach[2], D. Vollmann[2], C. Unterberg[2], S. Andreas[2]. *[1]Georg-August-Universität Göttingen, Kardiologie und Pneumologie, Göttingen, Germany; [2]University of Goettingen, Cardiology and Pneumology, Goettingen, Germany*

Background: Recently new therapeutic options related to implantable cardioverter defibrillator (ICD) or pacemaker (PM) for the treatment of sleep apnea have been proposed. While it has been reported that the prevalence of sleep apnea is significantly increased in PM patients in comparison to the normal population, so far this has not been evaluated for ICD patients.
Aim: The aim of this study was to investigate the prevalence of sleep apnea and to determine possible risk factors for sleep apnea in a patient population with implanted ICDs.
Methods: Patients of our out-patients' clinic with an age between 18 and 80 years and a dual chamber ICD were screened for sleep apnea with an ambulatory polygraphy device regardless of symptoms susceptible for sleep apnea. Sleep apnea was considered at an apnea-hypopnea index (AHI) >15/h.
Results: A total of 57 patients (79% male) were investigated. Underlying heart disease was coronary artery disease in 70% of the patients, followed by dilated cardiomyopathy (23%). Data is given in table 1. The prevalence of sleep apnea was 26%. No significant difference could be found for gender, age, heart rate, ejection fraction (EF) or body mass index (BMI) between patients with and without SA.

Table 1

	No. of patients	AHI [/h]	mean SO2 [%]	heart rate [/min]	EF [%]	BMI [kg/m²]	gender [m/f]	age [years]
all patients	57	7.8 ± 3.5	94 ± 1	62 ± 3	40 ± 6	28 ± 1	45/12	64 ± 6
AHI<15/h	42	3.4 ± 1.7	95 ± 1	61 ± 3	40 ± 7	28 ± 2	31/11	65 ± 6
AHI>15/h	15	20.2 ± 2.7	94 ± 1	64 ± 3	40 ± 5	29 ± 1	14/1	62 ± 5
p-value		<0.0001	n. s.	n. s.	n. s.	n. s.	n. s.	n. s.

Conclusion: The prevalence of sleep apnea in ICD patients was lower than reported for PM patients, but higher than in the normal population. Risk factors for sleep apnea could not be determined in this patient population.

P1754 Patients with recurrent ventricular tachyarrhythmias after ICD implantation: an indication for prolonged remote telephonic monitoring?

A. Schuchert[1], B. Schumacher[2], G. Hindricks[3], H. Schmidinger[4], L. Jordaens[5], P. Brugada[6] on behalf of Home-ICD Investigators.
[1]University-Hospital Hamburg-Eppendorf, Heart Center, Hamburg, Germany; [2]Heart Center, Neustadt an der Saale, Germany; [3]Heart Center, Leipzig, Germany; [4]University-Hospital, Wien, Austria; [5]University-Hospital, Rotterdam, Netherlands; [6]OLV Ziekenhuis, Aalst, Belgium

Background: Seamless remote telephonic monitoring could be beneficial in ICD patients with recurrent ventricular tachyarrhythmias after device implantation. The aim of the present study was to identify ICD patients with recurrent ventricular tachyarrhythmias prior to the onset of the recurrent episodes.
Methods: The European multi-center study included 266 patients (ejection fraction 39 $\pm$ 15%) with class I ICD indications who received the single (n=235) or dual-chamber (n=29) ICD Belos or Lexos VR-T/DR-T (Biotronik). All ICDs provide the automatic transtelephonic monitoring feature "Home Monitoring": The ICDs automatically transmit daily or in case of an arrhythmic event the stored data via a modified mobile phone to an evaluation center which forwards it to the responsible physician. Total follow-up duration lasted 312 $\pm$ 125 months. The clinical data of patients with >1 appropriate therapy (Group A) were compared to patients with 1 (Group B) as well as without any appropriate therapy (Group C) during follow-up.
Results: There were 41 patients in Group A, 16 patients in Group B, and 208 patients in Group C. Patients in Group A had 355 ventricular fibrillation (VF) and 2260 ventricular tachycardia (VT) episodes successfully treated with 2783 antitachycardia pacing (ATP) and 546 shocks. Group B experienced 34 VF and 66 VT episodes terminated with 62 ATP and 35 shocks. The ICD indication "monomorphic VT" was similarly distributed in Group A (n = 27), Group B (n = 10), and Group C (n = 115) as well as the frequency of aborted sudden cardiac death with 9 (Group A), 5 (Group B), and 66 (Group C) patients. Other clinical data in Group A and B were also not significantly different to patients of Group C. The time duration until the first shock was 128 $\pm$ 101 days in Group A and 241 $\pm$ 92 days in Group B ($p < 0.05$).
Conclusions: Recurrent VT/VF episode had 21% of all patients including 15% with more than one episode. As the clinical findings were unable to predict the patients with VT/VF episodes after implantation, seamless transtelephonic monitoring helps to detect the first recurrent VT/VF episode early. Transtelephonic monitoring should be prolonged in patients with their first recurrent VT/VF episode within the first 3 to 6 months after device implantation, because these patients often had additional VT/VF episodes after their first event.

P1755 Is a too short adjusted duration of the safety-timer function in ICD patients still a cause for inappropriate therapy?

A. Schuchert[1], T. Lawo[2], D. Schmitz[3], H.-J. Bondke[4], U. Wiegand[5], T. Zerm[6], T. Meinertz[7]. *[1]University-Hospital Hamburg-Eppendorf, Heart Center, Hamburg, Germany; [2]Clinic Bergmannsheil, Bochum, Germany; [3]St. Johannis Hospital, Dortmund, Germany; [4]University-Hospital Charite, Berlin, Germany; [5]University-Hospital Lübeck, Lübeck, Germany; [6]Karl-Gustav University, Dresden, Germany; [7]University-Hospital Hamburg-Eppendorf, Heart Center, Hamburg, Germany*

Enhanced detection algorithms in implantable defibrillators (ICDs) withhold ventricular therapies in case of atrial tachyarrhythmias. Most defibrillators have a so-called safety timer function, which delivers the therapy after a programmable time duration. The nominal setting of the safety-timer (30 seconds) frequently caused inappropriate therapies during atrial tachyarrhythmias despite proper arrhythmia discrimination. The aim of the study was to assess how the time duration of the safety-timer function is adjusted and whether too short duration of the safety timer is still a reason for inappropriate therapies.
Methods: the study included 106 patients who had received as first implant the Deikos A + ICD with the enhanced detection algorithm SMART (Biotronik Germany). Indications for ICD implantation were ventricular tachycardia in 63, ventricular fibrillation in 32, and other indications in 11 patients. The duration of the safety timer was programmed at the discretion of the physician. Inappropriate therapies were analysed in relation to the duration of the safety timer.
Results: during 6 $\pm$ 4 months follow-up 166 of the 258 spontaneous tachyarrhythmias were ventricular tachycardia/fibrillation episodes. The ICD detected all ventricular tachycardia/fibrillation episodes correctly. The remaining 92 episodes were atrial tachyarrhythmias. Of them, 44 were sinus tachycardia in 8 patients and 48 atrial fibrillation/flutter in 16 patients. The devices withheld any therapy in 90 episodes. The remaining two episodes were inappropriately classified. In case with correct arrhythmia discrimination the safety-timer duration was programmed to 30 seconds in 9 episodes (1 patient), to 2 minutes in 32 episodes (5 patients) and to 5 minutes in 51 episodes (12 patients). The duration of the safety timer was set to 5 and 12 minutes during the two episodes of inappropriate arrhythmia classification.
Conclusions: the ICD with the enhanced detection algorithm SMART classified 98% of the 92 atrial tachyarrhythmia episodes correctly. In most patients with atrial tachyarrhythmia events the duration of the safety timer was set from 2 to 5 minutes, which seemed to be sufficient. The delivery of inappropriate therapies was not associated with too short duration of the safety timer.

P1756 Lack of association between ventricular pacing and ventricular tachyarrhythmias episodes prompting ICD intervention in a MADIT II-like population: the SEARCH-MI registry preliminary results

M. Russo[1], C. Pignalberi[1], G. Boriani[2], A. Proclemer[3], M. Lunati[4], E. Santi[5], W. Rauhe[6], M. Santini[1] on behalf of the Search-MI registry investigators. *[1]S. Filippo Neri Hospital, Cardiology, Rome, Italy; [2]S. Orsola Hospital, Cardiology, Bologna, Italy; [3]S.M. della Misericordia Hospital, Cardiology, Udine, Italy; [4]Niguarda Hospital, Cardiology, Milan, Italy; [5]MEDTRONIC, CRM, Roma, Italy; [6]S. Maurizio Hospital, Cardiology, Bolzano, Italy*

Recent reports stated the Pacing Induced Tachycardia phenomenon in ICD recipients; others raised the suspicion that pacing itself could be arrhythmogenic. The SEARCH-MI registry is an ongoing survey on the application of MADIT II trial results in the "real clinical world": 303 patients with previous myocardial infarction and LVEF$\leq$30%, with a mean NYHA class of 2.4 and without arrhythmia history were implanted with different kind of Medtronic ICDs (single, dual chambers and CRT/ICD) starting from July 2002 and reached at least one follow-up. After a mean follow-up period of 11 months 11.2% of patients experienced an appropriate device intervention due to various types of ventricular tachyarrhythmias. A previous interim analysis, presented elsewhere, failed to demonstrate any predictive variable for appropriate device intervention (with the exception of diabetes) comparing the groups with and without ventricular arrhythmias. In particular, in the analysis performed to compare patients with high percentage of Ventricular Pacing (VP$>$50%) and low percentage of Ventricular Pacing (VP$\leq$50%), no significant differences in appropriate device intervention recurrence were observed. In order to detect the arrhythmogenic effect of ventricular pacing we have compared its percentage in an intra-patient basis between follow-up with and without episodes: where it was possible we considered the mean percentage of pacing in at least three follow-up visits without episodes; data about pacing percentage were derived by printouts of the device interrogation or by memory data saved on floppy disk. The patients with CRT/ICD were excluded from the analysis.
Results: up to now 34 patients in our registry experienced at least an appropriate device intervention. Twenty-five of them had follow-up with and without episodes; the mean percentage of ventricular pacing in follow-ups without episodes was 11.9% and in follow-ups with episodes was 10.0%; the difference wasn't statistically significant (p=0.457). This behaviour was similar for every patient considered in the analysis.
Conclusions: in patients with post-infartual cardiomyopathy and heavily depressed ejection fraction ($\leq$30%), implanted with ICDs according to primary prevention of sudden death, an intra-patient preliminary analysis did not show a significant correlation between the ventricular pacing and the incidence of ventricular tachyarrhythmias prompting device intervention.

P1757 NT-ProBNP predicts sustained ventricular arrhythmias in ischaemic patients with implantable defibrillators

E.M. Kanoupakis[1], H.E. Mavrakis[1], E.M. Kallergis[1], D. Nikitovic[1], E.G. Nyktaris[1], E.G. Manios[1], P.E. Vardas[2]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: A significant new cardiac marker in the prognosis of ischemic cardiomyopathy N-terminal pro brain natriuretic peptide (NT-proBNP) has recently been reported. Given the high incidence of sudden death in patients with congestive heart failure we examined the value of NT-proBNP in predicting the occurrence of malignant arrhythmias in patients with implantable cardioverter-defibrillators.
Methods: Baseline plasma concentrations of NT-proBNP were measured using ELISA in 25 patients (mean age 66$\pm$8 years) with ischemic cardiomyopathy and a left ventricular ejection fraction $\leq$35%. In all patients an internal cardioverter-defibrillator had been implanted for primary prevention of sudden death according to MADIT I criteria.
Results: The implantable cardiac defibrillators were interrogated at 1-year follow-up to identify the type of arrhythmias patients had developed. NT-proBNP concentrations were significantly higher in patients who developed sustained monomorphic ventricular tachycardia (SVT) or ventricular fibrillation (VF) compared with those having only episodes of non-sustained ventricular tachycardia (NSVT), (1024 $\pm$ 462 vs. 675 $\pm$ 320 pmol/L). By regression analysis, NT-proBNP was found to be a powerful predictor of sustained monomorphic ventricular tachycardia (R=0.423, p=0.035).
Conclusion: Increased circulating levels of NT-proBNP predict the appearance of sustained ventricular tachycardia and may serve as an additional criterion defining patients at high risk for sudden cardiac death.

RENAL DYSFUNCTION AND ANAEMIA

P1758 Age and female sex are major determinants of renal dysfunction in heart failure patients admitted to community hospital

B. Kozlowski, M. Michalkowska, M. Prejbisz, K. Wolkowska, W. Pikto-Pietkiewicz, T.J. Pasierski. *Miedzylesie General Hospital, Dept. of Cardiology, Warsaw, Poland*

Impaired renal function among patients with heart failure is a sign of poor prognosis that also limits full availability of pharmacological therapy. Prevalence of renal dysfunction was evaluated in consecutive series of heart failure patients admitted to the cardiology department of community hospital. Creatinine clearance (CrCl) was assessed with Cockroft-Gault formula with additional correction to ideal body mass and with MDRD equation.

Group of 122 consecutive patients (mean age 69) included 75 male (mean age 65,8 ys) and 47 female (mean age 74,1ys). Aetiology of HF was ischaemic/post MI in 38%, 52% had preserved ejection fraction (EF>or=40%). Mean NYHA class was 2,27. Creatinine clearance calculated with correction to ideal body mass was 19,6% lower than original Cockroft-Gault formula and calculated with MDRD formula was 5,6% lower. Mean uncorrected CrCl was 58,3ml/min and revealed abnormal renal function (CrCl<90ml) in 89% patients. Dysfunction was mild (CrCl 89,9-60 ml/min) in 28,6%, moderate (CrCl 59,9-30 ml/min) in 48,3%, and severe (CrCl <30 ml/min) in 12,2%. Corrected CrCl was on average 46,9ml/min and revealed abnormal renal function in 96,8% HF patients. After correction renal dysfunction was mild in 20,4%, moderate in 54,9% but severe in 21,3%. There was strong negative correlation between corrected CrCl and age (r= 0,671, p<0,05). Women were significantly older than men (74,1 vs 65,8 ys, p <0,05) and had significantly lower corrected CrCl (35,7 vs 53,9ml/min, p<0,05). Patients with EF>or=40 were significantly older compared to population with EF<40, (71,07 vs 66,6 ys, p<0,05) and had lower CrCl(44,3 vs 50,3 ml/min, p=0,09). Multiple regression analysis showed that age (t= -8,44, p<0,05) and female sex (t= -3,24, p<0,05) were independent predictors of corrected CrCl. No significant correlation between corrected CrCl and ischaemic/nonischaemic aetiology, EF or NYHA class was found. When using MDRD equation for CrCl calculation, significant correlation with age (t= -4,98, p<0,05) and weaker correlation with female sex (t= -1,96, p= 0,05) were also present.

Renal dysfunction is extremely common in hospitalised heart failure patients. Its major determinants are advanced age and to lesser degree sex. Correction for ideal body mass increased number of patients classified as severe renal dysfunction.

P1759 NT-proBNP testing is useful for evaluation of dyspneic patients with impaired renal function: a proBNP investigation of dyspnea in the Emergency Department (PRIDE) substudy

J. Januzzi, S. Anwaruddin, D. Krauser, R. Tung, A. Baggish, R. Cameron, D. Lloyd-Jones. *Massachusetts General Hospital, Cardiology Department, Boston, United States of America*

Background: Chronic kidney disease (CKD) is prevalent in patients with congestive heart failure (CHF). CKD may affect NT-proBNP and BNP levels in patients both with and without acute CHF.

Methods: The PRIDE Study was a prospective study testing NT-proBNP (Elecsys® proBNP, Roche Diagnostics, Indianapolis, IN) in 599 dyspneic patients with suspected acute CHF. Glomerular filtration rate (GFR) was estimated using the Modified Diet in Renal Disease (MDRD) equation. Multivariate logistic regression analysis determined independent predictors of NT-proBNP levels. Linear regression analysis determined the relationship between NT-proBNP and GFR. The comparative effect of renal function on BNP in 209 patients with acute CHF was also examined.

Results: GFR ranged from 14.8 to 252 ml/min. The prevalence of CHF risk factors and incident CHF increased with lower GFR (all p<0.001). Multivariate analysis identified GFR as an independent predictor of NT-proBNP levels (p<0.001). An inverse correlation existed between NT-proBNP levels and GFR in all patients (r=-0.55, p<0.001), those without acute CHF (r=-0.41, p<0.001), and those with acute CHF (r=-0.34, p<0.001). An inverse correlation also existed between BNP levels and GFR in patients with acute CHF (r=-0.18, p=0.02). Utilizing optimal cut-points, NT-proBNP was 85% sensitive and 88% specific for acute CHF in those with a GFR ≥60 ml/min. For those with GFR <60ml/min, sensitivity was 97% and specificity was 68%. A cutpoint of 1200 pg/ml in patients with GFR <60 ml/min improved the specificity of NT-proBNP to 72%. Even in the presence of CKD, NT-proBNP remained the single strongest predictor of death by 60-days following presentation (HR=1.57, 95% CI=1.2-2.0, p=0.0004).

Conclusions: NT-proBNP levels are higher in patients with CKD, largely related to higher CHF risk factor prevalence and more incident CHF in these subjects. Contrary to prior assertions, NT-proBNP provides valuable clinical utility in the diagnosis and prognosis of acute CHF in dyspneic patients with mild to moderate impairments in renal function.

P1760 The significance of an elevated N-terminal pro-B-type natriuretic peptide level in end stage renal disease

R. Sharma[1], D.C. Gaze[2], D. Pellerin[3], R. Mehtha[4], P.O. Collinson[5], S.J. Brecker[6]. *[1]St George's Hospital, Department of Cardiology, London, United Kingdom; [2]St George's Hospital, Department of Nephrology, London, United Kingdom; [3]The Heart Hospital, Department of Cardiology, London, United Kingdom; [4]Southampton General Hospital, Department of Statistics, Southampton, United Kingdom; [5]St George's Hospital, Department of Biochemistry, London, United Kingdom; [6]St George's Hospital, Department of Cardiology, London, United Kingdom*

Background: Elevated baseline levels of natriuretic peptides occur in a proportion of patients with end stage renal disease (ESRD). The significance and mechanisms responsible for this remain unclear. The aim of this study was to identify baseline characteristics and determine the prognostic significance of those renal failure patients with raised N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

Methods: 84 patients (mean age 52 ± 12 years, 75 male) referred for renal transplantation (mean creatinine 608 ± 272mmol/L) were prospectively studied over a mean follow-up period of 1.66 ± 0.58 years. All had coronary angiography, dobutamine stress echocardiography and baseline biochemical markers. Severe coronary artery disease (CAD) was defined as luminal stenosis > 70% in at least 1 vessel by visual estimation. A baseline NT-proBNP level > 125pg/mL was taken as significantly elevated.

Results: 50 (59%) patients had significantly elevated NT-proBNP levels. Using Kaplan-Meier survival analysis, this was associated with significantly increased mortality (p = 0.05). These patients had significantly impaired left ventricular (LV) fractional shortening (31 ± 10% vs 41 ± 9%, p = 0.04), lower mitral annular peak systolic velocity (0.06 ± 0.02 m/sec vs 0.09 ± 0.02 m/sec, p = 0.01) higher LV end diastolic diameter (5.1 ± 0.9 cm vs 4.4 ± 0.8 cm, p = 0.04), and higher LV end systolic diameter (3.1 ± 0.8 cm vs 2.5 ± 0.7 cm, p = 0.008) compared to those with NT-proBNP levels < 125pg/mL. Diastolic function was significantly impaired in the NT-proBNP positive group (E/Ea 14 ± 7 vs 11 ± 4, p = 0.03, E/Vp 2.2 ± 0.8 vs 1.8 ± 0.5, p = 0.05), as was LV mass index (186 ± 92g/m^2 vs 140 ± 48 g/m^2, p = 0.03). Age (55 ± 10 years vs 49 ± 13 years, p = 0.02) and the proportion of patients on dialysis (68% vs 29%, p 0.001) were significantly higher in the NT-proBNP positive group. Diabetes, the percentage of patients with severe CAD and inducible regional wall motion abnormality were similar in both groups. Stepwise logistic regression analysis identified dialysis (OR 12.6, 95% CI 2.9, 45, p = 0.001) and mitral annular peak systolic velocity (OR 5.8 95% CI -9.7, -2.1 p = 0.004) to be independently associated with an elevated NT-proBNP.

Conclusions: A significantly elevated NT-proBNP level was present in 59% patients with ESRD referred for renal transplantation, especially those on dialysis, and was associated with significantly increased mortality. Its presence signifies LV dilatation and impaired systolic and diastolic function. There was no association with severe CAD or inducible ischaemia.

P1761 ACE-inhibitor therapy and renal function: 1-year outcome in patients with chronic heart failure in daily clinical practice

R. Winkler, A. Kilkowski, A. Jost, K. Muth, B. Rauch, J. Senges on behalf of HeLuMa Study Group. *Herzzentrum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany*

Background: ACE- Inhibitors (I) improve prognosis in patients (P) with CHF but influences renal function. Renal insufficiency itself has a negativ prognostic impact on the outcome in CHF.

Aim of the study: 1-year outcome in CHF-P with and without ACE-I in relation to renal function (glomerular filtration rate [GFR]).

Patients and Methods: 2042 P with ACE-I, 510 P without ACE-I, from the regional, prospektive HELUMA CHF registry (ejection fraction <40%, non-valvular genesis), not on AT-II blockers. GFR was calculated with the Cockcroft-Gault-formula.

Results: see table and figure.

Conclusion: 1) In daily clinical practice a strong relation between renal function and 1-year mortality is found. This relation is not restricted to impaired renal function.

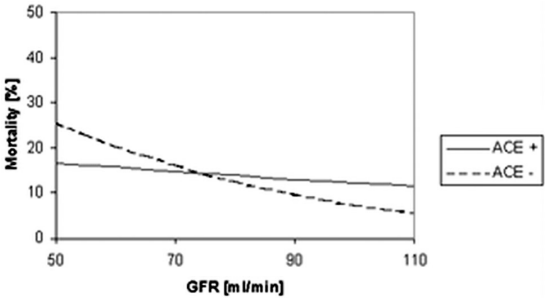


Fig. 1. Logistic regression curve: relation of ACE-I therapy and GFR on outcome.

Table 1. 1-year mortality in relation to GFR and ACE-I

GFR (ml/min)	ACE +	ACE-	p-value
<50	17%	25%	<0,05
75	14%	14%	0,7
100	12%	8%	0,1
>125	11%	6%	<0,05

2) In P without ACE-I mortality is highly correlated to renal function, while this correlation is only with ACE-I.
3) A reduction in GFR from 125 ml/min to 75 ml/min (often clinicaly not detected by Serum-Kreatinine) is associated with a two fold higher mortality in patients without ACE-I.

P1762 Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure

C. Opasich[1], M. Cazzola[2], S. De Feo[3], L. Scelsi[4], O. Febo[5], R. Moratti[6], R. Ferrari[7], L. Tavazzi[4]. *[1]Fondazione Salvatore Maugeri, Cardiology, Pavia, Italy; [2]Policlinico San Matteo, Haematology, Pavia, Italy; [3]Fondazione S Maugeri, Cardiology, Pavia, Italy; [4]Policlinico San Matteo, Cardiology, Pavia, Italy; [5]Fondazione S Maugeri, Cardiology, Montescano, Italy; [6]Policlinico San Matteo, Laboratory of Chemical analysis, Pavia, Italy; [7]University of Ferrara, Cardiology, Ferarra, Italy*

Background: Anaemia is often observed in pts with chronic heart failure (CHF), and it may be associated with a worse prognosis.
Aim: To identify the mechanisms of anaemia in individual CHF pts.
Methods: One-hundred forty-eight consecutive CHF pts in stable clinical conditions (absence of physical findings of congestion, significant changes in diuretics, weight or blood pressure in the last 4 weeks) and with haemoglobin (Hb) concentration <13 (if males) or <12 g/dL (if females) were enrolled. Factors responsible for anaemia were investigated by evaluating endogenous erythropoietin (Epo) production, serum cytokines levels (tumor necrosis factor-alpha (TNF-a) and its 2 soluble receptors (sTNFR-I and sTNRF-II), interleukin-6 (IL-6), and interleukin-1 receptor (-1Ra), C-reactive protein (CRP), body iron status (serum iron, serum ferritin and soluble transferrin receptor) and iron supply for erythropoiesis.
Results: The majority of pts were males (74%); 39% of pts were in NYHA class II, 47% in III and 14% in IV. The aetiology of CHF was ischemic in 48% of cases, idiopathic in 30%. Mean LV ejection fraction was 31±12%. Most pts (57%) had anaemia of chronic disease; among them, 92% presented evidence of a defective endogenous Epo production as indicated by an observed/predicted log(serum Epo) ratio <0.8 and/or a defective iron supply for erythropoiesis as judged by low transferrin saturation and/or increased value of soluble transferrin receptor. In pts with chronic disease anaemia, serum erythropoietin levels correlated with the severity of cardiac disease (NYHA II 8.4±7.6; NYHA III 29±37; NYHA IV 53.4±74 mU/mL: F=6.7; p=0.001), with CRP (r=-0.25; p=0.021) and IL-6 (r=0.57; p=0.0001). IL-6 resulted the only independent predictor of serum Epo values at the multiple regression analysis (β=0.49; p<0.0001). At the univariate analysis Hb was significantly correlated with gender (females 10.4±0.9 vs males 11.1±1.0 g/dL; p=0.0002), and inversely related with serum creatinine (r=-0.42; p<0.001), urea (r=-0.29; p=0.008), sTNFR-I (r=-0.44; p<0.001), IL-6 (r=-0.41; p=0.001) and Epo levels (r=-0.21; p=0.04). Multiple regression analysis showed that serum creatinine (β=-0.43, p<0.000009), sex (β=-0.38, p=0.00005) and serum Epo (β=-0.20, p=0.02) were independently correlated with anaemia.
Conclusions: In our study, about half of anaemic CHF pts showed anaemia of chronic disease with blunted endogenous erythropoietin production and/or defective iron supply for erythropoiesis. Determination of the individual mechanisms of anaemia in CHF could allow a rational therapeutic approach to anaemia.

P1763 Impaired renal clearance explains elevated Troponin T concentrations in heart failure patients

M. Aksoy[1], N. Aksoy[1], S. Soydinc[2], Z. Celen[3], M. Tarakcioglu[3], M.H. Dinckal[2], V. Davutoglu[2], I. Akdemir[2]. *[1]Gaziantep, Turkey; [2]Gaziantep university, Cardiology, Gaziantep, Turkey; [3]Gaziantep University, Gaziantep, Turkey*

Low-level elevation of serum cardiac troponin T (cTnT) has been documented in heart failure patients and it was theorized that the levels cTnT in heart failure patients reflect cellular injury and ongoing degradative processes of the contractile apparatus. However, whether these increases are specific to myocardial injury or nonspecific is not completely clear. We hypothesized that impaired renal function in HF leads to a diminished clearance rate that can cause the measurable increase in basal cTnT concentrations.
Methods and Results: The present study evaluated 126 patients with advanced HF who had angiographically documented no significant coronary stenosis, and normal serum creatinine and blood urea nitrogen at study entry. cTnT assay was drawn at the time of initial presentation. Left ventricular ejection fraction (LVEF) and left ventricular diastolic dimension (LVDd) were measured echocardiographically. Glomerular filtration rate (GFR) was measured with the plasma clearance of 99mTc DTPA as an accurate index of GFR.
Although normal serum creatinine (0.8±0.2 mg/dL) and urea 24±8 mg/dL at study entry, mean GFR was found low (55±15 mL/min) in the cohort. High (>0.01 ng/mL) initial serum concentrations of cTnT were detected in 81 patients (64%). Among patients with detectable cTnT, mean levels were 0.17±0.25 ng/mL, and the range was 0.02 ng/mL through 1.1 ng/mL. Echocardiographic mean LVEF was 0.32±0.09, LVDd was 59.6±5.2 mm. The 4 quartiles of GFR (<38, 39 to 56, 57 to 68, and >69 mL/min) had mean cTnT leves (0.29±0.37, 0.16±0.18, 0.10±0.06 and 0.03±0.02 ng/mL, respectively) and differences between the quartile mean cTnT concentrations are statistically significant (p=0.01). Mean cTnT leves were 0.24±0.38, 0.16±0.21, 0.11±0.18 and 0.06±0.08 ng/mL, in quartiles of LVEF 1 through 4 (p=0.09) and 0.17±0.43, 0.17±0.23, 0.14±0.21 and 0.10±0.11 ng/mL in quartiles of LVDd 1 through 4 (p=NS), respectively. After logarithmic transformation of skewed variables, the independence of the associations was evaluated in a multiple linear regression analysis and increasing levels of cTnT were independently and negatively associated with only GFR (p=0.02).
In our study, renal function correlated significantly, and more strongly than left ventricular function with the unexplained cTnT elevations in HF patients. This supports our hypothesis that impaired renal function leads to a diminished clearance rate that can be a prominent pathophysiological mechanism in the elevation of cTnT concentrations in HF.

P1764 Low hematocrit as a predictor of prognosis in congestive heart failure

E.N. Tapanlis, D.N. Chrissos, A.A. Katsaros, N.C. Korovesi, P. Missovoulos, E. Hatzistamatiou, A. Kakavas, I.E. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Introduction: Anemia is a high–cardiac output state and therefore its development in the presence of underlying heart disease often precipitates heart failure. It is also a common problem in congestive heart failure (CHF). The purpose of this study is to determine the correlation between low values of hematocrit (HEM) and prognosis of CHF-patients.
Methods: We recorded 134 consecutive hospitalized P (96 males and 38 females of mean age 69.54±11.32 years) with CHF -NYHA functional class III or IV and left ventricular ejection fraction <30%- for a two-year period. We classified the P in groups I and II with HEM values lower or higher respectively than the mean value -found to be 37.83±6.79%- and we then estimated their functional status, morbidity and mortality. The groups did not differ concerning other blood parameters, sex, age, etiology of CHF, any comorbid conditions, echocardiographic markers of cardiac function and adherence to therapy. Data were expressed as "mean value ± standard deviation" and statistical analysis was performed by the student's t-test method and by the X^2 method. P<0.05 was considered statistically significant.
Results: At the end of the follow-up period, we realized that NYHA functional class -although did not differ between the groups at the beginning- was significantly higher at group I compared to group II (3.55±0.50 versus 3.23±0.76, p<0.01). Moreover, -by measurement of the relative risk (RR)- we detected almost threefold hospital readmissions and more than threefold deaths due to deterioration of symptoms of CHF in group I (RR=2.81, p<0.01 and RR=3.68, p<0.05 respectively).
Conclusions: Patients with congestive heart failure and low hematocrit appear to have impaired functional capacity and aggravated morbidity and mortality. Therefore, it should be taken into account that successful management of anemia of the above patients could contribute substantially to improvement of their prognosis.

P1765 Correction of anaemia with subcutaneous erythropoietin and intravenous iron: effect on NT-proBNP levels and clinical evolution in patients with severe chronic heart failure and mild renal dysfunction

J. Comin-Colet[1], J. Bruguera[1], C. Garcia[1], B. Garcia-Bascunana[1], M. Cladellas[1], E. Martinez[2], G. Soria[2], R. Serrat[1]. *[1]Hospital del Mar, Heart Failure Unit. Cardiology Department, Barcelona, Spain; [2]Laboratori de Referencia de Catalunya, Departament Analisi Cliniques, Barcelona, Spain*

Background: There is little information about the influence of treatment with erythropoietin (rHuEPO) and intravenous iron sucrose (IVI) on neurohormonal activation and hospitalization in anemic HF patients with mild renal dysfunction.
Aims and Methods: To evaluate the hypothesis that correction of anemia with rHuEPO and IVI would improve functional status, neurohormonal activation and reduce hospitalization of NYHA class III-IV HF patients with anemia (hemoglobin (Hb)<12mg/dL)and mild renal dysfunction (serum creatinine<2.0 mg/dL), the evolution of hospitalization, functional status and NT-proBNP levels of 28 patients referred to our nurse-led HF clinic was analyzed according to assignation to control group (no anemia treatment; n=18) or to intervention group (treatment of anemia with subcutaneous rHuEPO and IVI to maintain Hb>12.5 g/dL; n=10).
Individuals of control group were matched to patients of intervention group by age, sex, ejection fraction, creatinine, NYHA functional class and NT-proBNP levels.
Baseline characteristics did not differ between groups (including cardiovascular drugs and time of follow up) and were: age=71.5±8.0 years; men=64.3%; LVEF=33.6±10.4%; NYHA functional class=3.1±0.3; Hb=10.3±1.6 mg/dL; serum creatinine=1.6±0.5 mg/dL; serum NT-proBNP=4288.9±4480.5 pg/mL (4108.4±3335.7 intervention vs 4385.1±5094.5 control; p=ns); HF etiology=

60.7%(17) ischemic, 39.3%(11) non-ischemic (p< 0.05:statistically significant; qualitative data:%(n);quantitative data: mean ± SD).
Results: After a mean follow up of 7.5±2.7 months, intervention group patients (10) compared to control group patients (18) had higher levels of Hb (13.7±1.2 vs 10.8±0.9; p<0.001), lower levels of NT-proBNP (2144.0±2534.2 vs 10344.3±8126.6; p=0.022) and better NYHA functional class (1.7±0.7 vs 3.2±0.7; p<0.001).
At this time, rate of worsening heart failure (WHF) (30% vs 72.2%; p=0.03), number of WHF episodes (0.3±0.7 vs 2.8±3.7; p=0.041), mean hospital stay (1.0±2.8 vs 14.2±18.1; p=0.007), number of hospitalizations (0.2±0.4 vs 1.7±2.7; p=0.027) and the need of intravenous diuretics (30% vs 72.2%; p=0.03) were all reduced in the intervention group compared to control group.
Conclusions: Correction of anemia with rHuEPO and IVI improves neurohormonal profile, hospitalization, rate and number of WHF episodes and functional status of patients with chronic advanced heart failure, anemia and mild renal dysfunction. Reduction of NT-proBNP levels (a surrogate of prognosis) in treated patients might suggest a potential benefit of this approach on mortality.

P1766 Heart failure is related to haemoglobin concentration in acute coronary syndromes

R.A. Archbold[1], A. Al-Hajiri[1], R. Liew[2], A. Suliman[2], K. Ranjadayalan[2], C.J. Knight[1], A. Deaner[1], A.D. Timmis[1]. [1]*London Chest Hospital, Cardiology Department, London, United Kingdom;* [2]*Newham University Hospital NHS Trust, Cardiology Department, London, United Kingdom*

Background: Anaemia has been identified as a major determinant of outcome in patients with cardiovascular disease, particularly heart failure (LVF). In this study we have examined the relationship between haemoglobin concentration ([Hb]), LVF and mortality in acute coronary syndromes (ACS).
Methods: Cross sectional cohort study of 2431 patients with ACS. Hospital outcomes (LVF, cardiac death) were analysed by quartiles of admission [Hb] (Q1 <12.5, Q2 12.5-13.7, Q3 13.8-14.8, Q4 >14.8 g/dL).
Results: There was a close inverse relationship between the frequency of LVF and admission [Hb], (Q1 22.9%, Q4 11.2%; p (trend) <0.0001), the odds of LVF being 0.45 (95% CI 0.33-0.62) for Q4 relative to Q1. Admission [Hb] was also associated with age, gender, renal dysfunction, smoking and heart rate but despite multiple adjustment for these and other baseline variables, the effect of [Hb] was diminished only slightly, the odds of LVF for Q4 relative to Q1 increasing to 0.56 (0.37-0.84). The association of [Hb] with LVF was not a reflection of the severity of myocardial injury, rates of infarction (54.0% v 41.5%; p<0.0001) and mean (SD) peak CK values (758 [1129] v 547 [1169] iu/L; p=0.01) being higher in Q4 compared with Q1. This may explain why admission [Hb] was not associated with cardiac death which occurred in 2.8% of Q4 and 3.8% of Q1 patients (p=NS).
Conclusion: In patients with ACS, anaemia predisposes to LVF but not cardiac death. Predisposition to LVF appears to be a direct effect of anaemia, and is not attributable to myocardial injury, which is paradoxically less severe in patients with anaemia.

P1767 Serum of anaemic heart failure patients inhibits haematopoiesis

P. Van der Meer[1], E. Lipsic[1], B.D. Westenbrink[1], E. Vellenga[2], R.G. Schoemaker[1], D.J. Van Veldhuisen[1], A.A. Voors[1], W.H. Van Gilst[1]. [1]*University Medical Center Groningen, Cardiology Department, Groningen, Netherlands;* [2]*University Medical Center Groningen, Hematology, Groningen, Netherlands*

Background: Anemia is common in patients with chronic heart failure (CHF) and is associated with an impaired prognosis. It has been shown that only a minority of patients with CHF had renal impairment or underlying hematinic deficiencies. Therefore, we hypothesize that serum of anemic heart failure patients reduces hematopoietic activity in the bone marrow.
Methods and Results: We included 98 patients with advanced stable CHF (LVEF 26±1%, age 66±2 years and 80% male). Seventeen patients were anemic (17.3%) of whom ten had an unexplained anemia (normal hematinics and no renal failure). We matched these 10 anemic patients with 10 non-anemic patients based on age, sex and LVEF. Serum of anemic CHF patients inhibited in vitro the proliferation of bone marrow derived erythropoietic cells of healthy donors by 16%, compared to non-anemic CHF patients (p=0.003; figure 1A). Levels of Ac-SDKP, a strong hematopoiesis inhibitor, were significantly higher in anemic CHF patients compared to non-anemic CHF patients (p=0.018; figure 1B). Ac-SDKP levels strongly correlated to hematopoietic activity (r=-0.64, p=0.001).
Conclusion: Serum of anemic CHF patients inhibits hematopoiesis. The clear correlation between Ac-SDKP levels and hematopoietic activity suggests an inhibitory role of Ac-SDKP on hematopoiesis in anemic CHF patients, which might be overcome by treating these patients with recombinant human erythropoietin.

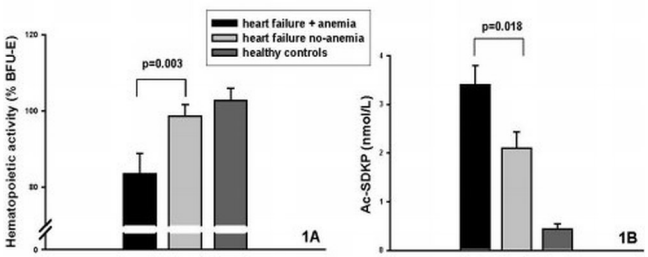


Figure 1

P1768 Does the treatment with erythropoietin decrease the left ventricular filling pressure in patients with chronic heart failure?

B. Cosyns[1], M. Mantia[2]. [1]*Braine-l'Alleud, Belgium;* [2]*Hopital de Braine, Cardiology, Braine l'Alleud, Belgium*

Background: Anemia is frequently found in patients with congestive heart failure (CHF). There is now evidence that early correction of the CHF anemia with subcutaneous erythropoietin (EPO) improves symptoms, renal function, exercise capability, and dramatically reduces the need for hospitalization.
However,the effect of this correction on left ventricular filling pressure (LVP) remains an unanswered question.
The ratio of transmitral early diastolic velocity (E) to mitral annulus early diastolic velocity (Em) has been shown to provide a good estimate of LVP.
Aim: Therefore, we prospectively studied the LVP in 18 patients with severe HF, chronic kidney disease (CKI), and anemia (Hb<12g/dl) before and after correction of their anemia with EPO.
Results: As expected, we have observed a decrease in the mean NYHA functional class from 3.5 to 2.2. The mean Hb level increased from 10.1 g/dl to 13.1 g/dl. The serum creatinine decreased by 15.6%. The need for oral loop diuretics was decreased by 35%. The mean follow-up period was 10.2 months. The rate of hospitalisation was decreased by 82% compared to the period of time before entering the study.
The E/Em ratio was 16 ± 8 at the beginning of the study and was reduced to 8 ± 7 at the end of the follow-up period. The change in E/Em ratio was well correlated to the improvement of clinical data.
Conclusion: Clinical improvement of CHF patients treated with EPO is well correlated with the decrease of the E/Em ratio. This indicates that one part of the beneficial effect of EPO treatment is related to LVP decrease.

P1769 Cystatin C may be related to heart failure severity independently of glomerular filtration rate (GFR)

P. Rozentryt[1], J.U. Nowak[2], A. Brachowska[2], L. Polonski[2], S.D. Anker[3], J. Deja[4], W. Bartnik[4]. [1]*Zabrze, Poland;* [2]*Silesian Center for Heart Diseases, III Department of Cardiology, Zabrze, Poland;* [3]*National Heart & Lung Institute., Clinical Cardiology, London, United Kingdom;* [4]*Institute of Oncology, Biochemical Lab., Gliwice, Poland*

Cystatin C plasma level is inversly related to GFR, and is useful estimator of filtration. Cystatin C belongs to cystein proteinase inhibitors family and was shown to play a role in regulation of inflammation. Higher inflammatory activation and worse renal function have all been demonstrated to be assocaieted with heart failure severity. Natriuretic peptide plasma level has been proved to reflect clinical severity of the syndrome. Our aim was to compare cystatin C concentration in heart failure patients and in control subjects carefuly mathed for GFR, and later on to assess whether cystatin C is related to heart failure severity.
In 98 heart failute patients (82M, age: 56±17y, NYHA: 2,7±0,7, EF: 21±5%) and in 20 control subjects (16M, age: 58±18y) carefuly matched for comorbidities, we measured cystatin C plasma level by nephelometry, creatinine by standard method and we estimated GFR using MDRD formulation. Mean values were compared by student-t test and shown in the table.
Later on in heart failure group, linear correlation coefficients were computed between NTproBNP plasma levels and large set of clinical, biochemical and body composition variables. For parameters correlated significantly, multivariable analysis was performed (step forward regression) with NTproBNP as dependent variable. In this model, parameters that retained significant independent predictive power (adjusted R2=.46616, p<.0000 were: lean tissue content (p<.0005), choloesterol (p<.004), cystatin C (p<.008), VO2max (p<.01), EF (p<.04). Neither NYHA class nor MDRD GFR were still significant predictors of NTproBNP.

Renal function and cystatin C

	Creatinine [mcmol/L]	GFR [ml/min·1,73m^2]	Cystatin C [mg/L]
Heart failure N=98	1,16±0,44	83,7±19	1,27±0,46
Healthy controls N=20	1,02±0,2	81,0±29	1,03±0,19
p values	0.177	0.61	0.027

Conclusions: Cystatin C plasma level may reflect heart failure severity independently of renal function

P1770 Anaemia as a risk factor in heart failure

S.M.A. Ferreira, G.V. Guimaraes, F.D. Cruz, F. Bacal, V.S. Issa, P.V. Pires, E.A. Bocchi. *Heart Institute (Incor), University of Sao Paulo Medical School, Sao Paulo, Brazil*

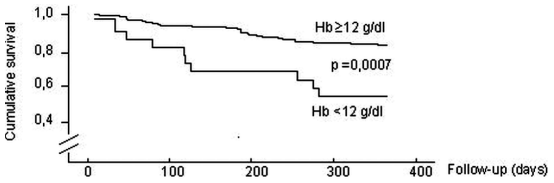
Background: Anaemia in patients (pts) with heart failure (HF) is associated with poor prognosis. There are few data about anaemia in HF brazilian population.

Methods and results: 180 pts of the study REMADHE were followed >12 months. Anaemia (Hb<12.0 g/dl) was detected in 19 (10.5%) pts and it was more common in women than men (20% vs. 7%, respectively, p=0,03) (table). In anaemic pts, 12-month survival was 54.6% compared to 82.9% in non-anaemic pts (p=0.0007) (figure).

Baseline clinical characteristics

	Anaemic pts (n=19)	Non-anaemic pts (n=161)	p
Age (years)	47.0±13.6	50.9±13.4	NS
Male (%)	47	74	0.03
LVEDD (mm)	71.1±11.8	71.4±9.1	NS
LVEF (%)	37±9	35±9	NS
Haemoglobin (g/dl)	10.9±0.9	14.4±1.4	<0.001
Serum sodium (mEq/l)	137.8±3.1	138.7±3.7	NS
Serum creatinine (mg/dl)	1.8±1.9	1.2±0.3	NS
Body mass index (kg/m^2)	24.7±4.5	26.7±5.1	NS
Ischaemic aetiology (%)	16	29	NS
Idiopathic aetiology (%)	26	29	NS
Chagas aetiology (%)	21	24	NS

PTS, patients; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction.



12-month survival curve in CHF patients

Conclusion: Anaemia is a significant predictor of poor outcome in this population.

P1771 Prevalence of anaemia in hospitalised patients with congestive heart failure (CHF) due to left ventricular systolic dysfunction

K.H. Ryu, S.W. Han, Y. Lee. *Konkuk university hospital, Cardiology Department, Seoul, Korea, Republic of*

Background: There is growing evidence that anemia is common in CHF patients and possibly related to symptoms and prognosis. But, there is considerable disagreement about the prevalence of anemia in CHF patients.

Methods: In 128 consecutive patients(60 male, 69.1?12.7 yrs) admitted with CHF due to left ventricular systolic dysfunction (LV ejection fraction less than 40%), demographic features and serum hemoglobin(Hgb), creatinine, echocardiographic findings were evaluated. Anemia was considered to be present when the Hgb on admission <12g/dL. Results: Fifty eight (45.3%) of the 128 patients were considered as anemic and 25 (19.5%) showed Hgb level less than 10g/dL on admission. Anemia was more frequent in female than male (67.2% vs 32.8%, p<0.01). Forty five (77.6%) out of 58 anemic patients showed normocytic normochrmic anemia, 6 were macrocytic. Microcytic anemia suggestive of iron deficiency state was revealed in 7 (12.1%) cases. Serum Hgb level was significantly lower in CHF patients with NYHA class 4 (10.9?6.1) than class 2 and 3 (12.6?2.7, 12.4?6.0g/dL respectively, p<0.01). LVEF was not significantly different with functional class. Serum Hgb level was reduced as serum creatinine level increase(r=0.288, p<0.001). But, Hgb level was not significantly lower than those without renal insufficiency (serum Cr >1.5mg/dL) (12.1?5.7 vs 11.3?5.7g/dL).

Conclusion: Anemia is a common finding in hospitalized patients with CHF and associated with severity of symptom. Mainly normocytic normochromic anemia is found among the patients with anemia and suggested that pathogenesis other than iron deficiency is the main mechanism of anemia in patients with CHF.

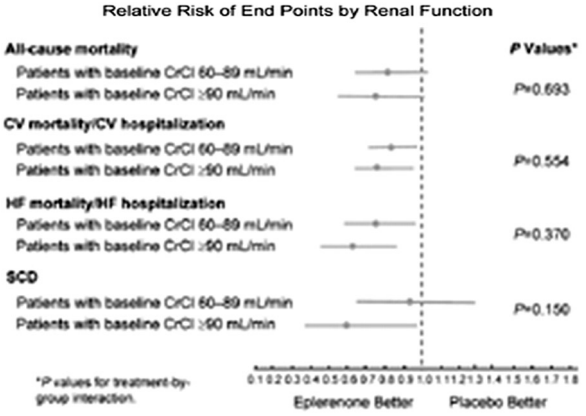
P1772 Effect of eplerenone in patients with normal renal function and mild renal insufficiency: results from the EPHESUS trial

R.G. Wilcox[1], E. Ambrosioni[2], R. Patni[3], R. Mukherjee[3], B. Pitt[4] on behalf of EPHESUS Investigators. *[1]Queen's Medical Centre, Department of Medicine, Nottingham, United Kingdom; [2]Universita degli Studi di Bologna, Bologna, Italy; [3]Pfizer, Inc, New York, United States of America; [4]University of Michigan Medical Center, Ann Arbor, United States of America*

Patients with renal insufficiency are at increased cardiovascular (CV) risk. This analysis of EPHESUS examines the effect of eplerenone (EPL) on outcomes in post-AMI HF patients with mild renal insufficiency and normal renal function at baseline (calculated creatinine clearance [CrCl] of 60–89 mL/min and ≥90 mL/min, respectively). As EPL is contraindicated in patients with CrCl <50 mL/min in Europe, these patients are not included.

In EPHESUS, patients with post-AMI HF and LVSD (EF=40%) on standard therapies were randomized 3–14 days after AMI to EPL (25 mg-50 mg QD; n=3319) or PBO (n=3313). This analysis by CrCl was performed using a Cox proportional hazards regression model with treatment group as the factor, stratified by geographic region. The estimated 95% CIs were based on the Wald test.

Approximately 2/3 of patients in EPHESUS had either normal renal function (N=1878) or mild renal insufficiency (N=2470). Risk reductions with EPL relative to placebo are given in the Figure. The incidence of hyperkalemia (serum potassium ≥6.0 mmol/L) was similar for both treatment groups in patients with mild renal insufficiency (EPL 3.8%, PBO 3.9%; P>0.20), and in patients with normal renal function (EPL 3.4%, PBO 2.4%; P>0.20). No deaths were adjudicated to hyperkalemia in EPL-treated patients and discontinuations due to hyperkalemia were <1.0% in both treatment groups.



Figure

In EPHESUS, EPL demonstrated consistently positive risk reductions in all-cause mortality, CV mortality/CV hospitalization, HF mortality/HF hospitalization, and sudden cardiac death in patients with normal renal function and in those with mild renal insufficiency. The rate of hyperkalemia in EPL-treated patients with mild renal insufficiency was low, and similar to that with PBO.

P1773 The beneficial effect of erythropoietin on cardiac function in patients with anaemia and chronic kidney disease. A randomised control study

K. Pappas, C. Gouva, P. Nikolopoulos, K. Katopodis, K. Naka, K. Siamopoulos, L. Michalis, J. Goudevenos. *Ioannina, Greece*

Introduction: Whether the correction of anemia with erythropoietin (EPO) in patients with chronic kidney disease (CKD) has any benefit on cardiac function is not clear. Most studies are based on indices of systolic function such as ejection fraction (EF) and left ventricular mass (LVM) and their results are conflicting.

Aim: The aim of the present study was to evaluate the effect of EPO on conventional and new indices of systolic and diastolic cardiac function in patients with anemia.

Methods: Thirty one patients with CKD (stage 3 or 4) were randomized in two groups. Fifteen patients (group I) were receiving EPO and sixteen (group II) were r not treated with EPO. Transthoracic echocardiography was performed in all patients at baseline and one year later. Systolic function was assessed with conventional methods (EF, and LVM). Diastolic function was assessed with mitral inflow indices (E and A wave velocities, Edt E deceleration time and E/A) and new preload - independed indices of mitral annulus velocities with Tissue Doppler Imaging (Em, Am) The elevated ratio E/Em seems to be a sensitive prognostic marker for cardiovascular events and is related to left ventricular filling pressure. A novel index of global cardiac function, Tei index, was calculated from mitral inflow and ejection time with doppler echocardiography.

Results: At baseline there were no significant differences in demographic characteristics, systolic pressure levels (132± 5 mmHg vs 134 ± 3 mmHg) and Hb levels (9,2 ± 0,6 vs 9,1 ± 0,5 g/dl). All indices of systolic and diastolic cardiac function between the two groups were not significantly different. Most of the patients had very good systolic cardiac function, increased LVM and impaired diastolic function. At the follow up study, one year later, there was significant difference in Hb levels (11,3 ± 0,5 in group I vs 9,3 ± 0,5 in group II, p < 0.005) and in echocardiographic parameters of systolic and diastolic function: EF %:(70,9 ± 7,6 vs 63,4 ± 9,33; p<0.02), LVM gr (209,6 ± 71 vs 278,5 ± 71,9; p<0.02), Edt ms (233,9± 98 vs 166,9 ± 45,1; p<0.02), Tei index (0,35 ± 0,12 vs 0,51 ± 0,17; P<0.007) and E/Em (9,7 ± 2,4 vs 14,8 ± 5,2; p<0.002) while blood pressure level were within normal values for both groups.

Conclusions: Correction of anemia with EPO in patients with CKD and good systolic cardiac function has beneficial effects on cardiac structure and function. The most significant differences were observed in the new echocardiographic indices we used, such as the Tei index and the E/Em ratio.

P1774 Addition of an angiotensin receptor blocker to standard heart failure therapy reduces morbidity in patients with reduced renal function

A. Ishani[1], I.S. Anand[2], M.A. Kuskowski[1], T. Rector[1], J. Cohn[3] on behalf of Val-Heft investigators. *[1]VA Medical Center, Minneapolis, MN, United States of America; [2]Edina, United States of America; [3]University of Minnesota, Minneapolis, MN, United States of America*

Background: Reduced renal function is a known risk factor for hospitalization and death in patients with heart failure (HF). Whereas ACE-inhibitors (ACE-I) or alternatively angiotensin receptor blockers (ARB) are standard therapy in HF, they are underutilized in patients with renal dysfunction (RD), and it is unclear whether they have similar beneficial effects in patients with HF and RD.
Methods: Patients (n=5010) randomized to placebo or valsartan in the Valsartan Heart Failure Trial (Val-HeFT) were retrospectively divided into subgroups with normal or abnormal kidney function according to baseline estimated glomerular filtration rate (eGFR) above or below of 60 ml/min/1.73m^2. Cox proportional hazards regression of all-cause mortality, first morbid event, and first hospitalization for heart failure were conducted to confirm that RD was a risk factor and compare treatment effects (valsartan vs. placebo) in patients with normal and abnormal renal function by testing for an interaction while controlling for several other known risk factors.
Results: Patients with eGFR $<$ 60mL/min/1.73 m^2 were older, more likely to be male, have lower diastolic blood pressure, BMI, left ventricular ejection fraction, and hemoglobin. They were more likely to be on diuretics and have worse NYHA class. Also they were less likely to be on ACE inhibitors, beta-blockers, and digoxin compared to those with normal kidney function. Adjusted hazard ratios (HR) confirmed that RD was an independent risk factor for death (HR 1.48, 95% CI 1.27-1.72), first morbid event (HR 1.56 95% CI 1.32-1.83) and first hospitalization for heart failure (HR 1.61 95% CI 1.36-1.91). In patients with normal renal function, valsartan reduced the risk of first morbid event (n=2083, HR 0.83, 95% CI 0.65-1.06) and first hospitalization for heart failure (n=2083, HR 0.82, 95% CI 0.63-1.05). The risk reduction attributed to valsartan was not significantly different in the subgroup with RD for first morbid event (n=2915, HR 0.68, 95% CI 0.58 - 0.80) or first hospitalization for heart failure (n=2915 HR 0.68, 95% CI 0.58 - 0.81), (p for interaction $>$ 0.1 for all comparisons).
Conclusion: These data confirm that renal dysfunction (eGFR $<$ 60mL/min/1.73 m^2) is an independent predictor of worse outcomes in patients with HF. However, the beneficial effects of valsartan in reducing mortality and morbidity were not significantly different in the presence of renal dysfunction. Given the excess risk of outcomes and similar valsartan efficiacy in those with RD, valsartan could benefit an even greater number of patients with RD.

P1775 Predictors and impact on outcome of new onset anaemia in chronic heart failure

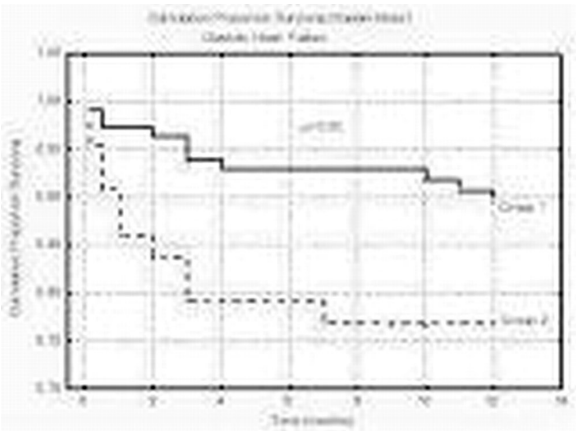
M. Komajda[1], S.D. Anker[2], A. Charlesworth[3], W.J. Remme[4], C. Moullet[5], K. Swedberg[6], J.G.F. Cleland[7], P.A. Poole-Wilson[8] on behalf of for the COMET Investigators. *[1]Pitie Salpetriere Hospital, Departement de Cardiologie, Paris Cedex 13, France; [2]Charite Campus Virchow-Klinikum, Cardiology, Berlin, Germany; [3]University Hospital, Department of Cardiovascular Medicine, Nottingham, United Kingdom; [4]Sticares Cardiovascular Research Found, Rhoon, Netherlands; [5]F. Hoffmann - La Roche Ltd, Basel, Switzerland; [6]Sahlgrenska University Hospital Ostra, Department of Medicine, Goteborg, Sweden; [7]University of Hull, Department of Cardiology, East Yorkshire, United Kingdom; [8]Imperial College London, Cardiac Medicine, London, United Kingdom*

Background: Anaemia is associated with poor prognosis in patients with chronic heart failure (CHF). However, the impact of New Onset Anaemia (NOA) on outcome remains largely unknown in this condition.
Objectives: We evaluated the predictors and the role of new onset anaemia defined by Hb $<$ 12.5 g/dl in non anaemic patients at baseline on mortality in 2996 CHF patients enrolled in the COMET trial over an average of 58 months of follow-up.
Results: At baseline, 10.9% of male patients and 24.5% of female patients had Hb $<$12.5g/dl and 2.2% of male patients and 4.1% of female patients Hb $<$11g/dl. New onset anaemia occurred in 13.1% at year 1 and, cumulatively, in 25% at year 5 (17% male subjects, 35% female subjects). Predictors of NOA were carvedilol (C) vs metoprolol (M) treatment (RR = 1.36, 95% CI, 1.13 – 1.62, p $<$ 0.0009) increasing age (RR = 1.16/10 years, 95% CI, p $<$ 0.001 female gender (RR = 1.74, 95% CI, 1.41 – 2.14, p $<$ 0.0001, diabetes (RR = 1.34, 95% CI, 1.09 – 1.64, p $<$ 0.005), stroke (RR = 1.37, 95% CI, 1.02 – 1.85, p = 0.03) increasing creatinine (RR = 1.05 per 10μMol/l, 95% CI, 1.03 – 1.07, p $<$ 0.0001). Increasing BMI (RR = 0.86 per 5 unit increase, 95% CI, 0.77 – 0.97, p = 0.01), LVEF (RR = 0.91 per 5 unit increase 95% CI, 0.86 – 0.97, p = 0.005), sodium (RR = 0.82 per 5 mM/l increase 95% CI, 0.71 – 0.93, p = 0.003) and Hb (RR = 0.51 per 1 g/dl increase 95% CI, 0.16 – 0.55, p = 0.0001) were associated with lower risk of NOA. Patients with moderate NOA had a markedly increased risk of mortality (RR = 1.67, 95% CI 1.38 – 2.03 p $<$ 0.001) and this was further increased in patients with severe NOA $<$ 11 g/dl (RR = 2.27, 95% CI 1.73 – 2.98, p $<$ 0.0001). Reduction of $\geq$ 3 g/dl of Hb was associated with a marked increase in mortality (RR = 2.13, 95% CI, 1.5 – 2.92, p $<$ 0.0001). Hb $<$ 12.5 g/dl increased the risk of hospitalisation by 17%. Despite a mild and sustained decrease in Hb in C vs M treatment, (-0.2g/dl, 95% CI, 0.3-0.1, p = 0.003 at year 1), no significant interaction between Hb strata and treatment on mortality was observed.
Conclusion: NOA is frequent and associated with increased mortality in CHF. Specific baseline demographic characteristics are associated with NOA. Carvedilol is associated with a slight reduction in Hb concentration. However, this effect does not impact on the beneficial effect of Carvedilol on mortality in CHF patients.

P1776 Influence of low level of haemoglobin on clinical picture and survival in patients with diastolic and systolic heart failure

M. Roik, S. Stawicki, M.H. Starczewska, A. Solarska-Polchlopek, D. Kosior, O. Warszawik, G. Horszczaruk, G. Opolski. *University Hopsital, 1 st Department of Cardiology, Warsaw, Poland*

Anemia (A) is common in patients with chronic heart failure (CHF). In pts with severe CHF lower hemoglobin concentrations is associated with an adverse prognosis and reduced the quality of life.
The aim of this was to compare the prevalance of A in pts wits SHF and DHF and impact on the clinical picture and survival during 1-year.
Methods: Of the 501 consecutive CHF pts in NYHA II-IV class hospitalised in Dept. of Cardiology from 2002-2003 we identified 394 with performed echocardiography examination and estimation of ejection fraction (EF). Pts were divided into two groups dependably on EF: DHF with EF$>$45% (n=155) and SHF with EF=$<$45%, (n=236). After the measurment of hemoglobin level we divied the pts in SHF and DHF on A pts (with hemoglobin level $<$ 12) and non-A pts (hemoglobin level $>$ 12). Patients were followed up for one year.
Results: In pts with SHF 50 pts (21%) were A. In clinical picture A pts with SHF were more common female gender and renal dysfuction (RD) (p $<$ 0.05). No differences in age, hypertension, DM, prior renal dysfunction, NYHA class and EF were observed. The 1-year mortality was significantly higher in pts with A and SHF, respectively (40% vs. 25%, p $<$ 0.05). In pts with DHF 38% of pts were A. A pts with DHF were older, with prior history of RD and RD were present in lab test during the admission in compare with pts DHF without A (p $<$ 0.05). Hypertension, DM, etiology, NYHA class and EF did not differ the A and non-A pts in DHF. A also had a significant impact on mortality in this group (p $<$ 0.05).



The Kaplan-Meier curve

Conlusions: A is common in pts with SHF and DHF and some findings are present in this group. Survival in A pts with SHF or DHF are worse than in pts without A.

HEART FAILURE: SURVEYS: NEW RESULTS

P1777 Heart failure in subjects over 80 years: a representative French nursing homes survey

A. Benetos[1], O. Hanon[2], G. Jondeau[3], J.F. Aupetit[4], P. De Groote[5], H. Gallois[6], M. Komajda[7], F. Forette[2] on behalf of French Society of Cardiology - French Society of Gerontology Geriatric. *[1]Hôpital Brabois, Centre de gériatrie, Vandoeuvre-les-Nancy, France; [2]Hopital Broca, Service de gériatrie, Paris, France; [3]Hopital Ambroise Pare, Service de cardiologie, Boulogne, Billancourt, France; [4]Centre Hospitalier St-Joseph/St-Luc, Service d'explorations fonctionnelles, Lyon, France; [5]Hôpital cardiologique, Service de cardiologie C, Lille, France; [6]Information Servier, Direction Scientifique France, Neuilly Sur Seine, France; [7]Centre Hospitalier Pitie-Salpêtrière, Institut de Cardiologie, Paris, France*

Background: The prevalence and management of heart failure (HF) in very elderly subjects (^{3}80 years) living in nursing homes in France are not known.
Objective: To determine, in an observational study, prevalence of HF, modalities

of diagnosis and treatment in a population of subjects over 80 years, living in nursing homes.
Methods: In 2004, a representative sample of nursing homes in France, based on their location and status (private or public), was derived from the French Nursing Homes survey by SFC and SFGG. In order to assess the prevalence of HF in patients over 80 years of age, practitioners in these nursing homes were asked to determine the number of patients suffering from HF within their establishment and to provide information pertaining to the management of the last two patients each had examined.
Results: In this national representative sample of 287 nursing homes (n=14 843 subjects), a prevalence of 31% of HF was determined in the group of elderly patients over 80 years
(3 146/10 233). For the 561 last examined patients (mean age 87 $\pm$ 5 years, 60% of women, history of hypertension 67% and coronary heart disease 43%), a moderate HF was established in 49% of cases and a severe HF in 33% of cases. The diagnosis of HF was based at least on two set of parameter in 80% of cases including clinical examination (79%) and/or echocardiography (64%) and/or electrocardiogram (57%) and/or Chest X-ray (32%). When performed, echocardiography, concluded to a systolic dysfunction in 51% of cases. Mean number of drugs taken by patient was 7.4 $\pm$ 2.8, only 4% had no pharmacological treatment. The treatments used for heart failure were diuretics in 78%, ACEI in 51% (in systolic dysfunction 60%), digitalis in 28%, spironolactone in 21% (in moderate HF 20%), beta-blockers in 16% and angiotensin II receptor blockers in 9%. Other treatments were nitrates in 43%, calcium antagonists in 16%, aspirin in 40%, anticoagulants in 23% and anti-arrhythmic agents in 22%.
Conclusions: The prevalence of heart failure in subjects over 80 years living in nursing home is high (31%). Echocardiography is often performed (64%) but recommended drugs remain underused (ACEI [51%]), beta blockers [16%]).

P1778 Congestive heart failure patients managed by GPs or cardiologists: the result of PRINCEPS studies

G. Jondeau[1], I. Leurs[2], F. Allaert[3]. [1]*Hopital Ambroise Pare, Service de Cardiologie, Boulogne-Billancourt, France;* [2]*AstraZeneca, Rueil Malmaison, France;* [3]*Centre d'evaluation CHRU, Dijon, France*

Aim: Compare patients with ambulatory congestive heart failure (CHF) managed by GPs and cardiologists working in and out of the hospital.
We compared the answer obtained to the same questionnaire in 2002-2003 from 1717 GPs, 527 cardiologists working out of the hospital, and 270 cardiologists working in hospital.
Results: Data were obtained for 3782 ambulatory CHF patients treated by GP, 463 patients treated by cardiologists working in hospital, 1505 patients treated by cardiologists working out of hospital.
Patients treated by GPs and cardiologists have different clinical characteristics (table)
These differences may explain why ACEI at recommended dosage (according to ESC recommendations) were used less often by cardiologists working either at the hospital (42% of patients) or out of hospital (50% of patients) than by GP (55% of patients). On the contrary, beta-blockade were used more often by cardiologists working at the hospital (65% of patients) or out of the hsopital (66% of patients), than by GP (20% of patients).

Patients according to treating physician

	hospit cardio	out of hospit cardio	GPs	p
age (yo)	65	68	71	<0.001
females (%)	28	28	38	<0.001
previous hospitalisation (%)	63	50	39	<0.001
NYHA II/III-IV (%)	48/43	59/30	63/29	<0.001
ischemic/HTN (%)	39/52	35/54	18/76	<0.001

Conclusion: in patients managed by GP, CHF is more recent, less symptomatic, more often related to HTN, with fewer previous decompensations. This difference may partly explain why GP use higher doses of ACEI but less beta-blockade that cardiologists working either at the hospital or out of the hospital for these CHF patients.

P1779 Inadequate recall of advice on diet and lifestyle in patients with heart failure: experience from the Euro Heart Failure Survey

M. Lainscak[1], I. Keber[2], M.J. Lenzen[3], F. Follath[4], K. Swedberg[5], M. Komajda[6], J.G.F. Cleland[7]. [1]*Murska Sobota, Slovenia;* [2]*Clinical Centre Ljubljana, Department of vascular disease, Ljubljana, Slovenia;* [3]*Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands;* [4]*University Hospital Zürich, Department of Medicine, Zürich, Switzerland;* [5]*Sahlgrenska University Hospital/Östra, Department of Medicine, Göteborg, Sweden;* [6]*Hôpital Pitié Salpétriere, Department of Cardiology, Paris, France;* [7]*University of Hull, Department of Cardiology, Kingston upon Hull, United Kingdom*

Background: Non-pharmacological measures including lifestyle advice, diet, vaccination, and specific therapy are part of the standard management of heart failure. However, there is little information on whether patients with heart failure recall receiving such recommendations and whether they admit to following them. We aimed to obtain information on the patients perception about being given non-pharmacological measures advice, and whether they follow the advice they remember.
Methods: The EuroHeart Failure Survey screened unselected consecutive deaths and discharges in 24 countries belonging to the ESC during 2000-2001. In this report we focus on those who attended the interview 12 weeks after discharge, and had evidence of left ventricular systolic dysfunction (LVSD – 1309 patients) or preserved left ventricular function (PLVF – 599 patients). Data on clinical characteristic and treatment were retrieved from medical documents and on non-pharmacological advice from the interview. Health and quality of life were assessed by a seven-category descriptive scale.
Results: LVSD patients were younger (64 (12) years vs. 69 (11) years), more frequently men (76% vs. 52%), and less frequently in NYHA class III/IV (25% vs. 32%). Estimated health (3.9 (1.4) vs. 3.8 (1.4)) and quality of life (4.2 (1.5) vs. 4.2 (1.5)) were similar between groups. Patients with and without LVSD reported awareness of heart problems in similar proportions but more LVSD patients were satisfied that their condition had been explained (83% vs. 74%). General lifestyle and dietary advice was more frequent recalled in LVSD patients: cholesterol or fat intake (67% vs. 62%), calorie intake (62% vs. 56%), alcohol (50% vs. 39%), and smoking (51% vs. 41%). Heart failure-specific advice such as exercise (65% vs. 58%), to decrease dietary salt intake (48% vs. 41%), to check weight regularly (51% vs. 41%), and to avoid the use of NSAID (21% vs. 17%) was also more frequently recalled by LVSD patients. This was not true of advice on influenza vaccination (40% vs. 39%).
Conclusions: Recall of both general and specific advice about lifestyle and diet is unsatisfactory in patients with heart failure. Those with LVSD seemed to have better recall compared to those with PLVF, which could reflect the effects of age or greater attention to care because of successful outcome trials and current guidelines.

P1780 Determinants of left ventricular systolic function recovery after an acute coronary syndrome; prospective randomised study

F. Sampaio[1], P. Mateus[2], N. Bettencourt[2], C. Dias[2], L. Simoes[2], V. Gama[2]. [1]*Porto, Portugal;* [2]*Centro Hospitalar Vila Nova de Gaia, Cardiologia, Vila Nova Gaia, Portugal*

Introduction: Ischemic heart disease after acute coronary syndrome (ACS) is a major cause of heart failure in western societies. However, factors that may influence left ventricular function (LVF) recovery after myocardial infarction are still uncertain.
Purpose: To identify variables that may influence LVF evolution one year after hospitalisation due to ACS.
Methods: 104 patients hospitalised with ACS between 1/7/2001 and 31/12/2002 and with systolic dysfunction (SD) - defined as echocardiographic ejection fraction (EF) $\leq$45% - were randomly allocated to a planned coronary follow-up clinic (FUP) or a general cardiology clinic (GC); in both groups patients were also randomly referred to a structured cardiac rehabilitation program (CRP). EF was reassessed at one year. We compared differences between patients who recovered left ventricular function (EF $>$ 45% - group 1) and those who did not (group 2).
Results: One year after discharge, 44.2% of the patients (mean age 56 years, 77.7% male) recovered function. Group 1 patients were more frequently overweight (body mass index $\geq$25) than group 2 patients (77.7% vs 47%, p=0.015). There were no significant differences in gender, age, hypertension, diabetes, dyslipidemia, smoking habits or family history between the groups. A previous history of cardiovascular events was more frequent in group 2 (11.1% vs 35.3%, p=0.03). Cardiac catheterization was performed before discharge in 88.8% and 88.2% in groups 1 and 2 respectively; p=NS); no differences were found in the distribution of coronary stenosis between the 2 groups. Angioplasty was performed in 54.2% in group 1 and 50% in group 2 (p=NS). There were no differences in the use of angiotensin converting enzyme inhibitors (83.3% vs 87.5%), beta blockers (87.5% vs 87.5%), nitrates (37.5% vs 33.3%), aspirin (95.8% vs 95.8%), statins (79.1% vs 75%) or diuretics (20.8% vs 45.8%). Heart failure symptoms were referred by 20.8% of group 1 and 38.5% of group 2 patients, and NYHA class $>$ 2 was observed in 16.6% in group 1 vs 30.7% in group 2; these differences, however, had no statistical meaning. There were no differences in function recovery between patients randomized to FUP or GC (38.5% vs 54.5%, p=NS). 87.5% of patients who completed CRP had a normal EF at one year compared to 32.7% of patients not referred to that program (p=0.009).
Conclusion: Enrollment in a structured CRP was the only variable that influenced LVF evolution and seems to be an important therapeutic measure in patients with SD after ACS; our data suggest that these programs should be more widely applied.

P1781 Between-speciality differences in the management of heart failure in Europe despite evidence-based guidelines – the SHAPE survey

W.J. Remme[1], J. McMurray[2], J. Lopez Sendon[3], A. Cohen Solal[4], F. Zannad[5], S. Boccanelli[6], B. Rauch[7], K. Keukelaar[8] on behalf of the SHAPE Study Group. *[1]Sticares Cardiovascular Research Foundation, Rhoon, Netherlands; [2]University of Glasgow, Glasgow, United Kingdom; [3]Hospital Universitario Gregorio Marano, Madrid, Spain; [4]Hopital Beaujon, Clichy, France; [5]Hopital Jeanne d' Arc, Dommartin-les-Toul, France; [6]San Giovanni Hospital, Division of Cardiology, Roma, Italy; [7]Klinikum der Stadt Ludwigshafen am Rhe, Ludwigshafen am Rhein, Germany; [8]Sticares Cardiovascular Research Fnd, Rhoon, Netherlands*

Background: European cardiologists(C) are likely to follow evidenced-based guideline-directed strategies in their management of heart failure(HF). Whether other specialists involved in HF care, e.g. internists(I) and geriatricians(G)do likewise, is unknown. To get insight in HF management between different specialities the Study group of Heart failure Awareness and Perception in Europe (SHAPE) surveyed 4000 specialists, 50%C and 50%I/G in France, Germany, Italy, the Netherlands, Poland, Romania, Spain, Sweden, and the UK.
Methods: A questionnaire with 32 questions (in their native language)was provided concerning knowledge of HF, how they would diagnose and treat HF, side effects of medications, non-pharmacological treatments and HF care programmes. Treatment questions related to HF with systolic dysfunction (LVEF<40%).
Results: Whereas 98% and 85%(IG) and 99% and 79%(C) would use an ECG and chest x-ray, respectively, as diagnostic routine (NS), 43% and 78%(I/G) and 82% and 90%(C) would use echocardiography with and without Doppler, respectively, (p>0.0001). 56%I/G and 58%C would use BNP/proBNP. ACE inhibitors would be prescribed in >90% of patients by 64%I/G and 82%C (p<0.0001). Only 39%I/G would use a beta-blocker in >50% of their patients, compared to 73%C, and 26% I/G would never prescribe a beta-blocker in patients with mild symptoms on ACE inhibition and diuretics versus 11%C (both p<0.0001). Although approximately 50% in both groups would start treatment in HF with fluid overload with a diuretic, 18%I/G would treat with diuretics only in mild, stable heart failure versus 7%C (p<0.0001). In patients with worsening heart failure, in sinus rhythm and on optimal doses of ACE inhibitors, beta-blockers and diuretics, 51%I/G and 59%C would add spironolactone (p<0.0001), whereas 14%I/G and 11%C would add digoxin. Recommended ACE inhibitor dose levels were prescribed by 26-76%I/G and by 40-89%C (p<0.0001). Beta-blockade was considered the most important innovation in the last decade by 81%I/G and 95%C, angiotensin II antagonists by 54%I/G and 30%C, and cardiac resynchronization therapy and ICD by 17%I/G and 34%C (all p<0.0001).
Conclusion: Between-specialty differences in the management of heart failure persist despite the availability of evidence-based HF guidelines. Significantly less uptake of recommended management strategies in internist and geriatric practices indicate the need for education of these essential health care providers.

P1782 Prognostic value of chronic obstructive pulmonary disease in heart failure patients: data from the Val-HeFT trial

L. Staszewsky[1], S. Masson[1], E. Carretta[1], M. Amigoni[1], M. Wong[2], I. Anand[3], J.N. Cohn[4], R. Latini[1] on behalf of the Val-HeFT investigators. *[1]Mario Negri Institute, Department of Cardiovascular Research, Milano, Italy; [2]VA Greater, Healthcare System, Los Angeles, California, United States of America; [3]University of Minnesota Medical School, VA Medical Center, Minneapolis, Minnesota, United States of America; [4]University of Minnesota Medical School, Minneapolis, Minnesota, United States of America*

Chronic obstructive pulmonary disease (COPD), like heart failure (HF), is a mayor cause of death and disability. There is little information on the prognosis of pts who present with both of these diseases.
Aim: To evaluate the prognostic value of COPD in pts with HF and to assess the relationship between COPD and biomarkers of HF severity.
Methods: 5010 pts with HF included in the Val-HeFT trial, were grouped according to the presence (n=628) or absence of COPD (n=4382) at randomization.Their baseline clinical, biohumoral and echocardiographic characteristics were compared.The independent prognostic role of COPD in predicting 23-month mortality was analyzed by a nested multivariate Cox proportional hazard model.
Results: Compared to no-COPD, pts with COPD were older, more likely to have a history of coronary heart disease and diabetes, higher heart rate, more severe symptoms, a poorer quality of life and less likely to have beta-blocker therapy. LVIDd and LVEF were not different. BNP was slightly increased (105 vs 97 pg/mL, p=0.0475), while norepinephrine (447 vs 386 pg/mL, p<0.0001) and inflammatory markers were consistently increased (neutrophils 66.9 vs 63.5%, p<0.0001; CRP 4.9 vs 3.1 μg/mL, p<0.0001) in COPD pts. All cause mortality was higher in COPD than in no-COPD pts (27.4 vs 18.4%, p<0.0001). When concomitant treatment was included in the model, COPD was no longer an independent predictor of mortality (Table 1), but remained an independent predictor of all-cause hospitalizations.
Conclusion: Pts with COPD were more symptomatic which was not explained by worse LV function but was associated with worse outcomes. COPD was not an independent predictor of mortality but it predicted all-cause hospitalizations. The prevalence and role of COPD in HF is important and the accurate diagnosis of COPD would optimize HF pts management.

Table 1. COPD vs no-COPD

Mortality	HR (95%IC)	p
Univariate analysis	1.57 (1.33-1.85)	<0.0001
Nested multivariate analysis (variables in the model)		
– Clinical	1.23 (1.01-1.49)	0.0366
– Clinical + echocardiographic	1.25 (1.03-1.52)	0.0215
– Clinical + echocardiographic + treatment	1.20 (0.99-1.45)	0.0669
– Clinical + echocardiographic + treatment + biomarkers	1.15 (0.95-1.40)	0.1538

HR: hazard ratio

P1783 Factors precipitating heart failure hospitalisation: a novel analysis of the Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme

M. Mcentegart[1], S. Yusuf[2], M.A. Pfeffer[3], E.L. Michelson[4], J. Ostergren[5], C.B. Granger[6], K. Swedberg[7], J.J.V. McMurray[8]. *[1]Western Infirmary, Cardiology, Glasgow, United Kingdom; [2]HGM-McMaster Clinic, Hamilton, Canada; [3]Brigham and Women's Hospital, Cardiology, Boston, United States of America; [4]AstraZeneca LP, Wayne PA, United States of America; [5]Karolinska Hospital, Stockholm, Sweden; [6]Duke University, Cardiology, Durham, United States of America; [7]Sahlgrenska University Hospital/Ostra, Medicine, Goteborg, Sweden; [8]Western Infirmary, Cardiology, Glasgow, United Kingdom*

Purpose: although heart failure (HF) hospitalisations (and associated morbidity and health care costs) are increasing, our knowledge of their precipitants is limited. The CHARM programme used a novel approach to investigate this problem. Investigators were asked to prospectively record possible precipitants at the time of HF admission, using a structured questionnaire. This information was obtained in patients with preserved as well as reduced LVEF.
Methods: the CHARM programme comprised 3 randomised, double-blind, trials (CHARM-Alternative: LVEF ≤40%, ACE inhibitor intolerant; CHARM-Added: LVEF ≤40%, ACE inhibitor treated; CHARM-preserved: LVEF >40%), comparing candesartan to placebo in 7599 patients. A list of 11 possible specific precipitants (concomitant medication in the prior 48 hours, arrhythmias, any other non-cardiac factor, excess salt or dietary non-compliance, high output state, non-compliance with medication, precipitating valve disease, inappropriate decrease in cardiac medication, acute myocardial ischaemia/infarction and excess alcohol) were offered. An "other" precipitating factor (with free text) could also be chosen. More than one factor could be selected but investigators were also asked to identify the primary precipitant.
Results: over 38 months mean follow-up, 2011 patients accounted for 4169 admissions with HF. When asked about any precipitant(s) possibly contributing to admission, concomitant medication (56.3%), arrhythmias (25.4%), and non-compliance (22.4%) were most frequently identified, while no specific precipitant was identified in 26% of cases. Precipitating factors were generally similar in patients with HF and reduced or preserved LVEF, though use of calcium channel blockers and non-steroidal anti-inflammatory drugs, atrial fibrillation, anaemia and valve disease were more frequent in patients with preserved LVEF, while inappropriate reduction in cardiac medication was more frequent in patients with reduced LVEF. When asked about the primary precipitant, an "other" factor was selected in 55.7% of admissions. While concomitant medication was the most frequently identified contributing factor it was identified as the primary precipitant in <2% of admissions.
Conclusions: identification of the factors that precipitate HF admissions, and particularly the primary precipitating factor, is difficult even in a clinical trial setting. While a few specific factors are thought to commonly contribute to admissions with HF, the primary precipitant, when identified, is one of a wide range of infrequent factors.

P1784 One year with RiksSvikt a national heart failure registry

M. Edner[1], Å Jonsson[2], U. Dahlstrom[3]. *[1]Danderyd Hospital, Medicine Dept., Danderyd, Sweden; [2]Ryhovs hospital, Medicine, Ryhov, Sweden; [3]Linköping University Hospital, Cardiology, Linköping, Sweden*

Recent reports have indicated that echocardiography is underused when diagnosing heart failure as well as recommended medical treatments as ACE-inhibitors/Angiotensin II-blockers (ARB's) and beta-blockers.
In order to find out to what extent guidelines concerning heart failure care are followed in Sweden, a national heart failure registry, RiksSvikt, was started in 2003.
Methods: To explore the interest of such a register all hospitals in Sweden were contacted before starting. A protocol including 85 variables concerning social status, concomitant diseases, ECG, chest X-ray, echocardiography and treatment was created. The database which is internet-based is situated at Uppsala Clinical Research Center, UCR. The users are working on-line and short "guidelines reports" are one line created by which it is possible to compare the own hospi-

tal/unit with the rest of Sweden. A more extensive statistical analysis of the data is performed on an annual basis.
Results: At the end of 2004, 35 hospitals and 4 primary care units had reported 3105 patients with a mean-age of 73,6 range 19-97 years to RiksSvikt. ECG was performed in 97% of the pts and almost 40% had atrial fibrillation. 89% of the men and 85% of the women had had an echocardiography performed ($p<0.001$). In pts with a left ventricular systolic dysfunction, left ventricular ejection fraction <40%, ACE/ARB were prescribed in 88%, range 50-100%, men 90 and woman 85%, $p<0.01$. Beta-blockers were prescribed in 89%, range 42-100%, men 88 and woman 89%. Aldosteron-antagonists are used in 44% of the pts, range 9-100%.
Conclusions: Even though collected data should be interpretated carefully there is a very wide range in the prescription of ACE/ARB and beta-blockers. Wether there is a real gender prescription difference has to be further explored. However, hospitals and primary care units are encouraged to participate in RiksSvikt and to contribute to an improved heart failure care in Sweden.

P1785 International variations in the treatment and co-morbidity of left ventricular systolic dysfunction: data from the Euro Heart Failure survey

M. Lainscak[1], J.G.F. Cleland[2], M. Lenzen[3], F. Follath[4], M. Komajda[5], K. Swedberg[6]. [1]*Murska Sobota, Slovenia;* [2]*University of Hull, Department of Cardiology, Kingston upon Hull, United Kingdom;* [3]*Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands;* [4]*University Hospital Zürich, Department of Medicine, Zürich, Switzerland;* [5]*Hôpital Pitié Salpétriere, Department of Cardiology, Paris, France;* [6]*Sahlgrenska University Hospital/Östra, Department of Medicine, Göteborg, Sweden*

Background: There is extensive evidence of the beneficial effects of angiotensin converting enzyme inhibitors (ACE) and beta-blockers (BB). In patients with left ventricular systolic dysfunction (LVSD) these therapies together with spironolactone are recommended, but many patients do not appear treated in accordance with guidelines. This may be inappropriate, reflecting a lack of adequate organisation of care. Alternatively, it may be appropriate not to implement treatment in a high proportion of patients because it is contra-indicated due to co-morbidity.
Methods: The EuroHeart Failure Survey screened unselected consecutive deaths and discharges in 24 counties belonging to the ESC during 2000-2001. We divided countries into original EU countries, new EU countries, Georgia and Russia and Israel. 10,701 patients (23%) of all patients screened had suspected or confirmed heart failure (HF) and 3,658 had documented LVSD. HF treatment guidelines mostly encompass patients with LVSD which were the focus of this report. Clinical characteristics including co-morbidity and pharmacological treatment were recorded.
Results: The mean age of the 3,658 patients with LVSD was 67 (13) years and 29% were women. Diabetes mellitus, major renal dysfunction, and respiratory disease were present in 28%, 20%, and 27%, respectively. ACE inhibitors, BB, and spironolactone had been prescribed to 78%, 46%, and 29% of patients by the time of discharge. The presence of renal dysfunction was associated with lower use of ACE inhibitors (74% vs. 83%, $p<0.001$). BB were less often used in patients with respiratory disease (32% vs. 53%, $p<0.001$). Co-morbidity did not appear to affect the use of spironolactone. At least 50% of the target dose was often prescribed to patients with a specific co-morbidity: ACE inhibitors for 59% of patients with glomerular filtration rate <60ml/min, BB to 58% of patients with respiratory disease, and spironolactone to 70% of patients with a history of renal dysfunction. Many patients received agents that have no well established role for the management of HF; nitrates (50%), and aspirin (54%). Importantly, There were few international differences in the uptake of key therapies within Europe. However, patients in new EU countries, Russia and Georgia, were more likely to be prescribed BB and spironolactone.
Conclusions: International guidelines appear successful in creating a relatively uniform approach to the management of important aspects of treatment for HF. Relevant co-morbidity seems to be responsible for a substantial reduction in the prescription of ACE inhibitors and BB.

P1786 Clinical profile and in hospital mortality of octogenarians enrolled in Euro Heart Failure Survey I

M. Komajda[1], O. Hanon[2], M. Hochadel[3], F. Follath[4], K. Swedberg[5], A. Gitt[6], J.G.F. Cleland[7]. [1]*Pitie Salpetriere Hospital, Departement de Cardiologie, Paris Cedex 13, France;* [2]*Broca Hospital, Department of Geriatrics, Paris, France;* [3]*Institut für Herzinfarktforschung, Ludwigshafen, Germany;* [4]*University Hospital, Zurich, Switzerland;* [5]*Sahlgrenska University Hospital Ostra, Department of Medicine, Goteborg, Sweden;* [6]*Institut für Herzinfarktforschung, Oberarzt Kardiologie, Ludwigshafen, Germany;* [7]*University of Hull, Department of Cardiology Unit, East Yorskshire, United Kingdom*

Background: Heart failure (HF) is a disease of the elderly. Data suggest that advanced elderly patients with HF have multiple comorbid factors and poor outcome.
Objectives: We compared the clinical profile and in hospital mortality in 2780 octogenarians (GR1, median age = 85) and 7912 younger patients (GR2, median age = 69) enrolled in 116 hospitals across 24 ESC countries participating in the Euro Heart Failure Survey I. Legend (*) = $p < 0.00001$.
Results: GR1 patients were more often referred to general medicine/geriatrics (73% vs 44% (*) and more likely to be women (63% vs 41% (*). An history of atrial fibrillation/SVT was more frequent (49% vs 40% (*) whereas ischaemic aetiology was less common (55% vs 62% (*). Co-morbid factors were much more prevalent in GR1, including stroke/TIA (22% vs 15%), dementia (22% vs 8%), renal dysfunction (21% vs 16%), arthritis (13% vs 10%) and infection (41% vs 30%), except diabetes (22% vs 29%) (all*). More GR1 patients had 3 (19% vs 14%), 4 (9% vs 6%), ≥ 5 (6% vs 4%), comorbid factors (all*). ECG and X-ray were performed equally in both groups but ejection fraction determination (38% vs 66% (*), coronary angiography and stress tests were less commonly performed in GR1. Systolic function was more often preserved (EF > 45% or systolic function formal/mildly reduced) in GR1 (61% vs 49%)(*). In hospital mortality (13% vs 5%, OR = 2.72 (95% CI 2.35 - 3.16)(*) and during 12 week follow-up (12% vs 6%, OR = 2.05 (95% CI: 1.73 - 2.43)(*) were also higher in GR1. Non cardiovascular death in hospital was more frequent in GR1 (7% vs 3%)(*). Finally, fewer GR1 patients were in Class NYHA I/II at interview (65% vs 75%) (*).
Conclusion: In this large cohort of in hospital HF octogenarians, demographic data including gender and aetiology, are different from those observed in younger heart failure patients. Preserved systolic function and co-morbid factors are considerably more prevalent. Finally, in hospital and short term mortality are significantly increased.

P1787 Risk factors for development of heart failure impair left ventricular performance in patients with coronary artery disease

E.N. Tapanlis, D.N. Chrissos, A.A. Katsaros, N.C. Korovesi, P.N. Stougiannos, A.N. Kartalis, D.S. Sirogiannidis, I.E. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Introduction: It has been proven that arterial hypertension, diabetes mellitus, dyslipidemia, tobacco use and obesity are important risk factors (RF) for development of heart failure (HF), principally in the presence of underlying coronary artery disease (CAD). The purpose of this study is to evaluate the impact of the above RF on noninvasive echocardiographic markers of left ventricular performance in patients (P) with HF owing to CAD.
Methods: 238 consecutive hospitalized P with HF due to CAD (185 males and 53 females of mean age 67.62±13.09 years) were studied for an eighteen-month period and were divided in P with no RF, P with 1-2 RF and P with ≥3 RF. The groups did not differ concerning sex, age, etiology of HF, any comorbid conditions, blood parameters, and adherence to therapy. Left ventricular end-diastolic diameter (EDD), end-systolic diameter (ESD) and ejection fraction (EF) were measured by 2-D echocardiography. EF less than 40% -using the Teicholz method- was considered as HF index. E/A ratio of the transmitral flow (TMF) was measured by pulsed-wave Doppler echocardiography -E and A are respectively the early and the late peak diastolic velocity of TMF (cm/sec). The restrictive TMF pattern (E/A >2) indicates advanced diastolic abnormality. Data were expressed as "mean value ± standard deviation", statistical analysis was performed by the student's t-test method and by the X^2 method and $p<0.05$ was considered statistically significant.
Results: It was revealed that P with ≥3 RF had significantly greater mean EDD and mean ESD (61.38±9.53mm and 50.93±11.59mm respectively) compared to P with 1-2 RF (57.79±10.25mm and 47.21±12.08mm respectively) and to P with no RF (56.65±7.93mm and 45.73±8.73mm respectively) ($p<0.05$ for both parameters). Significant differences concerning the mean EF were not detected between the three groups of P (30.65±8.67%, 32.37±6.92% and 31.85±7.12% respectively, p=NS). Furthermore, a significantly higher percentage of P with 1-2 RF (32.33%) and of P with ≥3 RF (45.90%) compared to P without RF (13.64%) manifested the restrictive TMF pattern ($p<0.05$ and $p<0.01$ respectively).
Conclusions: The coexistence of at least three RF for HF development -regarding patients with CAD- appears to have a negative effect on echocardiographic indices of left ventricular performance like EDD and ESD. Besides that, it seems that the presence of at least one RF may lead to severe diastolic dysfunction of the restrictive filling pattern. Thus, one should examine the possibility of improving cardiac function by altering the aforementioned risk factors.

P1788 Length of hospital stay and readmission rates in heart failure patients

S. Watkins[1], C. Young[2], E.A. McCandless[1], H.J. Dargie[1]. [1]*Glasgow, United Kingdom;* [2]*Tauranga, New Zealand*

Introduction: The prevalence of heart failure in the UK population is high, especially in the elderly. This is expected to increase further as the age of the population continues to rise. Up to 30% of heart failure patients are admitted every year, accounting for a significant proportion of our National Health Service (NHS) expenditure. We prospectively studied admissions with heart failure to a Glasgow teaching hospital to gain insight into the factors affecting the length of hospital stay and readmission.
Methods: Data was collected for each patient admitted to our cardiology ward with a diagnosis of acute heart failure from February to September 2004. We obtained information on patient demographics and factors associated with length

of admission and readmission. Within 48 hours of admission the caring physician would set a planned discharge date.
Results: Sixty patients were admitted during the study period. Mean age was 71 years (SD=9 years, Range 44–92) and 41 (68%) patients were male. Two patients died during their admission. The median length of stay was 9 days (Range 3–27). Twenty-five patients (42%) were discharged on the planned discharge date. One patient was discharged early whereas 31 (52%) had there discharge deferred. The number of extra hospital days per patient varied from 1 to 15 days with an overall extra 150 hospital days being required. Reasons for deferred discharge included persistent symptoms in 12 of 31 (39%), deranged electrolytes – 4 (13%), further investigations 4 (13%), transport 3 (10%) and other sporadic issues. Thirty-eight patients (66%) were referred to the heart failure liaison service (HFLS) for home follow-up. Seven patients (12%) required hospital readmission. Three patients had two admissions, 3 had three admissions and one required five admissions. There was no statistically significant difference in the median length of stay in those patients with a single hospital admission (8 days) and those with multiple admissions (10 days) with heart failure (p=0.2).
Conclusion: Deferred discharge following an admission with heart failure is common and is mainly due to persistent symptoms and deranged electrolytes. Hospital readmission following discharge is not infrequent despite HFLS referral and is not due to shorter initial hospital stay. Both of these factors contribute to the increasing burden of heart failure on our NHS resources.

P1789 Differences in characteristics of patients with acute heart failure under 70 years, 70 to 79, and over 80 years of age

V.-P. Harjola[1], K. Siirila-Waris[1], J. Melin[2], K. Peuhkurinen[3], M.S. Nieminen[1] on behalf of FINN-AKVA study group. *[1]Helsinki University Central Hospital, Division of Cardiology, Helsinki, Finland; [2]Central Finland Central Hospital, Department of Medicine, Jyvaskyla, Finland; [3]Kuopio University Hospital, Department of Cardiology, Kuopio, Finland*

Introduction: Acute heart failure (HF) is a complex syndrome with high individual variation. This analysis evaluates the age specific differences in patients presenting with acute HF in a nationwide study.
Methods: 622 pts were recruited from 14 different hospitals. The criteria for acute HF as defined by the new ESC guidelines were applied. Patients were grouped according to age on admission to hospital.
Results: As described in table one, in age group >80 years, patients are mainly females, very few have dilated cardiomyopathy, fewer have previous CABG. On the other hand, ejection fraction (EF) is better in the older patients than in the younger patients. Chronic atrial fibrillation is common in the oldest patient group. In contrast, the youngest group consists mainly of men. In this age group, dilated cardiomyopathy is more common, and consequently larger left ventricular end diastolic diameter and lower EF are observed. Chronic renal failure was equally prevalent in all patient groups.

Age group	<70 years	70-79 years	≥ 80 years
n (%)	174 (28)	232 (37)	216 (35%)
age (mean±SD)	62.0±7.2	75.4±2.9	85.4±3.8
female (%)	25.9a b	47.0ac	71.8bc
history of heart failure (%)	42.3b	47.8c	61.1bc
history of coronary heart disease (%)	37.4	57.8	66.7
previous CABG (%)	13.1	14.7c	6.0c
dilated cardiomyopathy (%)	21.1ab	6.0a	4.6b
ejection fraction (%)	40.2±15.8ab	46.2±15.5a	48.6±16.7b
diabetes mellitus (NIDDM) (%)	34.5	29.3	29.6
admitted from elsewhere than home (%)	17.8	19.0	29.6
chronic atrial fibrillation (%)	20.0b	25.4	34.7b
pacemaker:all/VVIR mode (%)	6.9/4.6	8.6/4.8	13.0/11.1

P<0.05 between a) group 1 and 2, b) group 1 and 3, c) group 2 and 3

Conclusion: At younger age, patients with acute HF present more often with dilated cardiomyopathy, and male gender is predominant. In contrast, over one third of the patients are 80 years old or older and are mainly female with better LV systolic function and atrial fibrillation. Diabetes is seen in a surprisingly high proportion in all patients with acute HF.

P1790 Survey of patients in the Heart Failure Clinic: what are their perceptions and priorities?

S.M. Deepak, W. Khan, T. Coppinger, C. Waywell, N.H. Brooks. *Wythenshawe Hospital, NHS Trust, Cardiology, Manchester, United Kingdom*

Background: Heart failure (HF) affects multiple aspects of patients' lives. Heart failure clinics (HFC) with palliative care and rehabilitation support were established in response to the National service framework (NSF) and National institute of clinical excellence (NICE) guidance. Plans exist to introduce community HFC and HF specialist nurses in England. We sought patients' views to guide future service provision.
Methods: Questionnaires were sent to 138 consecutive attendees at our HFC to assess their understanding of and fears about HF and their ability to self titrate medications. The first 100(72%) responses in a month were analysed.
Results: 80 were men, mean age 69yrs. 83 were retired, 11 were off work due to their illness and 6 were still working. All understood the diagnosis of HF. On who best enabled them to understand their illness, responses were: doctor in the HFC 54, specialist nurse at the HFC 51, doctor at the outpatient clinic 22, GP (General Practitioner) 22, ward doctor 20, ward nurse 4. Initial reactions to the diagnosis were: shock 40, fear 18, expected 19, depressed 12, disbelief 13, just another disease 12, surprised 5, relieved 4. 74 patients expressed multiple concerns including disabling symptoms and suboptimal quality of life. Other specific concerns were death 11, fear of another heart attack 9, uncertainty 6. 28 felt their concerns were addressed at the HFC, 40 partly addressed and 32 not addressed. 80 patients did not see the palliative care specialist of which 32 were unaware of the service. Of the 20 who used it, 16 found it beneficial. 60 responders attended the rehabilitation programme; 10 were unaware of the service. Of the attendees 24 participated in the exercise programme, 1 in the rehabilitation talks and 35 both. 26 attendees found both, 31 only the exercise and 3 only the talks beneficial. 90 patients were confidant to self titrate their medications with instructions at the time of their HFC visit and/or with telephonic advice, 10 were not confident/unable to do so. 40 patients choose to attend a HFC at their local GP surgery and 52 considered home visits by a specialist HF nurse as helpful.
Conclusion: Patients concerns regarding death, heart attack, uncertainty, disability and initial shock need greater attention. Uptake of rehabilitation was greater than of palliative care, but both were deemed beneficial. Most patients will adjust their medications with HFC advice. Community HFC and HF specialist nurses received a mixed response.

P1791 Prevalence and prognostic significance of ST elevation in aVR: insights from the Global Registry of Acute Coronary Events Electrocardiographic Substudy

A.T. Yan[1], S. Goodman[1], B.M. Kennelly[2], F.A. Anderson[3], J. Allegrone[4], P.G. Steg[5] on behalf of The GRACE investigators. *[1]St. Michael's Hospital, Department of Cardiology, Toronto, Canada; [2]Hoag Memorial Hospital, Newport Beach, United States of America; [3]University of Massachusetts, Medical School, Worcester, United States of America; [4]University of Massachusetts, Division of Cardiovascular Medicine, Worcester, United States of America; [5]Hôpital Bichat, Paris, France*

Background: There are limited data on the prevalence and independent prognostic value of ST elevation in lead aVR among contemporary unselected patients with non-ST acute coronary syndromes (ACS).
Methods: GRACE is a prospective observational study in 15 countries that recruited less selected ACS patients compared to clinical trials. In this electrocardiographic substudy (N=7900), the admission electrocardiograms were analyzed by a blinded core laboratory. Patients with ST elevation in leads other than aVR or confounders interfering with ST-segment assessment (N=2838) were excluded. We examined the prevalence and independent prognostic significance of ST elevation in aVR, adjusting for tertiles of the GRACE risk score (a validated predictor of mortality).
Results: Among 5062 non-ST ACS patients, 292 (5.8%) and 76 (1.5%) had ST elevation of 0.5-1 mm and >1mm in aVR, respectively. ST elevation in aVR was associated with advanced age, higher heart rate, worse Killip class, presence of ST depression in other leads, and higher GRACE risk score on presentation (all P<0.0001). While the use of revascularization in hospital was similar, the 6-month mortality rate was higher among patients with ST elevation in aVR (table). However, after adjusting for tertiles of GRACE risk score, ST elevation in aVR was not an independent predictor of mortality (Table). The results were similar after stratifying for ST depression in other leads, and using the composite endpoint of death or myocardial (re)-infarction during index hospitalization and at 6 months.

ST elevation in aVR	6-mo mortality (%)	P for trend	Adjusted odds ratio(95% CI)	P values
None	8.0		referent	–
0.5-1 mm	13.3	<0.001	1.09 (0.73-1.64)	0.67
>1 mm	19.4		1.07 (0.53-2.16)	0.85
≥0.5 mm	14.7		1.09 (0.76-1.56)	0.65

Conclusions: In this large contemporary cohort of less selected ACS patients, the prevalence of ST elevation in aVR was lower than previously reported. Although ST elevation in aVR was associated with other adverse prognostic factors and higher 6-mo mortality, it was not an independent predictor of worse outcome and did not provide incremental prognostic value beyond comprehensive risk stratification using the validated GRACE risk score.

P1792 Temporal trends in the pharmacological treatment of congestive heart failure in Denmark, 1995-2002

G.H. Gislason[1], J.N. Rasmussen[2], S.Z. Abildstrom[1], P. Buch[1], S. Rasmussen[2], M. Madsen[2], L. Kober[3], C. Torp-Pedersen[1]. *[1]Bispebjerg University Hospital, Department of Cardiovascular Medicine, Copenhagen, Denmark; [2]National Institute of Public Health, Copenhagen, Denmark; [3]Rigshospitalet, Department of Cardiology, Copenhagen, Denmark*

Purpose: in the last decade, new pharmacological treatment regimes have sub-

stantially improved the prognosis in congestive heart failure (CHF). We studied the temporal trends in the pharmacological treatment of CHF in Denmark, 1995-2002.

Methods: we identified patients with first admission for CHF in 1995-2002 who survived 30 days after discharge. By linkage of administrative registers we identified patients who claimed at least one prescription of beta-blocker, ACE inhibitor, loop-diuretic or spironolactone within 90 days from discharge. Odds ratios (OR) were calculated from logistic regression models, adjusted for age and gender.

Results: we identified 95,872 patients with first admission for CHF; 78,218 (81.6%) survived 30 days. In 1995-2002, the prescription rate of beta-blockers increased from 13.0% to 39.1% (OR=4.5; p<0.0001), ACE inhibitors from 38.0% to 48.7% (OR=1.6; p<0.0001) and spironolactone from 10.7% to 27.9% (OR=3.2; p<0.0001) (Fig. 1). However, the use of loop-diuretics fell slightly from 83.7% to 80.3% in 1995-2002 (OR=0.8; p<0.0001). Men had higher prescription rate of all medications than women (adjusted for age). The prescription rate fell with increasing age (adjusted for gender) for all medications, except loop-diuretics were the use increased with higher age.

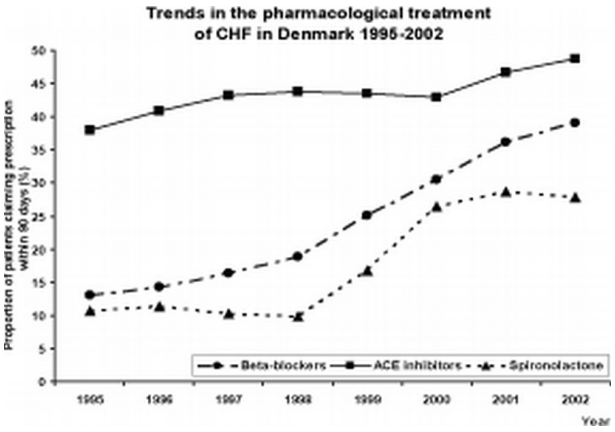


Figure 1

Conclusions: there was a substantial increase in the use of beta-blockers and spironolactone after first admission for CHF in 1995-2002, but only modest increase in the use of ACE inhibitors. Approximately half of patients with CHF have left ventricular dysfunction and thus the current figures indicate widespread impact of recent guidelines and trial results. Further studies will demonstrate adherence to treatment.

P1793 Baseline predictors of first rehospitalisation in heterogenous community based heart failure disease management program

L.L. Quek[1], H.C. Tan[2], P. Chai[2], A.R. Omar[2], Y.H. Seow[2], N. Suppiah[2], L.K. Tay[2], Y.H. Chan[3]. *[1]National University Hospital, Cardiology, Singapore, Singapore; [2]National University Hospital, Cardiology, Singapore, Singapore; [3]National University of Singapore, Biostatistics Unit, Singapore, Singapore*

Purpose: The aim of the Heart Failure Disease Management (HFDM) Program is to reduce clinical and financial outcomes. HFDM has been shown to reduce rehospitalisations. We sought to determine baseline predictors of the first rehospitalisation of patients enrolled in the HFDM Program in our heterogeneous Asian population.

Methodology: We enrolled 255 chronic heart failure (CHF) patients (58% male) with a mean age of 63 + 27 years and a mean LVEF of 27 + 13%. The multidisciplinary HFDM team consists of CHF cardiologist, CHF nurses, dietitian, physiotherapist, pharmacist, medical social worker, utilizing current evidenced based clinical practices, intensive and continuing education to patients and their caregivers and frequent monitoring through telemanagement and clinical consultations.

Results: The rehospitalisation rate for patients on the program was 16.9%. The median time to rehospitalisation was 57 days. Multivariate analysis showed patients with Diabetes Mellitus (p=0.012), Indian race (p=0.017) and a low 6 Minute Walk Test Result (<300 metres) (p = 0.035) were significantly associated with first rehospitalisations.

Conclusion: The rate of rehospitalisation in our heterogeneous community based multidisciplinary approach HFDM program is low. CHF patients with Diabetes Mellitus, Indian race and with a low 6 Minute Walk Test Result predict first rehospitalisations. As such clinical measures can be taken to reduce rehospitalisations in the HFDM program.

P1794 Presentation, acute cardiac care, and prognosis of acute heart failure in age groups under 70 years, 70-79 years , and 80 years or older

V.-P. Harjola[1], K. Siirila-Waris[1], J. Melin[2], K. Peuhkurinen[3], M.S. Nieminen[1] on behalf of FINN-AKVA study group. *[1]Helsinki University Central Hospital, Division of Cardiology, Helsinki, Finland; [2]Central Finland Central Hospital, Department of Medicine, Jyvaskyla, Finland; [3]Kuopio University Hospital, Department of Cardiology, Kuopio, Finland*

Background: Age is a well-known prognostic factor in chronic and acute heart failure (HF). However, little is known about the differences in presentation, acute cardiac care and prognosis in patients over 80 years of age.

Objective: Demonstrate differences in presentation (according to current ESC guideline), use of acute cardiac care resources, and prognosis between patients under 70 years of age (A), 70-79 years (B) and 80 years or older (C).

Method: FINN-AKVA is a prospective, national multicenter study. 622 consequtive patients hospitalized for acute heart failure were enrolled to the study. Medical history and medication were evaluated during hospital stay. P<0.05 between [1]group 1 and 2, [2] group 1 and 3, [3]group 2 and 3

Results: Congestive heart failure was the most prevalent presentation, and most prevalent in patients under 70 (A:71.3%[1], B:61.6%[1], C:63.4%). Pulmonary oedema tended to be more prevalent in the oldest (A:18.4%, B:26.3%, C:32.9%). On the other hand, cardiogenic shock was rare in our population and absent in the oldest patient group (A:2.3%, B:4.3%[3], C:0.0%[3]). CCU stay was shortest in the oldest age group. Pulmonary artery catheter monitoring (A:6.3%, B:6.5%, C:0.9%) and invasive ventilator therapy (A:6.9%,B:4.3%,C:1.9%), vasopressors and dobutamine, as well as, CABG and PCI during initial hospitalisation were much less frequently used in the oldest patient group (CABG A:5.6%[2], B:6.0[3], C:0.5[2 3]; PCI A:8.0, B:5.6[3], C:2.3[3]), and do-not-resuscitate (DNR) decision the most frequently. However, the length of hospital stay did not differ between the age groups. Interestingly, use of levosimendan was not significantly dependent on the age group. CPAP mask ventilation was independent of age (A:23.4%, B:29.7%, C:22.2%), as well, whereas invasive ventilation was significantly less used in the oldest patients (A:6.9%, B:4.3%, C:1,9%). In-hospital (A: 5.2%, B:7.3%, C:8.3%) and 6-month all-cause mortality (A:16.7%[1,2], B:24.6%[1], C:31.5%[2]) were the highest in the oldest patient group.

Conclusion: Acute heart failure is presented quite similarly in different age groups. Less resources are applied to patients over 80 years of age compared to patients less than 80 years of age. Although cardiogenic shock seems to be less common in the oldest patients, they have the worst in-hospital and 6-month outcome. Almost one third of them die within 6 months. However, DNR decisions are quite seldom made in this population of poor prognosis.

MISCELLANEOUS VALVE DISEASE

P1795 Stented bioprosthetic valve haemodynamics. How much is the supra-annular implant better than the intra-annular one?

L. Badano[1], S. Musumeci[2], D. Pavoni[2], R. Frassani[2], E. Mazzaro[2], P. Gianfagna[2], P.M. Fioretti[2], U. Livi[2]. *[1]Gemona del Friuli, Italy; [2]A.O. S Maria della Misericordia, Cardiovascular Science Department, Udine, Italy*

Background and Aim: Use of stented bioprostheses in elderly patients with degenerative aortic stenosis despite being desirable, raises concerns about the harmful effects of residual obstruction to left ventricular outflow tract (LVOT). To overcome this problem new bioprostheses have been designed for supraannular implant. However, the actual hemodynamic advantage of supra-annular implant (SAI) of stented bioprostheses over intra-annular one has not been fully investigated. Accordingly, we compared hemodynamic performance of the same stented bioprosthesis (except for the sewing ring design) manufactured by the same manufacturer (Sorin Biomedica, Saluggia, Italy) implanted in the supra-annular (Soprano®) and in the conventional intra-annular (Pericarbon More®) seating in two age, gender, and body size matched elderly patient groups with degenerative aortic stenosis and small aortic annulus at preoperative echocardiography (i.e LVOT diameter < 23 mm).

Methods: 24 patients with intra-annular implant and 29 with SAI, with similar age (74±5 and 76±6 years, p= 0.12), gender (males 46% and 59%, p= 0.44), and body surface area (1.77±0.2 and 1.86±0.2 m^2, p= 0.14), underwent echocardiography at 9±2 and 5±3 months after surgery, respectively (p= 0.001).

Results: The two patient population showed similar preoperative LVOT diameter (2.08±0.2 cm and 2.1±0.2 cm; p= 0.62), average size of the implanted prosthesis (21.3±1.7 mm and 21.7±1.4 mm; p= 0.46), and mean transprosthetic flow rate (259±81 and 227±64 ml/s; p= 0.14). Mean (9±4 mm Hg and 17±8 mmHg, p<0.0001), and peak (17±8 mm Hg and 39±13 mmHg; p<0.0001) gradients were lower, and effective orifice area (EOA) (1.85±0.4 cm^2 and 1.51±0.5 cm^2, p=0.011) was higher in patients with SAI. Valvular resistance was lower (505±246 and 1108±795, p=0.001), and the incidence of patient-prosthesis mismatch (i.e EOA<0.85 cm^2/m^2) decreased from 50% to 27%, (p<0.0001), with no case of severe mismatch (i.e EOA<0.6 cm^2/m^2), using SAI.

Conclusions: Our study demonstrates that SAI is associated to a significantly better hemodynamic performance of stented bioprostheses. With SAI, EOA in-

creased by 22%, transprosthetic gradients decreased by 56%, and valve resistance to flow decreased by 54%.

P1796 Early and midterm results of aortic valve replacement using the Sorin Pericarbon Freedom Stentless aortic bioprosthesis: the Italian multicenter clinical experience

A. Fabbri[1], P. Ius[2], A. Mazzucco[3], C. Zussa[4], C. Valfre[2], L. Martinelli[5], R. Casabona[6], A. Mazzola[7]. [1]*Vicenza, Italy;* [2]*Treviso, Italy;* [3]*Verona, Italy;* [4]*Mestre, Italy;* [5]*Genova, Italy;* [6]*Torino, Italy;* [7]*Teramo, Italy*

Objectives: The aim of this prospective study was to evaluate early and midterm results of aortic valve replacement (AVR) with Sorin Pericarbon Freedom Stentless bioprosthesis (SPF)
Materials and Methods: From January 2002 to December 2003, in 8 Italian cardiac-surgery departments, 223 patients (M/F=92/131; mean age 73±8 yrs, range: 20-91 yrs) underwent aortic valve replacement with the SPF. Indications were: aortic stenosis 54% of patients, aortic regurgitation in 7%, combined lesions in 39%. Preoperatively 29.6%, 56.6%, and 13.7% of patients were in NYHA class I/II, III and IV, respectively. Concomitant procedures were performed in 72 patients (32,8%) (CABG:25,2%). CPB time was 118.6±39.3 minutes, and aortic cross clamping was 91.7±31.4 minutes. Sizes ranged from 19 to 29 mm (23.4±2.1). Each patient underwent a clinical and echocardiographic assessment preoperatively and 1, 6 and 12 months postoperatively. 12 months follow-up was 97,5% complete. SPF has been implanted using either running or interrupted suture for the inflow rim,and appropriate prosthesis tailoring and trimming.
Results: Hospital mortality was 3,5% (n=8). There were 10 late deaths (4.6%), only one of these was valve related (haemorrhage during reoperation for active endocarditis). Valve related complications included: thromboembolic events in 4 patients (1.8%), endocarditis in 3 (1.3%), structural valve deterioration in 1 (0.4%), and nonstructural dysfunction in 11 (5.1%). There were two reoperations (0.9%), one for structural deterioration and one for active bacterial endocarditis. After 12-months, 99% of patients were in NYHA I-II.

Hemodynamic at 6 months

	21 mm	23 mm	25 mm	27 mm
peak gradient [mmHg]	19.7±9.4	18.5±10.5	12.5±5.5	11.1±5.2
mean gradient [mmHg]	8.9±4.2	8.3±5.1	5.1±2.4	4.7±2.3
EOA [mm^2]	1.53±0.57	1.61±0.54	2.10±0.57	2.42±0.53
EOAI [mm^2]	0.93±0.31	0.94±0.33	1.13±0.32	1.30±0.30

Conclusions: Our data suggest that SPF stentless bioprosthesis provides excellent early and mid term results in terms of hemodynamics (tab1), mortality and valve related complications.

P1797 Long-term results of aortic valve replacement with Edwards Prima Stentless Bioprosthesis

S. Auriemma, M. Brunelli, P. Magagna, M. Paccanaro, F. Rulfo, A. Fabbri. *San Bortolo Vicenza Hospital, Division of Cardiac Surgery, Vicenza, Italy*

Objective: The Edwards Prima stentless valve (EPSV) is a bioprosthesis made of porcine aortic root. Long-term survival and freedom from valve-related events are unknown. The aim of this study is to evaluate late clinical outcomes after aortic valve replacement with EPSV implanted as a miniroot in patients with aortic valve disease.
Methods: Between 1993 and 2004, 318 patients (age 69+9 y, range 37-83 y; 232 males) underwent aortic valve replacement with EPSV. Preoperatively, 102(32%), 162(51%), and 54(17%) patients were in NYHA class I/II, III and IV, respectively. Aortic stenosis, aortic incompetence and combined lesions were present in 124(39%), 114(36%) and 41(13%) of them. 20(6%) patients were referred for an acute aortic dissection, 20 (6%) for an aortic root aneurysm and in 139(44%) patients an aneurismal dilatation of the ascending aorta was associated.Ascending aorta was replaced in 159 patients (50%); aortic arch replacement was required in 10 (3%) patients. CABG surgery was performed in 86 patients (27%). Follow-up was based on clinical and echocardiographic assessment (Table 1).
Results: Operative mortality was 5% (n=17). There were 49 late deaths. Valve-related mortality occurred in 10 patients. Actuarial survival at 5 and 10 years was 85% and 68%, respectively. Actuarial freedom from valve reoperation and structural valve deterioration at 10 years were 100% and 98.8%. Actuarial freedom from embolic events and endocarditis at 10 years were 94.8% and 98.3% respectively.

Table 1. Echocardiographic follow-up

	Discharge	Six Months	1 Year
Mean Dp (mmHg)	14±5	12±3	10±6
LVOTd (cm)	1.8±0.1	1.9±0.3	2.5±3.1
LVIDd (cm)	4.9±0.08	5.1±0.8	5.1±0.8
LVIDs (cm)	3.6±1	3.4±0.8	3±0.1
PWd (cm)	1.2±0.02	1.1±0.03	1.2±0.2
Isd (cm)	1.3±1	1.2±0.2	1.3±0.2

Conclusion: The EPSV used as a miniroot provided excellent early and long term results in terms of survival and freedom from major complications.

P1798 Incidence of intracardiac thrombus and thromboembolism early after bioprosthetic mitral versus aortic valve implant

A.I.O. Ramos[1], H.M. Magalhaes[2], Z.M. Meneghelo[2], D.J. Togna[2], A.S. Arnoni[2], L. Machado[2], L.S. Piegas[2]. [1]*Instituto Dante Pazanese de Cardiologia, Dept of Valve Disease, Sao Paulo, Brazil;* [2]*Sao Paulo, Brazil*

Although the bioprosthetic valves are not much thrombogenic, the current guidelines recommend anticoagulation therapy in the mitral and aortic position in the first three months after implantation.
Aim: to know the incidence of intracardiac thrombus and thromboembolism and identify risk factors for thrombus formation in the first three months after implantation of a bioprosthetic valve in patients without oral anticoagulation
Methods: One hundred fourteen patients with bioprostheses in mitral or double position and 70 patients with aortic bioprostheses were submmited to transesophageal echocardiographic (TEE) performed at 8,4±3 days and three months later (97,4±21,7 days) after valve replacement.
Results: The sinus rhythm was found in 71% of the patients. The incidence of thrombus was significantly higher in patients with mitral or double prostheses than in those with aortic prostheses in both period of time, respectively (early-14,1%x2,1%, p<0,001, 3-month-31,7%x3,1%). The variables included in the regression analysis model are: cardiac rhythm, left atrium (LA) diameter, LA empty peak flow velocity, LA spontaneous contrast, immediate post-operative complications, prostheses position. The prostheses in the mitral or double position was identified as the only independent risk factor for LA thrombus formation in both period of time. Among the 181 patients with clinical follow-up, three patients died (1,6%) and eight patients with bioprosthetic mitral valve (3,4%) had a cerebral embolism.
Conclusion: 1) the prosthesis in the mitral or double position were identified as the independent risk factor for LA thrombus formation, 2) it may not be necessary to put patients with aortic bioprosthetic valve on oral anticoagulation therapy.

P1799 Sorin bicarbon mechanical heart valve in the over 70 year old patient: a hazardous choice?

R. Ascione[1], L. Culliford[2], C.A. Rogers[2], J. Wild[2], A.J. Bryan[2], G.D. Angelini[2]. [1]*Bristol Royal Infirmary, Bristol Heart Institute, Bristol, United Kingdom;* [2]*Bristol Royal Infirmary, Bristol Heart Institute, Bristol, United Kingdom*

Objective: To assess the safety and efficacy of Sorin Bicarbon bileaflet mechanical valve in elderly patients.
Methods: Data for consecutive 567 patients undergoing valve replacement with Sorin Bileaflet (SB) with or without concomitant surgery between April 1996 and November 2001 were extracted from a prospective database. Patients were grouped by age: A) < 70 years, and B) ≥ 70years, and their in-hospital and mid-term valve-related outcome analysed.
Results: Six hundred sixteen SB valves were implanted in 567 patients in 334 aortic (58.9%), 184 mitral (32.5%), and 49 double valve procedures (8.6%). There were 437 (median age 61 years (95% confidence interval (CI) 54 - 66) and 130 (median age 72 years (95% CI 71 - 74) patients in groups A and B respectively. Elderly patients were more likely to present with coronary disease, and to undergo concomitant coronary surgery (all p<0.01). In-hospital mortality was 2.8% and 2.3% (p=0.79) and neurological complications 1.4% vs 3.8% (p=0.026) in groups A and B respectively. The older group tended to stay longer in ITU and hospital post-operatively, (p=0.0514 and 0.0037 respectively), but no other in-hospital differences were observed between groups. One-year valve-related mortality was 1% (95% CI 0.3 - 2.3%) and 3.2% (95% CI 1.0 – 7.4%) in groups A and B respectively. Cumulative 3-year haemorrhagic event was 16.3% (95% CI 12.6%-20.9%) and 13.2% (95% CI 7.8%-21.8%) and cumulative 3-year thromboembolic and major haemorrhagic event was 10.2% (95% CI 7.3-14.2%) and 7.1% (95% CI 3.4-14.4%) in groups A and B respectively.
Conclusions: The use of Sorin Bicarbon bileaflet in over 70 year old patients is safe and effective with no increased risk of mid-term valve-related mortality, bleeding or thromboembolism when compared with a younger cohort.

P1800 Initial clinical experience with hand-held device (Thrombocheck) for the detection of bileaflet prosthetic valve malfunction

S. Ben Zekry, A. Sagie, I. Ben-Dor, D.A. Weisenberg, H. Nukrian, A. Battler, Y. Shapira. *The Dan Sheingarten Echocardiography Unit and Valvular Clinic, Cardiology Dept., Petach Tikva, Israel*

Background and aim of the study: Early recognition of subclinical prosthetic valve malfunction may promote early treatment and avoidance of serious complications. Echocardiography cannot be applied on a daily basis. Therefore a hand – held device (Thrombocheck©) capable of detecting subtle changes in the acoustic sounds of prosthetic valve has been developed for routine home monitoring of heart valve function. We report our initial clinical experience with this device.
Methods: Seventy one consecutive patients with one or more bileaflet prosthetic mechanical valves at any position were assessed both by transthoracic echocardiography (TTE) and by Thrombocheck©. These patients attended our clinic for either routine echocardiography (62 patients) and for detection of prosthetic valve

malfunction (9 patients). Cinefluoroscopy and transesophageal echocardiography were used selectively to confirm prosthetic valve malfunction.
The Thrombocheck© was held for one minute in subxhiphoid position perpendicular to the patient, and indicated normal function (OK), abnormal function (Warning) or no signal.
Results: The study patients had in total 82 bileaflet valves: 47 mitral, 31 aortic and 4 tricuspid. Eight patients (11.3%) had "no signal" indication. Of the remaining 63 patients, there were 10 patients (18.9%) with "warning" alarm, of whom 8 had current abnormal leaflet motion, one patient has a recent history of abnormal leaflet motion, and one patient had no evidence of prosthetic valve malfunction. The sensitivity and specificity for detecting abnormal prosthetic valve malfunction were 90% and 98%, respectively.
Conclusion: Thrombocheck© had an excellent sensitivity and specificity for the detection of prosthetic valve malfunction in a cohort of patients with bileaflet mechanical prosthetic heart valves.

P1801 Coagulation activity in the left atrium of patients with mitral stenosis

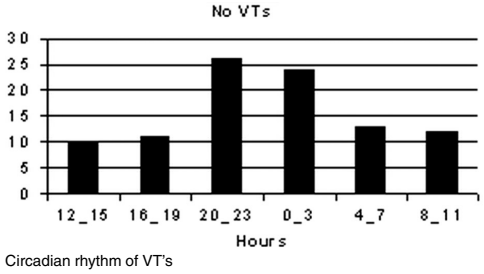
S. Kiatchoosakun[1], U. Suongto[2], N. Komanasin[2], C. Wongvipaporn[1], S. Silaraks[1], P. Mongkolwongroj[2], P. Tatsanavivat[1]. *[1]Khon Kaen University, Medicine, Khon Kaen, Thailand; [2]Khon Kaen university, Department of Clinical Microscopy, Khon Kaen, Thailand*

Background: Systemic thromboembolism is a serious complication in patients with mitral stenosis (MS). However, the pathogenesis of thromboembolism in MS is not clearly understood.
Objective: To investigate the hemostatic status of the right and left atria in patients with MS.
Methods: We determined the plasma levels of biochemical markers of thrombin generation (thrombin-anti-thrombin complex, fibrinogen and factor XIII) and fibrinolysis (D-dimer) in specimen of blood from right and left atrium in 35 consecutive patients with moderate to severe MS who underwent percutaneous ballon mitral valvuloplasty.
Results: Thrombin anti-thrombin complex and D-dimer in left atrium were significantly higher than those in right atrium (75.41 μg/L vs 28.99 μg/L; $p<0.001$ and 772.19 μg/L vs 430.96 μg/L; $p<0.001$, respectively). There was no statistically significant difference between right and left atrium fibrinogen level and factor XIII(320.9 mg/dL vs 315.38 mg/dL; and 132% vs 134%;$p > 0.05$, respectively). Levels of thrombin anti-thrombin complex and D-dimer did not correlate with the intensity of left atrium spontaneous echo contrast, left atrial size, mean left atrial pressure and mitral valve area.
Conclusion: Our study demonstrates that coagulation activity is increased in the left atrium of patients with mitral stenosis and may contribute to the pathogenesis of thromboembolism in mitral stenosis.

P1802 Circadian pattern of nonsustained VT in patients with significant aortic valve stenosis

E.H. Orlowska-Baranowska[1], R. Baranowski[2], J. Stepinska[2]. *[1]Institute of Cardiology, Valvular heart diseases, Warszawa, Poland; [2]Institute of Cardiology, Warsaw, Poland*

Ventricular arrhytmias, especially ventricular tachycardia [VT] may play an important role in sudden death of pts with aortic stenosis [AS]. The relation of circadian pattern of nonsustained VT was analysed in patients with significant [AS].
Material and methods: We reviewed Holter reports of 740 pts with AS (before valve replacement). Mean age was 63±10. Nonsustained VT was recorded in 58 pts. The number of episodes was 96 (1-9 in one pt). In 31 of them the history of palpitations and/or syncope was present. Two of them underwent cardiac arrest. In sinus rhythm were 54 pts, in atrial fibrillation 4 pts. We analysed circadian pattern, heart rate before the onset of VT and coupling interval.
Results: The number of evolutions was 3-24, the rate of nsVT 100-210/min. Mean heart rate before nsVT was 69/min. Mean coupling interval was 433±81ms (400-1040ms). The most frequently nsVTs were recorded between 20pm and 3am.



Circadian rhythm of VT's

Conclusions: Nonsustained VT is recorded in 8% of patients with significant aortic valve stenosis. It is mainly not related with patients activity and increased heart rate. The relationship between nsVT and symptoms like palpitations and syncope seems to be doubtful in this group of patients.

P1803 Degenerative severe aortic stenosis with and without concomitant coronary artery disease: clinical and anatomo-pathological differences

P. Stutzbach[1], P. Roura[2], R. Laguens[2], J. Scaglia[2], P. Gonzalez[2], C. Perel[1], R.R. Favaloro[2]. *[1]Favaloro Foundation, Valvular Heart Disease, Buenos Aires, Argentina; [2]Favaloro Foundation, Valvular Heart Disease, Buenos Aires, Argentina*

Background: Degenerative aortic stenosis (AoS) is often associated with atherosclerosis in the literature. However, it is not clearly understood why not all patients with AoS develop coronary artery disease (CAD). Our aim was to compare clinical and anatomo-pathological characteristics in patients with isolated AoS to those in patients with AoS and concomitant CAD (AoS+CAD).
Methods: We analyzed 443 patients with severe symptomatic AoS (area $<1cm^2$) who underwent aortic valve replacement. Diagnosis of coronary artery disease was made at presurgical evaluation assessed by coronary arteriography. Mean age was 71.3±5 years; 175 (39%) were female. Anatomo-pathological variables were studied with the following score: valvular thickening: mild (twofold or less the normal thickness) 1, moderate (twofold to fourfold) 2, and severe (fourfold or greater) 3; calcification degree: mild (<25%) 1, moderate (25-50%) 2, and severe (>50%) 3; and inflammation: mild 1, moderate 2, and severe 3.
Results: CAD was present in 203 patients (46%). Differences in clinical characteristics and symptoms in the group with AoS versus those with AoS+CAD were: female sex 40% vs 28% ($P<.001$); diabetes 10% vs. 20.6% ($P=.002$) dyspnea 78% vs 66% ($P<.001$), angina 39.5% vs 63.8% ($P<.001$), and syncope 17.9% vs 18.5% ($P=.9$). Doppler echocardiography showed: interventricular septum 14.6±3.2mm vs 13.8±2.4mm ($P<.05$), mean aortic gradient 60±20mmHg vs 47.9±18.4mmHg ($P<.001$), aortic area 0.59±0.16cm^2 vs 0.69±0.76cm^2 ($P<.001$). Age, hypertension and hyperlipidemia were not significant. Anatomo-pathological analysis showed: thickening: 2.3±0.59 vs. 2.07±0.61, $P<.001$; calcification degree 2.7±0.60 vs. 2.20±0.60, $P<.001$. There were no significant differences in inflammation degree.
Conclusion: Patients with AoS+CAD present with a greater prevalence of diabetes and less hemodynamic severity of the AoS. The anatomo-pathological findings show that there is a greater degree of aortic valve thickening and calcification in patients without CAD. These findings suggest that CAD leads to an earlier occurrence of symptoms in degenerative AoS.

P1804 Aortic stenosis and bleeding risk due to acquired Von Willebrand syndrome

M. Gomez Perez[1], R. Serrat[2], M. Cladellas[2], L. Molina[2], C. Roqueta[2], R. Manteiga[3], J. Bruguera[2]. *[1]Barcelona, Spain; [2]Hospital Del Mar, Cardiology, Barcelona, Spain; [3]Laboratori de Referència de Catalunya, Haematology, Barcelona, Spain*

Introduction: Aortic stenosis (AE) has been associated with high risk of bleeding due to an acquired Von Willebrand Factor (VWF) deficiency.
Objectives: To know the prevalence of VWF deficiency in AE and its clinical implications. To correlate this deficiencies with echocardiographic parameters of severity of AE.
Material and methods: In 125 patients with severe AE were prospectively analysed the VWF (VW antigen and VW ristocetine). We investigated bleeding history (modified Rappaport questionnaire) and clinical conditions of determination of VWF. Patients were divided in two groups: stable condition (ambulatory) and admitted in Emergency Unit by unstable condition.
Results: 16% of patients presented VWF deficiency. In all patients with VWF deficiency, the blood sample were obtained in stable condition (n=62). Therefore, all patients admitted in Emergency Unit (n=60) showed normal or elevated levels of VWF (97 vs 240; $p<0.01$). The abnormal elevation of VWF was observed in this situations: acute heart failure (56%), acute coronary syndrome (32%) or fever (12%), associated to VIII factor of coagulation cascade ($r=0.87$, $p<0.001$). 35% of patients with low levels of VWF presented haemorragic disorders like: bowel bleeding, epistaxis or echymosis (73% of them were taken AAS, clopidogrel or anticoagulant drugs). Levels of VWF correlated with echocardiographic data: maximal transvalvular gradient ($r= -0.67$, $p<0.001$), mean transvalvular gradient ($r= -0.7$, $p<0.001$) and aortic valve area ($r= -0.58$, $p<0.001$).
Conclusions: Determination of VWF in severe AE is useful because there is a risk of bleeding associated to VWF deficiency, specially associated to antiagregation or anticoagulation therapy. We recommend to determinate VWF in stable clinical condition (because it may be an acute phase reactant). VWF deficiency correlated with severity of valve disease by echocardiographic parameters

P1805 Clinical and bacteriological data of PM/ICD patients affected by systemic infection submitted to transvenous lead removal

C. Bartoli[1], G. Arena[1], E. Soldati[1], G. Giannola[2], F. Lapira[1], G. Zucchelli[1], A. Di Cori[1], M.G. Bongiorni[1]. *[1]Ospedale di Cisanello, Dipartimento CardioToracico, Pisa, Italy; [2]Ospedale di Cisanello, Dipartimento CardioToracico, Pisa, Italy*

The infection of pacing (PM) and defibrillating (ICD) systems is a rare but serious complication. We report clinical and microbiological characteristics of a large pop-

ulation of patients affected by systemic infection that underwent to transvenous lead extraction.
Materials: we evaluated 81 patients (66 males, age 66±18), with systemic infection related to PM (73) or ICD (8). Infection occurred early (onset of symptoms within 8 weeks after the last intervention) in 28.1% pts and late in 71.9%. Mean duration of symptoms was 7.63 months. In 60% (49/81) of pts systemic infection was associated with local infection in 39 pts local signs started before systemic infection, while simultaneously in 10 pts. Clinically relevant complications (pulmonary embolism, pulmonary and vertebral septic foci, septical shock, superior vena cava syndrome) were observed in 16.05%. These pts had a duration of infection significantly longer than the pts without complications (11.69 months vs 6.52).
Results: Biological cultures (haemocultures or culture of material from the pocket) were positive in 87.5% of pts, while microbiological cultures of the leads were positive in 81.2%; the results of cultures were concordant in 80%. Staphylococcus Aureus (S.A.) and coagulase negative bacteria were isolated in 82%. In 19% of pts without local infection Gram + Cocchi were isolated, while in pts with local infection was isolated a wide spectrum of bacteria: Gram - Cocchi, anaerobial bacteria and myces. S.A. was not significantly related neither with local infection or with early or late occurrence of infection. Transvenous removal of leads was successful in all pts. Antibiotic therapy based on leads cultures was continued for 4-8 weeks after removal. After a mean follow-up of 12±2 months no recurrence of infection was observed.
Conclusions: Most PM and ICD infection are caused by S.A. and coagulase negative bacteria. There is a strong concordance between biological and lead cultures while there is no association between causing microorganism and clinical presentation The best treatment is leads removal and an appropriate antimicrobial therapy based on leads cultures.

P1806 Prognosis of Staphylococcal aureus infective endocarditis in Argentina: the EIRA-2 study

E. Ferreiros[1], J.H. Casabe[2], J.C. Modenesi[2], F. Nacinovich[1], S. Swieszkowski[2], H. Cohen Arazi[2], C. Cortes[2], S. Varini[2]. *[1]Buenos Aires, Argentina; [2]Sociedad Argentina de Cardiología, Buenos Aires, Argentina*

Objective: To determine the epidemiological and clinical characteristics, and the hospital evolution of Staphylococcal Aureus infective endocarditis (SAIE) in Argentina.
Methods: The EIRA-2 survey was a prospective, multicenter study conducted in 82 hospitals representing 16 out of 24 provinces of Argentina. Patients with diagnosis of definite IE according to Duke criteria were surveyed during an 18-month period.
Results: 390 episodes of IE were reported; mean age was 58.5±17.3 years, male sex 70%. See Table: * p < 0.01; ** p = NS

Table

	SAIE	non SAIE	OR (CI 95%)
IE episodes (n)	108	282	–
Age (years; mean±SD)	57.0±17.6	59.0±17.1 **	–
Male sex (%)	68.5	70.6 **	0.9 (0.5-1.5)
Underlying heart disease (%)	58.3	67.4 *	0.7 (0.4-0.99)
Prosthetic valve IE (%)	14.8	16.3 **	0.9 (0.4-1.7)
Degenerative valve disease (%)	11.1	11.7 **	0.9 (0.4-2.0)
Rheumatic valve disease (%)	0.9	7.1*	0.1 (0.01-0.9)
Congenital heart disease (%)	3.7	11.7*	0.29 (0.08-0.9)
Prior invasive procedures (%)	33.3	22.0*	1.8 (1.1-3.0)
Hemodialysis (%)	21.3	10.6*	2.3 (1.2-4.3)
Heart Failure (%)	34.3	36.9 **	0.9 (0.5-1.5)
Stroke (%)	17.6	11.3*	1.7 (1.0-3.2)
Embolism (%)	8.3	2.8*	3.1 (1.06-9.2)
Surgical Treatment (%)	20.4	28.4 **	0.6 (0.36-1.2)
Hospital mortality (%)	34.3	20.9*	2.0 (1.2-3.3)

Conclusion: Patients with staphylococcal aureus IE have a higher risk profile. They have less underlying heart disease (rheumatic and congenital), and have more frequently underwent prior invasive procedures and hemodialysis. Staphylococcal aureus IE patients have a worse prognosis, their incidence of stroke, embolism and hospital mortality are higher than non-SAIE. These results suggest that more aggressive measures are needed in order to improve the prognosis of Staphylococcal Aureus IE.

P1807 Early and late outcome of patients with infective endocarditis along a 17-year period (1987-2004)

M. Delgado[1], M. Anguita[1], J.C. Castillo[2], M. Ruiz[1], D. Mesa[1], J.M. Arizon[1], J. Suarez de Lezo[1], F. Valles[1]. *[1]Hospital Reina Sofia, Servicio de Cardiologia, Cordoba, Spain; [2]Hospital Reina Sofia, Servicio de Cardiologia, Cordoba, Spain*

Infective endocarditis is a serious disease with a high mortality rate in the sort term although little is known about long term prognosis. The aim of this study is to asses the early outcome and the predictors of mortality in the long term. We have studied a series of 253 consecutive cases of infective endocarditis diagnosed at our centre between 1987 and 2004. Mean age was 49±19 years (range 1-84) and 64% were male. 68% of cases were native valve endocarditis and 32% prosthetic valve endocarditis. The microorganisms more frequently isolated were staphylococci (35%) followed by streptococci (22%), enterococus (14%) and others (16%). Blood cultures were negative in 13% of cases. 52% of patients underwent surgery during the active phase (20% emergency surgery and 32% elective surgery). In hospital mortality was 17% and it was reduced from 22% in the former years (1987-2005) to 13% in the latter (1996-2004). Cumulative survival at 15 years is 91% for survivors to the active phase (overall survival of 75%). In the Cox-regression analysis, long term mortality independent predictors were: previous episode of infective endocarditis (OR 4.09, p<0.01), severe complications during active phase (OR 5.21, p<0.01), age>65 years (OR 2.91, p<0.01) and negative blood cultures (OR 2.5, p<0.01). Probability of survival of patients with none of this predictors is 95% at 15 years. In conclusion, the in hospital mortality rate of patients with infective endocarditis is 17% however, this rate has been reduced to 13% in recent years. Long term prognosis is good for survivors to the active phase.

P1808 Infective endocarditis in intravenous drug addicts with and without HIV infection

E. Cecchi[1], D. Forno[2], M. Imazio[2], I. Dal Conte[3], F. De Rosa[3], F. Pomari[2], M. Moratti[2], R. Trinchero[2]. *[1]Torino, Italy; [2]Osp. Maria Vittoria, Cardiologia, Torino, Italy; [3]Università di Torino, Clinica di Malattie Infettive, Torino, Italy*

Clinical, echocardiographic and diagnostic features of Infective Endocarditis (IE) have been described in intravenous drug addicts (IVDA). Rarely the possible influence of coexistent HIV infection has been considered.
Objective: To compare clinical features of IE in IVDA with and without HIV infection.
Methods: 202 consecutive patients IVDA with suspected IE have been enrolled since 1992. Clinical, microbiologic, and echocardiographic data were prospectively collected and analysed. HIV infection was found in 102 out of 202 IVDA (50.5%). Among IVDA with HIV infection we found 40 patients with IE (39.2%; group 1), while IE was recorded in 55 patients out of 100 IVDA without HIV infection (55.0%; group 2).
Results: Clinical, microbiologial, and echocardiographic features are reported in the Results table.
The diagnostic accuracy of Duke criteria was similar in the studied groups. During follow-up a similar rate of embolic complications was found in the studied groups (respectively 50.0% vs 64.0%; p=NS). 2-months all cause mortality was higher in IVDA with HIV infection (12.5% vs 0.2%; p<0.05):3 out 5 deaths were in advanced AIDS patients. Surgery was performed more frequently in IVDA without HIV infection (27.3% vs 7.5%; p<0.05).

Feature	GROUP 1: IVDA HIV+	GROUP2: IVDA HIV-	P
Age (years)	31.1±6.5	31.7±6.2	NS
Male gender	20(50%)	46 (83.6%)	<0.001
Negative blood culture	8(20%)	7(12.7%)	NS
Stafilococcus aureus	22(55%)	29(52.7%)	NS
Streptococci	4(10%)	7(12.7%)	NS
Positive echocardiogram	35(87.5%)	53 (96.4%)	NS
Isolated right side vegetations	24(60%)	30(54.5%)	NS
Vegetations length (mm)	13.64±6.83	23.67±6.87	<0.001

Conclusions: Despite a similar clinical presentation, IVDA without HIV infection have bigger vegetations with a trend to more embolic complications. Two-months cardiac mortality is higher in HIV infection due to cases with end stage AIDS. Surgery is performed less frequently in these patients compared with IVDA without HIV infection.

P1809 Infective endocarditis: characteristics and mortality in a Spanish hospital – 1985-2002

T. Centella[1], P. Martin[2], P. Catalan[3], E. Oliva[4], I. G Andrade[4], M.J. Lamas[4], A. Epeldegui[4]. *[1]Ramon y Cajal H., Cardiothoracic surgery, Madrid, Spain; [2]Hospital Ramón y Cajal, Infectious Diseases, Madrid, Spain; [3]Hospital Ramón y Cajal, Cardiology, Madrid, Spain; [4]Ramón y Cajal, Cardiothoracic surgery, Madrid, Spain*

Introduction: Infective endocarditis remains a frequent disease with high mortality (15-27%) sometimes due to an increased frequency of intravenous drug users, and invasive procedures involving intravenous devices, prosthetic valves, and pacemaker implantation.
Objective: The study aim was to describe the characteristics, treatment and mortality of native and prosthetic valve endocarditis at a single institution from the last eighteen years.
Patients and methods: Retrospective study of 526 patients with infective endocarditis in our hospital between 1985 and 2002.
Results: There were 526 patients (388 male and 138 female), mean age 41,8 years (1 to 87). 408 patients (77,6%) had native valve endocarditis and 118 (22,4%) had prosthetic valve endocarditis: early in 27 patients [up to 60 days alter surgery] and late in 91 patients [later than 60 days]. Blood cultures were positive in 91,6%. The predominant organism in native valve endocarditis was Staphylococcus aureus (44,55%) and Staphylococcus epidermidis in prosthetic valve

endocarditis (32,2%). The hospital mortality was 14,1% (n=74). The in-hospital mortality of patients with native endocarditis was 9,8% (n=40) and with prosthetic endocarditis 28,8% (n=34). 142 patients required surgery (27,5% of them urgently and 28,9% emergently). The surgical mortality was 18,3% (12,1% native endocarditis and 29,4% prosthetic endocarditis). This mortality was related to urgent surgery ($p<0,036$) in patients with native valve endocarditis. Severe sepsis was the most frequent cause of mortality in both groups (35,41% in medically treated patients and 23,1% in a group of combination of antibiotics and surgery).
Conclusions: Infective endocarditis is a serious condition with high mortality in patients treated in our series in a tertiary medical centre. Our data show that the presence of severe sepsis has a bad prognosis. Urgent surgery and prosthetic endocarditis increase surgical mortality.

P1810 Overt and silent cerebral embolism due to infective endocarditis

T.T. Hryniewiecki[1], M. Grabowski[2], E. Smaga[3], E. Poniatowska[2], I. Rawczynska-Englert[2], J. Stepinska[2]. *[1]Institute of Cardiology, Dpt.of Acquired Valvular Heart Disease, Warsaw, Poland; [2]Institute of Cardiology, Dpt.of Acquired Valvular Heart Disease, Warsaw, Poland; [3]Institute of Cardiology, Warsaw, Poland*

Central nervous system (CNS) embolism is well-known serious complication of infective endocarditis (IE) and it could modify therapeutic decision making.
In some cases embolism causes small focal changes in brain not enough to develop clinical symptoms – so called "silent embolism". CNS embolism silent and overt could be especially significant during and post extracorporeal circulation (ECC). The most dangerous is intracerebral bleeding in heparinized patients.
The aim of the study was to establish frequency of cerebral embolism overt and silent in patients with infective endocarditis.
Material and methods: Study group consisted of 50 pts (33 male, 17 female) with infective endocarditis (age from 22 to 75 years, mean 50 years): 20 pts with prosthetic valve endocarditis (9 pts on mitral, 7 pts on aortic, 4 on mitral and aortic prosthesis) and 30 pts with native valve endocarditis (13 pts on mitral valve, 10 on aortic valve, 7 on both).
Diagnosis of IE was established according to the Duke criteria. All pts underwent neurologic evaluation and CNS imaging (NMR, in case of contraindications CT scan).
Results: Vegetations were found in 38 patients (16 pts on aortic valve, 13 pts on mitral valve, 9 pts on both). Overt CNS embolism was confirmed (on NMR or CT scan) in 17 (34%) pts. In the latter 33 pts (66%) no clinical manifestation of CNS embolism occurred. In this group 12 (36%) pts had new ischaemic focal lesions. In general cerebral embolism occurred in 57,5% of pts with endocarditis, among them in 6 pts without vegetation (12%). In the silent embolism group one patient died due to cerebral hemorrhage before operation and another two died due to post ECC neurological complications.
Conclusions: 1. Neurologic imaging should be performed in all patients with infective endocarditis because cerebral embolism is frequent and serious complication of the disease also in patients without neurological symptoms.
2. Cerebral embolism could occurs even in patients without echocardiographically confirmed vegetation.

P1811 Changing patterns of infective endocarditis in congenital heart disease

S. Di Filippo[1], F. Delahaye[2], B. Semiond[3], W.H. Neches[4], F. Sassolas[3], M. Celard[3], A. Bozio[3]. *[1]Hôpital Cardiovasculaire Louis Pradel, Cardiologie Pédiatrique Dept., Lyon 03, France; [2]Hopital Cardiologique Louis Pradel, Cardiologie A, Lyon, France; [3]Hôpital Cardiovasculaire, Cardiologie Pédiatrique, Lyon Cedex 03, France; [4]Children's Hospital of Pittsburgh, Pediatric Cardiology, Pittsburgh, United States of America*

Aim: This study was to assess the current patterns of infective endocarditis (IE) in children and adults with congenital heart diseases (CHD).
Patients and methods: From 1966 to 2001, 153 IE occurred: 81 before 1990 (period I) and 72 after 1990 (period II).
Results: The proportion of tetralogy of Fallot decreased, of non operated ventricular septal defect, Rastelli repair and palliated cyanotic CHD increased. Age was significantly higher in period II. Twenty-five percent of the cases in period I and 19% in period II had received appropriate prophylaxis for an at-risk procedure. Non compliance with antibiotic prophylaxis was more frequent in period II (15.3% versus 3.7%). Postoperative cases were more frequent in period I; dental cause was the second most frequent event in period I (20.5%) and the most frequent in period II (32.4%). Cutaneous causative infections increased from 5% to 17%. The proportion of negative blood cultures lessened (19.8% to 6.9%, $p = 0.03$). Streptococcus was the commonest causative organism in both periods. The incidence of severe heart failure decreased (20% to 4.4%) and cardiac complications lessened (30.7% to 17.8%). Early surgery was more frequently performed in period II (34.7% versus 27.8%). Overall mortality was 25% in period I and 8.3% in period II ($p = 0.06$). The IE-related death rate was higher in period I (11% versus 2.8% in period II, $p < 0.05$).
Conclusion: Microbiological diagnosis improved and mortality of IE in CHD decreased. However, neither the incidence of IE nor the dental causes decreased. Prophylaxis patient education should be improved in patients with CHD.

P1812 Infective endocarditis associated myocardial infarction

A.A. Demin[1], V.P. Drobysheva[2]. *[1]& Clinical Pharmacology Dept, Head of Internal Medicine, Novosibirsk, Russian Federation; [2]Medical Academy, Internal Medicine, Novosibirsk, Russian Federation*

Infective endocarditis(IE)associated myocardial infarction (MI) is serious complication influencing prognosis.
Aim: To study pathogenesis of MI in IE.
Methods: Clinical, biochemical, microbiological and ultrasonic techniques were used. Alongside with usual search of valve vegetations the attention was stressed on their arrangement in relation to a mouth of coronary arteries. Morphological researches included the macro- and microscopic analysis.
Results: MI developed in 9% of 230 patients with active IE (1985-2004). Development of MI was associated with poorer prognosis of IE. MI manifested with pain in 43% and was painless in 57% of these cases. In 29% of patients initial manifestations of MI were disturbances of cardiac rhythm and conduction, and acute left ventricular failure. This precluded timely ECG diagnosis. However repetitive ECG recordings allowed to confirm MI in all patients. Elevation of troponins helped to diagnose MI in 81% of cases. Possible causes of MI were shutting of coronary artery mouth by vegetation from an aortic valve cusp (47%) and/or lowering of perfusion pressure in coronary arteries because of severe aortic insufficiency (62%). Disturbances of hemostasis with activation of its vascular and platelet elements and hypercoagulation found in all patients with IE also facilitated development of MI.
Conclusion: The data obtained supplement pathogenesis of MI in IE for new ways for treatment.

P1813 TGF beta and factor XIIIa are constituants of the carcinoid heart endocardial layer – a study by confocal laser microscopy

B. Maisch[1], D. Diepholz[2], R. Funck[2], A. Wilke[2], R. Arnold[3]. *[1]Marburg, Germany; [2]Philipps-University, Department of Internal Medicine - Cardiology, Marburg, Germany; [3]Philipps-University, Department of Gastroenterology, Marburg, Germany*

The detailed composition of the carcinoid right ventricular endocardial layer and the pathogenesis are still unresolved. One common explanation is that fibrosis occurs as a consequence to microlesions induced by high levels of circulating serotonin and bradykinin.
Methods: The right ventricular endomyocardial biopsies of 7 patients (5 female, mean age 43,9 + 11,4 y) with established carcinoid syndrome and right ventricular disease were analysed immunohistochemically by confocal laser microscopy for the composition of the the carcinoid endomyocardial tissue components using specific antibodies against collagen I and III, factor XIIIa, TGF beta and laminin.
Results: The main component of the carcinoid membrane is collagen I, followed by collagen III. The layer is extremely rich with nuclei. - In the subendocardium the laminin surrounds hypertrophic and pycnic myocytes with lipofucein deposits. The regular structure of normal endomyocardium is disolved, disarray becomes a prominent feature. The carcinoid membrane itself does not contain laminin, however. – In the borderzone between the carcinoid membrane and the myocardium a lining of TGF beta positive cells is found regularly. From there factor XIII positive cells disperse into the surrounding myocytes.
Conclusion: To the best of our knowledge this is the first description that the 2 proteins TGF beta and factor XIIIa are regular constituants in the carcinoid fibrous plaque in right ventricular endomyocardium. Both proteins are known to contribute to inflammation and healing in general. Their presence in the endomyocardium substantiates the "response to injury hypothesis" for the pathogenesis of the carcinoid heart.

P1814 Infective endocarditis in Whipples disease: 5 cases and literature revue

H. Aiouaz[1], M. Celard[2], A. Mercusot[1], F. Vandenesch[2], D. Vital Durand[3], H. Rousset[3], F. Delahaye[1]. *[1]Hopital Louis Pradel, Service cardiologie 1, Bron, France; [2]Hopital Louis Pradel, Service de bactériologie, Lyon, France; [3]Centre hospitalier Lyon-Sud, Service de medecine interne, Pierre-Benite, France*

Background: Whipple's disease is an exceptional cause of blood culture negative infective endocarditis (23 cases since 1976). The diagnosis is difficult, especially when the usual systemic context of the disease is missing.
Methods and results: Among 702 cases of infective endocarditis hospitalized in our institution between 1991 and 2004, 5 cases of infective endocarditis occurred in patients with Whipple's disease. All were men, mean age was 53 years. The clinical presentation was mostly cardiac. A cerebral embolus occurred in 2 cases and heart failure caused by valve insufficiency occurred in 3 cases. Valve location was mostly aortic (4 cases); it was mitral and aortic in 2 cases. Valve vegetations were always present. Valve lesions were very severe in 1 case, with an annular abscess. Low grade fever (<38.2°C) was present in 4 cases, and there was weight loss in 2 cases. The only extracardiac signs were arthralgias or arthritis, which were previously considered as seronegative rheumatoid arthritis in one

case, spondylarthritis in one case and psoriatic arthritis in one case. All other clinical manifestations of Whipple's disease, namely digestive, lymphoid, ocular and neurologic manifestations, were missing in all cases. The duodenal biopsy, which was performed in 4 cases, was always negative. This differs from the literature, in which an extracardiac location was found in 11 out of 17 cases. All our patients underwent cardiac surgery, for heart failure caused by aortic insuffisiency in 3 cases and for risk of embolus reccurence in 2 cases. The diagnosis was made on pathological specimens, which showed macrophage infiltration with periodic acid Schiff positive granulations, and positive Tropheryma whipplei specific polymerase chain reaction (PCR).
Conclusion: This series confirms the existence of almost pure endocarditis forms of the Whipple's disease in which the only extracardiac signs are rhumatologic manifestations, and it reinforces the value of histolopathological and PCR examination of the cardiac valves after valve surgery.

P1815 Protein S-100 as a new marker of cerebral embolism in the course of infective endocarditis

T.T. Hryniewiecki[1], M. Grabowski[2], J. Janas[3], E. Poniatowska[1], J. Stepinska[1]. *[1]Institute of Cardiology, Dpt.of Acquired Valvular Heart Disease, Warsaw, Poland; [2]Institute of Cardiology, Dpt.of Acquired Valvular Heart Disease, Warsaw, Poland; [3]Institute of Cardiology, Dpt.of Biochemistry, Warsaw, Poland*

Central nervous system (CNS) embolism is a frequent and could be serious complication of infective endocarditis (IE). It happens even in patients without echocardiographically confirmed vegetation. In some cases embolism causes small focal brain damage not enough to develop clinical symptoms or even CNS imaging changes. Fast and cheap method to identify patients with CNS embolism would be very useful because it could modify therapeutic decision making.
Protein S-100 is a relatively novel serum marker of brain damage. It has high sensitivity and could be measured by a simple and fast blood test.
The aim of the study was to evaluate usefulness of measurement of protein S-100 serum concentration to identify patients with cerebral embolic complication in the course of infective endocarditis.
Material and methods: Study group consisted of 30 pts (18 male, 12 female) with infective endocarditis (age from 25 to 76 years, mean 51 years): 11 pts with prosthetic valve endocarditis (4 pts on mitral, 4 pts on aortic, 3 on mitral and aortic prosthesis) and 19 pts with native valve endocarditis (8 pts on mitral valve, 7 on aortic valve, 4 on both).
Diagnosis of IE was established according to the Duke criteria. All pts underwent neurologic evaluation and CNS imaging (NMR or in case of contraindications CT scan).
S-100 serum levels were measured in all patients by a two-site radioimmunoassay technique (Sangtec).
Results: CNS embolism was confirmed (on NMR or CT scan) in 16 (53%) pts. Among them 7 pts (43%) have no clinical manifestation of embolism. Protein S-100 concentration was significantly (p = 0,05) higher in pts with (0,19 $\pm$ 0,24 pg/l) than in pts without CNS embolism (0,1 $\pm$ 0,11 pg/l). Protein S-100 level was elevated in 13 (82%) of pts with embolism and only in 2 pts without.
Conclusions: 1. Elevated serum protein S-100 concentration may suggest cerebral embolic complication in patients with infective endocarditis
2. Protein S-100 could be a useful marker in diagnosis and therapeutic decision making in patients with infective endocarditis.

P1816 Myocardial 123I-metaiodobenzylguanidine scintigraphic uptake and heart rate variability in patients with mitral valve prolapse

E.A. Zacharis[1], G.E. Kochiadakis[1], S.I. Koukouraki[2], M.E. Marketou[1], A.P. Patrianakos[1], N.S. Karkavitsas[2], P.E. Vardas[3]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Dept. of Nuclear Medicine, Heraklion, Greece; [3]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: Mitral valve prolapse (MVP) is associated with autonomic nervous system abnormalities. We undertook this study to evaluate myocardial sympathetic innervation and cardiac vagal activity by simultaneous assessment of 123-I-metaiodobenzylguanidine (MIBG) scintigraphy and heart rate variability (HRV), in patients with MVP.
Methods: MIBG myocardial scintigraphy and time-domain heart rate variability (HRV) were analysed in 30 patients with MVP (19 female, 36$\pm$12 years) and 25 healthy controls. None of the participants had any other disease that may have affected myocardial adrenergic innervation or autonomic nervous system. A 24-hour ECG ambulatory Holter monitoring was performed in all the subjects who also underwent a planar and a SPECT myocardial imaging of the heart after intravenous infusion of 5mCi MIBG. Heart to mediastinum ratio (H/M) was used for quantitative assessment of adrenergic innervation, 10 minutes and 4 hours after drug infusion, while SPECT scintigraphy evaluated the regional distribution of adrenergic activity. The percent washout rate (WR) was determined for the 4-hour period.
Results: Forty percent of the MVP was located in the posterior leaflet, 40% in the anterior leaflet and 20% in both leaflets. Patients with MVP showed enhanced WR (7.7 $\pm$ 3.4 in MVP versus 2.2 $\pm$ 2.3 in controls) and regional adrenergic innervation defects mostly in the inferoposterior and septal walls in anterior MVP and in inferior and lateral walls in posterior MVP. HRV analysis revealed a significant reduction of cardiac vagal tone in MVP patients (pNN50 (%): 4.6$\pm$2.2, rMSSD (ms): 16.9$\pm$6.5, SDNN (ms): 210$\pm$68) compared to controls (pNN50 (%): 8.6$\pm$5.1, rMSSD (ms): 32.9$\pm$7, SDNN (ms): 160$\pm$77, $p<0.05$ for all). WR correlated adversely with pNN50 (r= - 0.65, p= 0.02) and tended to correlate with rMSSD (r= - 0.059, p= 0.055).
Conclusions: Patients with MVP revealed an increased clearance of MIBG uptake and regional myocardial adrenergic innervation defects, which are related to a depressed cardiac vagal tone. These findings add important information to existing knowledge concerning the disturbed autonomic drive in MVP syndrome but further studies are necessary to assess if these findings are the cause or the result.

P1817 Ventricular remodelling after undersised mitral annuloplasty in patients with ischaemic valve regurgitation

I. Capecchi, S. Gelsomino, M. Chioccioli, C. Rostagno, S. Caciolli, P. Stefano, G.F. Gensini. *Careggi Hospital, Cardiac Surgery, Florence, Italy*

Objective: Restrictive Mitral annuloplasty has been widely used for repair in ischemic mitral regurgitation (IMR).This study was aimed to explore if such technique translate in a significant postoperative left ventricular (LV) remodelling.
Methods: We reviewed 90 patients (mean age 58$\pm$10 years, 64.4%male) who survived undersized mitral annuloplasty (UMA)between 2002 and 2004.The entire population had associated coronary graft surgery (mean graft 2.7$\pm$0.6,artery graft score 61.50).Associated mitral procedures were: para-commissural "edge-to-edge"(n=13) and secondary cordae resection (n=9). Ventriculoplasty was associated in 7 patients. Mean follow-up was 21$\pm$10 months.
Results: Results are summarized in table I

Indices of global LV remodelling

	Preroperative	Postoperative	p
MR	3.3$\pm$0.5	1.08$\pm$1.02	<0.001
EDVI(ml/m^2)	83.5$\pm$28	100$\pm$18	0.02
ESVI(ml/m^2)	51.7$\pm$16	40.5$\pm$18	0.04
SV(ml)	54$\pm$18	98$\pm$42	0.01
ERO(cm^2)	32$\pm$12	10$\pm$2	<0.001
RV	50$\pm$16	15$\pm$7	<0.001
RF	43$\pm$11	21$\pm$11	<0.001
LVEF (%)	38$\pm$13	43$\pm$9	0.04
ESWSm (Kdine/m^2)	171$\pm$64	66$\pm$27	<0.001
ESWSc (Kdine/m^2)	297$\pm$86	210$\pm$61	<0.001
SI	0.82$\pm$0.07	0.67$\pm$0.04	0.03

Abbreviations:MR=Mitral Regurgitation (Grade 0-4); EDVI= End diatolivc volumr index; ESVI= End systolic volume index; SV=Stroke Volume; ERO=Effective regurgitant orifice; RV= Regurgitant Volume; RF=Regurgitant fraction; LVEF=Left ventricular ejection fraction; ESWSm End-systolic meridional wall stress;ESWSC= End-systolic circumferential wall stress; SI= Sphericity Index.

Conclusions: Excellent result of combined UMA and coronary artery bypass were obtained. Residual mitral regurgitation was absent/minimal at follow up, associated with significant LV remodelling.

AORTA AND PERIPHERAL ARTERIES

P1818 Loeys-Dietz syndrome: a new aortic aneurysm syndrome with an aggressive clinical course and widespread vascular involvement

J. De Backer[1], B.L. Loeys[2], P.J. Coucke[3], J. Chen[2], H.C. Dietz[2], A. De Paepe[3]. *[1]Ghent, Belgium; [2]Mc Kusik Nathans Institute, Genetic Medicine, Baltimore, United States of America; [3]Centre for Medical Genetics, Ghent, Belgium*

Familial Thoracic Aortic Aneurysms (FTAA) comprise a genetic and clinical heterogeneous group of disorders. Recently, a new thoracic aortic aneurysm syndrome, the Loeys-Dietz syndrome (MIM #609192) has been reported. This autosomal dominant disease is caused by mutations in either Transforming Growth Factor Beta Receptor 1 or 2 genes (TGFBR1 or 2). Here we provide a detailed clinical description of 11 independent families in whom a causal mutation was identified (6 subjects from 4 families with TGFBR1 and 11 subjects from 7 families with TGFBR2 mutations). Affected subjects are characterized by the triad of widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm/dissection. Other findings were present in multiple systems and include craniosynostosis, structural brain abnormalities, congenital heart disease (atrial septum defect and patent ductus arteriosus), and aneurysms with dissection throughout the arterial tree.
While some individuals with mutations in TGFBR1 or TGFBR2 show some overlap with Marfan (MFS) syndrome (variable evidence for bone overgrowth and aortic root dilatation and/or dissection), none satisfied the clinical-diagnostic criteria for MFS. More importantly, all affected individuals showed manifestations in multiple organ systems that are not associated with MFS. Aneurysms tend to be

particularly aggressive, with rupture at an early age or at a size not associated with high risk in MFS. Two young patients also died from dissections outside the ascending aorta: one died from a cerebral bleeding whereas the other had an abdominal aortic dissection. These findings are important for the management of these patients: an even more stringent follow-up and earlier surgical intervention seem appropriate and imaging studies of the total body arterial tree by MRA or CT-scan are strongly indicated.

P1819 Contrast transoesophageal echocardiography, a significant breakthrough in the assessment of aortic disease

Z. Gomez Bosch, A. Evangelista, G. Avegliano, M.T. Gonzalez-Alujas, C. Orihuela, J. Rodriguez, I. Ferreira, J. Soler-Soler. *Hospital Vall d'Hebron, Cardiologia Dept., Barcelona, Spain*

Transoesophageal echocardiography (TOE) has become a technique of choice in the assessment of aortic disease. However, there are some limitations which can be important in therapeutic management.
Methods: 85 patients with aortic disease were assessed by conventional transthoracic echocardiography (TTE) and by TOE using echo-colour Doppler information and after contrast administration (Optison iv, 1-2ml in both TTE and TOE). Two independent observer assessed the diagnostic benefits of using contrast echo in the recorded images.
Results: In 18 acute dissections (8 type A and 10 type B), conventional TTE gave correct diagnosis in 10 cases and 15 with contrast echo. Contrast in TOE enabled retrograde type dissection diagnosed in 2 cases. In 34 repaired type A dissections conventional echo did not visualized the entry tear in 14, whereas contrast identified all them (9 in the upper part of ascending aorta and 5 in abdominal aorta). In 33 type B dissections contrast helped to localize the entry tear in 5 cases, identified correctly the true lumen in 7, and gave information on the flow of false lumen in most cases.
Conclusions: The use of contrast improves the diagnosis of aortic dissection by transthoracic echocardiography. Contrast provides crucial information in localising the entry tear in hidden aortic segments, helps in true lumen identification and is basic in the assessment of false lumen flow by transoesophageal echocardiography.

P1820 Preferential storage of matrilysin and plasmin in cystic medial necrosis of human aortic aneurysms and dissections

L. De Figueiredo Borges[1], P. Sampaio Gutierrez[1], M. Lecharpentier[2], B. Franc[2], G. Jondeau[3], Z. Touat[4], O. Meilhac[4], J.B. Michel[4]. *[1]Heart Institute (InCor), Laboratory of Pathology, Sao Paulo, Brazil; [2]CHU Ambroise Paré, Laboratoire d'anatomopathologie, Boulogne, France; [3]CHU Ambroise Paré, Consultation Marfan, Boulogne, France; [4]CHU X. Bichat, INSERM Unité 698, Paris, France*

Background: Aneurysms and dissections of the ascending aorta are usually non-atherosclerotic, non-inflammatory vascular diseases, sharing similar histopathological features, characterized by areas of smooth muscle cell disappearance and degradation of collagen and elastic fibres, both predominating in mucoid areas (known as "cystic media necrosis"), related to the accumulation of either isolated glycosaminoglycans or proteoglycans. In view of these morphological alterations, we explored the topography of matrix protease storage in these diseases.
Material and methods: 5μm-thick sections of formalin-fixed, paraffin embedded human aortas were used to detect, by immunohistochemistry, the presence of MMP-3 (stomelysin), MMP-7 (matrilysin) and plasminogen/plasmin in the medial layer; in parallel, serial sections were stained with hematoxylin, eosin and Alcian blue (for mucoid material). Aortas from 12 patients with thoracic aortic aneurysms (6 with Marfan's syndrome) and 6 with acute dissection were analysed. Cases particularly rich in mucoid content were selected. Additionally, 6 normal aortic fragments obtained at coronary artery bypass surgery were studied as controls.
Results: In all cases except controls, stromelysin and, most remarkably, matrilysin, accumulated in the areas of cystic medial necrosis, whereas plasmin/plasminogen was situated in the periphery of these regions. Outside these mucoid areas, MMP-3 was distributed throughout the media, mostly in the intercellular space. MMP-7 predominated in the external half of the media, presenting both an intra- and extracellular localisation. The same pattern of distribution was seen in normal aortas, in the absence of mucoid areas.
Conclusions: Considering that matrilysin (and stomelysin) acts on versican, the main proteoglycan in aortic wall, on other extracellular matrix molecules including fibronectin, collagens and elastin, on serine-protease inhibitors, and on other secreted gelatinases (MMP-2 & -9), these enzymes could be directly involved in tissue remodelling. Tissue-adsorbed plasminogen/plasmin could play a critical role in the in situ activation of MMPs. Their exact colocalization with areas of cystic medial necrosis, suggests a major role for this association in the pathologies of the ascending aorta.

P1821 Prophylactic treatment of type II endoleak at the time of endovascular abdominal aortic aneurysm repair

M. Zanchetta[1], S. Ronsisvalle[2], M. Zennaro[1], F. Faresin[2], M. Riggi[2], L. Pedon[1]. *[1]Department of Cardiovascular Disease, Cittadella, Italy; [2]Department of Vascular Surgery, Cittadella, Italy*

Purpose: Type II endoleak may be defined as blood flow outside the stent graft but within the aneurysm sac from aortic side branch vessels, such as inferior mesenteric, lumbar, accessory renal, sacral and hypogastric arteries. The management of type II endoleak still remains contentious, varying from early or late interventions to conservative or surgical approach. Our purpose was to report the first clinical use of intraoperative fibrin glue aortic side branch embolization in order to prevent reperfusion type II endoleak and to assess its incidence following endovascular abdominal aortic aneurysm repair using this new technique.
Methods: Between June 2003 and December 2004, sixty four consecutive patients, 93% males, mean age 74.3 ± 7.0 years (range 64-86), underwent elective intraoperative fibrin glue (Tissucol®) aortic side branch embolization. A mean value of 3.5 of aortic side branches per patient was found on the preoperative angiogram. There were fifty eight bifurcated Talent and eight bifurcated AneuRx devices used in our series. After performing angiography, the bifurcated body of the prostheses with its integral iliac leg was deployed just below the renal arteries in the usual fashion, followed by the deployment of controlateral limb. Intraoperative fibrin glue aortic side branch embolization technique can be summarized as follows. Firstly, after the deployment of the bifurcated body of the prostheses, the angiographic Pig-tail catheter was withdrawn, leaving a 0.035 standard guide-wire in place. Secondly, a proper sealing of distal neck was obtained by inflating the balloon into the ipsilateral iliac leg. After the deployment of the controlateral iliac extension, a 23 mm britetip sheath was advanced over the wire into the aneurysm sac and an aneurysmogram was performed by injecting the contrast media by hand. During the fibrine glue injection (5.0 ml), a proper sealing of the distal neck was obtained by inflating the balloon into the ipsilateral iliac leg. Subsequently, an aneurysmogram was repeated in order to verify aortic side branch occlusion.
Results: Successful intraoperative fibrin glue embolotherapy was obtained in all patients. Complete sealing of the aortic side branches was achieved in 63 patients (98.4%), confirmed by the lack of contrast filling into the aneurysm sac at the CT-scan follow-up (mean 9.3 ± 4.4 months).
Conclusions: The intraoperative fibrin glue aortic side branch embolization appears to be a suitable procedure. This preventive strategy provides easier aortic side branch occlusion than transarterial and translumbar embolotherapy.

P1822 Early prognosis of acute type B aortic dissection: analysis of risk factors in 70 consecutive patients

J. Perunicic[1], R. Lasica[1], B. Vujisic-Tesic[1], M. Asanin[1], I. Mrdovic[1], M. Pejic[1], P. Djukic[1], P. Mitrovic[2]. *[1]University Clinical Centre, Institute for Cardiovascular Diseases, Belgrade, Serbia and Montenegro; [2]Beograd, Serbia and Montenegro*

Aims: The purpose of this prospective study was to assess the risk factors for the early outcome of acute type B aortic dissection (AAD-B) as well as patients' survival related to the treatment.
Methods and results: From 1998 to 2004, 70 patients with AAD-B (68.6% males, average age 62 ± 9.62) were treated in our Institute. The overall in-hospital mortality was 15.7% (11 patients). 62 patients (88.5%) received drug treatment (Group I), while 86 patients (11.5%) were treated surgically (Group II). Only those patients with complicated AAD-B were treated surgically. In-hospital mortality was lower in Group I (12.9%) than in Group II (37.5%) (p=0.01). 25 patients (37.5%) suffered in-hospital complications caused by AAD-B, the most often being acute renal failure (7 patients, or 28%), hypotension/shock (6 patients, or 24%), mesenteric ischemia-infarction (3 patients, or 12%), and limb ischemia (2 patients, or 8%). The following presenting variables as mortality predictors were identified by logistic regression analysis: in-hospital complications (OR, 21,20; 95% CI, 2,71-165,90; p= 0,003), relapsing pain (OR, 20,43 95% CI, 2,58- 161,65, p= 0,004), uncontrolled hypertension (OR, 13,90, 95% CI, 2,99- 64,59, p= 0,001), unthrombosed false lumen (OR, 8,76; 95% CI, 1,12- 68,45; p= 0,038), pain intensity on admission > 8/10 (OR, 6,03; 95% CI, 1,69-21,43; p= 0,005), initial pain intensity > 8/10 (OR, 4,90; 95% CI, 0,98- 24,40; p= 0,052), syncope (OR, 4,41; 95% CI, 1,34-14,48; p= 0,014), maximum diameter of dissected descending aorta >4,75 cm (OR, 1,71; 95%CI, 1,18-2,48; p=0,004) and/or maximum diameter of dissected abdominal aorta > 3,35cm (OR, 1,76; 95%CI, 1,24-2,49; p=0,001). The most important early mortality predictors shown by Cox's multivariant analysis were uncontrolled hypertension (OR, 20,69; 95%CI, 2,60-164,62; p= 0,004) and maximum diameter of dissected aorta > 4,75 cm (OR, 6,30; 95%CI, 1,33-29,93; p=0,020).
Conclusion: In-hospital mortality in AAD-B is quite high. Intensity of AAD-B complications is important and considerably contributes to increased early mortality. Knowledge of early mortality risk key factors may help a better choice of treatment and mortality decrease in these patients.

P1823 Advantages of contrast transoesophageal echocardiography during aortic endovascular therapy

Z. Gomez Bosch[1], A. Evangelista[1], G. Avegliano[1], M. Matas[2], J. Maeso[2], V. Fernandez-Valenzuela[2], M.T. Gonzalez-Alujas[1], J. Soler-Soler[1]. [1]*Hospital Vall d'Hebron, Cardiologia Dept., Barcelona, Spain;* [2]*Hospital Vall d'Hebron, Cirugía vascular, Barcelona, Spain*

Aortic endovascular treatment has become an extended therapeutic alternative in descending thoracic aorta diseases. Angiography and transoesophageal echocardiography (TOE) during the procedure is crucial for a correct stent-graft placement.

The aim of this study was to assess the usefulness of contrast echocardiography to improve TOE information.

Methods: 33 endovascular procedures were performed in thoracic aorta in acute dissection (n:1), chronic dissection (n:7), aneurysm (n:14) and post-trauma (n:11). 1-4 stent were implanted in each procedure (1.4±1).Conventional TOE and then contrast (Optison 1-3ml) were used consecutively.

Results: In spite of echocardiographic and colour Doppler information contrast added significant information during the procedure for the identification of the true lumen in 3 cases, in the assessment of the residual false lumen flow in 8 cases, and in persistent thoracic arterial trunk flow (left subclavian artery, left carotid artery and celiac trunk) in 14 cases. After stent implantation during the procedure 13 endoleaks were found, colour Doppler failed to identify the type of endoleak in 6 cases. Contrast was critical in the diagnosis of these endoleaks (5 type I and 2 type III), quantification of its severity (2 severe) and management (balloon inflation and new stent implantation) in 7 cases.

Conclusions: Transoesophageal echocardiography is most useful in monitoring the correct stent-graft implantation in the thoracic aorta. However, the use of contrast shows significant improvement, especially in the identification and quantification of endoleaks, and in the assessment of residual false lumen and thoracic arterial trunks flows.

P1824 Intercostal island dilatation after aortic replacement in Marfan patients

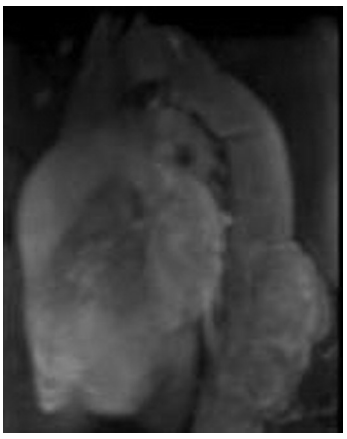
P. Symersky[1], J.W.J. Vriend[2], B.J.M. Mulder[2], B.A.J.M. de Mol[1]. [1]*academic medical center, cardiothoracic surgery, amsterdam, Netherlands;* [2]*academic medical center, cardiology, amsterdam, Netherlands*

Background: Reimplantation of intercostal arteries (ICA' s) as an island is a common strategy to avoid ischemic damage to the spinal chord during descending aortic replacement. However, remnants of native aortic tissue in Marfan patients may be prone to dilatation and rupture.

Aim: To study the prevalence of late aortic complications after island reimplantation and the relationship with island size.

Methods: Retrospective observational design. Clinical records, operative reports and MR and/or CT angiograms of all Marfan patients followed in our tertiary referral center were reviewed.

Results: A total of 96 Marfan patients were identified. Five patients had undergone descending aortic replacement with island reimplantation of the ICA's. Mean follow-up in these patients was 47 months (range 12 to 61 months). The number ICA's reimplanted as an island ranged from 4 to 9. Increases in maximal aortic diameter at the level of the intercostal island ranged from 2 to 24 mm. Diameters in the islands with 9 and 7 ICA's increased by 12 mm (35 to 47) and by 24 mm (36-60), respectively. The first patient suffers from dyspnea as a result of compression of the left bronchus by the dilated patch, and the second had a blowout of the island for which an endovascular stent-graft was introduced to prevent exsanguination. The patients with the small islands (4 ICA's) had a diameter increase by 4 mm (37 to 41) and 13 mm (50 to 63), respectively. The fifth patient with 5 ICA's and a follow-up of only 12 months had an increase of 3 mm (from 43 to 46 mm).



A dilated intercostal island.

Conclusions: All intercostal islands dilate in Marfan patients with mid-term follow-up. The amount of dilatation seems related to the size of the island (i.e. the number of ICA's included). Island size should be limited.

P1825 Ambulatory arterial stiffness index (AASI), a novel measure of arterial stiffness, provides additional prediction of cardiovascular mortality

E. Dolan[1], L. Thijs[2], Y. Li[2], N. Atkins[1], P. McCormack[1], E. O Brien[1], J.A. Staessen[2], A. Stanton[1]. [1]*ADAPT Centre, Beaumont Hospital, Dept. Clinical Pharmacology, Dublin, Ireland;* [2]*University of Leuven, Molecular and Cardiovascular Research, Leuven, Belgium*

Background: While arterial stiffness predicts cardiovascular outcome, its measurement is not readily available in clinical practice. We hypothesize, that the dynamic relationship between systolic blood pressure (SBP) and diastolic blood pressure (DBP) over twenty-four hours, provides further early insight into arterial stiffness. Even prior to manifesting a widened average pulse pressure (PP), subjects with stiffened arteries will demonstrate greater increments in SBP than in DBP with increasing distending pressure. The objective of this study was to determine the additional predictive value of a novel measure of this phenomena, termed the ambulatory arterial stiffness index (AASI), over and above mean PP.

Methods: At baseline, whilst not on antihypertensive medication, 11,291 patients (5326 male, mean age 54.6 years) underwent ambulatory BP monitoring (ABPM). Using all BP readings from each individual we plotted DBP against SBP, and calculated the regression slope. AASI was defined as one minus this regression slope. We dichotomized AASI using the upper boundary of the 95th prediction interval in relation to age using a database of normotensive subjects. After a median follow-up of 9.4 years there were 566 cardiovascular deaths

Results: In a Cox proportional-hazard model AASI was an independent predictor of cardiovascular mortality. The resultant unadjusted and adjusted (adjusted for sex, age, smoking history, diabetes, previous cardiovascular events, BMI, MAP and PP) relative hazard rates (RHR) for an abnormal AASI were 2.02 (95% confidence intervals;1.57-2.60, $p<0.0001$) and 1.53 (1.19-1.98, $p=0.001$) respectively. The fully adjusted RHR for stroke mortality was 2.39 (1.54-3.69, $p<0.0001$). Unlike PP, AASI predicted cardiovascular mortality in those with normal daytime ambulatory pressures (<135/85 mmHg) with a fully adjusted RHR of 2.06 (1.17-3.61, $p < 0.01$). The substitution of mean SBP for MAP did not materially alter any of the above hazard ratios.

Conclusions: This novel dynamic index of arterial stiffness, which can be readily determined from ambulatory blood pressure recordings, is strongly and independently associated with cardiovascular risk. AASI appears to particularly improve on average PP in the prediction of stroke and in the identification of cardiovascular risk amongst normotensive subjects.

P1826 Mechanisms and consequences of luminal renewal of parietal thrombus in Abdominal Aortic Aneurysm

Z. Touat[1], V. Ollivier[2], J. Day[2], M.G. Huisse[2], P. Rossignol[2], O. Meilhac[2], M.C. Guillin[2], J.B. Michel[2]. [1]*INSERM, Paris, France;* [2]*INSERM - U698, CHU X. Bichat, Paris, France*

It has been shown that the mural thrombus plays a role in abdominal aortic aneurysm (AAA) expansion through its biological activity. In the present study, we explored the mechanisms of thrombus renewal at the luminal interface. We collected 20 mural thrombi of AAA during surgery, of which corresponding blood samples had been taken before, together with blood samples of 20 matched healthy individuals. The luminal layer showed, by immunohistochemistry, fibrin-rich areas, where GPIIIa and P-selectin colocalized with PMNs. Mural thrombi were dissected into 3 layers: luminal, intermediate and abluminal, and incubated for 24H at 37°C.

Luminal eluates exhibited a diminished clotting time compared to those from the other two layers ($p<0.005$). This procoagulant activity was only partly prevented by anti-TF antibody; and the enrichment in TF was similar in eluates from the 3 layers. In contrast, the concentration of microparticles, p-selectin, sGPV and sCD40L released by the luminal layer was increased compared to other layers ($p<0.005$). The microparticles are principally of platelet and PMN origin (59% ± 14 and 36% ± 12, respectively) but were negative for a macrophage marker. Moreover, the removal of microparticles from the luminal eluate increased the clotting time ($p<0.05$). Our investigations were then extended to plasma, showing an increase in markers of platelet and coagulation activation (Table) ($p<0.005$.)

Table 1. Results

Thrombus	Microparticles (nb/μL)	p-selectin (ng/mL)	sCD40L (pg/mL)	sGPV (ng/mL)	TAT (mg/mL)
Luminal	1124 ± 279 **	1450 ± 262 **	288 ± 60 **	514 ± 97 **	7.15 ± 2.9
Intermediate	332 ± 69	291 ± 45	70 ± 17	136 ± 23	11.3 ± 3.4
Abluminal	232 ± 97	265 ± 43	69 ± 27	98 ± 22	4.9 ± 1.7
Plasma					
Patients	5906 ± 1163 **	108.6 ± 9.8 **	240.6 ± 29 **	63.6 ± 7.5 **	7.4 ± 1.3 **
Controls	819 ± 136	40.8 ± 2.3	48.8 ± 4.5	39 ± 4.4	3 ± 0.4

In conclusion, we observed that the luminal layer of the AAA thrombus has an intense procoagulant activity which could be related to platelet aggregation and activation, microparticle release and associated PS-exposure. These constituents

could be used as plasma markers in patients, providing evidence of thrombus activity. These data open new therapeutic avenues, using inhibitors of platelet activation for preventing aneurysm expansion.

P1827 High dose of beta-blockers and tight heart control reduce the incidence of myocardial ischaemia in patients undergoing major vascular surgery

H.H.H. Feringa[1], J.J. Bax[2], M.D. Kertai[3], O. Schouten[1], S.H. Meij[4], H. Boersma[4], J. Klein[3], D. Poldermans[5]. *[1]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands; [2]University hospital Leiden, Cardiology, Leiden, Netherlands; [3]Erasmus MC, Anaesthesiolgy, Rotterdam, Netherlands; [4]Erasmus Medical Centre, Cardiology Dept., Rotterdam, Netherlands; [5]Erasmus MC - Anesthesiology, Rotterdam, Netherlands*

Background: Perioperative myocardial ischemia is an important risk factor for adverse cardiac outcomes after major vascular surgery. In a large number of studies beta-blockers have shown a beneficial effect on post-operative outcome, however, some studies failed to demonstrate such a cardioprotective effect. We hypothesized that tight heart rate control during surgery using high dose beta-blockers, is associated with a reduced incidence of myocardial ischemia and improved outcome.
Aim: The present study examines the influence of different doses of beta-blockers on heart rate control, the incidence of myocardial ischemia and post-operative outcome.
Methods: The study population consisted of 142 patients undergoing major vascular surgery. Patients were screened for cardiac risk factors and beta-blocker use. Dosage of beta-blockers was expressed as percentage of the maximum recommended dose. Myocardial ischemia was assessed by continuous 12-lead electrocardiographic monitoring (12-lead ECG), starting 12 hours before surgery and continuing for 3 days after. Troponin T level was measured on day 1, 3 and 7, after surgery and before discharge.
Results: In this study cohort (mean age: 68±11 years, 79% male), myocardial ischemia occurred in 55/142 (39%) patients. In these patients, perioperative heart rate was significantly higher (81 (±12) vs 72 (±12) beats/minute, $p<0.0001$), and the dosage of beta-blockers was significantly lower (12% vs 27% of maximum dose, p=0.001), compared to patients without myocardial ischemia. The incidence of positive troponin T was higher in patients with myocardial ischemia, compared to patients without myocardial ischemia (29% vs 13%, p=0.02). Using multivariable logistic regression analyses and adjusting for cardiac risk factors, pre-operative heart rate (OR per 5 beats/minute: 1.16, 95% CI: 1.02-1.31, p=0.02) and dosage of beta-blockers (OR per 10% of maximum dose: 0.74, 95% CI: 0.62-0.88, p=0.001) were significantly associated with myocardial ischemia.
Conclusion: High doses of beta-blockers and tight heart rate control are associated with a reduced incidence of perioperative myocardial ischemia in patients undergoing major vascular surgery.

P1828 Aortic stiffness in systemic sclerosis is increased independently of the extent of skin involvement

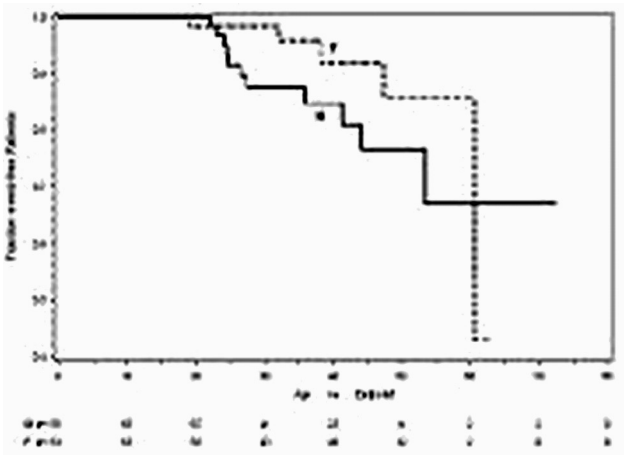
I. Moyssakis[1], E. Gialafos[1], V. Vassiliou[2], D. Papadopoulos[1], V. Votteas[1], P. Sfikakis[2]. *[1]Laiko Hospital, Cardiology Department, Athens, Greece; [2]Laiko Hospital, Rheumatology, Athens, Greece*

Objective: To study the stiffness of large arteries in relation to the extent of skin and lung fibrosis, the aortic distensibility in patients with diffuse and limited Systemic Sclerosis (SSc) was examined.
Material and Methods: Consecutive patients (55 with diffuse and 51 with limited SSc) without signs and symptoms of heart failure or previous history of arterial hypertension, underwent echocardiography and lung function tests. Aortic stiffness was determined non-invasively by aortic distensibility and aortic strain measurements in all, as well as in 50 healthy subjects, matched for age and gender.
Results: Aortic distensibility in patients with either diffuse ($2.03 \pm 0.26 \times 10^{-6}$ cm^2 dyn^{-1}) or limited SSc (2.12 ± 0.33) was similarly decreased compared to controls (2.49 ± 0.36, $p<0.001$). Moreover, aortic strain was significantly reduced in both patient groups (6.48+0.36% and 6.58+0.40%) than controls (7.2+0.41%, $p<0.001$), confirming that aortic stiffness is increased in SSc independently of the extent of skin involvement. Left ventricular performance was similar between patients and controls, while left ventricular mass (117±21g/m^2 and 113±18 vs. 82±15) and pulmonary hypertension (20% and 17.6% vs.0%) were significantly increased in both SSc groups ($p<0.01$ and $p<0.05$ respectively), the latter associating with aortic distensibility and strain in multivariate analysis (p=0.016 and p=0.037 respectively). No association with serum levels of C-reactive protein, or lung function abnormalities indicative of pulmonary fibrosis, were found.
Conclusions: Stiffness of the aorta is increased in patients with established SSc regardless of the extent of the inflammatory fibrotic process in the skin and lung, suggesting that additional pathogenetic mechanisms contribute to the compromise of large arteries.

P1829 Gender related difference in elective aortic root surgery in Marfans syndrome

J. Timmermans, G.H.J. Boers, J.R.M. Cruysberg, B.C.J. Hamel, S. Teerenstra, F.W.A. Verheugt. *Radboud University Nijmegen Medical Centre, Department of Cardiology, Heartcenter, Nijmegen, Netherlands*

Background: Male (m) Marfan patients (pts) are thought to have more severe disease than female (f) pts and, therefore, suffer more events. Since elective aortic (Ao) surgery is recommended at a Valsalva sinus diameter of 50-55 mm, the need for surgery may be biased in favour of m because the Valsalva sinus diameter is related to BSA, which is larger in m.
Methods: We studied the gender difference in the need for first elective Ao surgery and assessed age, BSA, Ao root diameter and Ao parameters indexed for BSA (Ao index and Ao ratio) between m and f with and without surgery. Yearly echo was done. End of F/U was defined as the last visit in the non-event group and time of Ao F/U surgery in the event group.
Results: In 131 adult pts (68 m, 63 f, mean age 29.5 yr range, 16-65 yr) surgical events occurred in 11 m and in 5 f (p=0.15 m vs f). Mean F/U to endpoint in the event-free group was 7 yrs (1-6 yrs) and 10 yrs (4-14 yrs) in the event group. In both groups there is a significant difference in BSA between m and f (2.1 vs 1.8 m^2, $p<0.0001$ and 2.2 vs 1.9 m^2, p=0.006). The Ao diameter was greater in m than in f in the event-free group at inclusion and at end of F/U (40 vs 37 mm, p=0.0004 and 43 vs 39 mm, $p<0.0001$). The Ao diameter at surgery was the same for m and f (55 vs 54 mm). Ao index was higher for f at inclusion (26 vs 22 mm/m^2, p=0.02) and endpoint (29 vs 25 mm/m^2, p=0.008). In the event group Ao ratio was higher for f at inclusion (16 vs 14, p=0.02) and at endpoint (17 vs 16, p=0.07). In the event group age at elective surgery tended to be higher in f (39 vs 32 yr, figure).



Freedom of aortic surgery

Conclusion: In our selected group of Marfan pts we could not demonstrate more severe disease in male pts, but it seems they are operated upon earlier than women.

P1830 Impaired aortic properties in patients with chronic heart failure as assessed by cardiovascular magnetic resonance

N.P. Nikitin, P.H. Loh, R. de Silva, E.I. Lukaschuk, A.L. Clark, J.G.F. Cleland. *University of Hull, Academic Dept. of Cardiology, Kingston-upon-Hull, United Kingdom*

Aortic properties change with age and in cardiac disease. In patients with chronic heart failure (CHF) it may contribute to patients' symptoms. In this study we used cardiovascular magnetic resonance (CMR) to assess the size and distensibility of the ascending and descending aorta in CHF patients with impaired and preserved left ventricular (LV) systolic function and compared it with younger and older normal subjects.
Methods: The study population included 209 patients with signs and symptoms of compensated CHF (NYHA functional class II or III). One hundred and forty patients (aged 69±10 years) who had LV systolic dysfunction (LV ejection fraction <45%) formed Group I, and 69 patients (aged 69±11 years) with preserved LV systolic function (LV ejection fraction =45%) formed Group II. The control population included 14 older volunteers aged 66±14 years (Group III) and 21 younger subjects aged 32±4 years (Group IV) with no known cardiac disease. The subjects underwent cine CMR on a 1.5T Signa CV/i GE Medical Systems scanner to characterise LV function and to assess cross-sectional areas and distensibility of the ascending aorta (AA) and the descending aorta (DA).
Results: There were no differences in age between groups I, II and III. Systolic blood pressure was significantly ($p<0.05$) higher in group II and Group III as compared with Group IV. Diastolic blood pressures were not significantly different between the groups. The distensibility index (DI) of the AA and the DA

was closely correlated with age (r = -0.67 and -0.68 respectively) in the entire study group. Aortic size increased and aortic distensibility declined with age. CHF patients (Groups I and II) demonstrated aortic dilatation and increased stiffness compared to both younger and older groups of normal volunteers.
Conclusion: Patients with CHF show impaired elastic properties of the ascending and the descending aorta. Diminished aortic distensibility is present in patients with both impaired and preserved LV systolic function.

e-POSTER SESSION 5

MODERATED e-POSTERS: NUCLEAR CARDIOLOGY: FROM DIAGNOSIS TO PROGNOSIS

P1831 Adenosine triphosphate with thallium predicts prognosis in patients with coronary artery disease

M.I. Coma-Canella[1], J. Palazuelos[1], M.J. Garcia-Velloso[2]. *[1]Clinica Universitaria de Navarra, Dept of Cardiology, Facultad de Medicin, Pamplona, Spain; [2]Clínica Universitaria de Navarra, Nuclear Cardiology, Pamplona, Spain*

Aim: To assess the value of adenosine triphosphate (ATP) and single photon emission computed tomography (SPECT) to stratify risk in coronary artery disease (CAD).
Methods: 299 patients (188 men, aged 64±10 years) with suspected or known CAD and inability to perform physical exercise underwent SPECT studies with ATP infusion (0,160 mg/kg/min during 6 minutes). ATP was used instead of adenosine because previous studies have shown similar results but ATP has a much lower cost. Thallium-201 was injected in the fourth minute of infusion. Stress images were adquired 10 minutes and rest images 4 hours after ATP infusion. Perfusion defects were divided into mild, moderate or severe according to the extension and intensity of hypoperfusion. Non-reversible defects were considered more severe than reversible defects. Total follow-up time in this study was 815.51 years with a mean time of 2.72 (1.7) years per patient. Clinical variables with well-known influence in prognosis were compared with SPECT.
Results: Total cardiovascular events (CVE) were 115. Forty three of them were hard events (HE), defined as death or non-fatal myocardial infarction. The mean of total CVE was 0.38 (0.7) with a range from 0 to 5. There was an event rate of 11.75 (95%CI: 9,79 to 14,11) events per one thousand patients per month (11.75/1000p/m); that is an event rate of 17% per year. In the univariate statistical analysis, the variables with clinical relevance to predict HE were: age >55 (risk 4,49 times vs <55, p=0.023), diabetes mellitus (risk 2.26 times vs non diabetes, p=0.016), ejection fraction <0.5 (risk 2.92 times vs EF>0.5, p=0.005) and severe perfusion defects (risk 4.85 times vs non severe defects, p=0.0002). Heart to lung ratio (HLR)>0.3 increased the risk of total CVE (risk 1,77 times vs HLR <0.3, p=0.01). In a multivariate analysis only age >55, diabetes and severe perfusion defects were statistically related to HE.
Conclusion: ATP can be used as a pharmacological stress test in patients who cannot perform physical exercise. Perfusion thallium defects elicited by ATP had a stronger correlation with prognosis than clinical variables such as age, diabetes or low ejection fraction.

P1832 Long-term prognosis in patients with chronic ischaemic left ventricular dysfunction is affected by revascularisation strategy

C. Pollack[1], J.P. Hellermann[2], M. Namdar[1], P.T. Siegrist[1], P. Koepfli[1], T. Schepis[1], M. Genoni[3], P.A. Kaufmann[1]. *[1]University Hospital Zurich, Nuclear Cardiology, Zurich, Switzerland; [2]Cardiovasculare Centre, University Hospital, Zurich, Switzerland; [3]University Hospital, Cardiac Surgery, Zurich, Switzerland*

Background: The relative benefits of coronary artery bypass graft surgery (CABG) versus percutaneous transluminal angioplasty (PTCA) in patients with chronic ischemic left ventricular (LV) dysfunction (LVD) are largely unknown.
Aim: To assess the impact of revascularization strategy on long-term prognosis in patients with LVD.
Methods: We assessed the follow up (f/u) of 102 patients with chronic ischemic LVD who underwent FDG und NH3 PET scan for assessment of hibernating myocardium (= NH3/FDG mismatch). Patients werde grouped according to the presence (hibernating) or absence of viable myocardium (no hibernating).
Results: see Table 1.

	Hibernating		No Hibernating	
	CABG (n = 29)	PTCA (n = 21)	CABG (n = 27)	PTCA (n = 25)
age, years	59±9	56±13	64±9	65±7
gender, male	86%	86%	78%	88%
LV EF (%)	33±11	28±9	30±7	35±3
3-vessle disease	93%	62%	44%	48%
mean f/u, years	4.2±2.4	4.9±2.5	4.4±2.6	4.6±1.6
first year mortality	13.0%	13.2%	20.0%	6.0%
survivors, end of f/u	51.4%	71.8%	49.4%	80.4%

Conclusion: Our results demonstrate a strong association between CABG and increased first year mortality compared to PTCA in the absence of myocardial viability assessed by PET. The long-term follow up, however, reveals a markedly reduced survivors rate in CABG compared to PTCA irrespective of presence or absence of viable myocardium.

P1833 Myocardial SPECT and suspected acute coronary syndrome: previous myocardial infarction and/or diabetes are strong predictors of ischaemia in patients with normal troponin levels

A. Jain[1], E. Macias[2], A.H. Elmegadmi[2], E.J. Smith[2], C. Randall[2], N.W. Garvie[2]. *[1]London, United Kingdom; [2]Barts and The London NHS Trust, Cardiology, London, United Kingdom*

Introduction: ECG and cardiac troponin are routinely used to risk stratify patients who present with suspected acute coronary syndrome, If dynamic ECG changes are absent, and the 6 hour troponin level remains normal, the risk of future cardiac events is deemed as low, allowing the patient to be discharged earlier. Such patients are often referred subsequently for investigation by exercise treadmill test or myocardial perfusion SPECT (MPS), in order to exclude an ischemic cause for their symptoms. The overall diagnostic yield of MPS in this situation is, however, low. We have investigated the hypothesis that a history of previous myocardial infarction (MI) or diabetes mellitus (DM) will improve the diagnostic yield of MPS, and therefore assist in the identification of those patients who are most in need of follow-up investigation.
Methods: The study group comprised 81 patients (32 male) who had presented with troponin negative and ECG negative suspected acute coronary syndrome. Troponin was assayed at 12 hours and deemed normal if the level was recorded as <0.4ng/ml. Each patient subsequently underwent MPS according to standard protocol (2 day protocol, Tc-Myoview) as an outpatient. Treadmill, adenosine, or dobutamine stress was used as clinically indicated. Image interpretation was informed by attenuation-correction.
Results: 16/81 (20%) of the study group had a history of MI, 25/81 (31%) had DM. Overall, 15/81(18%) of the total group had ischaemia on MPS, but this value fell to 7% if DM or prior MI was excluded. 8/16 (50%) of patients with a history of MI had ischaemia on MPS, a five-fold increase when contrasted against the 10% (7/65) of patients with no record of infarction. 6/25 (24%) of diabetic patients had ischaemia, compared to 9/56 (16%) of non-diabetic patients. 7/16 (44%) of patients with previous myocardial infarction were also diabetic and 71% of these had MPS scans which were positive for ischemia.
Conclusion: In patients who present with acute chest pain but with no subsequent troponin or ECG abnormality, stress/rest MPS has a low overall diagnostic yield for ischemia. In this situation a history of either myocardial infarction or diabetes mellitus is strongly predictive for the presence of ischemia, and therefore significantly improves the cost-effectiveness of investigation by MPS.

P1834 Predictors of congestive heart failure in diabetic cardiomyopathy using cardiac sympathetic nerve activity

I. Samuil, M. Nagai, F. Hana. *Kawasaki, Kanagawa, Japan*

Diabetic cardiomyopathy is associated with abnormalities in cardiac sympathetic nerve activity which contribute to the high morbidity and moratlity. Myocardial scintigraphy with (123)I-labeled metaiodobenzlguanidine (MIBG) is used to study the predictive values for cardiac complications.
Methods: MIBG scintigraphy was performed for 52 patients diagnosed as diabetic cardiomyopathy (38 males and 14 females, mean age 48 ± 12 years). Early and delayed images were obtained in 15 minutes and 5 hours after administration of (123)I-MIBG. The heart to mediastinum ratio for (123)I-MIBG activity was calculated (H/M). The myocardial washout ratio (WOR) was determined as percent change in activity from 15 minutes to 5 hours after isotope administration as well as the extent score and severity score. Echocardiography as well as measurement of plasma brain natriuretic peptide (BNP) were done. Patients were followed for 18 months with end points of cardiac events (congestive heart failure or arrhythmia requiring hospitalization and cardiac death).
Results: congestive heart failure occurs in 28 patients (54%), arrhythmia in 24(46%) and cardiac death in 6 (11.5%). Patients were divided into two groups. Group A (24 patients) with left ventricular ejection fraction >45% and BNP <200 pg/ml and group B (28 patients) with left ventricular ejection fraction <45% and BNP >200 pg/ml. Multivariate analysis identified WOR as the only significant predictor of cardiac death (r =1.182, p<0.001) and cardiac events (r=1.082, p<0.05) in group A patients with preserved left ventricular function while left ventricular ejection fraction and the delayed H/M were the most powerful predictors for the cardiac events in group B (r=0.005, p< 0.01 and r=0.004, p<0.01) among other parameters, age, heart rate, NYHA class, WOR, left ventricular end diastolic dimension, left ventricular end systolic volume and left ventricular wall thickness. Kaplan-Meier survival curves revealed the prognosis become poor in patients with low H/M ratio. Low H/M ratio was associated with type I diabetes, female, high NYHA class and low fraction shortening.
Conclusion: (123) I-MIBG scintigraphy is useful noninvasive tool for assessment of myocardial sympathetic nerve activity which is useful for predicting cardiac events in patients with diabetic cardiomyopathy.

P1835 Acute reversible heart failure caused by scorpion envenomation is associated to transitory myocardial perfusion disturbance

A.B. Figueiredo[1], A.O. Pintya[1], F. Caligaris[1], P. Cupo[1], S.E. Hering[1], A. Pazin-Filho[1], J.A. Marin-Neto[1], M.V. Simoes[2]. [1]*Faculdade de Medicina RP - USP, Hospital das Clinicas, Ribeirao Preto, Brazil;* [2]*Faculdade de Medicina de Ribeirao Preto - USP, Divisao de Cardiologia, Ribeirao Preto, Brazil*

Acute left ventricular (LV) dysfunction may occur in patients with severe scorpion envenomation (SE), but its mechanisms remain unclear, and its prognosis is unpredictable. Myocardial perfusion (MP) disturbance has also been described in this clinical context.

Purpose: we aimed at investigating the temporal relationship between MP abnormalities and LV dysfunction in patients with SE.

Methods: Twelve consecutive patients (8 males, 9±3 y.o.) presenting in the emergence room with severe (n=9) and moderate (n=3) SE based on clinical manifestations were investigated. Patients underwent EKG-synchronized Tc99m-Sestamibi Single Photon Emission Tomography (G-SPET) within 72 h (acute) and 15 days (follow-up) after the acute event onset. G-SPET images were interpreted using a visual semi-quantitative score for assessment of MP (0=normal, 4=absent) and wall motion (WM; 0=normal, 4 = akinesia) using a 17-segment LV model. Summed MP and WM scores (SMP and SWM, respectively) were calculated for every patient. Global LV ejection fraction (LVEF) was automatically calculated by using the QGS® software.

Results: Eight out of 9 patients with severe SE presented extensive WM and MP abnormalities associated to global LV dysfunction and pulmonary congestion. Among the 3 patients with moderate SE only 1 presented mild WM abnormality and a normal LVEF. The SWM score (n=12) was 22±20, SMP score was 10±9, and LVEF was 44±18%. A positive correlation between the SWM and SMP was found (R=0.76, p=0.004). In addition, a significant negative correlation was obtained between SMP score and the LVEF (R=-0.72, p=0.013). A total of 204 segments were analyzed, and a significant topographic correlation between segmental WM and MP changes was obtained (Chi-Square, $p<0.0001$). In the segments showing normal WM (n=102), concordant normal MP was seen in 95 segments (93%); and among the 102 segments with abnormal WM, 72 presented concordant reduction in MP (71%). The follow-up G-SPET showed significant recovery of SWM (1.4±4.6, p=0.004), SMP (1.41±3.4, p=0.004), and LVEF (65±8%, p=0.007). The LVEF improvement was significantly correlated to the SMP score amelioration (r=0.85, p =0.007).

Conclusions: Myocardial perfusion disturbance is common in severe scorpion envenomation and is topographically correlated to the segmental LV dysfunction. The LV function improvement correlates with the recovery of MP. These findings suggest that myocardial perfusion disturbance is an important mechanism of this form of reversible acute heart failure.

P1836 Relation between coronary flow reserve and flow mediated dilation index in patients with peripheral artery disease

P. Perrone-Filardi[1], A. Silvestro[2], T. Pellegrino[3], G. Brevetti[2], L. Corrado[2], M. Cafiero[2], M. Chiariello[2], A. Cuocolo[3]. [1]*Napoli, Italy;* [2]*"Federico II" University, Cardiology, Naples, Italy;* [3]*"Federico II" University, Nuclear Medicine, Naples, Italy*

Purpose: The aim of this study was to assess the relationships between brachial artery flow-mediated dilation (FMD) and coronary flow reserve (CFR) in patients with peripheral artery disease (PAD) without coronary artery disease (CAD).

Methods: We studied 30 consecutive patients (26 men; mean age of 65±9 years) with PAD, asymptomatic for cardiac symptoms and with normal stress SPECT cardiac imaging. Thirteen other patients (7 men, mean age 59±10 years) without PAD or CAD constituted the control group. All patients and controls, underwent dipyridamole (0.74 mg/kg) sestamibi imaging. Myocardial blood flow (MBF) was estimated by measuring first transit counts in pulmonary artery and myocardial counts from SPECT images. On a separate day the same acquisitions were repeated after tracer injection under resting conditions. Estimated CFR was expressed as the ratio MBF stress/MBF rest. In all patients with PAD, flow mediated dilation index of the brachial artery was assessed by ultrasound.

Results: Patients with PAD were separated in 2 groups, considering the median value of overall FMD (6.85%): group 1 (n=16) with FMD above the median (mean 8.78±1.3%) and group 2 (n=14) with FMD below the median (mean 5.14±0.94%). Sestamibi estimated CFR was significantly reduced in group 2 compared with group 1 (1.0±0.4 vs 1.5±0.4, $P<0.005$). These observations were not dependent on the threshold value that was arbitrarily chosen to define the severity of impairment of arterial reactivity, as there was a significant correlation for the entire group of patients with PAD between FMD and sestamibi estimated CFR ($r = 0.56$, $P<0.002$). In the 13 controls, estimated CFR was 2.2±0.5, significantly higher compared to both groups of patients with PAD ($P<0.05$ vs group 1 and $P<0.001$ vs group 2, respectively).

Conclusion: Estimated CFR was significantly reduced in patients with PAD compared to controls and CFR impairment correlates with the degree of peripheral endothelial dysfunction, asymptomatic for CAD.

METABOLIC SYNDROME, DIABETES AND MECHANISMS OF ATHEROGENESIS

P1837 Advanced glycation end products (AGEs) enhance the vascular smooth muscle cell proliferation in diabetic vasculopathy: the potential role of AGEs in the restenosis of diabetic patients after stenting

Y.W. Yoon[1], H.M. Kwon[1], K.C. Hwang[2], E.Y. Choi[1], B.K. Hong[1], S.J. Lim[1], H.S. Kim[1]. [1]*Yongdong Severance Hospital, YUMC, Cardiology Department, Seoul, Korea, Republic of;* [2]*Yonsei Cardiovascular Center, Department of Cardiovascular Research, Seoul, Korea, Republic of*

Background: Advanced glycation endproducts (AGEs), irreversible non-enzymatic glycation of macromolecules enhance the local oxidant stress and immunoinflammatory reaction in diabetic vasculopathy through its receptor RAGE. Recently, AGEs have been reported to play a role in neointimal formation in the animal model of arterial injury. However, the potential role of AGE in vascular smooth muscle cell (VSMC) proliferation remains unclear. Therefore, we sought to determine whether the activation of VSMC proliferation by AGE is associated with activation of the mitogen-associated protein kinase (MAPK) system, an important signaling pathway associated with VSMC proliferation. Furthermore, we also investigated the association between serum level of AGEs with formation of ROS and expression of RAGE.

Methods & Results: Blood samples were collected from the diabetic CAD patients and the serum levels of AGEs were analyzed by the fluorescent intensity method. In vitro smooth muscle cell culture was done using the different levels of AGEs containing serum of the patients. Smooth muscle cell proliferation was assessed using MTT analysis. Western blotting was performed to assess the activation of MAPK system and protein kinase C in the smooth muscle cells. Increasing concentration of AGEs was associated with increased smooth muscle cell proliferation and was associated with activation of ERK and Protein kinase C. The expression of RAGE was assessed by RT-PCR and the formation of ROS was evaluated using H2DCFDA. The possible inhibition of smooth muscle cell proliferation by AGE inhibitor, Aminoguanidine, was assessed. The formation of ROS was significantly correlated with increasing concentration of AGEs. Aminoguanidine (5-50 μg/ml) significantly inhibited activation of ERK and PKC by AGEs and inhibited the formation of ROS.

Conclusions: High serum level of AGEs can indeed activates VSMC proliferation and increase the oxidative stress in vitro. Aminoguanidines significantly inhibited smooth muscle proliferation through inhibition of AGEs and its receptor RAGE. Activation of ERK, PKC and increased formation of ROS may be the possible mechanism of AGEs induced vasculopathy. Increased VSMC proliferation by AGEs may affects the high in-stent restenosis rate in diabetic CAD patients treated with stenting.

P1838 Effects of rosiglitazone alone and in combination with atorvastatin on serum inflammatory biomarkers in patients with type 2 diabetes mellitus

C.S. Chu, K.T. Lee, M.Y. Lee, S.T. Lee, K.H. Cheng, W.C. Voon, S.H. Sheu, W.T. Lai. *Kaohsiung Medical University Hospital, Cardiology, Kaohsiung, Taiwan*

Combination therapy of PPAR-gamma agonist rosiglitazone (R) and HMG-CoA reductase inhibitor atorvastatin (A) has beneficial effects on both glycemic control and lipid composition in patients (pts) with type 2 diabetes mellitus(DM).

Aim: To evaluate the effects of combination therapy with R and A on vascular inflammatory biomarkers of atherosclerosis in pts with type 2 DM.

Methods: Total 30 pts (mean age 59) with type 2 DM and hyperlipidemia were enrolled to receive R monotherapy (4 mg/day) for 3 months, and then A (10 mg/day) was added with R for the following 3 months. Inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP), matrix metalloproteinase-9 (MMP-9), soluble CD40 ligand (sCD40L), adiponectin (all by ELISA methods) as well as lipid profiles were measured at baseline, after R monotherapy and after combination therapy of R and A, respectively.

Results: With treatment of R alone for 3 months, hs-CRP decreased significantly by 25.6% and adiponectin raised by 1.92 fold (both $P<0.05$).There was a trend of reduction in both MMP-9 and sCD40L, but total and LDL cholesterol were elevated after R alone therapy. With combination therapy of R and A for the following 3 months, hs-CRP further significantly decreased and adiponectin further increased. MMP-9 and sCD40L levels were further significantly decreased compared with baseline. The total and LDL cholesterol levels were also significantly reduced compared with baseline.

Table 1. Serial changes of the biomarkers

	Baseline Month 0	RSG Month 3	RSG+ATV Month 6
hs-CRP, mg/L	3.78 ± 3.62	2.06 ± 1.96*	1.21 ± 1.01*#
Adiponectin, ug/mL	10.2 ± 7.2	23.8 ± 21.4*	29.6 ± 24.7*#
sCD40L, ng/mL	1.97 ± 0.91	1.78 ± 1.05	1.50 ± 1.07*#
MMP-9, mg/dL	422.8 ± 99.5	390.2 ± 78.8	360.0 ± 45.0*#

RSG: rosiglitazone; ATV: atorvastatin; *p < 0.05 vs pretreatment; #p < 0.05 vs after RSG 3 months'treatment.

Conclusion: Combination therapy with rosiglitazone and atorvastatin not only significantly improved lipid profiles, but increased adiponectin and reduced vascular biomarkers of hs-CRP, MMP-9 and sCD40L in pts with type 2 DM. The strategies of combination therapy with rosiglitazone and atorvastatin offer additive benefits in reducing cardiovascular risk factors for patients with type 2 DM.

P1839 Additive beneficial effects of ramipril combined with simvastatin in the treatment of type II diabetic patients

K.K. Koh[1], S.H. Han[2], M.J. Quon[3], W.-J. Chung[1], E.K. Shin[1]. *[1]heart center, ghil hospital, cardiology, Incheon, Korea, Republic of; [2]Ghil hospital, Gachon medical school, Cardiology, Incheon, Korea, Republic of; [3]NIH, Diabetes Unit, Bethesda, United States of America*

Background: We compared vascular and metabolic responses to statin and angiotensin converting enzyme inhibitor therapies either alone or in combination in type II diabetic patients.
Methods: This was a randomized, double-blind, placebo-controlled cross-over trial with three treatment arms (each 2 months) and two washout periods (each 2 months). Fifty patients were given simvastatin 20 mg and placebo, simvastatin 20 mg and ramipril 10 mg, or ramipril 10 mg and placebo daily during each 2 month period.
Results: Ramipril alone or combined therapy significantly reduced blood pressure and simvastatin alone or combined therapy significantly changed lipoproteins. All three treatment arms significantly improved flow-mediated dilator response to hyperemia relative to baseline measurements. However, these parameters were changed to a greater extent with combined therapy when compared with simvastatin or ramipril alone ($P<0.001$ by ANOVA). When compared with simvastatin or ramipril alone, combined therapy significantly reduced high sensitivity C-reactive protein levels (P=0.004 by ANOVA). Interestingly, combined therapy or ramipril alone significantly increased plasma adiponectin levels and insulin sensitivity (determined by QUICKI) relative to baseline measurements. These changes were significantly greater than in the group treated with simvastatin alone (P=0.013 for adiponectin and P=0.015 for QUICKI by ANOVA).
Conclusions: Ramipril combined with simvastatin improves endothelial function and reduces inflammatory marker to a greater extent than monotherapy with either drug in type II diabetic patients.

P1840 Symptomatic diabetic macrovascular disease is associated with an increase in platelet microparticle levels

K.T. Tan[1], M.H. Tayebjee[2], H.S. Lim[2], G.Y. Lip[2]. *[1]University of Birmingham, University Department of Medicine, Birmingham, United Kingdom; [2]City Hospital, University Dept of Medicine, Birmingham, United Kingdom*

Introduction: Platelet activation, with consequent platelet microparticle(PMP) formation, has been shown to be increased in type 2 diabetes and atherosclerosis.
We hypothesised that patients with both diabetes and clinically detectable atherosclerotic disease have greater levels of PMPs in their blood, compared to patients with type 2 diabetes who have no clinical evidence of macrovascular disease.
Methods: 21 diabetic patients with no clinical evidence of macrovascular disease and 18 patients with diabetes and known atherosclerosis were recruited. 21 controls were recruited from healthy volunteers. Blood was collected into citrated Vacutainers (BD Biosciences) for ELISA and Diatube-H Vacutainers (BD Biosciences) for the flow cytometric determination of platelet microparticle levels.
Results and Discussion:

Patient details and results

	Controls (n=21)	Diabetes (n=21)	Diabetes with Atherosclerosis (n=18)	P-value
Age	66.8(12.6)	68.4(6.1)	71.0(5.9)	0.335
Males (%)	38.1	61.9	61.1	0.221
SBP (mmHg)	132(14)	136(17)	133(16)	0.655
DBP (mmHg)	77(12)	76(8)	70(7)	0.067
HbA1c	5.5 (5.2-5.8)	6.6 (6.0-7.4)	7.2 (6.8-7.8)	0.03
Cholesterol (mmol/l)	5.4(0.9)	4.6(0.9)	4.0(0.7)	0.02
Triglycerides (mmol/L)	1.4 (1.0-1.8)	1.8 (1.2-2.7)	1.4 (0.7-2.1)	0.191
HDL (mmol/l)	1.5(0.3)	1.2(0.2)	1.3(0.3)	0.004
Platelet Count	269(75)	307(123)	295(104)	0.468
Aspirin Use(%)	–	42.9	94.4	0.001
Hip/Waist Ratio	–	1.06(0.05)	1.05(0.05)	0.574
PMP/ml ($x10^5$)	1.09 (0.53-1.46)	1.68 (0.79-2.78)	3.33 (1.70-8.01)	0.045
sP-selectin (ng/ml)	40 (34-52)	40 (35-48)	49 (35-47)	0.046

Results presented as mean (SD) or median (IQR) for normally and non-normally distributed data respectively. SBP Systolic blood pressure, DBP Diastolic blood pressure, HbA1c Glycosylated haemoglobin, HDL High-density lipoprotein, PMP Platelet microparticles

Patients with diabetes but no evidence of macrovascular disease have increased levels of PMPs. However, the presence of clinically apparent macrovascular disease is associated with even higher levels of PMPs. Therefore, PMPs may represent a novel marker of high risk diabetes.

P1841 Impact of advanced glycation end products (AGEs) on inflammation in atherosclerosis

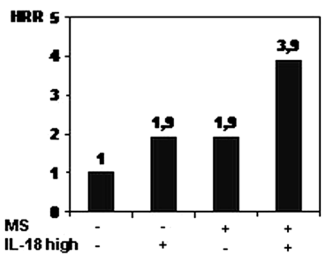
C. Reiss[1], A. Yilmaz[2], F. Traeg[2], M. Klein[3], D. Raithel[3], M. Pischetsrieder[4], W.G. Daniel[2], C.D. Garlichs[2]. *[1]Medical Clinic II, University Erlangen, Molecular Cardiology, Erlangen, Germany; [2]University of Erlangen-Nuremberg, Medical Clinic II, Erlangen, Germany; [3]Clinical Center, Clinic for Vascular Surgery, Nuremberg, Germany; [4]University of Erlangen-Nuremberg, Institut for Pharmacy/Food Chemistry, Erlangen, Germany*

Background: Diabetic patients often suffer from vascular atherosclerotic complications such as myocardial infarction or stroke. An important pathway involved in accelerated atherosclerosis in diabetes is the increased formation of advanced glycation end products (AGEs) generated by nonenzymatic, irreversible glycation of proteins and lipids. The interaction of AGEs with their specific receptors (e.g. RAGE) activates key signal transduction pathways which lead to altered gene expression and the release of proinflammatory mediators. Therefore the aim of our study was to investigate if the quantity of AGEs in human atherosclerotic plaques correlates with the frequency of different inflammatory cells.
Methods: We investigated 65 carotid endarterectomy specimens by immunohistochemistry with antibodies against macrophages (MP, anti-CD68), dendritic cells (DC, anti-fascin, anti-CD83), T-lymphocytes (TC, anti-CD3) and HLA-DR. AGEs were immunohistochemically stained with a monoclonal antibody against AGE-Carboxymethyllysin (AGE-CML). Using a computer-assisted image analysis system (Nikon DXM 1200) AGE-positive area was analyzed and compared to the total plaque area (%AGE/P). Additionally, the number of different inflammatory cells was analyzed in the plaque.
Results: AGEs were detected extracellular as well as within cells around the lipid core and in the plaque shoulders, indicating an uptake of AGEs by e.g. macrophages. An increase in %AGE/P was shown for advanced atherosclerotic plaques compared to initial stages. We observed a significant correlation between the %AGE/P and the number of mature DCs (r=0.43; p=0.002), MPs (r=0.27; p=0.04), TCs (r=0.39; p=0.009) and HLA-DR+-cells (r=0.40; p=0.002). There was a trend to higher %AGE/P values in plaques of patients with acute ischemic complications (e.g. TIA).
Conclusion: In the present study, we show a significant association between the amount of AGEs and the severity of inflammation in human atherosclerotic plaques. As inflammation is an important pathogenic factor in atherogenesis, particularly for the occurrence of plaque complications, these results point out the impact of AGEs in atherosclerosis.

P1842 Metabolic syndrome, inflammation and cardiovascular prognosis

C. Espinola-Klein[1], H.J. Rupprecht[2], C. Bickel[2], A. Schlitt[2], K. Lackner[3], J. Meyer[3], T. Muenzel[2], S. Blankenberg[2] on behalf of the Atherogene study. *[1]Universität zu Mainz, II. Medizinische Klinik, Mainz, Germany; [2]University Hospital, 2nd Department of Internal Medicine, Mainz, Germany; [3]University Clinic, Department of Clinical Chemistry, Mainz, Germany*

Background: Patients with the metabolic syndrome (MS) are at increased risk for cardiovascular atherosclerosis. Recent findings suggest an elevation of inflammatory markers in patients with the MS. Aim of this study was to evaluate the impact of elevated interleukin-18 (IL-18) on the long-term prognosis of patients with atherosclerosis in accordance to the MS.
Methods and Results: We included 1303 patients with coronary artery disease (CAD). Patients with at least 3 of the following criteria were defined to suffer from the MS: triglycerides $>$ 150mg/dL, high density lipoprotein-cholesterol $<$ 50mg/dL, body-mass-index $>$ 30, blood pressure $>$ 135/85mmHg, fasting blood glucose $>$ 110mg/dL. In 586 patients (45%) at least 3 components of the MS were present. Over that, IL-18 was evaluated in all patients. IL-18 was significantly higher in patients with the MS (63.4 vs. 58.4 pg/mL; $P < 0.0001$). Cardiovascular mortality could be evaluated in 1290 patients (99%) after a median follow-up of 5.5 years. Patients with the MS had a significantly higher cardiovascular mortality (MS yes: 14.9%, no: 7.9%, $P<0.0001$). Patients were divided into two groups according to the median Il-18 level (60.4 pg/mL). Elevation of IL-18 further in-



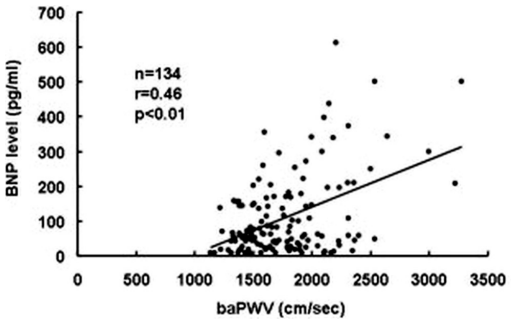
Cardiovascular mortality

creased cardiovascular mortality (P < 0.0001). Hazard risk ratio is shown in the figure. Patients with elevated IL-18 and at least 3 components of the MS had a 4-fold higher cardiovascular risk compared to patients with low Il-18 and less than 3 components of the MS.
Conclusion: Elevation of Il-18 significantly increased cardiovascular mortality in patients with CAD in accordance to the MS.

P1843 Aortic stiffness is an independent determinant of plasma brain natriuretic peptide level in patients with coronary artery disease

S. Sakuragi[1], K. Okawa[2], N. Tokunaga[2], M. Kakishita[2]. *[1]Tottori Municipal Hospital, Department of Cardiology, Tottori, Japan; [2]Tottori Municipal Hospital, Department of Cardiology, Tottori, Japan*

Plasma brain natriuretic peptide (BNP) level has been reported to be elevated in some patients with coronary artery disease (CAD) in the absence of CHF, however, the underlying mechanism of this elevation in BNP has not been fully evaluated. Because pulse wave velocity (PWV), which is an index of atherosclerosis, has been reported to be higher in patients with CAD, there is a possibility that enhanced aortic stiffness may cause increased BNP level in CAD patients. In this study, we examined the influence of aortic compliance on BNP level in patients with CAD by measuring brachial-ankle PWV (baPWV), which can be measured automatically using newly developed device in Japan.
Methods and Results: We enrolled 134 patients with CAD determined by coronary angiography (103 men and 31 women, 68±9years) and patients were classified into quartiles on the basis of the BNP level. The baPWV was used as an index of aortic compliance. Patients in the highest BNP level quartile were older, had lower LVEF and had higher baPWV than the other categories of patients, whereas there was no difference in the number of diseased coronary arteries. In univariate analysis, baPWV significantly correlated with BNP level (r=0.46, p<0.01, figure). By multivariate logistic regression analysis, baPWV and LVEF were independently associated with the highest quartile of BNP level (p=0.03 and p=0.02, respectively). In the highest baPWV quartile, the time to ST depression in exercise testing was significantly shorter than the other categories of patients.



Correlation between baPWV and BNP level

Conclusion: These findings indicate that baPWV, which can be easily measured, is an independent determinant of BNP level in CAD patients. Lower myocardial ischemic threshold may cause the increased BNP level in patients with severe aortic stiffness.

P1844 The protein kinase C-pathway is involved in transcriptional regulation of C-reactive protein synthesis in human hepatocytes

Y. Ivashchenko[1], F. Kramer[1], S. Schäfer[1], A. Bucher[2], V. Hombach[2], A. Busch[1], O. Ritzeler[1], J. Torzewski[3]. *[1]Sanofi-Aventis, Cardiovascular Research, Frankfurt, Germany; [2]University of Ulm, Internal Medicine II, Ulm, Germany; [3]Univ. Klinik Ulm, Abt. Innere Medizin II - Kardiologie, Ulm, Germany*

Objective: C-reactive protein (CRP) is the prototype acute phase protein and a cardiovascular risk factor. Interleukin-1beta (IL-1beta) and interleukin-6 (IL-6) stimulate CRP synthesis in hepatocytes. We searched for additional pathways regulating CRP expression.
Methods and results: Primary human hepatocytes (PHHs) were treated with IL-1beta, IL-6 and protein kinase C (PKC)-activator phorbol12,13-dibutyrate (PDBu). CRP was analysed by quantitative RT-PCR and ELISA. PDBu significantly induced CRP transcription by 21.0 ± 9.24-fold and protein release by 2.9 ± 0.5-fold. Transcriptional regulation was studied in detail in HepG2 cells stably transfected with the 1kb CRP promoter (HepG2-ABEK14 cells). In these cells, PDBu significantly induced CRP transcription by 5.39 ± 0.66-fold. Competetive inhibition with bisindolylmaleimide derivative LY333531 abolished PDBu-mediated promoter activation. Competetive inhibition with IkB-kinase-inhibitor I229 also inhibited PDBu-effects. Importantly, interleukin-8 (IL-8) significantly induced CRP-release in PHHs by 58.675 ± 19.1-fold, which was blockable by LY333531.
Conclusions: This study describes a novel PKC-dependent transcriptional regulation of CRP gene expression, which, in analogy to the classical IL-1beta and IL-6 pathways, is operational in hepatocytes only. It also identifies IL-8 as a potential physiological PKC-activator. HepG2-ABEK14 cells may be useful for high throughput screening (HTS) to identify inhibitors of CRP synthesis for the prevention of cardiovascular disease.

P1845 Altered balance between circulating endothelial progenitor cells and apoptotic endothelial cells in patients with coronary artery disease

V. Ivanov[1], I. Popovici[1], L. Guzun[2], V. Cobets[1], L. Ciobanu[1], S. Costin[1], M. Popovici[3]. *[1]Institute of Cardiology, Moldavian Society of Cardio, Chisinau, Moldova, Republic of; [2]CFR Clinic, Romanian Society of Cardio, Brasov, Romania; [3]Moldavian Research Institute of, President, Moldavian Society of Cardiology, Chisinau (Kishinev), Moldova, Republic of*

Intact endothelial cell (EC) layer and endothelialization processes are asssential to maintatin the vascular integrity. Although recent studies provided evidence for the role of circulating endothelial progenitor cells (EPCs) in the repair of injured vessels, more studies are certainly needed to substantiate the consistency of these findings. Therefore, we determined the number and functional activity of circulating EPCs in 24 patients with angiographically-demonstrated coronary artery disease (CAD) and 15 healthy volunteers. Quantification of circulating EPCs was performed with double labeling for CD34 and VEGFR2 by FACS analysis. Adhesiveness, survival and the phenotype of EPCs from both groups were assesssed using fibronectin-coated culture dishes. In addition, we have quantitatively determined the number of circulating apoptotic ECs using FACS analysis of annexin V/PECAM double-labeled cells. Apoptotic ECs were also confirmed by TUNEL staining. The number of circulating EPCs was markedly reduced in CAD than in control (35.7±24 cells/mL blood vs 86.6±21.7 cells/mL blood, p<0.006). These finding were corroborated by 147.5±24% increase in circulating apoptotic ECs when compared with the control (p<0.001). The percent of EPCs attached to the culture substrate was lower in CAD than in controls (52.7±25.8% vs 92.07±8,12%, p<0.001) and the number of EPCs which survived 7 days in culture was found to be significantly less in CAD than in control (94.9±35.5 cells/mm^2 vs 496.6±146.9 cells/mm^2). These both functional parameters of cultured EPCs and the number of circulating apoptotic ECs correlated significantly with the number of affected coronary arteries (R=-0.695, R= -0.716, R= +0.74, respectively).
Conclusion: The present study demonstrate that patients with CAD exhibit reduced levels and functional impairment of EPCs, which were associated with increased numbers of circulating apoptotic ECs. Both, EPCs levels and function, and apoptotic ECs correlate with the number of affected coronary arteries. Thus, CAD is characterized by a disturbed balance between the number and function of circulating EPC and the occurrence of EC apoptosis. This markers could provide means of risk stratifying patients for likelihood of CAD progression and of developing plaque disruption and acute coronary events.

P1846 The LPL-D9N polymorphism is a marker for myocardial infarction in type 2 diabetes

M.C. Izar[1], T. Helfenstein[1], S.S.M. Ihara[2], W.G.M. Relvas[1], L.E.S.A. Pinto[1], M.I.H. Fonseca[1], S.W. Han[3], F.A.H. Fonseca[1] on behalf of GOLD Investigators. *[1]Federal University of Sao Paulo, Medicine, Sao Paulo, Brazil; [2]Federal University of Sao Paulo, Pathology, Sao Paulo, Brazil; [3]Federal University of Sao Paulo, Biophysics, Sao Paulo, Brazil*

Background: Although type 2 diabetes has been considered at equivalent coronary risk, it has been debated if all diabetics should be classified at higher risk. Polymorphisms of genes affecting lipid metabolism may predispose diabetic patients to myocardial infarction (MI). We investigated whether multiple genetic testing could add in the prediction of risk in diabetics.
Methods: A prospective multicenter study was conducted in 990 diabetic, middle-aged individuals of both sexes (386 with MI, 604 without MI) from 27 institutions in Brazil. Apo AI-Msp I, Apo C3-Sst I, CETP-Taq I, Apo E, LPL-D9N, PON 1-Gly192Arg, and both Mwo I and Avr II-LCAT polymorphisms have been tested by PCR-RFLP.

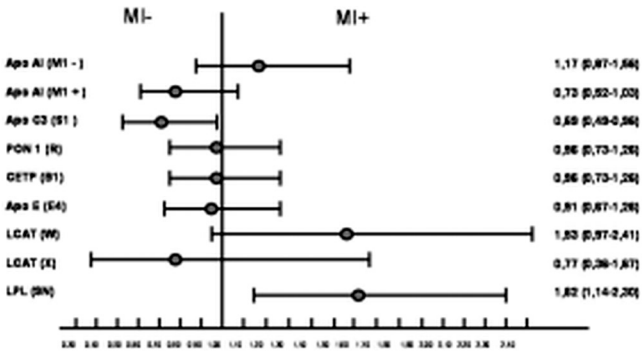


Figure 1

Results: Among studied polymorphisms, LPL-9N allele was associated with a 62% increase in risk, while Apo C3-S1 exerted a very modest protective effect on the occurrence of MI in diabetic individuals (Figure 1). Apo AI-M2- allele was associated with higher HDL-C levels, in statin naïve patients. In a logistic regression model the risk of MI was associated with male sex, age as risk factor, smoking habit, BMI, and with the LPL-9N allele.
Conclusion: Genetic predisposition for MI in diabetics can be based, at least in part, in genes regulating key enzymes or apolipoproteins related to the metabolism of triglyceride-rich lipoproteins, namely, LPL-D9N and Apo C3-Sst I. Analysis of multiple genes is reasonable to assess the individual genetic burden of MI in diabetic patients.

P1847 Renin inhibitor, aliskiren, prevents vulnerable plaque development in a mouse model of unstable plaque

L. Mazzolai, M. Korber, J.F. Aubert, K. Bouzourene, D. Nussberger, D. Hayoz. *University Hospital, CHUV, Angiology Unit, Dept of Internal Medicine, Lausanne, Switzerland*

Mechanisms responsible for transforming a stable into a vulnerable plaque remain elusive. Using an atherosclerotic mouse model (ApoE-/-) with increased endogenous Ang II production (two-kidney, one clip renovascular hypertension, 2K1C) we showed that Ang II induces a switch towards a vulnerable plaque phenotype, independently from its effect on blood pressure. The aim of the present work was to assess to what extent we can modulate atherosclerotic lesion development by blockade of the renin-angiotensin system (RAS). Sham and 2K1C-ApoE-/- mice were untreated or treated for 3 weeks with the specific renin inhibitor Aliskiren (intraperitoneal minipumps) at a dose of 50 mg/kg/day. This dose has been found to optimally block the RAS. At 3 weeks, mean blood pressure (MBP) and plasma renin activity (PRA) were measured and tissues were analyzed histomorphologically. Aliskiren decreased MBP in both sham operated (94±4 mmHg vs untreated 119±2 mmHg; $p<0.05$) and 2K1C hypertensive mice (95±4 mmHg vs untreated 150±5 mmHg; $p<0.05$). PRA was significantly ($p<0.05$) decreased in sham controls from 5,4±1.8 ng/ml/hr to 2±0.2 ng/ml/hr and in 2K1C from 17±6 ng/ml/hr to 1.9±0.7 ng/ml/hr (n=8 in each group). Histo-morphological analysis revealed that renin inhibition effectively prevented the development of vulnerable plaques in 2K1C-ApoE-/- mice. These results confirm the beneficial effect of RAS blockade on atherogenesis and reveal the potential of renin inhibitors to stabilize atherosclerotic lesions.

P1848 ^{18}F-fluorocholine images macrophages in atherosclerotic plaques

C. Matter[1], M.T. Wyss[2], P. Meier[1], N. Spaeth[2], B. Weber[2], T.F. Luscher[1], A. Buck[2], P.A. Kaufmann[3]. *[1]University of Zurich, Cardiovascular Research, Zurich, Switzerland; [2]University Hospital, Nuclear Medicine, Zurich, Switzerland; [3]University Hospital, Nuclear Cardiology, Zurich, Switzerland*

Background: Most of the current imaging modalities of atherosclerosis visualize plaque morphology. An important additional aspect of plaque imaging is visualization of enhanced lesion metabolism which has been investigated with 18F-fluorodeoxyglucose (18F-FDG). An increased choline uptake has also been identified in tumor cells and was related to an upregulation of choline kinase and choline transport mechanisms. Recently, we reported enhanced uptake of 18F-fluorocholine (18F-FCH) into macrophages surrounding an abscess. As macrophages are important determinants of plaque vulnerability, 18F-FCH might be a useful tracer to characterize vulnerability of a plaque.
Methods and Results: Thus, we injected 18F-FCH or 18F-FDG intravenously into atherosclerotic apolipoprotein E null (ApoE-/-) mice (n=5). En face analysis of aortas isolated 20 min after injection of the radiotracers demonstrated a selective uptake of 18F-FCH which was 4.9-fold higher in plaque areas compared to areas without lesions. Comparisons between fat staining and autoradiographies after injections of 18F-FCH revealed a highly significant correlation ($r=0.989$, $P<0.0001$). In contrast, 18F-FDG uptake correlated poorly with plaques ($r=0.098$, $P<0.707$). Histological analyses of cross sections 20 min after coinjections of 18F-FCH and 14C-FDG confirmed superior plaque imaging with 18F-FCH that colocalized with macrophages as documented by anti-CD68 staining (n=3): Signal-to-noise ratios of radiotracer uptake on cross sections were 3.5 for 18F-FCH, 2.9 for 18F-FDG and 2.5 for 14C-FDG.
Conclusions: 18F-FCH identifies murine plaques more precisely than 18F-FDG. Its enhanced uptake in macrophages may render this tracer a promising candidate for imaging vulnerable plaques.

P1849 Repetitive hypoxia decreases matrix metalloproteinase and increases PAI-1 levels in human monocyte derived macrophages

A. Death[1], J.D.L. Lattimore[2], K.C.Y. McGrath[1], T. Tsatralis[1], S. Nakhla[1], I. Wilcox[2], D. Celermajer[2]. *[1]Heart Research Institute, Sydney, Australia; [2]Royal Prince Alfred Hopsital, Cardiology, Sydney, Australia*

Purpose: Obstructive sleep apnoea (OSA) is associated with systemic hypertension and (most likely) coronary artery disease. Both of these pathologies involve extensive matrix remodelling. An underlying problem in OSA is sustained and/or repetitive hypoxia at the level of the vessel wall and vascular cells. We investigated whether repetitive and sustained hypoxia affects matrix remodelling by studying macrophage protease activities and expression.
Methods: Human monocyte-derived macrophages were cultured for 8-10 days and then exposed to 30 minute cycles of alternating 2%/21%, or constant 2% sustained hypoxic conditions, or to control conditions (constant 21% oxygen) for 48 hours. mRNA was measured by real-time PCR, protein by western (PAI-1), zymography (MMP-9) or ELISA (TIMP-1).
Results: Hypoxic conditions were confirmed by a decrease in HIF mRNA levels (50% down-regulation, $P<0.001$), as measured by real-time RT-PCR. Using gelatin zymography, we next determined that activity of the major arterial macrophage protease, metalloproteinase-9 (MMP-9), was decreased by repetitive (88±3%, $P<0.05$) and sustained 2% (61±11%, $P<0.05$) oxygen conditions, compared with control levels (100±3%). The decrease in MMP-9 activity correlated with a corresponding increase in the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1), under both repetitive (125±5%, $P<0.05$) and sustained 2% (126±10%) oxygen conditions. We also showed that the plasmin system is dysregulated by hypoxia with repetitive and sustained 2% oxygen conditions increasing plasminogen-activator inhibitor (PAI)-1 levels (by 125±5% and130±4%, respectively, $P<0.01$) as measured by western analysis.
Conclusions: Our findings thus show repetitive and sustained hypoxia lead to significantly altered expression of the matrix turnover system, which may contribute to the association between OSA and cardiovascular disease.

P1850 Bone morphogenetic proteins and inhibitory smads regulate cellular phenotype in atherosclerosis

A. Qasim[1], N.G. Figg[2], P.L. Weissberg[2], C.M. Shanahan[2]. *[1]Cambridge, United Kingdom; [2]University of Cambridge, Division of Cardiovascular Medicine, Cambridge, United Kingdom*

Pathological vascular smooth muscle cell (VSMC) and bone marrow stromal cell (BMSC) phenotypes contribute to calcification and lipid accumulation in atherosclerosis. We and others have previously shown the influence of transforming growth factor beta superfamily members including bone morphogenetic proteins (BMPs) on VSMC and BMSC differentiation. Signal transduction for this process is through the Smad family of intracellular proteins, and is regulated by the inhibitory Smads 6 and 7.We investigated the role of BMPs and I-Smads in human VSMC and BMSC differentiation.
In vitro VSMCs and BMSCs responded to osteogenic differentiation medium (ODM) with calcification and increased alkaline phosphatase (AP) activity. BMP-2 stimulation also caused calcification in VSMCs and BMSCs cultured in 1% foetal calf serum (FCS), but not in 10% FCS. Adenoviral overexpression of Noggin, an extracellular BMP inhibitor found in serum that binds directly to BMPs 2, 4 and 7, blocked the osteogenic effects of ODM on BMSCs and VSMCs.
Adenoviral Smad 6 overexpression inhibited calcification and abolished the rise in AP activity of VSMCs and BMSCs in ODM ($p<0.01$). Oil red-O staining showed that Smad 6 overexpression led to lipid accumulation in cytoplasmic vacuoles. In BMSCs this was associated with a significant rise in adipogenic markers (Western blot) PPAR-gamma, CEBP-alpha, SREBP-1 and adipsin; a fall in smooth muscle markers a-smooth muscle actin and calponin; and reduced expression of the osteogenic transcription factor cbfa-1. The effects on VSMCs were less marked with increased SREBP-1 and adipsin expression. Smad 7 transduction partially inhibited the osteogenic effects of ODM, consistent with partial inhibition of bone morphogenetic protein (BMP) signalling. Immunohistochemistry showed high levels of I-Smad expression in VSMCs in normal arteries, with a significant reduction in I-Smad levels in VSMCs in atherosclerosis ($p<0.01$).
These findings demonstrate the importance of BMP signalling and I-smad fucntion in regulating VSMC and BMSC phenotype, and suggest that reduced I-Smad expression in VSMCs in atherosclerotic arteries contributes to their pathological differentiation.

P1851 Association of serum soluble heat shock protein 60 with carotid atherosclerosis-clinical significance determined in a follow-up study

K. Mandal[1], Q. Xiao[2], F. Oberhollenzer[3], J. Willeit[4], Q. Xu[2], S. Kiechl[4]. *[1]London, United Kingdom; [2]St George's Hospital Medical School, Cardiological Sciences, London, United Kingdom; [3]Hospital of Brunneck, Department of Internal Medicine, Brunneck, Italy; [4]University of Innsbruck Medical School, Clinics of Neurology, Innsbruck, Austria*

Background: Previous work has shown heat shock protein 60 (HSP60), a mitochondrial protein, to be present in circulating blood and its increased levels to be associated with atherosclerosis. The present follow-up study was designed to further scrutinize this association and assess their value in predicting development and/or progression of lesions in the same population.
Methods: To explore the association of soluble HSP60 (sHSP60) with progressive atherosclerosis, we conducted a population-based follow-up study with 684 subjects aged 40-79 years. All participants were subjected to serial (5 yearly, 1995-2000) measurement of sHSP60 levels, ultrasonography to assess carotid atherosclerosis and evaluation of other cardiovascular risk factors.
Results: Our data confirm the consistency of sHSP60 levels in the population

over a 5-year observation period (r=0.40, p<0.001). Circulating sHSP60 levels were significantly elevated in subjects who, developed new plaques (OR-1.55, 95%CI 1.12-2.14; p=0.009) or showed progression of early carotid atherosclerotic lesions (OR-1.26, 95%CI 1.04-1.54; p=0.02). Multiple logistic regression analysis showed this association to be independent of age, sex and other cardiovascular risk factors. We were able to show a positive correlation between sHSP60 and markers of infection, including anti-LPS antibodies (r=0.28, p<0.001), anti-HSP65(mycobacterial) antibodies (r=0.27, p<0.001), anti-HSP60(human) antibodies (r=0.26, p<0.001), anti-chlamydia IgG (r=0.07, p=0.08) and anti-CMV antibodies (r=0.09, p=0.02). These associations were consistently seen, both in 1995 and 2000 evaluations. Furthermore, presence of laboratory/clinical evidence of chronic infection enhanced the predictive significance of sHSP for early progressive atherosclerosis. Odds ratio of sHSP60, for incident carotid atherosclerosis was 2.0 (model adjusted for age, sex, and baseline atherosclerosis) which increased to 4.2 (multivariate adjustment), when high sHSP60 coexisted with chronic infections.

Conclusion: These findings, confirm a sustained presence of sHSP60 in subjects with early progressive carotid atherosclerosis. This possibly indicates the involvement of sHSP60 in activating proinflammatory processes associated with early atherogenesis and could be used as a marker for disease progression.

P1852 (W) Oxidised LDL correlates with interferon regulatory factor 1: a link between oxidative stress and macrophage inflammatory response involving PPARgamma

P. Holvoet[1], D. Dekeyzer[2], M. Doukoure[3], E. Deridder[2], K. Bishay[3], W. Verreth[2], N. Benhabiles[3], G. Marguerie[3]. [1]*CEHA, Leuven, Belgium;* [2]*Katholieke Universiteit Leuven, CEHA, Leuven, Belgium;* [3]*Clinigenetics, Nimes, France*

Background: We have demonstrated a relation between the metabolic syndrome and high oxidized LDL that predicted risk of future MI. Macrophages oxidize LDL that induces a macrophage inflammatory response. It is not clear which genes in macrophages mediate these processes in vivo.

Methods and Results: We isolated macrophages, by laser capture, from porcine coronary plaques: seven type I, eight type II, and five type III lesions according to the Stary classification. We compared gene expression in macrophages with that in monocytes on microarray. Out of 1659 deregulated genes in macrophages, 43 genes correlated with plaque complexity, and nine of these correlated with oxidized LDL. The interferon regulatory factor 1 (IRF1) that regulates the macrophage response in host defense was the strongest independent covariate of oxidized LDL. IRF1 correlated with genes involved in monocyte chemotaxis and proliferation; macrophage differentiation; LDL aggregation and oxidation; foam cell formation; and inflammatory response. IRF1 expression was 4-fold higher in RNA extracts of complex human plaques, compared to control monocytes. We confirmed microarray data with quantitative RT-PCR. Oxidized LDL correlated negatively with superoxide dismutase (SOD1), an important inhibitor of the oxidation of LDL. We investigated the relation between IRF1, SOD1 and the oxidation of LDL further in obese, hyperlipidemic, diabetic (DKO) mice that show accelerated atherogenesis and impaired cardiac function as the consequence of high oxidative stress and inflammation. Compared to lean mice, IRF1 expression was higher in the aortic arch of DKO mice. Diet-restricted induced weight-loss in these mice was associated with lower oxidative stress and inflammation, resulting in inhibition of atherosclerosis. Weight-loss was associated with lower IRF1 and higher SOD1 expression. Because we observed a negative correlation between IRF1 and SOD1 expression, we searched for a molecular mechanism. PPARgamma expression, that correlated negatively with plaque oxidized LDL, correlated positively with SOD1 and negatively with IRF1.

Conclusion: Oxidized LDL correlated positively with IRF1 that mediates an atherogenic inflammatory response in macrophages. It correlated negatively with SOD1, a predictor of infarct size in man. In aggregate, our data support a molecular mechanism of positive regulation of SOD1 by PPARgamma that also could sequester IRF1 and thereby inhibit several atherogenic processes regulated by IRF1 and induced by oxidized LDL.

CMR: ATRIA, VALVES AND CORONARIES

P1853 Phase contrast magnetic resonance imaging as an accurate tool of atrial septal defect sizing: a comparison with transoesophageal echocardiography

S.P. Chin[1], T.K. Ong[1], R. Annuar[2], K.H. Sim[1], C.K. Liew[1], H.B. Liew[1], W.L. Chan[1], S. Hasri[3]. [1]*Sarawak General Hospital, Cardiac Department, Kuching, Malaysia;* [2]*University Malaysia Sarawak, Faculty of Medicine and Health Science, Kuching, Malaysia;* [3]*National Heasrt Institute, Paediatric Cardiology, Kuala Lumpur, Malaysia*

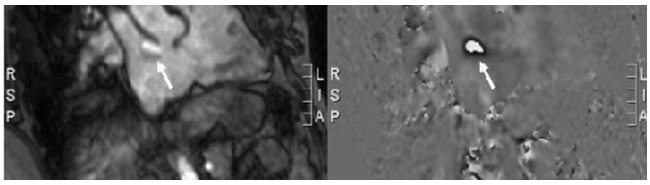
Background: trans-oesophageal echocardiography (TOE) is a trusted method of sizing atrial septal defects (ASD) prior to percutaneous closure but is invasive, uncomfortable and may carry a small risk of morbidity and mortality. Magnetic resonance imaging (MRI) may be useful non-invasive alternative in such patients who refuse or are unable to tolerate TOE and may provide additional information on shape of ASD.

Objective: to validate the accuracy of ASD sizing by MRI compared to TOE.

Method: 12 patients (mean age 30 years; range 11-60) scheduled for ASD closure underwent TOE, T2-weighted spin-echo MRI (T2W-MRI) in 4 chamber and sagittal views and Phase-Contrast MRI (PC-MRI) with reconstruction using the two orthogonal planes of T2W images as planning. The average of 3 of the longest measurements for all imaging modalities was calculated for each patient.

Results: mean maximum ASD length on TOE 18.8±4.6mm. Mean length by T2W-MRI imaging 20.0±5.0mm. Mean length by PC-MRI 18.3±3.6mm. There is significant correlation between TOE with T2W-MRI and PC-MRI (Pearson r=0.69, p=0.02 and r=0.59; p=0.04 respectively). The mean difference between TOE and T2W-MRI was -1.2mm [95%CI -3.7,1.3] and between TOE and PC-MRI was 0.5mm [95%CI -1.9,2.9]. Bland-Altman analysis also determined general agreement between both MRI methods and TEE. The ASDs were egg-shaped in 2 cases, circular in 1 patient and oval in other patients.

Conclusions: ASD sizing by MRI using T2W and Phase-Contrast protocols correlated well with TOE estimates. PC-MRI provides additional information on ASD shapes.



Phase-contrast imaging of ASD.

Diagram: [left] Phase-contrast imaging of ASD (white arrow) in planar orientation and [right] after flow velocity encoded reconstruction.

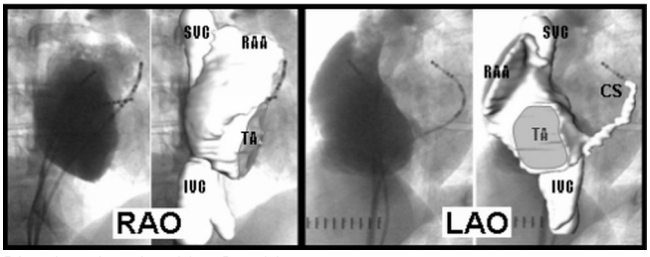
P1854 MRI-based 3D modelling of the right atrium allows for pre-procedural ablation planning

J. Ector[1], S. De Buck[2], S. Dymarkowski[3], J. Bogaert[3], F. Maes[2], H. Heidbuchel[1]. [1]*UZ Gasthuisberg, Cardiology, Leuven, Belgium;* [2]*UZ Gasthuisberg, ESAT, Leuven, Belgium;* [3]*UZ Gasthuisberg, Radiology, Leuven, Belgium*

Background: Three dimensional (3D) models of the left atrium are frequently used as a roadmap for atrial fibrillation ablation. Similar 3D models of the right atrium (RA) might enhance mapping and ablation in right-sided procedures, but are difficult to create due to incomplete filling of the right atrium with contrast agent. We wanted to develop an approach to 1) create detailed 3D models of the RA and 2)integrate these models with fluoroscopic images for online ablation assistance.

Methods: Cardiac MRI images without gadolinium contrast were acquired in 39 pts referred for ablation. A balanced fast-field MRI sequence (slice thickness 6 mm) was acquired in 3 orthogonal planes during different breath holds in all patients. In 11/39 pts, this basic sequence was compared to a 3D MRI acquisition sequence with 0,75 mm slice thickness and respiratory gating. 3D models were created by manual contouring of the endocardial cavity. Contours were cross-checked in other imaging planes to verify correct delineation. Integration of 3D models in the fluoroscopic framework was achieved using in-house developed software.

Results: The 3D MRI sequence was superior to the basic MRI sequence in visualising fine anatomical structures. A Eustachian valve >10 mm on angiography was visualised in 3/11 pts with an available 3D MRI sequence but could not be seen in models of the same patients based on the basic sequence. Based on the 3D model, a difficult coronary sinus (CS) catheterisation was predicted in 3/11 pts. In two of them, CS catheterisation was only possible using a special guiding sheath.



RA angiography and overlying 3D model

Conclusions: We developed software, acquisition and modelling algorithms to create detailed 3D models of the RA. They allow for pre-procedural planning and may facilitate complex ablation cases.

P1855 3D assessment of left atrial and ventricular volume throughout the cardiac cycle with magnetic resonance imaging

T. Germans, R. Nijveldt, A.M. Beek, M.J.W. Goette, A.C. van Rossum. *VU University Medical Centre, Cardiology Department, Amsterdam, Netherlands*

Background: Left atrial (LA) volume and function reflect diastolic filling properties of the left ventricle (LV), though volume measurement is challenging due to its complex geometry. With cine MRI, LA and LV volumes can be assessed throughout the cardiac cycle.
Aim of study: To determine LA volumetric dynamics throughout the cardiac cycle and its relation to LV volume change.
Methods: 12 asymptomatic volunteers were investigated. Cine images were acquired of LA and LV with a temporal resolution of 47 milliseconds with a 1.5 Tesla MRI-scanner. LV and LA contours were drawn semi-automatically and reconstructed into 3D volumes. Volumes were indexed to body surface area.
Results: Mean age was 32.4 years (23.9-51.6). Mean LA maximum volume was 53 ml/m^2 (34-64) and LV end diastolic volume was 105 ml/m^2(74-129). Ratio between maximum LA and LV volume was 0.5(0.41-0.73). Mean LV stroke volume (LVSV), which is comprised of LA reservoir volume, conduit volume and booster pump volume was 60 ml/m^2(40 -84), see figure 1. LA reservoir volume contributed 35 percent (27%-47%), left atrial conduit volume 41 percent (23%-53%) and booster volume 22 percent (13-35%) to total LVSV.

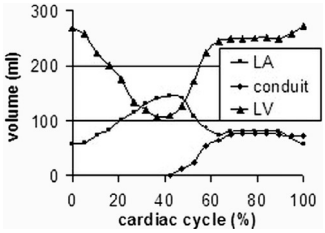


Figure 1

Conclusions: Assessment of left atrial and left ventricular volume throughout the cardiac cycle is feasible and may be a sensitive indicator of diastolic function.

P1856 Etiologic evaluation of ischaemic mitral regurgitation using cardiac MRI

E.Y. Choi[1], Y. Jang[1], Y.G. Ko[1], S.J. Rim[1], J.W. Ha[1], N. Chung[1], B.W. Choi[2]. *[1]Yonsei Cardiovascular Center, Cardiology Division, Seoul, Korea, Republic of; [2]Yonsei Cardiovascular Center, Radiology, Seoul, Korea, Republic of*

Background: we intended to evaluate the 3 dimensional geometric changes and the effect of revascularisation in patients with ischaemic mitral regurgitation (IMR) using cardiac magnetic resonance imaging (MRI).
Methods: twenty-three patients with IMR, 10 patients with dilated cardiomyopathy with MR (DCM-MR), and 7 control subjects were enrolled. Haemodynamic indices, severity of MR, geometric parameters of mitral apparatus and myocardial viability were evaluated in all patients and re-evaluated 6 months after revascularisation in IMR patients.
Results: mitral tenting area (TAA) (334.1±111.7 mm^2 vs. 222.9±123.0 mm^2, p=0.16), sum of tenting angle(TA) (72.9±12.9 ° vs. 51.5±11.1°, p<0.001) at mid-systolic phase were increased in IMR patients compared with DCM-MR. In IMR, MR severity was positively correlated with sum of tethering length (r=0.522, p=0.011), LVESV (r=0.551, p=0.006), TAA(r=0.613, p=0.002) and TA(r=0.713, p<0.001). Among 10 patients with viable myocardium, who had been revascularised without surgical repair of mitral apparatus, MR severity was decreased (28.3±10.4% vs. 16.5±7.6%, p=0.009) in 7 patients as decrease of sum of tethering distance(51.2±13.9 mm vs. 40.2±9.1mm, p=0.034), tenting area (299.2±93.8 mm^2 vs. 215.0±63.6 mm^2, p=0.036) and sum of tenting angle (72.9±12.9 ° vs 56.2±14.8 °, p=0.015) at 6 months after revascularisation.
Conclusion: IMR was related with geometric change in the mitral apparatus. Cardiac MRI can be an effective tool for evaluating these geometric changes and making treatment plan.

P1857 A hybrid approach for quantification of aortic valve stenosis using cardiac magnetic resonance imaging and echocardiography: comparison to right heart catheterisation and standard echocardiography

D. Haghi, T. Suselbeck, S. Fluechter, G. Kalmar, J.J. Kaden, T. Poerner, M. Borggrefe, T. Papavassiliu. *University Hospital Mannheim, Cardiology Department, Mannheim, Germany*

Background: Doppler echocardiography has gained widespread clinical acceptance as the standard method for evaluation of aortic stenosis, but poor acoustic windows, heavy calcification or flow acceleration in the left ventricular outflow tract may lead to inaccurate assessment of aortic valve area (AVA). To find an alternative to the standard continuity equation for calculation of AVA (method A), we replaced Doppler-derived stroke volume by right heart catheterization-derived stroke volume (method B) and cardiovascular magnetic resonance (CMR)-derived stroke volume (method C) and compared the results.
Methods: 20 consecutive patients with aortic stenosis admitted for right heart catheterization underwent transthoracic echocardiography and CMR within a time period of 3 weeks. Additionally, continuous-wave Doppler spectra of the aortic valve were acquired during catheterization and following CMR.
Results: There was no statistically significant difference for mean AVA between the three methods. Mean AVA was 0.88 ± 0.25 cm^2 by method A, 0.82 ± 0.23 cm^2 by method B and 0.84 ± 0.21 cm^2 by method C (p not significant). Mean difference between methods A and B was 0.01 cm^2 and the limits of agreement were -0.35 to 0.37. Mean difference between methods A and C was -0.01 cm^2 and the limits of agreement were -0.36 to 0.34. Mean difference between methods B and C was -0.02 cm^2 and the limits of agreement were -0.35 to 0.31.
Conclusion: The hybrid method for determination of AVA using CMR is an excellent alternative to the standard continuity equation or the hybrid method using right heart catheterization.

P1858 Contrast enhanced magnetic resonance imaging: a novel approach for identifying the infarct related artery in patients with non-ST elevation myocardial infarction

J. Heitner[1], I. Klem[2], J. Kevin Harrison[2], M. Manesh Patel[2], R.M.J. Robert M Judd[2], T.M.T. Thomas M Todoran[2], M.H.S. Michael H Sketch[2], R.J.K. Raymond J Kim[2]. *[1]New York Methodist Hospital, Cardiology, Brooklyn, United States of America; [2]Duke University, DCMRC, Durham, United States of America*

Background: Patients with non-ST elevation myocardial infarction (NSTEMI) often have multi-vessel disease and/or non-occlusive stenosis. Thus, determining the infarct related artery (IRA) using coronary angiography in NSTEMI patients can be difficult. Contrast enhanced magnetic resonance imaging (ce-MRI) has the ability to identify small areas of myocardial necrosis. The purpose of this study was to define whether ce-MRI improves the diagnostic ability of cardiac catheterization in identifying the IRA in patients with NSTEMI.
Methods: Patients with no prior history of coronary artery disease admitted to the coronary care unit with NSTEMI underwent ce-MRI prior to cardiac catheterization. Images were interpreted by readers blinded to patient care related decisions. The interventional cardiologists were blinded to results of the ce-MRI and documented each coronary vessel territory on a 17-segment model and assigned the IRA. The ce-MRI was interpreted blinded to angiography and also evaluated using this 17-segment model. The IRA was defined as the artery that supplied the territory with sub-endocardial infarction by ce-MRI. Ce-MRI was considered indeterminate if there was no evidence of infarction by ce-MRI or if there was >1 coronary artery territory of infarction.
Results: Forty patients, mean age 62 years, 51% female, were studied. Ten patients had insignificant coronary artery disease (<50% epicardial stenosis) by cardiac catheterization, 10 had 1-vessel disease, 10 had 2-vessel disease, and 9 had 3-vessel disease. Nineteen patients underwent revascularization (PCI, n=10; CABG, n=9). Cardiac catheterization identified the IRA in 19 of the 40 (48%) patients. Ce-MRI identified the IRA in a significantly larger number of patients 34 of 40 (85%), p<0.01. Of the 6 patients that were indeterminate by ce-MRI, 3 were due to inability to visualize the infarct, 1 was due to infarct in more than one coronary vascular territory, and 2 patients had a scar pattern consistent with infiltrative cardiomyopathy. The addition of infarct location by ce-MRI identified the IRA in 13 patients in which the IRA could not be determined by cardiac catheterization alone. Three patients underwent PCI of an artery that was not the IRA by ce-MR.
Conclusion: Use of ce-MRI to identify IRA in NSTEMI patients may be a novel approach to help guide appropriate coronary revascularization strategies.

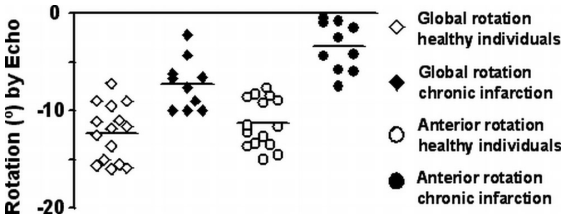
ECHOCARDIOGRAPHY, DOPPLER

P1859 Regional myocardial rotation by speckle tracking echocardiography is a powerful method for assessment of ischaemic dysfunction

T. Helle-Valle[1], T. Edvardsen[1], H.J. Smith[2], N.F. Osman[3], B.H. Amundsen[4], H. Ihlen[1], O.A. Smiseth[1]. *[1]Rikshospitalet University Hospital, Dep. of Cardiology, Oslo, Norway; [2]Rikshospitalet University Hospital, Dep. of Radiology, Oslo, Norway; [3]Johns Hopkins University, Baltimore, United States of America; [4]NTNU, Dep of Circulation and Medical Imaging, Trondheim, Norway*

Background and aims: we have recently demonstrated that speckle tracking echocardiography (STE) can quantify LV rotation in healthy individuals. The present study investigates if LV rotation by STE can serve as a diagnostic method in patients with ischaemic dysfunction, and if segmental rotation may be more specific and sensitive than global apical rotation.
Methods: in 15 healthy volunteers and 10 patients with old anterior infarctions, LV apical short-axis images were obtained by gray scale echocardiography and

rotation was derived from circumferential displacement of speckle patterns. MR-tagging served as reference method. Global rotation was estimated as average angular displacement of four regions of interest (ROI), automatically distributed around the myocardial wall. Regional rotation of the anterior segment was calculated as angular displacement of the anterior ROI. Rotation by MR-tagging was analyzed using Harmonic Phase (HARP).
Results: (x ± SD): global apical rotation by STE was lower in patients than in healthy individuals (12.3 ± 2.9° vs. 7.3 ± 2.6°, p = 0.0040, sensitivity = 0.70 and specificity = 0.73). Regional differences between patients and healthy individuals were even more pronounced (11.3 ± 2.5° vs. 3.4 ± 2.5°, p < 0.0001, sensitivity = 0.90 and specificity = 1.0). Correlation between STE and MR-tagging was excellent (r = 0.93, p < 0.0001).

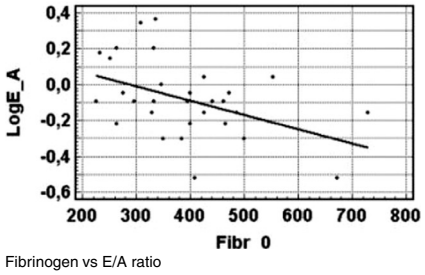


Conclusions: regional myocardial rotation by STE was a powerful marker of myocardial ischaemia, and was superior to global apical rotation. These results suggest that segmental analysis of rotation by STE may represent a new non-invasive modality to diagnose ischaemic heart disease.

P1860 Inflammatory markers are related to left ventricular dysfunction in first myocardial infarction treated with primary percutaneous intervention

J.D. Kasprzak[1], K. Kolodziej[2], M. Krzeminska-Pakula[2], L. Chrzanowski[2], M. Wraga[2], P. Lipiec[2], J. Drozdz[2]. [1]*Lodz, Poland;* [2]*Medical University, II Chair of Cardiology, Lodz, Poland*

Aim: Novel inflammatory and neurohumoral markers are recognized as prognostic factors in acute coronary syndromes. The aim of the study was to assess the relationship of initial levels of interleukins (IL) 1 and 10, monocyte chemotactic protein (MCP-1), apoptosis marker s-FASl, WBC and CRP with echocardiographic variables and NT-proBNP in patients with first myocardial infarction (MI) treated with primary PCI (pPCI).
Methods: 85 patients (20 females) aged 61±9 years admitted with first ST-elevation MI and treated with pPCI. IL-1, IL-10, MCP-1, sFASl, NT-proBNP, fibrinogen and CRP were sampled prior to intervention and echocardiogram was done on day 3. left ventricular (LV) mass and size, left atrial size, ejection fraction (EF) and mitral E/A ratio were measured and analyzed for relationships with biochemical markers.
Results: IL, sFASl and MCP-1 were not related with echocardiographic variables except for positive correlation of MCP-1 and LV mass (p=0.003, r=0.36). However, EF was significantly correlated with initial log NT-proBNP, WBC and (trend) fibrinogen (p=0.005, 0.04 and 0.078; r values -0.35, -0.23 and -0.32, resp.). Optimal multiple regression model included NT-proBNP and WBC (p=0.022 and 0.03; multiple r=-0.58, p=0.009). Log E/A significantly correlated with initial fibrinogen and logtransformed NT-proBNP, CRP (p=0.013, 0.039 and 0.011; r values -0.45, -0.27 and -0.30, resp.). In multivariate analysis only fibrinogen had significant negative relationship with E/A (graph).



Fibrinogen vs E/A ratio

Conclusion: Cytokines and apoptosis marker measured on admission do not correlate with early post-MI LV function. More stable, classic markers of inflammation are related to EF (WBC toghether with NT-proBNP); interestingly, the relationship of fibrinogen and E/A ratio was detected.

P1861 Euglycemic hyperinsulinemic clamping enhances myocardial wall motion in dysfunctional, but metabolically viable segments

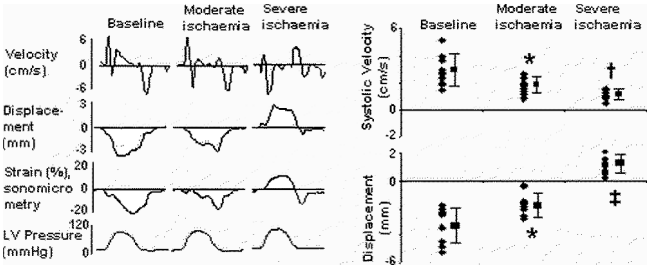
L.J. Klein[1], C.M.C. Van Campen[1], A.P. Van der Weerdt[1], G.T. Sieswerda[1], O. Kamp[1], A.A. Lammertsma[2], F.C. Visser[1]. [1]*VU University Medical Centre, Cardiology Department, Amsterdam, Netherlands;* [2]*VU University Medical Centre, PET Centre, Amsterdam, Netherlands*

Background: Euglycemic hyperinsulinemic clamping (EHC) is a technique used to improve myocardial glucose uptake before the injection of 18F-fluorodeoxyglucose (FDG) to determine viability with positron emission tomography (PET). Viability determined by this technique compares well to viability determined by low-dose dobutamine echocardiography. We investigated whether EHC enhances segmental wall-motion and whether it had a similar agreement as LDD with FDG-PET scanning.
Methods: Forty-five patients, referred for viability assessment, underwent LDD echocardiography and echocardiography during EHC procedure used to prepare the patient for the myocardial PET-scan. Myocardial segmental response during LDD and EHC was scored by a thirteen segment model. In the same thirteen segments, myocardial uptake of 18F-FDG was determined by visual analysis. Dysfunctional segments with improvement of contractility were considered to show contractile reserve (viability by LDD/EHC). Dysfunctional segments showing > 50% 18F-FDG-uptake were considered metabolically viable by PET.
Results: Three hundred sixty segments showed dysfunction by baseline LDD echocardiography and 364 by baseline GIK echocardiography. Of these segments, 160 (LDD) and 162 (GIK) showed contractile reserve, whereas 211 (LDD) and 214 (GIK) showed metabolic viability. Agreement was 71% by LDD vs. PET and 69% by GIK vs. PET. Sensitivity was 63% and 62%, respectively and specificity was 82% and 80% respectively. LDD and GIK echocardiography had an agreement of 94% (kappa 0.91) with each other.
Conclusion: GIK infusion determines contractile reserve as accurate as LDD infusion and has a similar agreement with 18F-FDG uptake > 50% by PET as LDD infusion. However, metabolic viability was present more frequently than contractile reserve in dysfunctional segments. Results are in line with previously published results.

P1862 Myocardial displacement imaging is superior to velocity imaging for grading of ischaemic dysfunction

H. Skulstad, S. Urheim, T. Edvardsen, E. Lyseggen, K. Andersen, H. Ihlen, O.A. Smiseth. *Rikshospitalet University Hospital, Department of Cardiology, Oslo, Norway*

Background and aim: since the LV apex is relatively stationary during the heart cycle systolic myocardial displacement, calculated as the velocity-time integral, is a measure of longitudinal shortening. The aim of this study was to compare myocardial displacement imaging and velocity imaging for grading of myocardial function during acute ischaemia.
Methods: in 10 anaesthetised dogs we reduced LAD flow about 50% (moderate ischaemia) and 100% (severe ischaemia). In the long-axis of the mid anterior LV segment we measured myocardial peak ejection velocity and systolic displacement by tissue Doppler imaging (TDI). Displacement was calculated as the time integral from end-diastole to end-systole and displacement towards apex was assigned negative values. Strain by sonomicrometry was used as reference method.
Results: peak systolic velocity as well as displacement decreased significantly ($p<0.01$) with ischaemia. Peak velocity during moderate and severe ischaemia showed only minimal difference and there was substantial overlap between individual values. Displacement, however, differentiated well between moderate and severe ischaemia. Systolic displacement and strain correlated better (r=0.92) than peak ejection velocity and strain (r=0.74).
Fig. left: representative traces. Fig. right: Individual values with mean ± SD. *$p<0.01$ vs baseline, †$p<0.05$ vs moderate ischaemia and ‡$p<0.01$ vs moderate ischaemia.



Figure

Conclusion: systolic displacement was superior to peak ejection velocity for grading of ischaemic dysfunction. This difference was explained by inclusion of the isovolumic contraction phase in the displacement analysis. Displacement imaging is a promising modality which needs further clinical testing.

P1863 Successful revascularisation can be monitored by SRI

M. Gori[1], J. D'hooge[2], P. Claus[2], L. Herbots[2], B. Bijnens[2], F.E. Rademakers[2], G.R. Sutherland[3]. [1]*Bergamo, Italy;* [2]*University Hospital Gasthuisberg, Department of Cardiology, Leuven, Belgium;* [3]*St George Hospital, Department of Cardiology, London, United Kingdom*

Background: ultrasound strain and strain rate imaging (SRI) has been proposed as a method to monitor functional changes during patient follow-up.
Aim: to test whether SRI is able to identify successful revascularisation in patients with single vessel coronary artery disease (CAD).
Methods: we prospectively enrolled 10 patients with angina pectoris having single vessel CAD (>70%) treated with PTCA. Myocardial Velocity Imaging data sets were taken one day before and 6 weeks after the procedure using a GE Vivid7. Data were acquired for individual myocardial walls at high frame rate (>180Hz) and analysed using dedicated software (SPEQLE) to extract end-systolic strain in an 18-segment model. The functional improvement, expressed as the change in longitudinal deformation, was correlated against longitudinal function pre-PTCA using linear regression and expressed as a Pearson's correlation coefficient.
Results: a good correlation (r=0.65; p<0.001) was found between pre-PTCA longitudinal function and functional recovery (Fig. 1).

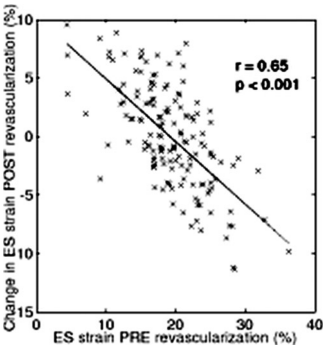


Figure 1

Conclusion: dysfunctional segments improved systolic function after successful PTCA while segments with high end-systolic deformation before revascularization normalised (i.e. decreased) systolic function after therapy. Most likely, this is due to a compensatory mechanism where normal segments compensate for the reduced function in adjacent ischaemic ones. SRI thus showed to be a reliable technique for therapy monitoring.

P1864 Improvement of regional myocardial diastolic function in patients with coronary artery disease undergoing percutaneous coronary intervention as assessed by strain rate imaging

H. Tanaka, H. Kawai, K. Tatsumi, T. Kataoka, T. Onishi, T. Mizoguchi, M. Yokoyama. *Kobe univercity graduate school of medicine, Cardiovascular and Respiratory Medicine, Kobe, Japan*

Background: percutaneous coronary intervention (PCI) has been known to improve global left ventricular diastolic dysfunction in patients with coronary artery disease (CAD), however the effect of PCI on regional myocardial diastolic function is unclear. Strain rate (SR) imaging can be used to analyze regional myocardial function objectively. The aim of this study was to investigate the effect of PCI on global and regional left ventricular diastolic function as assessed by SR imaging.
Methods: we studied 32 patients with CAD and myocardial ischaemia, who underwent successful PCI. Perfusion scintigraphy served as a gold standard to define regional myocardial ischaemia. We performed echocardiography to obtain SR imaging and transmitral flow velocity (E, A and E/A ratio) before and 12 to 48 hours after PCI and measured segmental peak SR in systole (SSR) and early diastole (ESR) in each of the 18 segments of the myocardium from the apical views.
Results: we could measure SSR and ESR in 401 segments (154 ischemic and 247 nonischaemic segments) of 480 possible segments obtained from 32 patients. There was no significant change in SSR with PCI in both ischaemic and nonischemic segments. ESR in the ischaemic segments was significantly smaller compared with ESR in the nonischaemic segments at rest (1.81±0.73/s vs 2.01±0.68/s, P<0.01). PCI caused significant increase in ESR in the ischemic segments from 1.81±0.73 to 2.28±0.91/s (P<0.0001), but no significant change in ESR in the nonischaemic segments (2.01±0.68/s vs 2.12±0.64/s). There were no significant changes with PCI in E, A or E/A ratio in the entire group. However when patients was dichotomised into two groups according to the magnitude of changes in ESR in the ischemic segments with PCI, E and E/A ratio were significantly increased in patients with more increase in ESR in the ischemic segments.
Conclusions: the results of this study suggested that regional myocardial relaxation in the ischaemic segments was reduced at rest and augmented after PCI in patients with CAD, and that the improvement of left ventricular early diastolic filling was associated with the magnitude of improvement of regional myocardial relaxation.

P1865 E/Em is strongly associated with B-type natriuretic peptide levels in patients with acute myocardial infarction

C. Papadopoulos, E.G. Dalamaga, T.D. Karamitsos, G. Giannakoulas, M. Anifanti, H.I. Karvounis, G.E. Parharidis, G.E. Louridas. *AHEPA University Hospital, 1st Dardiology Department, Thessaloniki, Greece*

The ratio of early transmitral flow velocity (E) to early diastolic mitral annulus velocity (E/Em) has recently been shown to be an accurate noninvasive predictor of elevated left ventricular (LV) filling pressure early after acute myocardial infarction (AMI). Additionally plasma B-Type Natriuretic Peptide (BNP) has evolved as a powerful predictor of survival in this clinical setting.
Aim: The present study was designed to investigate the possible association of these two specific indices early in the course of the post-infarction period.
Methods: Forty-nine patients (mean age 58±12, 42 males) with a first anterior ST segment elevation AMI, who underwent successful (angiographically documented) reperfusion, with thrombolysis, angioplasty or surgery, comprised the study population. At discharge, Color Tissue Doppler Imaging was performed to assess the systolic (Sm) and early diastolic (Em) mitral annulus velocity. Conventional Doppler echocardiography was used to evaluate E, E/A ratio, Decceleration Time and the Myocardial Performance Index. Two-dimensional echocardiography was undertaken to measure Ejection Fraction, LV End-Systolic and End-Diastolic Volume index, using Simpson's formula and finally Left Atrial size and the Sphericity index. Additionally BNP plasma levels were recorded at the same day, using a specific commercially available immunoassay. E/Em was reassessed at 3 months follow-up. Pearson's correlation coefficient was used to correlate E/Em with BNP. Finally a multivariable linear regression analysis was performed in order to estimate which of the obtained parameters were the major predictors of BNP levels.
Results: There was a statistically significant positive correlation between E/Em and BNP levels at baseline (R=0.509, p=0.013) that remained unaffected 3 months following discharge (R=0.759, p=0.018). Additionally, regression model analysis revealed that E/Em (t=24.4, p<0.001), CPK MB levels (t=4.01, p=0.02), Sm (t=-4.00, p=0.02) and LV End-Systolic Volume index (t=3.38, p=0.043) were the most significant predictors of BNP levels.
Conclusions: E/Em is strongly associated with BNP levels in patients with acute myocardial infarction. Measurement of this index may assist in the risk stratification of patients in this setting.

P1866 Can reperfusion be predicted by acute thickening of the at risk myocardium in STEMI? Full pressure vs pressure limited reperfusion

E. Merli[1], S. Sutcliffe[2], T. Karu[2], A. Baltabaeva[2], A. Marciniak[2], S.J. Brecker[2], N. Bunce[2], G.R. Sutherland[2]. [1]*St George's Hospital, Department of Cardiology, London, United Kingdom;* [2]*St George's Hospital, Department of Cardiology, London, United Kingdom*

Introduction: Experimental studies have shown that if an acute transmural myocardial infarction is reperfused at full pressure there is an immediate and persisting increase in end-diastolic wall thickness due to massive intramural oedema with the amount of oedema inversely related to the % residual stenosis in the infarcted related artery. To determine if these findings are paralleled in the clinical setting and whether the resultant myocardial substrate differs after PCI vs thrombolysis (the latter having a higher incidence of residual flow limiting stenosis in the culprit vessel), the following study was undertaken.
Methods: 44 consecutive patient with STEMI were enrolled. 20 patients underwent primary PCI (group 1) and 24 had thrombolysis (group 2). All thrombolysed pts routinely underwent Day 2 control angiography. Of these 13/24 required secondary PCI for residual vessel stenosis. All 44 patients underwent day 1-5 M-mode and 2-D grey scale echocardiography to determine the myocardial area at risk and evolution of wall thickness. The left ventricle was divided into 16 standard segments. Regional end-diastolic wall thickness (EDWT) was measured and EDWT in distal non infarct segments was compared to EDWT in infarct segments after thrombolysis and after primary or secondary PCI.
Results: A total of 704 segments were analysed: 232 infarct and 472 normal distal segments. Post-primary PCI 18/20 had TIMI 3 flow. Post-thrombolysis 15/24 had TIMI 3 flow, 4 TIMI 2, 1 TIMI 1 and 4 TIMI 0. Mean EDWT of infarct segments post thrombolysis compared to distal normal segments (Group 2) did not differ (p=n.s.) but was significantly thicker than the thin wall of segments with no reflow. However infarct zone wall thickness after PCI was significantly increased compared to distal normal segments (p<0,001). In the 13 thrombolysed pts with a flow limiting stenosis, there was a marked increase in EDWT following the secondary PCI (p< 0,001).
Conclusions: In STEMI, full-pressure reperfusion is characterised by increased EDWT, consistently measurable by echo. In contrast, pressure limiting reperfusion (typical for thrombolysis) results in normal EDWT. Persistently thin segments (<80% distal wall EDWT) represent areas of no-reflow. This confirms experimental data that PCI and thrombolysis can differ in their resultant myocardial substrate.

P1867 Prediction of left ventricular function after myocardial infarction: comparison of ejection fraction by Simpson method, tissue Doppler derived mitral annular velocities and global strain imaging

E.B. Kaya, N. Ozer, E. Ozturk, E. Atalar, K. Ovunc, S. Aksoyek, S. Kes, F. Ozmen. *Hacettepe University, Cardiology, Ankara, Turkey*

Background: The accurate assessment of left ventricular (LV) global and regional systolic function remains an important issue in clinical practice. Conventional echocardiographic techniques that are used to evaluate wall motion have several important limitations.
Aim: To evaluate the feasibility of 2-dimensional global longitudinal strain and mean mitral annular velocity for quantitative echocardiographic assessment of myocardial function and compare with conventional echocardiographic indeces of ventricular function, in patients with acute myocardial infarction (AMI)
Methods: Seventy-two patients (55 male, mean age: 59 ± 12) with acute myocardial infarction and forty age-matched healthy subjects were included in the study. Conventional echocardiography with tissue Doppler and strain and strain rate imaging was performed during initial hospital admission. Peak systolic myocardial velocities were recorded from 4 different sites on the mitral annulus corresponding to the septum, lateral, inferior and anterior sites of the left ventricle. In addition, global longitudinal strain (GLS) and GLS rate were calculated from 12 segments (apical 2 and 4 chamber views).
Results: The patients with AMI had a significantly reduced mean mitral annular systolic velocity compared with healthy subjects (5,52 ± 1,78 vs 9,80 ± 1,13 cm/s, P < 0,001). There was a good linear correlation between ejection fraction and the mean pik systolic mitral annular velocity (r = 0,73, p < 0,001). When patients were divided into 2 different groups with respect to ejection fraction = 50% or < 50%, a cut off value of mean systolic mitral velocity of = 8,01 cm/s had a sensitivity of 97,2%, specificity of 93,3%, positive predictive value of 97,2% and negative predictive value of 93,3% in predicting EF = 50%. Similarly, global systolic longitudinal strain and strain rate parameters were lower in patients with AMI (-11,23 ± 2,83% vs -19,11 ± 2,05%, P < 0,001 for GLS; 1,00 ± 0,05 vs 1,54 ± 0,07, P < 0,001 for GLS rate). There was also a good linear correlation between EF and GLS and GLS rate (r = 0,74, 0,69, p < 0,001). A cut off value of GLS = -15,35% had a sensitivity of 94,4%, specificity of 100% in predicting preserved left ventricular function in patients with acute myocardial infarction.
Conclusions: Mean mitral annular motion and mean myocardial systolic strain and strain rate parameters correlated well with the left ventricular ejection fraction. Thus quantification of global myocardial systolic function with these techniques improves evaluation of cardiac function after myocardial infarction.

P1868 Assessment of regional myocardial function after acute myocardial infarction in mice: a strain rate study

H. Thibault[1], L. Gomez[1], A. Bardet[1], N. Chavanis[1], M. Scherrer-Crosbie[2], M. Ovize[1], G.A. Derumeaux[3]. *[1]Faculté de médecine LYON Nord, EMIU N°0226, Lyon, France; [2]Massachusetts General Hospital, Boston, United States of America; [3]Lyon, France*

Background: The noninvasive assessment of murine myocardial function has drawn increasing interest. Recently, tissue Doppler imaging (TDI) has been demonstrated to be feasible to quantify regional myocardial function in mice. The objective of this study was to assess whether myocardial systolic velocities (Vs) and strain rate (SR) could accurately identify left ventricular (LV) dysfunction after distal left anterior descending coronary artery (LAD) occlusion.
Methods: Echocardiographic studies (13 MHz, Vivid 7, GE) were performed in 3 groups of adult wild type mice (2 months): 7 normal controls, 5 sham-operated and 19 distal LAD occlusion mice at 72 hour interval. TDI was obtained from short axis views (mid and apical level) in order to measure endocardial Vs (Vs endo, cm/sec, ROI: 0.2x0.2 mm) and SR (sec-1, ROI: 0.6x0.6 mm) in the anterior (AW) and posterior walls (PW)at frame rates > 300/sec.
Results: Myocardial velocities and SR were obtained in all mice with adequate tracings. Pre-operatively there was no significant difference in ejection fraction (EF, Simpson), Vs endo and SR between the 3 groups. After LAD occlusion, EF significantly decreased in infarcted mice (45±1.3% versus 78±1% in controls and 82±1.6% in sham, p<0.05). Vs endo significantly decreased both in the infarcted area (antero-apical segments) and in the remote area (mid PW) versus controls and sham at 72 hour echographic studies (table, * = p<0.05). At the opposite, SR significantly decreased only in the infarcted area but not in the remote area.

	Controls	Sham-operated	LAD-occlusion
Mid PW: Vs endo	3.2±0.5	3±0.4	1.7±1*
Mid PW: SR	34±7	30±6	23±5
Mid AW: Vs endo	-1.9±0.4	-1.9±0.4	-0.5±0.4*
Mid AW: SR	29±6	31±5	11±8*
Apex PW: Vs endo	2.8±0.3	2.7±0.5	1.2±0.4*
Apex PW: SR	26±4	27±4	12±5*
Apex AW: Vs endo	-1.7±0.2	-1.5±0.4	-0.25±0.4*
Apex AW: SR	20±3	25±4	4±8*

Conclusion: Myocardial velocities and SR can be measured noninvasively in mice using TDI. SR is superior to velocities in identifying necrotic segments after LAD occlusion.

P1869 Coronary flow velocity pattern after percutaneous coronary intervention by transthoracic Doppler echocardiography as a predictor of left ventricular function and in-hospital complication in AMI

Z.-P. Li[1], J. Feng[1], X.-H. Feng[1], W. Gao[2], J.-M. Mao[1]. *[1]Peking Universith Third Hospital, Department of Cardiology, Beijing, China; [2]Peking University Third Hospital, Cardiology department, Beijing, China*

Background: Recently, it was reported that the degree of microvascular injury and left ventricular function recovery during the chronic period can be predicted after treatment of the infarct-related artery based on the coronary flow velocity (CFV) pattern assessed using a Doppler guidewire. The aim of this study was to examine that the relationship of CFV pattern at 3 days after percutaneous coronary intervention (PCI) by transthoracic Doppler echocardiography (TTDE) and left ventricular function and in-hospital complication in acute myocardial infarction (AMI).
Methods: The study population consisted of 51 consecutive patients with a first anterior AMI successfully treated with PCI. We examined the left anterior descending coronary artery distal CFV pattern and wall motion score index (WMSI) and left ventricular ejection fraction (LVEF) at 3 days after PCI by TTDE. In accordance with previous findings, patients were divided into two groups based on diastolic deceleration time (DDT): DDT> 600ms(group A, n=21) and DDT=600ms (group B, n=30).
Results: Peak creatine kinase concentrations were higher in the group B than that in the group A (4284±3358U/L vs. 2156±1053U/L, P<0.05).WMSI were higher in the group B than that in the group A (1.56±0.18 vs. 1.32±0.14, P<0.01). LVEF were lower in the group B than that in the group A (50±5 vs. 56±5, P<0.01).All patients who died in hospital (n=2) were in group B. Congestive heart failure(CHF) and malignant arrhythmia were observed more frequently in the group B than group A(43% vs. 4.7% and 70% vs. 29%,P<0.05). Pericardial effusion were observed more frequently in group B than in the group A, too(50% vs. 14%, P<0.05).
Conclusions: These findings suggest that the CFV pattern at 3 days after PCI was correlated with left ventricular function; DDT=600ms was a marker of more complications in-hospital in AMI.

P1870 Flow-mediated dilation and gender in coronary artery disease – arterial size determinates gender differences in flow-mediated dilation

K. Mizia-Stec, Z. Gasior, M. Mizia, S. Gomulka, E. Jastrzebska-Maj, D. Jakubowski, W. Walkowicz, W. Skiba. *Silesian University School of Medicine, Department of Cardiology, Katowice, Poland*

Risk of atherosclerosis and its complications differs between male and female subjects. It probably results in gender differences of endothelial function reflected by endothelium-dependent vasodilation.
Aim: To compare flow-mediated vasodilatation (FMD) in males and females with CAD, and to determine potential factors influencing FMD.
Methods: 96 patients with stable CAD (CCS II-III): group A - 76 males (mean age: 60.1 ± 10 years), and group B - 20 postmenopausal females (mean age: 57.7 ± 10 years) were included into the study. Clinical data, pharmacotherapy, concomitant diseases, and FMD were all assessed. FMD was measured with high-resolution ultrasound as the percent change of brachial artery diameter (BAd) after a 3-minute occlusion (%FMD), and following the administration of 0.4 mg sublingual nitroglycerin (%NTG-MD).
Results: The %FMD was significantly decreased (p<0.05), and BAd was significantly increased (p<0.001) in males compared to females examined (Table 1). Clinical data, pharmacotherapy, concomitant diseases were comparable in the study groups.
In the CAD group %FMD was related to BAd (r= -0.462, p<0.001), BMI (r=0.300, p<0.05), and HDL-Ch (r= -0.257, p<0.05) in the univariate analysis, and BAd (r= -0.343, p<0.01) in the multivariate analysis. The NTG-MD correlated negatively with BAd (r= -0.573, p<0.001), and positively with EF (r=0.334, p<0.01) in the univariate analysis, and BAd (r= -0.288, p<0.05) in the multivariate analysis.

Table 1

	BAd (mm)	%FMD	%NTG-MD
Males	4.41 ± 0.6 **	8.9 ± 6.7 *	15.3 ± 9.6
Females	3.79 ± 0.5	12.9 ± 5.9	20.2 ± 12.3

* p<0.05, **p<0.001 vs Females

Conclusion: Males and females with CAD show differences in endothelium-dependent vasodilatation that seem to secondarily result from differences in the brachial artery diameter. Thus, regardless of gender FMD% values should be adjusted to the brachial artery diameter.

P1871 Relation between stress hyperglycemia and coronary flow reserve of non-culprit coronary artery in patients with acute myocardial infarction

Y. Takei, N. Tanaka, S. Kurohane, M. Manaka, T. Chikamori, K. Takazawa, A. Yamashina. *Tokyo Medical University, 2nd Department of Internal Medicine, Tokyo, Japan*

Background: Although stress hyperglycemia on admission is associated with increased mortality in patients with acute myocardial infarction (AMI), the mechanism is still unknown. The purpose of this study was to investigate the influence of stress hyperglycemia on coronary flow reserve (CFR) in the culprit and non-culprit coronary arteries after successful treatment for AMI.
Methods: Fifteen patients with AMI who had not been diagnosed as diabetic previous to their admission, were evaluated. Stress hyperglycemia was defined as a plasma glucose level on admission (Ad-Glu) of >140mg/dl. Fourteen days after successful coronary revascularization, CFR was measured by transthoracic Doppler echocardiography before and 1-hour after oral glucose loading. We divided the patients into two groups by their Ad-Glu (H group:>140mg/dl, n=8, N group: <140mg/dl, n=7).
Results: The CFR in the culprit coronary artery did not change significantly after glucose loading (H: 2.0±0.2 to 1.9±0.2; p=ns, N:2.4±1.1 to 2.4±0.9; p=ns, respectively). The mean diastolic velocities in the non-culprit coronary artery under the baseline condition during glucose loading was similar in both groups. The mean diastolic velocities in the non-culprit coronary artery under the hyperemic condition after glucose loading in the H group was lower than that in the N group (H: 36.4±1.6 cm/s. vs N:45.6±8.3cm/s, p=0.02). In the H group, CFR in the non-culprit coronary artery after glucose loading was significantly lower than that before glucose loading (from 2.1±0.2 to 1.8±0.2, p=0.01). Although CFR in the non-culprit coronary artery before glucose loading did not differ significantly between the two groups (H: 2.1±0.2 vs N: 2.2±0.1, p=ns), after glucose loading CFR in H group was lower than that in N group (H: 1.8±0.2 vs N: 2.1±0.2, p=0.02).
Conclusions: Acute hyperglycemia attenuated CFR in the non-culprit coronary artery in the H group. These results suggest that a reduced CFR in the non-culprit coronary artery during hyperglycemia might be one of the cause for death despite of successful treatment for AMI.

P1872 Transthoracic Doppler coronary flow in patients with anterior myocardial infarction undergoing rescue percutaneous coronary intervention: angiographic, function recovery, and clinical correlates

E. ElSharkawy[1], A. Zaki[1], A. Farah[1], M. Sobhy[1], M. Rashwan[2]. *[1]Faculty of Medicine, Cardiology, Alexandria, Egypt; [2]Alexandria, Egypt*

Background: Noninvasive Transthoracic Doppler recording is a feasible attractive method to characterize different coronary flow velocity (CFV) patterns, however, its clinical application in the setting of percutanous coronary intervention (PCI) need to be emphasized.
Objectives: To correlate CFV patterns of left anterior descending artery (LAD) with angiographic findings, and to determine its impact on left ventricular (LV) function recovery and clinical outcomes following rescue PCI in patients with anterior myocardial infarction.
Methods: 40 consecutive patients were studied 12 hours after PCI, using high frequency transducer and 2nd harmonic imaging of LAD, to measure diastolic flow data [peak and mean diastolic velocities (PDV and MDV), deceleration time (DEC), pressure half time (P1/2)], and to record retrograde systolic wave (RSW). Coronary angiographic data included epicardial flow grade (TIMI), and myocardial blush grade (MB). LV function recovery was determined by Doppler Tissue imaging of myocardial velocities within infarct segments. Clinical outcomes included in-hospital and three months major cardiac events (MACES).
Results: Following PCI 32 patients achieved TIMI flow grade III flow (80%), while 26 patients had MB grade III (65%). PDV and MDV were significantly higher in TIMI grade III (43.7±10.2 vs. 19.9±4.4 cm/sec p<0.014, and 20.41±7.8 vs. 11.32±4.92 cm/sec p<0.007 respectively), while DEC time and P1/2 time were significantly longer in MB grade III (383.96±82.36 vs. 174.24±62.92 msec p<0.001, and 134.1±38.18 vs. 76.9±15.49 msec p<0.01 respectively). RSW was recorded in 22 patients (55%). RSW correlated to lower grades of myocardial blush (MB grade 0-2) than TIMI flow(14/22 vs. 8/22 P<0.05), and associated with lower percent changes of myocardial velocities (41.18±57.81% vs. 160.25±109.69% p<0.01), as well as, higher incidence of MACES (6/22 vs. 0/18 p<0.01).
Conclusions: Noninvasive Transthoracic Doppler study of coronary flow provides intimate correlation to essential angiographic, functional, and clinical data in the setting of rescue PCI where coronary flow velocities correlated with epicardial flow grade, time intervals related to myocardial blush grade, and the presence of systolic retrograde wave carried a poor clinical outcome.

P1873 Transthoracic measurement of left coronary artery flow reserve improves the diagnostic value of routine dipirydamole-atropine stress echocardiogram

J.D. Kasprzak[1], P. Lipiec[2], P. Wejner-Mik[2], J. Drozdz[2], A. Plachcinska[3], J. Kusmierek[3], M. Krzeminska-Pakula[2]. *[1]Lodz, Poland; [2]Medical University, II Chair of Cardiology, Lodz, Poland; [3]Medical University, Dept. of Nuclear Medicine, Lodz, Poland*

Aim: Coronary flow reserve (CFR) of left interior descending (LAD) branch of the left coronary artery can be noninvasively studied using transthoracic Doppler echocardiography and vasodilator challenge. Usual CFR protocol with adenosine is, however, less efficient for wall motion abnormalities (WMA) assessment. We hypothesized that CFR in LAD can be effectively studied during peak phase of high-dose dipyridamole-atropine stress protocol (DIP)
Methods: We studied 64 patients (pts, age 58±9, range 36-77, 20 females) undergoing routine workup for myocardial ischemia using a rapid (0,84mg/kg over 4 min) infusion of DIP with atropine up to 1mg iv in negative cases. 20 pts had previous MI and mean CCS class was 2.4. All patients underwent coronary angiography and gated SPECT (55/64) as reference. CFR was measured without contrast enhancement during peak phase of DIP using 5MHz 7v3 probe (Siemens Sequoia 256C).
Results: Significant (≥50%) LAD disease was present in 42 pts, including 7 with total occlusion. CFR calculation was feasible in 53 pts (83%). 11 pts had undetectable distal LAD flow signal due to total occlusion in 6 cases or critical (95%) stenosis of LAD in 3 cases (specificity 81% for severe LAD disease). Recorded CFR ranged 1.3-4.1 (2.2±.7) corresponding with resting and peak LAD flow of 14-60 (28±9) and 29-119 (58±21)cm/s, respectively. Lower CFR was characteristic for significant LAD disease: 1.97±.62 vs 2.55±.57, p=0.0015 and correlated with LAD %stenosis: r=0.44, p=0.008. Optimal cutoff for 50% stenosis was CFR=<2.1 (ROC AUC 0.776, sens.68% and spec. 84%). There were no false positives with CFR=<1.8 and no false negative results in CFR. In 17 patients without WMA in LAD territory abnormal CFR identified LAD disease with 82% (14/17) positive predictive value. In WMA-negative DIP 6/9pts with disease LAD had abnormal CFR whereas in WMA-positive DIP 12/13 pts with normal LAD had normal CFR. Accuracy using either abnormal WMA or CFR as criterion for positivity increased from 75% to 85%. No test with both abnormalities was false positive for the detection of coronary disease.
Conclusions: CFR of LAD can be measured as an extension of routine DASE with success rate of 83% (most cases of recording failure correspond with critical LAD disease and resting WMA). The method is 74% accurate and significantly improves the detection of multivessel disease involving LAD even in studies without inducible WMA. This is translated into 10% gain in overall test accuracy.

P1874 Evaluation of left anterior descending coronary artery stenosis of intermediate severity using transthoracic coronary flow reserve and dobutamine stress echocardiography

P. Meimoun[1], J.C. Tcheuffa[2], V. Louzoun[2], S. Sayah[2], T. Benali[2], A. Luycx-Bore[2], H. Zemir[2], C. Tribouilloy[3]. *[1]CHU Compiegne, Service de Cardiologie, Compiegne, France; [2]CH Compiegne, Service de Cardiologie, Compiegne, France; [3]CHU, Service de Cardiologie, Amiens Sud, France*

Background: the physiological significance of left anterior descending artery (LAD) stenosis of intermediate angiographic severity is of clinical importance and difficult to assess non invasively. Assessment of coronary flow reserve (CFR) with transthoracic Doppler echocardiography (TTE) is a new tool and could provide in this setting a non invasive and rapid evaluation of stenosis severity.
Objective: to evaluate the value of CFR measurement determined by TTE, compared with dobutamine stress echocardiography (DSE), in the setting of LAD stenosis of intermediate angiographic severity.
Methods: 51 consecutive stable patients in sinus rhythm (33 men, 65±12 years, left ventricular ejection fraction 59±7%), without previous anterior myocardial infarction and with an angiographic proximal LAD stenosis of intermediate severity (56±8% QCA, one-vessel disease) were prospectively studied. Coronary flow velocity was measured in the distal part of the LAD by TTE, at rest and during continuous infusion of 0.14 mg/kg/mn of adenosine within 2 minutes, using a high frequency transducer, in the modified parasternal or 3 apical view. CFR was calculated as the ratio of hyperemic to basal mean (mean CFR) and peak (peak CFR) diastolic flow velocity. DSE was performed immediately after the adenosine test to assess ischemia in the LAD territory (% maximum predict heart rate = 94±8).
Results: adequate recording of CFR was possible in 46 patients. Of the 35 pts with a CFR=2 (peak CFR = 2.7 ± 0.6), DSE was normal in 34. Of the 11 pts with a CFR<2 (peak CFR = 1.7 ± 0.2),7 had an abnormal response with DSE, in the LAD territory. In this range of intermediate stenosis there was a poor correlation between % LAD diameter stenosisand CFR. In patients with positive DSE, CFR was 1.6 ± 0.2 compared to 2.7 ± 0.6 in patients with normal DSE (p<0.05). The sensitivity, specificity, positive and negative predictive values of TTE CFR for detecting ischemia on DSE were 88%, 89%, 64% and 97% respectively with an overall agreement of 89% between the two tests.
Conclusion: given its high negative predictive value, non invasive CFR could be a useful aid in reaching clinical decisions promptly at bedside, in patients with moderately severe lesion of the proximal LAD.

COMPUTERS IN CARDIOLOGY

P1875 Development of the filtering device based on adaptive and inherent scaling through synchronous frequency sampling

M. Mita[1], T. Ono[1], M. Hirano[2]. [1]*Iwate Medical University, Biomedical Engineering, Morioka, Japan;* [2]*Iwate College of Nursing, Takizawa, Japan*

The electrocardiogram (ECG) gives information not only about the activity of the heart but also about many organic activities. Finding specific information from its signal has very important meaning because it helps clinical diagnosis and treatment. We have developed a device for separating a cardiac signal and its baseline from a source signal. In this way, influence can be avoided on those overlapping frequency components.
Methods: This device is designed by the theory of a scaling filter based on adaptive and inherent scale through synchronous frequency sampling.
The block diagram of the device which is loaded with two FPGAs(Field Programmable Gate Array) is illustrated in Fig1. The one prepares for an adaptive scale recognizing the waveform of each cardiac signal, and the other decodes memory address in haste for adaptive and inherent scale as synchronous frequency sampling. It can process in parallel with real time.
Results: The filter based on adaptive and inherent scale through synchronous frequency sampling is implemented on the one board using by FPGAs. The device extracts cardiac signals and its baseline successfully on time. The high efficient coding from the scaling compresses the signal information less than 1/100 than that of crude samples. It reconstructs the source completely.

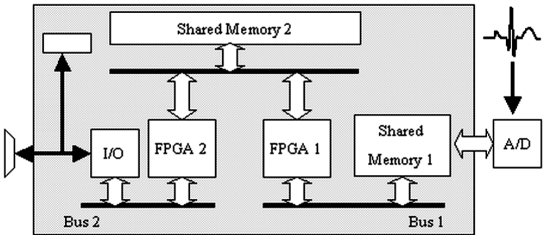


Figure 1. Block diagram of the device

Conclusion: Through this device, we can fetch the pathological signals from fluctuating signals with random noise and follow up those changes with longterm high efficiency recordings. A device we developed, is applicable to other fluctuating physiological signals in general.

P1876 Regulation of heteromeric Kir2.x channels by alpha-1a adrenergic receptors is based on inhibitory effects of novel PKC (nPKC) isoenzymes on Kir2.3 channel subunits

C.A. Karle[1], C. Kiesecker[2], D. Scherer[1], E.P. Scholz[1], M. Pirot[1], S. Kathofer[1], D. Thomas[1], E. Zitron[1]. [1]*Medical University Hospital Heidelberg, Department of Cardiology, Heidelberg, Germany;* [2]*Medical University Hospital Heidelberg, Department of Cardiology, Heidelberg, Germany*

Introduction: In the heart, the inwardly rectifying potassium current IK1 is essential to maintain the resting membrane potential. There is an increasing body of evidence that heteromeric assembly of Kir2.1, Kir2.2 and Kir2.3 potassium channels underlies a main part of this current. It has been demonstrated in human cardiomyocytes that activation of adrenergic alpha-1a receptors leads to an inhibition of IK1 currents. However, the molecular basis of this regulation has not been elucidated yet.
Methods: Human adrenergic alpha-1a receptors and Kir2.1, Kir2.2 and Kir2.3 channels were co-expressed in Xenopus oocytes and experiments were performed using two-microelectrode voltage-clamp.
Results: Activation of co-expressed adrenergic alpha-1a receptors had differential effects on Kir2.x channels in heteromeric composition: A pronounced inhibitory effect could only be observed in Kir2.1/Kir2.3 heteromers and Kir2.2/Kir2.3 heteromers, but not in Kir2.1/Kir2.2 heteromers. Thus, only heteromeric channels containing Kir2.3 channel subunits were sensitive to this regulation suggesting a central role of this channel.
The signal transduction pathways underlying this regulation were studied by the use of specific activators and inhibitors of protein kinases. We found that the effect of alpha-1a receptors on Kir2.3 channel subunits was mainly dependent on PKC and could be suppressed by PKC inhibitors staurosporin and chelerythrine. Moreover, an identical inhibitory effect could be induced by unspecific PKC activator PMA, but not by thymeleatoxin, a specific activator of conventional PKC isoenzymes (cPKC). In conclusion, this effect is probably mediated by novel PKC isoenzymes (nPKC).
Conclusion: Activation of adrenergic alpha-1a receptors has inhibitory effects on IK1 in native human cardiomyocytes. On the basis of our results, phosphorylation of Kir2.3 channel subunits by novel protein kinase C isoenzymes (nPKC) plays a central role in mediating this effect and leads to a current reduction in heterotetrameric Kir2 channels composed of different subunits. These findings elucidate molecular aspects of the adrenergic regulation of IK1 in the heart.

NEW PERSPECTIVES IN TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

1900 Echocardiocardiography improve accuracy of a clinical risk score in patients with suspected pulmonary embolism

J. Kjaergaard[1], B.K. Schaadt[2], J.O. Lund[2], C. Hassager[3]. [1]*University Hospital of Gentofte, Dept. of Cardiology, Hellerup, Denmark;* [2]*University Hospital of Gentofte, Dept. of Clinical Physiology, Hellerup, Denmark;* [3]*Rigshospitalet, Dept. of Cardiology B, Copenhagen, Denmark*

Background: Clinical risk score in combination with D-dimer measurements is a safe way of excluding pulmonary embolism (PE) but the positive predictive value is low. Trans-thoracic Echocardiography (TTE) is not a first-line diagnostic test in patients with suspected PE, although well established for risk stratification in patients with confirmed PE.
We aimed at evaluating the value of modern echocardiographic evaluation of the Right Ventricle (RV) in a consecutive series of 300 hemodynamically stable patients with suspected PE referred for ventilation/perfusion scintigraphy (V/Q scan).
Methods: 283 V/Q scans were of sufficient quality to allow interpretation by two expert readers as suggestive of PE or no PE. TTE with Doppler, 2D and Tissue Doppler Imaging (TDI) on the Philips SONOS 7500 and Q-lab software was done in standard views. Analysis of TTE, ECG and clinical data was blinded to the results of the V/Q scan.
Results: High vs. Low/Intermediate Wells clinical risk category (Odds Ratio, OR 3.0, p=0.08, Area under the ROC curve (AUC)=0.53) did not contain significant diagnostic information. Presence of RV strain on ECG, defined as negative precordial T-waves, SIQIIITIII or RBBB (OR 4.5, $p<0.0001$, AUC=0.65) and maximal D-dimer (OR 1.15, $p<0.0001$, AUC 0.79) had univariate diagnostic value. TTE in categories of
1. RV anatomi: RV end-diastolic diameter (RVED) (OR 3.0, $p<0.0001$, AUC=0.67),
2. RV pressure: tricuspid regurgitation maximal velocity (OR 4.2, $p<0.0001$, AUC 0.72) and acceleration time of the pulmonary flow (PA acc. time) (OR 0.96, $p<0.0001$, AUC=0.78) and
3. RV systolic performance: RV outflow tract fractional shortening (RVOT fs) (OR 0.95, $p<0.0001$, AUC=0.69), Tricuspid plane elevation (TAPSE) (0.50, $p<0.01$), AUC=0.62), RV Index of Myocardial Performance (OR 9.3, $p<0.002$, AUC 0.67) and Strain of the RV mid segment by TDI (OR 1.03, $p<0.003$, AUC 0.65) all held significant diagnostic information.
The RVED, the PA acc. time, and RVOT fs was chosen for the multivariate analysis by greater univariate AUC in each category. The multivariate analysis showed incremental value from adding ECG to Wells risk category, (AUC=0.65), D-dimer (AUC=0.83) and the echocardiographic parameters (AUC=0.88).
Conclusion: TTE provides incremental diagnostic information in patients with suspected PE, in addition to providing important prognostic information. TTE could be consideredas a part of the initial diagnostic strategy for the assessment of patients with suspected PE.

1901 Value of hand-carried ultrasound device in triage patients with suspected pulmonary embolism in emergency department

N. Mansencal[1], A. Vieillard-Baron[2], J.C. Farcot[1], M. El Hajjam[2], G. Dufaitre[1], D. Brun-Ney[2], P. Lacombe[2], O. Dubourg[1]. [1]*Hopital Ambroise Pare, Service de Cardiologie, Boulogne-Billancourt, France;* [2]*Boulogne, France*

Background: The diagnosis of pulmonary embolism (PE) remains difficult in emergency department. Hand-carried ultrasound device (HCU) has been proposed as an echocardiographic tool at the bedside. The aim of our study was to determine the value of HCU for triage patients with suspected PE referred to emergency department.
Methods: We prospectively studied 103 consecutive patients with suspected PE in emergency department. After a clinical probability scoring system and D-dimer assessment, 27 patients were excluded (considered as no PE) and the other 76 patients (mean age 62 $\pm$ 17 years) underwent venous ultrasonography, transthoracic echocardiography using HCU and helical CT. Patients with normal CT and with deep venous thrombosis or with high clinical probability underwent pulmonary angiography or lung scan. Each exam was obtained in a blind fashion. The diagnosis of deep venous thrombosis rested on venous incompressibility. Following echocardiographic parameters were systematically performed: (1) right to left ventricular end-diastolic area (RVEDA/LVEDA) ratio in apical four-chamber view with a cut-off value of 0.6; (2) assessment of right ventricular regional wall motion.
Results: Pulmonary embolism was present in 31 patients. The sensitivity (Se) and specificity (Sp) of venous ultrasonography was respectively 58% and 93%. The echocardiographic feasibility was 99% for RVEDA/LVEDA ratio and 97% for

right ventricular dysfunction assessment. The Se of RVEDA/LVEDA ratio and assessment of right ventricular regional wall motion assessment was 55% and 35% and the Sp was respectively 69% and 93%. The efficiency of echocardiography using RVEDA/LVEDA ratio was better in patients with dyspnea (Se 73%, Sp 67% vs. 42% and 74% in pts with chest pain). Using HCU, the Se and Sp of a combined strategy (echocardiography with RVEDA/LVEDA ratio and venous ultrasonography) was respectively 87% and 69%. The Se of this combined strategy was significantly improved as compared to venous ultrasonography alone (p = 0.01), even when the Sp was lower (p = 0.003). In patients with dyspnea or with high clinical probability, this combined strategy was particularly relevant with high sensitivities (respectively 95% and 100%) and specificities of 69% and 83%.
Conclusion: This prospective study suggests that HCU may be a reliable tool using 2D simplified criterion for triage patients with suspected PE in emergency department. This strategy is particularly relevant in patients presenting with dyspnea.

1902 N-terminal pro-BNP testing combined with echocardiography for risk stratification of acute pulmonary embolism

L. Binder[1], B. Pieske[2], M. Olschewski[3], A. Geibel[4], B. Klostermann[2], C. Reiner[2], S.V. Konstantinides[2]. *[1]Laboratory Chemistry, University of Goettingen, Goettingen, Germany; [2]Georg August University of Goettingen, Department of Cardiology and Pulmonology, Goettingen, Germany; [3]Biostatistics, University of Freiburg, Freiburg, Germany; [4]Cardiology and Angiology, University of Freiburg, Freiburg, Germany*

Natriuretic peptides BNP and NT-proBNP have recently emerged as promising parameters for risk assessment in acute PE. However, their positive predictive value is low, and the prognostic implications of NT-proBNP elevation alone are questionable. The present study investigated whether combination of NT-proBNP testing with echocardiography may identify both low-risk and high-risk patients with pulmonary embolism (PE). We prospectively included 124 consecutive patients with proved PE. All underwent echocardiography, NT-proBNP and cardiac troponin T and I testing on admission. The primary end point was in-hospital death or major complications. The median NT-proBNP concentration was 7,176 pg/mL in patients with an adverse clinical outcome as opposed to 864 pg/mL in those with an uncomplicated course ($p<0.001$). The NT-proBNP cut-off level of 1,000 pg/mL (determined by ROC analysis) had a high negative predictive value (95% for a complicated course, 100% for death), but neither NT-proBNP >1,000 pg/mL (OR, 1.82; 95% CI, 0.29-11.29; p=0.52) nor cardiac troponin T >0.04 ng/mL (OR, 3.23; 95% CI, 0.79-13.22; p=0.10) independently predicted an adverse outcome. Combination of NT-proBNP testing with echocardiography identified 3 major risk groups: 1) patients with low NT-proBNP levels (reference group; n=44); 2) high NT-proBNP and a negative echocardiogram (n=37); and 3) patients with a positive echocardiogram (n=30). Of note, an enlarged (dysfunctional) right ventricle on the echocardiogram was almost never (except for 3 patients; 2.4%) encountered in the absence of NT-proBNP elevation. Complication rates (primary end point) in the 3 groups were 4.6%, 13.5%, and 36.7% respectively, and mortality rates 0, 0, and 16.7% respectively. Multiple logistic regression showed that a positive echo was associated with a 12-fold elevated risk of an adverse outcome compared to the patients with low-proBNP (p=0.002), while, in the presence of NT-proBNP elevation alone, the risk was slightly but not significantly higher comapared to the reference group (p=0.17). Combination of cardiac troponin testing with echocardiography yielded similar complication rates in the lowest-risk group and a similar magnitude of risk elevation for the highest-risk patients, but it also increased the number of intermediate-risk groups without providing additional prognostic information.
Thus, our results support a simple and practical risk stratification algorithm for patients with PE, using NT-proBNP testing as an initial step which should be followed by echocardiography if elevated levels of the biomarker are found.

1903 Biomarker-based risk assessment model in acute pulmonary embolism

M. Kostrubiec[1], P. Pruszczyk[1], A. Bochowicz[1], R. Pacho[2], M. Szulc[1], A. Kaczynska[1], G. Styczynski[1], A. Kuch-Wocial[1]. *[1]Medical University of Warsaw, Internal Medicine and Hypertension, Warsaw, Poland; [2]The Medical University of Warsaw, The Dep. of Radiology, Warsaw, Poland*

Aims: Despite growing interest in biomarkers application for risk evaluation in acute pulmonary embolism (APE), no decision-making levels have been defined.
Methods and results: We developed a biomarker-based risk stratification in 100 consecutive, normotensive on admission, APE patients (35M, 65F, 62±18yrs). On admission serum NT-proBNP and cardiac troponin T (cTnT) levels were assessed, and echocardiography was performed. All-cause 40-day mortality was 15%, while APE mortality was 8%. In univariable analysis, cTnT>0.07μg/L predicted all-cause mortality, HR 9.2 (95%CI: 3.3–26.1, p<0.0001), and APE mortality, HR 18.1 (95%CI: 3.6–90.2, p=0.0004); similarly NT-proBNP>7600ng/L predicted all-cause deaths and APE mortality, HR 6.7 (95%CI: 2.4-19.0, p=0.0003) and 7.3 (95%CI: 1.7-30.6, p=0.007), respectively. NT-proBNP<600ng/L indicated uncomplicated outcome. Multivariable analysis revealed that serum cTnT>0.07μg/L was the highest independent predictor, while NT-proBNP, hypotension and echocardiographic parameters were non-significant. APE mortality in patients with NT-proBNP>600ng/L and cTnT>0.07μg/L reached 33%. NT-proBNP<600ng/L indicated group without deaths. APE mortality for patients with NT-proBNP>600ng/L and cTnT<0.07μg/L was 3.7%. Incorporation of echocardiographic data did not improve group selection.
Conclusion: Simultaneous measurement of serum cTnT and NT-proBNP allows for precise APE prognosis. Normotensive patients on admission with cTnT>0.07μg/L and NT-proBNP>600ng/L are at high risk of APE mortality, while NTproBNP<600ng/L indicates excellent prognosis.

1904 Value of brain natriuretic peptide in pulmonary arterial hypertension

M.H. Williams[1], C.E. Handler[1], M.R. Akram[1], D. Nair[2], C.P. Denton[3], C.J. Smith[4], C.M. Black[3], J.G. Coghlan[1]. *[1]Royal Free Hospital NHS Trust, Department of Cardiology, London, United Kingdom; [2]Royal Free Hospital NHS Trust, Department of Biochemistry, London, United Kingdom; [3]Royal Free Hospital NHS Trust, Academic Department of Rheumatology, London, United Kingdom; [4]Royal Free and UCL Medical School, Primary Care and Population Sciences, London, United Kingdom*

Aims: N-terminal brain natriuretic peptide (NT-pro-BNP) is used to diagnose left heart failure but its role in pulmonary arterial hypertension (PAH) and right heart failure is unclear. In our previous study we proposed a level of 395 pg/ml as a cut-off for excluding scleroderma associated PAH (SSc-PAH). This study was done to evaluate the accuracy of this proposal. We also investigated whether NT-pro-BNP could be used as prognostic indicator in SSc-PAH, and whether serial levels could be used as a means of monitoring disease progression and response to therapy.
Methods: we measured six minute walk distance (SMWD), cardiopulmonary haemodynamics, or estimated pulmonary artery pressure (PAP) (by echocardiography) and NT-pro-BNP, in 109 pts with systemic sclerosis (SSc), both with and without PAH, and without significant left heart failure (pulmonary capillary wedge pressure < 15 mmHg), diagnosed by right heart catheterisation (mean PAP >25 mmHg) (follow-up: 1 month - 18 months, mean 10 months). We recorded their WHO class and estimated survival using Kaplan-meier analysis. NT-pro-BNP levels, SMWD and WHO class were serially monitored in those patients with SSc-PAH.
Results: there were 41 control pts with SSc and normal mPAP, they had a mean BNP level of 139 pg/ml(stdev 151 pg/ml). The 68 pts with SSc-PAH had a significantly higher mean BNP level of 1474 pg/ml (stdev 2642 pg/ml) p = 0.0001. Baseline NT-pro-BNP positively and significantly correlated with mPAP ($r=0.7;p<0.0001$), pulmonary vascular resistance ($r=0.71;p<0.0001$), right atrial pressure {$r=0.53;p<0.0001$}, and inversely and significantly with cardiac index {$r=-0.5;p<0.0001$}, mixed venous oxygen saturations {$r=-0.46;p=0.013$} and SMWD ($r=-0.46;p<0.0001$).
At a cut-off of 395 pg/ml our study revealed a sensitivity of 56% and a specificity of 95.1% for predicting the presence of SSc-PAH. A cut-off of 90 pg/ml revealed a specificity of 51% and a sensitivity of 90% for excluding SSc-PAH.
1 year survival was 83.3%. For every 10 fold increase in NT-pro-BNP level, there was a 4-fold increased risk of dying (p=0.004 baseline level and p=0.035 for follow-up level).
Conclusion: raised BNP levels are directly related to the severity of PAH. This study validates our previous cut-off of 395 pg/ml for identify patients with SSc-PAH. An NT-pro-BNP level of 90 pg/ml appears to rule out patients with SSc-PAH. Baseline NT-pro-BNP levels (and more so change in NT-pro-BNP levels) are highly predictive of survival. NT-pro-BNP may have a role as a screening test for SSc-PAH and as a means of monitoring response to therapy.

1905 Predictive value of tricuspid regurgitation area in idiopathic pulmonary arterial hypertension patients treated according to current guidelines

A. Manes, M. Ferlito, F. Pelino, G. Rocchi, K. Vaziri Farahani, L. Bacchi-Reggiani, N. Galie', A. Branzi. *University of Bologna, Institute of Cardiology, Bologna, Italy*

Background: Non-invasive echocardiographic and Doppler parameters such as pericardial effusion size, right atrial area, right ventricular (RV) Tei index and left ventricular remodelling index were found to be correlated to the prognosis of patients with idiopathic pulmonary arterial hypertension (IPAH). However, these findings were assessed in small series of patients treated with conventional therapies or specific treatment such as intravenous prostanoids.
Aim: The objective of this study was the evaluation of the predictive role of Echocardiographic and Doppler parameters in a large series of IPAH patients treated with contemporary targeted treatments according to current guidelines.
Methods: 121 patients (mean age: 49±17 years; 65% females) with IPAH [NYHA functional class I (10%), II (40%), III (42%) and IV (8%)] underwent prospectively a complete Echocardiographic and Doppler examination before the initiation of the specific therapy. Treatment strategy followed current guidelines: all patients were anticoagulated, 16 (13%) patients, responders to acute vasoreactivity test, were treated only with high doses of Calcium-channel blockers; all other patients were treated with either a prostanoids (oral, inhaled, subcutaneous or intravenous), an endothelin receptor antagonist (bosentan, sitaxentan or ambrisentan) or a phosphodiesterase-5 inhibitor (sildenafil) or a combination of them when required.
Results: after a mean follow-up 23±16 months (range 1-51 months), 18 patients

died and 3 underwent lung transplantation. At the univariate analysis relating the echocardiographic and Doppler parameters with the survival, the following parameters reached a statistical significance: area of tricuspid regurgitation (p=0.004), RV end-systolic area (p=0.02), RV Tei index (p=0.04), moderate-to-severe pericardial effusion (p=0.05), end-diastolic area of RV (p=0.05). In the Cox stepwise regression analysis only the area of tricuspid regurgitation (p=0.006) and the RV Tei index (p=0.04) were related to survival. At three years the survival of patients with a tricuspid regurgitant area below the median (5.5 cm^2) was 91% as compared to 66% of patients with a tricuspid regurgitant area above the median ($p<0.01$ by Log Rank Test).
Conclusion: In this large series of IPAH patients treated with contemporary strategies, Doppler-assessed area of tricuspid regurgitation before the initiation of the therapy appears to be a strong predictor of survival.

NEW APPROACHES IN VALVE SURGERY

1906 Edge-to-edge mitral valve repair for isolated prolapse of the anterior leaflet due to degenerative disease

C. Fucci[1], G. De Cicco[1], G. Coletti[1], P. Faggiano[2], P. Garyfallidis[2], R. Lorusso[3]. *[1]Civic Hospital, Cardiac Surgery Unit, Brescia, Italy; [2]Civic Hospital, Cardiology Divisio Policardiografia, Brescia, Italy; [3]Ospedale Civile, Cardiac Surgery Division, Brescia, Italy*

Background: Mitral valve repair (MVR) for isolated anterior leaflet dysfunction (IALD) represents a surgical challenge, often requiring complex reconstructive procedures, and a well established risk factor for less satisfactory postoperative outcome. Edge-to-edge (ETE) technique has been proposed as a potential option to treat mitral insufficiency in this setting. We reviewed our experience with the use of a such a technique to neutralized IALD due to degenerative disease.
Methods: From October 1886 till June 2004, 789 patients underwent MVR for valve regurgitation at our Institution. IALD due to degenerative disease (Barlow) was the cause of mitral insufficiency in 82 patients, and from 1992 sixty-eight patients underwent ETE procedure for anterior mitral leaflet prolapse or flail (double-orifice procedure in 40 patients, and paracommissural ETE repair in 28 cases, respectively). Mitral valve annuloplasty was performed in the majority of the patients. Associated procedures consisted of aortic valve replacement in 2 patients, tricuspid valve repair in 4, and CABG in 4 cases.
Results: Mean follow-up (100% complete) was 68±22 months (range 9-137 months). The cumulative 10-year survival was 89±4%, and 10-year freedom from reoperation was 92±4%. Echocardiographic evaluation at follow-up revealed no residual MI in 34 patients, trivial MI in 24 cases, and mild to moderate MI in 6 patients.
Conclusions: Our experience with ETE indicates that this MVR procedure provides satisfactory results in the treatment of ILAD considered a risk factor for suboptimal postoperative results, and it represents our technique of choice in such a pathological setting at our Institution.

1907 Systematic reductive annuloplasty of mitral and tricuspid orifices in patients with end-stage ischaemic dilative cardiomyopathy

Z. Jonjev[1], B. Mihajlovic[2], M. Fabri[2], S. Nicin[2], N. Radovanovic[2] on behalf of Clinic of Cardiovascular Surgery Sremska Kamenica, Serbia&Montenegro. *[1]Institute of Cardiovascular Disease, Clinic of Cardiovascular Surgery, Sremska Kamenica, Serbia and Montenegro; [2]Institute of Cardiovascular Disease, Clinic of Cardiovascular Surgery, Sremska Kamenica, Serbia and Montenegro*

Objective: Patients with ischemic dilative cardiomyopathy (IsDCM) exhibit extensive remodelling of the left ventricle, annular dilatation, and significant mitral and tricuspid regurgitation. These changes increase perioperative morbidity and mortality, and emphasize patient candidacy for heart transplantation. The aim of this study is to show immediate and long-term results after reductive annuloplasty of double (mitral and tricuspid) orifices[RADO procedure], performed at the time of coronary artery by-pass grafting(CABG), as an alternative to heart transplantation.
Methods: There were 226 consecutive patients (205 males, 21 females) with ischemic dilated cardiomyopathy, mean ejection fraction below 30%, and mean left ventricle end-diastolic internal diameter greater than 7.0 cm. In addition to myocardial revascularization, Carpentier's mitral annuloplasty and posterior semicircular reductive annuloplasty were performed in 37 and 189 patients, respectively. In 214 patients (94.69%) a modified De Vega's tricuspid annuloplasty was performed.
Results: Postoperative 30-day mortality was 7.5% (17 pts). Survival rates after 5 and 10 years were 61.5±4.0% and 38.05±8.0%, respectively. Significant reduction in daily doses of medications and high freedom from decompensation were also observed.
Conclusion: Reductive annuloplasty of mitral and tricuspid orifices performed at the time of myocardial revascularization could be successfully used as an alternative or a bridge for heart transplantation in patients with end-stage IsDCM. The elimination of valvular incompetence combined with CABG results in improvement of immediate and long-term morbidity and mortality. Thus, our method should not be recognized as a valve repair, but ventricular repair procedure as well.

1908 The effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease

C.A. Abreu Filho[1], L.A.O. Dallan[2], L.A.F. Lisboa[2], G.S. Spina[3], M. Scanavacca[3], E.A. Sosa[3], J.A.F. Ramires[3], S.A. Oliveira[2]. *[1]Instituto da Coração - HC-FMUSP, Department of Cardiovascular Surgery, São Paulo, Brazil; [2]Heart Institute HCFMUSP, Department of Cardio-thoracic surgery, Sao Paulo, Brazil; [3]Heart Institute HCFMUSP, Department of Cardiology, Sao Paulo, Brazil*

Background: Although the "Cox-Maze III" procedure is effective for treating permanent atrial fibrillation (AF), its high complexity limits its use. The saline-irrigated cooled-tip radiofrequency ablation (SICTRA) is an alternative source of energy used to ablate AF. The aim of this study was to evaluate the effectiveness of the SICTRA for the treatment of permanent AF in patients with rheumatic mitral valve (MV) disease.
Methods: Between February 2002 and April 2003, 70 patients with permanent AF and rheumatic mitral valve MV disease were randomly assigned to undergo a modified Maze III procedure using SICTRA associated with MV surgery (Group A) or MV surgery alone (Group B). Groups A and B were similar in terms of baseline characteristics.
Results: Postoperatively, hospital mortality was 2.3% (1 death) in group A versus 0% (no deaths) in group B (p = 1.00). The additional time required for the left sided radiofrequency (RF) ablation in group A was 14.2±5.1 minutes and 12.3±4.2 minutes for the right-sided one. The mean postoperative follow-up periods were 13.8±3.4 and 11.5±7.3 months, respectively, in groups A and B. The overall mid-term survival was 95.1% in group A and 92.8% in group B (p = 1.00). The cumulative rates of sinus rhythm (SR) were 79.4% in group A and 26.9% in group B ($p < 0.05$). Doppler-echocardiography documented biatrial transport function in 90.3% of group A patients in SR.
Conclusions: The SICTRA is effective for treating permanent AF associated with rheumatic MV disease.

1909 Beneficial effects of surgical ventricular restoration and restrictive mitral annuloplasty in patients with ischaemic dilated cardiomyopathy

S. Tulner, J.J. Bax, G.B. Bleeker, P. Steendijk, R.J.M. Klautz, M.J. Schalij, R.A.E. Dion, E.E. van der Wall. *LUMC, Cardiology Department, Leiden, Netherlands*

Background: Surgical ventricular restoration (SVR) and restrictive mitral annuloplasty (RMA) are increasingly applied in patients with ischemic dilated cardiomyopathy. The effects of combined SVR/RMA on clinical parameters, LV reverse remodeling, LV dyssynchrony, RV reverse remodeling, and severity of tricuspid regurgitation and pulmonary artery pressure were studied.
Methods: 21 patients with ischemic dilated cardiomyopathy (NYHA class III/IV, LVEF <30%) underwent SVR; 14 patients underwent additional RMA, and 8 additional tricuspid ring annuloplasty. Clinical parameters (NYHA, Quality of Life questionnaire, 6-minute walk test) and echocardiographic parameters were assessed at baseline and 6 months after surgery. LV volumes, LVEF, RV dimensions, severity of tricuspid regurgitation, and pulmonary artery pressure were measured by echocardiography, and LV dyssynchrony by tissue Doppler imaging.
Results: All patients survived 6 months follow-up. All clinical parameters improved significantly at 6-months follow-up. LVEF improved from 27±10% to 36±11% ($P<0.01$). LV end-diastolic volume decreased from 248±78 ml to 152±50 ml ($P<0.001$), and LV end-systolic volume from 186±77 ml to 101±50 ml ($P<0.001$). LV dyssynchrony decreased from 61±41ms to 12±12 ms ($P<0.001$). RV annular diameter decreased from 30±7 mm to 27±6 mm, RV short-axis from 30±9 mm to 27±7 mm, and RV long-axis from 90±7 mm to 79±10 mm (all $P<0.05$). Finally, significant reductions in severity of tricuspid regurgitation (from 1.3±1.1 to 0.9±0.6, P=0.001) and pulmonary artery pressure (42±11 to 28±10 mmHg, P=0.015) were observed.
Conclusion: The combined approach of SVR and RMA resulted in improvement of clinical parameters, significant LV reverse remodeling and reduced LV dyssynchrony at 6-months follow-up. In addition, RV reverse remodeling was noted with reductions in tricuspid regurgitation and pulmonary artery pressure.

1910 20-years outcome differences after aortic valve replacement for aortic regurgitation depending on the adherence to guidelines

A. Sambola[1], P. Tornos[2], A. Evangelista[2], Z. Gomez[2], A. Martin[1], G. Permanyer-Miralda[2], J. Soler-Soler[1]. *[1]University Hospital Vall d'Hebron, Cardiology, Barcelona, Spain; [2]University Hospital Vall d'Hebron, Cardiology, Barcelona, Spain*

Purpose: The influence of adherence to guidelines on outcome after aortic valve replacement for aortic regurgitation (AR) is still not well known. We retrospectively

assess the impact of adherence to the current guidelines criteria on postoperative outcome in severe AR.
Methods and Results: Two-hundred ten patients underwent surgical correction for pure severe AR between 1982 and 2002. One-hundred seventy patients (135 m, 35 f; age 50±14 y) who had available echocardiographic preoperative register were prospectively followed-up for 10±6 years (1-22 y). Follow-up was complete in 99%. Regarding the timing of surgical indication patients were divided in Group A (adherence to guidelines) and Group B (not adherence to guidelines). Not adherence to guidelines was defined by the presence of at least one of the following: 1) CF III-IV 2) ESD>or=55 mm 3) Ejection fraction (EF)<45%. Group A were 52 pts (31%) and Group B 118 pts (69%). Overall mortality was 57 pts. Perioperative mortality was 11 pts (6%): 2 pts (4%) in Group A and 9 pts (8%) in Group B (p=ns). Overall mortality was 46 pts. Non-cardiac death 17 pts (5 pts in Group A and 12 pts in Group B) and cardiac mortality 29 pts (4 in Group A and 25 pts in Group B). Causes of cardiac death differed between Groups A and B: heart failure and sudden death were more frequent in Group B than in Group A (17 pts vs 1 pt, p=0.03). Survival rates by actuarial analysis were: 88±5% at 10 y and 71±2% at 20 y in Group A and 71±5% at 10 y and 64±5% at 20 y in Group B (p=0.032). Final echocardiographic dimensions among survivors were EDD 53±6; ESD 37±7; EF 55±10% in Group A and EDD 59±12; ESD 44±13; EF 48±16% in Group B p=0.009, p=0.008, p=0.042, respectively.
Conclusions: Our results suggest clearly the benefit in increased long-term survival and preservation of LV function among patients with AR operated following guidelines recommendations.

1911 Myocardial bridge: surgical outcome and midterm follow up

R. Parvizi, H. Javadzadegan, A. Sajjadieh Khajouei. *Tabriz university of Medical sciences, Madani Hospital, Tabriz, Iran (Islamic Republic of)*

Myocardial bridge consists of muscle fiber bundle lining on the epicardial coronary artery for variable distance. Although myocardial bridge is associated with benign prognosis, their presence has also been considered a cause of angina, myocardial infarction, malignant arrhythmia and sudden death. There is not a general consensus about therapeutic strategies in symptomatic patients whith myocardial bridge (medical therapy, coronary artery bypass surgery, coronary stenting, supra arterial myotomy).We report results of surgery and long-term follow up in 26 patients who had disabling symptoms due to myocardial bridge refractory to medical therapy.
From 1998-2003 among more than 18800 coronary angiography which was performed in our centre 290 (1.5%) cases had the angiographic diagnosis of myocardial bridge out of them 26(9%) patients underwent surgical myotomy for treatment of myocardial bridge causing significant systolic arterial compression. The patients (19 male-7 female) had history of typical chest pain and positive exercise test. All of them were studied with radionucleotide imaging study preceding angiography that was positive for ischemia in 20 cases(76%). Coronary angiography and left heart catheterization in all patients revealed impaired blood flow due to myocardial bridge in left anterior descending artery and there was additional atherosclerotic stenosis of coronary arteries in 6 and mitral valve disease in one patients. supra arterial myotomy was performed in all patients.
There was no mortality or major intraoperative complication. Post operative scintigraphic and angiographic studies demonstrated restoration of coronary blood flow and myocardial perfusion without significant residual compression of the artery. Except in one patient who had recurrent anginal chest pain after operation and coronary angiography showed residual narrowing in LAD despite myotomy and underwent CABG of LIMA to distal LAD. During 7-81 month of follow-up (mean: 34.2± 21) only two patients had symptoms of angina that was not shown significant residual compression in angiography and symptoms controlled by medical treatment. In conclusion surgical relief of myocardial ischemia due to myocardial bridge can be accomplished with very low operative risk and excellent prognosis.

CLINICAL VALUE OF MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY

1958 Usefulness of real-time myocardial perfusion imaging to evaluate alterations of myocardial blood flow after elective percutaneous coronary interventions

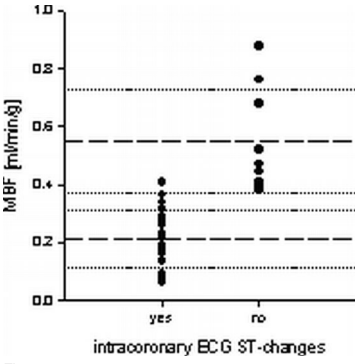
G. Korosoglou, B. Geiger, A. Hansen, S.E. Hardt, E. Giannitsis, H.F. Kuecherer. *University of Heidelberg, Dept. of Cardiology, Heidelberg, Germany*

Introduction: Release of cardiac enzymes has been reported in patients with stable angina who undergo elective percutaneous coronary interventions (PCI) and has been associated with adverse clinical outcomes. The aim ofthe present study was to investigate, whether impaired microvascular integrity can be detected using myocardial contrast echocardiography (MCE) in patients undergoing elective PCI and whether it is related to the release of troponin T.
Methods: We investigated consecutive patients with stable angina (n=19) who were scheduled for elective angioplasty with stent placement. MCE was performed before, 2-4 hours after and 24 hours after the coronary intervention. Contrast images were analyzed visually and quantitatively measuring the peak signal intensity (A) and the slope of signal intensity rise (β) in 16 myocardial segments. The product of A*β was calculated in each segment, to estimate the regional myocardial blood flow. Troponin T was collected serially before PCI, 2-4 hours after and 24 hours after PCI.
Results: Five patients (26%) had elevated troponin T 24 hours after PCI (range between 0.03 and 0.46 μg/l). Eight patients (42%) including all 5 patients with elevated troponin T levels, demonstrated impaired microvascular integrity between 2 and 4 hours after PCI, in at least 2 myocardial segments (range 2 to 4) within the perfusion territory where PCI was performed. Of 11 patients without evidence of impaired myocardial perfusion by MCE, none had elevated troponin T at follow-up. Quantitative analysis of myocardial blood flow showed that impaired perfusion after PCI was reversible. Thus, A*β significantly decreased at 2-4 hours after PCI (3.4±1.6 vs. 8.8±3.4 dB/s initial, *p<0.01) and returned to baseline after 24 hours (7.4±3.1 vs. 3.4±1.6 dB/s, #p<0.01). The perfusion defect size 2-4 hours after PCI was closely related to troponin T levels after 24 hours (r^2 =0.80, p<0.0001).
Conclusion: Impaired microvascular integrity is partially present in patients with stable angina who undergo elective PCI, is to a large extent reversible and is closely related to the release of troponin T. Because judgment of interventional success has shifted downstream to the adequacy of tissue level perfusion contrast echo may be useful to monitor such alterations of myocardial tissue perfusion.

1959 Is there a minimal perfusion threshold that prevents myocardial ischaemia in humans

R. Vogel, A. Indermühle, C. Seiler. *University Bern, Cardiology, Bern, Switzerland*

Background: During percutaneous coronary intervention, myocardial perfusion of the related territory decreases depending on the development of the coronary collateral circulation. Objective of this study was to determine whether there is an absolute perfusion threshold preventing myocardial ischaemia in humans.
Methods: Myocardial blood flow (MBF, ml/min/g) is gold standard to quantitatively assess the regional blood supply and, as we have shown recently, can be obtained by quantitative myocardial contrast echocardiography (qMCE). During angioplasty of 37 coronary stenoses in 30 patients with stable coronary artery disease, MBF of the related territory was measured by qMCE. For the duration of the one-minute vessel occlusion, an intracoronary ECG was obtained from the guide wire and ST-segment changes of > 0.1mV defined insufficient perfusion to prevent myocardial ischaemia.
Results: Perfusion analysis by qMCE was successfully performed in 33 of 37 cases. MBF during occlusion varied between 0.060-0.876ml/min/g (0.304±0.196ml/min/g. Sufficient perfusion was found in 9 territories ranging from 0.381-0.876ml/min/g (0.549±0.179ml/min/g). Insufficient perfusion was found in 24 territories ranging from 0.060-0.408ml/min/g (0.212±0.099ml/min/g). A perfusion threshold of 0.374ml/min/g determined sufficient perfusion with 100% sensitivity and 96% specificity (Figure).



Figure

Conclusion: In humans with coronary artery disease, myocardial blood flow of > 0.374ml/min/g prevents ischaemia as documented by intracoronary ECG. Accordingly, this suggests the existence of an analogue threshold for myocardial viability that can be determined by qMCE at rest.

1960 Prediction of transmurality of acute myocardial infarction – comparison between myocardial contrast echocardiography and radionuclide perfusion imaging

S.A. Hayat[1], R. Janardhanan[1], J.C. Moon[2], D. Pennell[2], R. Senior[1]. *[1]Northwick Park Hospital, Dept. of Cardiology, Harrow, United Kingdom; [2]Royal Brompton Hospital, Department of CMR, London, United Kingdom*

Background: It is well established that contrast enhanced cardiovascular MRI(CMR) can be used to assess transmural extent of infarction (TEI). We

sought to determine the relative accuracy of myocardial contrast echocardiography (MCE) and Tc-99m sestamibi (SPECT) to predict TEI after AMI.
Methods: MCE, SPECT and CMR were performed in 40 patients with AMI 7-10 days post thrombolysis. CMR was used to divide TEI into 5 groups: 0%,1-25%,26-50%,51-75% and 76-100%. TEI scores in dysfunctional segments were compared to qualitative MCE scores (0-absence of contrast, 1-heterogenous opacification, & 2-homogenous opacification) and SPECT (0-normal perfusion, 1-mild reduction, 2-moderate reduction, 3-severe reduction & 4-absent uptake).
Results: There was a significant relationship ($p<0.0001$) between decreasing contrast intensity assessed qualitatively by MCE and increasing TEI on CMR as was the case for SPECT(Fig 1). Segmental concordance between MCE and CMR (kappa 0.50) was superior than for SPECT and CMR (kappa 0.38). The accuracy of MCE (77%) to predict >50% TEI (non-viable myocardium) was significantly ($p<0.03$) superior to SPECT (70%). Absence of uptake on MCE and SPECT virtually ruled out <50% TEI (negative predictive values:93% and 89% respectively). TEI of <25% has been shown to be an excellent predictor of long term improvement of contractile function, and again we found MCE to be significantly more sensitive than SPECT in differentiating between < and >25% TEI(84%vs76% $P<0.05$).

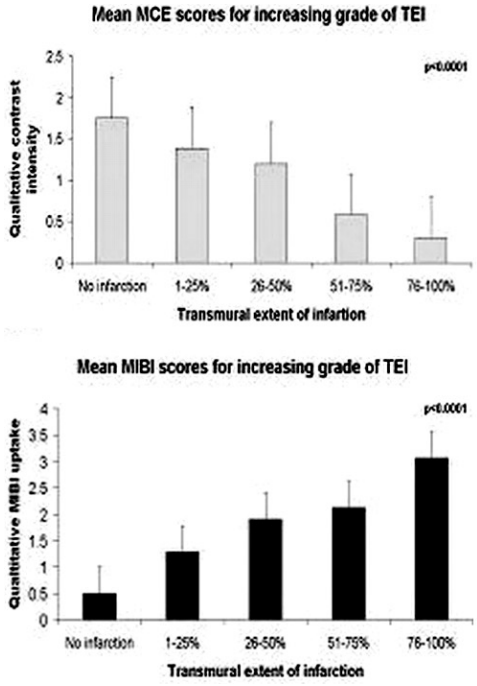


Figure 1.

Conclusion: Both MCE and MIBI correlate well with TEI. However, MCE is significantly more accurate in predicting greater than 50% transmural extent of infarction and more sensitive in identifying >25% TEI than MIBI.

1961 Value of combined dobutamine stress echocardiography and myocardial contrast echocardiography in detecting coronary artery disease

C. Aggeli[1], P. Misovoulos[2], D. Soulis[2], C. Kokkinakis[2], G. Roussakis[2], E. Christoforatou[2], S. Brili[2], C. Stefanadis[2]. *[1]Athens, Greece; [2]Hippokration Hospital, Cardiology Dept., Athens, Greece*

Myocardial contrast echocardiography (MCE) is a newly introduced technique used for the evaluation of myocardial perfusion in patients with suspected coronary artery disease.
Aim: To evaluate the accuracy of MCE and wall motion analysis (WMA) during dobutamine stress echo for the diagnosis of coronary artery disease.
Methods: We studied 336 patients (mean age 63±10, men 279) who underwent dobutamine (up to 50μg/kg/min)-atropine stress testing and coronary angiography within one month, during the period 2003-2004. Both WMA and MCE (using repeated boluses of SonoVue, Bracco) were performed at rest and peak stress. MCE images were acquired using low mechanical-index in 3 apical views after acquisition of standard rest and poststress images. Wall motion and MCE components of the study were interpreted sequentially, blinded to other data. The diagnosis of coronary artery disease was based on the induction of reversible wall motion and perfusion abnormalities.
Results: Coronary artery disease was detected in 261(77%) patients. Sensitivity of MCE was higher than that of WMA at maximal stress (92% vs. 69%, $p<0.001$). Specificity was lower for MCE compared with WMA (64% vs. 79%, $p<0.01$). Sensitivity of MCE in single vessel disease was higher compared to WMA (85% vs. 56%, $p<0.001$). Similarly, sensitivity of MCE in multivessel disease was higher compared to WMA (96% vs. 75%, $p<0.001$). The combination of both MCE and WMA demonstrated the best balance for sensitivity and specificity (85% and 78%, respectively).
Conclusion: The combination of myocardial contrast echocardiography and wall motion analysis during dobutamine stress echo has high diagnostic accuracy in detecting coronary artery disease.

1962 Manual thrombus-aspiration reduces microvascular obstruction after PCI in unselected STEMI patients: MCE substudy of the randomised REMEDIA trial and insight into the pathogenesis of no-reflow

L. Galiuto, F. Burzotta, B. Garramone, M. De Vita, R. Mongiardo, M.A. Mazzari, A.G. Rebuzzi, F. Crea on behalf of REMEDIA investigators. *Policlinico A. Gemelli Rome, Italy, Cardiology Department, Rome, Italy*

Background: The effective role of microembolization in the genesis of no-reflow after PCI is still unclear. We designed a prospective randomized trial (REMEDIA) in order to assess the role of a new thrombus-aspirating device in preventing distal microembolization after PCI. A subgroup of consecutive patients entered the myocardial contrast echocardiographic (MCE) substudy, thus deriving further insight into the pathogenesis of no-reflow.
Method: A total of 34 patients with first STEMI were enrolled in the MCE substudy of the REMEDIA trial at the time of PCI: 17 were randomized to be pretreated with thrombus-aspiration with the Diver CE device before primary stenting of the culprit lesion and 17 were treated with standard PCI. At day 1 and 7 after PCI, myocardial contrast echocardiography (MCE) was performed using continuous infusion of Sonovue® (Bracco) and real-time imaging by CPS technology (Sequoia, Siemens). Regional wall motion score index (WMSI), contrast score index (CSI), endocardial length of wall motion abnormality (WML) and of contrast defect (CDL) were calculated
Results: While at day 1 no differences between the two study groups were observed, at 7 days WMSI, CSI, WML and CDL were significantly lower in patients treated with thrombus-aspiration filter device (2±0.5 vs 1.6±0.6, $p<0.05$; 2.4±0.5 vs 1.9±0.8, $p<0.02$; 5.5±2.9 vs 2.8±3.8, $p<0.02$; 3.6±2.3 vs 1.4±2.5, $p<0.05$, respectively.)
Conclusions: Thrombus-aspiration used at the time of PCI significantly reduces the extent of microvascular obstruction and myocardial dysfunction. This beneficial effect is not evident 1 day after PCI, but it appears after 7 days. These observations bear important therapeutic implications and also shear some light into the pathogenesis of no-reflow. In fact, not only microembolization plays a role in the genesis of no-reflow, since the phenomenon is reduced by filters, but additional factors, such as microvascular costriction, are responsible for the initial extent of no-reflow, that is similar despite the use of filters and it is then spontaneously reversible.

1963 Value of quantitative adenosine and dobutamine stress real-time myocardial contrast echocardiography for identifying coronary artery disease in different territories

I. Kowatsch[1], J.M. Tsutsui[2], A. Osorio FF[2], M.L.Z. Trindade[2], J.C. Frizera[2], V.T. Hota[2], J.F. Ramires[2], W. Mathias Jr[2]. *[1]University of Sao Paulo Medical School, Heart Institute (InCor), Sao Paulo, Brazil; [2]University of São Paulo Medical School, Heart Institute (InCor), São Paulo, Brazil*

Aim: We sought to determine the value of myocardial blood flow reserve (MBFR) obtained by adenosine and dobutamine stress real-time myocardial contrast echocardiography (RTMCE) for detecting global, regional, single-vessel and multivessel coronary artery disease (CAD).
Methods: We prospectively evaluated 54 patients (mean age 60±9 years, 33 men) with known or suspected CAD who underwent RTMCE at rest and during 2 modalities of pharmacologic stress within a period of 6 h. Adenosine RTMCE was performed using continuous infusion of 140mcg/kg/min of adenosine for 6 min. Dobutamine RTMCE started at least 4 h later with infusion of scalar doses from 5 to 40mcg/kg/min + up to 2.0 mg of atropine. Quantifications of microbubble replenishment velocity (beta) and myocardial blood flow (Axbeta) were performed off line using specific software (Q-Lab).Quantitative coronary angiography was performed in all patients within one week and CAD was define as >50% diameter stenosis. Anterior coronary territory (CT) was defined as that supplied by the left anterior descending coronary artery, while posterior CT as that supplied by right coronary or left circumflex.
Results: There were 25 patients with CAD, 24 in anterior CT, 20 in the posterior CT, 11 with multivessel CAD and 14 with single-vessel CAD. The cut-off value of beta reserve and MBFR obtained by dobutamine stress were 2.42 and 2.50, and

The diagnostic parameters

		Sensitivity	Specificity	Accuracy
Global	Dobutamine	84%(70-98%)	76%(60-91%)	80%(69-90%)
Global	Adenosine	72%(60-91%)	79%(65-94%)	76%(64-87%)
Anterior Territory	Dobutamine	81%(66-98%)	79%(63-94%)	80%(69-91%)
Anterior Territory	Adenosine	65%(47-84%)	81%(67-96%)	74%(62-85%)
Posterior territory	Dobutamine	74%(54-93%)	79%(65-94%)	77%(65-89%)
Posterior territory	Adenosine	84%(70-98%)	76%(60-91%)	80%(69-90%)

by adenosine 1.92 and 2.5, respectively. The diagnostic parameters are in the Table below. The sensitivity of RTMCE for detecting single-vessel and multivessel CAD were 75%, 55% using dobutamine and 93% and 86% using adenosine stress.
Conclusion: Quantitative dobutamine stress RTMCE holds slightly superior diagnostic accuracy than adenosine for detecting CAD.

ACS: LESSONS FROM RANDOMISED TRIALS

1964 The time course of patient management and disease events in the acute coronary syndrome; findings from the RITA 3 trial

P.A. Poole-Wilson[1], S.J. Pocock[2], M. Abdalla[2], K.A.A. Fox[3], R.A. Henderson[4], D.J. Wheatley[5], T.R.D. Shaw[3], T.C. Clayton[2] on behalf of the Randomized Intervention Trial of unstable Angina (RITA). *[1]National Heart & Lung Institute, Dept. of Cardiac Medicine, London, United Kingdom; [2]LSHTM, London, United Kingdom; [3]Edinburgh, United Kingdom; [4]Nottingham, United Kingdom; [5]Glasgow, United Kingdom*

In the acute non-ST-elevation coronary syndrome, the benefit from early invasive coronary intervention compared to a strategy of later symptom guided intervention may vary over time. In RITA3 (Randomised Intervention Trial of unstable Angina 3) we randomly assigned 895 patients to coronary angiography (median 2 days after randomisation) and intervention and 915 patients to a symptom guided strategy. The co-primary combined endpoint (death, non-fatal myocardial infarction (MI), or refractory angina) showed benefit from intervention after 4 months (risk ratio 0.66, 95% CI 0.51–0.85, p=0.001) and after 12 months (p=0.003) largely due to a 53% reduction in the occurrence of refractory angina. Death and myocardial infarction were similar in both treatment groups at 4 and 12 months. Patients in both groups were at highest risk of death, MI or refractory angina in the first 7 days (incidence rate over 40 times higher than in months 5 to 12 of follow-up). In the first 72 hours after randomisation the event rates per 1000 patient.days for death or non-fatal myocardial infarction were 5.6 in the intervention arm and 3.7 in the conservative arm. The rate after 28 days was < 0.1/1000 patient.days. At 7 days, there were 6 deaths and 22 MIs in the intervention group (4 and 14 procedure related respectively) and 3 deaths and 17 MIs in the conservative group. After 28 days the respective figures were 15 (7 procedure related) and 24 in the intervention group, and 9 and 25 in the conservative group. Any intervention policy needs to recognise the very high risk of events in the first week, and the substantial minority of patients not needing intervention. Intervention may be best targeted at higher risk patients since the early hazards of the procedure are then offset by reduced subsequent events.

1965 NSTE-ACS patients with an elevated cardiac troponin T and NT-pro-BNP on admission did not benefit from an early invasive strategy

A. Hirsch[1], F. Windhausen[2], J.P. van Straalen[3], J. Fischer[3], G.T.B. Sanders[3], J.H. Cornel[4], J.G.P. Tijssen[2], R.J. de Winter[2] on behalf of the ICTUS investigators. *[1]AMC, Cardiology, Amsterdam, Netherlands; [2]AMC, Cardiology, Amsterdam, Netherlands; [3]AMC, Clinical Chemistry, Amsterdam, Netherlands; [4]MCA, Cardiology, Alkmaar, Netherlands*

Background: The ICTUS trial compared an early invasive (EI) strategy aiming at coronary angiography (CAG) and revascularization within 24-48 hrs, with a "selective invasive" (SI) strategy, in 1200 nSTE-ACS patients with an abnormal cardiac Troponin T. In the SI group, CAG and revascularization was performed in the event of refractory angina or ischemia on the pre-discharge exercise test. We could not demonstrate that an EI strategy is superior to a SI strategy. Subgroup analyses of other strategy trials revealed that benefit from an EI strategy was confined to patients at intermediate or high risk for adverse outcomes. Thus, we assessed whether an elevated NT-pro-BNP concentration on admission is associated with adverse outcomes and whether patients with an elevated NT-pro-BNP benefit from an EI strategy.
Methods: In 1133 out of 1200 patients a blood samples was available for central analyses of NT-pro-BNP. The incidence of death and myocardial infarction (MI) by one year was established for two groups: NT-pro-BNP $\geq$ 600mg/L (n=564) and NT-pro-BNP $<$600mg/L (n=569). In patients with NT-pro-BNP $\geq$ 600mg/L, we assessed whether an EI strategy reduces death and MI compared to the SI strategy. Cumulative incidence rates were calculated according to the Kaplan-Meier method and significance of differences between groups were assessed using the log-rank test.
Results: Patients with a NT-pro-BNP $\geq$ 600mg/L level on admission more often had a history of previous MI and hypertension, but were less often male compared to patients with a NT-pro-BNP $<$ 600mg/L. Mortality was 4.4% in the NT-pro-BNP $\geq$ 600mg/L group versus 0.9% in the NT-pro-BNP $<$ 600mg/L group (p=0.002). The rate of MI was 11.5% in the NT-pro-BNP $\geq$ 600mg/L group versus 13.9% in the NT-pro-BNP $<$ 600mg/L group (p=0.21). Among patients with a NT-pro-BNP $\geq$ 600mg/L, mortality was similar in the EI versus SI strategy (4,7% vs 4.2%, p=0.79). However the incidence of MI was significantly higher in patients randomized to an EI strategy (14.5% vs. 8.5%, p=0.02).
Conclusion: An elevated NT-pro-BNP level was strongly associated with mortality in cardiac Troponin T positive nSTE-ACS patients. The high mortality in patients with NT-pro-BNP $\geq$ 600mg/L could not be reduced with an EI strategy. The incidence of MI was not significantly different between patients with and without elevated NT-pro-BNP levels. However we observed a higher incidence of MI among patients with NT-pro-BNP $\geq$ 600mg/L randomized to an EI strategy compared to an SI strategy.

1966 The evaluation of strategies to triage intermediate risk ACS patients: the STATUS trial

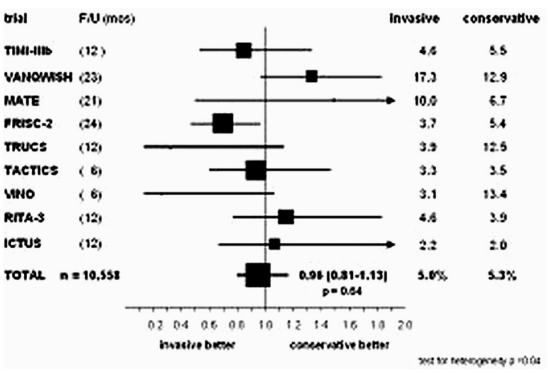
J.L. Navarro Estrada[1], F. Rolandi[2], P. Averbuj[2], M.U. Zafar[3], M. Santra[3], J. Barbiere[3], J.H. Chesebro[3], M.E. Farkouh[3]. *[1]Buenos Aires, Argentina; [2]Hospital Italiano de Buenos Aires, Unidad Coronaria, Buenos Aires, Argentina; [3]Mount Sinai Hospital, Cardiology, New York, United States of America*

Background: Cardiac troponins are important markers to diagnose acute myocardial infarction (MI) but their value in guiding management is still controversial. Using a randomized design, we sought to compare the utility of a strategy utilizing stress testing (ST) versus a troponin-I (TnI) guided strategy (TG) for risk stratification and management of pts with intermediate risk (IR) unstable angina.
Methods: Pts were randomized to either ST or TG with all pts having CK-MB measurements. ST pts underwent a cardiac stress test if ruling out for MI after a12 hr CPU stay. TnI was collected in ST but not reported. Pts assigned to the TG had blood drawn for TnI at 0 and 6 hours after arriving in the ED. TG pts were admitted to CCU if either measurement of TnI was greater or equal to 0.4 ng/ml with the subsequent clinical course dictated by the attending physician. The primary endpoint was one of the cluster of death, nonfatal MI and repeat hospitalization at 6 months.
Results: Of the 578 pts with IR ACS, 241 were randomized(n=119 in ST and n=122 in TG). Baseline characteristics were similar in both arms. At 6 months, only 1 patient died overall (assigned to TG). No patient suffered an MI. There was a trend towards a lower rate of readmission due to recurrent ACS in the stress test arm (5.9% versus 8.2%, p=0.62). At 6 months, the cumulative survival free from death, MI and rehospitalization because of ACS was similar for both arms (p=0.84). The proportion of pts requiring CCU admission was significantly higher in TG compared with ST (49.2% vs. 31.9%, p=0.002). The median CPU stay was only slightly lower in pts in TG compared to ST (18 vs. 22 hours, p$<$0.01). In a retrospective analysis of ST, 29 pts (25%) who had safely undergone stress testing and discharged home were subsequently found to have had some mild elevation in TnI.
Conclusions: For pts with IR ACS, an ST based strategy is likely as safe as a TG based approach in triaging pts with acute chest pain with a significant reduction in the need for hospitalization from a CPU. Importantly, pts with mild TnI elevations can safely undergo stress testing. Further studies into combining the ST and TG strategies are warranted.

1967 Early invasive management of acute coronary syndromes without ST elevation does not improve long-term mortality: insights from the randomised trials

F.W.A. Verheugt, M.A. Brouwer. *Radboud University Nijmegen Medical Centre, Department of Cardiology, Heartcenter, Nijmegen, Netherlands*

Background: Randomized trials from the 80s and early 90s evaluating an early invasive strategy failed to show a benefit over a conservative approach, but in recent studies the composite of death, MI and revascularisation/recurrent ischemia has been reduced by early intervention. However, by the necessarily open design MI and revascularisation/recurrent ischemia are relatively weak endpoints. Since MI is both an entry criterion and an endpoint, it is difficult to evaluate, since it may be induced by intervention and, therefore, its definition in the trials is cumbersome. Thus, long term mortality is the best outcome parameter to evaluate the above strategies.
Methods and Results: We analyzed the 10 trials carried out between 1996 and



Long-term mortality

2004, which randomized 10,558 patients with non ST elevation acute coronary syndromes to an early invasive or an ischemia-guided conservative strategy.
Conclusion: Although most trials on non ST elevation ACS reported a reduction in the composite of death, MI and revascularisation/recurrent ischemia, an early invasive strategy does not lead to improved survival on the long term. These findings should be clearly mentioned in current and future guidelines.

1968 Three-year mortality of patients with non-ST segment elevation acute coronary syndromes who are not eligible in clinical trials according to the reason for ineligibility

V. Delgado[1], S. Diez-Aja[2], F. Miranda-Guardiola[2], E. Borquez[2], F. Verbal[2], X. Bosch[2]. [1]*Hospital Clinic, Cardiovascular Institute, Barcelone, Spain;* [2]*Hospital Clinic, Cardiovascular Institute, Barcelone, Spain*

Objective: To determine the prevalence and long-term mortality of patients (pts) with non-ST segment elevation acute coronary syndromes (ACS) who are not eligible in randomised clinical trials (RCT) according to the reason for ineligibility.
Methods: Common causes of exclusion in RCT were prospectively assessed in a cohort of 452 pts with ACS with a complete follow-up to 3 years.
Results: Forty-one percent of pts had some of the reported exclusion criteria in recently published RCT on anthithrombotic therapy. Non-eligible pts were older (68 ± 10 vs 65 ± 11 yrs; p=0.001), with a higher frequency of arterial hypertension (62% vs 52%; p=0.03), diabetes (34% vs 26%; p=0.05), peripheral vascular disease (30% vs 17%; p=0.001), heart failure (15% vs 3%; p<0.0001), and ST-segment depression (60% vs 43%; p<0.0001). The 3-year mortality rate was 25% in non-eligible pts compared to 9% in eligible pts (p<0.001) with a RR of 2.5 (95% CI, 1.5-4.4). The RR of mortality for each exclusion criteria are shown in the figure 1.

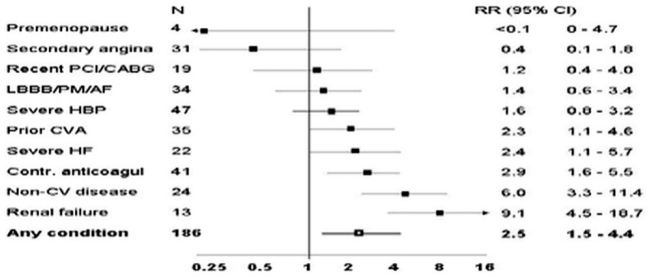


Figure 1

Conclusion: Patients with ACS who are not eligible in RCT have a much higher risk profile and a threefold long-term mortality than eligible pts, especially pts with renal dysfunction, those with contraindications to anticoagulation and those with heart failure.

1969 What are the future targets of therapy beyond intensive statin therapy? An analysis from PROVE IT-TIMI 22

K.K. Ray[1], C.P. Cannon[2], C.M. Gibson[3], R. Cairns[4], A.J. Kirtane[3], C.M. McCabe[2], E. Braunwald[2]. [1]*British Heart Foundation International Fellow, TIMI Study Group, Boston, United States of America;* [2]*Brigham & Women's Hospital, Medicine, Boston, United States of America;* [3]*Beth Israel Deconess Medical Centre, Medicine, Boston, United States of America;* [4]*Nottingham Clinical Reseach Institute, Nottingham, United Kingdom*

Background and Aims: intensive statin therapy with on a background of aggressive medical therapy and therapeutic revascularisation reduces clinical events after acute coronary syndromes (ACS). However, recurrent events remain high. We sought to identify the characteristics of patients with adverse events in the intensive treatment arm of PROVE-IT-TIMI 22 as potential future targets for risk factor reduction.
Methods: 2099 patients allocated to atorvastatin 80mg on average 7 days after ACS were evaluated using a case cohort design to identify univariate predictors, which were then included in a multivariable model. We evaluated the composite of acute cardiac events (death, MI or unstable angina (UA)).

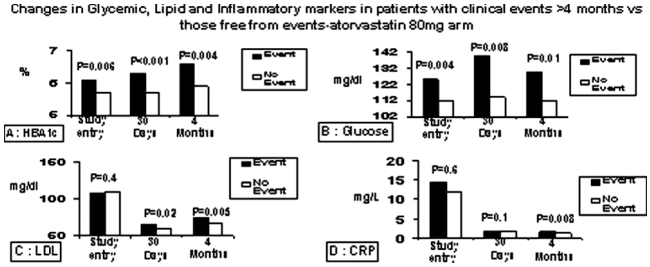


Figure 1

Results: there were 233 events (11.1%), of which 93 occurred <4 months and 140 occurred >4 months. Patients who developed clinical events (n=233)were older (61 vs 58y, p<0.0001), more likely to have diabetes (26% vs 18%, p=0.002), hypertension (62% vs 50%, p=0.0004), a higher TIMI risk score, a higher fasting glucose or HgbA1c at enrollment. Among patients initially event free who subsequently had events >4 months (Figure 1)HgbA1c (A),glucose (B), LDL (C), and HDL were higher at 30 days and 4 months and CRP (D)was higher at 4 months compared with those who remained event free. Independent predictors of events > 4 months were age, gender, 4 month LDL, HBA1c and CRP. In contrast age was the only significant baseline characteristic associated with events <4 months.
Conclusion: among aggressively treated ACS patients receiving intensive statin therapy, older patients and males remain at high-risk. Poorly controlled metabolic, lipid or inflammatory markers are associated with recurrent events and may be important future targets for additional therapy.

GROWN-UP CONGENITAL PATIENTS FOR THE CARDIOLOGISTS: INTERDISCIPLINARY APPROACH

1978 Organisation of care for adults with congenital heart disease in Europe

P. Moons[1], P. Engelfriet[2], H. Kaemmerer[3], F.J. Meijboom[4], E. Oechslin[5], B.J.M. Mulder[2] on behalf of the Expert committee of Euro Heart Survey on Adult Congenital Heart Di. [1]*Catholic University of Leuven, Center f. Health Services & Nursing Res., Leuven, Belgium;* [2]*Academic Medical Center, Department of Cardiology, Amsterdam, Netherlands;* [3]*Deutsches Herzzentrum, Ped.Cardiol & Congenital heart disease, Munich, Germany;* [4]*Thoraxcenter Erasmus MC, Department of Cardiology, Rotterdam, Netherlands;* [5]*University Hospital, Division of Cardiology, Zurich, Switzerland*

The growing number of adults with congenital heart disease urged the development of recommendations for the management of these patients and for the organisation of health care. Because it is unknown to what extent these recommendations are followed, the Euro Heart Survey on Adult Congenital Heart Disease (ACHD) was initiated. The aim of the present study was to assess how the care for adults with congenital heart disease is provided in Europe.
Methods: In this survey, 71 centres voluntarily participated, of which 48 were specialist and 23 non-specialist centres. Specialist centres were those complying with the following criteria: (1) paediatric cardiology or congenital cardiac surgery available; (2) at least one cardiologist dedicated to ACHD; and (3) more than 200 patients under regular follow-up. Relying on the existing recommendations, we have devised a 20-item questionnaire to evaluate the structure of ACHD programmes in Europe. To test the content and face validity, as well as the feasibility of the questionnaire, this questionnaire was reviewed and commented on by the expert committee of this Euro Heart Survey.
Results: In specialist centres, a median of 500 outpatient visits was made annually. Fifty ACHD hospital admissions and 42 ACHD cardiosurgical procedures were recorded per year. In the non-specialist centres, 75 outpatient visits, 10 hospital admissions, and 4 congenital heart surgery were recorded in ACHD patients per year. In 90% of the specialist centres, the care for ACHD patients was provided by specialized cardiologists with an adult medical background. In only 40% of the specialist centres, a cardiologist with paediatric background was involved. A paediatric cardiologist, a congenital heart surgeon, and an electrophysiologist were available in about 80% of the centres. Only 42% of the centres had one or more specialist nurses in ACHD. We found that only 18.8% of the specialist centres complied with the standards for optimal structure. The criteria that appeared to be most difficult to achieve were 50 congenital heart operations or more per year and the involvement of specialist nurses. Sixty-one percent of the non-specialist centres had a formal collaboration with a specialist centre.
Conclusion: This survey indicated that the provision of care for adults with congenital heart defects in Europe can be considered as suboptimal. In order to complete the successes of cardiac surgery in infants and children, continuous efforts to implement the recommendations on the organisation of care from childhood until adulthood are imperative.

1979 Prolonged long-term survival in adults with Eisenmenger syndrome compared to other forms of pulmonary arterial hypertension related with congenital systemic-to-pulmonary shunt

J.M. Oliver[1], E. Diaz Caraballo[1], P. Gallego Garcia De Vinuesa[2], A. Gonzalez[1], J. Ruiz Cantador[1], A. Sanchez Recalde[1], A. Aroca[1], J.A. Sobrino[1]. [1]*La Paz University Hospital, Adult Congenital Heart Disease Unit, Madrid, Spain;* [2]*Virgen Macarena University Hospital, Seville, Spain*

Background: In the setting of pulmonary arterial hypertension (PAH) related with congenital systemic-to-pulmonary shunt (CSPS), three clinical situations can be distinguished: Eisenmenger reaction, hyperkinetic PAH with dominant left-to-right shunt and severe PAH despite of effective surgical repair or restrictive shunt. Analysis of differences in long-term survival in these forms of PAH secondary to CSPS could have influence on early recommendations for new therapies with pulmonary vasodilators.
Methods: We retrospectively analyzed 66 patients who had pulmonary systolic

pressure > 75 mm Hg, no right ventricular outflow tract stenosis and CSPS, among 2,568 patients > 15 years with congenital heart disease (CHD) seen between 1989 and 2005. Mortality and Kaplan-Mayer curves for actuarial survival after the age of PAH diagnosis or the age of 15 years were compared by log rank test.
Results: Overall prevalence of PAH was 2.6%. Mean age was 41 ± 18 years (range 16-86) and 67% were female. The study population was divided into Eisenmenger reaction (41 patients); hyperkinetic PAH (19 patients) and severe PAH with repaired in childhood or restrictive shunt(6 patients). Complex CHDs were responsible for Eisenmenger's reaction in 68% of the cases, but only 12% of hyperkinetic PAH or repaired/restrictive shunt had a complex CHD. After diagnosis, 42% of adults with hyperkinetic PAH had still criteria for surgery and were subsequently operated on. Overall mortality during 14±10 years of follow-up was 25%. Mortality was 14% in Eisenmenger syndrome, 33% in hyperkinetic PAH and 50% in repaired/restrictive shunt. Actuarial survival in Eisenmenger syndrome was 97%, 94%, 90%, and 80% at 5, 10,15 and 25 years of follow-up, respectively, compared with 86%, 64%, 42%, and 21% in hyperkinetic PAH (log rank 12,7; p<0.001). The group with repaired/restrictive shunt had poor prognosis in terms of lifespan: 40% died at 6 years of diagnosis and none survived more than 11 years of follow-up. Despite no early postoperative major complications, long-term mortality in late repaired hyperkinetic PAH was 37% and all deaths occurred in those with persistent PAH after surgery.
Conclusions: Despite the higher number of complex CHD associated with Eisenmenger syndrome, long-term survival of Eisenmenger reaction with adequate medical care is much better than other forms of PAH related to CSPS, even when repaired. Patients with severe PAH despite of effective surgical repair or restrictive shunt have the worst prognosis.

1980 Outcome of pregnancy in patients after repair of aortic coarctation

J.W.J. Vriend[1], W. Drenthen[2], P.G. Pieper[2], J.W. Roos-Hesselink[3], D.J. van Veldhuisen[2], B.J.M. Mulder[4]. *[1]Academic Medical Center, Dept. of Cardiology B2-216, Amsterdam, Netherlands; [2]University Hospital, Cardiology, Groningen, Netherlands; [3]Erasmus Medical Center, Cardiology, Rotterdam, Netherlands; [4]Academic Medical Center, Cardiology, Amsterdam, Netherlands*

Background: Nowadays most women born with aortic coarctation reach childbearing age. However, data on outcome of pregnancy in women after repair of aortic coarctation are scarce. Aim of this study was to report on maternal and neonatal outcome of pregnancy in women after aortic coarctation repair.
Methods and results: The CONCOR national registry on congenital heart disease in the Netherlands was reviewed for women of childbearing age (= 18 years old) with a history of aortic coarctation repair. Medical history and maternal, obstetrical and neonatal outcome were determined. Fifty-four of the 100 women included, had a history of pregnancy. The 54 women had 126 pregnancies resulting in 98 births. There were 22 miscarriages (miscarriage rate 19%), 5 elective abortions, and 2 neonatal deaths. There were 85 (87%) vaginal deliveries, 7 (7%) vaginal deliveries with epidural analgesia and 6 (6%) caesarean sections. A total of 26 pregnancies (22%) were complicated by a hypertensive disorder of pregnancy, with preeclampsia in 5 pregnancies. During pregnancy, 5 patients had an increase = 15 mmHg across the site of repair at echocardiography, but only 1 patient required reintervention for recoarctation after delivery. Four of the 98 children (4%) had a congenital heart defect.
Conclusion: Pregnancy is well tolerated in women after repair of aortic coarctation. However, an excess of miscarriages and hypertensive disorders of pregnancy were found.

1981 Complications associated with cardiac pacing in congenital heart disease patients

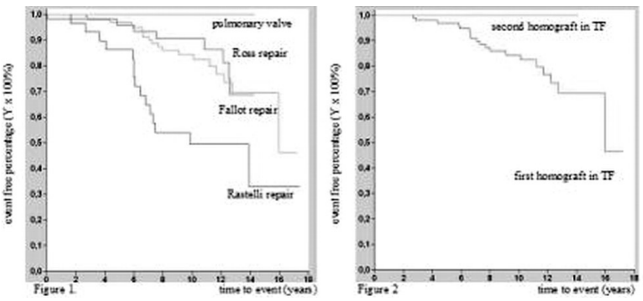
A.A. Khan[1], G.P.D. Gerhard-Paul Diller[2], R.S. Richard Sutton[3], J.C. Johanthan Clague[3], J.T. Jan Till[3], M.G. Michael Gatzoulis[2], M.M. Michael Mullen[2]. *[1]Royal Brompton Hospital, Adult Congenital Heart Disease Program, London, United Kingdom; [2]Royal Brompton Hospital, Adult Congenital Heart Disease Program, London, United Kingdom; [3]Royal Brompton Hospital, Department of Pacing, London, United Kingdom*

Objective- To evaluate incidence, type and clinical manifestations of pacemaker related complications in congenital heart disease(CHD) patients (pts) during long term follow-up.
Methods and Results: We reviewed all 169 pts (85 male) with CHD, in whom a pacemaker had been implanted.Median follow-up was 5.7 years (25 days - 30 years,1335 pts-years).Nine pts died (2 within 30 days of implantation), none due to pacemaker related complications.Major complications occurring in 19 pts (=14.3/1000 pts-yrears) were:(i) Infection in 12 pts (2 within 60 days of implantation; isoltaed lead infection in 3 pts, combination of lead and generator pocket infection in 8 pts;recurrent infection 3 pts).Blood cultures were positive in only 2 of these pts.Clinical signs were low grade fever (8/12), local pain and tenderness (4/4 pts with pocket infection).Echocardiography revealed lead vegetations in only 1 patient.(ii)Cerebrovascular accidents (CVA) in 5 pts(1 transient, 4 persistent deficits,all in pts with endocardial leads),(iii)pulmonary embolism in 1 patient and (iv) obstruction of the superior caval vein in 1 patient.Infection was more common in pts with prosthetic material(RR=3.9,p=0.02),while CVA were more common in pts with an intracardiac shunt(RR=9.9,p=0.01).
Minor complications were:Lead fracture in 4 pts, lead displacement in 6 pts(5 atrial, 1 ventricular),pacemaker sysndrome in 2 pts,oversensing requiring revision in 2 pts and difficulties with lead positioning in 8 pts(1 transposition of the great arteries(TGA),3 congenitally corrected TGA,2 double outlet ventricle, 1 atrial septal defect,1 ventricualr septal defect).
Conclusion: Pacemaker complications are not uncommon in CHD Pts,involving mainly thromboembolism (cerebral and pulmonary)and infections.In our cohort,infections were associated with the presence of prosthetic material, while cerebrovascular accidents occurred only in pts with endocardial leads amd were associated with intracardial shunts.Whether this represents a causal relationship needs to be elucidated.

1982 Single centre experience of homograft survival in adult congenital heart disease

E. Troost[1], W. Daenen[2], B. Meyns[2], M. Gewillig[3], K. Van Deyk[1], W. Budts[1]. *[1]University Hospitals Leuven, Cardiology, Leuven, Belgium; [2]University Hospitals Leuven, Cardiac Surgery, Leuven, Belgium; [3]University Hospitals Leuven, Paediatric Cardiology, Leuven, Belgium*

Background: Homografts have no lifelong survival and redo surgery remains unavoidable. The relationship between homograft survival and the type of surgical intervention remains unclear. We were interested in the survival patterns of homografts on the subpulmonary ventricle.
Methods: Two-hundred-and-ten consecutive patients with homograft implantation were selected from the data base of congenital cardiology. All patients' files were reviewed. Survival analysis was plotted by a Kaplan Meier curve and log-rank testing was performed. P<0.05 was considered as significant.
Results: Fifty-three patients (30 male) underwent a Ross repair at the age of 18±8y. In 18 patients (13 male, age 14±7y) a homograft was implanted in pulmonary position as redo surgery several years after pulmonary valvotomy. Twenty-nine patients (18 male, age 7y, range 0-30y) underwent a Rastelli repair for transposition of the great arteries or truncus arteriosus. Finally, in 110 patients with tetralogy of Fallot (TOF, 66 male), the first homograft was inserted at the age of 16±11y. Most of the latter underwent previous surgical correction with a transannular patch in the right ventricle outflow tract. The survival curves of the first homograft are plotted in Figure 1. The survival of the first homograft, used for Rastelli repair, was significantly lower when compared with the other survival curves (P<0.05). However, the survival of the second homograft used in patients with TOF tended did not differ from the first one (P=0.36, Figure 2).



homograft survival curve

Conclusions: In complex surgical interventions, homograft survival seems to be shorter than in simple surgical repair. In addition, our data suggest that the survival of a second homograft after TOF repair is as good as the survival of the first one.

1983 Pulmonary hypertension in atrial septal defect: natural history and effect on interventional outcome in adults

R. Rosenhek[1], H. Gabriel[2], F. Rader[2], N. Loho[2], M. Heger[2], T. Binder[2], G. Maurer[2], H. Baumgartner[2]. *[1]Wien, Austria; [2]Medical University Vienna, Department of Cardiology, Vienna, Austria*

Background: The natural history of pulmonary hypertension in atrial septal defect (ASD) during adult life and its effect on outcome after late ASD closure has insufficiently been studied.
Methods: 190 patients (136 female, 50±18 yrs, range 16 to 83 yrs) who presented with unrepaired ASD during adult life were included. The relation between pulmonary artery pressure (PAP) and age, defect size, right ventricular (RV) enlargement and symptoms at presentation was studied. Furthermore, the effect of late ASD closure on PAP and the relation between initial PAP and postinterventional outcome was evaluated.
Results: Only 4 of 190 pts presented with severe pulmonary vascular disease (pulmonary vascular resistance > 5 Wood units). All 4 were younger than 30 yrs at presentation and two of them had Eisenmenger physiology. In the remaining 186 pts, PAP was not significantly related to ASD size but correlated closely with age (r=0.6; p<0.0001). Mean syst. PAP was 33±9 mmHg in pts presenting in

their 4th decade and increased to 40±12 and 60±17 in those presenting in their 6th and 8th decade, respectively. PAP was strongly related to symptoms and to RV size at presentation. All 186 pts underwent ASD closure. PAP and RV size decreased and symptoms improved in general. However, 11% of the patients remained symptomatic, PAP remained elevated (> 35 mmHg) in 34% and RV enlarged (> 40mm) in 19%. PAP was again closely related to age (r=0.6; p<0.0001). By univariate analysis, age, PAP, RV size and symptoms at presentation but not ASD size were related to postprocedural outcome with regard to symptoms, PAP and RV size. By multivariate analysis postinterventional PAP and RV size were strongly related to their respective preinterventional values. Furthermore, in multivariate analysis, PAP at presentation was the strongest predictor of postprocudural symptoms.
Conclusion: Severe pulmonary vascular disease is very rare in ASD and occurs in general during early adulthood. PAP however, continuously increases with age. With rising PAP, the likelihood of an unfavorable outcome after ASD closure with regard to symptoms and persisting elevated PAP increases. Therefore, ASD should be closed as soon as possible even in pts presenting during advanced age.

THE NEED FOR PERFUSION: MECHANISMS OF ANGIOGENESIS AND ANGIOADAPTATION

1984 "Side Population" stem cells residing in healthy arteries of adult mouse could participate in vasculogenesis and arterial remodelling

J. Sainz, A. Al Haj Zen, G. Caligiuri, C. Demerens, D. Urbain, M. Lemitre, A. Lafont. *Faculté de Médecine Necker, Inserm EMI 0016, Paris, France*

Background: Eversince circulating hematopoietic stem cells and endothelial progenitor cells were identified in peripheral blood, much work has been devoted to evaluate their contribution to angiogenesis and their participation in vascular repair after injury. In contrast, we do not know whether the normal arterial wall harbors permanently-residing stem cells like many other adult organs.
Objective: The aim of the present study was to identify tissue-residing stem cells within normal adult murine arteries, and to further explore their potential implication in vascular biology, physiology and pathology.
Methods and Results: All experimental procedures involving animals were performed on five to eight weeks-old C57Bl/6 female mice. We characterized stem cells termed Side Population or SP cells in the tunica media of normal murine arteries, using the Hoechst-based method which has become widely used to isolate tissue-residing stem cells. These cells were not hematopoietic stem cells since they did not form hematopoietic colonies when cultured on methylcellulose-based medium (experiments, n=3). To assess arterial SP cell vascular plasticity, SP cells were cultured for two weeks in medium containing either VEGF or TGF-beta. Importantly SP cells differentiated in vitro, either into endothelial cells or into smooth muscle cells, as revealed by the presence of CD31, VE-cadherin and von Willebrand Factor or of alpha-smooth muscle actin and calponin, respectively (experiments, n=4). Moreover, when cultured on undiluted Matrigel basement membrane matrix, these cells generated in two weeks vast vascular-like branching structures composed of both vascular cell types as illustrated by the presence of VE-cadherin-positive cells and alpha-smooth muscle actin-positive cells (experiments, n=4). Last, after having demonstrated that arterial SP cells specifically expressed the ABCG2 transporter, similarly to SP cells from other tissues, we proceeded to ABCG2 histological immunostainings on stenosed, aneurysmal and atherosclerotic arteries. A high proportion of ABCG2-positive cells were found in the neointima as well as in aneurysmal and atherosclerotic lesions, suggesting these SP cells could be involved in the corresponding pathological processes.
Conclusion: Our results bring to light a new cellular actor which could not only participate in arterial homeostasis, angiogenesis and vasculogenesis, but also be involved in pathological vascular remodeling.

1985 Differentiation and function of endothelial progenitor cells: which impact has the micro-environment?

P. Gerzer[1], A.H.P. Linke[2], N. Kraenkel[1], V. Adams[1], S. Erbs[1], G. Schuler[1], R. Hambrecht[1]. *[1]University of Leipzig, Heart Center, Department of Cardiology, Internal Medicine, Leipzig, Germany; [2]University of Leipzig, Heart Center, Department of Cardiology, Internal Medicine, Leipzig, Germany*

Intracoronary and intramyocardial injection of blood-derived endothelial progenitor cells (EPC) has been shown to contribute to an improvement of cardiac function after myocardial infarction. The underlying mechanisms are only partially understood. It was the aim of the present study to determine whether EPCs are terminally committed to an endothelial lineage or whether their fate can still be changed by a specific micro-environment.
Methods: Blood-derived mononuclear cells were cultured in endothelium-specific medium supplemented with growth factors for 4 days. (At this time, adherent cell are considered to be EPCs and are, therefore, used in clinical studies.) Adherent EPCs were now grown for 7 additional days in a basal endothelial medium (BEM) supplemented with VEGF (200 ng/ml) to induce an endothelial lineage commitment, in epidermal growth factor (EGF, 100 ng/mL) to promote differentiation in epithelial cells and in interleukin 2 (IL2, 1200 IU/mL) to support a development into lymphocytes. Adherent EPCs raised for 7 days in basal endothelial medium that did not contain cytokines or specific growth factors served as control (Con). After this time period, adherent cells were detached and analysed for the expression of CD34 (stem cell marker), CD3 (lymphocyte markers), E-cadherin (epithelial marker), and KDR (endothelial marker) using FACS analysis. The functional properties of EPCs were assessed by matrigel and migration assay.
Results: Culture of EPCs in BEM supplemented with VEGF significantly enlarged the proportion of CD34+/KDR+ cells by 48±8% (p<0.05) as compared to Con. Additionally, the migratory capacity of EPCs was increased after exposure to VEGF by 116±25% and the ability of EPCs to incorporate into vascular networks by 112±14% (p<0.05 vs. Con). When EPCs were grown in BEM+IL2 an lymphocyte lineage commitment with an increase in the number of CD3+ cells by 156±34% (p<0.05 vs. Con) was observed, accompanied by a reduction in the amount of CD34+/KDR+ stem cells with an endothelial phenotype by 60±6% in comparison with Con. IL2 significantly attenuated the ability of EPCs to incorporate into vascular structures by 68±10% and their migratory capacity by 61±9% (p<0.05 vs. Con). Culture of EPCs in BEM containing EGF resulted in an epithelial lineage commitment with a significant expansion of CD34+/E-Cad+ cells by 75±15% as compared to Con (p<0.05).
Conclusion: These data suggest, that the mico-environment in which EPCs are homing impacts substantially on the fate of these cells and might therefore modulate the therapeutic potential of EPCs.

1986 RoY- a novel synthetic peptide induces angiogenesis in a mechanism that is independent of VEGF expression

C. Weiss[1], A. Raiter[1], A. Battler[2], B. Hardy[3]. *[1]Tel-Aviv University School of Medicine, Felsenstein medical Research Center, Petah-Tikva, Israel; [2]Rabin Medical Center and Tel-Aviv Univ, Cardiology and Felsenstein Med Res, Petah-Tikva, Israel; [3]Tel-Aviv University School of Medicine, Felsenstein Medical Research Center, Petah-Tikva, Israel*

Background: We have identified a novel 12 amino-acid synthetic peptide, RoY, selected from a phage display peptide library by screening against endothelial cells under hypoxia. RoY peptide specifically binds endothelial cells, induces potent angiogenesis under hypoxia as manifested in vitro by proliferation, migration and tube formation of endothelial cells.
Objectives: To elucidate the mechanism of RoY peptide angiogenic activity under hypoxia by gene expression and signal transduction
Methods: Endothelial cells were incubated in serum free media with RoY peptide (10ng/ml) for 3 and 24 hours under hypoxia followed by RNA extraction. cDNA was labeled with dUTP-biotin and hybridized with Gene Array membranes (96 genes, SuperArray, Bethesda, MD). Results were validated using RT-PCR method. VEGF gene expression was quantified by Real Time PCR using TaqMan probes and normalized with GAPDH.
ERK signaling using anti phospho-ERK was determined by western blot analysis of cell lysates prepared from endothelial cells incubated with RoY peptide (100ng/ml) in starvation conditions for different times.
Results: Gene array, confirmed by RT-PCR, revealed up-regulation of angiogenesis growth factors Angiopoitin-2 and bFGF, Up-regulation of chemokine CCL20 and of the anti-apoptotic gene TNF-RSF10D. In contrast, determination of VEGF gene expression in endothelial cells incubated with RoY peptide for 3 or 24 hours resulted in no significant up-regulation (1.03-1.17 peptide/control fold expression). Since it is generally considered that growth factors primarily stimulate the ERK pathway under hypoxia, we studied activation of ERK. RoY peptide induced ERK phosphorylation 15 minutes post incubation with endothelial cells.
Conclusion: RoY is a synthetic peptide that exhibits angiogenic properties under hypoxia by up regulation of growth factors, cytokines and anti apoptotic genes. RoY peptide activity is VEGF independent thus suggests a way to bypass classical VEGF angiogenic system.

1987 Anti-angiogenic action of PPARg ligands through COX-2-mediated MMP-9 expression and release

E. Scoditti[1], M. Massaro[2], M.R. Montinari[2], M.A. Carluccio[1], C. Storelli[2], A. Distante[1], R. De Caterina[3]. *[1]Institute of Clinical Physiology, CNR, Lecce, Italy; [2]University of Lecce, Department of Biology, Lecce, Italy; [3]"G. d'Annunzio" University-Chieti, Director, University Cardiology Division, Chieti, Italy*

Angiogenesis contributes to diabetic vascular complications. The pro-inflammatory COX-2 gene is involved in angiogenesis, partially through a link with endothelial matrix metalloproteinases (MMPs). We used the thiazolidinedione(TZD) rosiglitazone (RSG), a peroxisome proliferator-activated receptor (PPAR)γ ligand, as a tool to assess the role of PPARγ in angiogenesis, on the basis of recent reports of RSG as an anti-angiogenic agent. To this purpose, we investigated RSG effects on endothelial proliferation, COX-2 expression and related MMP release in human umbilical vein endothelial cells (HUVEC) challenged with proinflammatory (cytokines) and mitogenic (phorbol myristate acetate-PMA) stimuli.
Methods and Results: By immunocytochemistry and immunofluorescence we first investigated the subcellular localization of PPARγ in HUVEC, and observed

a clear nuclear localization of the receptor. In the absence of any toxicity and anti-proliferative effects, RSG, at concentrations 10 μmol/L, significantly ($p<0.01$) reduced MMP-9 release (by 40%, Western blot and zymography) and COX-2 expression and activity (by 50%, Western blot and immunoassays for 6-keto-PGF1a), through inhibition of the p65 NF-κB component nuclear translocation (immunofluorescence and gel shift assays). This effect was mimicked by GW1929, a non-TZD PPARγ ligand, and completely reverted by the PPARγ antagonist bisphenol-A-diglycidyl ether (BADGE), as a test for specificity. Since the extracellular signal-regulated kinase (ERK1/2) is involved in signaling upstream of COX-2 and MMP-9 expression, we investigated the effect of RSG on ERK1/2 activation. RSG treatment reduced ERK1/2 activation. Correspondingly, RSG, as well as the ERK1/2 inhibitor PD98059 and the COX-2 inhibitor NS398 inhibited endothelial migration in a scratch wound model and capillary-like endothelial tube formation in a matrigel system, confirming ERK1/2 and COX-2 involvement in the anti-angiogenic effects of RSG.
Conclusions: The anti-angiogenic action of PPARγ ligands occurs, at least in part, through the inhibition of COX-2-related MMP-9 release by an upstream interference with ERK activation.

1988 Aspirin but not clopidogrel attenuates collateral artery growth in an experimental peripheral artery disease setting

S. Grundmann[1], I. Hoefer[2], S.H. Schirmer[3], N. van Royen[4], I. Buschmann[5] on behalf of the Art.Net.-Investigators. [1]*Research Group for Arteriogenesis, Department of Cardiolgy, Freiburg, Germany;* [2]*Perfusion Technologies GmbH, Freiburg, Germany;* [3]*Research Group for Arteriogenesis, Department of Cardiology, Freiburg, Germany;* [4]*Academic Medical Center, Cardiology, Amsterdam, Netherlands;* [5]*Charite, Department of Cardiology, Berlin, Germany*

Collateral artery growth (arteriogenesis) proceeds by way of leukocyte/monocyte homing to recruited pre-existing arteriolar connections. After transmigration through the vessel wall into the peri-vascular tissue, monocytes mature into macrophages and release a variety of cytokines and growth factors that in turn lead to growth of the anastomoses into functional collateral arteries. This important rescue mechanism for occlusive arterial diseases (e.g. CHD, PAD) thus shares many common features with inflammatory processes. The aim of the current study therefore was to examine the effects of different platelet inhibitors with and without anti-inflammatory properties on arteriogenesis.
Methods: After ligation of the right femoral artery, 54 New Zealand White rabbits were divided into three groups, n=18 each. Group 1 received 10mg/kg aspirin once daily per os, whereas group 2 received clopidogrel in the same manner. Group 3 served as control and received solvent only. Seven days later, collateral conductance was measured in-vivo via fluorescent microspheres, injected at six different pressure levels (n=6 per group). Post-mortem high-resolution angiograms were used to quantify the number of detectable collateral arteries (n=6 per group). Quantitative immunohistochemistry and flow cytometry were performed to investigate the mechanisms of substance action.
Results: While clopidogrel neither affected angiographic appearance nor collateral conductance, aspirin significantly reduced the arteriogenic response (Collateral Conductance: Solvent: 50.70 ± 11.52; Clopidogrel: 49.53 ± 14.22; Aspirin: 32.55 ± 9.54 ml/min/100mmHg; $p<0.05$). These data were confirmed by a significant inhibition of vascular smooth muscle cell proliferation, leukocyte migration and leukocyte activation under aspirin treatment.
Conclusion: In a PAD setting, clopidogrel acts neutral on natural adaptive arteriogenesis. Aspirin significantly inhibits arteriogenesis in this model, most likely due to its anti-inflammatory effects. This observation might be of potential value for the prescription of the appropriate platelet inhibitor in case of occlusive arterial diseases. Clinical studies are on the way to evaluate this important experimental finding.

1989 Complex effect of atorvastatin on angiogenic gene expression in normoxic and hypoxic microvascular endothelial cells

A. Loboda[1], A. Jazwa[1], A. Jozkowicz[1], G. Molema[2], J. Dulak[1]. [1]*Jagiellonian University, Dept. of Cell. Biochemistry, Krakow, Poland;* [2]*University of Groningen, Dept. Pathology Laboratory Medicine, Groningen, Netherlands*

Background: Hypoxia is the crucial modulator of angiogenesis. Statins, the inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase were also reported to affect blood vessel formation. However, very limited data are available on effects of statins on angiogenic gene expression in hypoxia. Therefore, here we investigated the effect of atorvastatin in normoxic and hypoxic human microvascular endothelial cells (HMEC-1).
Methods and Results: As expected, hypoxia (1% oxygen, 6-24 hours) strongly upregulated the expression of pro-angiogenic VEGF-A but, unexpectedly, it significantly decreased pro-angiogenic IL-8, as shown by real-time RT-PCR and verified by ELISA. Array analysis for the angiogenic transcriptome showed that hypoxia increased the expression of pro-angiogenic VEGF-D and endoglin. On the other hand, anti-angiogenic thrombospondin-1 (TSP-1) and tissue inhibitor of matrix metalloproteinases-1 and 2 (TIMP-1 and TIMP-2) were down-regulated. Atorvastatin at physiologically relevant concentration (0.1-1 μM) enhanced the expression of VEGF-D and endoglin in normoxia, but in hypoxia it attenuated their expression. On the other hand atorvastatin inhibited TSP-1 and IL-8 synthesis in normoxia, diminished hypoxia-induced VEGF production and further aggravated the decrease in expression of IL-8 and TSP-1 caused by hypoxia. The inhibitory effect of atorvastatin in hypoxia is exerted through attenuation of HIF-1 transcription factor activity.
Conclusions: The effect of atorvastatin on angiogenic gene expression in hypoxic HMEC-1 cells appears to be complex, as it inhibits the production of both pro-angiogenic VEGF-A, VEGF-D and IL-8 as well as anti-angiogenic TSP-1, but in normoxia enhances the expression of VEGF-D and endoglin. Interestingly, hypoxia itself influences in the opposite way the expression of two pro-angiogenic genes, augmenting VEGF and decreasing IL-8. In microvascular endothelial cells, the major players in angiogenesis, atorvastatin seems to exert mostly anti-angiogenic effect.

DRUG-ELUTING STENTS: BARE METAL STENTS STILL IN ISSUE IN 2005?

1998 Results following implantation of drug-eluting stents in large coronary vessels: any benefit compared to bare metal stents?

E. Tsagalou[1], A. Chieffo[1], I. Iakovou[2], L. Ge[2], F. Airoldi[1], M. Montorfano[1], M. Carlino[1], A. Colombo[2]. [1]*San Raffaele Hospital, Milan, Italy;* [2]*Columbus Hospital, Milano, Italy*

Background: Implantation of drug eluting stents (DES) has been reported to decrease the rate of restenosis, compared to bare metal stents (BMS), in coronary arteries with reference diameter ranging from 2.5 to 3.5 mm. Whether this favorable effect would persist in the subset of lesions located on large vessels has not yet been clarified.
Methods: All consecutive patients who underwent percutaneous coronary interventions on de novo coronary artery lesions with implantation of BMS (BMS group, n=381) between June 2001 and March 2002 and DES (DES group, n=318) between April 2002 and April 2004, and had stents dilated with a final balloon ≥3.5mm in diameter were analyzed.
Results: Patients treated with DES had a greater prevalence of hypertension (69% versus 54%, p=0.0001) and hypercholesterolemia (68% versus 53%, p=0.0001). The mean baseline reference vessel diameter (3.24±0.54mm for BMS and 3.16±0.52mm for DES, p=0.036) was bigger in the BMS group while the mean stent length per lesion was longer in the DES group (25±13mm for DES versus 20±9mm for BMS, p=0.0001). The average follow up period was 8.5±2.6 months. There was a significant decrease in the major adverse cardiac events (MACE) in the DES group (10.9% versus 21.3%, p=0.0001), mainly driven by a significant decrease in target vessel revascularization (9.1% versus 19.7%, p=0.0001). At the multivariate analysis diabetes mellitus, post procedural reference diameter, use of DES and stent length per lesion were all predictors of target lesion revascularization (TLR).
Conclusions: Drug eluting stent implantation in relatively large native coronary arteries is associated with a significant decrease in MACE mainly due to the reduction of TVR.

1999 Low incidence of revascularisation of bare metal stents in the era of drug eluting stents

H.A. Jilaihawi[1], S.Q. Khan[2], J.D. Skehan[1], J. Kovac[1]. [1]*Glenfield Hospital, Department of Cardiology, Leicester, United Kingdom;* [2]*University of Leicester, Department of Cardiovascular Sciences, Leicester, United Kingdom*

The use of drug eluting stents has dramatically reduced the impact and incidence of both angiographic and clinically significant in-stent restenosis. However, in parallel to this development, there has been an ongoing improvement in bare stent technology. We were keen, therefore to study the incidence and determinants of clinically significant in-stent restenosis and the influence of stent type deployed on this endpoint.
Methods: We studied information contained in our database pertaining to patients undergoing coronary stenting between the 1st of January 2003 and 7th November 2004. The end point of clinically driven Percutaneous Target Lesion Revascularisation (TLR) at 12 months was used, defined as return for intervention to the same lesion within the specified follow-up period after the original intervention. This was used as the dependent variable and entered into a multivariate binary logistic regression model with diabetes, clinical instability, total stent length, minimum stent diameter and individual type of stent (drug eluting Taxus and Cypher or most commonly used bare metal stents including Zeta, Driver and Sonic) used as covariates.
Results: 1112 patients underwent stenting to an average of 1.4 vessels using a mean total stent length of 23.4 mm and an average minimum diameter of 3.1mm. The TLR rate was 4.9% of all patients at 12 months (54 cases). It was higher in diabetics (7.3% of 219 patients; p=0.04), and in unstable cases (6.7% of 208 patients;p=NS). It was lower in those receiving drug eluting stents (2.8% of 109 patients;p=NS) relative to those receiving only bare metal stents, although even in

thosereceiving the latter TLR was low (5.1% of 1003 patients). With regard to specific commonly used bare metal stents there were slight albeit statistically insignificant differences. TLR was seen in 5.8% of 467 Zeta cases, 4.9% of 329 Driver and 5.4% of 93 Sonic cases. In the multivariate model only diabetes was a significant predictor of TLR, perhaps due to the overall low event rate observed. Overall 1 year mortality was low (2.8%) and unrelated to prior need for TLR (p=0.669).
Conclusion: Clinically significant restenosis with need for revascularization is currently low in our practice, perhaps suggesting that more expensive strategies such as drug eluting stents to reduce this phenomenon should be reserved for patients at higher risk such as diabetics or those with unstable coronary artery disease. There may be a lower incidence of TLR with new non steel stent platform designs relative to other bare metal stents.

2000 Randomised trial comparing sirolimus eluting stents versus bare metal stents in severely diseased spahenous vein graft treatment: six month clinical and angiographic outcome

P. Vermeersch[1], G. Vanlangenhove[2], C. Convens[2], C. Stockman[2], F. Van den Branden[2], S. Verheye[2], P. Van den Heuvel[2]. *[1]Hove, Belgium; [2]AZ middelheim, Cardiology, Antwerpen, Belgium*

Background: Drug eluting stents (DES) have been shown to be highly succesfull in reducing restenosis in native coronary disease. Percutaneous treatment of saphenous vein grafts (SVG) with DES remains controversial. Since the mechanism of in-stent restenosis in SVG differs from native coronary arteries, the benefit of DES as yet remains to be shown in randomized trials. We therefor initiated a randomized trial comparing DES with bare metal stent (BMS)in SVG treatment.
Methods: 75 patients with at least one de novo lesion in a SVG were randomized in a double-blind fashion between sirolimus eluting stent (SES)and BMS. Both groups recieved the same post-procedural standard of care. Clinical and 6-month angiographic and intravascular (IVUS) follow-up was performed.
Results: All patients have reached the 6-month angiographic follow-up date.
In total 94 lesions were treated in 82 grafts. Acute clinical and angiographical succes was 100%.Table 1 shows the angiographic results of the first 60 patients. During the first 6 months one patient(pt) died in the SES group. Target vessel (TV) failure occurred in 14 patients in the BMS group and in 3 patients in the SES group.

Table 1

	cypher	bare metal stent	p -value
MLD pre (mm)	1.14±0.54	1.15±0.53	
reference diameter pre(mm)	3.27±0.57	3.38±0.79	
% stenosis pre	66±15	66±14	
MLD post (mm)	2.95±0.44	2.83±0.55	
reference diameter post(mm)	3.49+/_0.49	3.44±0.68	
% stenosis post	15+/_7	17±8	
MLD at follow-up(mm)	2.46±0.63	1.84±0.91	
reference diameter at follow-up(mm)	3.35±0.49	3.30±0.61	
% stenosis at FU	27±15	46±22	
binary restenosis%	6	38	=0.001
late loss in stent (mm)	0.50±0.51	0.99±0.57	<0.0005
late loss in lesion (mm)	0.53±0.49	1±0.57	<0.0005
length of the lesion	19.72±9.3	17.42±10.15	

Conclusions: SES implantation in SVG results in a significant reduction in late loss and binary restenosis, resulting in less TV revascularization.

2001 Do drug-eluting stents reduce in-hospital events compared to bare metal stents? First results of the prospective Basel stent cost-effectiveness trial (Basel Stent Kosten Effektivitaets Trial)

C. Kaiser[1], H.P. Brunner-La Rocca[2], A. Zutter[2], A. Bernheim[2], S. Osswald[2], P. Buser[2], A. Linka[2], M. Pfisterer[2]. *[1]Basel, Switzerland; [2]University Hospital, Cardiology, Basel, Switzerland*

Background: Drug-eluting stents (DES) have been proven to reduce restenosis and improve outcome of coronary interventions in selected patients compared to bare metal stents (BMS). However, there is no prospective randomised data comparing DES and BMS regarding in-hospital events in a real world setting.
Methods: The Basel stent cost-effectiveness trial (BASKET) is the first prospective randomised trial to compare DES and BMS in consecutive, non-selected patients on a "all-comer" basis. Between May 2003 and June 2004 all patients referred for interventional therapy of coronary disease were randomised to receive either sirolimus-eluting, paclitaxel-eluting or BMS irrespective of clinical presentation or lesion characteristics. Only exclusion criteria were no consent, in-stent-restenosis and vessel size ≥4mm. Clinical follow-up for major events is performed after 6 and 18 months including stress myocardial perfusion scintigraphy after 6 months. This first analysis compares in-hospital major events, i.e. death, non-fatal myocardial infarction and target lesion/vessel revascularisation (TLR/TVR) up to discharge.
Results: A total of 806/988 patients (82%) could be enrolled, while 46 patients were treated for in-stent-restenosis and 136 did not consent or appropriate stent sizes were not available. Overall in-hospital mortality was 1.2%, infarction rate 1.5% and the rates of TVR 2.2% or TLR 0.9% for a total event rate of 4.0%. There were no differences between subgroups with DES vs. BMS (Table 1). Major predictors of in-hospital events were acute infarction, 3vessel-disease and number of stented segments.

In-Hospital MACE:

	BASKET (all, n=806)	BASKET (SIR, n=261)	BASKET (PAC, n=276)	BASKET (BMS, n=269)	p-value
Death (%)	1.2	0.8	1.1	1.5	
Non fatal MI (%)	1.5	1.5	0.7	2.2	
Target vessel revascularisation (%)	2.2	1.5	2.6	2.6	
Target lesion revascularisation (%)	0.9	0.8	0.7	2.2	
Any event (%)	4.0	3.1	3.2	5.6	0.25
Stent thrombosis (%)	0.7	0.8	0.7	0.7	

SIR: sirolimus-eluting stents. PAC: paclitaxel-eluting stents, BMS: bare metal stents.

Conclusions: Thus, in an unselected large patient population, DES did not reduce in-hospital events compared to BMS.

2002 The European multicenter, randomised, double-blind study of the sirolimus-eluting stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS): 3-year clinical outcomes

V. Legrand[1], J. Schofer[2], Y. Taeymans[3], B. Reimers[4], F. van den Branden[5], G. Breithardt[6], H. Gershlick[7], W. Wijns[8]. *[1]La Reid, Belgium; [2]center for cardiology and vascular int, Hamburg, Germany; [3]university hospital, Gent, Belgium; [4]cardiology, Mirano, Italy; [5]Middelheim Ziekenhuis, Antwerp, Belgium; [6]university hospital, cardiology and angiology, münster, Germany; [7]glenfield hospital, Leister, United Kingdom; [8]Cardiovascular center, Aalst, Belgium*

The randomized double-blind E-SIRIUS trial enrolled 352 patients at 35 centers in Europe and Israel to compare the safety and efficacy of the Sirolimus-eluting stent (SES, n = 175) vs the identical appearing bare-metal stent (BMS, n = 177) in the treatment of native de novo coronary artery lesions. The primary endpoint was in-stent minimum lumen diameter (MLD) at 8-month follow-up. Among the secondary endpoints were major adverse cardiac events (MACE) at 1, 6, 9 and 12 months – and annually up to 5 years –, as well as target lesion revascularization (TLR), target vessel revascularization (TVR) and target vessel failure (TVF) at 9 months. The superiority of the SES over the BMS was clearly demonstrated angiographically, with a binary in-lesion restenosis rate at 8 months of 5.9% (vs BMS 42.3%). At 2 years, the clinical benefit of the SES over the BMS was maintained, with a statistically significantly lower incidence of major adverse cardiac events (10.3% vs 29.9%). This difference in incidences was primarily driven by a significant difference in TLR rates (5.1% vs 26.6%). With event-free survival curves for SES and BMS patients still diverging at 2 years, there was no indication of a "late catch-up" phenomenon. Three-year clinical follow-up of patients enrolled in E-SIRIUS will be analyzed by July 2005. Results for the overall patient cohort will be available at the time of presentation.

2003 Differential use of bare metal short stents and drug eluting stents for selected lesions yields a low restenosis rate while reducing costs of PCI

U. Dietz, C. Dauer, H. Lambertz. *German Clinic For Diagostic, Cardiology Dept., Wiesbaden, Germany*

We have shown that routine use of a short stent (<8mm) (SS) is feasible in about 60% of all PCI yielding a restenosis rate of 14%. We investigated the feasibility and restenosis rate of a protocol where either an SS or a drug eluting stent (DES) was used in lesions that are not suitable for short stenting or in those with a high likelihood for restenosis (e.g., small vessel diameter) after bare metal SS, in a prospective study. The interventional protocol demanded stent implantation in every lesion according to the following criteria: (1) implantation of a single bare metal SS (MultiLink) if the vessel diameter was >2.6mm and the length of vessel obstruction >30% was < 10mm after preceding PTCA; (2) in all other lesions, a DES (Cypher or Taxus) was implanted. The protocol was followed in 150 con-secutive patients and 161 lesions, respectively. Among patient characteristics 72/150 (48%) had unstable angina pectoris and 36/150 (24%) diabetes. The reference diameter was 2.8 ± 0.3mm, the MLD 0.7 ± 0.2mm, and the lesion length 11 ± 4mm. An SS was found to be suitable in 124/161 (76%) of lesions; DES were implanted in 37/161 (23%) of lesions. In 5 lesions an additional stent had to be used after an SS. Placement of 3 DES was not possible; a longer bare metal stent was implanted instead. The length of the SS was 8.4 ± 0.4mm and of the DES 22 ± 12mm. Angiographic success was achieved in 97% (156/161) of lesions and procedural success in 96% (144/150) of patients. During the 6 month follow-up, 1 patient suffered a myocardial infarction. Angiographic control was performed after 6 months in 140 of 144 patients. Restenosis was found in 12/148 (8.1%) lesions; of those 10/114 occurred after SS and 2/34 after DES. All in-stent restenoses were classified as focal lesions. Reintervention was performed in 10 lesions with a resulting TLR of 10/148 (6.8%).
Conclusion: the differential use of bare metal short stents and drug eluting stents according to prognostic lesion characteristics yields an acceptable restenosis rate at reduced costs compared to routinely used DES.

REAL-TIME 3D ECHO: A CLINICAL REALITY?

2009 Value of real time three-dimensional dobutamine stress echocardiography in patients qualification towards severe ischaemic mitral regurgitation to cardiosurgical treatment

J. Kochanowski, P. Scislo, D. Kosior, R. Piatkowski, S. Stawicki, G. Opolski. [2]*Warsaw Medical University, Cardiology, Warsaw, Poland*

The aim of our study was to evaluate the optimal surgical approach in pts with severe post myocardial infarction (AMI) mitral regurgitation (MR) based upon real time three-dimensional dobutamine stress echocardiography (DSE 3DRT)–coronary artery by-pass grafting alone (CABGa) or CABG with mitral reconstruction(CABGmr).

Material and methods: The study group was 32 pts (F/M 10/22, mean age 63±11 year) with severe MR assessed by echo during 2-8 weeks after AMI. All pts were qualified to CABG due to multiple vessel coronary disease and significant LV dysfunction (EF<40%,WMSI 1.9±0.5). Control group was 32 healthy subject matched with age and sex.

Prior to surgery, 2-D and 3DRT evaluation were performed in all study pts, for precise evaluation of mitral valve apparatus and 3D MR degree assessed by 3D-PISA, 3D-vena contracta and mitral deformation indexes (MDI). DSE 3DRT examinations were performed for evaluation of LV viability and MR. 3DRT echo were done with Sonos 7500 and iE 33, Philips. DASE were done according the standard protocol and were digitally recorded for assessment by 2 independent cardiologists.

Results: Group I (Gr. I)was with 12 pts with no significant impact of DBX infusion of MR severity assessed in DSE 3DRT; Group II (Gr. II) were 15 pts in whom significant MR severity decrease without significant influence on WMSI and MDI improvement in comparison to Gr. I. Five pts with significant MR severity decrease and MDI improvement, with non-significant improvement of WSMI during DBX infusion in comparison with Gr. I and II was considered as Group III (Gr. III) during further analyses (Tbl I). Pts from Gr. I and II were offered CABGmr; Gr. III was assigned to CABGa.

After CABGa (Gr. III) there were 3 pts with small MR, 2 mild and no severe. After CABGmr (Gr. I + II) there were 20 pts with small MR, 7 mild and no severe.

Table 1. Influence of DSE 3DRT on the mitral valve deformation indexes and WMSI

MDI and WMSI	Control group 32 pts	Before DASE 32 pts	No influence on MR 12 pts (Gr. I)	Decreased MR 5 pts (Gr. III)	Decreased MR 15 pts (Gr. II)
Tenting area (cm^2)	0.5±0.2	3.6±1.0	3.4±1.0	0.8±0.4*	3.2±1.0
Coaptation height (cm)	0.3±0.1	1.4±0.4	1.3±0.4	0.5±0.1*	1.2±0.5
Systolic mitral annulus area (cm^2)	7.2±1.0	11±2.1	11±2.0	8.0±1.0°	10±2.1
WMSI	1.0	1.9±0.5	1.7±0.5	1.4±0.5[a]	1.7±0.5

*p<0,001 vs Gr I and II, ° p<0,05 vs Gr I and II, [a]p=0,27 vs Gr I and II

Conclusion: DSE 3DRT is a precise method to evaluate the exact surgical approach to pts with severe MR with ischemic etiology followed AMI assigned to CABG.

2010 3D real time dobutamine stress echocardiography vs 2D stress echocardiography at patients with coronary artery disease

P. Scislo[1], J. Kochanowski[2], R. Piatkowski[2], D. Kosior[2], G. Opolski[2]. [1]*Warsaw, Poland;* [2]*The Warsaw Medical University, Department of Cardiology, Warsaw, Poland*

The aim of the study was to assess a new 3D real time quantification method used during diagnostic dobutamine stress echocardiography at patients with clinical suspicion of coronary artery disease.

We analyzed 37 patients (pts) referred to diagnostic stress echocardiography (DSE) before planned coronarography. DSE was done using full dose protocol (0-10-20-30-40 - mcg/min dobutamine + atropine if needed in 5-3-3-3 minutes) on Philips iE33 system with 3D Qlab advanced package. On the end of each step 2D (DSE) and 3D (3DDSE) full volume were digitally recorded.

First independent observer assessed LV contractility using standard 17 segment model (subjective classification: normo, hipo, akinesis). Second independent observer, using 3D Advanced tool reconstructed 17 segments 3DLV shape. Contractility of each segment 3DLV were analyzed using contractility curves.

All patients had coronary angiogram.

We compare diagnostic values of standard DSE and 3DDSE in comparison to results of coronary angiogram.

Table 1. Diagostic parameters of 3DDSE and DSE

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
3DDSE	90%	96%	90%	96%
DSE	80%	88%	72%	92%

Conclusion: Because of three dimensional real time analysis 3D dobutamine stress echo has better diagnostic value than standard 2D assessment in identification of patients suspected of caoronary artery disease.

2011 Quantification of left ventricular volumes and ejection fraction by real-time three-dimensional echocardiography: comparison with cardiovascular magnetic resonance

E. Claver, R. Leta, S. Pujadas, P.A. Kociubinski, F. Carreras Costa, G. Pons-Llado. *Hospital Sant Pau, Department of Cardiology, Barcelona, Spain*

Three-dimensional echocardiography (3DE) is a potentially useful tool for the assessment of left ventricular (LV) volumes and function. Comparison studies with an established reference standard, as cardiovascular magnetic resonance (CMR) are, however, scarce.

Objective: We sought to analize the ability of 3DE in the assessment of LV volumes and ejection fraction (EF) in non selected patients, using CMR as a gold standard.

Methods: 25 patients (19 men; age 55.4±17 years), in whom a CMR study (Philips Intera 1,5T) including a complete assessment of LV function was performed, were studied immediately after by 3DE (Philips Sonos 7500). LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and LV EF were calculated by both techniques by two independent observers blinded to the results of each other. 3DE images were postprocessed offline using the software TomTec 4D LV Analysis® (TomTec Imaging Systems® GmbH). The semi-automatic border detection was used in all cases, although it could be modified manually, according to the investigator criteria. The analysis using 3DE was performed in all cases by a second investigator blinded to the results of the first one and to those from the CMR. Results are expressed as mean±standard deviation (SD), except for accuracy (mean±2 SD, following Bland-Altman analysis for the agreement). SE means standard error.

Results: In 20/25 patients (80%) acoustic window was judged as adequate. Results including all 25 patients from the study group are shown in the Table. Results considering only those 20 patients with adequate acoustic window did not significantly improve respect to those from the whole group.

Table

	3DE	CMR	r	Accuracy (%)	P	3DE interobserver
EDV	143±50 ml	154±51 ml	0.62	9±53	0.19	6 (SE 5.4)
ESV	66±30 ml	67±38 ml	0.65	1.8±82	0.87	0.54 (SE 5.9)
EF	54±11%	58±15%	0.65	7.1±35	0.09	4.5 (SE 2.2)

Conclusions: In non selected patients, 3DE is only moderately reliable in the assessment of LV volumes and EF when compared with CMR. 3DE tends to underestimate EDV and, as a consequence, also left ventricular EF, in comparison with CMR. Dependency from the observer and quality of the acoustic window do not seem to be determinant factors in these results.

2012 Accuracy and feasibility of online 3D echo for measurement of LV parameters

C. Jenkins[1], J. Chan[2], L. Hanekom[2], T.H. Marwick[2]. [1]*University of Queensland, School of Medicine, Brisbane, Australia;* [2]*University of Queensland, School of Medicine, Brisbane, Australia*

Background: The clinical application of real-time 3D echo (RT3D) to LV volume calculation has been limited by use of off-line, semi-automated measurement in at least 8 views. The availability of on-line software with less user interaction may increase the feasibility of RT3D for clinical use. We sought to compare off- and on-line approaches against magnetic resonance imaging (MRI).

Methods: Pts who presented to the clinical laboratory for evaluation of LV parameters (n=110, 94men, age 63+10) were studied with 2DE, online and offline RT3D and MRI. RT3D measurements were obtained a semi automated LV border detection based on tracing (online; QLab, Philips, Andover) and edge detection (offline; 4D LV analysis, Tomtec, Germany). MRI images were obtained using true FISP during breath-hold (Siemens Sonata 1.5T) and 3D volumes and EF were measured using CIM software (Auckland University).

Results: All echo techniques underestimated LV volumes (see Table), but EF estimations were similar. The best correlation was between MRI vs offline 3D. The correlation of online RT3D with MRI was significantly better than 2DE approach (EDV Z=4.2; ESV Z=4.44; EF Z=4.32, all p<0.01). However, correlation of offline RT3D with MRI was significantly better than online 3DE (EDV Z=2.57, p<0.05; ESV Z=2.42, p<0.05; EF Z=3.82, p<0.01). Images were considered to be good quality (endocardium visualized in all walls) in 50 pts; discrepancies between online and offline RT3D and MRI were similar with good and poor quality images. Wall motion abnormalities were present in 98 pts; discrepancies with MRI were similar in pts with and without wall motion abnormalities.

Table 1

	EDV (MRI 180 + 55mls)	R (echo vs. MRI)	F (echo vs. MRI)	ESV (MRI 93 + 50mls)	R (echo vs. MRI)	F (echo vs. MRI)	EF (MRI 50 + 13%)	R (echo vs. MRI)	F (echo vs. MRI)
Offline RT3D	164+49	0.86*	1.24 P=0.12	83+39	0.91*	1.66*	51+10	0.81*	1.72*
Online RT3D	136+37	0.78*	2.17*	72+31	0.86*	1.66*	49+11	0.64*	1.33 P=0.07
2D Echo	110+32	0.71*	2.89*	59+27	0.80*	3.52*	48+12	0.61*	1.26 P=0.22

P<0.01*

Conclusions: Online measurement of LV volumes is feasible and more accurate

than with 2D. Differences in the 3D techniques may due to amount of interpolation and user interaction with each technique.

2013 Feasibility and accuracy of real-time transthoracic three-dimensional echocardiographic assessment of ventricular septal defects

A. Van den Bosch[1], A. Ten Harkel[2], J.S. McGhie[3], J.W. Roos-Hesselink[3], M.L. Simoons[3], A.J.J.C. Bogers[4], F.J. Meijboom[3].
[1]Thoraxcenter, erasmus MC Rotterdam, Cardiology Dept., Rotterdam, Netherlands; [2]Erasmus MC, Pediatric cardiology, Rotterdam, Netherlands; [3]Thoraxcenter, erasmus MC Rotterdam, Cardiology, Rotterdam, Netherlands; [4]Erasmus MC, Cardiac-thoracic surgery, Rotterdam, Netherlands

Background: The aim of this study was to evaluate the feasibility and accuracy of real-time transthoracic 3D echocardiography (RT-3DE) in the determination of the position, size and shape of VSDs.
Methods: Between July and December 2004, 25 patients who were scheduled for surgical closure of a VSD, were enrolled in the study. The VSD localisation, shape and measurements of minimal and maximal diameter from 'en face' LV and 'en face' RV view were assessed from the 3D data set. These 3D data were compared with measurements and descriptions done by the surgeon during the surgical procedure. RT-3DE was performed with Hewlett-Packard Sonos 7500 echo-system and off-line analysis with TomTec Echoview® software.
Results: Acquisition of RT-3DE datasets was feasible in 22 of the 25 (88%) patients. In 3 patients, the quality of the transthoracic 3D echo was too poor to allow 3D reconstruction. The time of 3D data acquisition was 4 $\pm$ 2 min. Reconstruction time was 23 $\pm$ 16 minutes. The localization and number of the VSD were determined correctly by RT-3DE in all 22 patients. There was a good correlation between RT-3DE and surgery for the maximal VSD measurements from 'en face 'RV view (r = 0.95) and 'en face 'LV view (r = 0.91).

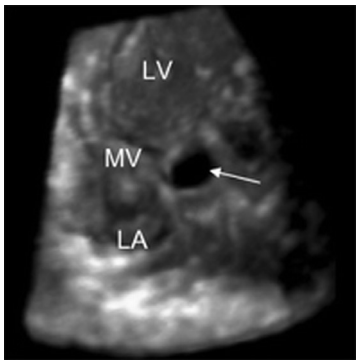


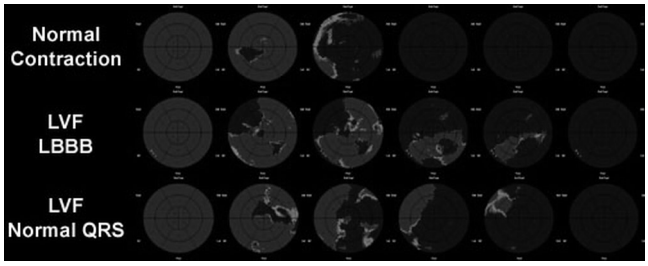
Figure 1. VSD from LV view

Conclusion: Real-time 3D echocardiography is feasible for quantitative assessment of VSDs and allows accurate determination of VSD size and localization. After a short learning curve, RT-3DE is applicable in daily clinical practise.

2014 Contraction front mapping: novel 3D echocardiographic technique for high resolution visualisation of left ventricular mechanical contraction

S. Kapetanakis[1], E. Ho[2], S.P. Turner[2], M.T. Kearney[3], M.J. Monaghan[2]. *[1]Kings College Hospital, Cardiology dept, London, United Kingdom; [2]King's College Hospital, Department of Cardiology, London, United Kingdom; [3]King's College, London, United Kingdom*

Introduction: LV Mechanical Dyssynchrony (LVMD) has emerged as a therapeutic target in resynchronisation therapy (CRT). Real-Time 3D Echo (RT3DE) offers superior spatial resolution of LV structure and function and utilising this we developed Contraction Front Mapping (CFM), a novel modality to combine temporal and spatial visualisation of the contraction of the LV.
Methods: 20 patients were investigated on clinical grounds (65% male). 16 patients had LV dysfunction, of which 9 had left bundle branch block on ECG and one had a permanent pacemaker (PPM). Of the 4 patients with normal function, 1 had a PPM. CFM was derived by representing the myocardium that reaches peak contraction every 25 milliseconds, using a bulls-eye display of the LV, based on RT3DE.
Results: In 6 of the 9 patients with LBBB, a U-shaped contraction wave was noted, with maximum delay in the postero-lateral region. In 1 patient, a similar pattern was noted at the antero-septal region, while 2 patients had homogenous activation of the LV. In the 6 with normal conduction and LVF, 3 had homogenous conduction, while 1 had antero-apical delay (anterior MI) and 2 had U-shaped activation, with delay in the postero-septal region. Pacing induced early activation of the septal region. There was homogenous contraction in those with normal function.
Conclusions: Contraction Front Mapping is a robust tool for non-invasive visualisation of spatial and temporal distribution of LVMD. In keeping with other studies



Contraction Mapping

utilising invasive mapping of LV electrical activation, LBBB activation is variable, while abnormal contraction patterns are seen even in patient with normal QRS morphology. This may be valuable in patient selection for CRT.

SPORTS CARDIOLOGY: NEW HURDLES

2023 Pre-participation screening strategies for prevention of sudden death in young competitive athletes: 12-lead ECG makes the difference

D. Corrado[1], C. Basso[2], M. Schiavon[3], B.J. Maron[4], G. Thiene[2]. *[1]Division of Cardiology, University of Padova, Padova, Italy; [2]University of Padova, Cardiovascular Pathology, Padova, Italy; [3]Center for Sports Medicine, Padova, Italy; [4]Minneapolis Heart Institute, Minneapolis, United States of America*

Preparticipation screening (PPS) by history, physical examination and 12-lead ECG, that is in practice in Italy for more than 25 years, has proven to identify competitive athletes with hypertrophic cardiomyopathy (HCM) and prevent sudden death (SD) during a long term follow-up. We performed a cost-effectiveness analysis of the Italian PPS compared to that recommended by the American Heart Association (AHA; i.e. essentially based on history and physical examination, without 12-lead ECG) for identification of cardiovascular diseases at risk of SD during sports Among 33,735 young competitive athletes (age 35 years or less) screened in Padova from 1979 to 1996, only 3,016 (8.9%) were referred for further examination due to positive history, abnormal physical examination or ECG abnormalities (specificity $>$90%). A cardiovascular disease at risk of SD was actually detected by PPS in 43 athletes (in 81% because of 12-lead ECG abnormalities): HCM in 22, arrhythmogenic right ventricular cardiomyopathy/dysplasia in 8, dilated cardiomyopathy in 4, Marfan syndrome in 3, long QT syndrome in 2, premature coronary artery disease in 2, myocarditis in one, and subvalvular aortic stenosis in one. Only 10 (23%) of these 43 athletes had a positive family history, an abnormal physical examination, or both at PPS and would have been identified by the AHA screening (77% lower sensitivity). The cost to initially screen 33,735 athletes and to further evaluate those with abnormal response was 1,223,170 euros for Italian screening modality, whereas it would have been 754,990 euros for AHA protocol. The cost for each correct diagnosis by the Italian and the AHA protocol was estimated at 28,450 and 75,500 euros, respectively. Assuming that 10% of affected athletes identified by both PPS modalities will live an additional 20 years, the cost per year of life saved was estimated at 14,220 and 37,750 euros, respectively. Thus, the Italian PPS protocol based on history, physical examination and 12-lead ECG was more efficient and cost-effective than that recommended by the AHA (without ECG) for identification of athletes with cardiovascular disease at risk of SD.

2024 Cardiac function by strain imaging: key to the increased performance capacities of endurance trained athletes

J. Claessens[1], P.H. Claessens[2], C.H.R. Claessens[3], M. Claessens[4], M. Claessens[5]. *[1]Antwerp, Belgium; [2]Sint Jozef Hospital, Cardiology, Malle, Belgium; [3]Hospital Sint Jozef, Turnhout, Belgium; [4]Academic Hospital Gasthuisberg, Leuven, Belgium; [5]Rubenslei, Outpatients'cardiological clinic, Antwerp, Belgium*

Background: to increase the performance capacity of a triathlete, a variety of adaptations are necessary. The heart is the central and the most important limiting factor. The structural heart adaptations in triathletes have important repercussion on cardiac function. In particular, left ventricular diastole shows specific characteristics that determine the performance capacity.
Methods: 40 male triathletes were compared with 31 active male controls and with 112 patients with ischemic heart disease. All subjects underwent tissue doppler imaging and strain imaging.
Results: in particular the late diastolic filling period in triathletes has specific characteristics. Pulsed doppler tissue imaging demonstrated in triathletes specific characteristics of both the late passive diastolic filling period and the early active diastolic relaxation period. Extremely striking were the significant differences between the three groups concerning the strain values at the basal and the mid septum in the longitudinal axis by aortic valve closure and by mitral valve

opening. Fascinating were the values of the enddiastolic strain by the end of the a-wave: negative in triathletes, near zero in normal controls and marked positive in coronary patients (figure 1).

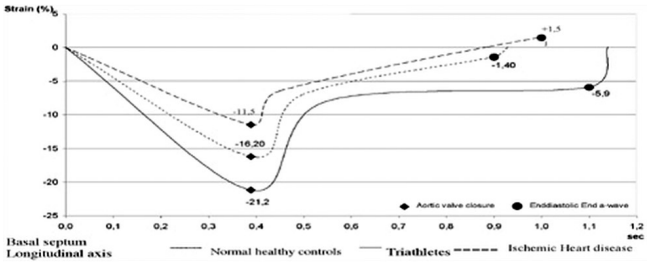


Fig.1

Conclusions: the marked negative enddiastolic strain in triathletes can be explained by an increased muscular tone after a rapid and almost complete early diastolic filling of the left ventricle. These specific systolic and especially supernormal diastolic properties of the left ventricle with an increased diastolic reserve, enhance the aerobic capacities so that performance capacity can be greatly improved.

2025 Troponin, B-type natriuretic peptide and echocardiographic abnormalities suggest that transient myocardial damage occurs following an ultra-endurance triathlon

A. La Gerche, K. Connelly, D. Mooney, A. MacIsaac, D. Prior. *St Vincents Hospital, Cardiac Investigation Unit, Fitzroy, Australia*

Introduction: There has been speculation that ultra-endurance exercise may have deleterious consequences on cardiac function, resulting in cardiac arrhythmias and sudden cardiac death.
Methods: We tested 27 athletes (20 male,7 female) one week before, immediately after, and one week after competing in the Australian Ironman Triathlon. Tests included cardiac troponin I (cTnI) and B-type natriuretic peptide (BNP) assays as well as comprehensive echocardiographic systolic and diastolic function assessment. Echo analysis was performed blinded by 2 observers.
Results: Twenty-five athletes completed the race and testing procedures. After the race, cTnI and BNP were significantly elevated. Right ventricular fractional area change (RVFAC) and right ventricular annular displacement (RVAD) were significantly reduced post-race. Echocardiography revealed segmental wall motion abnormalities in 7 athletes and reduced left ventricular ejection fraction (LVEF) in that group post-race. Findings normalized by 1 week following the event (see Table).

Table 1

	Pre-race	Post-race	1 week	p value
Subjects with elevated cTnI (>0.15 mcg/L)/total subjects #	3/25	14/25	0/25	0.02
BNP ng/L	11.9	41.5	15.6	<0.001
LVEF (%)	60.4	57.1	59.9	0.26
LVEF (%) in athletes with abnormal wall motion	56.5	45.9	57.5	0.001
Abnormal wall motion/total subjects ##	1/25	7/25	0/25	<0.05
RVFAC (%)	0.47	0.39	0.45	<0.001
RVAD (mm)	21.7	19.1	24.1	<0.001

mean increase in cTnI =0.31mcg/L## mean increase in no. of abnormal segments =5

Conclusion: The elevated biochemical markers and functional abnormalities of the left and right ventricles suggest that transient myocardial damage occurs following competition in ultra-endurance sporting events. This may predispose to subsequent cardiac complications.

2026 Clinical profile of young competitive athletes who died suddenly from arrhythmogenic right ventricular cardiomyopathy /dysplasia: implications for preparticipation screening

D. Corrado[1], C. Basso[2], M. Schiavon[3], G. Thiene[2]. *[1]Division of Cardiology, University of Padova, Padova, Italy; [2]University of Padova, Cardiovascular Pathology, Padova, Italy; [3]Center for Sports Medicine, Padova, Italy*

Background: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a leading cause of sudden death (SD) in young competitve athletes. Such a disease is rarely identified during life because of insufficient clinical suspicion.
Methods: The aim of the present study was to characterize the clinical markers that would enable the detection of potentially fatal ARVC/D at preparticipation athletic screening. To this purpose we reviewed the clinico-pathologic findings of 22 young competitive athletes (20 males and 2 females, aged 22±7years) who died suddenly of ARVC/D proven at autopsy.
Results: Each athlete died either during (17) or after (5) intense exertion on the athletic field. Fifteen athletes had experienced one or more symptoms 2 to 25 months before SD including syncope in 10 (exertional in 6 and recurrent in 3),palpitations in 14, and chest pain in 3. Right precordial inverted T-waves (beyond lead V1) had been recorded in 15 of 17 athletes (88%) with an available ECG, right precordial QRS duration > 110 msec in 13 (76%), and ventricular arrhythmias with a left bundle branch block pattern in 13 (76%), in the form of isolated/coupled premature ventricular beats in 9, non-sustained ventricular tachycardia in 3, and sustained ventricular tachycardia in one. Ventricular dilatation was documented by echocardiography in 6 of 8 athletes (right ventricular in 4 and biventricular in 2) and it was deemed to be consistent with athlete's heart. Limited exercise testing induced ventricular arrhythmias in 6 of 12 athletes (50%). Sub-maximal exercise testing, available in 5 athletes, showed a "pseudo" normalization of right precordial repolarization abnormalities in all.
Conclusions: the majority of young competitive athletes who died suddenly from ARVD/C experienced symptoms, ECG abnormalities and ventricular arrhythmias that could raise the suspect of the underlying cardiovascular disease at preparticipation evaluation and lead to further testings for a definitive diagnosis. Right precordial T-wave inversion (beyond V1) is a high sensitive clinical marker for potentially fatal ARVC/D in young competitive athletes. These observations have important implications for designing preparticipation screening strategies aimed to identify young competitive athletes at risk of arrhythmic cardiac arrest.

2027 Tissue Doppler analysis of the systolic mitral annulus motion in top level athletes

F. van Buuren[1], T. Butz[2], E. Oepangat[2], C. Langer[2], A. Fruend[3], L. Faber[2], D. Horstkotte[2], K.P. Mellwig[2]. *[1]Bad Oeynhausen, Germany; [2]Heart Center NRW, Ruhr Univ Bochum, Department of Cardiology, Bad Oeynhausen, Germany; [3]Heart Center NRW, Ruhr Univ Bochum, Institute of Physical Therapy, Bad Oeynhausen, Germany*

Introduction: The differentiation between hypertrophic cardiomyopathy (HCM) and athletes heart (AH) sometimes is difficult. The analysis of the systolic velocity (S') of the mitral annulus (MA) by Doppler tissue imaging (DTI) was proposed in literature as a method to identify HCM at a preclinical stage with a S' velocity of <9 cm/s. The aim of our study was to investigate the systolic velocity of the MA in top level handball players of the german first national league in order to reconsider the usefulness of the suggested normal range of S'.
Methods: We examined 83 athletes by conventional echocardiography according to the ASE guidelines. Systolic and diastolic function was additionally assessed by flow Doppler analysis of the left ventricular filling, and by pulsed DTI of the MA.
Results: In all athletes systolic function was normal and no structural heart disease was found. The mean left ventricular enddiastolic index was 29±3 mm/m^2. Enddiastolic thickness of the septum was 10±2 mm, of the posterior wall 9±2 mm. Mass index of the left ventricle was 212±15 g/m^2. Exercise testing showed a peak oxygen consumption of 54±7 ml/kg/min representing an average predicted peak oxygen consumption of 126% (min. 115%, max. 131%). Mean systolic velocity S' was 10.4±2.3 cm/s at the lateral and 9.4±1.5 cm/s at the septal MA. S' was <9 cm/s in 15 (18%) athletes at the lateral and in 25 (30%) at the septal MA. S' waves of <9 cm/s at both sides of the MA were seen in 9 athletes (11%); none of these had any clinical or echocardiographic abnormalities, or a functional limitation.
Conclusion: DTI can be of diagnostic importance to distinguish between AH and HCM but the validity of the suggested cutoff value of S' (9 cm/s) has to be evaluated by further trials.

2028 Is low grade valvular heart disease a limiting factor in competitive sports?

C. Langer[1], K.P. Mellwig[1], A. Fruend[2], H.K. Schmidt[1], F. van Buuren[1], T. Butz[1], D. Horstkotte[1]. *[1]Heart Center NRW, Ruhr Univ Bochum, Department of Cardiology, Bad Oeynhausen, Germany; [2]Institute of Physical Therapy, Heart Center NRW, Ruhr Univ Bochum, Bad Oeynhausen, Germany*

Introduction: low grade valvular heart disease (LGVD; any echocardiographically detected valve defect I°) is a frequent finding in cardiac and non-cardiac patients as well as in healthy individuals. Data about cardiopulmonary capacity in patients with LGVD are scarce. In this study we examined national top athletes with LGVD by cardiopulmonary exercise testing (CPX) and compared these data with results of athletes without LGVD.
Methods: 19 German male top athletes active in highly dynamic and moderately static sports (handball n=9, football n=10) with normal left ventricular size, geometry and function were identified to have LGVD: aortic regurgitation n=1; combined aortic lesion n=3; mitral regurgitation n=8; pulmonary regurgitation n=4; and tricuspid regurgitation n=3. Peak oxygen uptake (peak VO2) and predicted

Table 1

	Age		peak VO2		pred VO2 max	
	years	p	mL min^{-1} kg^{-1}	p	%	p
Football LGVD (n=10)	22.7±2.5	0.1487	58.7±4.8	0.789	124.1±12.3	0.8008
Football control (n=10)	22.2±2.9	0.1487	59.4±4.5	0.789	122.7±7.9	0.8008
Handball LGVD (n=9)	24.4±3.1	0.4468	53.3±3.7	0.2994	118.8±10.9	0.5068
Handball control (n=9)	24.7±3.2	0.4468	55.8±5.1	0.2994	121.9±10.4	0.5068

maximum oxygen uptake (pred VO2 max) were documented by CPX for athletes with and without LGVD (no echocardiograhically detected valve defect).
Results: all groups demonstrated a cardiopulmonary capacity above average irrespective of LGVD. There were no significant differences between the LGVD groups and their corresponding control groups.
Conclusion: LGVD is not a limiting factor for adequate cardiopulmonary capacity in top athletes active in highly dynamic and moderately static sports like handball and football. Athletes with LGVD are not limited compared to those without LGVD.

NOVEL BIOCHEMICAL AND GENETIC RISK FACTORS FOR CAD

2029 LpPLA2: a novel risk factor for CVD

M. Persson[1], J.-Å Nilsson[1], B. Hedblad[2], J.J. Nelson[3], G. Berglund[1].
[1]Malmo University Hospital, Clinical Research Department, Malmoe, Sweden; [2]Epidemiology, Department of Community Medicine, Malmö, Sweden; [3]GlaxoSmithKline, Worldwide Epidemiology, NC, United States of America

Introduction: Lipoprotein associated phospolipase A2 (LpPLA2) is a pro-atherogenic enzyme participating in the oxidative modification of LDL to release oxidized fatty acids and lyso phosphatidylcholine. Recent epidemioloy studies have indicated that LpPLA2 may be a new independent risk factor for CVD. We explored this association within a large, population-based cohort.
Methods: The Malmö Diet and Cancer Study is a population based prospective cohort study of which a random sample of 6103 subjects participated in a cardiovascular substudy between November 1991 and February 1994 (mean age 58 years; 58% women). Baseline examinations included blood pressure, BMI, lipids, glucose, hsCRP and disease and risk factor history. Subjects were followed for a mean of 9.5 years for incidence of fatal or non-fatal CVD (myocardial infarction, acute coronary event and ischemic stroke). LpPLA2 was measured at baseline on previously frozen samples using a high throughput radiometric activity assay. Subjects with prevalent CVD at baseline (n=254) were excluded from the analysis and this present study consists of 5186 subjects.
Results: At baseline, LpPLA2 levels were higher in men than in women and in current smokers. LpPLA2 was positively correlated with age, total-cholesterol, LDL-C and triglycerides, and negatively correlated with HDL-C. During approximately 10 years follow-up, 259 subjects experienced an event. LpPLA2 was higher in subjects who developed an event vs event-free subjects (50.2 vs 45.1 nmol/min/mL, $p<0.001$). In a proportional hazards model adjusted for age and gender, the hazard ratio (HR) (95% confidence interval (CI)) comparing the highest tertile of LpPLA2 to the lowest tertile demonstrate a nearly two-fold increase in risk of future CVD event (HR 1.96, 95% CI 1.39-2.75). Further adjustment for traditional risk factors (smoking, hypertension, BMI), lipids, and high sensitive CRP attenuated the association but LpPLA2 remained an independent predictor of events (HR 1.55, 95% CI 1.03-2.31, p=0.031).
Conclusions: Elevated levels of LpPLA2 activity appear to be an independent risk factor for future coronary events over a long follow-up period in this population-based cohort.

2030 Leptin but not adiponectin is a predictor of recurrent cardiovascular (CV) events in males: data from the LIPID study

S. Soderberg[1], D. Colquhoun[2], A. Keech[3], P. Nestel[4], C. Pollicino[3], E. Barnes[3], J. Simes[3], A. Tonkin[4] on behalf of the LIPID study group.
[1]Ornskoldsvik, Sweden; [2]Core Research, Brisbane, Australia; [3]NHMRC Clinical Trials Centre, Sydney, Australia; [4]Monash University, Melbourne, Australia

Background: obesity is characterised by high circulating leptin levels whereas adiponectin levels are low. These adipocyte-derived hormones may be a key link between obesity and development of CV disease through effects on blood pressure, platelet aggregation, arterial thrombosis, and inflammatory vascular responses. Notably, high leptin but a low adiponectin level strongly associates with other components of the metabolic syndrome. We thus hypothesized that a high leptin (but low adiponectin) predicts CV events in CHD patients in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.
Methods: 184 male subjects who had suffered a recurrent CV event during an average 2.5 years following blood collection were matched with 184 randomly selected other males who were free of further events during the same period. There were insufficient matched pairs to assess the relationship in women. Plasma leptin and adiponectin were measured by RIA. Relationships with CV events were adjusted for the published LIPID risk score, treatment allocation and obesity using a multivariate conditional logistic regression model. Hormone levels were also examined as quartiles.
Results: plasma leptin was significantly higher among male cases than male controls 7.0 vs 5.3 ng/mL; P=0.003), and correlated with risk score (p=0.01). The relative risk of recurrent CV events increased across leptin quartiles ($<$3.8 through $>$10.3 ng/mL; P for trend=0.002); Odds ratio was 3.0 for subjects in highest vs. lowest quartile. Association between leptin and CV events remained significant after adjustment for obesity (BMI=$>$30) alone or for LIPID risk score, adiponectin and treatment with pravastatin, but was attenuated after adjusting for all of the above. Low adiponectin did not predict recurrent CV events.
Conclusion: plasma leptin was a strong predictor of recurrent CV outcomes (CV death, non-fatal myocardial infarction, stroke) in male patients with previous acute coronary syndromes. It appears to partly mediate the obesity-related risk for CV disease, but also confers additional risk independent of obesity.

2031 N-terminal pro brain natriuretic peptide is inversely related to metabolic cardiovascular risk factors – a paradoxical relationship to the metabolic syndrome

M.H. Olsen[1], T.W. Hansen[2], M.K. Christensen[3], F. Gustafsson[4], K. Wachtell[5], T. Joergensen[2], K. Borch-Johnsen[6], P. Hildebrandt[4].
[1]Niva, Denmark; [2]Glostrup University Hospital, Research Center for Prevent and Health, Copenhagen, Denmark; [3]Glostrup University Hospital, Clinical Physiol. and Nuclear Medicine, Glostrup, Denmark; [4]Frederiksberg University Hospital, Department of Internal Medicine, Copenhagen, Denmark; [5]Department of Cardiology, Rigshospitalet, University of Copenhagen, Denmark; [6]Gentofte University Hospital, Steno Diabetes Center, Copenhagen, Denmark

Aim: To investigate the relationship of N-terminal pro brain natriuretic peptide (Nt-proBNP) to metabolic and hemodynamic cardiovascular (CV) risk factors in the general population.
Methods: From a population based sample of 2656 people, aged 41, 51, 61 or 71 years, we selected 2070 patients without prior stroke or myocardial infarction, who did not receive any CV, anti-diabetic or lipid-lowering treatment in 1993-94. Traditional CV risk factors, 24-hour blood pressures, left ventricular (LV) mass and ejection fraction (EF) by echocardiography, pulse wave velocity (PWV), urine albumin/creatinine ratio (UACR) and serum Nt-proBNP was measured in 1993-94. The metabolic syndrome was defined in accordance with the definition of the European Study Group of Insulin Resistance (EGIR).
Results: Higher log(Nt-proBNP) was in multiple regression analysis related to female gender (b=-0.38), 10 years older age (b=0.31), higher clinic pulse pressure (b=0.19), lower serum total cholesterol (b=-0.15), lower log(serum insulin) (b=-0.09, all $P<0.001$), lower LVEF (b=-0.08), higher logUACR (b=0.05, both $P<0.01$), lower body mass index (b=-0.06), lower log(serum triglyceride) (b=-0.05), lower heart rate (b=-0.05), higher log(LV mass index) (b=0.04) and history of diabetes, (b=0.04, $P<0.05$) (adj.R^2 =0.35, $P<0.001$). The metabolic syndrome was associated with lower Nt-proBNP (35 pg/ml vs. 48 pg/ml, $P<0.001$), and shifted the positive relationship between pulse pressure and Nt-proBNP to the right (log[Nt-proBNP]=[0.032$\pm$0.005]*pulse pressure+[1.79$\pm$0.26]) vs. log[Nt-proBNP]=[0.029$\pm$0.002]*pulse pressure+[2.35$\pm$0.10]). In other words, subjects with the metabolic syndrome had higher BP for a given level of Nt-proBNP.
Conclusion: The metabolic syndrome was associated with lower Nt-proBNP and shifted the positive relationship between Nt-proBNP and pulse pressure to the right creating a possible link between the metabolic syndrome and hypertension.

2032 Inflammatory genotypes predisposing to premature coronary artery disease in a large discordant sibship collection and utility as risk predictors

B.D. Brown[1], R.L. Lawrence[1], A.J. Balmforth[1], L. Stenier[2], A.S. Hall[1].
[1]University of Leeds, Institute for Cardiovascular Research, Leeds, United Kingdom; [2]Roche Molecualr Systems, California, United States of America

Background: An increasing body of evidence supports the role of inflammation in the development and complications of atherosclerosis. To date, it remains less clear whether this observation represents cause or effect. We believe one possible solution is to investigate the genetic substrate in affected individuals.
Aims: Evaluate the role of 51 variants in 35 candidate genes of cellular adhesion, chemotaxis and cellular signalling in a large discordant sibship population.
Methods: Using a multilocus assay we evaluated the genotype frequency of 2871 individuals in 930 discordant sibships affected by premature CAD (MI/PCI/CABG/Angina prior to 66th birthday). After checking for genotype errors using the Graphical Representation of Relationships software data was analysed using the Family Based Association Test (FBAT) software.
Results: Examination for genotyping errors identified several monozygotic twin pairs and one half sibling. These families were excluded from further analysis. Power calcualtions revelaled the cohort to have $>$90% power with a rare allele frequecny of $<$26% and below, assuming an additive model of inheritance. Allele frequencies in cases and controls were in Hardy-Weinberg Equilibrium (if rare allele frequency $>$1%). We observed the following significant associations- IL4R Ser478Pro (p=0.023); IL9 Thr113Met (p=0.033); IL1 alpha Thr549Cys (p=0.018); C5 Ile802Val (p=0.021). 34.2% of unaffecteds compared to 40.2% affecteds had three or more of the four alleles associating with disease (p=0.003). In a binary logistic regression model, with affected status as the dependent variable, possessing three or more of the disease alleles increased the risk of developing disease by 32.0% (95% CI 1.046-1.666; p0.019).
Conclusions: We have identified four polymorphisms of inflammatory gene variants that are significantly associated with CAD. Our large family based cohort provides the power to reliably detect an effect if present but also avoid false positive results attributable to population admixture. Furthermore, we have demonstrated how this knowledge can be combined to form the basis of a clinically useful tool.

2033 The ScaI Atrial Natriuretic Peptide gene polymorphism is associated with nonfatal myocardial infarction and extent of coronary artery disease

M. Gruchala[1], W. Sobiczewski[2], R. Targonski[2], A. Rynkiewicz[2]. [1]Wejherowo, Poland; [2]Medical University of Gdansk, First Department of Cardiology, Gdansk, Poland

Background: There is growing evidence from recent studies that atrial natriuretic peptide (ANP) plays an important part in coronary blood flow regulation and in atherosclerosis. Transition T2238?C in the atrial natriuretic peptide (ANP) precursor gene which leads potentialy to the translation of ANP with two additional arginines, has been suggested to be associated with salt-sensitive hypertension. According to our knowledge this study is the first one looking for potential association of the ScaI ANP gene polymorphism with the history of nonfatal myocardial infarction and extent of coronary artery disease (CAD).
Methods: The study was performed in 847 consecutive, Caucasian patients: 719 males and 128 females with significant coronary artery stenosis confirmed by elective coronary angiography (at least one coronary artery with >50% lumen narrowing). Screening for the T2238?C substitution was performed by polymerase chain reaction of genomic DNA, followed by ScaI digestion and agarose gel electrophoresis.
Results: We found a significant association of the A2A2 ScaI ANP genotype with higher incidence of positive history of nonfatal myocardial infarction (OR, 1.85; 95% CI, 1.33-2.58) and multiple-vessel CAD (OR, 1.45; 95% CI, 1.02-2.06). The ScaI ANP genotypes distribution did not differ in terms of age, sex, body mass index, plasma lipids, hypertension, diabetes mellitus and family CAD history in studied groups.
Conclusions: Our results suggest that the ScaI ANP polymorphism may be associated with nonfatal myocardial infarction and extent of CAD. However, the precise mechanism of this association remains to be determined.

STEM CELLS IN HEART FAILURE

2039 Evaluation of human cardiac growth reserve by means of cell ploidy and CDK inhibitors

F. D'Aurizio[1], P. Machin[1], L. Mariuzzi[1], N. Finato[1], D. Cesselli[1], A.P. Beltrami[2], U. Livi[3], C.A. Beltrami[1]. [1]Policlinico Universitario, Cattedra di Anatomia Patologica, Udine, Italy; [2]Policlinico Universitario, Dip. Ricerche Mediche e Morfologiche, Udine, Italy; [3]Unita' di Cardiochirurgia, Azienda Ospedaliera S. M. Misericordia, Udine, Italy

Aims: 1. To compare myocyte ploidy of normal and failing hearts;
2. To correlate DNA content, cell cycle associated proteins and age related antigens to myocyte hypertrophy and senescence.
Materials and Methods: Myocytes were enzimatically dissociated from left ventricles of 6 (3 per gender) ischemic dilated human hearts and from 4 control hearts (3 women, 1 men). A FISH staining for chromosome X,Y and 18 was utilized to estimate DNA ploidy. Ki-67 was utilized to evaluate, by means of immunofluorescence and confocal microscopy, the fraction of cycling myocytes, whereas p16 and p27 identified the fraction of senescent myocytes. Telomeric length, assessed by Q-FISH, was utilized as an additional marker of cell aging. Cell volume was evaluated by confocal microscopy and morphometry.
Results: Pathological hearts, in comparison with normal ones, were characterized by a significant increase in polyploid (77.4% vs 44.4%, $p<0.001$), p16 positive (21.4% vs 4.6%, $p<0.001$) and p27 positive (32.5% vs 13.6%, $p<0.001$) myocytes. Both in control hearts and in failing human hearts, cell ploidy, p16 and p27 expression were associated with cell volume, being the larger myocytes, polyploid and senescent ($p<0.001$). Although Ki-67 positive myocytes were significantly more numerous in failing hearts with respect to control ones (46.6% vs 23.9%, $p<0.001$), pathological hearts displayed a larger fraction of Ki-67 positive myocytes arrested in G1 phase of the cell cycle, since they co-expressed p16 (33.6% vs 11.5, $p<0.001$) or p27 (36.4% vs 21.2, $p<0.001$).
Conclusion: In the myocardium we could identify two major classes of cells: a diploid one (constituted by small, p16, p27 negative cells) and a polyploid one (comprising the largest, p16, p27 positive cells). Cycling myocytes were identified in both groups, but in the latter, Ki-67 was preferentially expressed by cells arrested in the G1 phase. The recent demonstration of a cardiac stem cell pool (Beltrami et al., 2003) resident in the mammalian heart, supports the view of a cardiac hierarchical model of cellular differentiation and maturation that parallels the well established and characterized hematopoietic one. Under this light, the diploid cell compartment would be enriched in cells of the so-called transit amplifying pool, while the polyploid one would represent a population of cells that has reached growth arrest and terminal differentiation. This way, the proportion between diploid and polyploid cells would reflect the cardiac growth reserve and could be used as a marker of failing heart.

2040 Regeneration versus left-ventricular function recovery after revascularised acute anterior wall myocardial infarction. A randomised study

J. Suarez de Lezo[1], M. Romero[1], A. Torres[2], I. Herrera[2], M. Pan[1], I. Urena[1], J. Herrador[1], D.J. Pavlovic[1]. [1]Reina Sofia Hospital, Cardiology, Cordoba, Spain; [2]Reina Sofia Hospital, Hematology, Cordoba, Spain

The favourable influence of early revascularization on left ventricular (LV) function in patients (pts) with acute myocardial infarction (AMI) has been widely studied. Stem-cell derived myocardial regeneration could provide substantial benefit for pts with revascularized AMI. However, it is still difficult to differentiate both effects in clinical studies.
Methods: From a randomized trial currently underway, we selected 30 consecutive pts with anterior wall AMI who were revascularized with drug-eluting stents and then randomly assigned either to intracoronary infusion of bone-marrow stem-cells (Group I; n=10), systemic mobilization of stem-cells with granulocyte-colony stimulating factor (G-CSF) (Group II; n=10) or to the control group (Group III; n=10). All pts were treated early with systemic fibrinolytics followed by stent revascularization within 0 to 5 days of the onset of symptoms. Pts from group I received direct intracoronary infusion of autologous bone-marrow cells 5 to 10 days after AMI. A ten-day course of 10 μg/kg/day of G-CSF was administered to pts from group II, starting on post-AMI day 5. Angiographic LV-function studies were performed at baseline and at 3-month follow-up. Functional recovery was defined as the absolute gain achieved in ejection fraction (EF).
Results: There were no differences among groups in clinical parameters, AMI size in terms of peak creatine-kinase (CK) or baseline LV-function. All pts survived. Table shows the baseline and follow-up findings. The gain in EF was significantly higher in pts from group I.

	Group I (n=10)	Group II (n=10)	Group III (n=10)	P<
Peak CK-mb (IU/L)	464±264	579±472	248±197	ns
Baseline EF (%)	37±5	39±5	38±6	ns
Baseline ACS	32±12	36±11	28±14	ns
3-month EF (%)	56±7	43±13	43±8	0.02
3-month ACS (%)	12±11	24±15	21±14	ns
Gain in EF	20±8	4±13	6±10	0.01
Reduction in ACS	20±15	12±11	5±12	0.1

ACS: Abnormal Contracting Segment

Conclusions: Regenerative therapy with intracoronary infusion of bone-marrow stem-cells seems to be an effective adjunctive treatment leading to further functional recovery in pts with revascularized anterior wall AMI.

2041 Intracoronary bone marrow cell transfer prevents the progression of diastolic dysfunction in patients after acute myocardial infarction

G.P. Meyer[1], A. Schaefer[2], M. Fuchs[1], G. Klein[1], M. Kaplan[1], K.C. Wollert[1], H. Drexler[1]. [1]Medizinische Hochschule Hannover, Kardiologie und Angiologie, Hannover, Germany; [2]Hannover, Germany

Background: We have recently shown in the randomized-controlled BOne marrOw transfer to enhance ST-elevation infarct regeneration (BOOST) trial, that intracoronary autologous bone marrow cell (BMC) transfer improves left ventricular (LV) ejection fraction recovery in patients after acute myocardial infarction (AMI). However, the impact of BMC therapy on LV diastolic function in patients after AMI has remained uncertain.
Methods and Results: Using (tissue) Doppler echocardiography, we evaluated the effects of BMC-transfer on LV diastolic function in patients enrolled in the BOOST trial. After successful primary percutaneous coronary intervention (PCI) for acute ST-elevation MI, patients were randomized to a control (n=30) or BMC-transfer group (n=30). Diastolic function was determined 4.5?1.5 days after PCI, at 6 months, and at 18 months by measuring transmitral flow velocities (E/A ratio), diastolic myocardial velocities (Ea/Aa ratio), isovolumic relaxation time (IVRT), and deceleration time (DT). All analyses were performed in a blinded fashion. In the control group, significant decreases of E/A ratios at 6 and 18 months and of Ea/Aa ratio at 18 months, and a significant increase of DT at 18 months as compared to baseline were observed. By contrast, E/A and Ea/Aa ratios, and DT remained unchanged in the BMC group. IVRT was increased significantly in both groups after 18 months.
Conclusion: Intracoronary autologous BMC-transfer attenuates the progression of diastolic dysfunction in patients after AMI.

2042 Improvement of left ventricle function (LVP) in patients with AMI after infusion of bone marrow stem cells (BMSC)

S. Grajek[1], M. Popiel[2], P. Breborowicz[1], M. Lesiak[1], R. Czepczynski[3], L. Gil[4], K. Sawinski[4], A. Cieslinski[1]. [1]Institute of Cardiology, First Department of Cardiology, Poznan, Poland; [2]First Department of Cardiology, Poznan, Poland; [3]Department of Endocrynology, Poznan, Poland; [4]Department of Haematology, Poznan, Poland

Aim: to assess LVF in pts with AMI after i.c. infusion of BMSC.
Material and methods: 30 pts with first anterior AMI after PCI of LAD were ran-

domized; 19 were into BMSC group (BG), 11 into control group (CG). 14 pts in BG and 7 pts in CG group have finished 6 month follow-up (FU) and 10 pts in both groups have finished one-year FU. BMSC were administered via infarct-related artery (IRA). In ECHO study contractility index (CI) was calculated. Tc-99m-MIBI SPECT was performed and perfusion index (PI) was calculated at 5-8 days at rest (PI 7day) and after 6 months at rest (PI 6mR) and with dipyridamole (PI 6mD). CI and PI were calculated for segments supplied with blood by IRA; CI-ira and PI-ira. Radionuclide ventriculography (RNV) after 5-10 days (RNV 7 day) and after 6 months (RNV 6m) was made to obtain EF.

Results: Results of CI and PI are displayed in tables. RNV was 46,52%±19,79 in BG and 41,54%±6,97 in CG at start (NS) and 50,35%±7,22 in BG and 39,85%±8,95 in CG after 6 months (p=0,009).

Results

group	CI 3day	CI 10day	CI 6m	CI-ira3d	CI-ira10	CI-ira6m
BMSC	n=19	n=19	n=14	n=19	n=19	n=14
mean	1,63	1,57	1,47	2,34	2,22	2,07
SD	0,21	0,18	0,16	0,43	0,41	0,34
Control	n=11	n=11	n=7	n=11	n=11	n=7
mean	1,66	1,59	1,72	2,45	2,21	2,58
SD	0,18	0,25	0,29	0,25	0,40	0,37
p	NS	NS	0,02	NS	NS	0,005

	PI 7day	PI 6mR	PI6mD	PI-ira7day	PI-ira6mR	PI-ira6mD
BMSC	n=19	n=14	n=14	n=19	n=14	n=14
mean	2,47	2,29	2,11	3,12	2,62	2,46
D	0,64	0,40	0,39	0,84	0,70	0,86
Control	n=11	n=7	n=7	n=11	n=7	n=7
mean	2,48	2,53	2,46	3,06	3,08	3,20
SD	0,55	0,43	0,37	0,56	0,54	0,58
p	NS	NS	0,03	NS	0,07	0,05

Conclusion: patients with AMI who received BMSC present with better LVF; both contractility and perfusion indeces (CI,PI) and ejection fraction (RNV) compared to control group after 6-months FU.

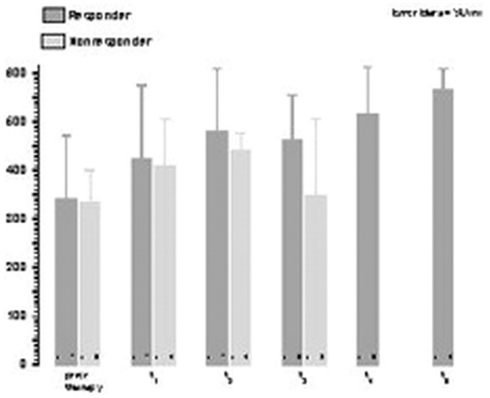
2043 Stem cell therapy increases exercise tolerance in patients with heart failure

A. Gutersohn[1], U. Duehrseln[2], A. Huettmann[2], T. Neumann[3]. *[1]Rhede, Germany; [2]University Hospital, Bone Marrow Transplantation, Essen, Germany; [3]University Hospital, Cardiology, Essen, Germany*

Background: Bone marrow (BM) derived stem cells may contribute to organ regeneration. Granulocyte colony stimulating factor (G-CSF, Filgrastimâ) stimulates BM stem cell mobilisation. In an attempt to restore cardiac function we started a phase II trial with G-CSF in pts. NYHA class III-IV.

Methods: We included 13 pts and 14 pts on heart transplantation list served as control pts. G-CSF was given subcutaneously at doses maintaining leukocyte count at 50000/ml. Four ten-day G-CSF courses each followed by a 10 day pause were performed. To prevent thrombotic events enoxiparin (40 mg/d) was given in addition. As a surrogate marker for BM-stem cell mobilisation CD34+ blood cells were measured. To assess cardiac function echocardiography, magnet resonance tomography, ergometry and 6 min-walk-test (6MWT) were performed every 10 days.

Results: 1. Although G-CSF stimulation was administered continuously 4 pts. had only poor CD34 mobilisation. 2. After 3 months 9 pts (69%) had a reduction in their NYHA class and were defined as responder 4 (31%-non responder) had no change or worsening of NYHA class. 3. Interestingly 3 of the 4 non responders had poor or no CD34+ cell increase. In the responder group all pts. hand an increase of their walking distance (mean + 48,3% vs. −12,5%; p=0,025) in the 6MWT. There was no improvement in the control group.



6 min walk test

Conclusion: G-CSF therapy in patients with heart failure increases exercise tolerance to which extend BM-derived stem cells mediate this effect remains speculative.

2044 Assessment of segmental left ventricular function by tissue tracking imaging after transplantation of autologous bone marrow stem cells in patients with acute myocardial infarction

W. Ruan[1], C.Z. Pan[1], Y.L. Li[1], J.B. Ge[1], X.H. Shu[2]. *[1]Zhongshan Hospital, Fudan University, Department of Cardiology, Shanghai, China; [2]Zhongshan Hospital, Department of Cardiology, Shanghai, China*

Objective: To use tissue tracking imaging (TT)to assess the segmental function after autologous Bone Marrow Stem Cell (BMCs) transplantation in patients with acute myocardial infarction(AMI).

Methods: Sixteen AMI patients proven by coronary angiography of anterior descending coronary artery occlusion were randomized into two groups. Group A patients were treated with transplantation of BMCs (n=8), and group B with standard therapy (n=8). Tissue Doppler Imaging (TDI) was performed at one week and three months follow-up, and tissue tracking (TT) was applied each time to obtain segmental displacement (Ds) and delayed longitudinal contraction (DLC) of 18 segmental from the apical four chamber (4-Ch), three chamber (3-Ch) and two chamber (2-Ch) views at basal, mid and apical segment. DLC was obtained on the quantitative displacement curve and a fraction of DLC from total segments was calculated. The Ds and DLC results were compared with the results from left ventricular ejection fraction (LVEF) and 201thallium scintigraphy.

Results: (1) Ds of the ischemic segments increased significantly in Group A three months after transplantation compared with one week follow-up ($p<0.05$), whereas no significant change between one week and three month follow-up in Ds was found in Group B ($p>0.05$). (2) Percentage of DLC from total segments decreased significantly in Group A three months after transplantation compared with one week after it (25% vs 9%, $p<0.05$). DLC also decreased in Group B (29% vs 14%), but the change was not significant ($p>0.05$). (3) LVEF of Group A increased from one week to three months after transplantation (53%±9% Vs 57%±12%, $p>0.05$), but LVEF of Group B decreased from one week to three months (54%±5% Vs 52%±7%, $p>0.05$)201-thallium Scintigraphy of Group A revealed an increased myocardial perfusion in the infracted zone, and SPECT score decreased significantly from 21.75±9.6 to 18.75±11.8($P<0.05$) at three months compared with one week follow-up. In Group B, myocardial perfusion remained unchanged and SPECT score slightly decreased from 21.75±8.35 to 20.75±10.43 ($P>0.05$) three months compared with one week follow-up.

Conclusions: Ds and DLC obtained by tissue tracking could be effective modalities to evaluate the efficacy of BMCs transplantation therapy.

MEDIATORS OF STEM CELL DIFFERENTIATION AND THERAPEUTIC SUCCESS

2045 Serotonin 5-HT2 receptors are essential for in-vitro cardiac differentiation of mouse embryonic stem cells

F. Stillitano[1], L. Sartiani[1], S. Brogioni[1], S. Suffredini[1], M. Jaconi[2], A. Mugelli[1], E. Cerbai[3]. *[1]University of Florence, Center of Molecular Medicine, Florence, Italy; [2]University Hospital of Geneva, Geriatrics and Rehabilitation Dept, Geneva, Switzerland; [3]University of Florence, Center of Molecular Medicine, Florence, Italy*

Background: Identification of factors regulating cardiac differentiation of embryonic stem cells (ES) is important to obtain a cell source suitable for cardiac cell transplantation therapy. In the developing heart, serotonin (5-HT) plays a crucial role during embryogenesis via type 2 receptor subtypes (5-HT2). The role of 5-HT2 during cardiac differentiation of ES cells is unknown.

Methods and results: Mouse ES (mES) spontaneously differentiate toward a cardiac phenotype in-vitro via formation of embryoid bodies (EBs); 5-HT content in the differentiation medium assayed by HPLC was about 5 μM. RT-PCR analysis of 5-HT2 revealed that 2A, 2B and 2C isoforms are selectively expressed during cardiac differentiation, while absent in undifferentiated mES. Functional coupling of 5-HT2 was tested by fluorescence detection of intracellular calcium levels at the confocal microscope. In myocytes isolated from EBs, exposure to either 5-HT (1 μM) or alphaMe-5-HT (100 nM, a 5-HT2 selective agonist) decreased intracellular calcium. This effect was accompanied by a reduction of T-type Ca-current caused by acute exposure to 5-HT (1 μM) of patch–clamped cells. To establish the contribution of 5-HT2 to cardiac differentiation, mES were grown in the presence of mianserin (1-10 μM, a 5-HT2 antagonist) or SB215505 (1 μM, a selective 5-HT2B antagonist). Clusters of pulsating cardiomyocytes were observed in >20% of EBs at day 7 of differentiation. In contrast, only 6% of EBs grown in the presence of 1 μM mianserin showed beating foci. No pulsating activity was detected if mianserin was raised to 10 μM. SB215505 (1 μM) reduced the appearance of beating foci to 16%. Accordingly, 5-HT2 blockade impaired expression of cardiac transcription factor MEF2C, which was present in control conditions (mRNA relative expression/GADPH 0.18%±0.033) and undetectable in the mianserin-treated EBs. Finally, expression of structural cardiac genes was markedly affected, being ventricular myosin light chain present in control condition (mRNA relative expression/GADPH 1.2%±0.23), and undetectable in mianserin-treated EBs.

Conclusions: these data show for the first time that 5-HT2 isoforms are selectively expressed in cardiomyocytes differentiated from mES and have a functional role in modulating intracellular calcium handling. Their pharmacological blockade during differentiation suppresses/reduces the occurrence of spontaneous con-

tractile activity, the expression of cardiac specific transcription factors and sarcomeric proteins. Thus, serotonin via 5-HT2 stimulation plays a key role in cardiomyocyte development.

2046 Exercise training promotes the release of early tissues-committed stem cell from the bone marrow in rats with chronic myocardial infarction

A.H.P. Linke, N. Kraenkel, V. Adams, S. Erbs, M. Sandri, S. Gielen, G. Schuler, R. Hambrecht. *University of Leipzig, Heart Center, Department of Cardiology, Internal Medicine, Leipzig, Germany*

Recently, the liberation of different populations of tissue-lineage committed stem cells from the bone marrow has been described in response to myocardial infarction (MI). Those cells are believed to contribute to tissue regeneration after injury. Exercise training is also known to increase the number of circulating stem cells. Therefore, aim of the present study was to elucidate, whether exercise training promotes the release of tissue-committed stem cells, in particular in rats with chronic myocardial infarction.

Methods: Male Wistar Kyoto rats underwent LAD ligation (MI) or were sham-operated (Sham). Three weeks afterwards, animals of both groups were subjected to an inactive control group (Sham-C n=12; MI-C, n=12) or a training group (Sham-T, n=12; MI-T, n=12). Animals in the training groups were running on a treadmill with a speed up to 30 m/min one hour daily for a period of four weeks. The number of sca1+ stem cells was analysed in the blood by FACS and is expressed as number per 100000 "gated events". The expression of vimentin, von Willebrand factor (vWF), and myogenin as a marker of fibroblast, endothelial, and skeletal muscle lineage-commitment, respectively, was determined in circulating cells by RT-PCR and normalized to the expression of 18SrRNA. Hemodynamics were assessed by echocardiography and conductance catheter.

Results: The number of circulating sca1+ stem cells did not differ between Sham-C (1155±172 cells) and MI-C (922±171 cells). However, the expression of the fibroblast-lineage marker vimentin was significantly elevated 3fold in circulating cells of the MI-C group. Exercise training significantly increased the amount of sca1+ cells in chronic MI (MI-T: 1581±222 cells, $p<0.05$ vs. MI-C) but not in sham-operated animals (Sham-T: 1316±230 cells). The expression of vWF and myogenin in circulating cells was found to be augmented 4fold and 7fold, respectively, in rats with chronic MI after exercise training compared to all other groups ($p<0.05$). Additionally, exercise training in chronic MI normalized the expression of vimentin in circulating cells.

Conclusion: These data suggest that exercise training in an animal model of chronic MI promotes the release of endothelial and skeletal muscle lineage-committed cells from the bone marrow. The ongoing tissue analysis will reveal, whether those endothelial and skeletal muscle progenitors contribute to tissue regeneration and whether the attenuation of fibroblast progenitors in response to exercise training is associated with a reduced myocardial scar formation in chronic MI.

2047 Absence of cell fusion of stem cells with cardiac myocytes in mismatched heart transplantation

A. Angelini[1], C. Castellani[1], M. Della Barbera[1], M. Valente[1], A. Gambino[2], A.L.P. Caforio[3], G. Gerosa[2], G. Thiene[1]. *[1]Universita' di Padova, Dept. of Cardiovascular Pathology, Padova, Italy; [2]University of Padua, Cardiovascular Surgery, Padua, Italy; [3]University of Padua, Cardiology, Padua, Italy*

Purpose: Different research group have proposed different mechanism for the apparent transformation of stem cells into cardiomyocytes. Some attribute this trasformation to the transdifferentiation potential of stem cells, others to cell fusion.

Aim: Aim of our study was to evaluate the transdifferentation and/or fusion phenomena of stem cells in mismatched heart transplantation.

Methods: Endomyocardial biopsies were obtained from the right ventricles of male patients (n=17, mean age 43,5± 23, 95 years) who had undergone sex-mismatched orthotopic heart transplantation. Endomyocardial biopsies from a non-transplanted male served as control. Cells from recipient origins were identified by fluorescence in situ hybridization for combined XY-chromosome (Vysis) on paraffin sections of each biopsies. Biopsies at 3 different time points were examined in all the patients. Rejection scores (according to a modification of ISHLT grading sistem) were calculated for all patients.

Results: Cardiomyocytes of recipient origin were detected in 15 of 17 patients with a mean percentage of 0,20 ± 0,12% (in young patient: 0,35± 0,07%; in adult patients: 0,19± 0,12%).

Cardiomyocytes of male origin (myosin positive, and CD45 negative) were located as single cells, not found in clusters, and were located in normal myocardium tissue. The nuclei of these Y-chromosome positive cardiomyocytes never showed more than two signals, one for Y-chromosome and one for X-chromosome. There was an increase of recipient-derived cells in the donor hearts over time. Regression analysis showed a positive correlation between the Y-chromosome positive cardiomyocyte and the rejection index (r2= 0,07; p= 0,023) suggesting that colonization could be more pronounced when cardiac injury was more severe.

Conclusions: Our results support the idea that the phenotypic transformation in this human cronic heart injury, rappresented by rejection phenomena following mismatched heart transplantation, is the result of transdifferentiation of male stem cells (beeing atrial or circulating cells) in new cardiomyocytes.

2048 Fusion between myoblasts and pig cardiomyocytes is the mechanism of survival of XENP transplanted human skeletal myoblasts in pig heart

L. Ye[1], K.H. Haider[2], S.J. Jiang[2], P.K. Law[3], E.K.W. Sim[1]. *[1]National University of Singapore, Surgery, Singapore, Singapore; [2]University of Cincinnati, Department of Pathology, Cincinnati, United States of America; [3]Cell Transplants Singapore Pte Ltd, Singapore, Singapore*

Introduction: Little information is available regarding the in vivo behavior of human skeletal myoblasts due to the ethical issues and difficulties of using human subjects as models. We employed a xenotransplant animal heart model to investigate the differentiation of human skeletal myoblasts after myocardial implantation.

Methods: Human skeletal myoblasts were labeled with Lac-z reporter gene for identification after cell transplantation into porcine heart. Porcine heart model of myocardial infarction was developed by coronary artery ligation and grouped as DMEM injected (group-1 n=10), human skeletal myoblast transplanted (group-2 n=12). After 3-weeks, 5ml DMEM with or without $3x10^8$ skeletal myoblasts were intramyocardially injected into the center and peri-infarction. Animals were maintained on immunosuppression for 6-weeks after cell transplantation using Cyclosporine-A. Pigs were euthanized and hearts were explanted at 2, 6 and 12-weeks post-treatment and processed for histological studies.

Results: Extensive survival of human skeletal myoblasts as revealed by Lac-z expression was only found in pig heart from group-2. Most of the Lac-z positive tissue had the typical phenotype of pig cardiomyocytes from group-1. Counterstaining the Lac-z positive tissue with specific anti-pig IgG antibody demonstrated that the Lac-z positive tissue was actually pig heart tissue. Triple counterstaining with DAPI revealed that Lac-z expression nuclei were centrally located in the pig cardiomyocytes suggesting that human skeletal myoblasts integrated into host pig cardiomyocytes to form mosaic muscle fiber. Fluorescent in situ hybridization (FISH) further confirmed that skeletal myoblast nuclei integrated into pig cardiomyocytes. The Lac-z expression mosaic fiber expressed fast or slow isoforms of human skeletal muscle myosin heavy chain instead of human cardiac connexin-43 and troponin-I. Human HLA class I and II expression was down-regulated on Lac-z expression mosaic fibers. No infiltration of pig CD4+ or CD8+ lymphocytes was observed at the site of human skeletal myoblast survival. Cytoflorimetric analysis of pig serum revealed that anti-human skeletal myoblast antibody was transiently present in pig serum (<2-weeks after cell transplantation) at very low level.

Conclusion: Human skeletal myoblasts do not differentiate into cardiomyocytes. Fusion between human skeletal myoblasts and pig cardiomyocytes is the mechanism of xenotransplanted human skeletal myoblasts survival in pig heart.

2049 Intramyocardial administration of hepatocyte growth factor naked DNA plasmid improves left ventricular regional and global function in dogs with heart failure

H. Sabbah, M. Imai, S. Rastogi, R.C. Gupta. *Henry Ford Health System, Detroit, United States of America*

Background: Gene transfection of hepatocyte growth factor (HGF) limits coronary occlusion-reperfusion injury and enhances myocardial angiogenesis. We examined the effects of direct intramyocardial injections of naked plasmid encoding human HGF on regional and global LV function in dogs with microembolization-induced heart failure (HF).

Methods: A randomized, blinded, placebo-controlled study was performed in 21 dogs with LV ejection fraction (EF) <40%. All dogs underwent a mid-sternotomy to perform 10-16 intramyocardial HGF injections in the anterolateral (AL) and anteroapical (AA) LV wall regions and were followed for 3 months. One group (n=7) received high dose (HD) HGF (total of 4.0 mg). A second group (n=7) received low dose (LD) HGF (total of 0.4 mg) and a third (n=7) received an equal number and volume of saline injections as the HD and LD groups and served as sham-operated control. LV EF and percent segmental systolic shortening (PSSS) were measured from left ventriculograms obtained before (PRE) and 3 months after therapy (POST). PSSS was assessed using the rectilinear system whereby the LV silhouettes were divided into 6 segments namely, anterobasal (AB), AL, AA, posteroapical (PA), posterolateral (PL) and posterobasal (PB).

Results: LV EF decreased from PRE to POST in control and the LD HGF dogs but increased in HD HGF dogs (Table). PSSS decreased in all 6 LV segments in

LV EF and Segmental Systolic Shortening

	Sham-Controls		LD HGF		HD HGF	
	PRE	POST	PRE	POST	PRE	POST
LV EF (%)	37 ± 1	29 ± 1*	37 ± 1	33 ± 1*	37 ± 1	41 ± 1*
AB (%)	35 ± 3	25 ± 3*	44 ± 4	40 ± 3	37 ± 3	35 ± 4*
AL (%)	34 ± 3	25 ± 2*	32 ± 4	28 ± 4*	30 ± 3	36 ± 3*
AA (%)	32 ± 2	24 ± 2*	33 ± 7	30 ± 6	27 ± 3	34 ± 3*
PA (%)	30 ± 2	23 ± 2*	36 ± 5	29 ± 5*	35 ± 4	31 ± 3*
PL (%)	33 ± 4	26 ± 3*	26 ± 3	22 ± 4*	26 ± 3	21 ± 3*
PB (%)	20 ± 3	17 ± 4*	17 ± 5	16 ± 3	23 ± 4	17 ± 3

*p<0.05 PRE vs. POST

control and LD HGF dogs. In HD HGF dogs, PSSS increased in AL and AA, was unchanged in AB and PA and decreased in PL and PB segments.
Conclusions: In HF dogs, intramyocardial injections of HD HGF improve regional and global LV function. HGF may be useful adjunctive therapy for treating HF.

2050 Human embryonic stem cells induce immunity when transplanted to immunologically competent mice

K.H. Grinnemo[1], A. Mansson-Broberg[2], H. Teerijoki[3], M. Kumagai-Braesch[2], O. Hovatta[2], C. Sylven[2], M. Corbascio[2], G. Dellgren[2]. *[1]Huddinge University Hospital, Cardiothoracic surgery, Stockholm, Sweden; [2]Stockholm, Sweden; [3]Turku Centre for Biotechnology, Turku, Finland*

Objective: Human embryonic stem cells (hESCs) can potentially be used to replace damaged and dysfunctional cells in different clinical settings. A recent study has demonstrated evidence suggesting that hESCs are immunologically privileged and may thereby possess the ability to circumvent rejection. In order to test this hypothesis, hESCs were transplanted into the myocardium of immunologically competent C57Bl/6 mice.
Methods: We used microarray analysis to study the expression of transplantation antigens like MHC class I and II, before and after IFN-g treatment and the expression of costimulatory molecules. hESCs were also injected into the myocardium of C57Bl/6 mice (n=24) and the hearts were harvested at different time points between 1 day and 10 days. Surviving stem cells were evaluated by FISH and we studied the immune response by using antibodies towards CD3, CD4, CD8 and CD11b (activated macrophages) and comparing this reaction to control mice (n=24). A MLR (n=10) was performed three weeks after the intramyocardial injection, where we used blocking antibodies towards LFA-1, CD40L and B7 molecules.
Results: hESCs could be demonstrated initially after transplantation by FISH, but were absent at four days after transplantation. hESCs were acutely rejected as demonstrated by the infiltration of CD11b+ macrophages, CD4+ and CD8+ T-cells. When splenocytes from transplanted recipients were exposed to hESCs in a mixed leukocyte reaction (MLR), proliferation was demonstrated. Blocking LFA-1, CD40L, or B7 molecules inhibited this proliferation.
Conclusion: For the first time we describe that hESCs induce an immune response when transplanted to immunocompetent mice, which is depending on the same signalling pathways necessary for inducing allogeneic and xenogeneic rejection.

CRT FOR EVERY DRUG RESISTANT HEART FAILURE PATIENT?

2051 Diastolic function or diastolic asynchrony fails to predict a favourable response to cardiac resynchronisation therapy

J.(W.H.) Fung, Q. Zhang, H. Lin, J. Chan, H. Chan, L. Kum, J.E. Sanderson, C.M. Yu. *The Chinese University of Hong Kong, Medicine & Therapeutics, Hong Kong, Hong Kong*

Introduction: Recently studies show that assessment of systolic asynchrony is a major predictor of a favorable response to cardiac resynchronization therapy (CRT).It is not known, however, whether diastolic function and diastolic asynchrony will predict left ventricular (LV) reverse remodeling.
Methods: 76 patients (aged 65±11years, 67% male,59% non-ischemic etiology) received CRT were prospectively studied by echocardiography and clinical assessment at baseline and 3-month follow up. Diastolic function was assessed by transmitral early (E) and late diastolic filling, tissue Doppler imaging (TDI) for myocardial early (Em) and late (Am) diastolic velocities, and E/Em as a marker of filling pressure. LV systolic and diastolic asynchrony were assessed by the time to peak myocardial contraction (Ts) and early diastolic relaxation (Te).
Results: There was improvement of 6-minute Hall-Walk distance, quality of life and symptoms after CRT($p<0.001$).LV reverse remodeling is evident by the reduction of LV end-systolic (136±66 vs 107±59cm^3,$p<0.001$) and end-diastolic ($p<0.001$)volumes.Ejection fraction was increased (28.3±10.1 vs 35.9±10.7%$p<0.001$).For diastolic function, there was significant reduction of transmitral E velocity (79.7±30.9 vs 68.5±27.2cm/s, p=0.003), without change in A velocity (80.2±24.6 vs 75.1±27.6cm/s, p=NS) or E/A ratio.By TDI, despite the improvement of mean Sm (3.01±1.19 vs 3.34±1.05cm/s, p=0.03), the mean Em was actually reduced (3.70±1.88 vs 3.03±1.45cm/s, p=0.002). The E/Em was unchanged (31.1±23.1 vs 28.8±30.6, p=NS). Systolic asynchrony index (standard deviation of Ts of 12 LV segments) (r=-0.72, $p<0.001$) and systolic septolateral delay (r=-0.42, $p<0.001$) correlated significantly with reverse remodeling. However, diastolic asynchrony index (standard deviation of Te of 12 LV segments) (r=-0.10, p=NS), septolateral delay in early diastole (r=-0.04, p=NS)and diastolic parameters did not correlated with reverse remodeling. Although responders of LV remodeling were more frequently found to have abnormal relaxation pattern than pseudonormal or restrictive filling pattern (64 vs 30%, Chi2=8.7, p=0.01), this was significant in multivariate regression analysis.
Conclusions: CRT improves systolic function, though early diastolic function may have been worsened as evident by TDI. LV Reverse remodeling response is predicted by the severity of pre-pacing systolic asynchrony, but not diastolic asynchrony or diastolic filling pattern. Therefore the benefit of CRT in heart failure is on systolic rather than diastolic function.

2052 Severe right ventricular dysfunction predicts lack of left ventricular ejection fraction improvement following cardiac resynchronisation therapy

G. Magrini[1], L. Scuteri[1], R. Rordorf[2], N. Ajmone Marsan[1], F. Frattini[1], M. Landolina[1], S. Ghio[1], L. Tavazzi[1]. *[1]IRCCS Policlinico S. Matteo, Cardiologia, Pavia, Italy; [2]Pavia, Italy*

Purpose: the role of right ventricular (RV) function, an important prognostic factor in heart failure pts, has not been investigated as a potential marker of responsiveness to cardiac resynchronization therapy (CRT). Aim of this study is to evaluate the role of RV function in predicting short-term left ventricular (LV) EF improvement in pts treated with CRT.
Methods: 20 pts with dilated cardiomyopathy (6 ischemic, 14 idiopathic; NYHA class 2.7±0.6, LVEF 20±5%, QRS 162±24msec) underwent echocardiographic evaluation before and 1 months after biventricular pacing implantation.
Results: we identified a group of 6 pts with severe RV dysfunction defined on the basis of Tricuspidal Annular Plane Systolic Excursion (TAPSE)≤14mm (A) and a group of 14 pts with TAPSE>14mm (B). In the two groups there were no differences in age, LVEF, myocardial performance index, NYHA class and QRS duration. Intra and interventricular dyssynchrony defined as septal to lateral delay in peak velocity at TDI and interventricular mechanical delay (IVMD) were similar in the two groups (66±22msec vs 65±8msec and 59±10msec vs 60±6msec). RV dysfunction in group A compared to group B was confirmed by: RV Tei index (0.9±0.1 vs 0.5±0.1, P=0.04), RV fractional area shrinkage (26% vs 46%, $P<0.01$), free RV wall peak regional velocity and strain at TDI (basal segment: 4±0.6cm/sec vs 7±0.7cm/sec, P=0.01; -11±3% vs -20±2%, P=0.02; medium segment 2.5±0.5cm/sec vs 4.8±0.6cm/sec, P=0.03; -8±2% vs –24±3%, $P<0.01$). Following the implantation dyssynchrony indices were similarly improved in the two groups (IVMD: from 59±10 msec to 17±4 msec in group A and from 60±6 to 22±6 msec in group B; septal to lateral delay: from 66±22 to 36±10 in group A and from 65±8 to 44±12 in group B).
At 1 month after implantation, LVEF of pts with severe RV dysfunction was lower compared to pts with better preserved RV function (22±2% vs 29±2%, P=0.05) with a notably difference in LVEF improvement (+2±0.7% vs +8±1%, P=0.001) and LV remodelling (reduction in LV end-systolic volume -8±8ml vs -40±5ml, $P<0.01$). NYHA class improvement was significantly higher in group B compared to A (-0.7 vs -0.1, P=0.02).
Conclusions: severe RV dysfunction may predict poor short term LVEF improvement and LV remodelling after effective CRT. Echocardiographical evaluation of RV function may help in identifying non-responder to CRT.

2053 Echocardiographic assessments of cardiac dyssynchrony in patients of end stage heart failure: a "responsible approach

R.R. Kasliwal, N.S. Chouhan, P. Gupta, G. Manohar, S. Manocha, S. Tandon, S. Mittal, S. Shrivastava. *Escorts Heart Institute & Research Centre, Cardiology, New-Delhi, India*

Background: Non-response to cardiac resynchronization therapy (CRT) was reported in 20% to 30% of patients when selection was done on basis of wide QRS complex, reason being the persistence of left intra-ventricular dyssynchrony due to discordance between the site of the left ventricular (LV) pacing and the site of the maximum LV delay. We evaluated the presence of LV dyssynchrony and site of maximum intra-ventricular delay using two-dimensional echocardiography (2D-Echo) and tissue Doppler imaging (TDI) in consecutive patients with heart failure.
Methods: Ninety-six consecutive patients with heart failure (LV ejection fraction <35%, New York Heart Association class III-IV) were included in the study. 24 patients had normal QRS complex (QRS duration <120 ms), 40 patients had an intermediate QRS duration (120-150 ms) and 32 patients had a wide QRS complex (>150 ms). Cardiac dyssynchrony [intra-ventricular dyssynchrony & inter-ventricular] were assessed in all patients using 2D Echo & TDI technique. Intra-ventricular dyssynchrony was defined as an electromechanical delay >60 ms on TDI between different left ventricular walls along with prolonged aortic pre-ejection period (PEP >140ms) & septal-posterior wall delay (>130ms). Inter-ventricular dyssynchrony was defined as delay between RV free wall and inter-ventricular septum of > 40ms along and aortic PEP and Pulmonary PEP difference of >40ms.
Results: Significant intra-ventricular dyssynchrony was observed in 29.17% of patients with narrow QRS complex, 45% with intermediate QRS duration, and 78.13% with wide QRS complex. Significant inter-ventricular dyssynchrony was observed in 41.67% of patients with narrow QRS complex, 52.5% with intermediate QRS complex, and 56.3% with wide QRS complex. Most delayed activation on TDI was reported in lateral (24%), posterior (26%), anterior (16%), inferior (18%), anterior septal (6%) and septal (2%) walls accordingly. Inter-observer and intra-observer agreement for assessment of intra-ventricular dyssynchrony by TDI were 90% and 96%, respectively.
Conclusion: A wide QRS complex may not be synonymous with substantial left ventricular dyssynchrony: 21.87% of heart failure patients with QRS duration

>150ms do not exhibit intra-ventricular dyssynchrony, while 29.17% of patients with normal QRS do. In patients with mechanical dyssynchrony the lateral wall is not always last to activate. The combination of 2D-Echo & TDI derived markers may allow more accurate prediction of response to CRT by providing better assessment of intra-ventricular dyssynchrony and site of maximum intra-ventricular delay.

2054 Diastolic function and diastolic asynchrony fail to predict a favourable response to cardiac resynchronisation therapy

J.W.H. Fung[1], Q. Zhang[1], H. Lin[1], Y.S. Chan[1], H.C.K. Chan[2], G.W.K. Yip[1], A. Chan[1], C.M. Yu[3]. *[1]The Chinese University of Hong Hong, Department of Medicine & Therapeutics, Hong Kong, China; [2]Alice Ho Miu Ling Nethersole Hospital, Department of Medicine, Hong Kong, China; [3]The Chinese University of Hong Kong, Div.Cardiology, Dept Medicine & Therapeutics, Shatin, Hong Kong*

Introduction: Cardiac resynchronization therapy (CRT) has been shown to improve symptoms, prognosis, systolic function and causes left ventricular (LV) reverse remodeling. Recently studies show that assessment of systolic asynchrony is a major predictor of a favorable response to CRT. It is not known, however, whether diastolic function and diastolic asynchrony will predict LV reverse remodeling.
Methods: 76 patients (aged 65±11 years, 67% male, 59% non-ischemic etiology) received CRT were prospectively studied by echocardiography and clinical assessment at baseline and 3-month follow up. Diastolic function was assessed by transmitral early (E) and late diastolic filling, tissue Doppler imaging (TDI) for myocardial early (Em) and late (Am) diastolic velocities, and E/Em as a marker of filling pressure. LV systolic and diastolic asynchrony were assessed by the time to peak myocardial contraction (Ts) and early diastolic relaxation (Te) using the 6-basal, 6-mid segmental model.
Results: There was improvement of 6-minute Hall-Walk distance, quality of life and symptoms after CRT (all $p<0.001$). LV reverse remodeling is evident by the reduction of LV end-systolic (136±66 vs 107±59cm^3, $p<0.001$) and end-diastolic ($p<0.001$) volumes. Ejection fraction was increased (28.3±10.1 vs 35.9±10.7%, $p<0.001$). For diastolic function, there was significant reduction of transmitral E velocity (79.7±30.9 vs 68.5±27.2cm/s, p=0.003), without change in A velocity or E/A ratio. By TDI, despite the improvement of mean Sm (3.01±1.19 vs 3.34±1.05cm/s, p=0.03), the mean Em was reduced (3.70±1.88 vs 3.03±1.45cm/s, p=0.002). The E/Em was unchanged (31.1±23.1 vs 28.8±30.6, p=NS). Systolic asynchrony index (standard deviation of Ts of 12 LV segments) (r=-0.64, $p<0.001$) and systolic septolateral delay (r=-0.42, $p<0.001$) significantly correlated with reverse remodeling, but not diastolic asynchrony index (standard deviation of Te of 12 LV segments) (r=-0.17, p=NS) or septolateral delay in early diastole (r=-0.07, p=NS). Although responders of LV remodeling were more frequently found to have abnormal relaxation pattern than pseudonormal or restrictive filling pattern (64 vs 30%, Chi^2 =8.7, p=0.01), this was not significant in multiple regression analysis.
Conclusions: CRT improves systolic function, though early diastolic function appears to be worsened by TDI. LV Reverse remodeling response is predicted by the severity of pre-pacing systolic asynchrony, but not diastolic asynchrony or diastolic filling pattern. Therefore the benefit of CRT in heart failure is on systolic rather than diastolic function.

2055 Long-term efficacy of cardiac resynchronisation therapy (CRT) in patients with normal QRS duration

M. Gasparini[1], P. Galimberti[2], F. Regoli[2], C. Ceriotti[2], M. Bonadies[2], D. Pini[3], M. Mangiavacchi[3], E. Gronda[3]. *[1]Milano, Italy; [2]Istituto Clinico Humanitas, Elf1, Rozzano (Milano), Italy; [3]Istituto Clinico Humanitas, Heart Failure, Rozzano (Milan), Italy*

CRT is known to be effective in patients (pts) with heart failure (HF) and prolonged QRS. The effects of CRT on HF pts with normal QRS duration remain unclear. Aim of the study was to compare long term effects of CRT in pts with Normal duration QRS (<120 ms-NQRS) and in those with Wide QRS (>120 ms-WQRS).
Methods: From Oct'99 toDec'04, 408 pts (mean age 65 ± 10 yrs, mean LVEF 29 ± 6%, mean QRS 168 ± 31 ms, mean 6-minute walking test (6MWT) 336 ± 117 m) underwent successful CRT. F.u. was performed every 6 months (mean f.u.: 30 ± 11 months). 48/408 pts (12%) had NQRS. Pts were not pre-selected by echo dyssynchrony criteria. Baseline characteristics of the 2 groups did not differ, except for larger left ventricular end-systolic volume (LVESV) in WQRS ($p<0.005$).
Results: see Table 1.
1) Significant improvements in NHYA class and 6WT were detected in both groups with no statistical difference.
2) Significant reduction of LVESV and increases in LVEF were observed in both groups; during f.u., NQRS maintained significantly lower ESV ($p<0.001$) and a trend towards significantly greater increase of LVEF (p=0.08) was noted.
3) A significantly lower cardiac mortality rate in NQRS compared to WQRS (0,0%/yr vs 5,7%/yr; log rank p=0.04) was detected.
Conclusions: In our experience CRT yielded similar long-term improvements in both groups regarding functional capacity. However the effects of CRT on cardiac function and cardiac mortality rate seemed to be better in NQRS group. Our data suggest that CRT could be indicated even in pts with refractory HF and normal QRS duration.

Table 1

	LVEF(%)*		LVESV(ml)*^		6mWT(m)*		NYHA III-IV(%)*	
	NQRS	WQRS	NQRS	WQRS	NQRS	WQRS	NQRS	WQRS
Baseline	30.5 (6,2)	29.1(6,3)	121(41)	148(61)	322(118)	327(119)	81	88
6 months	39,8(10,7)	36,5(10,1)	92(41)	118(61)	447(102)	427(108)	4	15
12 months	42,1(11,9)	38,0(10,6)	84(46)	110(56)	481(80)	451(105)	5	10
24 months	46,8(13,9)	40,4(12,0)	84(51)	103(61)	500(84)	480(96)	12	9
36 months	43,2(15,6)	42,4(12,7)	95(51)	90(58)	560(40)	520(129)	0	4

* significance value of the model $p < 0.001$; ^ significantly lower LVESV maintened throughtout follow up for NQRS compared to WQRS ($p<0.001$). Values are expressed as means with SD standard deviation between parentheses.

2056 Randomised comparison of simultaneous biventricular stimulation vs. optimised interventricular delay in patients treated with a biventricular cardioverter-defibrillator

G. Boriani[1], H.J. Trappe[2], K.H. Seidl[3], R. Grove[4], J. Vogt[5], W. Danschel[6], A. Schuchert[7], P. Djiane[8] on behalf of RHYTHM II ICD Study. *[1]Institute of Cardiology, Cardiology Dept., Bologna, Italy; [2]Marienhospital Universitatsklinik, Cardiology, Herne, Germany; [3]Klinikum Ludwigshafen, Cardiology, Ludwigshafen, Germany; [4]Schuchtermann-Klinik, Cardiology, Bad Rothenfelde, Germany; [5]Herzzentrum Nordrhein-Westfalen, Cardiology, Bad Oyenhausen, Germany; [6]Ambulantes Herzzentrum, Cardiology, Chemnitz, Germany; [7]Universitat-Klinikum Eppendorf, Cardiology, Hamburg, Germany; [8]Hopital St Marguerite Cantini, Cardiology, Marseille, France*

Purpose: Cardiac resynchronization therapy (CRT) has demonstrated to be an effective therapy in patients with advanced chronic congestive heart failure (CHF) under optimal drug regimen. Some studies suggest that the optimization of the interventricular (V-V) pacing delay may further improve the left ventricular (LV) function.
The RHYTHM II ICD trial was designed to asses by a prospective randomized study design whether customizing the V-V delay after implantation of a cardioverter-defibrillator with biventricular pacing capabilities (CRT-D device) improves long-term clinical outcomes, compared to the delivery of simultaneous biventricular pulses.
Method: This study included 121 CHF patients, 83% male, mean age 67 yrs, 63% ischemic, 93% NYHA class III. At baseline the mean intrinsic QRS width was 175 ms (90% with left bundle branch block), the mean LV ejection fraction was 22% and the mean LV end-diastolic diameter was 71 mm. ACE-Inhibitors or angiotensin receptor blockers, beta-blockers and diuretics were given in 85%, 76% and 89% pts, respectively. All patients received an Epic HF CRT-D device (St Jude Medical), and were randomly assigned in a 1:3 ratio to either simultaneous (SIM n=30) or optimized (OPT n=91) biventricular pacing. V-V was optimized before hospital discharge to maximize the LV outflow tract velocity time integral at echocardiographic evaluation.
Results: In the OPT group, the V-V delay ranged from 0 to 80 ms, with similar proportions of patients being paced right ventricular and left ventricular first, and 25% of patients were stimulated at an OPT V-V delay of 0 ms. In the whole cohort, 6 months of pacing with the CRT-D device were associated with 1) a 113-m increase in distance covered during the 6-minute hall walk (6-MHW) test ($P =0.0002$ vs. baseline), 2) an improvement in NYHA functional class in 69% of the patients ($P <0.0001$ vs. baseline), and c) an improvement in mean quality of life (QOL) score from 45 down to 27 ($P <0.0001$ vs. baseline). The magnitude of changes in 6-MHW distance, NYHA functional class, or QOL scores between baseline and 6 months were similar in both SIM and OPT study groups.
Conclusion: The clinical use of a CRT-D system with independent programming of V-V pacing delay was associated with significant improvements in functional capacity and quality of life. V-V optimization had no significant effect on clinical outcomes at 6 months.

TREATMENT OF ENDOTHELIAL DYSFUNCTION

2073 Genetic deletion of caveolin-1 results in enhanced circulating NO, vessel relaxation and decreased systolic blood pressure variability in vivo

F. Desjardins, M. Pelat, I. Lobysheva, C. Dessy, O. Feron, J.L. Balligand. *Universite Louvain (UCL), Dept. of Medicine, Pharmacology Unit, Brussels, Belgium*

The endothelial NOS (eNOS) is a key regulator of blood pressure (BP), but the impact of genetic alteration of its allosteric regulators, such as caveolin-1 (cav1), on vascular nitric oxide (NO) production, BP and heart rate (HR) homeostasis in vivo is unknown.
Using chronically implanted telemetry devices, we studied HR and BP and their variability in non-anesthetized, unrestrained mice deficient for cav1 (and wild-type littermate controls; n=6 each). The contractile response of isolated vessels from the same mice was also studied in vitro. NO production was directly assayed by

EPR in blood as circulating Hb-NO or from isolated vessels using [Fe(II)(DETC)2] as spin-trap. Compared with WT, cav1-/- mice had normal systolic BP and circadian cycle and slightly elevated diastolic BP (96.6 ± 1.8 vs. 89.6 ± 1.1 mmHg; $p<0.05$). Systemic NOS inhibition with L-NAME resulted in higher SBP increase in Cav1-/- (161 ± 2.4 vs. 149 ± 4.6 mmHg; $p<0.05$), suggesting higher basal NOS activity in their vessels. Spectral analysis showed a lower SBP variability in the very low frequency band (VLF, <0.4Hz; -20%, $p<0.05$) indicating enhanced SBP buffering by NO that was also abrogated by NOS inhibition. In agreement with this interpretation, circulating Hb-NO levels were higher in cav1-/- mice compared with WT (188 ± 24%; n= 9, $p<0.05$), and were strikingly reduced upon animal treatment with L-NAME in the drinking water (to 35 ± 10%; n=4,$p<0.01$). Isolated vessels from cav1-/- also produced more NO in response to the calcium ionophore, ionomycin (152 ± 5% of WT) and to carbamylcholine (178 ± 26% of WT; n=4-5, both $p<0.05$). Similarly, KCl-preconstricted aortic segments from cav1-/- relaxed more to acetylcholine than WT and this was abrogated by NOS inhibition.

In conclusion, the vascular phenotype of cav1-/- mice fully validates the inhibitory role of cav1 on eNOS activation in response to specific agonists (e.g. acetylcholine) in vitro and in vivo. Their increased vascular production of NO is translated into decreased sytolic BP variability, a parameter with prognostic importance in human cardiovascular diseases. This highlights the potential interest of pharmacologic cav1 modulation for the treatment of cardiovascular disorders.

2074 Improvement of endothelial dysfunction by intravenous transfusion of different subpopulations of vascular progenitor cells

S. Wassmann[1], T. Czech[2], N. Werner[2], M. Boehm[2], G. Nickenig[2].
[1]Universitaetskliniken des Saarlandes, Medizinische Klinik-Innere Medizin III, Homburg/Saar, Germany; [2]Universitaetskliniken des Saarlandes, Medizinische Klinik-Innere Medizin III, Homburg/Saar, Germany

Vascular function is influenced by the effective regeneration of the endothelium. Cellular restoration may be affected by circulating progenitor cells. Therefore, we investigated the effect of vascular progenitor cells on endothelial dysfunction in atherosclerotic mice.

Methods and Results: Apolipoprotein E-deficient (ApoE-/-) mice were splenectomized and treated with high-cholesterol diet for 5 weeks, resulting in marked impairment of endothelium-dependent vasodilation as compared with wild-type mice (organ chamber experiments with isolated aortic segments). Intravenous transfusion of spleen-derived mononuclear cells (MNCs) isolated from wild-type mice on 3 consecutive days restored endothelium-dependent vasodilation in the ApoE-/- mice, as measured 7 days after transfusion. This effect was still observed 45 days after transfusion. Histological analyses of aortic tissue identified fluorescent-labeled exogenously applied progenitor cells which expressed CD31 in the endothelial layer of atherosclerotic lesions. Progenitor cell treatment led to increased vascular NOS activity (arginine-citrulline conversion assays). To characterize the responsible cell type within the MNC fraction, MNC subpopulations were isolated by magnetic bead separation. Transfusion of either in vitro-differentiated Ac-LDL/lectin-positive endothelial progenitor cells, CD11b-positive monocytes/macrophages, CD45R-positive B-cells, or Sca1-positive cells significantly improved endothelial function, although these treatments were not as effective as transfusion of total MNCs. Depletion of MNCs of either CD11b-positive, CD45R-positive, or Sca1-positive cells before transfusion resulted in a significantly attenuated effect on endothelial function as compared to undepleted MNCs; however, endothelium-dependent vasodilation was still significantly improved as compared to saline-treated ApoE-/- mice.

Conclusions: Intravenous transfusion of spleen-derived MNCs improves hypercholesterolemia-induced endothelial dysfunction in ApoE-/- mice. Beside endothelial progenitor cells, other subpopulations within the mononuclear cell fraction seem to be responsible for this effect as well.

2075 Treatment with granulocyte colony stimulating factor improves endothelial function despite concomitant increase of C-reactive protein

I. Ikonomidis[1], J. Lekakis[2], C. Papadimitriou[2], P. Katchichti[2], A. Protogerou[2], C. Papamichail[2], A. Dimopoulos[2], M. Mavrikakis[2].
[1]Athens, Greece; [2]Alexandra General Hospital, Clinical Therapeutics Dept., Athens, Greece

Granulocyte colony stimulating factor (GCSF) is used in mobilisation of endothelial progenitor cell. Concerns have been raised about GCSF-induced inflammation within the vascular wall. We examined the effects of GCSF administration on endothelium in vivo.

Methods: We studied 59 women with excised breast cancer. Forty-two received a 5-day course of s.c. GCSF (5μg/kg), o.d. after adjunctive chemotherapy and 17 received placebo. Flow-mediated, endothelium-dependent dilatation (FMD%) and nitrate-mediated, endothelium-independent dilatation (NMD%) of the brachial artery was assessed by ultrasonography at baseline before chemotherapy (FMD, NMD 0), before (FMD, NMD 1) and 2 hours (FMD, NMD 2) after the first s.c. injection of GCSF or placebo and at the end (FMD, NMD 3) of a 5-day treatment with GCSF or placebo. CRP serum levels were also assessed at the above periods.

Results: FMD increased 2 hours after the first GCSF injection (FMD2) and remained improved at the end of GCSF treatment (FMD3) compared to FMD before treatment (FMD1) ($P<0.05$, table). NMD remained unchanged throughout the study. CRP was increased at the end of GCSF treatment (CRP3). ($p<0.05$). There were no changes of FMD, NMD and CRP after placebo treatment.

Table

	0	1	2	3
FMD (%)	4.9±3.2	4.3±3.3*	6.2±3.4	5.7±2.8
NMD (%)	15.8 ±7.3	14.9±8	13.3±4.1	14.5±4.5
CRP (mg/l)	0.6±0.2	0.59±0.2	0.75±1	1.4±2*

$p<0.05$ for FMD1 vs. FMD2 and FMD3 and for CRP 3 vs. CRP0, CRP1, CRP2

Conclusion: Treatment with GCSF improves endothelial function despite a concomitant increase of CRP levels and thus, may be safely used to facilitate neovascularisation and rendothelialisation after endothelial cell damage.

2076 Swiss dark chocolate improves endothelial and platelet function

F. Hermann[1], L.E. Spieker[2], F. Ruschitzka[2], M. Hermann[2], T.F. Lüscher[2], W. Riesen[3], G. Noll[2], R. Corti[2]. *[1]University Hospital, Dept. of Cardiology, Zurich, Switzerland; [2]University Hospital, Dept. of Cardiology, Zürich, Switzerland; [3]The Institute for Clinical Chemistry, Kantonsspital St. Gallen, St. Gallen, Switzerland*

Aims: Dark chocolate, but not white chocolate contains high amounts of polyphenols, a heterogeneous class of antioxidants. Polyphenols have shown to positively influence endothelial function and platelet reactivity in healthy volunteers. To assess the effects of chocolate on individuals with known impaired endothelial function and platelets hyper-reactivity, a homogenous population of healthy chronic smokers was selected.

Methods and Results: In 25 healthy smokers (mean age 26±1 years), flow-mediated dilation (FMD) measured using high-sensitive ultrasonography of the brachial artery, shear stress-dependent platelet adhesion (SSDPA) and total antioxidant status (TAS) were assessed before and after ingestion of 40 grams of Swiss dark chocolate (74% cocoa), or Swiss white chocolate (4% cocoa), respectively.

Two hours after intake of dark chocolate, FMD improved from 4.4%±0.9 to 7.0%±0.7 (P=0.026), while SSDPA was reduced from 5.0±0.6% to 3.2±0.4% (P=0.03).

The beneficial effect of dark chocolate on FMD lasted for 8 hours. White chocolate had no effect on FMD nor platelet function. TAS improved significantly after 2 hours of ingestion of dark chocolate (1.2±0.02 mmol/l to 1.3±0.02 mmol/l, P=0.03), but remained unchanged in the white chocolate group.

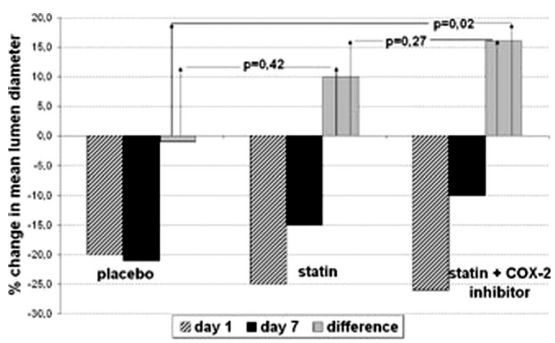
Conclusions: Dark chocolate improves endothelial function, antioxidant status and reduces platelet adhesion in smokers most likely via a reduction of oxidative stress.

2077 Seven days of anti-inflammatory therapy improves endothelial function in patients with non ST segment elevation acute coronary syndromes

M. Chyrchel, D. Dudek, J. Legutko, T. Rakowski, S. Bartus, L. Rzeszutko, A. Dziewierz, J.S. Dubiel. *Institute of Cardiology, Jagiellonian University, Krakow, Poland*

Background: Endothelial inflammatory activation is associated with profound impairment in vasodilator endothelial function. We earlier proved that short term aggressive treatment with statins and cyclooxygenase-2 (COX-2) inhibitors reduce CRP level – major inflammatory marker. The aim of the present study was to analyze the impact of the same therapy directly on endothelial function in patients with Non–ST segment elevation Acute Coronary Syndromes (NSTE ACS).

Methods: In 23 pts with NSTE ACS and elevated CRP level endothelial function was assessed by coronary Acetylocholine (Ach) test within non – culprit vessel. Quantitative coronary angiography (QCA) was done at baseline and after highest dose of Ach. Vessel response was calculated as a percent change of mean lumen diameter (% change of Mean Lumen Diameter (LD)). Then pts were randomized



Figure

to three groups of therapy A (n=7) placebo, B (n=8) 80 mg atorvastatin, C (n=8) 80 mg atorvastatin and 25 mg rofecoxib. After 7 days of therapy control test was performed within the same, indicatory segments. Recovery of endothelial function in all groups was calculated as delta in % changes of Mean LD between day 1 and day 7.

Results: At day 1 significant decrease in Mean LD between baseline and the highest dose of Ach was observed in all groups: -20% (group A), -25% (B) and -26% (C). After 7 days of therapy these changes averaged - 21% (A), -15% (B) and -10% (C). Differences between day 1 and day 7 were -1%, +10% and +16% respectively (Figure).

Conclusions: In 93% of pts with NSTE ACS profound endothelial dysfunction was observed. Short term therapy with 80 mg of atorvastatin and COX-2 inhibitor significantly improved endothelial function.

METABOLIC SYNDROME

2079 Models for immediate classification of gluco-metabolic state in patients with coronary artery disease

J. Ohrvik[1], M. Bartnik[2], K. Malmberg[2], L. Ryden[2] on behalf of the Euro Heart Survey Investigators. *[1]Uppsala University, Center for Clinical Research, Vasteras, Sweden; [2]Karolinska Hospital, Cardiology, Stockholm, Sweden*

Objectives: Abnormal glucose regulation (AbnGR) has serious prognostic implications in patients with coronary artery disease (CAD). This study tried to develop classification criteria, based on easily available clinical data, useful in acute CAD and to limit the number of oral glucose tolerance tests (OGTT) needed for accurate characterization.

Methods: CAD patients were enrolled at 110 centers in 25 countries. Fasting plasma glucose (FPG) and 2-h post load glucose were obtained in patients without known AbnGR. The gluco-metabolic status was classified according to WHO as normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or diabetes and compared with ADA 1997 and 2003 criteria (normal FPG <6.1 and <5.6 mmol/L respectively). Classification methods – ordinal logistic regression and a single hidden layer neural network (NNET) – were assessed to find rules to characterize the metabolic status.

Results: OGTT was performed in 1 867 patients. They were classified as normal (870), IFG or IGT (678) and diabetes (319). Many patients with newly detected diabetes (93) and IGT (385) had been missed even with the new ADA criterion. The best classification algorithm for gluco-metabolic status – a NNET with three neurons in the hidden layer – using FPG, age and high density lipoprotein cholesterol as input variables (see Table 1) reached a 96% diagnostic accuracy concerning specificity – i.e. almost everyone classified as having IFG, IGT or diabetes had AbnGR.

Table 1

Classification by WHO criterion	Classification by neural network			Total
	Normal glucose regulation	Impaired glucose regulation	Diabetes	
Normal glucose regulation	446 (95.5)	21 (4.5)	0	467
Impaired glucose regulation	236 (67.6)	102 (29.2)	11 (3.2)	349
Diabetes	59 (33.9)	51 (29.3)	64 (36.8)	174
Total	741 (74.8)	174 (17.6)	75 (7.6)	990

Glucose regulation predicted by a neural network including fasting plasma glucose, high density lipoprotein cholesterol and age applying ten-fold cross validation. Data presented as counts (row%).

Conclusions: FPG alone has a limited capacity to identify CAD patients with AbnGR. An OGTT should become a diagnostic routine for evaluation of total risk in all CAD patients classified as having NGR applying the classification algorithm based on the NNET.

2080 Recognising abnormal glucose regulation in patients with coronary artery disease

M. Bartnik[1], J. Ohrvik[2], L. Ryden[3], K. Pyorala[4], E. Standl[5], K. Malmberg[6], M.L. Simoons[7] on behalf of the Euro Heart Survey Investigators. *[1]Karolinska Institute, Karolinska Hospital, Cardiology Department, Stockholm, Sweden; [2]Karolinska Institute, Department of Medical Epidemiology and, Stockholm, Sweden; [3]Karolinska Hospital, Department of Cardiology, Stockholm, Sweden; [4]Kuopio University Hospital, of Medicine, Kuopio, Finland; [5]Teaching Hospital, Medicine (Endocrinology), Munich-Schwabing, Germany; [6]Karolinska Hospital, Department of Cardiology, Stockholm, Sweden; [7]Thoraxcenter, Erasmus University, Cardiology, Rotterdam, Netherlands*

Background: Patients with coronary artery disease (CAD) and abnormal glucose regulation are at high risk for subsequent cardiovascular events underlying the importance of accurate glucometabolic assessment in clinical practice.

Our aim was to investigate different methods to identify glucose disturbances among patients with CAD.

Methods: Consecutive patients referred to a cardiologist due to CAD were prospectively enrolled at 110 centres in 25 countries. Fasting and 2-h post 75-g glucose load glycemia were requested in patients without known glucose abnormalities. The glucometabolic status was classified following the WHO (1999) and the ADA (1997 and 2003) criteria as normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or diabetes, respectively.

FINDINGS Fasting and 2-h post load glycemia were available in 1867 patients, out of whom 870 (47%) had normal glucose regulation, 87 (5%) IFG, 519 (32%) IGT and 319 (17%) diabetes. Normal fasting glycemia (<5.6 mmol/l) was found in 65% of patients with IGT and 29% with newly detected diabetes. If the new ADA criterion for fasting glycemia was applied, abnormal glucose regulation would have remained undetected in 48% (478) of patients. Attempts were made to find a satisfactory classification algorithm based on variables easily available in clinical practice.

INTERPRETATION We conclude that an oral glucose tolerance test is required for assessment of glucometabolic status in patients with CAD and should become a routine for evaluation of the total risk. A neural artificial network model including fasting plasma glucose, age and HDL-cholesterol, may allow for reduction of necessary glucose tolerance tests by 25%.

2081 Body mass index, weight modification and risk of late onset diabetes in post MI patients: results from the gissi prevenzione trial

A. Macchia[1], G. Levantesi[1], G. Tognoni[1], L. Tavazzi[2], F. Valagussa[3], R. Marchioli[1]. *[1]Consorzio Mario Negri Sud, Clinical Pharmacology and Epidemiology, Santa Maria Imbaro, Italy; [2]IRCCS Policlinico San Matteo, Department of Cardiology, Pavia, Italy; [3]Ospedale San Gerardo, Department of Cardiology, Monza, Italy*

Although body mass index (BMI) increases the risk of late onset diabetes in subjects free of cardiovascular disease, the independent prognostic impact in patients with previous myocardial infarction (MI) is not well known. Moreover, the impact of weight variation in post-MI patients on late onset diabetes is not reported.

GISSI-Prevenzione was a multicenter, open-label, randomized trial that has been conducted in 11,323 patients with recent (<3 months) MI testing the efficacy of n-3 polyunsaturated fatty acids (PUFA) 1 g/d, vitamin E 300 mg/d, both, or neither. Mean follow-up duration was 3.5 years. We excluded from this analysis 4,296 patients without measurement of BMI both at baseline and the first follow-up visit scheluded at 6 months, those with diabetes at baseline, and those who died prior to the first visit. Cox regression models adjusted for baseline BMI and relevant prognostic indicators were fitted. BMI was analyzed according to statistical quintiles and weight changes were evaluated into six categories according to BMI variation (from >10% of BMI reduction to >10% of BMI increase).

Incidence of late onset diabetes steeply increased with increasing BMI levels, from 9.6% in the 1st quintile (Q) of BMI to 18.3% in the 5th Q (OR Q5 vs. Q1 = 1.95 [1.58-2.41], p for trend < 0.0001). Body weight variation significantly changed the risk of late onset diabetes (Figure 1).

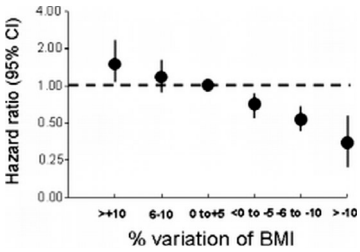


Figure 1

In post MI patients, BMI strongly influenced the risk of late onset diabetes. Weight loss and gain were significantly associated with decrement and increase of risk of becoming diabetic, respectively.

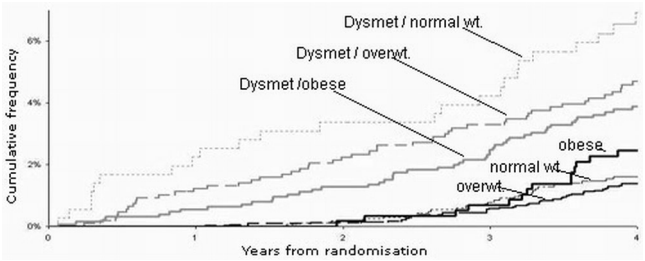
2082 Dysmetabolic status, and not obesity per se, is associated with increased cardiovascular mortality in patients with stable coronary disease

C. Daly[1], K.M. Fox[1], M. Bertrand[2], R. Ferrari[3], W. Remme[4], M. Simoons[5] on behalf of The EUROPA investigators. *[1]Royal Brompton Hospital, Cardiology Dept., London, United Kingdom; [2]INSERM, Lille, France; [3]Arcispidele S Anna, Cardioloy, Ferrara, Italy; [4]STICARES, Rhoon, Netherlands; [5]Thoraxcenter, Rotterdam, Netherlands*

The metabolic syndrome(MetSyn) predicts adverse cardiovascular (CV) outcome. Increasing levels of obesity are closely linked with increasing prevalence of MetSyn but it is not clear if obesity per se has a negative effect on CV mortality. We investigated this in 8397 patients with known coronary artery disease(CAD)in EUROPA, a trial of the effects of perindopril on CV events in stable CAD with 4.2 year follow up.

Patients were categorised as having dysmetabolic status if they had either diabetes (DM) or MetSyn. MetSyn was defined by the presence of at least 3 of the following: BP >130/85 or antihypertensive medication; HDL <1.0 mmol/l (male),

and <1.3 mmol/l (female); Body Mass Index > 30; fasting plasma glucose >6.1 mmol/l. The population was also stratified according to BMI, with a BMI < 25 considered normal weight, BMI 25-30 overweight and BMI > 30 obese.



Figure

MetSyn without DM was identified in 1183 patients(14%) and DM in 1502(18%). Stratified by BMI and dysmetabolic status the probability of CV death was increased by dysmetabolic status, but not by overweight or obesity (Fig). With normal weight without dysmetabolic status as reference, the RR of CV death associated with obesity and dysmetabolic status was 2.4 [95% CI 1.5-3.7], p<0.001, overweight and dysmetabolic status was 3.0 [95% CI 1.9-4.7], p<0.001, and normal weight and dysmetabolic status was 4.1 [95% CI 2.9-6.9] p<0.001. Patients who were overweight or obese without DM or MetSyn were not at increased risk of CV death. Obesity is not an independent predictor of CV death in patients with CAD. All patients with CAD should be screened for DM and MetSyn not just those who are overweight or obese, as normal weight individuals with dysmetabolic features are at particularly high risk of CV death.

2083 Metabolic syndrome independently predicts impaired coronary collateral vessel development in patients with obstructive coronary artery disease

M.B. Yilmaz[1], V. Caldir[2], Y. Guray[2], U. Guray[2], H. Altay[2], B. Demirkan[2], S. Cay[2], S. Korkmaz[2]. [1]*Turkiye Yuksek Ihtisas Hospital, Cardiology Clinic, Ankara, Turkey;* [2]*Turkiye Yuksek Ihtisas Hospital, Cardiology Clinic, Ankara, Turkey*

Collateral vessel development is triggered by the pressure gradient between the coronary bed of the arteries, and is caused by coronary obstruction and myocardial ischemia. Presence of well-developed collateral vessels feeding the jeopardized myocardial area may limit the infarct size following coronary occlusion and may even provide a survival benefit. It is not well established why some patients with coronary artery disease develop coronary collaterals while others do not. Metabolic Syndrome (MS), defined as cluster of risk factors, has been identified as a secondary target for cardiovascular risk reduction by new guidelines. However, affect of MS onto coronary collateral development (CCV) has not been investigated.

Methods: 596 consecutive patients (337 male, 259 female with mean age 56±8 years), who underwent coronary angiography at our centre and were found to have total occlusion of right coronary artery (RCA), were prospectively enrolled into our study. Patients were, then, classified into two groups as first with good CCV (Rentrop 2-3, Group 1) and poor CCV (Rentrop 0-1, Group 2)

Results: There were significant differences in terms of body mass index (kg/m^2), glucose, triglyceride and duration of angina pectoris in years between Group 1 and 2. Prevalence of DM was 27.1% in Group 1, whereas, 44% in Group 2 (p<0.001). Presence of MS was significantly higher in Group 2 than in Group 1 (78.4% vs. 49.2%, p<0.001). In multivariable logistic regression analysis (MLRA), duration of angina pectoris (Beta=0.347, 95% confidence interval: 0.266-0.453, p<0.001), presence of DM (Beta=1.829, 95% confidence interval: 1.021-3.279, p=0.042), poor wall score (Beta=2.379, 95% confidence interval: 1.356-4.173, p=0.003) and presence of MS (Beta=2.993, 95% confidence interval: 1.541-5.813, p=0.001) were independent predictors of angiographically determined poor collateralisation. After adjusting for DM, MS persisted to predict poor collateralization independently (Beta=2.235, 95% confidence interval: 1.113-4.930, p=0.046). When we included components of MS individually into MLRA, instead of MS itself after adjusting for, DM again, it was noticed that increased waist circumference (Beta= 2.055, 95% confidence interval: 1.322-3.194, p=0.001) and presence of impaired fasting glucose (^{3}100 mg/dl) (Beta= 1.365, 95% confidence interval: 1.009-1.489, p=0.050) were independently associated with poor collateralization.

Conclusion: MS is associated with poor CCV, which might account for poor outcomes. The risk individually seems to be associated with high blood glucose and abdominal obesity.

2084 Evidence of myocardial insulin resistance and coronary microvascular dysfunction in patients with familial combined hyperlipedaemia

H. Kindler[1], M.T. Khan[1], Y. Bouchareb[1], D.J. Betteridge[2], R.P. Naoumova[1], P.G. Camici[1]. [1]*Imperial College School of Medicine, MRC Clinical Sciences Centre, Faculty of Med., London, United Kingdom;* [2]*University College, Middlesex Hospital, London, United Kingdom*

Background: Familial combined hyperlipedaemia (FCHL) is the most common inherited disorder of lipid metabolism which affects up to 2% of the population and is known to be associated with premature cardiovascular mortality. In addition to coronary artery disease these patients have whole body insulin resistance. We hypothesize that patients with FCHL will have impaired glucose uptake and insulin resistance at myocardial level as well as coronary microvascular dysfunction.

Methods: We studied 13 FCHL patients aged 54±7 years and 27 healthy controls (HC) aged 51±8 years (p=ns). All patients were receiving maximal lipid lowering treatment with statins ± fibrates. Myocardial glucose uptake (MGU) during euglycaemic hyperinsulinaemic clamp was measured in all patients and 14 HC by means of positron emission tomography (PET) and F18-fluorodeoxyglucose. Myocardial blood flow (MBF) at rest and during iv adenosine (ADO, 140 μg/kg) was measured in all patients and 13 HC with PET and oxygen-15 labelled water. The coronary flow reserve (CFR) was calculated as ADO-MBF/Rest-MBF.

Results: MGU in FCHL patients was significantly reduced compared to HC (0.35±0.16 vs 0.61±0.08 μmol/min/g; p<0.0001). Resting MBF was comparable in FCHL patients and HC (1.04±0.21 vs 0.95±0.16 ml/min/g; p=ns) whereas ADO-MBF (2.47±0.81 vs 3.57±1.08 ml/min/g; p<0.007) and CFR (2.43±0.86 vs 3.89±1.39; p<0.004) were severely blunted in patients compared to HC.

Conclusions: The main finding of the present study is that FCHL patients are characterized by severe reduction of MGU which suggests insulin resistance at myocardial level in addition to a marked impairment of coronary microvascular function. Myocardial insulin resistance could contribute to the higher cardiovascular morbity and mortality in FCHL patients and, possibly, should be treated.

INFLAMMATION AND IMPAIRED METABOLISM IN CHRONIC HEART FAILURE

2099 Expression of the insulin-like growth factor system in chronic human heart failure

P. Trigo Trindade[1], C. Morandi[2], J.C. Pache[3], H. Ross[4], A. Kalangos[3], L. Gullestad[5], M. Brink[2]. [1]*Hopital Universitaire de Geneve, Centre de Cardiologie, Geneve 14, Switzerland;* [2]*University Hospital, Kardiobiologie, Basel, Switzerland;* [3]*University Hospital, Geneva, Geneva, Switzerland;* [4]*Toronto General Hospital, Toronto, Canada;* [5]*Rijkshospitalet, Oslo, Norway*

Background: apoptosis is considered to play a role in the progression of chronic heart failure (CHF). The IGF system is known to act in favour of cell survival in cell culture and animal models. To determine whether this system plays a role in human CHF, we examined the expression of members of the IGF system in tissue of failing left ventricles in relation to apoptotic markers.

Methods: tissue was harvested from the left ventricle at cardiac transplantation (n=15) and at autopsy after non cardiac death (controls; n=4). Competitive RT-PCR and immunohistochemistry were used to analyze expression levels of messenger RNA of IGF-I, its receptor IGF-IR, IGF-II and IGF-IIR and of IGF-I and -II protein. Markers of apoptosis were examined by immunohistochemistry on paraffin sections. Caspase-3 was quantified by counting positive objects in four different sections of 6 failing and 4 control tissues.

Results: in failing myocardium, mRNA levels of IGF-I (1175 ± 261 fg) were significantly lower than IGF-II (8678 ± 2305 fg). However, IGF-I expression was higher in the failing samples than in controls(545 ± 105 fg). In contrast, the expression of IGF-IR was lower in the failing ventricles (682 ± 108 fg) than in the control samples (1086 ± 95 fg). In distinction to IGF-I, IGF-II expression was decreased in failing myocardium compared to controls (17228+5201 fg). Immunohistochemical staining for IGF-I protein was heterogenous in cardiomyocytes, but also present in vascular smooth muscle cells and interstitial fibrous tissue. In contrast, staining for IGF-II was homogeneously present in all cardiomyocytes and absent in fibrous tissue. Bax and Bcl-2 was recognized in failing myocardium, and occasionally caspase-3 positive cells were identified. Although rare, the numbers of caspase-3 positive cells in failing myocardium were increased compared to controls (2.3 cells/cm^2 vs 0.4 cells/cm^2, p< 0.001).

Conclusions: these data show that members of the IGF system are differentially expressed in the human failing heart and that apoptosis is present, even though at a low rate. As IGF-I and IGF-II both act via the IGF-IR, the combined changes in these factors may ultimately modulate apoptosis in CHF.

2100 Differences in endothelial function and inflammatory process between patients with ischaemic and dilated heart failure

D. Tousoulis[1], C.A. Antoniades[2], M. Kotsopoulou[1], E. Bosinakou[1], C. Pitsavos[1], C. Tentolouris[1], A. Trikas[1], C. Stefanadis[1]. [1]*Hippokration Hospital, Cardiology, Athens, Greece;* [2]*Athens, Greece*

Heart failure (HF) is associated with endothelial dysfunction and increased inflammatory process.

Aim: We investigated the differences in endothelial function and levels of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-a) between patients with coronary artery disease (CAD), ischaemic HF (IHF), dilated HF (DHF) and healthy controls.

Methods: In this study were included 26 patients with CAD (57.8±1.8 years old), 48 patients with IHF (68.1±1.2 years old), 20 patients with DHF (57.86±3.6 years old) and 14 healthy controls (aged 44.4±4.4 years old). Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from rest to the maximum flow during reactive hyperemia or after sublingual nitroglyceride administration respectively. All patients with HF were NYHA II to IV. All values are expressed as mean±SEM.

Results: EDD was greater in healthy (102±14.7%) than in IHF (42.4±2.7% $p<0.01$), DHF (53.7±4.4% $p<0.01$) or CAD (71.2±7.3%, $p<0.05$). EDD was lower in IHF compared to DHF ($p<0.05$) and significantly higher in CAD compared to both IHF($p<0.05$) and DHF ($p<0.05$). EID was similar between groups. TNF-á and IL-6 were lower in the control group (1.42±0.14 and 1.51±0.65 pg/ml respectively) compared to CAD (2.08±0.15 and 4.18±0.83 pg/ml respectively, $p<0.05$ for both), IHF (3.68±0.32 and 7.35±0.56 g/ml $p<0.01$ for both), and DHF (4.05±0.7 and 6.24±0.71 pg/ml $p<0.01$ for both). Although TNF-a and IL-6 serum levels were lower in CAD compared to both IHF ($p<0.05$ for both) and DHF ($p<0.05$ for both), there was no significant difference between IHF and DHF groups.

Conclusions: Impaired endothelial function and increased inflammatory process were found in both types of heart failure. Although TNF-a and IL-6 levels were not different between ischaemic and dilated heart failure, a greater endothelial dysfunction was observed in patients with ischemic compared to those with dilated cardiomyopathy, implying that the underlying atherosclerosis may participate in this process.

2101 Infarcted human heart absorbs soluble IL6 receptors

K. Kaminski[1], I. Wojtkowska[1], S. Dobrzycki[2], P. Kralisz[2], K. Nowak[2], P. Prokopczuk[2], M. Kozuch[1], W.J. Musial[1]. [1]*Medical University in Bialystok, Department of Cardiology, Bialystok, Poland;* [2]*Medical University, Invasive Cardiology, Bialystok, Poland*

Interleukin 6 is one of the typical pleiotropic cytokines which affects both inflammatory reaction and myocardial response to harmful stimuli. It is induced during myocardial infarction and in heart failure, but its role remains largely unrevealed. Soluble forms of IL6 receptors (sIL6R and sgp130) may strongly affect the effects of this cytokine.

We have undertaken a study to assess the production of interleukin 6 and its soluble receptors by human heart during ischemia and reperfusion. In our pilot study we included 10 patients (mean age 67,1) with first myocardial infarction, no co-morbidity, left anterior descending (LAD) artery occlusion and otherwise normal coronaries. Blood samples from coronary sinus and aorta were drawn before, ca. 2 minutes after angioplasty and 20 minutes later. Venous blood of 19 healthy volunteers served as control. Plasma concentrations of IL6, sIL6R and sgp130 were measured using ELISA kits.

All blood samples from patients with AMI presented significantly higher IL6 and significantly lower sgp130 concentrations than the control group. We did not notice significant transcardiac gradient of IL6 neither during ischemia nor after reperfusion. Surprisingly, during ischemia there was significantly higher concentration of both soluble IL6 receptors in aorta than in coronary sinus. This difference disappeared immediately after reperfusion.

IL6 concentration is increased and sgp130 concentration is decreased in the acute phase of myocardial infarction. During ischemia there is a transcardiac gradient of sIL6R and sgp130, which disappears instantly after reperfusion. Such difference may indicate that large amounts of soluble IL6 receptors are bound to cell surface in the infarcted heart thus affecting the signal transduction. Nevertheless this finding requires further elucidation.

Table I

	IL6 (pg/mL)	IL6 (pg/mL)	IL6 (pg/mL)
Control group		1.8 ± 1.2	
Time	Before PCI	Instantly after PCI	Later after PCI
Coronary sinus	10.9 ± 12.5 ##	11.9 ± 12.6 ##	14.6 ± 15.1 ^^ ##
Aorta	11.1 ± 9 ##	12.3 ± 10.3 ##	13.2 ±10.7 ##
	sIL6R (ng/mL)	sIL6R (ng/mL)	sIL6R (ng/mL)
Control group		31.8 ± 9.2	
Time	Before PCI	Instantly after PCI	Later after PCI
Coronary sinus	27.9 ± 6.3**	29.2 ± 6.9	28.6 ±9
Aorta	35.6 ±8.9	31 ± 7.1	27.5 ± 11.6 ^^
	sgp130 (ng/mL)	sgp130 (ng/mL)	sgp130 (ng/mL)
Control group		270.7 ± 46.5	
Time	Before PCI	Instantly after PCI	Later after PCI
Coronary sinus	197.5 ± 29.9** ##	205.4 ± 33 ##	198.1 ± 25.9 ##
Aorta	226.7 ± 24 ##	205.4 ± 33 ##	205 ± 21.9 ^^ ##

** $P<0.01$ vs Aorta ## $P<0.01$ vs Control group ^^ $P<0.001$ vs Before PCI

2102 Attenuated specific immunity in chronic heart failure

S. von Haehling[1], E.A. Jankowska[2], G. Foldes[2], K. Strohschein[2], W. Doehner[2], S.D. Anker[2]. [1]*National Heart and Lung Institute, Department of Clinical Cardiology, London, United Kingdom;* [2]*National Heart and Lung Institute, Clinical Cardiology, London, United Kingdom*

Background: Chronic heart failure (CHF) is a state of chronic immune activation. Although the role of pro-inflammatory cytokines has been studied in detail, the role of leukocyte subsets and their antigen presenting capacity remains unclear.

Methods: We prosepectively enrolled 63 CHF patients (age 67.9±1.3 y [mean±SEM], NYHA 2.4±0.1, left ventricular ejection fraction 31±2%, white blood cell count [WBC] 7.5±0.3/nL, CRP 9.7±1.0 mg/L, creatinine 120±5 μmol/L) and 17 healthy control subjects (age 62.4±2.6, WBC 7.4±0.4, CRP 9.9±1.8, creatinine 81±4). Flow cytometry was performed using EDTA anticoagulated whole blood after staining with CD4/CD8/CD3, CD14/CD19, and CD95/human leukocyte antigen (HLA)-DR. Data were analysed using scatter plot gating.

Results: Lymphocyte distribution differed between CHF patients and controls: CD3 positive T cells 15±1 vs. 18±2%, p=0.1, CD4 positive T helper cells 9±0.6 vs. 12±1%, p=0.04, CD8 positive cytotoxic T cells 2.6±0.4 vs. 3.0±0.9%, p=NS, CD19 positive B-lymphocytes 2.6±0.2 vs. 4.4±0.7%, p=0.002. The relative number of CD95 positive lymphocytes in CHF patients was reduced compared to controls (21±1 vs. 37±2%, p=0.03). However, the relative number of CD95 positive granulocytes in CHF was increased compared to healthy controls (59±2 vs. 53±3%, p=0.048). The relative number of HLA-DR positive lymphocytes was reduced in CHF patients as compared to controls (21±1 vs. 26±3%, p=0.037). In monocytes, there was no difference in absolute number, CD95 or HLA-DR expression.

Conclusion: CHF is associated with attenuated specific immunity as characterized by reduced T helper and B cell numbers and diminished antigen presenting capacity. The latter is reflected by reduced HLA-DR expression. Overactive innate responses may suppress specific immune responses.

2103 C-reactive protein, heart rate variability, and prognosis in community subjects with no apparent heart disease

A. Sajadieh[1], O.W. Nielsen[2], V. Rasmussen[3], H.O. Hein[4], J.F. Hansen[2]. [1]*Herlev, Denmark;* [2]*Bispebjerg Hospital, Cardiology, Copenhagen NV, Denmark;* [3]*Hvidovre Hospital, Cardiology, Copenhagen, Denmark;* [4]*Copenhagen University Hospital, Epidemiological Research Center, Copenhagen, Denmark*

Background: Increased C-reactive protein (CRP) and reduced heart rate variability (HRV) are both markers of poor prognosis in different populations. An association between reduced HRV and increased CRP has been reported, suggesting an interaction between the inflammatory and autonomic systems. This may theoretically lead to increased cardiovascular mortality, but has not been studied.

Methods and Results: 643 middle-aged and elderly subjects with no apparent heart disease were selected from community and studied by interview, clinical and laboratory examination and 24-h Holter monitoring. Four time domain measures of HRV were studied. All were followed for up to five years. Both CRP and three of four HRV measures were significantly associated with increased rate of death or acute myocardial infarction after adjustment for traditional risk-factors. In a Cox model with CRP, SDNN (standard deviation for the mean value of the time between normal complexes) and their interaction term, the interaction term proved significant implying that the increased risk seen in subjects with high CRP or reduced SDNN is mainly due the increased risk in the group with both increased CRP and reduced SDNN, while subjects "high CRP and high SDNN" or "low SDNN and low CRP" had the same good prognosis as subjects with "low CRP and high SDNN" (Table 1). In a Cox-model with traditional risk factors, "high CRP and low SDNN" was the strongest predictor of events after age: Hazard Ratio 2.47, 95% CI: 1.36-4.48, p=0.003.

Table 1. Five-year event rates in groups of apparently healthy middle-aged and elderly subjects stratified based on SDNN and CRP

	Number of subjects/events	Event rate
CRP≤3 μg/ml and SDNN>=100 ms	307/22	7.2%
CRP≤3 μg/ml and SDNN<100 ms	72/3	4.2%
CRP>3 μg/ml and SDNN>=100 ms	178/16	8.9%
CRP>3 μg/ml and SDNN<100 ms	86/19	22.1%

$p<0.0001$ (Log-Rank).

Conclusions: The prognostic burden of increased CRP is mainly carried by subjects with reduced SDNN and vice versa, suggesting that the interaction between inflammatory and autonomic systems may be of crucial prognostic significance.

2104 Two sides of the coin-glutathione-peroxidase 1 and homocysteine in cardiovascular disease

R. Schnabel[1], E. Lubos[1], K.J. Lackner[2], H. Rupprecht[1], C. Bickel[3], L. Tiret[4], T. Muenzel[1], S. Blankenberg[1] on behalf of AtheroGene.
[1]Johannes-Gutenberg-Universität, II. Med. Clinic, Mainz, Germany; [2]Johannes Gutenberg-University, Department of Clinical Chemistry, Mainz, Germany; [3]Bundeswehrzentralkrankenhaus, Department of Internal Medicine, Koblenz, Germany; [4]Faculté de Médecine Pitié-Salpêtrière, INSERM U525, Paris, France

Background: Homocysteine plasma levels have been associated with cardiovascular risk. Experimental data suggest that anti-oxidative glutathione peroxidase (GPx)-1 activity modulates cardiovascular risk associated with homocysteine plasma levels.
Methods and Results: In 643 patients with suspected coronary artery disease we performed a prospective study to assess the risk of homocysteine plasma levels and glutathione-peroxidase (GPx)-1 activity on long term cardiovascular risk with a median follow-up of 7.1 years. Both, homocysteine plasma levels as well as GPx-1 were among the strongest univariate predictors of future cardiovascular risk. Homocysteine levels were significantly elevated in individuals with future cardiovascular events (15.4 versus 13.4 μmol/l; P<0.0001), GPx-1 activities were lower (45.3±13.1 U/g Hb vs. 50.2±11.0 U/g Hb; P<0.0001). These associations remained nearly unaffected if adjusted for cardiovascular confounders. In patients with GPx-1 activity below the median, homocysteine plasma levels above the median were significantly associated with a 3.2 fold (95% CI 1.8 - 5.6; P<0.0001) increase in cardiovascular risk whereas it loses its independent risk prediction in individuals with increased antioxidative capacity reflected by high GPx-1activity. In contrast to single determination, combined assessment of homocysteine plasma levels and GPx-1 activity revealed a sifgnificant increase in C-statistics of cardiovascular risk predictive models from 0.72 including traditional risk factors to 0.75 additionally including homocysteine plasma levels and GPx-1 activity.
Conclusion: Plasma homocystine levels and GPx-1 acitivity are complementary in identifiying individuals at high cardiovascular risk. Joint determination of both biomarkers provide substantial information on top of classical risk factors in cardiovascular risk assessment.

MANAGEMENT AND PROGNOSTIC ASSESSMENT IN DECOMPENSATED HEART FAILURE

2105 Prolonged neurohormonal and inflammatory activation in acute heart failure: the uncontrolled spark?

W.G. Stough[1], M. Gheorghiade[2], G. Cotter[1], C.M. O'Connor[1], K.F. Adams Jr[3]. *[1]Durham, NC, United States of America; [2]Chicago, IL, United States of America; [3]University of North Carolina, Heart Failure Programme, Chapel Hill, United States of America*

Purpose: Previous studies have shown that patients admitted with acute heart failure (AHF) have a high rate of recurrent AHF (up to 40% in the first month), and this recurrence is related to increased short and long term mortality. Neurohormonal and inflammatory activation is commonly identified in patients with AHF, and has been associated with this adverse outcome especially after discharge. However, serial changes in specific cytokines and endothelin-1 and their independent relationship to in hospital outcomes has not been well studied.
Methods: PRESERVD-HF was a prospective, randomized trial of nesiritide or dobutamine in 51 patients with ischemic heart disease (IHD) admitted with acute decompensated heart failure judged to be eligible for vasoactive medication. For the purpose of the biomarker analysis, blood was obtained at baseline, 8, 56, and 80 hours post randomization (mean one day after admission). Patients were monitored for the occurrence of worsening heart failure or death during hospitalization.
Results: Significant changes in neurohormonal and inflammatory markers were not observed during the admission (Table). Although the number of adverse outcomes was limited (6), multivariable modeling demonstrated that IL-6 and endothelin-1 (ET-1) were predictors of short term (during the admission) recurrent AHF and death.

Table

Biomarker	Baseline	Last Value	p-Value
Endothelin-1	4.1 (2.5, 6.6)	4.4 (1.9, 6.6)	0.578
TNFalpha	5.6 (4.1, 9.5)	6.3 (4.1, 8.1)	0.161
IL-6	7.5 (5.3, 12.5)	7.5 (5.1, 12.7)	0.344
IL-1	0.14 (0.02, 0.28)	0.09 (0.02, 0.27)	0.892
IL-10	1.9 (1.4, 3.0)	2.3 (1.3, 3.7)	0.159

*Values are median (25th, 75th)

Conclusions: Selected neurohormonal and inflammatory activation persists throughout the first few days of admission in patients with IHD hospitalized for AHF, and it could be one of the pathophysiological causes for the high rate of early recurrent AHF in these patients. IL-6 and ET-1 may be important mediators of this association.

2106 Effect of inotropes on the course of serum levels of circulating cytokines and soluble cytokines receptors in patients with acutely decompensated chronic heart failure. Results from the CASINO study

S.G. Foussas[1], M. Zairis[2], N. Patsourakos[1], M. Glyptis[1], D. Beldekos[1], C. Ntellos[1], D. Babalis[3], D.V. Cokkinos[4] on behalf of the CASINO Study Group. *[1]Tzanio Hospital, Cardiology Dept., Piraeus, Greece; [2]Piraeus, Greece; [3]Western Attica General Hospital, Cardiology, Athens, Greece; [4]Onassis Cardiac Surgery Center, Cardiology Dept., Athens, Greece*

Background: We sought to investigate the effect of treatment with levosimendan, or dobutamine on the course of the serum levels of tumor necrosis factor alpha (TNFa), soluble TNFa receptor 1 (sTNFaR1), soluble TNFa receptor 2 (sTNFaR2), interleukin-6 (IL-6) and soluble IL-6 receptor (sIL-6R) in patients enrolled in the CASINO study.
Methods: The CASINO was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study which investigated the hypothesis that a 24-hr treatment with levosimendan would result in better survival than treatment with either placebo or dobutamine, in 299 patients who were hospitalized for acutely decompensated severe (New York Heart Association class III/IV) low-output chronic heart failure (CHF). For the purpose of the present substudy, we serially measured the serum levels of TNFa, sTNFaR1 sTNFaR2, IL-6 and sIL-6R upon randomization as well as 8; 16; 24 and 48 hrs later, in all patients.
Results: There were no significant differences concerning the baseline characteristics, concomitant drug therapy and the serum levels of the study cytokines or their soluble receptors upon randomization among the patients assigned to levosimendan, dobutamine, or placebo. There was no any significant change in the serum levels of the study cytokines or their soluble receptors in patients assigned to placebo or dobutamine during the 48 hrs study period. Patients assigned to levosimendan did not have any significant change in serum levels of IL-6 (p for trend=0.8) or sIL-6R (p for trend=0.6) during the 48 hrs study period. However, a significant decrease in the serum levels of TNFa (p for trend <0.001), sTNFaR1 (p for trend=0.008), and sTNFaR2 (p for trend<0.001) was observed in these patients.
Conclusions: The present results suggest that in patients with acutely decompensated severe low-output chronic heart failure treatment with dobutamine has no any effect on circulating levels of proinflammatory cytokines or their soluble receptors. Conversely, treatment with levosimendan is associated with a significant decrease in serum levels of tumor necrosis factor or its soluble receptors.

2107 Fluid restriction in the management of decompensated heart failure: influence of admission serum sodium

B. Travers[1], C. O'Loughlin[1], M. Ledwidge[1], K. Mcdonald[2]. *[1]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland; [2]St. Vincent's University Hospital, Cardiovascular Research Director, Dublin 4, Ireland*

Background: Preliminary data previously presented from our unit indicated that fluid restriction (FR) did not improve the management of patients hospitalised with decompensated heart failure (DHF). However, it remains unknown whether benefit can be seen in the subgroup of patients presenting with low serum sodium.
Aim: The purpose of this analysis is to ascertain whether serum sodium influences response to FR.
Methods: This is a prospective randomised study where patients admitted with Class IV heart failure (HF) are assigned to either fluid restriction (FR) or free fluid (FF) within 24 hours of admission. Patients in both groups monitor and record their fluid intake on a daily basis with assistance form a HF nurse specialist. Patients in the FR arm are limited to one litre of fluid in a 24 hour period. Compliance with fluid intake is measured on daily basis. The primary end-point is time to clinical stability (CS) defined as stable dry weight, off intravenous therapy (IVT) for DHF for at least 2 days, on stable oral therapy for at least 2 days with no worsening of renal function (increase in serum creatinine by 25% from baseline). Time to discontinuation of IVT is a pre-specified secondary end-point. Both time points are assessed by HF cardiologist blinded to the patient intervention.
Results: In this ongoing study, 63 patients have been randomised: 33 to FR (age 75.4±10.5 yrs, male 42.4%, ischaemic 75.8%); 30 patients to FF(age 73.4 ± 12.9, male 51.7%, ischaemic 53.6%). In the FR arm daily compliance was 58 ± 32%. There was a significant difference in average daily fluid intake between the groups (FR: 1074.6 ± 324 mL; FF: 1459.1± 631.4 mL, p= 0.012). There was no significant difference in time to CS between groups (FF: 6.3±3.7 days vs. FR: 5.5±2.2 days, P=NS) or in IVT (FF: 3.0±5.9 days vs. FR: 2.6±4.6 days, p=NS). There was no significant difference in serum sodium levels between groups at baseline or on reaching CS (Baseline: FF: 137.9 ± 2.9 mEq/L, FR: 137.5 ± 4.3 mE/L; CS; FF: 137.4 ± 3.2 mEq/L, FR 137.8 ± 3.8 mEq/L). Multivariable analysis demonstrated that baseline sodium level (range FF: 126 to 141 mEq/L, FR: 123 to 141 mEq/L) was not an independent predictor of response to FR with regard to either time to CS (p=0.119) or time to discontinuation of IVT (p=0.221)
Conclusion: These data demonstrate that FR does not influence time to CS in patients admitted with DHF. Furthermore, there is no influence of admission serum sodium on the clinical impact of FR. FR should not be a routine strategy inthe management of this patient population.

2108 A novel clinical prognostic score for short-term and long-term prognosis in patients after acute cardiogenic pulmonary oedema

M. Fiutowski[1], T. Waszyrowski[1], M. Krzeminska-Pakula[2], J.D. Kasprzak[2]. [1]*Jonscher Hospital, Cardiology Dept., Lodz, Poland;* [2]*Medical Univeristy, Cardiology, Lodz, Poland*

Background: congestive heart failure is a very common disorder connected with high mortality. Only a few data concerning the prognosis in patients (pts) after acute episode of heart failure and no prognostic scales are used in this condition to date.
Aim: this study was performed to develop a simple score predicting in-hospital and 2-year prognosis in pts after cardiogenic pulmonary oedema (CPO) based on the clinical variables available on patient presentation.
Methods: 276 consecutive pts (128 males, 148 females; median age 70 years) admitted to two departments of cardiology with CPO between 1998-2000 (mean duration of hospital stay 12±7 days) were followed-up for a period of 498±272 (range 5-932 days) with regard to mortality.
Results: deuring hospitalisation 58 pts (21%) died and 218 (79%) were discharged. The completeness of 2-years follow-up was 94%. Of those 205 Pts discharged from the hospital, 81 (40%) were dead at two years, which corresponds with overall 2-year mortality of 53%. Univariate and multivariate statistical analysis revealed that the most significant predictors for in-hospital mortality were: acute myocardial infarction (RR=2,12; 95%CI 1,36-3,31), heart rate >115/min. (RR=2,13; 95%CI 1,33-3,4), systolic blood pressure =<130mmHg (RR=3,61; 95%CI 2,21-5,89) and white blood cells count >11500/mm^3 (RR=2,26; 95%CI 1,39-3,65) on presentation. The presence of each factor was scored 1 point and the sum was calculated to provide Pulmonary Oedema Prognostic Score (POPS). Pts with POPS=0 had 2% in-hospital and 40% 2-year mortality rate whereas mortality in Pts with POPS 4 was 64% during hospitalisation and 82% during follow-up. Receiver operating characteristics analysis was applied proving satisfactory discriminative ability of POPS for in-hospital (AUC=0,78) and 2-year (AUC=0,66) prognosis. Score above 1 had sensitivity of 79%, specificity of 62%, 36% positive and 92% negative predictive value for in-hospital mortality (RR=4,43; 95%CI 2,46-7,99) and sensitivity of 60%, specificity of 68%, 68% positive and 60% negative predictive value for 2-year mortality in patients after CPO (RR=1,71; 95%CI 1,35-2,17).
Conclusions: it is possible to determine short-term and long-term prognosis in patients with pulmonary oedema based on 4 simple clinical predictors during the acute episode. Pulmonary oedema prognostic score is a simple bedside tool allowing a satisfactory prediction of in-hospital and 2-year prognosis after acute cardiogenic pulmonary oedema. This index can be easily used in each patient on presentation after ECG, blood pressure and white cell count are obtained.

2109 B-type natriuretic peptide (BNP) and N-terminal proBNP are comparably useful for disease monitoring in acute heart failure treated with intravenous positive inotropic drugs

G. Falkensammer[1], G. Poelzl[2], R. Zwick[2], A. Hammerer-Lercher[3], A. Griesmacher[1], B. Puschendorf[3], O. Pachinger[2], J. Mair[2]. [1]*Central Institute for Med and Chem Laborator, Innsbruck, Austria;* [2]*University of Innsbruck, Internal Medicine, Cardiology, Innsbruck, Austria;* [3]*Innsbruck Biocenter, Division of Clinical Biochemistry, Innsbruck, Austria*

B-type natriuretic peptide (BNP) reflects the severity of heart failure (HF), and BNP concentrations have been reported to decrease with improving hemodynamic status during tailored intravenous treatment in acute HF. The aim of this study was to compare the abilities of BNP and N-terminal proBNP (NT-proBNP) for disease monitoring of acutely decompensated HF patients.
We investigated 30 consecutive patients (aged 39 to 83 years, 26 male, 4 females) with acute HF (all NYHA class IV) who were admitted to our coronary care unit (CCU) for treatment with intravenous positive inotropic drugs (20 levosimendan, 6 milrinone, 4 dobutamine). A Swan-Ganz katheter was placed in all patients for invasively monitoring hemodynamic changes during drug treatment. EDTA blood samples were drawn at CCU admission (baseline) and after 24 hours of treatment. The plasma samples were immediately frozen until batch analysis of BNP on an ADVIA Centaur analyser and NT-proBNP on an Elecsys analyser. Hemodynamic measurements included the pulmonary capillary wedge pressure (PCWP). Patients were divided into two groups according to the PCWP after 24 hours of therapy. A cut-off value of 16 mmHg was chosen. After 24 hours of therapy BNP and NT-proBNP levels decreased. The decrease of the BNP and NT-proBNP levels was more pronounced, although statistically not significant, in those patients showing a PCWP <16 mmHg (responders) (BNP mean -36% of baseline, range from -68% to +45%; NT-proBNP mean -34% of baseline, range from -72% to +20%) than in those with a PCWP = 16 mmHg (non-responders) after 24 hours of treatment (BNP mean -19% of baseline, range from -67% to +319%; NT-proBNP mean -28% of baseline, range from -78% to +791%). Absolute concentrations of BNP and NT-proBNP correlated at baseline (r = 0.548; p<0.01) as well as after 24 hours of treatment (r = 0.595; p<0.01). Only BNP levels significantly correlated with PCWP values at baseline (r=0.427 p<0.05). No significant correlations were found after 24 hours of treatment. We found an equal but only moderate diagnostic performance of BNP and NT-proBNP levels to discriminate between patients with PCWP <16 mmHg and = 16 mmHg after 24 hours of treatment. The areas under curve for BNP (0.67) and NT-proBNP (0.74) did not differ significantly.
The diagnostic performances of BNP and NT-proBNP to identify hemodynamic responders during intravenous positive inotropic drug treatment of acutely decompensated HF are only moderate. Despite their different biological half-lives both markers are comparably useful.

2110 Prognosis of decompensated heart failure: does NT-proBNP predict prognosis in patients with preserved systolic function?

L. Fonseca[1], S. Ferreira[2], A. Azevedo[3], R. Almeida[4], H. Guerrero[1], S.U. Ferreira[1], A. Ferreira[2], P. Bettencourt[2]. [1]*Fac. Medicina Porto, Hospital S. Joao, Internal Medicine, Porto, Portugal;* [2]*Porto Medical School, Unidade de I&D Cardiovascular, Porto, Portugal;* [3]*University of Porto Medical School, Hygiene and Epidemiology, Porto, Portugal;* [4]*Hospital de S.João, Cardiology, Porto, Portugal*

Introduction: Left ventricular (LV) preserved systolic function (SF) is a common finding in Heart Failure (HF) patients. Data from ambulatory and hospitalised patients indicate that HF with preserved SF and HF with depressed SF have similar morbidity. However, mortality is higher in the latter group. Predictors of prognosis in HF patients with preserved SF are far less known than in patients with depressed SF. We intended to evaluate the prognostic value of NT-proBNP variations during hospitalisation for decompensated HF and compare the morbidity between HF patients with preserved and depressed LVSF.
Methods: This study included 310 patients admitted with decompensated heart failure between November 2002 and April 2004. Patients discharged alive from the hospital were followed for up to 6 months. The primary endpoint was death or hospital readmission. NT-proBNP was measured at admission and discharge in a subsample of 224 patients. Patients were classified in three groups: A - decreasing NT-proBNP levels by at least 30%, n=122; B - no meaningful modifications on NT-proBNP levels, n=65; and C - increasing NT-proBNP levels by at least 30%, n=37. Cox regression was used to evaluate readmission-free survival.
Results: Patients with preserved LVSF (n=213) were older (73.2±11.2 vs 70.6±12.5 years), more frequently female (72.2% vs 45.1%), had lower prevalence of ischaemic heart disease (26.8% vs 59.6%) and higher prevalence of hypertension (56.4% vs 50%) and atrial fibrillation (55.7% vs 35.1%) than patients with depressed LVSF (n=97). NT-proBNP decreased in both groups (9048±19688 to 6004±14854 vs 13786±20862 to 10168±20200 pg/ml). NYHA functional class was similar in the two groups, both at admission (3.4±0.7 vs 3.4±0.7) and at discharge (2.0±0.4 vs 2.1±0.5). The hazard ratio (HR) of death or readmission for patients with depressed LVSF (vs patients with preserved LVSF) was 1.17 (95%CI: 0.81-1.69). When compared to group A, patients of groups B (preserved LVSF - HR:2.45, 95%CI: 0.96-6.23; depressed LVSF - HR: 2.64, 95%CI: 1.49-4.70) and C (preserved LVSF - HR: 3.24, 95%CI: 1.32-7.96; depressed LVSF - HR: 6.19, 95%CI: 3.29-11.65) had worse outcome.
Conclusions: HF patients have a high morbidity after hospitalisation regardless of systolic function. These results suggest that in HF patients with preserved systolic function NT-proBNP can play a role as a tool to identify patients at risk of adverse outcome.

NEW INSIGHTS INTO CARDIAC IMAGING

2123 The role of contrast-enhanced real-time 3D stress echocardiography in diagnosing coronary artery disease

C. Aggeli[1], P. Misovoulos[2], G. Roussakis[2], C. Kokkinakis[2], E. Christoforatou[2], S. Brili[2], J. Barbetseas[2], C. Stefanadis[2]. [1]*Athens, Greece;* [2]*Hippokration Hospital, Cardiology Dept., Athens, Greece*

Background: Stress echocardiography is a clinical procedure, routinely used for the diagnosis of coronary artery disease. Incomplete data and misaligned prestress and poststress views are known limitations of conventional stress echocardiography.
We tested the hypothesis that left ventricular wall motion abnormalities during stress echo could be measured more accurately from real-time 3D (RT3D) data sets, which allow the offline selection of nonforeshortened apical views, by comparing 2D and RT3D.
Methods: 45 patients (mean age 63±12, 17men) who referred for coronary angiography, underwent dobutamine stress with 2D and RT3D echo. A bolus of SonoVue infusion was done at rest and peak stress to better evaluate wall motion abnormalities. Wall motion score index was calculated using both techniques, while regional wall motion score index was calculated as well for the left ventricular apex, separately. All images were obtained at baseline and peak stress from apical 4-, 2-, 3-chamber views. 2D and 3D images were interpreted by two expert readers blinded for other data.
Results: 30 patients had coronary artery disease. Wall motion score indexes, assessed by 2D and RT3D echo, were similar at rest but were different at peak stress (1.27±0.3 vs. 1.25±0.29, p<0.001, respectively). Regional wall motion score index at peak was different between 2D and 3D stress echo (128±0.4 vs. 124±0.3, p<0.001, respectively). Overall sensitivity, specificity, and accuracy

were similar for 2D and 3D stress echo (79% vs. 80%, 83% vs. 85% and 82% vs. 84%, respectively). Concordance between two techniques for normal vs. abnormal perfusion was 87% (k=0.74) whereas discrepancies between them were more notable in the LAD territory.
Conclusions: Contrast-enhanced RT3D stress echo is an accurate method to identify coronary artery disease. It has potential benefits for the evaluation of the left ventricular apex, by eliminating off-axis acquisition errors.

2124 How to distinguish between physiological and pathological post-systolic-thickening. An experimental strain rate imaging study

F. Weidemann[1], J. Broscheit[2], B. Bijnens[3], P. Claus[3], G.R. Sutherland[4], W. Voelker[2], G. Ertl[2], J. Strotmann[2].
[1]University Hospital, Medical Clinic, Dept. of Cardiology, Wurzburg, Germany; [2]University Hospital Wuerzburg, Cardiology, Wuerzburg, Germany; [3]University Hospital Gasthuisberg, Cardiology Dept., Leuven, Belgium; [4]St George Hospital, Cardiology, London, United Kingdom

Background: The ongoing thickening after aortic valve closure (post-systolic thickening=PST) is an established marker for acute ischemic myocardium. In addition, late activated segments and pharmacological interventions can also induce post-systolic thickening. Thus, the aim of this study was to distinguish between ischemic (pathological) and non-ischemic (physiological) PST.
Methods: In an experimental pig-model (n=11) regional deformation of the inferolateral wall during normal perfusion and regional ischemia was measured using ultrasonic Strain Rate Imaging. Ischemia was induced by an active coronary hypoperfusion in the circumflex coronary artery. Measurements were done at 1) baseline, 2) during akrinor, 3) dobutamine and 4) esmolol infusion and 5) during a preload increase by saline infusion. In all segments where thickening was ongoing after aortic valve closure the amount of PST was calculated by the difference of maximal strain minus systolic strain. In addition, peak strain rate during the isovolumetric relaxation period was extracted.
Results: During normal perfusion 79% of the segments (n=40) developed PST. This physiological PST averaged 5±4% and was most frequently during esmolol infusion (n=11). Peak isovolumetric strain rate averaged -2.1±2.0 s-1 in segments with physiological PST. During coronary hypoperfusion 96% of the ischemic segments developed PST. The amount PST averaged 14±11%, was highest during dobutamine infusion (25±13%) and lowest during esmolol infusion (5±5%). In contrast to normal perfused segments, peak isovolumetric strain rate was positive and averaged 2.0±1.5 s-1 in these segments with pathological PST. Using a cut-off value of =0 s-1 for isovolumetric strain rate pathological PST was detected with a sensitivity of 100% and a specificity of 87%.
Conclusions: By extracting peak isovolumetric strain rate pathological PST can be precisely differentiated from physiological PST.

2125 Non invasive coronary angiography with 64-multislice-spiral-CT: Ready to replace diagnostic angiography in patients with suspected CAD?

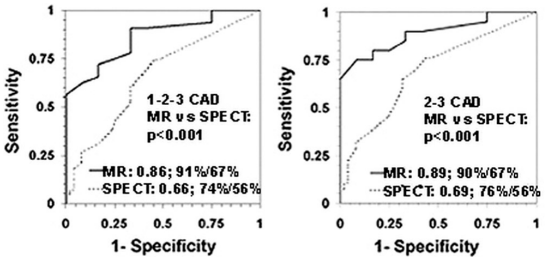
A. Knez[1], A. Becker[2], C. Becker[3], F. Ziegler[2], M. Reiser[3], A. Leber[3].
[1]University of Munich, Medical Hospital I, Munich, Germany; [2]Klinikum Großhadern, Medical Hospital I, Munich, Germany; [3]Klinikum Großhadern, Departement of Radiology, Munich, Germany

The recent introduction of 64-Multislice-Spiral-CT (64-MSCT) promises further improvement of image quality that may allow a more precise evaluation of coronary stenosis. The aim of the present study was to evaluate the diagnostic accuracy of 64-MSCT compared to conventional angiography in a clinical setting.
79 consecutive patients with stable angina (male=65, age=62±9 y) were included. 64-MSCT studies (Sensation64, Siemens) were performed within two days before coronary angiography using a standardized protocol (80 cc contrast media, collimation 64 x 0,6 mm, scan time =165 ms, retrospective ECG-trigger). 30 patients with heart rates >65 bpm received oral beta-blockade (50 to 100 mg metoprololtartrate). Analysis of the angiograms with QCA (Quantcor QCA, Siemens) and quantitative analysis of the CT data set (NeoImagery, Insight) were performed by experienced blinded readers. After the MSCT scan 6/79 subjects with non diagnostic CT- image quality (artifacts= 3, poor signal/noise ratio= 2) has to be excluded from further evaluation. Therefore 1025 segments were available for comparison between 64-MSCT and QCA. Overall correlation between the degree of stenosis between both methods was r = 0.64. Sensitivity for the detection of stenosis <50%, >50%, >75% was 79%, 74% and 81% respectively, specificity was 97%. If the analysis was restricted only to lesions that require revascularisation sensitivity improved to 89%. 24 lesions were missed and 14 were underestimated. Of 8 stenoses >75% that were missed 6 were detected but underestimated and 2 could not be visualised due to their location in a side branch (luminal diameter < 2 mm).
64-MSCT is a clinically robust modality that allows quantification of coronary stenosis with good sensitivity and excellent specificity. Major limitations are still the limited accuracy to exactly quantify luminal obstructions, to assess heavy calcified segments as well as distal segments with luminal diameters < 2mm. This restrictions still hampers the application of 64-MSCT technology as a real substitute for diagnostic angiography in a symptomatic patient population.

2126 Comparison of MR perfusion imaging with single photon emission computed tomography: a multicenter multivendor dose finding study

J. Schwitter[1], W. Bauer[2], A.C. van Rossum[3], M. Lombardi[4], N. Al-Saadi[5], S. Flamm[6], M. Marquardt[7], L. Johannson[8]. *[1]University Hospital Zurich, Div.of Cardiology,Dept.Internal Medicine(DIM), Zurich, Switzerland; [2]Dept. of Cardiology, University Hospital Wuerzburg, Wuerzburg, Germany; [3]Dept. of Cardiology, VU Medical Center, Amsterdam, Amsterdam, Netherlands; [4]Istituto di Fisiologia Clinica, CNR, Pisa, Italy; [5]University Hospital Berlin, Charite - Berlin Buch, Berlin, Germany; [6]Radiology, St. Luke's Episcopal Hospital Houston, Houston TX, United States of America; [7]GE Healthcare, Statistics, Munich, Germany; [8]GE Healthcare, Uppsala, Sweden*

Background: For ischemia detection single center studies suggested MR perfusion imaging as an alternative to single photon emission computed tomography (SPECT). However, the performance of MR perfusion imaging and optimum CM dose in a multicenter setting is not known.
Goal: To compare diagnostic performance of MR perfusion imaging at optimum CM dose vs quantitative coronary angiography (QCA) and SPECT in a large multicenter, multivendor trial.
Methods and Results: In 18 centers world-wide, 241 patients scheduled for QCA were enrolled. MR perfusion imaging and stress-rest 99mTc or 201Tl SPECT studies were performed within 4 weeks prior/after QCA. MR included a hyperemic first-pass (3 min adenosine, 0.14mg/kg/min IV) and rest study. Patients were randomised to 0.01, 0.025, 0.05, 0.075, or 0.1 mmol/kg GdDTPA-BMA (Omniscan, GE Healthcare). Coronary artery disease was defined as diameter stenosis >50% on QCA. Both, MR and SPECT data were scored blindly by 3 readers each, involving 16 segments/heart. The scores of the 3 MR and SPECT readers were averaged and ROC curves for both modalities were generated. 9% of patients experienced mild adverse events, no severe adverse events occurred. For MR and SPECT, 12.9% and 9.9% of the studies (ns) were non-evaluable, resp. Accuracy was lowest for lowest dose (on average 1.2 MR readers with a correct diagnosis/patient; p<0.003 vs other doses, Kruskal-Wallis). For ROC curves of the highest dose, see Figure (numbers are area under ROC, sensitivity, specificity), differences for lower doses ns.



Figure

Conclusions: In this largest multicenter, multivendor MR – SPECT perfusion trial, ROC analyses demonstrate good performance of MR perfusion imaging for detection of CAD. It may be used as an alternative for SPECT imaging in experienced centers.

2127 Non-viable myocardium may predict cardiovascular events in patients with severe ischaemic left ventricular dysfunction

M. Feola[1], G. Leonardi[1], S. Peano[2], A. Bianchi[2], F. Tassone[3], A. Biggi[2], E. Uslenghi[1]. *[1]Hospital Santa Croce-Carle, Dept of Cardiovascular Diseases, Cuneo, Italy; [2]Hospital Santa Croce-Carle, Nuclear Medicine, Cuneo, Italy; [3]Ospedale Santa Croce, Endocrinology Division, Cuneo, Italy*

Clinical prognosis could be predicted by the presence of hibernating myocardium revealed with fluorine F18 fluorodeoxyglucose (FDG) positron emission tomography (PET) in severe ischemic left ventricular dysfunction. This study analysed if the FDG PET might predict cardiovascular events independently to coronary revascularization.
Methods: All patients had previous myocardial infarction (MI) (>6 months) and left ventricular systolic dysfunction (LVEF<40%). FDG PET, transthoracic echocardiography,coronary angiography and TC99m single photon emission tomography (SPECT) were provided for all pts. All subjects underwent euglycemic hyperinsulinemic clamp before the injection of FDG. The results of PET/SPECT scans and echocardiograms were analysed semiquantitatively (dividing the left ventricle in 17 segments; score from 0=normal to 4=absence of detectable tracer uptake in one segment for PET/SPECT and score from 1=normal to 4=diskinetic segments) by two different operators. The dysfunctioning myocardium segment (echo score 2-3) was defined viable when the PET FDG segment uptake proved to be in the range from normal to moderately reduction (score 0-2). Inducible ischemia was revealed with rest/adenosine myocardial SPECT. Cardiac death, hospital admission for myocardial infarction or heart failure were considered cardiovascular events.

Results: Forty-four consecutive patients (36 males, mean age 64 ys) were studied. LVEF was 29.5±6.9%; 19 (43.1%) suffered an anterior MI, 16 (36.3%) non-q MI and 9 inferior MI. At coronary angiography 1/44 patient did not reveal any critical coronary stenosis, 18 (40.9%) had single-vessel disease, 11 (25%) two-vessel and 14 (31.8%) three-vessel disease. Twenty-four (54.5%) subjects were treated with coronary revascularization (3 with PTCA and 21 with CABG). Cardiovascular events occurred in 9/44 patients at 1-year follow-up (6 deaths and 3 readmission). Age (p=0.1), LVEF (p=0.2), wall motion score index (p=0.6), metabolic rate glucose (p=0.3), magnitude of inducible ischemia (p=0.2), presence of diabetes (p=0.8) and hypertension (p=0.9) were not different in the two groups. There were no differences in the prevalence of male gender (p=0.7) or rate of coronary revascularization (p=0.9). Patients who experienced cardiovascular events had larger non-viable myocardium (6.8±2.5 vs 4.5±2.6, p=0.02) but similar hibernating myocardium (1.7±1 vs 1.9±2, p=0.7) than subjects without events.
Conclusions: The magnitude of non-viable myocardium revealed with FDG PET predicts clinical prognosis independently to coronary revascularization procedures.

MULTIFOCAL PLAQUE INSTABILITY

2137 Periadventitial inflammation – a marker of systemic inflammatory activation and coronary death?

S. Dalager-Pedersen[1], W.P. Paaske[2], I.B. Kristensen[3], E. Falk[4]. *[1]Aarhus University Hospital, SKS, Dept. of Cardioth. and Vasc. Surgery T, Aarhus N, Denmark; [2]Aarhus University Hospital, SKS, Dept. of Cardioth. and Vasc. Surgery T, Aarhus N, Denmark; [3]University of Aarhus, Dept. of Forensic Medicine, Aarhus C, Denmark; [4]Aarhus University Hospital, SKS, Dept. of Cardiology B, Aarhus N, Denmark*

Periadventitial inflammation (PAI) may be important in atherosclerotic plaque growth and complications, and may be identified non-invasively using novel molecular imaging techniques.
Aim: To explore the distribution of PAI and atherosclerotic plaque in different arterial territories.
Methods: Predefined segments of left anterior descending (LAD), right coronary (RCA), and bilateral carotid, and superficial femoral arteries were obtained prospectively from 100 autopsies (70 men; 20-82 years, mean age 47.1±1.4); 27 of these subjects (18 men; 22-71 years, mean age 47.2±2.3) had died from coronary atherosclerosis. One subject dying with chronic lymphatic leukemia was excluded. The segments were sectioned and processed for microscopic examination (~48 sections per subject). Blinded typing of the hematoxylin and eosin stained sections (n=4755) was performed using the American Heart Association classification and the presence of plaque (type ≥IV) was recorded. PAI was quantified by counting periadventitial high power fields (PAI-HPF's) with ≥25 mononuclear round cells (x40 objective) around the vessel perimeter.
Results: PAI was quite common in the coronaries and the carotid bifurcation and highly associated with (but not exclusive to) atherosclerotic plaque and coronary death (table). The degree of PAI (PAI-HPF's) was much higher in coronary death both in the coronaries and the carotid bifurcation, suggesting a systemic inflammatory activation.

Table 1. Distribution of plaque and PAI in subjects and sections

	Subjects with Plaque		Subjects with PAI		Sections with Plaque		Sections with PAI		Mean PAI-HPF's per Section	
	CD+ (%)	CD- (%)	CD+ (%)	CD- (%)	CD+ (%)	CD- (%)	CD+ (%)	CD- (%)	CD+ (%)	CD- (%)
LAD	100	68.1	100	61.1	75.9	42.9	52.3	21.1	2.01*	0.39
RCA	88.9	50	92.6	55.6	77.0	29.2	52.2	20.8	2.12*	0.53
Right Carotid	92.6	65.3	85.2	43.1	44.6	22.8	32.0	9.46	1.14*	0.18
Right Carotid Bifurcation	92.6	62.5	70.4	29.2	81.5	41.7	44.4	13.9	2.06*	0.28
Left Carotid	92.6	74.6	85.2	44.4	43.1	24.3	30.1	9.64	1.03*	0.16
Left Carotid Bifurcation	92.6	71.8	77.8	33.8	80.0	46.7	48.8	15.1	1.91*	0.27
Right Femoral	74.1	30.6	37.0	16.7	37.0	13.2	9.72	2.96	0.23	0.04
Left Femoral	74.1	26.4	33.3	13.9	43.1	10.3	8.33	2.43	0.18	0.03

The mean number of PAI-HPF's per section in coronary (CD+) versus non-coronary death (CD-) were compared using the Mann-Whitney test.*P<0.0001

Conclusion: Quantification of PAI may be a new target for identification of high-risk patients.

2138 Vulnerable plaque detection using ultrasound radio frequency data analysis

G.A. Rodriguez-Granillo, H.M. Garcia-Garcia, J. Aoki, M. Valgimigli, C.A.G. van Mieghem, K. Tsuchida, A.T.L. Ong, P.W. Serruys. *Erasmus MC, Rotterdam, Netherlands*

Purpose: Thin-cap fibroatheroma (TCFA) lesions are the most prevalent substrate of plaque rupture, the main trigger of acute coronary syndromes (ACS). We sought to explore the incidence, distribution and characteristics of TCFA and its relationship with the clinical presentation using spectral analysis of Intravascular utrasound (IVUS) radiofrequency data [IVUS-Virtual HistologyTM (IVUS-VH)].
Methods: Fifty five consecutive patients with non-culprit, non-treated, angiographically non-obstructive (<50%) lesions were investigated with IVUS-VH. Spectral analysis of intravascular ultrasound radiofrequency data, obtained with a 30 MHz catheter, was performed with IVUS-VH software. The population was divided in two groups, stable patients (n= 32) and patients presenting with ACS (n=23). We classified TCFA lesions as focal (adjacent to non-TCFA), lipid-rich [>10% of the cross-sectional area (CSA)] plaques being in contact with the lumen. In addition, TCFA definition required a percent area obstruction (defined as Plaquearea/Vesselarea X 100) = 40%.
Results: ACS patients presented a significantly higher incidence of TCFA than stable patients (2.74±2.4 vs 1.34±1.8, p= 0.018). No relation was found between patient's characteristics such as gender (p= 0.917), diabetes (p= 0.217), smoking (p= 0.904), hypercholesterolemia (p= 0.663), hypertension (p= 0.251) or family history of coronary heart disease (p= 0.136) and the presence of TCFA.
Finally, we compared the severity (mean percent area obstruction 56.97±7.4 vs 54.75±6.0, p= 0.343) and the composition (mean percent lipid core 19.73±4.1 vs 18.05±3.0, p= 0.205) of TCFAs between stable and ACS patients and no significant differences were found.
Conclusions: In this in vivo study, IVUS-VH identified thin-cap fibroatheroma (TCFA), the major precursor of plaque rupture, as a multi-focal finding in acute coronary syndromes. This novel intravascular diagnostic tool has a potential role in vulnerable plaque detection and risk stratification.

2139 Three dimensional palpography: results of the IBIS trial

J. Schaar[1], F. Mastik[1], E.P. McFadden[1], D. Goedhart[1], P.J. de Feyter[1], A. Zalewski[2], A.F.W. van der Steen[3], P.W. Serruys[1]. *[1]Rotterdam, Netherlands; [2]GlaxoSmithKline, Philadelphia, USA; [3]ICIN, Interuniversity Cardiology Institute, Utrecht, Netherlands*

The Integrated Biomarker and Imaging Study (IBIS) was designed to investigate non flow-limiting atherosclerotic lesions in patients, with diverse clinical presentations, referred for percutaneous coronary intervention. These plaques were investigated at baseline and 6 month follow up with intravascular palpography, an IVUS derived technique, which can assess the mechanical properties of plaques and has proven to detect vulnerable plaques defined as thin cap fibroatheromas.
Methods and Results: Plaque deformability was classified according to the ROC classification as low strain spots (ROC I: 0.0 - <0.6%), moderate strain spots (ROC II: 0.6 - <0.9%), medium strain spots (ROC III: 0.9 - <1.2%), or high strain spots (ROC IV: >1.2%). The vulnerability of a vessel was described by the SMS-Index. It was calculated as the number of ROC III and IV scores that were measured in the ROI at cross-sections positioned uniformly over the length of the ROI and averaged over the number of those cross-sections and multiplied by 10. Thus, it is a measure that is normalized for the ROI length and IVUS catheter pullback speed. This SMS-Index describes the longitudinal extent of highly deformable plaques and is taken as a measure of their vulnerability.
Main results are given in the Table 1.

Table 1

Angina Class	Baseline	Follow Up	p-value
STEMI (n=12)	2.30 ± 1.80	1.15 ± 1.37	0.0003
unstable (n=16)	1.78 ± 1.78	1.41 ± 1.69	0.29
stable (n=24)	1.21± 1.06	1.17 ± 1.14	0.56
p- value	0.02	0.91	

Results of the IBIS trial

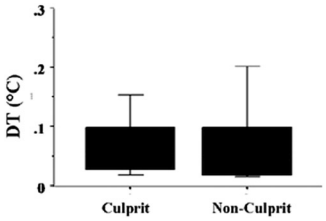
Conclusion: Multifocal plaque deformability, a possible marker of vulnerability, decreases over a 6-month period following myocardial infarction, while it remains unchanged in patients with stable and unstable angina. Notwithstanding differences on baseline palpogram, standard medical therapy fails to eliminate abnormal biomechanical plaque characteristics in patients with documented coronary artery disease.

2140 Local or widespread inflammatory involvement in patients with acute coronary syndromes?

K. Toutouzas, M. Drakopoulou, I. Mitropoulos, S. Vaina, V. Markou, E. Tsiamis, E. Bosinakou, C. Stefanadis. *Ippokration Hospital, Dept of Cardiology, Athens, Greece*

Background: There is a controversy whether inflammation is widespread, or limited to the culprit lesion (CL). Coronary thermography assesses the local inflammation in atherosclerotic lesions. C-reactive protein (CRP) is the most reliable marker for assessment of systemic inflammation. We investigated: 1) thermal heterogeneity in non-culprit lesions (NCL), and 2) the correlation of CRP with heat production of CLs and NCLs.
Method: We included patients (pts) suffering from stable angina (SA) or acute coronary syndromes (ACS). All pts should have at least two significant lesions at different vessels. CLs should be identified in all patients by ECG, wall motion abnormalities, scintigraphic perfusion defects, and/or coronary angiogram. Pts with chronic total occlusions and multiple significant lesions at the culprit vessel were excluded. Blood samples were taken in all pts and CRP was measured. We measured at each lesion the temperature difference (DT) between the atherosclerotic plaque and proximal vessel wall temperature using a thermography catheter (Medispes, Switzerland).

Results: Coronary thermography was performed in 84 lesions from 42 consecutive pts (23 with SA and 19 with ACS). Stenosis (%) was greater in the CL compared to the NCL (73.55±14.76% vs 66.42±11.96%, p=0.06). DT was similar in CL and NCL(0.09±0.10°C vs 0.08±0.10°C, p=0.86). A positive correlation between CRP values and DT in all lesions (n=84) was observed (p<0.001, R=0.52). An increase in DT by type of clinical syndrome was observed in both CL and NCL (CL; SA: 0.06±0.04°C, ACS: 0.13±0.14°C, p=0.03, vs NCL; SA: 0.05±0.06 vs ACS: 0.13 ±0.14°C, p=0.01).



TD-CL-NCL

Conclusion: Although a single lesion is clinically symptomatic, ACSs seems to be associated with diffuse thermal heterogeneity and inflammation.

2141 Levels of serum C-reactive protein is associated with degree of oxidant stress in coronary atherosclerotic plaques

Y. Nakagawa[1], Y. Kijima[2], A. Nishibe[1], M. Fukunaga[3], N. Ogaswara[1], S. Senda[3], T. Hata[1]. *[1]Higashi-Osaka City General Hospital, Department of Cardiology, Higashi-Osaka, Japan; [2]Higashi-osaka City General Hospital, Department of Cardiology, Higashi-osaka, Japan; [3]Kagawa University Hospital, Departmentd of Integrated Meddicine, Takamatsu, Japan*

Background: Oxidant stress plays an important role in the pathogenesis of atherosclerosis. We previously reported that tissues recovered by directionally atherectomized-coronary (DCA) from patients with unstable angina contain greater levels of 8-iso-prostaglandin F2alpha (8-iso-PGF2alpha), a marker for in vivo oxidant stress, than those from patients with stable angina. Thus oxidant stress may be correlated with plaque stability. It is reported that elevated high sensitive C-reactive protein (CRP) levels are associated with the presence of ruptured plaques, and now CRP is established as a predictor for cardiovascular events. We therefore hypothesized that elevated levels of CRP correlate with degree of oxidant stress in plaque of coronary artery.
Methods: We used 8-iso-PGF2alpha as a marker for in vivo oxidant stress. We measured its contents in directionally atherectomized-coronary (DCA) specimens in plaques from 16 patients with stable angina pectoris. Baseline CRP levels and coronary risk factors were evaluated before the intervention procedure.
Results: Levels of 8-iso-PGF2alpha contents in DCA specimens widely ranged from 1.0 ng/g tissue to 116.2 ng/g tissue. Patients were divided into 2 groups according to CRP level; the cutoff point was 0.10mg/dl, a median value. Levels of 8-iso-PGF2alpha were significantly elevated in plaques from patients with high CRP than those from patients with low CRP (30.50 ± 34.50 vs. 5.70 ± 4.10 ng/g tissue; P=0.02). Glucose concentrations, lipid profile, blood pressure, and smoking status were not associated with levels of 8-iso-PGF2alpha contents in DCA specimens.
Conclusions: Levels of serum CRP were associated with degree of oxidant stress in coronary atherosclerotic plaques. These results suggest that CRP is a marker to identify patients who are likely to have plaques with oxidant stress, that is, vulnerable plaques.

PLAQUE FEATURES IN ACUTE VASCULAR SYNDROMES

2143 Intracoronary thermography of culprit artery does not predict further cardiac events after acute coronary syndrome

D. Dudek[1], L. Rzeszutko[1], J. Legutko[1], A. Richter[2], M. Chyrchel[1], M. Wizimirski[1], J.S. Dubiel[1]. *[1]Institute of Cardiology, Jagiellonian University, Krakow, Poland; [2]Volcano Therapeutics Inc, Rancho Cordova, United States of America*

Background: Coincidence of increased vessel wall temperature and further cardiac events in patients with coronary artery disease has been reported in one clinical study. The aim of this study was to assess the relationship between culprit artery temperature profile in patients with acute coronary syndromes (ACS) assessed with thermography system (Volcano Therapeutics Inc.,USA) and further cardiac events.
Methods: 40 patients with ACS (24 pts with acute myocardial infarction and 16 pts with unstable angina) in whom intracoronary thermography of culprit artery was performed before percutaneous coronary intervention of culprit lesion were followed up for one year. We used 3,5-F catheter containing a self-expanding basket with 5 arms and a thermocouple on each arm measuring vessel wall temperature, as well as a central thermocouple measuring blood temperature, allowing detection of differences of 0,05°C. We assessed blood temperature (Tbl, °C) and the maximum temperature difference between blood and any thermal couple (delta Tmax, °C) during pullback (0,5mm/s). The incidence of major cardiac events (death, myocardial infarction, target vessel revascularization (TVR), nontarget vessel revascularization (nonTVR), and refractory angina) was correlated with vessel wall temperature profile of culprit artery.
Results: In 16 pts (40%) delta Tmax was =0,1°C. In 23 pts (57,5%) the highest delta Tmax was found in culprit segment and was significantly higher than in non culprit adjacent segments (delta Tmax = 0,092±0,03 vs. 0,062±0,01, p<0,001). In follow up period MACE occurred in 8 patients (20%). There were no death and myocardial infarction. TVR was performed in 2 patients (5%) and nonTVR in 3 patients (7.5%) due to atherosclerosis progression. 3 patients (7.5%) had refractory angina. We have found positive correlation between baseline HsCRP (r=0,4, p=0,01) and MACE. We have not found any correlation between any temperature measurements and MACE.
Conclusions: Cardiac events have not been correlated with temperature profile of culprit artery in patients with ACS. The results do not confirm clinical significance of thermography as diagnostic or prognostic tool in patients with ACS.

2144 Temperature difference of atherosclerotic plaque and normal vessel wall predict distal embolisation after percutaneous coronary stenting

S.Y. Choi, S.J. Tahk, B.J. Choi, M.H. Yoon, Z.G. Zheng, S.Y. Yoo, G.S. Hwang, J.H. Shin. *Ajou University Hospital, Cardiology, Suwon, Korea, Republic of*

Background: It has been known inflammatory response of activated macrophages increases the temperature in atherosclerotic plaque. The active Inflammation of plaque might be related with spontaneous or procedure-related distal plaque embolization but the relationship of plaque temperature and distal embolization after percutaneous coronary intervention (PCI) has not been evaluated yet.
Methods: We measured the temperature difference of atherosclerotic plaque and normal vessel wall in patients with coronary artery disease using RADI analyser system(RADI Medical System AB, Sweden) after zeroing just when the thermistor emerged from the tip of guiding catheter before PCI. Temperature measurements were repeated twice and the mean values were obtained. We also assessed the TIMI myocardial perfusion (TMP) grade evaluated by filling and clearance of contrast in the myocardium on angiogram before and after stenting. We divide patient into two groups, group A is reduction of TMP grade, group B contains no change and increased TMP grade after stenting compare to pre-PCI. Patients with acute myocardial infarction were excluded in this study.
Results: 26 lesions (left anterior descending coronary artery 16, left circumflex coronary artery 4, right coronary artery 6) in 25 patients (mean age 62±8, male 16). Group A contains 6 lesions (23%) when group B contains the other 20 lesions. Clinical and angiographic characteristics were similar between two groups except group A has more prevalence of UA(group A: 5(83.3%), group B: 5(25.0%), p=0.036). Difference of plaque temperature was significantly higher in group A than group B (group A: 0.30±0.24°C, group B: 0.11± 0.04°C, p= 0.004) There was no difference of procedural complication such as coronary dissection and no reflow but group A had high incidence of a CK-MB leakage after stenting(group A: 4(66.7%), group B: 2(10.0%), p=0.019). Multivariate analysis showed that the difference of temperature of plaque was the only independent predictor of reduction of TMP (olds ratio 2.32, 95% CI 0.56~5.52, p=0.0188).
Conclusion: Preprocedural temperature difference of atherosclerotic plaque and normal vessel wall was related with distal embolization assessing by TMP grade and CK-MB leakage after percutaneous coronary stenting. The Inflammation of plaque represented by temperature could predict the procedure-related microembolism of plaque after stenting reduction.

2145 Intravascular ultrasound assessment of remnants of the fibrous cap in ulcerated ruptured plaques

L.O. Jensen[1], G.S. Mintz[2], S.G. Carlier[2], K. Fujii[2], I. Moussa[3], G.W. Stone[3], M.B. Leon[2], J.W. Moses[3]. *[1]Odense University Hospital, Department of Cardiology, Odense, Denmark; [2]Cardiovascular Research Foundation, New York, United States of America; [3]Columbia-Presbyterian Medical Center, New York, United States of America*

Background: Ruptured plaques can be detected by intravascular ultrasound (IVUS), but the fibrous cap remnant often appears incomplete.
Methods: 97 patients with a ruptured plaque were analyzed. The IVUS cross-section with the largest intraplaque cavity and longest visible remnant of the fibrous cap was measured. Measurements included: cavity length, length of the fibrous cap remnant, and estimated length of the original fibrous cap that would have completely covered the mouth of the ruptured plaque.
Results: Out of 97 plaque ruptures only 53 contained measurable fibrous cap remnants. The intraplaque cavity measured 2.4±1.3mm^2 in area 3.1±1.6mm in length. The remnant did not cover the entire mouth of the cavity in any of the patients studied. The estimated length of the missing fibrous cap (1.16 ± 0.57mm) correlated significantly with the cavity area (r=0.517, p<0.001) and lesion external elastic membrane (EEM) area (r=0.330, p=0.016), lumen area (r=0.289,

p=0.036), and maximum plaque thickness (r=0.364, p=0.007). In 36 (68%) patients the rupture of the fibrous cap appeared to have occurred at the shoulder; the other ruptures occurred in the center of the cap. The length of the missing cap was significantly less in plaques with center rupture compared with shoulder rupture (0.91±0.42 vs. 1.27±0.60mm, p=0.017). However, the length of the missing fibrous cap was similar in stable and unstable patients.

Conclusion: In lesions with demonstrable plaque rupture, the fibrous cap remnant rarely covered the entire mouth of the rupture cavity. The missing remnant correlated with indices of plaque size and instability (cavity area). Possible explanations include (1) the remnant may be too thin to detect with IVUS, (2) the missing remnant may have embolized, and (3) there may have been conformation changes in lesion geometry post-plaque rupture.

2146 Reduced TIA-1 expression in vulnerable atherosclerotic plaques as a basis of cyclooxygenase-2-dependent plaque instability in humans

F. Cipollone, M. Fazia, A. Iezzi, C. Cuccurullo, S. Ucchino, F. Spigonardo, M. Bucci, A. Mezzetti. *Center for Excellence on Aging Sciences (CeSI, G. d'Annunzio University Foundation, Chieti, Italy*

Purpose: Inflammation plays a key role in metabolic events leading to rupture of atherosclerotic plaque. We showed that inducible isoforms of cyclooxygenase (COX-2) and PGE synthase (mPGES-1) are up-regulated in vulnerable plaques of symptomatic patients, and contribute to lesion instability through release of PGE2–dependent metalloproteinase (MMPs). However, the mechanisms regulating COX-2 overexpression, leading in turn to PGE2-dependent MMP biosynthesis, are still unclear. It is known that COX-2 expression is regulated by post-transcriptional mechanisms mediated by the AU-rich elements (AREs) within the COX-2 mRNA 3'untranslated region (3'-UTR). TIA-1, one of the identified RNA binding proteins, has been shown to suppress COX-2 expression in colon cancer cells by promoting translational silencing of the message through binding to COX-2 AREs. However, evidences do not exist yet about involvement of this mechanism in human atherosclerosis. The aim of this study was to evaluate TIA-1 expression in plaques of symptomatic and asymptomatic patients and to correlate it with COX-2/mPGES-1, MMP expression and with clinical features of plaque destabilization.

Methods: Plaques were obtained from 40 patients who underwent carotid endarterectomy and divided into 2 groups (symptomatic and asymptomatic) according to clinical evidence of recent TIA or stroke. Plaques were subjected to analysis of TIA-1, COX-2/mPGES-1, MMP-2 and MMP-9, by immunohistochemistry and Western blot; zymography was used to detect MMP activity. Immunohistochemistry was also used to identify CD68+ macrophages, CD3+ T-lymphocytes, and HLA-DR+ inflammatory cells.

Results: Percentage of macrophage- and T cell-rich areas was markedly higher in symptomatic plaques. TIA-1 expression was significantly lower in symptomatic plaques (9±3% vs 26±4%, P<0.0001), whereas COX-2 and mPGES-1 expression was significantly higher (21±4% vs 5±3%, and 29±7% vs 8±2%, respectively, P<0.0001) in this group. MMP-2 and MMP-9 expression and activity were also markedly (P<0.001) higher in symptomatic plaques. Immunofluorescent double staining showed that both COX-2 and TIA-1 were mainly expressed in macrophages. Interestingly, we observed a significant (P=0.001) inverse association between TIA-1 and COX-2 expression.

Conclusions: This study demonstrates that reduced TIA-1 expression is associated with enhanced inflammatory reaction and COX-2/mPGES-1 overexpression in carotid plaques of symptomatic patients, and this effect may contribute in turn to plaque destabilization by inducing COX-2-dependent MMP expression.

2147 Plaque characteristics are related to symptomatic carotid patients

W.E. Hellings[1], B. Verhoeven[2], F.L. Moll[1], C.A. Seldenrijk[3], D.P.V. de Kleijn[4], E. Velema[4], J.P.P. de Vries[5], G. Pasterkamp[6] on behalf of Athero-Express. *[1]University Medical Center Utrecht, Vascular surgery, Utrecht, Netherlands; [2]University Medical Center Utrecht, Vascular Surgery, Utrecht, Netherlands; [3]St. Antonius Hospital, Pathology, Nieuwegein, Netherlands; [4]Inter University Cardiology Institute, Utrecht, Netherlands; [5]St. Antonius hospital, Vascular surgery, Nieuwegein, Netherlands; [6]University Medical Center Utrecht, Experimental Cardiology, Utrecht, Netherlands*

Introduction: Carotid artery atherosclerotic disease may remain clinically silent or be responsible for cerebral ischemic events. It is suggested that a higher grade of carotid artery stenosis correlates with more clinical symptoms. It is unknown whether plaque phenotype is associated with clinical presentation.

Methods: We included 338 patients (232 men, 106 women) undergoing a carotid endarterectomy (CEA). The plaques were freshly harvested, stained and semiquantatively analyzed for the presence of macrophages(MF), smooth muscle cells(SMC), collagen and fat. The plaques were divided into 3 phenotypes based on the overall presentation and amount of fat: fibrous(32%), fibro-atheromatous(35%) and atheromatous(34%). At baseline, clinical symptoms and duplex measurements were retrieved from the medical record.

Results: Clinical symptoms were categorized as follows: ipsilateral stroke (26%), transient ischemic attack (TIA;36%), amaurosis fugax (AFX;13%) or asymptomatic (NO;24%). Atheromatous, lipid rich plaques were more prevalent in patients with stroke/TIA (Table 1). Collagen staining was less evident in symptomatic patients (p=0.001). No relation was observed between duplex measured stenosis and plaque type or clinical symptoms. In addition, the degree of SMC and MF staining didn't differ among patient groups.

Table 1

		Symptoms				p-value
		NO	AFX	TIA	Stroke	
Amount of lipid	N0	26.5%	37.8%	19.7%	14.6%	0.014
	< 40%	43.4%	48.9%	42.6%	46.1%	
	> 40%	30.1%	13.3%	37.7%	39.3%	
Macrophage	Moderate	50.0%	57.8%	44.2%	46.6%	0.45
	Heavy	50.0%	42.2%	55.8%	53.4%	
SMC	Moderate	30.9%	24.2%	33.3%	35.2%	0.63
	Heavy	69.1%	75.6%	66.7%	64.8%	
Collagen	Moderate	12.3%	13.3%	34.2%	24.7%	0.001
	Heavy	87.7%	86.7%	65.8%	75.3%	
Plaque overall	Fibrous	37.8%	46.7%	27.9%	24.7%	0.015
	Fibro-atheromatous	30.5%	42.2%	33.6%	37.1%	
	Atheromatous	31.7%	11.7%	38.5%	38.2%	
Duplex stenosis	50-64%	1.3%	2.3%	0.9%	6.0%	0.152
	65-89%	29.5%	31.8%	40.3%	38.6%	
	90-100%	69.2%	65.9%	58.8%	55.4%	

Conclusion: TIA and stroke are associated with the presence of atheromatous plaques whereas the plaques of asymtomatic patients are more fibrous with more intense collagen staining. The plaque phenotype of patients with amaurosis fugax resembles the plaque phenotype of asymptomatic patients. Further studies are required to understand why clinical presentation reflecting arterial predisposition for embolisation is associated with plaque phenotype.

2148 Incidence and clinical and angiographic correlates of ruptured plaques in saphenous vein grafts. An intravascular ultrasound study

J. Pregowski[1], P. Tyczynski[2], G.S. Mintz[3], R. Waksman[4], A. Witkowski[2], M. Kruk[2], A. Pichard[4], N. Weissman[4]. *[1]National Institute of Cardiology, Hemodynamics Department, Warsaw, Poland; [2]National Institute of Cardiology, Hemodynamics Department, Warsaw, Poland; [3]Cardiovascular Research Foundation, New York, NY, United States of America; [4]Washington Hospital Center, IVUS Core Lab, Washington, DC, United States of America*

Ruptured plaques (RPs) in native coronary arteries were well described with intravascular ultrasounds (IVUS).There is no IVUS report on RPs in saphenous vein grafts (SVGs). The aim of this study was to use IVUS to assess the incidence and clinical and angiographic correlates of RPs in SVGs.

We reviewed 791 IVUS SVG studies and identified 94 RPs in 76 SVGs in 73 patients. 23 pts had diabetes, 51 had hypetension, and 58 had hypercholesterolemia. 18 pts had recent MI, 27 had unstable angina, and 20 were stable. IVUS measurements were performed at sites of maximal plaque cavity (MPC), minimal lumen area (MLA), and distal and proximal references. Remodeling index (RI) was defined as ratio of SVG area at lesion site to mean reference. Angiographic analyses included presence of ulceration, intimal flap, aneurysm, and filling defect at the IVUS RP site; angiographically complex lesions contained at least one of these findings.

RP length measured 3.7±2.3mm, RP cavity measured 2.9± 1.9mm^2, and lumen area at the MPC measured 5.9±3.4 mm^2. MLA (4.5± 2.9mm^2) was located at the MPC site in only 52%. Calcium deposits were present in 59% of lesion sites. 76% of lesions were eccentric (maximum/minimum plaque thickness>3)and 70% of lesions had positive remodeling. 95% of lesions were angiographically complex. Clinical correlates of SVG RP are shown in the table. 21 pts had multiple RP's; these patients were more often female (38% vs 14% p=0.075) and diabetic (53% vs 27% p=0.083).

Table

	Ruptured plaques	Non-ruptured	P
Age (yrs)	68.6±10.5	67.7±9.2	0.5
Male	75%	77%	0.8
Diabetes	35%	30%	0.4
Hypertension	77%	63%	0.028
Hypercholesterolemia	91%	81%	0.053
Smoking history	56%	48%	0.3
Current smoking	13%	0.6%	0.1
Graft age (years)	12.3±4.8	8.6±5.2	<0.0001

RPs are detected by IVUS in 9.7% of SVGs, can be multiple, and occur even in patients with stable angina - but are almost exclusively in older SVGs with a complex angiographic appearance.

e-POSTER SESSION 6

MODERATED e-POSTERS: CMR AFTER MYOCARDIAL INFARCTION

P2159 Impact of no-reflow and infarct size on left ventricular remodelling in reperfused myocardial infarction: study by contrast-enhanced magnetic resonance imaging

A. Lombardo[1], L. Natale[2], B. Garramone[3], G.A. Lanza[3], A. Porcelli[2], L. Galiuto[3], F.A. Gabrielli[3], F. Crea[3]. *[1]Cardiology Institute, Universita' Cattolica, Roma, Italy; [2]Radiology Institute, Università Cattolica, Roma, Italy; [3]Cardiology Institute, Università Cattolica, Roma, Italy*

Left ventricular (LV) remodelling may occur after reperfused acute myocardial infarction (AMI). Among mechanisms involved in this process, residual microvascular and myocardial damage may play a role. Contrast-enhanced Magnetic Resonance Imaging (MRI) is effective in detecting no-reflow and infarct size

Aim: to assess the individual role of no-reflow and infarct size in predicting LV remodelling after reperfused AMI.

Methods: 28 patients with first AMI (anterior: 20, infero-lateral: 8) and successful primary coronary intervention were studied. End-diastolic (EDV) and end-systolic (ESV) LV volumes were assessed by echocardiography using Simpson's method within 24 hours and at 3-month follow-up. A >20% increase of EDV and/or ESV was considered indicative of LV remodelling. MRI was performed within 4 days with a 1.5 T scanner, using fast-gradient echo train for first-pass perfusion study and IR-prep fast gradient echo for delayed enhancement assessment. Gadolinium-DTPA was administered at the beginning and at the end of first-pass study (0.075 mmol/kg, 3 ml/sec). Delayed enhancement was evaluated after 15 min. Extent of no-reflow (first-pass and/or delayed hypoenhancement) and infarct size (delayed hyperenhancement) were evaluated using a score index on the basis of their transmural extension (<25%, 25-50%, 50-75%, >75%) in each segment of a 17-segments LV model.

Results: at follow-up 12 patients had LV remodelling. EDV and ESV increased from 103±28 ml to 155±35 ml and from 60±15 ml to 95±23 ml respectively in patients with LV remodelling. No-reflow was detected in 24 patients (86%). The score indexes for no-reflow and infarct size were 2.4±1.1 and 3.3±1.6 in patients with LV remodelling and 1.5±1.1 (p: 0.04) and 2.6±1.7 (p: NS) in those without LV remodelling. A higher number of segments with transmural extension>75% of both no-reflow and delayed hyperenhancement were found in patients with LV remodelling compared to those without LV remodelling (15 vs 1, p:0.008 and 37 vs 15, p:0.043).

Conclusions: in patients with reperfused AMI, 1) MRI detects a high incidence of no-reflow; 2) the effects of no-reflow on LV remodelling are stronger than those of infarct size; 3) transmurality extent >75% of both no-reflow and hyperenhancement is a major determinant of LV remodelling.

P2160 Microvascular obstruction after optimal treatment for acute myocardial infarction: a contrast-enhanced CMR study

R. Nijveldt[1], A.M. Beek[1], M.B.M. Hofman[2], A.C. van Rossum[1]. *[1]VU University Medical Center, Cardiology Dept., Amsterdam, Netherlands; [2]VU University Medical Center, Clinical Physics & Informatics, Amsterdam, Netherlands*

Background: Microvascular obstruction (MVO) is considered a major predictor of cardiac complications and mortality after acute myocardial infarction (AMI). Its incidence and significance in patients after optimal acute phase treatment (including primary stenting and clopidogrel) is unknown.

Objectives: To document the presence of MVO and its correlation to changes in left ventricular volumes, ejection fraction and total infarct size in patients optimally treated for AMI.

Methods: 23 patients with first AMI who were treated within 6 hours with primary stenting, abciximab, aspirin, heparin and clopidogrel underwent cine and contrast-enhanced (ce)CMR at 4-7 days and 3 months after admission. Left ventricular endsystolic volume (ESV), enddiastolic volume (EDV), ejection fraction (EF), total infarct size (TIS), and presence of MVO were determined in short axis views covering the whole left ventricle.

Results: 14 (61%) of patients had evidence of MVO at baseline. Compared to patients without MVO, patients with MVO had larger baseline TIS (p=0.002), and tend to show greater TIS reduction at follow-up, suggesting a higher degree of infarct involution and myocyte loss. ESV and EDV decreased significantly in patients without MVO, but did not change in patients with MVO (see table).

	Without MVO (n=9)			With MVO (n=14)		
	baseline	follow-up	p-value	baseline	follow-up	p-value
ESV	53.5	47.0	0.016	58.7	59.6	0.813
EDV	98.5	91.7	0.031	98.5	101.1	0.685
LVEF	48.1	50.7	0.161	41.1	43.3	0.156
TIV	11.5	7.7	0.010	34.2	26.8	0.001

Conclusions: CeCMR visualizes MVO in the majority of patients after AMI despite early and optimal revascularization. Patients with MVO have larger infarct size and no improvement of left ventricular volumes.

P2161 The incidence and time course of microvascular obstruction following an acute myocardial infarction

C. Bucciarelli Ducci[1], C. Bucciarelli-Ducci[2], P. Tejedor[2], T.A. Holly[3], E. Wu[3], J.C. Carr[4], F.J. Klocke[2], R.O. Bonow[3]. *[1]Università Roma/La Sapienza, Cattedra Cardiologia, Roma, Italy; [2]Feinberg Cardiovascular Research Insti, Chciago, United States of America; [3]Norhwestern University, Division of Cardiology, Chicago, United States of America; [4]Northwestern University, Radiology, Chicago, United States of America*

Background: Delayed contrast-enhanced MRI (ce-MRI) can delineate the size of acutely injured myocardium. Additionally, areas of absent contrast can also be seen due to poor contrast penetration and are thought to be related to microvascular obstruction or "no-reflow." The incidence and resolution of microvascular obstruction in acute myocardial infarction has not been completely described.

Methods: Cine and ce-MRI studies were performed on 33 patients within 3-4 days and 3 months after successful percutaneously reperfused ST-elevation myocardial infarction. Delayed contrast-enhanced images were obtained using a segmented inversion-recovery MRI technique 15-20 minutes after a 0.15-0.20 mmol/kg bolus injection of gadolinium. Multiple short axis views were acquired to encompass the entire left ventricle. Acute and chronic infarcts were defined as hyperenhanced areas, and microvascular obstruction (MO) was defined as areas of hypoenhancement.

Results: MO was seen in 17 (51%) patients on the acute ce-MRI study (MO present group). On follow-up imaging, MO was no longer detected and was replaced by hyperenhancement. Transmural infarction was observed in 12 (70%) patients in the MO present group and 4 (25%) patients in the MO absent group. At baseline, the MO group showed larger infarct mass, end-diastolic volume (EDV), and lower ejection fraction (EF) when compared to the MO absent group (55±23 vs, 27±15 g, p< 0.005; EDV, 181±31 vs. 139±41 ml, p<0.05; EF, 35±10% vs. 44±10%, p<0.05). At follow-up, EF increased in the MO absent group (44±10 to 51±7%, p<0.05) but not in the MO present group (35±10% to 36±9%, p=NS).

Conclusions: MO was observed acutely in over half of patients with successful percutaneously reperfused acute myocardial infarction, and these areas were no longer present after 3 months. The presence of MO is correlated with larger, and more frequently transmural infarcts and predicts lack of functional recovery.

P2162 Prognostic value of delayed contrast-enhanced cardiovascular magnetic resonance after reperfusion of acute myocardial infarction

M. Regenfus[1], C. Schlundt[1], C. Stingl[1], J. von Erffa[1], R. Kraehner[1], M. Schmidt[2], W. Adler[1], W.G. Daniel[1]. *[1]Friedrich-Alexander-Universitat, Internal Medicine, Erlangen, Germany; [2]Siemens, Medical Engineering, Erlangen, Germany*

Purpose: Delayed contrast-enhanced cardiovascular magnetic resonance (DE-CMR) can be used to assess myocardial viability. Its prognostic value after reperfusion of acute myocardial infarction (MI), however, is not known. We investigated whether DE-CMR is able to determine cardiac prognosis in patients with reperfused acute MI.

Methods: 102 patients (pts) with left ventricular (LV) dysfunction (EF 42±8%) were examined on a 1.5T scanner within 6±3 (4-10) days of an reperfused acute MI. Cine and DE-CMR (10 min after injection of 0.15 mmol/kg Gd-DTPA) was acquired and scored for regional wall thickening and contrast enhancement (HE) using a 17-segment model. Segments were considered to be viable if showing < 25% HE. LV ejection fraction (EF) was determined by planimetry. Serial clinical follow-up was obtained in all patients (mean follow-up 2.5±1.3 years) regarding occurrence of cardiac death, death attributable to any cause, reinfarction, further myocardial revascularization, and unstable angina or congestive heart failure requiring hospitalization. Patient-related and CMR data were analyzed in a multivariate Cox regression model.

Results: Among the 102 patients, there were 11 cardiac deaths and reinfarctions in the follow-up period, additionally there were 26 patients with further myocardial revascularization or hospitalization due to unstable angina or congestive heart failure. Patients with events at follow-up showed significantly lower EF (37±14% vs. 45±12%, p = 0.006) than patients without events. In patients with cardiac death or reinfarction, the dysfunctional area by CMR (65% vs. 48%, p = 0.02) and the dysfunctional but viable area by CMR (27% vs. 17%, p = 0.008) was significantly larger than in patients without such events. By multivariate analysis EF (hazard ratio 0.98, CI 0.95 to 1.0, p = 0.03) and the dysfunctional but viable area by CMR (hazard ratio 1.4, CI 0.9 to 3.0, p = 0.04) were related to occurrence of future events independent of the presence of risk factors for coronary arterosclerosis.

Conclusion: After reperfusion of acute MI, DE-CMR can be used to predict major adverse cardiac events.

P2163 Usefulness of a comprehensive assessment for predicting late systolic function after infarction with cardiac magnetic resonance imaging

V. Bodi Peris[1], M.P. López-Lereu[2], J. Sanchis[1], D. García[1], J. Núñez[1], M. Pellicer[1], F.J. Chorro[1], A. Llácer[1]. [1]*Hospital Clínic i Universitari, Cardiology, València, Spain;* [2]*ERESA, Cardiac Magnetic Resonance Imaging, València, Spain*

Purpose: To evaluate the usefulness of a comprehensive assessment of four cardiac magnetic resonance imaging (CMR)-derived myocardial viability indexes.
Methods: The study comprised 40 patients with a first ST-elevation myocardial infarction (MI), single-vessel disease and an open infarct-related artery (TIMI 3 flow and residual stenosis <50%, stent in 33 cases) 1 week and 6 months after MI. At the first week and using CMR, wall motion thickening (WM, abnormal if <2 mm) was quantified in all segments (s, 16-s model). Four viability indexes were determined: (a) Wall thickness (viability if >5.5 mm); (b) WM improvement with low-dose dobutamine (viability if >2 mm); (c) Perfusion (first-pass perfusion imaging, viability if normal enhancement without delay in contrast arrival); (d) Transmural extent of necrosis (viability if late enhancement <50%). At the sixth month, CMR was repeated in all cases. We investigated the utility of a comprehensive score based on the number of indexes suggesting myocardial viability at the first week (0 to 4) in predicting normal systolic function (WM >2 mm) at the sixth month.
Results: Out of 579 s properly analyzed at the first week and sixth month, we focused on 153 s which showed abnormal WM at the first week (26%). Of these 153 dysfunctional s, 59 (39%) exhibited a normal WM at the sixth month. The proportion of s showing normal WM at the sixth month increased in parallel to the number of indexes suggesting viability: 0 indexes: 0/13 s (0%), 1 index: 10/62 s (16%), 2 indexes: 7/27 s (26%), 3 indexes: 24/33 s (73%) and 4 indexes: 18/18 s (100%), $p< 0.0001$ for the trend. In a multivariate analysis including the score as well as all 4 indexes separately, the only independent predictors of preserved WM at the sixth month were the absence of transmural extent of necrosis (odds ratio with 95% confidence intervals (OR [95% CI]): 4.1 [1.1 to 15.5 p=0.03]) and the score (OR [95% CI]: 2.9 [1.6 to 5.3] for each additional positive index, $p <0.0001$).
Conclusions: CMR allows simultaneous assessment of several viability indexes. A comprehensive analysis is useful for predicting late systolic function after MI, and contributes independent information when compared with a separate study of these parameters.

P2164 Hepatocyte growth factor (HGF) affects chronic left ventricular remodelling after ischaemia and reperfusion in the rat heart in vivo

C. Waller[1], K.-H. Hiller[2], K. Bathe[3], K. Gollnau[3], G. Ertl[3], W.R. Bauer[3]. [1]*Wuerzburg, Germany;* [2]*Universitaet Wuerzburg, Physikalisches Institut, Wuerzburg, Germany;* [3]*Universität Würzburg, Medizinische Klinik und Poliklinik I, Würzburg, Germany*

Hepatocyte growth factor (HGF) is described as an antiapoptotic and angiogenic agent that protects the myocardium after acute ischämia and reperfusion. However, effects of HGF treatment during the chronic phase of left ventricular remodeling are not yet analyzed. We used serial Cine-MR imaging to quantify geometry and function in the rat heart in vivo.
After 60 minutes of occlusion and reperfusion of the LAD, animals were treated with 0.45 mg/kg/day of HGF recombinant protein administered via a jugular vene catheter and an implanted osmotic pump during 9 days (n=10). Ten animals were not treated and served as controls. Using MR-imaging in vivo, all animals were studied serially from the 1st to the 16th week after intervention and left ventricular geometry, function and infarct size were quantitatively determined. Finally, infarct size was measured histologically.
Infarct size determination using MR and histology showed a good correlation ($r=0.78$, $p<0.001$).
Results of Cine-MRI are shown in Table 1.

Table 1. Ischemia and Reperfusion Injury

	HGF-treatment		Untreated controls	
weeks	1	16	1	16
MR-infarct size (%)		26.3±2.8		25.5±4.4
HW/BW (mg/g)	2.39±0.12	2.08±0.13	1.81±0.12 *	1.87±0.13
LV ESV (ul)	186.8±25.5	437.1±77.5 #	149.3±29.8	265.4±55.1
LV EDV (ul)	271.1±30.6	592.2±94.7 #	255.7±29.5	319.1±50.0 #
SV (ul)	84.3±7.1	155.1±25.8 #	99.4±10.9	125.7±7.6
EF (%)	33.8±3.6	29.6±4.3	45.0±6.1	37.3±6.2
CO (ml/min)	24.4±2.8	48.0±8.1 #	28.0±3.5	35.6±2.3

*$p<0.01$ HGF-treatment vs. untreated controls, #$p<0.01$ 1. vs. 16. week

HGF treatment after ischemia and reperfusion injury results in a significant increase in stroke volume and cardiac output, however also an increase in left ventricular volumes and mass. We conclude that, in contrast to studies with shorter observation times, HGF-treatment improves cardiac performance but promotes left ventricular remodeling with a probably adverse effect on prognosis.

INFLAMMATION, OXIDATIVE STRESS AND LIPID LOWERING THERAPY IN ATHEROSCLEROSIS

P2165 A novel inhibitory effect of lectin-like domain of thrombomodulin on the neointima formation in mouse blood flow cessation model

Y.-H. Li[1], S.-L. Liu[2], G.-Y. Shi[2], P.-Y. Liu[1], H.-L. Wu[2]. [1]*National Cheng Kung Univ. Hospital, Dept. of Internal Medicine, Tainan, Taiwan;* [2]*National Cheng Kung University, Department of Biochemistry, Tainan, Taiwan*

Purpose: Thrombomodulin (TM) is a cell membrane-bound glycoprotein and functions as a cofactor to thrombin in the activation of protein C. TM protein structure includes an N-terminal lectin-like domain (D1), 6 epidermal growth factor repeats (D2), a serine-threonine-rich region (D3), a transmembrance domain (D4) and a short cytoplasmic tail (D5). Recent study demonstrated that TMD1 has direct anti-inflammatory effect. In the study, we investigated the effect of recombinant human TM on the neointima formation in mouse blood flow cessation model. The influence of TMD1 was specifically examined.
Methods: Human DNA fragments coding for TMD23 (residues Ala224-Ser497) or TMD123 (Ala1-Ser497) were cloned into expression vector pCR3-EK and transfected into HEK293 cells. TMD123 or TMD23 protein was purified, and both of them showed effective cofactor activity for thrombin-dependent protein C activation. Adult FVB mice were anesthetized and the right common carotid artery was ligated just proximal to the carotid bifurcation. Recombinant TMD123 (145μg/kg), equal dose of TMD23 or saline was administered intravenously immediately before and after carotid artery ligation. Additional TM (290μg/kg TMD123 or equal dose of TMD23) or saline was given once a day for an additional 48 hours postoperatively. The mice were sacrificed at 4 weeks. The carotid neointima area, media area, total vascular area and neointima/media (N/M) area ratio were calculated. Data were given as mean $\pm$ SEM. Comparisons between groups were made by one-way ANOVA.
Results: The total vascular area was largest (93752 ± 10089 vs 64481 ± 21030 vs $36800 \pm 13892 \mu m^2$, $p<0.05$) in mice receiving saline injection (n=5) than those receiving TMD23 (n=7) and TMD123 (n=6) showing a significant positive remodeling of ligated carotid artery in mice without TM supply. The lumen area was similar (11170 ± 1930 vs 14235 ± 7906 vs 7965 ± 3628 μm^2, p=NS) between groups. The neointima area (52353 ± 7219 vs 31431 ± 8301 vs 16048 ± 7394 μm^2, $p<0.05$) and media area (30228 ± 2672 vs 18814 ± 5546 vs 12984 ± 4039 μm^2, $p<0.05$) were significantly reduced in mice receiving TMD123 treatment. The N/M ratio was similar between mice receiving saline and TMD23, and significantly decreased in TMD123-treatment group (1.72 ± 0.11 vs 1.83 ± 0.21 vs 0.97 ± 0.24, $p<0.05$).
Conclusion: Early recombinant TM treatment in mice receiving carotid ligation might alter arterial remodeling and decrease the severity of neointima formation. TMD123 has better therapeutic effect in reducing neointima formation due to the anti-inflammatory effect of TMD1 in addition to the protein C activation from TMD23.

P2166 Production of C-reactive protein and serum amyloid A in response to inflammatory cytokines by human adipocytes

P. Calabro[1], D.W. Chang[2], J.T. Willerson[3], E.T. Yeh[4]. [1]*Institute of Molecular Medicine, Cardiology-University of Texas, Houston, United States of America;* [2]*MD Anderson Cancer Center, Plastic Surgery, Houston, United States of America;* [3]*Texas Heart Institute, Department of Cardiology, Houston, United States of America;* [4]*MD Anderson Cancer Center, Cardiology, Houston, United States of America*

C-reactive protein (CRP) and serum amyloid A (SAA) are major acute-phase proteins in humans, and elevated plasma levels of these proteins are risk factors for the development of cardiovascular disease. Both CRP and SAA were thought to be produced by hepatocytes in response to inflammatory stimuli. Recently, we have shown that CRP can be produced by vascular smooth muscle cells following inflammatory stimuli. Several studies have shown that adipose tissue can secrete a number of biologically active molecules, including several proinflammatory factors. Therefore, we tested the hypothesis that cells in adipose tissue can synthesize CRP and SAA in response to inflammatory stimuli.
Methods: Adipocytes and preadipocytes were isolated from abdominal adipose tissue and incubated with interleukin-1 and -6, tumor necrosis factor-alpha (TNF-alpha), lipopolysaccharide (LPS), or resistin, or a combination of these proteins, at different concentrations. After 48 hours, the supernatants were analyzed by using ELISAs specific for human CRP and SAA. In the modulation experiments, cells were treated with different antinflammatory agents.
Results: In adipocytes, all of the stimuli induced CRP production, which peaked in response to all the stimuli combined (an ~6-fold increase compared with control) and this was modulated by different drugs. In contrast, CRP was not produced by preadipocytes in response to any stimuli. In order to investigate the intracellular mechanisms involved in this process, we used specific inhibitors for AKT and MAPK, LY294002 and U0126, respectively, attempting to modulate CRP induction. Pretreatment of adipocytes with the inhibitors did not lead to a reduction in CRP production. Furthermore, SAA production was also induced in adipocytes by

LPS, TNF-alpha, and resistin, with a peak in production in response to the three together (an ~5 fold increase).
Conclusions: These results demonstrate we believe for the first time that human adipocytes can produce CRP in response to inflammatory cytokines and that this effect can be modulated by antinflammatory drugs. Moreover, under similar proinflammatory conditions adipocytes can produce also SAA, thereby suggesting a new link between obesity, fat tissue and vascular inflammation.

P2167 Up-regulated leukotriene formation in atherosclerosis

M. Back[1], Y. Sheikine[2], A. Leclercq[3], O. Meilhac[3], J.Z. Haeggstrom[4], S.E. Dahlen[5], J.B. Michel[3], G.K. Hansson[2]. *[1]Karolinska University Hospital, Center for Molecular Medicine, Stockholm, Sweden; [2]Karolinska University Hospital, Center for Molecular Medicine, Stockholm, Sweden; [3]Bichat Hospital, INSERM u460, Paris, France; [4]Karolinska Institutet, Medical Biochemistry and Biophysics, Stockholm, Sweden; [5]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden*

Leukotrienes are lipid mediators of inflammation that recently have been implicated in the pathogenesis of atherosclerosis. Metabolism of endogenous arachidonic acid from membrane phospholipids, via the 5-lipoxygenase pathway, yields the unstable epoxide LTA4. The subsequent reactions leads to formation of either LTB4 by the action of LTA4 hydrolase, or the cysteinyl-leukotrienes LTC4, D4 and E4, by conjugation with glutathione. The aim of the present study was to determine the leukotriene formation within the human vascular wall and to compare healthy and atherosclerotic vessels.
Human atherosclerotic tissues were obtained from patients undergoing carotid endarterectomy, and internal mammary arteries were used as controls. Leukotriene formation was measured using enzyme immuno assay on supernatants of vascular tissues incubated in DMEM at 37°C for 24 h. The tissues were subsequently homogenized and the protein fraction used for Western Blot determinations of LTA4 hydrolase.
The formation of LTB4 as well as cysteinyl-leukotrienes (measured as LTE4) was detected in both types of vessels examined. In addition, there were significantly greater amounts of LTB4 released from atherosclerotic vessels (1.89±0.24 pg/mg, n=3) compared with healthy vessels (0.82±0.25 pg/mg, n=4, $P<0.05$). Using Western blot analysis, LTA4 hydrolase was visualized as a 69 kDa protein in both atherosclerotic and normal vessels. Moreover, the area of the protein bands detected in atherosclerotic tissues represented 162±35% (n=3) of the bands detected in internal mammary arteries.
In summary, the results suggest that leukotrienes are locally produced within the human vascular wall and that the formation of LTB4 is significantly greater in atherosclerotic compared with healthy vessels. In addition, the greater levels of LTA4 hydrolase protein in atherosclerotic vessels indicate that this enzyme is upregulated during atherogenesis.

P2168 Asymmetric dimethyl arginine (ADMA), homocysteine and semicarbazide-sensitive amine oxidase activity (SSAO): new markers of oxidative stress in acute coronary syndromes

R. Marcucci[1], L. Raimondi[2], F. Sofi[1], A. Casini[3], A. Mugelli[2], C. Surrenti[3], R. Abbate[4], G.F. Gensini[1]. *[1]Hospital Careggi, Surgical and medical critical care, Florence, Italy; [2]University of Florence, Department of Pharmacology, Florence, Italy; [3]University of Florence, Department of Clinical Pathophysiology, Florence, Italy; [4]Florence, Italy*

High levels of Homocysteine (Hcy) are a well-established risk factor for atherosclerotic disease. One of the mechanism evoked to support its pathogenetic role in atherosclerosis is the induction of an oxidative stress. Ex-vivo reports documented an inhibitory effect of high levels of Hcy on the enzyme dymethyl arginine dymethylaminohydrolysis (DDAH) which converts the Asymmetric dimethyl arginine (ADMA) in citrullin. Elevated levels of ADMA, the most potent endogenous inhibitor of the nitric oxide synthase activity, are markers of endothelial dysfunction and are found elevated in patients with atherosclerosis. The semicarbazide-sensitive amine oxidase (SSAO) is a tissue-bound amine oxidase activity with adhesion properties highly expressed in the vasculature. For unknown reasons in the metabolic syndrome and in cardiovascular diseases, elevated levels are found but their pathological significance remains to establish. One hypothesis is that this enzymatic activity participate in generating endothelial dysfunction through the production of cytotoxic aldehydes and hydrogen peroxide.
The aim of this study was to evaluate Hcy, ADMA levels and SSAO activity in patients with acute coronary syndromes (ACS). 75 patients (age 62.6? 11.6; 70M/5F) with ACS (51 AMI, 24 UA) referred to the Cardiologic Unit of the University of Florence and 75 controls (age 61? 9.8; 69M/6F) were enrolled.
SSAO activity, ADMA and Hcy levels were significantly higher in patients than in controls (31.6 ± 4.6 pmol/mg/h vs 0-2 pmol/mg/h; 1851.58 ± 254.65 pmol/ml vs 520 ± 360 pmol/ml and 22.7 ± 18.4 μmol/L vs 12.3 ± 10.5 μmol/L).
SSAO activity significantly correlated with Hcy ($r=0.57$; $p=0.001$) and Hcy levels significantly correlated with ADMA ($r=0.49$; $p<0.005$). In addition, ADMA positively correlated with the extension of necrosis in AMI patients ($r=0.46$; $p<0.05$).
This is the first in-vivo demonstration that Hcy significantly correlates with ADMA levels in ACS. Furthermore, we found another possible factor which might play a role in the oxidative stress generated by hyperhomocysteinemia.

P2169 Reduced connexin43 expression decreases balloon-induced intimal hyperplasia in hypercholesterolemic mice

C.E. Chadjichristos[1], C.M. Matter[2], I. Roth[1], E. Sutter[1], G. Pelli[1], T.F. Luescher[2], B.R. Kwak[1]. *[1]University Hospital Geneva, Division of Cardiology, Geneva 4, Switzerland; [2]University Hospital Zürich, Cardiovascular Research, Zürich, Switzerland*

Activation and migration of arterial smooth muscle cells involved in intimal growth of atherosclerosis or restenosis correlate with increased expression of the gap junction protein connexin43 (Cx43). In order to determine whether the level of Cx43 expression is causally related to intimal hyperplasia, we performed balloon distension injury in the non-dissected proximal portion of the left common carotid artery of adult male Cx43+/-LDLR-/- mice, in which Cx43 expression levels are reduced by half, and in Cx43+/+LDLR-/- littermate controls. All animals were exposed to an atherogenic diet (1.25% cholesterol, no cholate) for 7 weeks. In addition, they received aspirin (16mg/kg/day) starting 1 week prior to surgery until sacrifice for preventing acute vessel closure. Both carotid arteries were harvested 1 hour, 1, 4, 7 and 14 days after injury following pressure fixation and serial cross sections were analyzed. Interestingly, we observed a progressive increase in Cx43 and alpha smooth muscle actin in immunostainings on carotids 4, 7 and 14 days after balloon distension underlining the relevance of Cx43 after vascular injury. At 14 days post-angioplasty, the remaining lumen of the carotids was significantly larger ($p<0.05$) in Cx43+/-LDLR-/- mice (87.6 ± 1.1 μm^2; n=9, mean ± SEM) than in Cx43+/+LDLR-/- control mice (62.9 ± 0.7 μm^2; n=9). Similarly, total counts of neointimal nuclei were significantly lower in Cx43+/-LDLR-/- (102±17) than in control Cx43+/+LDLR-/- mice (163 ± 24; $p<0.05$). In Cx43+/-LDLR-/- carotids with minimal restenosis, complete endothelial repair was found 14 days after injury.
In conclusion, we demonstrated for the first time that reducing Cx43 expression in vivo decreases intimal hyperplasia after balloon distension injury in hypercholesterolemic mice. The reduction in intimal hyperplasia in Cx43+/-LDLR-/- mice may result from a combination of restricted smooth muscle cell proliferation and accelerated endothelial repair. Our findings open novel therapeutic opportunities for reducing neointimal disease by decreasing Cx43-mediated gap junction communication.

P2170 Atorvastatin decreases circulating Fas concentrations in patients with high cardiovascular risk. Atorvastatin Inflammatory Markers (AIM) study; a sub-study of ACTFAST

L. Blanco-Colio[1], J.L. Martin-Ventura[1], E. de Teresa[2], C. Farsang[3], A. Gaw[4], G.F. Gensini[5], A. Langer[6], J. Egido[1] on behalf of the ACTFAST investigators. *[1]Fundacion Jimenez Diaz. Autonoma University, Vascular Research Lab., Madrid, Spain; [2]V. de la Victoria Hospital, University of Malaga &, Málaga, Spain; [3]1st Dept. Med. Semmelweis Univ., Budapest, Hungary; [4]University of Glasgow, Glasgow, United Kingdom; [5]Careggi Hospital, University of Florence, Firenze, Italy; [6]& Canadian Heart Research Center, Univ. of Toronto.St-Michael's Hospital, Toronto, ON, Canada*

Introduction: ACTFAST was a 12-week, prospective, multi-centre, parallel arm, open-label trial which enrolled subjects (either statin-free or statin-treated at baseline) with coronary heart disease (CHD) or CHD-equivalent (defined as diabetes, peripheral vascular disease or cerebrovascular disease) or a 10-year CHD risk > 20%.
Methods: AIM sub-study only included statin-free patients of the ACTFAST study. Subjects with LDL-C between 100-220 mg/dL (2.6-5.7 mmol/L) and triglycerides =600 mg/dL (6.8 mmol/L) were assigned to a starting dose of atorvastatin (10-80 mg/day) based on LDL-C at screening. After 6 weeks, where possible, subjects not reaching LDL-C target had their dose doubled. The primary endpoint was the proportion of subjects reaching LDL-C target (<100 mg/dL). Out of a number of inflammatory markers measured at baseline and at the end of the study, we focus here on soluble Fas (sFas) and soluble Fas ligand (sFasL). These proteins have been implicated in inflammation and apoptosis during atherosclerotic plaque development. Increased plasma levels of sFas has been shown in patients with congestive heart failure and sFasL levels was diminished in hyperlipidemic patients.
Results: Of the 2117 subjects enrolled in ACTFAST, 1,041 subjects were also included in the AIM study. At baseline, 52%, 14%, 12% and 22% of subjects were assigned to 10, 20, 40 and 80 mg, respectively. At study end, 85% of subjects reached LDL-C target. Geometric mean of sFas was reduced by atorvastatin treatment (7,392 vs 7,137 pg/mL; $p<0.05$). Reduction of sFas was observed with all doses tested (0.97 [0.94-0.99], 0.97 [0.93-1.00], 0.93 [0.88-0.97], 0.98 [0.94-1.01]; ratio and 95% confidence intervals for 10, 20, 40 and 80 mg, respectively). Interestingly, atorvastatin treatment was more effective in reducing sFas in diabetic subjects (N=442; 0.95 [0.93-0.97]) and in patients with metabolic syndrome (N=466; 0.95 [0.92-0.97]). However, atorvastatin did not modify the sFasL concentrations (58.8 vs 57.6 pg/mL).
Conclusions: Atorvastatin reduces sFas concentrations in high cardiovascular

risk patients. These data reveal a novel effect of atorvastatin and add support for the well-known anti-inflammatory properties of statins.

P2171 Rosuvastatin treatment protects against nitrate-induced oxidative stress via a direct interaction with the NAD(P)H oxidase pathway

A. Otto[1], D. Fontaine[2], J. Fontaine[2], G. Berkenboom[3]. *[1]ULB, Pharmacology Department, Brussels, Belgium; [2]ULB, Pharmacology Department, Brussels, Belgium; [3]Erasme Hospital ULB, Cardiology Department, Brussels, Belgium*

Nitrate tolerance is associated with an enhanced superoxide anion production and could be attenuated by statins as they interact with the two main (eNOS and NAD(P)H oxidase) pathways involved in this oxidative stress.
Methods: In wild-type (WT) and eNOS deficient mice (eNOS-/-), 3 types of treatment were given: group 1 received rosuvastatin (20 mg/kg/d p.o.) for 5 weeks and the last 3 days a cotreatment with the statin plus NTG (30 mg/kg/d, sub-cutaneous injections bid); group 2 received only NTG (30 mg/kg/d, b i d for 3 days) and group 3 served as control.Rings of thoracic aortas from these groups were studied in organ baths.
Results: Relaxations to NTG (0.1 nM to 0.1 mM) were determined on U44619, a thromboxane analogue, preconstricted rings and O2- production (counts/10s/mg) was assessed on aorta homogenates with the lucigenin enhanced chemiluminescence technique. In WT group 2, the concentration-response curves to NTG were significantly shifted to the right: the pD2 (-log NTG concentration evoking a half maximal relaxation) was 6.27±0.06 (n=7) vs 6.70±0.05 (n=8) in WT group 3 (not exposed to NTG) and O2- production was enhanced from 6,845±1,313 (n=9) to 24,477±4,927 (n=8 P<.01). In contrast, in WT group 1, the rightward shift was abolished: the pD2 value was 6.68±0.04 (n=8) (P<.001 vs group 2, WT) and O2- production was 12,171±780 (n=6, NS vs group 3 WT). In eNOS-/- groups 1 and 3, similar data were observed: the pD2 values were 7.66±0.12 and 7.87±0.17 (NS) vs 7.21±0.09 in eNOS-/- group 2 (n=5, P<.05). In both strains, this rosuvastatin-induced protection was abolished after incubation with mevalonate (100 μM), the product of HMG-CoA reductase enzyme reaction. Moreover, before NTG exposure, rosuvastatin treatment decreased p22phox (an essential NAD(P)H oxidase subunit) mRNA.
Conclusion: Long-term rosuvastatin treatment protects against nitrate tolerance by counteracting NTG-induced increase in O2- production. This protection involves a direct interaction with the NAD(P)H oxidase pathway and seems to be completely independent of the eNOS pathway.

P2172 HMG-CoA reductase inhibition by rosuvastatin increases eNOS expression in cytokine-treated human endothelial cells

M. Landsberger, F. Jantzen, S.B. Felix. *Ernst Moritz Arndt University, Department of Internal Medicine B, Greifswald, Germany*

Background: Endothelial dysfunction and atherosclerosis are associated inter alia with an inflammation-induced decrease in endothelial nitric oxide synthase (eNOS) expression. Both clinical and experimental data support the hypothesis that inhibition of HMG-CoA reductase by statins directly influences the initiation and progression of atherosclerosis. Therefore we analyzed the effects of rosuvastatin (RSV) on the expression of eNOS in TNF-alpha-treated human venous endothelial cells (HUVEC).
Methods: RSV concentrations tested were 0.01 to 1 μmol/l; total RNA and protein extracts were isolated from TNF-alpha-treated (10 ng/ml) HUVEC after 8 and 12 hours with standard procedures. Expression of eNOS mRNA was determined by TaqMan®, protein expression by Western blotting. Expression was calculated relative to the expression in cells treated with TNF-alpha in the absence of RSV.
Results and Conclusions: After 8 hours TNF-alpha reduced eNOS mRNA expression (1.0±0, n=5) compared to cells incubated with media in the absence of the cytokine (9.6±2.1-fold of TNF-alpha-treated cells, n=5, p<0.05). Incubation of the cells with RSV (0.1 μmol/l) in the absence of TNF-alpha increased the basal expression of eNOS mRNA (14.8±6.3-fold of TNF-alpha-treated cells, n=5, p<0.05). In TNF-a-treated cells RSV dose-dependently increased eNOS mRNA (0.01 μmol/l: 1.6±0.7, 1 μmol/l: 2.1±1.0; n=5) leading to augmented eNOS protein expression after 12 hours (0.01 μmol/l: 1.11±0.06, 1 μmol/l: 1.26±0.12, n=4, p<0.05 compared to TNF-a-treated cells). The effects on eNOS mRNA and protein expression mediated through RSV could be reversed by incubation of the cells with mevalonate indicating inhibition of HMG-CoA reductase as the underlying mechanism. Treatment with geranylgeranyl pyrophosphate, but not farnesyl pyrophosphate reversed the increase of eNOS mRNA and protein expression induced by RSV. We conclude that RSV - via inhibition of HMG-CoA reductase and subsequent blocking of isoprenoid synthesis - reverses the detrimental effects of TNF-alpha-induced reduction in eNOS expression. RSV may have beneficial effects on endothelial dysfunction associated with cardiovascular diseases beyond its effects on lowering cholesterol.

P2173 Effects of atorvastatin on soluble adhesion molecules levels in patients with or without mutations of LDL receptor or ApoB100 genes

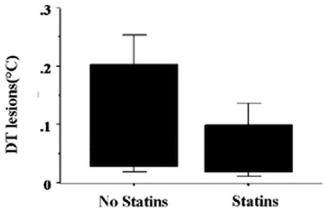
A. Bolewski[1], R. Plewa[2], T. Siminiak[3]. *[1]District Hospital, Poznan, Cardiology Department, Poznan, Poland; [2]University of Poznan, Department of Molecular Biology, Poznan, Poland; [3]District Hospital, Poznan, Cardiology Department, Poznan, Poland*

Background: Inflammatory processes play an important role in the pathogenesis of atherosclerosis. Several data suggest that cell adhesion molecules can initiate and progress the atherosclerosis.
Atorvastatin can reduce levels of proinflammatory markers (cytokines, cell adhesion molecules) in patients with hypercholesterolemia. The influence on these levels in patients with familial hypercholesterolemia is still not well known.
Aim: To investigate the effect of atorvastatin treatment on circulating cell adhesion molecules in patients with hypercholesterolemia with or without mutations of LDL receptor/ApoB100 gene.
Methods: The study group consisted of consecutive 34 hypercholesterolemic patients (mean serum cholesterol level 294±44 mg% (age 58±14, 13 females) without treatment with statins in the past. We analyzed the LDL receptor and ApoB100 genes using the single-strand confirmation polymorphism (SSCP) and direct sequencing technique.
We found 8 mutations in LDL receptor/ApoB100 genes (group A = mutation, B = no mutation). Circulating sVCAM-1, sICAM-1, sP-Selectin, sE-Selectin and sL-Selectin levels were determined by commercially available ELISA kits (R&D System Europe Ltd). Atorvastatin (Sortis, Pfizer) in dose 20 mg%/d was administered for following three months.
All statistical analyses were performed with Willcoxon paired and nonparametric test.
Results: Atorvastatin caused a significant decrease in the total (A: 34.7%, p=0,007; B: 30.0%, p<0.0001) and LDL-cholesterol (A: 46.2%, p<0.0001; B: 38.0%, p=0.007) levels compared both with baseline measurements.The sVCAM-1 (A: 20,3%, p=0.04; B: 9,8%, p=0.001) and sICAM-1 (A: 19.6%, p=0.007; B: 5.5%, p=0.04) plasma concentration derceased in both groups after the treatment. The significantly decreasing of sE-Selectin (43.1%, p=0.007) and sP-Selectin (20.0%, p=0.008) was observed only in group with mutation. There was no difference of sL-Selectin in both groups.
Conclusion: Short–term lipid lowering with middle dose of atorvastatin can decrease levels of endothelial adhesion molecules (sVCAM-1, sICAM-1) in hypercholesterolemic patients both with and without mutations of LDL receptor/Apo B100 gene. sP-Selectin, sE-Selectin decreased only in mutation group. There was no influence on levels of sL-Selectin. Atorvastatin might exert beneficial effect on inflammatory process.

P2174 Non-culprit significant lesions of patients with acute coronary syndromes have thermal heterogeneity: new implications of the pleiotropic effect of statins

M. Drakopoulou, K. Toutouzas, I. Mitropoulos, E. Tsiamis, S. Vaina, M. Vavuranakis, D. Tousoulis, C. Stefanadis. *Ippokration Hospital, Dept of Cardiology, Athens, Greece*

Background: Thermal heterogeneity has been demonstrated in culprit lesions (CL). It is not known whether increased plaque temperature is detected in non-culprit lesions (NCL) and the possible effect of statins. Aim of the study was to investigate: 1) thermal heterogeneity in NCL, and 2) the effect of statins on plaque temperature of NCL.
Method: We included patients (pts) suffering from stable angina (SA) or acute coronary syndromes (ACS). All pts had at least two angiographically significant lesions at different arteries. CLs were identified in all pts by a combination of ECG, wall motion abnormalities, scintigraphic perfusion defects, and/or coronary angiogram. Pts with chronic total occlusions and multiple significant lesions at the culprit vessel were excluded. We measured at each lesion the temperature difference (DT) between the atherosclerotic plaque and the proximal vessel wall temperature(Medispes, Switzerland).
Results: Study population included 42 pts: 23 with SA, 19 with ACS. Of them 29 pts received statins > 4 weeks and 13 were not receiving statins. DT was similar in CL and NCL (0.09±0.10°C vs 0.08± 0.10°C, p=0.86). Mean value of DT in all lesions (n=84) was higher in the untreated group compared to the treated group (treated: 0.06±0.05°C vs untreated: 0.11±0.13°C, p=0.009). A progressive increase in DT by type of clinical syndrome was observed in both CLs and NCLs (CL; SA: 0.06±0.04°C, ACS: 0.13±0.14°C, p=0.03, vs NCL; SA: 0.05±0.06°C vs ACS: 0.13±0.14°C, p=0.01).



Lesions - Statins

Conclusions: NCLs have thermal heterogeneity supporting the concept of global coronary instability. Pts under statin treatment have less thermal heterogeneity in NCLthan those not treated. Thus, statins seem to have a favourable effect on heat release from atherosclerotic plaques.

P2175 N-BNP and vascular disease among 20,536 patients in the MRC/BHF Heart Protection Study

J. Emberson[1], J. Armitage[1], L. Ng[2], L. Bowman[1], S. Parish[1], R. Collins[1] on behalf of Heart Protection Study Collaborative Group. *[1]Clinical Trial Service Unit, Nuffield Dept. of Clinical Medicine, Oxford, United Kingdom; [2]University of Leicester, Department of Cardiovascular Sciences, Leicester, United Kingdom*

Background: N-terminal pro-B-type natriuretic peptide (N-BNP) blood levels indicate the presence and severity of overt heart failure. However, the independent predictive value of N-BNP for occlusive vascular disease has not been established. In addition, while cholesterol lowering with statins reduces the risk of major vascular events in a wide range of people, it has been suggested that these benefits may not extend to patients with heart failure.
Methods: In the MRC/BHF Heart Protection Study (HPS), 20,536 people with coronary or other vascular disease were randomised to receive simvastatin 40mg daily or matching placebo for an average of 5 years. Patients with heart failure were eligible provided they were not breathless at rest. Baseline blood samples were used to stratify participants into five groups of N-BNP (<60; 60-187; 188-432; 433-953; and ≥954 fmol/ml). The incidence of major vascular events (MVE: i.e. major coronary events [MCE: non-fatal MI or coronary death], stroke, or revascularistion) and heart failure hospitalisation or death (HF) by baseline N-BNP level was assessed, as was the response to statin treatment.
Results: Participants with higher baseline N-BNP levels were older, and more likely to have pre-existing vascular disease and to be taking cardioprotective drugs, than subjects with lower baseline N-BNP levels. However, even after allowing for differences in these and other vascular risk factors, the risks of subsequent MVE, MCE, stroke, and HF were strongly associated with N-BNP levels. Compared with participants with baseline N-BNP level <60 fmol/ml, those with levels of at least 954 fmol/ml had relative risks for MVE of 2.4 (95% CI 2.2-2.6), for MCE of 3.7 (3.3-4.1), for stroke of 1.9 (1.6-2.3), and for HF of 12.6 (10.9-14.5). Allocation to simvastatin reduced the relative risk of MVE by 24% (19%-28%), with similar proportional reductions irrespective of baseline N-BNP (heterogeneity p-value = 0.41). Although there was a trend towards smaller proportional reductions in MCE with statin therapy among participants with higher baseline N-BNP, there was an opposite trend for strokes. Simvastatin allocation was also associated with a 14% (0%-25%) proportional reduction in HF.
Conclusion: Participants in HPS with baseline N-BNP levels suggestive of mild to moderate heart failure were at increased risk not only of HF hospitalisation or death but also of MVE. Statin allocation produced significant reductions in MVE among these high-risk individuals, with no evidence of any significant hazard.

P2176 Fluvastatin efficacy and safety profile in patients with moderate to severe renal impairment: results from the fluvastatin pooling analysis

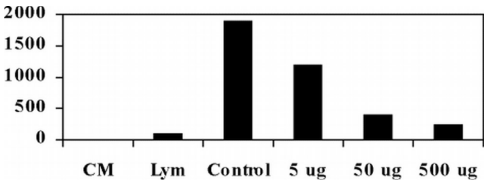
H. Holdaas[1], C. Wanner[2], C. Gimpelewicz[3], C. Abletshauser[4], M.P. Verpilleux[3], J.O. Logan[3], M. Bortolini[3]. *[1]Dept. of Medicine National Hospital, Renal Section, Oslo, Norway; [2]University Hospital, Division of Nephrology, Wuerzburg, Germany; [3]Novartis, Medical Department, Basel, Switzerland; [4]Novartis, Medical Department, Nuernberg, Germany*

Background: Over the past few years, strong evidence supporting the use of statins in diverse populations has emerged. Cardiovascular disease is a common cause of morbidity and mortality in patients with decreased renal function. There has been an emerging consensus that patients with chronic kidney disease (CKD) have to be treated intensively for dyslipidemia.
This analysis was conducted to evaluate the lipid modulating efficacy, clinical outcome and safety profile of fluvastatin in patients with moderate to severe renal impairment defined as creatinine clearance < 50 ml/min.
Methods/Patients: Data from 30 completed double-blind, randomized, placebo and active control studies, with at least 6 weeks of active treatment and daily fluvastatin doses of 20 mg, 40 mg, and 80 mg were included in a pooled database. Total cholesterol, LDL-C, HDL-C and triglycerides were evaluated at baseline and on study medication. A further analysis of clinical outcomes included only studies with duration of 1 year or longer in which clinical endpoints were collected and reviewed by blinded adjudication committees.
Results: The pooled database included 7,463 patients randomly assigned to fluvastatin treatment and 4,352 patients randomly assigned to placebo treatment. There were 810 fluvastatin-treated patients and 646 placebo-treated patients with moderate to severe renal impairment. Fluvastatin treatment resulted in mean reduction in LDL-C of 28.1%, (25.9% for the 20 mg dose and up to 31.2% for the 80 mg XL dose) in patients with renal impairment. The clinical outcome analyses included 1135 patients with moderate to severe renal impairment. The incidence of cardiac death or non-fatal MI was 7.4% in the fluvastatin group versus 12% in the placebo group. The risk of cardiac death or MI was reduced by 41.2%, OR 0.588 (0.392, 0.883) p = 0.0099. The safety profile was similar in both treatment arms.
Conclusions: This pooled analysis showed that fluvastatin is an efficacious, safe and tolerable drug for reducing cardiovascular endpoints in patients with moderate to severe renal impairment.

P2177 Direct atorvastatin anti-inflammatory effects. Atorvastatin blocks C-reactive protein production in cultured human hepatocytes

A. Merino Otermin[1], J. Calvo[2], A. Gaya[2], A. Berenguel[1], I. Segura[1], C. Imizcoz[1], E. Alegria[3], L. Badimon[4]. *[1]Clinica Rotger, Cardiologia, Palma de Mallorca, Spain; [2]Banc de Teixits de Les Illes Balears, Palma de Mallorca, Spain; [3]Clinica Universitaria, Pamplona, Spain; [4]ICCC/CSIC, Barcelona, Spain*

Several studies have shown that statins reduce C-reactive protein (CRP) levels. It is not known whether this effect is due to a direct anti-inflammatory action or if it is secondary to other not specified anti-atherosclerotic effects of this class of drugs. Blood CRP is mainly produced by hepatocytes.
Aim: to conduct an in-vitro experiment that shows if CRP production by cultured hepatocytes is blocked by atorvastatin.
Methods: we set up a model in which CRP was induced by a line of cultured hepatocytes (human hepatoma, Huh7) by stimulation with a supernantant of PHA stimulated lymphocytes which is rich in several citokynes (IL-1, IL-6, IL-8). Then we determined dose-response curves to assess the optimal cytokine concentration to induce CRP production by hepatocytes. Finally we added different concentrations of atorvastatin to determine its effect on CRP production. CRP was analyzed in the supernatants by ELISA with a detection range from 78 to 5000 pg/ml. Simultaneously we determined CRP production by the presence of specific messenger RNA by RT-PCR.
Results: they are shown in the figure which shows CRP (pg/ml) production by Huh7 hepatocyte line. The bar graph shows CRP levels in different conditions. Mean CRP in culture medium (CM). Supernatant of lymphocytes stimulated with PHA (Lym). CRP levels in hepacocytes stimulated by lymphocyte supernatant (Control) and after adding 5, 50 y 500 mM of atorvastatin.



CRP in cultured human hepatocytes

Conclusions: atorvastatin blocked CRP production by cultured human hepatocytes in a dose response manner. Atorvastatin has a direct anti-inflammatory effect by blocking CRP production in the liver.

P2178 CD40-Ligand during acute lipemia in healthy subjects

T. Kaelsch[1], E. Elmas[2], X.D. Nguyen[3], H. Leweling[4], M. Neumeier[5], H. Klueter[3], M. Borggrefe[2], C.E. Dempfle[2]. *[1]University Hospital Mannheim, 1st Department of Medicine, Mannheim, Germany; [2]University Hospital Mannheim, 1st Department of Medicine, Mannheim, Germany; [3]Institute of Transfusion Medicine, Faculty of Clinical Medicine Mannheim, Mannheim, Germany; [4]University Hospital Mannheim, 4th Department of Medicine, Mannheim, Germany; [5]University Hospital Mannheim, Department of Clinical Chemistry, Mannheim, Germany*

Background: In patients with chronic hypercholesterolemia, the CD40-CD40L dyad is upregulated, contributing to the initiation and progression of atherosclerosis. In acute alimentary lipemia, the response of platelets and monocytes to inflammatory stimulation and the role of CD40 ligand have not been described yet.
Methods and Results: Before and two hours after consumption of a defined fatty meal, whole blood samples of 31 healthy persons were incubated with endotoxin (LPS). CD40-ligand and CD62P expression on platelets and tissue-factor binding and CD41 expression on monocytes were measured with flow cytometry. Platelet-monocyte aggregates were measured by CD41 expression on platelets adherent to monocytes. Soluble CD40-ligand plasma levels were measured with an ELISA. With the intake of the fatty meal, serum triglyceride levels increased from 137.65 ± 60.52 mg/dl to 201.45 ± 74.98 mg/dl ($p<0.0001$) while white and red blood cell counts did not change significantly. After the meal, expression of CD40L on platelets, expression of CD62P on platelets, and plasma levels of soluble CD40L were significantly decreased. No significant changes after the meal were observed concerning tissue factor on monocytes and platelet-monocyte aggregates. Addition of LPS before and after the meal showed no significant effect concerning CD40-ligand or CD62P expression on platelets, whereas the amount of platelet-monocyte aggregates significantly increased under LPS stimulation after the fatty meal.
Conclusions: Acute hyperlipemia leads to a decreased expression of CD40L on platelets and a reduced plasma level of sCD40L under the suspicion of an increased turnover.

P2179 Short-term atorvastatin treatment prevents angiotensin-II induced oxidative stress and p67phox expression in rat heart and aorta

P. Wenzel, A. Daiber, M. Oelze, A. Muelsch, T. Muenzel. *Johannes-Gutenberg-Universitaet, II. Medizinische Klinik, Mainz, Germany*

Background: Inhibition of the assembly of NADPH oxidase or NOX homologue subunits in the membrane contributes to the pleiotropic effects of HMG-CoA-reductase-inhibitors caused by the inhibition of the mevalonate pathway. How NADPH oxidase and NOX assembly in the heart is influenced by a short term atorvastatin therapy was investigated in the present study.
Methods: 24 male Wistar rats (age: 8 weeks, weight 250-350 g) were treated for 7d with angiotensin-II (AT-II) (1mg/kgKG/d) and atorvastatin (ATOR) (10mg/kg/d). Drugs were administrated subcutaneously by osmotic pumps, solvents (NaCl and DMSO, respectively) served as controls (C). Hearts were homogenized and the heart membrane fraction (HM) was prepaired. Superoxide production was measured by lucigenin-derived chemiluminescence (LDCL) using 5μM lucigenin and a final protein concentration of 0.2mg/ml. The expression of p67phox, p47phox and rac-1 were determined by Western blot analysis.
Results: 7d AT-II infusion caused a siginificant increase in LDCL, which was prevented by ATOR co-treatment. ATOR alone did not increase LDCL. In HM of AT-II treated rats, the LDCL increase was abolished by in vitro addition of NADH or diphenylene iodonium (DPI), suggesting that NADPH oxidase or NOX homologues are the source of superoxide. The p67phox expression was increased about 7-fold in HM of AT-II treated rats, which was abolished by co-treatment with ATOR. ATOR treatment alone showed no difference as compared to control. The expression of rac-1 and p47phox was not altered by any treatment as compared to control.
Conclusion: Our results indicate that a short term ATOR therapy can normalize oxidative stress induced by AT-II infusion in rats. Additionally, endothelial dysfunction (measured by isometric tension studies in organ chambers) was prevented and LDCL was decreased in isolated aortic rings of AT-II treated rats. Our results point towards possible anti-oxidative side-effects of ATOR.

P2180 The influence of Cys152Trp mutation on the structure and function of LDL receptor in patients with familial hypercholesterolemia

R. Plewa[1], M. Luczak[1], A. Bolewski[2], J. Wierzchowiecki[2], T.L. Siminiak[3]. *[1]University of Poznan, Poland, Dept. Molecular Biol. & Biotechnology, Poznan, Poland; [2]District Hospital, Department of Cardiology, Poznan, Poland; [3]Univ. School of Medical Sciences, Dept. of Internal Medicine & Cardiology, Poznan, Poland*

Familial hypercholesterolemia, an autosomal dominant disorder caused by mutations in the low density lipoprotein receptor (LDLR) gene has been shown to be involved in pathogenesis of atherosclerosis and ischaemic heart disease. The LDL receptor is a trans-membrane glycoprotein, present on cellular surface, being responsible for mediation of the uptake and degradation of LDL, major cholesterol carrier in plasma. A large number of different mutations of the LDLR gene was identified.
In a screening of the LDLR gene mutations of 50 consecutive patients with familial hypercholesterolemia, we discovered a point mutation Cys152Trp in 4 exon. This mutation occurs in the fragment encode the ligand binding domain, which is made of seven repeats of 40 amino acids each. Each repeat contains six cysteine residues that form three desulfide bounds.
We used computer simulation to discover how Cys152Trp mutation influence the structure of the ligand binding domain of the LDL receptor. Because of Cys152Trp substitution, the cysteine with small side chain was replaced by large, aromatic ring, positively charged tryptophan. As a result there is lack of the one of disulfide bridges which stabilize the ligand binding domain. Moreover the steric hindrance caused by Trp, changes the pleated sheet structure in the place of mutation and it also causes appearance of two new such structures in eight amino acids from the mutation place. As a result this change of structure protein affects the binding capability of apolipoprotein by LDL receptor. The internalization of apolipoprotein B to the muted LDL receptor was additionally evaluated by flow cytometry assay, based on evaluation of LDLR expression after subsequent cell incubation with apolipoprotein B in vitro, confirming its functional impairment.
Thus, Cys152Trp mutation in the LDL receptor gene may be involved in the development of atherosclerosis in patients with familial hypercholesterolemia.

CMR: ISCHAEMIC HEART DISEASE

P2181 Association of cardiovascular risk scores with myocardial high-energy phosphate metabolism in men

R. Zwick[1], G. Klug[2], M.F. Schock[3], C. Wolf[3], M. Frick[2], W. Jaschke[3], O. Pachinger[2], B. Metzler[2]. *[1]Wien, Austria; [2]University Innsbruck, Cardiology, Innsbruck, Austria; [3]Innsbruck University, Radiology 1, Innsbruck, Austria*

Purpose: We intended to prove an association between human myocardial, high-energy, phosphate metabolism and cardiovascular risk scores.
Methods: Our study included 71 healthy, asymptomatic male patients (mean age 52.2±8.8) with normal ejection fraction. All underwent echocardiography and cycle ergometry to exclude a latent coronary insufficiency and/or a reduced left ventricular function. Blood was taken to evaluate cardiovascular risk scores (Procam, Framingham). Thereafter phosphorus-31, two-dimensional chemical shift imaging (31P 2D CSI) of the heart was performed in all subjects using a 1.5 Tesla whole-body magnetic resonance (MR) scanner. The ratios (R) between phosphocreatine (PCr) and beta-adenosine-triphosphate (beta-ATP) were calculated for the left ventricular myocardium and divided into tertiles (R1-R3).
Results: There was an overall difference of R1, R2, R3 within the cardiovascular risk scores (Procam; p = 0.046, Framingham; p = 0.019). Patients with the lowest R had a significant increased risk for future cardiovascular events than those in the highest tertile (Procam from 5.3±0.8 to 2.6±3.4; p = 0.014, Framingham from 11.7±1.0 to 8.5±1.1; p = 0.004).
Conclusions: We are the first to show an association between the high-energy, phosphate metabolism in the left ventricular myocardium and cardiovascular risk scores.

P2182 Contrast-enhanced adenosine-stress magnetic resonance imaging feasibility and practicability of a protocol for detection or exclusion of ischaemic heart disease in an outpatient setting

P. Bernhardt[1], K. Haase[2], G.E. Pilz[1], B. Höfling[1], O. Strohm[2]. *[1]Agatharied Hospital, MRI-Center, Hausham, Germany; [2]MRT-Zentrum am SGK, Sankt Gertrauden Krankenhaus, Berlin, Germany*

Background: Evaluating myocardial function, assessing ischemic myocardial areas and detecting myocardial viability are necessary diagnostic information for guiding further therapy in patients with angina. Aim of this study was to show feasibility and safety of a contrast-enhanced magnetic resonance imaging (ceMRI) protocol providing previous mentioned diagnostic possibilities and to demonstrate its applicability in daily routine.
Methods: Consecutive patients with angina were screened on a 1.5 Tesla system. Functional images were acquired for each patient. First-pass kinetics of Gadolinium-based contrast agent was measured after stress with adenosine infusion. After a second bolus injection of contrast agent "late enhancement" (MLE) sequences were acquired for the detection of myocardial necrosis. All patients with a relevant hypoperfusion underwent invasive coronary artery angiography.
Results: We enrolled 3,174 patients referred for ceMRI for detection or exclusion of ischemic heart disease. Hypoperfusion in more than one myocardial segment and affecting more than 25% of the myocardial wall diameter could be detected in 1,972 (62%) patients. Subendocardial hypoperfusion with limited duration could be shown in 897 (28%) patients. In 305 (10%) patients hypoperfusion could be excluded. MLE could be seen in 532 (17%) patients. Positive predictive value of ceMRI was 0.96 compared to invasive angiography data.
Conclusion: This compiled ceMRI protocol is suitable for detection or exclusion of ischemic heart disease in an outpatient routine with a high positive predictive value. We showed feasibility, applicability and safety of our protocol. CeMRI may serve as a useful surrogate for non-invasive diagnostic prior to invasive coronary angiography in many outpatients.

P2183 The importance of resting wall motion abnormalities for the diagnostic accuracy of a multicomponent stress CMR test

I. Klem[1], J.F. Heitner[2], S. Ambati[2], S. Greulich[1], M.A. Parker[2], U. Sechtem[1], R.M. Judd[2], R.J. Kim[2]. *[1]Robert-Bosch-Krankenhaus, Cardiology Dept., Stuttgart, Germany; [2]Duke University Medical Center, Durham, United States of America*

Background: A multicomponent cardiac magnetic resonance (CMR) stress test allows the assessment of wall motion abnormalities using Cine CMR (Cine), perfusion defects during Adenosine stress and at rest (Perfusion), and myocardial scarring with delayed-enhancement CMR (DE-CMR) in one single study. The utility of the individual CMR techniques for the detection of coronary artery disease (CAD) in the chronic setting is not yet established.
Purpose: To assess the diagnostic accuracy of Cine alone and the incremental effect of adding Cine to 1) Perfusion alone 2) to an algorithm which systematically integrates Perfusion and DE-CMR.
Methods: We prospectively enrolled 100 consecutive pts (age 58.0±11.5 yrs,

47F) without prior history of cardiac disease who were referred for coronary angiography (CA). A comprehensive study including Cine, adenosine and rest Perfusion, and DE-CMR was performed in 92 pts within 24 hrs of CA. Images were scored blinded to pt identity visually in the following manner: Perfusion alone; Cine alone; DE-CMR alone; Cine with Perfusion combined in that if either or both were abnormal the overall test was positive; Cine combined with an algorithm integrating Perfusion and DE-CMR in a specific manner. Pts were considered positive for CAD if there was ≥70% coronary stenosis on CA.
Results: Cine alone had a low sensitivity and moderate specificity for the detection of CAD (Table). The simple addition of Cine to Perfusion increased sensitivity at the cost of lower specificity. The accuracy of the combination of Cine and the algorithm was similar to the algorithm alone. (P=NS)

	Sensitivity	Specificity	Accuracy
Perfusion alone	84%	58%	68%
Cine alone	49%	73%	63%
DE-CMR alone	49%	98%	78%
Cine+Perfusion	89%	49%	65%
Algorithm	89%	87%	88%
Algorithm+Perfusion	86%	89%	88%

Conclusion: The presence of wall motion abnormalities alone, without evidence of perfusion defects or scar on DE-CMR should not be considered as indicative of CAD in a multicomponent CMR stress test in the non-acute setting.

P2184 The match between regional transmural flow and function during maximal vasodilation: a dipyridamole contrast magnetic resonance study

A. Pingitore, M. Lombardi, B. Scattini, G. Di Bella, G.D. Acquaro, D. De Marchi, V. Positano, E. Picano. *CNR Institute of Clinical Physiology, Pisa, Italy*

Background: Cardiac magnetic resonance (CMR) has the potential to evaluate quantitatively regional function and flow. With contrast, also perfusion can be quantitatively assessed both transmurally (TM) and separately in the subendocardial (ENDO) and the subepicardial (EPI) layers.
Aim: To assess the effects of high dose dipyridamole (D) stress test on the regional flow-function match in patients with normal and diseased coronary arteries.
Methods: Twenty-nine patients (age 60±6 years, 17 males) with normal resting function underwent perfusion CMR using a multislice echo-planar sequence for monitoring first pass kinetics of gadolinium at rest and after D (0.84 mg/kg in 10 minutes). Signal intensity upslope (UPS) as a measure of myocardial perfusion of TM, ENDO and EPI was assessed in a 16 segment model of left ventricle. A perfusion reserve index (PRI) was calculated as the ratio between D and resting UPS. Systolic wall thickening (SWT) was measured in the same myocardial segments. All patients underwent quantitative coronary angiography independently of test results. Myocardial segments were divided as follows: group I= 329 segments supplied by 87 non-stenotic (< 50% diameter reduction) coronary vessels; group II = 40 segments supplied by 7 coronaries with 50 to 70% stenosis; group III = 95 segments supplied by 14 coronaries stenosed >70%.
Results: See table.

Groups	PRI			SWT (%)	
	TM	ENDO	EPI	Rest	D
I (n=318)	2.7±1.7	2.4±1.4	2.8±2.4	96.1±43.3ˆ	113.5±54ˆ
II (n = 40)	2.2±0.9°	2.0±1.0°°	2.4±1.0°°	77.8±40.7	86.6±33.3°°
III (n = 90)	1.7±0.9*	1.6±0.9*	1.9±1.1*	71.2±33.3*	72±36.6*

*III vs I=p<0.001; °II vs III= p<0.01; °°II vs III= p=0.03; ˆI vs II= p<0.01.

Conclusion: During D, the reduction in transmural and subendocardial regional flow reserve is mirrored by a lack of hyperkinesia of segments subtended by critically stenosed coronary arteries. The degree in both the regional perfusion and functional impairment is somewhat linked to the anatomic severity of the coronary artery supplying those segments.

P2185 2D strain analysis allows accurate analysis of regional systolic left ventricular function as defined by magnetic resonance imaging

M. Becker[1], E. Bilke[1], A. Franke[1], H. Kuehl[1], M. Katoh[2], P. Hanrath[1], R. Hoffmann[1]. *[1]University Hospital Aachen, Cardiology Dept., Aachen, Germany; [2]University Hospital Aachen, Radiology Dept., Aachen, Germany*

Objective and quantitative regional left ventricular function assessment is desirable. We sought to evaluate a novel computer software (General Electric Ultrasound, Horton, Norway) which allows automatic frame-by-frame tracking of natural accoustic markers during the heart cycle yielding objective measures of contractility.
Methods: 35 patients with ischemic heart disease and 10 healthy students underwent cardiac magnetic resonance imaging (cMRI) to define regional left ventricular function as normokinetic, hypokinetic or akinetic in a 16 segment model.For each LV segment radial strain (RS), circumferential strain (CS), radial strain rate (RSR) and circumferential strain rate (CSR) were calculated using the novel computer software which allows radial and circumferential strain and strain rate analysis based on parasternal views. Obtained data were related to regional LV function defined by cMRI.
Results: Image quality allowed adequate strain and strain rate analysis from parasternal views in 88% of segments. Each of the strain and strain rate parameters obtained by 2D strain analysis was significantly different between segments defined as normokinetic, hypokinetic or akinetic by cMRI (see Table).

Strain and strain rate results

	Normokinesis (N=242 segments)	Hypokinesis (N=240 segments)	Akinesis (N=150 segments)	P
CS (%)	-20.8 ± 7.1	-13.4 ± 4.7	-8.4 ± 3.3	< 0.001
RS (%)	39.4 ± 12.0	23.7 ± 8.9	11.9 ± 4.7	< 0.001
CSR (1/sec)	-1.63 ± 0.29	-1.20 ± 0.28	-0.81 ± 0.31	<0.001
RSR (1/sec)	1.60 ± 0.28	1.21 ± 0.27	0.81 ± 0.31	< 0.001

RS analysis had the highest accuracy to detect hypokinesis/akinesis defined by cMRI (cut-off value <27.1 (%), sensitivity: 88.7%, specificity: 84.0%, ROC area 0.929). For CS ROC area was significantly smaller (0.846; p<0.001). RSR analysis allowed detection of hypokinesis/akinesis defined by cMRI with a sensitivity of 84.6% and a specificity of 84.8% using a cut-off value for RSR of <1.32 1/s (ROC area 0.912).
Conclusions: Strain and strain rate defined by a novel 2D strain software allows accurate analysis of regional systolic left ventricular function.However,the novel radial strain and strain rate analysis allows better prediction of regional LV function defined by cMRI than circumferential strain and strain rate analysis.

P2186 Magnetic and biological properties of MRI contrast agents for molecular imaging

M. Graefe[1], D. Stibenz[2], T. Dietrich[2], U. Thanabalasingam[2], P. Stawowy[2], Z. Yu[2], E. Nagel[2], K. Graf[2]. *[1]Deutsches Herzzentrum Berlin, Cardiology Dept., Berlin, Germany; [2]Deutsches Herzzentrum Berlin, Internal Medicine/Cardiology, Berlin, Germany*

Non invasive imaging techniques such as MRI support new approaches to visualise molecular and cellular structures in vivo. By use of specific contrast agents it becomes potentially possible to realize molecular imaging. Both, superparamagnetic iron particles and gadolinium based compounds targeted to molecular structures are presently under investigation for their applicability in molecular imaging. In the present investigation we compared four different iron based MRI contrast agents in respect to their magnetic and biological properties.
Methods: three contrast agents (CA) were coated with dextran and had diameters of 4nm (AD) and 10 nm (BD, DD) while one was citrate-coated (CC, 4 nm). Magnetic properties of all four compounds were measured in a special manufactured phantom using a 7T scanner (Bruker) by T2-fit (MSME), duration 11 min, TR 3540 ms, TE 3 to 5 ms echo time, matrix 128x128 pixels. The biological properties were characterized in cultures of murine endothelial cells (bEND.3). Cellular uptake was measured by "Berliner Blau" staining and estimation of cellular iron content by a photometric assay.
Results: the relaxivities were: AD: 47 (mM*s)-1; BD: 64 (mM*s)-1; DD: 117 (mM*s)-1; CC: 65 (mM*s)-1. The uptake into endothelial cells under static conditions was comparable for all dextran coated compounds and was measured as 10% of citrate coated particles. The iron concentration of citrate coated particles per cell reached 1000 pg iron/cell after 24 hours. The time course of cellular uptake of all three dextran coated particles showed a plateau which was reached after 2 hours while uptake of citrate coated particles was nearly linear for 24 hours.
Conclusion: the magnetic properties of all investigated contrast agents are comparable. However, they differed significantly in their biological properties. Uptake of citrate coated particles was strong and therefore those compounds are more applicable for unspecific in vivo labelling of living cells. Due to their low cellular uptake dextran coated particles are more suitable for specific ligand coupling and should be used for targeting of cellular and molecular structures.

ECHOCARDIOGRAPHY, DOPPLER

P2187 Relationship between sub-clinical abnormalities of global and regional left ventricular function and insulin resistance in severe obesity: a color (Doppler imaging study)

V. Di Bello[1], F. Santini[2], A. Di Cori[3], C. Palagi[3], M.G. Delle Donne[3], P. Fierabracci[2], E. Talini[2], A. Balbarini[3]. *[1]university of pisa, dipartimento cardio toracico, Pisa, Italy; [2]Dipartim. Endocrinologico Metabolico, Pisa, Italy; [3]University of Pisa, Cardiac and Thoracic Dept, Pisa, Italy*

Aim: Aim of the study was to evaluate the relationship between insulin resistance and pre-clinical abnormalities of Left Ventricular structure and function detected in severe obesity by Color Doppler Myocardial Imaging (CDMI)
Forty eight consecutive severely obese patients (11 males, 37 females, mean age 32.8±7 yr) were enrolled. Forty-eight sex- and age-matched non-obese healthy

subjects were also recruited as controls. All subjects underwent conventional 2D-Color Doppler echocardiography and CDMI. The homeostasis model assessment insulin resistance index (HOMA-IR) was used to assess insulin resistance.
Obese had a greater LVMh (58.8±14 g/m^2.7) than controls (37±8 g/m^2.7), p<0.0001), due to compensation response to volume overload caused by a greater cardiac output (p<0.02). Preload reserve was increased in obese, as demonstrated by the significant increase in left atrial dimension (p<0.0001); this volumetric increase activated the Frank-Starling mechanism and determined a significantly higher left ventricular ejection fraction (p< 0.03) if compared with controls. Obese patients had a slightly reduced LV diastolic function (transmitral E/A ratio: O: 1.1±0.8 vs. C: 1.5 ±0.5; p<.002). Cardiac deformation assessed by regional myocardial systolic strain and strain rate (SR) values was significantly lower (abnormal) in obese patients than in controls, both at septum and lateral wall level. These Strain and SR abnormalities were significantly related to BMI. In addition, the early phase of diastolic function, evaluated using SR, was compromised in obese patients (p<0.001). The HOMA-IR values in the obese patients were significantly higher (3.09 ±1.6) than those determined in control group (0.92 ± 0.5) (p<0.0001). The HOMA-IR values, in obese group, were significantly related with systolic strain and strain rate values sampled at septum level.
In conclusion, this study has confirmed the previous observations that obese patients showed systolic structural and functional abnormalities at a preclinical stage, and has demonstrated that those myocardial alterations could have a possible relationship with insulin resistance.

P2188 Weight reduction improves subclinical myocardial and vascular dysfunction in obese subjects

C. Wong[1], T. O'Moore-Sullivan[2], N. Byrne[3], L. Smith[2], T.H. Marwick[2]. [1]*University of queensland, School of medicine, Brisbane, Australia;* [2]*University of queensland, School of medicine, Brisbane, Australia;* [3]*Queensland University of Technology, Brisbane, Australia*

Recent work has suggested subclinical LV dysfunction and vascular changes to occur in pts with obesity and metabolic syndrome. We sought whether such changes were reversible through weight reduction.
Methods: Quantitative assessment of myocardial vascular function was performed at baseline and after 6 weeks of lifestyle intervention program in 105 subjects with significant risk factors but no cardiovascular disease. All subjects had normal LV EF. Sensitive ultrasonic tissue characterization techniques are used to assess myocardial function i.e. strain rate [SR], strain [e], and regional myocardial systolic velocity [sm], diastolic velocity [em]. Vascular structure and function were assessed using brachial artery reactivity [BAR] and carotid intima-medial thickness [cIMT].
Results: Weight loss of >1 kg was achieved by 23F and 24M (average -4% vs +1%, p<0.001), associated with a body fat reduction of -2% (vs +1%, p<0.001). There was significant improvement in subclinical myocardial diastolic dysfunction (em; Table), which was related to the magnitude of wt change (diff. in wt% to diff. in em; r=0.34, p=0.01) and vascular BAR (from a mean 6.7% to 8.6%), but no significant change in systolic parameters (sm, global strain 21% vs22% and strain rate 1.5 s-1 vs. 1.5 s-1) and cIMT (remained 0.61 mm). No significant differences were detected in pts who did not lose weight.

Table 1. Clinical and LV and vascular ultrasonic characterization measures at baseline and 6 weeks follow up, and comparison of diff. between the 2 groups

	wt stable (n=52,27F) 48±10y			wt reduction (n=47,23F) 47±11y			
	baseline	post intervention	diff.	baseline	post intervention	diff.	
Wt (kg)	95±22	96±22	0.9±2.0	98±23	94±22	-3.4±2.0	<0.001
sm (cm/s)	4.8±1.6	5.0±1.6	0.2±1.3	4.8±1.2	5.3±1.4	0.5±1.5	ns
em (cm/s)	5.5±2.0	5.5±1.7	0.1±1.5	5.5±1.9	6.4±1.9	0.9±1.7	<0.01
BAR %	6.4±4.2	6.2±5.3	0.20±5.5	6.7±4.9	8.6±4.9	2.2±5.5	<0.05

Conclusion: Weight reduction is associated with improvements in subclinical myocardial and vascular dysfunction.

P2189 Association of aortic stiffness and left ventricular diastolic function with microalbuminuria in type 2 diabetic patients

D. Duman[1], M. Karakas[2], R. Demirtunc[2], B. Erdogan[2], B. Karadag[3], D. Duman[4]. [1]*Haydarpasa Numune Hospital, Department of Cardiology, Istanbul, Turkey;* [2]*Haydarpasa Numune Hospital, Internal Medicine, Istanbul, Turkey;* [3]*IU Cerrahpasa Medical School, Cardiology, Istanbul, Turkey;* [4]*Istanbul, Turkey*

Aim: Microalbuminuria (MA) is an early marker of diabetic nephropathy and has been shown to strongly predict future cardiovascular morbidity and mortality in patients with type 2 diabetes. In this study, we tested the hypothesis suggesting that the presence of MA reflects impaired aortic elastic properties in type 2 diabetic patients.
Methods: Fifty type 2 diabetic patients with MA (urinary albumin 30-300 g/mg creatinine) and 49 type 2 diabetic patients without MA (urinary albumin < 30 g/mg creatinine) were recruited, matched for their sex, age, body mass index (BMI), diabetes duration and antidiabetic therapy. Their blood pressure was lower than 140/90 mmHg and none had known or suspected coronary heart disease. Fifty healthy volunteers were enrolled as the control group. Aortic strain and distensibility were calculated from the echocardiographically derived thoracic aorta diameters and the measurement of pulse pressure obtained by cuff sphygmomanometry.
Results: The mean aortic strain and distensibility were lower in type 2 diabetes patients with MA than in patients without MA (5.8 ± 3.8% vs. 8.6 ± 3.0%, p < 0.005 and 2.3 ± 1.9 vs. 3.2 ± 1.7 cm^2 /dyn/10^3, p < 0.01) The mean aortic strain and distensibility in both diabetes groups were decreased in comparison to the control group (7.4 ± 3.6% vs. 12.8 ± 5.6%, p < 0.005 and 2.6 ± 1.5 vs. 6.2 ± 3.2 cm^2 /dyn/10^3, p < 0.005 respectively). The aortic distensibility was significantly correlated with deceleration time (DT) and isovolumic relaxation time (IVRZ) (?= -0.39, p < 0.001 and ?= -0.35, p < 0.005). In linear regression analysis, the association of amount of secreted albumin into urine with echocardiographic parameters (aortic distensibility, ejection fraction, DT, IVRZ, peak early and late transmitral filling velocity ratio, peak early transmitral filling velocity, left ventricle mass index) was evaluated. It was observed that amount of albumin was significantly associated only with aortic distensibility (standardised b coefficent –0.33, p < 0.01, overall R^2 = 0.16) and DT (standardised b coefficent 0.32, p < 0.01, overall R^2 = 0.23).
Conclusions: These findings suggest that type 2 diabetic patients with MA had increased aortic stiffness compared to the patients without MA. Furthermore, aortic stiffness was also associated with left ventricular diastolic dysfunction in type 2 diabetes. Underlying impaired aortic elastic properties may explain the high cardiovascular mortality in type 2 diabetic patients with MA.

P2190 Impact of metabolic syndrome on subclinical changes of vascular structure and function in diabetic and non-diabetic subjects

C. Wong[1], B. Haluska[2], L. Jeffriess[2], T. O'Moore-Sullivan[2], T.H. Marwick[2]. [1]*University of queensland, School of medicine, Brisbane, Australia;* [2]*University of queensland, School of medicine, Brisbane, Australia*

Objectives: The metabolic syndrome (MS) is associated with adverse effects on the vasculature. We sought whether clustering of multiple components of MS had an additional impact on vascular structure and function in subjects with atherosclerotic risk factors, with and without diabetes mellitus (DM).
Methods: Vascular structure and function were assessed quantitatively in 144 men and 150 women with atherosclerotic risk factors. None had overt cardiovascular disease and all had a negative stress test. High-resolution ultrasound was used to assess vascular structure (carotid intima-medial thickness [IMT]) and function (brachial artery reactivity [BAR]), which was also assessed by tonometry (total arterial compliance [TAC]).
Results: Pts with MS (NCEP III criteria) had a higher risk for early atherosclerotic changes/reduced vascular function. The vascular parameters IMT, BAR and TAC were overall significantly different compared to those without MS. In non DM pts, MS was associated with reduced TAC and higher% of abnormal IMT (>0.70mm) (Table). Pts with DM and MS had no significant differences in cIMT and TAC, although BAR was worse compared to pts without MS. ACEi and statins were more commonly used in DM pts and may attenuate the effect of MS. In a regression model, MS was an independent predictor for TAC after adjustment for ACEi and statin use.

Table 1. Comparison of vascular profiles of non DM/DM groups according to MS profile

	Non DM (n=114, 60F)			DM (n=180, 90F)		
	MS-	MS+	p	MS-	MS+	p
BMI(kg/m^2)	34±8	45±12	<0.001	27±7	32±5	<0.001
ACEi %	0	7	ns	40	63	<0.05
Statin%	0	4	ns	7	8	ns
BAR%	7.0±4.4	5.7±4.2	ns	6.4±4.8	4.8±4.5	<0.05
Abn. cIMT	6%	22%	0.01	38%	38%	ns
TAC mmHg/ml	1.8±0.5	1.5±0.4	0.02	1.2±0.6	1.3±0.7	ns

Conclusion: Components of MS synergistically impact vascular changes in pts in both DM and non DM groups, although the effects of these disorders may be modulated by therapy.

P2191 Diastolic tissue velocity predicts exercise capacity in renal transplant recipients with glucose intolerance

D. Rakhit[1], K.A. Armstrong[2], N. Isbel[2], T.H. Marwick[2]. [1]*Brisbane, Australia;* [2]*University of Queensland, Brisbane, Australia*

Background: Impaired exercise capacity in renal transplant recipients (RTR) is attributed to deconditioning. We sought a direct myocardial contribution by examining the association between resting myocardial tissue velocities and LV mass with peak oxygen (VO2) uptake.
Methods: Resting 2D echocardiograms were obtained in 51 RTR with glucose intolerance (mean age 55 yrs, 61% male, median transplant duration 7.8 yrs) who underwent treadmill VO2 testing by expired gas analyses. Clinical and biochemical data were recorded. Echo measurements were LV cavity and wall thickness, LV mass indexed to height 2.7, relative wall thickness, left atrial volume and area, pulmonary venous doppler, LV and left atrial filling parameters, Tei index and ejection fraction (Simpson's biplane). Myocardial velocity during systole (Sm), early

(Em) and late diastolic filling were obtained from colour tissue doppler images of the septal and lateral mitral valve annulus.
Results: Mean peak VO2 was 18.9 ± 6.2 mL/kg/min. Em was the only independent echocardiographic predictor of peak VO2 (table). Clinical predictors of a lower Em were use of platelet inhibitors (p=0.02), metformin therapy (p=0.05), higher serum phosphate (p=0.003) and history of heart failure (p=0.002).

Variable	Univariate		Multivariate	
	B (95% CI)	p value	B (95% CI)	p value
Septal thickness (cm)	-5.1 (-10.5 to 0.3)	0.07		
LV mass index (g/m^2.7)	-0.09 (-0.2 to -0.008)	0.03		
Em (cm/s)	1.3 (0.2 to 2.4)	0.02	1.3 (0.2 to 2.4)	0.02
Sm (cm/s)	1.5 (0.2 to 2.9)	0.03		

Conclusion: Myocardial hypertrophy, subclinical LV dysfunction or diastolic abnormalities may contribute to impairment of exercise capacity in RTR. Abnormalities of early diastolic velocity predict peak VO2 in glucose intolerant RTR independently of LV mass.

P2192 Impaired subendocardial myocardial systolic function in patients with type II diabetes mellitus by Doppler myocardial imaging

Y.B. Deng, X.H. Shi, X.J. Bi, H.Y. Yang, C.L. Li. *Tongji Hospital, Department of Medical Ultrasound, Wuhan, China*

Objectives: Previous study has shown that subendocardial myocardium is vulnerable to the ischemia and subendocardial myocardial systolic function can be evaluated by observing the longitudinal systolic motion and systolic myocardial velocity gradient with Doppler myocardial imaging. This study sought to evaluate the subendocardial myocardial systolic function in patients with type II diabetes mellitus by Doppler myocardial imaging.
Methods: The study population consisted of 46 patients with type II diabetes mellitus and 23 healthy subjects. The Doppler myocardial images were recorded in parasternal long-axis plane and apical long-axis, two-chamber and four-chamber planes. The longitudinal systolic velocity was measured at the mitral annulus at 6 sites in the left ventricle corresponding to anteroseptal, anterior, lateral, posterior, inferior and posteroseptal walls and the mean value from the above 6 sites was calculated. In addition, the systolic myocardial velocity gradient was obtained from the left ventricular posterior wall in parasternal long-axis plane. Left ventricular ejection fraction was calculated with a bi-plane Simpson's method.
Results: Although the ejection fraction was not statistically different between the patients with type II diabetes mellitus (70±6%) and healthy subjects (69±5%, p > 0.05), the mean longitudinal systolic velocity at mitral annulus in patients with type II diabetes mellitus (6.0±1.5 cm/s) was significantly lower than that in healthy subjects (7.8±1.6 cm/s, p < 0.01). In addition, there was a significant difference in the systolic myocardial velocity gradient in the left ventricular posterior wall between patients with type II diabetes mellitus (1.4±1.0 1/s) and healthy subjects (2.4±2.2%, P < 0.01).
Conclusions: The present study showed decreased longitudinal systolic velocity at mitral annulus and systolic myocardial velocity gradient in patients with type II diabetes mellitus when compared with the healthy subjects with preserved global systolic function, indicating that the subendocardial myocardial systolic function is impaired in diabetes mellitus patients.

P2193 Relationship between blood glucose level and left ventricular performance in patients with diabetes mellitus?

M. Yazici[1], B. Ozin[2], K. Ozdemir[3], B. Altunkeser[3], R. Yazici[4], M. Kayrak[5]. *[1]Cardiology, Konya, Turkey; [2]Baskent Univetsity Medical Faculty, Cardiology, Ankara, Turkey; [3]Selcuk University Medical Faculty, Cardiology, Konya, Turkey; [4]Selcuk University Medical Faculty, Internal Medicine, Konya, Turkey; [5]Selcuk University Medical Faculty, Cardiology, Konya, Turkey*

Purpose: The relationship of blood glucose regulation status with left ventricular(LV) performance has not been thoroughly investigated. We have designed this study in order to investigate the relationship of parameters of blood glucose regulation status with LV myocardial performance index (MPI) which has recently become popular as a surrogate of global cardiac function, flow propogation velocity (FPV), myocardial velocities, and conventional echocardiographic velocities.
Methods: In 73 patients (mean age: 50+_11 years)with a diagnosis of DM of at least 6 months duration, whose blood pressure is less than or equal to 150/90 mmHg, who are on insulin or oral antidiabetic medication, FBG after 8 hours of fasting, PPBG, and HBA1C values were determined. Echocardiography was performed, LV ejection fraction (EF), left ventricular early (E) and late (A) filling velocities, and E/A ratio were determined. By using the tissue doppler imaging method, systolic myocardial velocities (Sm), early and late diastolic velocities (Em, Am) in four segments of the LV, ejection time, isovolumetric contraction and and relaxation times were determined and the MPI was calculated. By calculating the arithmetical mean value of the segmentary values, mean LV Sm, MPI, and Em/Am values were obtained. FPV in the LV inflow tract was determined. The relationship of the FBG, PPBG, and HbA1C with the echocardiographic parameters are shown in the table.
Results: No relation was found between FBG, PPBG, and HbA1C values and the LV MPI, Sm, FPV, and EF. However, there was a weak but significant positive correlation between both the conventional doppler derived E/A ratio, and the tissue doppler derived mean LV Em/Am ratio and FBG and PPBG (r=0.24, p=0.03, and r=0.31, p=0.009 for the E/A ratio, respectively; r=0.23, p=0.04, and r=0.29, p=0.01 for the Em/Am ratio, respectively).

	EF	E/A	MPI	Sm	Em/Am	Flow E	Flow A
FBG	0.01	0.24*	-0.13	0.07	0.23*	0.07	0.01
PBBG	0.01	0.31*	-0.19	-0.15	0.29*	0.13	0.17
HbA1C	0.06	-0.04	-0.11	-0.01	0.02	0.09	0.04

*p<0.05

Conclusion: The results study imply that the parameters of blood glucose regulation in patients with DM are related to parameters of LV filling, and therefore, diastolic function of the LV.

P2194 Early detection of cardiomyopathy in patients with b-thalassaemia major

K. Bouki[1], G. Pavlakis[2], K. Komninos[2], E. Bougatiotis[2], K. Kostopoulos[2], D. Vini[3], M. Drossou[3], E. Papasteriadis[2]. *[1]Athens, Greece; [2]General Hospital of Nikea, Cardiology, Pireaus, Greece; [3]General Hospital of Nikea, Hematology, Pireaus, Greece*

In patients with thalassaemia major cardiac failure secondary to iron overload remains the commonest cause of death.
Aim: To assess the accuracy of pulsed Tissue Doppler Imaging (TDI) for the early detection of cardiomyopathy related to iron overload and to compare TDI indices with myocardial T2 star magnetic resonance, in patients with b-thalassaemia major, before the developemend of overt heart failure.
Methods: We examined 66 patients with b-thalassemia major with no symptoms and signs of heart failure, whose myocardial iron overload was evaluated with the magnetic resonance imaging (MRI) method of T2star (T2*). All thalassemic patients had normal left ventricular (LV) ejection fraction by echocardiography and MRI, while 46 (70%) of them showed significant myocardial iron overload (T2* < 20 msec) in MRI. All patients, as well as 38 healthy controls, underwent conventional echocardiographic examination including pulsed TDI. The peak myocardial velocities during systole (s-wave), early diastole (e-wave) and late diastole (a-wave) were measured from the apical 4-chamber view, at the mitral (septal site) and tricuspid annulus(lateral site).
Results: Systolic and early diastolic myocardial velocities were significantly lower in thalassaemic patients compared to controls (see table). Among all the measured TDI echocardiographic parameters septal e-wave showed the strongest correlation (r=0,80, p<0.001) with T2*. Selecting a cut off value<10cm/sec for the septal e wave, myocardial iron overload was detected by DTI with a sensitivity of 87% and a specificity of 85%, in patients with b-thalassaemia major.

DTI myocardial velocities

	SSm	SEm	SAm	TSm	TEm	TAm
Patients	7.3±1.3	9.2±3.3	6.9±1.8	13.7±3.9	13.4±3.3	12.4±3.3
Controls	9.2±1.2	11.1±1.9	7.8±1.4	15.1±1.6	15.8±2.8	11.8±2.7
p value	<0.001	<0.002	0.009	0.04	<0.001	NS

SSm=Septal s-wave, SEm=Septal e-wave, SAm=septal a-wave, TSm=Tricuspid s-wave, TEm=Tricuspid e-wave, TAm=Trcuspid a-wave

Conclusions: Patients with b-thalassemia major and normal LV ejection fraction, show reduced systolic and early diastolic myocardial velocities by DTI. Moreover early myocardial velocity can predict with great accuracy the severity of myocardial iron overload and may represent an early sign of cardiomyopathy, despite preserved global function.

P2195 Right ventricular function in patients with beta thalassemia: relation to serum ferritin level

A.M. Hamdy[1], M.Y. Zein El-Din[2], M.A. Abdel-Hafez[2]. *[1]Cairo, Egypt; [2]Cairo, Egypt*

Background: Cardiac dysfunction is a major cause of death in patients (pts) with beta thalassemia. Right ventricular (RV) contribution to cardiac morbidity and mortality in these pts has been suggested. The purpose of this study is to assess RV function in pts with beta thalassemia (B-Th) using echocardiography and tissue Doppler imaging (TDI), and to detect the relation of serum ferritin level to RV dysfunction.
Method: 30 young pts with B-Th (11.7 ± 5.1 ys), and 15 age matched normal subjects (NL), were evaluated by conventional echo-Doppler and TDI. Measurements obtained included: RV end diastolic & end systolic diameters (RVEDD & RVESD), RV % fractional shortening (RVFS), RV pressure (RVP) calculated from tricuspid regurgitation (TR) if present, lateral and septal tricuspid annular systolic and diastolic velocities (Sa, Ea, Aa & Ea/Aa), and RV myocardial systolic and diastolic velocities at the basal RV segment (RVSm, RVEm, RVAm & RVEm/Am). Serum ferritin (Fe) level was measured in B-Th pts who were divided accordingly into 2 groups; G1 (10 pts) with Fe = or > 2000 ug/l & G2 (20 pts) with Fe <2000 ug/l. Pts with RVP >30 were considered to have pulmonary hypertension (PH).

Results: variable degrees of TR were detected in 18 pts with B-Th (8 pts from G1 and 10 pts from G2). Trivial TR was detected in 13 NL subjects. RVEDD, RVESD & RVP were higher and RVFS was lower in B-Th compared to NL (p=0.05, p<0.05, p<0.01 & p=0.05 respectively). Sa of both lateral and septal tricuspid annulus and RVSm were not significantly different in B-Th from NL. In contrast, compared to NL subjects, pts with B-Th had higher Aa at the lateral and septal tricuspid annular sites (p<0.0001 & p<0.005 respectively) and lower Ea/Aa at both annular sites (p<0.005 & p<0.0005 respectively). RVAm was higher (p<0.0005), and RVEm/Am was lower (p<0.0005) in B-Th compared to NL subjects. Patients with higher serum Fe level (G1) had significantly higher RVP compared to G2 (44.6 ± 17.3 vs 27.2 ± 3.7, p=0.001), higher RVEDD (2.2 ± 0.3 vs 1.7 ± 0.4 cm, p<0.005), and higher RVESD (1.8 ± 0.3 vs 1.4 ± 0.3 cm, p<0.005). Both Sa at the lateral annular site and RVSm were lower in G1 than G2 (10.0 ± 0.7 vs 11.4 ± 2.1 cm/sec, p<0.05 and 10.4 ± 0.9 vs 12.0 ± 2.3 cm/sec, p<0.05 respectively). PH was significantly associated with high serum Fe level (p= 0.015).
Conclusion: patients with beta thalassemia have RV diastolic dysfunction, pulmonary hypertension is common, and the presence of RV systolicdysfunction in these patients is related to the higher level of serum ferritin.

P2196 Survival in thalassemia major patients: prognostic value of Doppler-demonstrated left ventricular restrictive filling pattern

G. Efthimiadis[1], H. Hassapopoulou[2], D. Tsikaderis[1], H. Karvounis[1], G. Giannakoulas[1], G. Parharidis[1], G. Louridas[1]. *[1]AHEPA Hospital, 1st Department of Cardiology, Thessaloniki, Greece; [2]AHEPA Hospital, Thalassemia Unit, Thessaloniki, Greece*

Thalassemia major carries an adverse cardiovascular prognosis.
Aim: To evaluate the prognostic significance of Doppler-demonstrated left ventricular restrictive filling pattern in patients with thalassemia major.
Methods: We studied a cohort of 45 asymptomatic transfusion-dependent adult patients with thalassemia major with normal systolic function. All patients were receiving chelation therapy with desferrioxamine. The patients were regurarly evaluated by clinical examination and Doppler-echocardiographic studies throughout the 15 year follow-up period. Patients were categorized into two groups according to baseline data; those with and those without left ventricular restrictive filling pattern. We analyzed the incidence of cardiac death in the two groups. The impact of chelation therapy on ventricular filling pattern and survival was also examined.
Results: Nineteen patients (42.2 percent) had a restrictive and 26 (57.8 percent) a non-restrictive filling pattern of the left ventricle. During follow-up 11 patients died due to cardiac causes. Eight of the latter (72.8 percent) initially had a restrictive and 3 (27.2 percent) a non-restrictive filling pattern. Chi-square test of independence showed that left ventricular restrictive filling pattern was significantly associated with mortality (x2=5.55, p=0.018). By Kaplan–Meier survival analysis, mean survival in patients with left ventricular restrictive pattern was 11.1±1.2 years (confidence interval: 8.7-13.4 years), while mean survival in patients with non-restrictive filling pattern was 14.3±0.5 years (confidence interval: 13.3-15.2 years). The 15-year cumulative survival rate was 58% in patients with restrictive filling pattern of the left ventricle and 88% in patients with normal filling pattern, with log-rank statistic=6.02 (p=0.014). Poor compliance with chelation therapy was significantly associated both with left ventricular restrictive filling pattern (p=0.007) and high cardiovascular mortality (p=0.003).
Conclusions: Left ventricular restrictive filling pattern is an important predictor of cardiac mortality in patients with thalassemia major. Poor compliance with chelation therapy was found to be significantly associated with restrictive physiology and cardiac mortality.

P2197 Epicardial adipose tissue measured by echocardiography is an useful parameter predicting coronary artery disease

S.G. Ahn, J.H. Yoo, H.W. Han, J.H. Choi, S.Y. Choi, M.H. Yoon, S.J. Tahk, J.H. Shin. *Ajou University Medical Center, Departement of Cardiology, Suwon, Korea, Republic of*

Background: The significance of epicardial adipose tissue (EAT), which is frequently observed during transthoracic echocardiographic examination, is not well known. Aim of this study was to investigate the relationship of epicardial adipose tissue to coronary artery disease (CAD) and other established CAD risk factors.
Methods: We measured EAT thickness consecutively and prospectively in 148 patients (56 ± 11, 72 males) who underwent coronary angiography due to various reasons. EAT thickness were obtained on the free wall of right ventricle above aortic valve in parasternal long-axis view and short-axis view at mitral valve level at end-diastole. Anthropometric parameters such as body mass index, waist circumference, the percentage of total and truncal fat mass using dual-energy X-ray absorptiometry scanning and metabolic parameters such as plasma lipid profiles, high sensitivitity C-reactive protein (hs-CRP), fibrinogen, fasting glucose, insulin and cardiac enzymes were measured to evaluate the correlation with EAT.
Results: EAT thickness was increased significantly in 64 CAD patients compared with in patients with normal coronary artery (46.5 ± 32.9 mm vs. 23.8 ± 21.9 mm, p < 0.001). EAT thickness had a good correlation with age (r = 0.38, p < 0.001), the number of CAD risk factor (r = 0.248, p < 0.009), HDL cholesterol (r = - 0.29, p < 0.001), hs-CRP (r = 0.27, p = 0.006), fibrinogen (r = 0.25, p = 0.011), the presence of abdominal obesity (r = 0.31, p = 0.004), the percentage of truncal fat (r = 0.32, p = 0.017) and the presence of CAD (r = 0.38, p < 0.001). Receiver operating curve analysis revealed a fair correlation with the presence of CAD (Area under the curve 0.742, 95% confidence interval 0.663 to 0.821, p < 0.001). The best cut-off value of EAT thickness to predict CAD was 25.4 mm with 72% of sensitivity and 65% of specificity.
Conclusions: EAT, which can be measured easily during echocardiographic examination, could be not only a new useful parameter of CAD risk but also a new predictor of CAD. We suggest that it needs to be included the measurement of EAT thickness at routine echocardiographic examination.

P2198 Silent cardiac involvement in relation to age and activity in patients with rheumatoid arthritis: an echocardiographic study

M. Abd Elghany, M. Mokhtar, H. Darwish, O. Ragab, M. Abdallah. *Cairo, Egypt*

Introduction: Rheumatoid arthritis (RA) is a systemic disease that involves many organs. It is frequently accompanied by cardiac affection which can take many forms related to vasculitis and or granulomatous proliferation. Subclinical cardiac involvement may exist in a variable degree among both adult and juvenile RA patients. Its relation to disease activity and duration is not clear.
Methodology: This study was conducted on 60 patients fulfilling the American Rheumatism Criteria for the diagnosis of RA. Half of the patients had adult RA and half had juvenile RA. All had no symptoms of cardiac diseases. An echo Doppler study was performed and findings were correlated with age, onset, type and activity of RA.
Results: Silent cardiac involvement was found in 19 out of 30 adult RA patients(63%), in the form of diastolic dysfunction in 14 (46%), valvular lesions in 8 (26%) and pericardial effusion in 2 cases (6%). While in juvenile RA patients, 14 out of 30 (46%), had silent cardiac affection; in the form of diastolic dysfunction in 5 (16%) and valvular lesions in 12 (40%). A higher incidence of cardiac affection was detected in polyarticular onset RA (50%), compared to systemic onset (36%) and oligoarticular onset (14%). Active RA patients had more silent cardiac affection compared to non active cases (P<0.001).
Conclusion: Silent cardiac involvement in the form of echocardiographically detected diastolic dysfunction and valvular lesions is common among RA patients, particularly, adults, those with long disease duration, those who have polyarticular onset of the disease with increased number of swollen and tender joints and those with active disease.

P2199 Aortic stiffness is associated with haemodialysis-induced hypotension in patients undergoing chronic haemodialysis

D. Duman[1], B. Erdogan[2], R. Deirtunc[2], M. Karakas[2], B. Karadag[3]. *[1]Haydarpasa Numune Hospital, Department of Cardiology, Istanbul, Turkey; [2]Haydarpasa Numune Hospital, Internal Medicine, Istanbul, Turkey; [3]IU Cerrahpasa Medical School, Cardiology, Istanbul, Turkey;*

Aim: This study was designed to investigate the hypothesis that hemodynamic instability during hemodialysis frequently observed in patients undergoing chronic hemodialysis may be related to impaired aortic elastic properties.
Methods: Aortic elastic properties and left ventricular functions were evaluated in 61 chronic hemodialysis patients with (group I; n = 28) and without symptomatic hypotension episodes (group II; n = 33) during hemodialysis. Aortic strain and distensibility were calculated from the echocardiographically derived thoracic aorta diameters, and the measurement of pulse pressure obtained by cuff sphygmomanometry. Logistic regression analysis was performed in a model that includes clinical and biochemical data and aortic elastic properties measurements.
Results: Group I patients in comparison to group II patients, had increased aortic diameters (p < 0.01), lower mean aortic strain (5.0 ± 3.8% vs. 7.8 ± 3.0%, p < 0.005) and distensibility (2.3 ± 1.9 vs. 3.2 ± 1.7 cm^2 /dyn/10^3, p < 0.01). In a logistic regression model including clinical data and aortic elastic properties measurements, left ventricular systolic dysfunction, ischemic heart disease, decreased aortic strain and distensibility were found to be the main predictors of hemodialysis-induced hypotension.
Conclusions: These data suggest that hemodialysis-induced hypotension is strongly associated with impaired aortic elastic properties. Patients with ischemic heart disease, reduced left ventricular systolic function and impaired aortic elastic properties may have higher risk for hemodynamic instability during hemodialysis.

P2200 Abnormal left ventricular longitudinal contractile reserve in patients with end stage renal disease: assessment with pulsed-wave tissue Doppler exercise echocardiography

J.-W. Ha[1], S.W. Kang[2], J.M. Kim[2], J.A. Ahn[2], S.M. Kang[2], S.J. Rim[2], N. Chung[2]. *[1]Yonsei Cardiovascular Center, Cardiology Div., Int. Medic., Seoul, Korea, Republic of; [2]Yonsei Cardiovascular Center, Cardiology division, Seoul, Korea, Republic of*

Background: In patients with end-stage renal disease (ESRD), left ventricular

(LV) hypertrophy is common due to concomitant hypertension. LV longitudinal contraction results in apical displacement of the mitral annulus and it can be quantified using pulsed wave tissue Doppler imaging. Since pathologic LV hypertrophy is associated with myocardial fibrosis, particularly in the subendocardium, we hypothesized that mitral annular systolic velocity at rest and during exercise would be abnormal in patients with ESRD.
Methods and Results: Septal mitral annular systolic velocity (S') was measured at rest and during graded supine bicycle exercise (25W, 3 minutes increments) in 23 patients (19 male, mean age 52 years) with ESRD and 58 subjects (22 male, mean age 57 years) with control. LVEF was calculated from the echocardiographic m-mode from short axis image. LVEF at rest was significantly lower in patients with ESRD compared with that of control (59±11 vs 67±9%, p=0.0047). Although there was no significant difference in S' at rest between the groups (6.3±1.2 vs 6.3±1.1 cm/s, p=0.83), S' during exercise (6.9±1.4 vs 8.0±2.2 cm/s at 25 W, p=0.0109; 7.6±1.6 vs 9.1±2.1 cm/s at 50 W, p=0.0065) and change of S' with exercise (0.6±1.2 vs 1.6±1.6 cm/s from base to 25W, p=0.0054; 1.4±1.7 vs 2.6±1.7 cm/s from base to 50W, p=0.02) was significantly lower in patients with ESRD compared with control.
Conclusion: In conclusion, even though resting longitudinal contraction of patients with ESRD were comparable to the control, their longitudinal contractile reserve during exercise is reduced. The assessment of longitudinal function and functional reserve should be incorporated for the comprehensive evaluation of LV systolic function and maybe the better parameter for earlier detection of LV systolic dysfunction.

P2201 Tissue Doppler parameters predict outcome in chronic kidney disease

D. Rakhit[1], N. Isbel[2], T.H. Marwick[2]. [1]*Brisbane, Australia;* [2]*University of Queensland, Brisbane, Australia*

Background: cardiovascular disease is a major cause of morbidity and mortality in pts with chronic kidney disease (CKD). In these pts left atrial (LA) enlargement, LV hypertrophy, diastolic abnormalities and subclinical LV dysfunction are common. We sought whether LA size, LV mass, abnormal filling or tissue velocity were predictive of cardiac events (cardiac death, MI or acute coronary syndrome) or all cause mortality.
Methods: resting 2D echocardiograms were obtained in 155 pts with CKD (mean age 55yrs, 87 male, and 93 dialysis-dependent). LA volume was calculated from the minor axis in the parasternal long axis, and minor and major axes in the 4 chamber view. LV mass was calculated using ASE guidelines and indexed for body surface area. Colour tissue Doppler images of the septal and lateral mitral valve annulus were used to measure myocardial velocity during systole (Sm), early filling (Em), and late filling (Am).
Results: mean follow up was 1.7 yrs. There were 24 deaths and 20 cardiac events. Mean end diastolic dimension was 4.7 ± 0.9 cm, septal wall thickness 1.4 ± 0.9 cm. posterior wall thickness 1.2 ± 0.3 cm, LA volume 40.0 ± 18.8 cm^3, LV mass index 139.0 ± 57.3 g/m^2, average Sm 5.6 ± 1.9 cm/s, average Em 5.4 ± 2.3 cm/s and average Am 6.8 ± 1.8 cm/s. Average Em was the only independent predictor of death. Independent predictors of a composite of death plus cardiac events were average Sm and septal wall thickness (table).

	Death (Chi-square 9.3, p=0.002)	Death plus Events (Chi-square 12.2, p=0.002)
Em (cm/s)	HR 0.72, 95% CI 0.58–0.89, p=0.002	
Sm (cm/s)		HR 0.73, 95% CI 0.58–0.92, p=0.008
Septal wall thickness (cm)		HR 2.6, 95% CI 1.2–5.7, p=0.02

Conclusion: abnormal tissue velocities and septal wall thickness can predict events in pts with CKD.

P2202 Left ventricular function after endoscopic thoracic sympathectomy

C. Sousa[1], S. Goncalves[2], C. Amaro[2], P. Costa[2], L. Pereira[2], J. Cruz[3], F.J. Pinto[1]. [1]*Lisbon University Medical School, Cardiology Department, Lisbon, Portugal;* [2]*Univ Hosp Sta Maria, Dpt Cardiology, Lisbon, Portugal;* [3]*Univ Hosp Sta Maria, Cardiothoracic Surgery, Lisbon, Portugal*

Background: Endoscopic thoracic sympathectomy at T2-T4 is the current surgical treatment for primary axillary and palmar hyperhidrosis and facial blushing refractory to conventional treatment. However, the potential repercussion of thoracic sympathectomy on global and regional left ventricular function is unknown.
Objective: To assess the repercussion of thoracic sympathectomy on systolic and diastolic left ventricular function.
Methods: Comparative prospective longitudinal study of a group of patients that underwent thoracic sympathectomy, assessed before and 6 months after surgery. A complete echocardiographic study, including M Mode and 2D (left atrium and left ventricle dimensions, ejection fraction by Simpson's rule) Doppler flow (transmitral: e and a waves, e/a, deceleration time; aortic velocities) and tissue Doppler (septal and lateral mitral annulus: e', a', e'/a', e/e', systolic velocity) was performed in each patient.
Results: Thirty four patients (24 female and 10 male, mean age 25±6 years old) were studied at baseline and 6 months after surgery. The different variables that were analysed showed no significant differences except the following:

Table 1

Variables	Basal Study	6 months follow up	p
Heart rate	70±12	65±9	0.026
Ejection Fraction	76±6	73±5	0.002
e/a	2.25±0.6	1.97±0.4	0.03

Conclusions: In this group of patients that underwent thoracic sympathectomy there were no significant changes in global and regional left ventricular function during a follow up period of 6 months. The only observed changes may be only due to vagal predominance post operatively. Therefore, thoracic sympathectomy does not seem to affect LV function in the short run.

COMPUTERS IN CARDIOLOGY

P2203 Estimating heart rate variability using reveal plus EKG: validation using data collected from CARISMA

Messier[1], S. Lu[2], H. Huikuri[3], P.E. Bloch-Thomsen[4], R. Morch Olesen[4], L. Stylos[2], P. Talsma[5], D. Kaiser[2] on behalf of the CARISMA study team. [1]*LA BROQUE, France;* [2]*CRM research, Medtronic R&D, Minneapolis, United States of America;* [3]*Oulou University Hospital, cardiology, Oulou, Finland;* [4]*KAS Gentofte university, cardiology, Hellerup, Denmark;* [5]*Medtronic, Clinical research, Maastricht, Netherlands*

Heart rate variability (HRV) indices extracted from Reveal Plus devices (R+) could be useful in managing Risk Stratification in post-MI patients. The stored EKGs could be used for the prognosis of arrhythmic risk during the entire devices' service (> 2 years), eventually yielding "continuous" information on the autonomic system's evolution in specific pathologies. Technical limitations include short duration recordings (2 min EKG), low sampling rate (100 Hz) and non-linear compression (2:1 from 100 Hz). The extent of those limitations was established by comparing R+ derived HRV indices against those from corresponding 24-hour Holters (24Htr) taken during the 6 weeks post-MI follow-up of 288 patients in the CARISMA study.
Method: Over/under sensed triggered R+ episodes recorded on the same day as the reference 24Htr without arrhythmic events were selected. The compressed EKGs were extracted from save-to-disk files and interpolated to 250 Hz using a cubic spline interpolation. QRS complexes were automatically detected using the algorithm described by Cao (2001). Ectopic and erroneously coded beats were filtered from the RR interval series by rejecting changes in RR intervals greater than 20%. Standard deviation of normal-to-normal intervals (SDNN) was calculated using the filtered RR interval series. The avg R+ SDNN indices were correlated against indices from the 24-Htr using standard linear regression.
Results: 399 automatically triggered R+ episodes from 53 patients were included in this analysis. Of these, 22 patients had more than 5 episodes (of 2 minutes each) sampled on the 24-hr Holter day, yielding a correlation coefficient to 0.78.

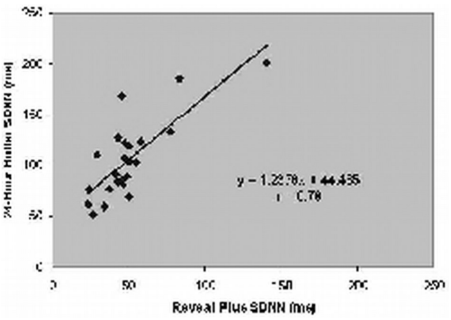


Figure 1

Conclusions: Signals obtained at the follow-up of the Reveal Plus can be processed to obtain Heart Rate Variability indices.

P2204 Inhibition of cardiac HERG channels by green tea flavenoid ECGC and grapefruit flavenoid morin: new mechanisms of blockade independent of the conventional binding sites

C.A. Karle[1], E.P. Scholz[1], C. Kiesecker[2], M. Pirot[1], D. Thomas[1], S. Kathofer[1], V.A.W. Kreye[3], E. Zitron[1]. [1]*Medical University Hospital Heidelberg, Department of Cardiology, Heidelberg, Germany;* [2]*Medical University Hospital Heidelberg, Department of Cardiology, Heidelberg, Germany;* [3]*University of Heidelberg, Dept. of Physiology and Pathophysiology, Heidelberg, Germany*

Background: Flavonoids are natural plant compounds, which occur ubiquitously in fruits and vegetables and reach high concentrations in tea and wine. In several epidemiological studies, a high nutritional intake of flavonoids was associated with

a reduced cardiovascular mortality. We have demonstrated in a previous study (Zitron et al., Circulation 2005 in press) that flavonoids are specific antagonists of cardiac HERG channels and that dietary intake of flavonoids may influence cardiac electrophysiology. Here we show that green tea flavonoid ECGC and grapefruit flavonoid morin inhibit HERG channels with highly unusual pharmacological properties and that both compounds do not bind to the conventional pore binding site.

Methods: HERG currents expressed in HEK cells and in Xenopus oocytes were measured with whole-cell patch clamp and two-microelectrode voltage-clamp.

Results: ECGC inhibited HERG currents in HEK cells with an IC50 of 8 micromol/l. The IC50 of morin measured in Xenopus oocytes was 111.3 micromol/l. The inhibitory effect of neither compound was reversible upon washout.

In general, HERG antagonists bind to the pore binding site Tyr-652/Phe-656. We tested the effect of ECGC and morin on HERG channels in which this binding site had been inactivated by mutating these residues to alanines. To our surprise, the potency of the inhibitory effect of ECGC and morin on these mutated channels was identical to the wild type channels.

Moreover, morin also induced a drastic shift of HERG current activation curves to more positive potentials. In mutated HERG channels lacking protein kinase A phosphorylation sites, the identical effect could be observed. Furthermore, this effect could not be suppressed by coapplication of proteinkinase inhibitor staurosporin.

Morin and ECGC also exhibited a positive use-dependence and a strong voltage-dependence of effects. Both compounds blocked HERG channels in the open and inactivated states.

Conclusions: Flavonoids ECGC and morin exhibit highly unusual properties of HERG channel blockade. In contrast to all HERG antagonists that have been characterised to date, these compound do not bind to the aromatic pore binding site Phe-656. Furthermore, morin induces a drastic modification of HERG activation properties without the involvement of protein kinases. These results suggest the existence of additional binding sites in the HERG channel structure which may be associated with the regulation of its biophysical properties.

POSTER SESSION 4

MODERATED POSTERS: HYPERTENSION/MYOCARDIAL-PERICARDIAL-CONGENITAL HEART DISEASE/SURGERY

P2205 Effect of angiotensin II receptor blockade on autonomic nervous system function in patients with essential hypertension

H. Krum[1], E. Lambert[2], E. Windebank[3], D.J. Campbell[4], M. Esler[2]. *[1]Green Lane Hospital, Auckland City Cardiovascular Research Unit, Auckland, New Zealand; [2]Baker Heart Research Institute, Melbourne, Australia; [3]Monash University, Dept of Epidemiology & Prev. Medicine, Melbourne, Australia; [4]St Vincents Institute of Med Research, Melbourne, Australia*

It has been postulated angiotensin receptor blockers (ARBs) reduce sympathetically-mediated increases in vascular tone. However, much of these data have been derived from pre-clinical models, with little evaluation in man. The present study therefore compared the effects of ARBs to placebo on autonomic function in patients with mild to moderate essential hypertension.

Patients were prospectively randomised to eprosartan 600 mg mane, losartan 50 mg mane or placebo in a cross-over study design. Each active period was 4-weeks with a 2-week wash-out. Autonomic assessments (plasma catecholamines, tritiated norepinephrine kinetics, microneurography, blood pressure (BP) and heart rate responses to cold pressor test (CPT) and heart rate variability (HRV) measures of parasympathetic activity, plasma angiotensin II measurement, was performed at the end of each period.

Compared to placebo, both ARBs reduced blood pressure and increased angiotensin II levels similarly, indicative of equivalent AT1 receptor blockade. There were no significant differences across the three treatment arms in plasma norepinephrine levels (supine or tilted), norepinephrine spillover rate or haemodynamic response to CPT. Sympathetic nerve firing rates did not change. Furthermore, there were no significant differences with respect to HRV measures between groups.

Comprehensive assessment of the autonomic nervous system in these patients demonstrated that neither eprosartan nor losartan exerted material anti-adrenergic effects, either on sympathetic outflow from the brain, or on presynaptic modulation of norepinephrine release. The findings of the present study therefore do not support earlier pre-clinical data suggesting that sympatho-inhibitory effects of ARBs may substantially contribute to BP lowering with these agents.

P2206 The effect of losartan versus atenolol on structure and function in subcutaneous small arteries in essential hypertension. A life substudy

M.H. Olsen[1], K. Wachtell[2], C. Aalkjaer[3], M. Mulvany[4], J. Rokkedal[2], H. Dige-Pedersen[5], H. Ibsen[2]. *[1]Niva, Denmark; [2]Glostrup University Hospital, Department of Internal Medicine, Copenhagen, Denmark; [3]Institute of Physiology, Århus University, Denmark; [4]Institute of Pharmacology, Århus University, Denmark; [5]Glostrup University Hospital, Clinical Physiol. and Nuclear Medicine, Glostrup, Denmark*

Background: Whether angiotensin II receptor blockers normalize vascular remodeling and improve endothelial function compared to beta-receptor blockers is unknown.

Methods: In 42 LIFE patients with hypertension and ECG left ventricular hypertrophy we isolated subcutaneous arteries (lumen=0.1-0.5 mm) and measured media/lumen ratio (M/L), nitroprusside- (NIR) and acetylcholine-induced relaxation (AIR) with a wire-myograph at baseline and after one year of antihypertensive treatment with losartan- vs. atenolol-based regimens. Furthermore, we measured 24-hour ambulatory systolic blood pressure (24-hour-SBP), intima-media thickness in the brachial (IMTb) and carotid artery (IMTc) with ultrasound.

Results: Blood pressures were reduced significantly and to the same degree in the two groups without any significant changes in the small arteries except for lumen (Table 1). However, M/L ratio decreased insignificantly in the losartan group whereas it increased insignificantly in the atenolol group creating an almost significant difference at one year (9.3% vs. 11.3%, P=0.08). The same diverging trend was seen in sensitivity to NIR (6.35 vs. 6.17, P=0.07). At baseline high M/L was associated with high IMTb (r=0.39, $P<0.05$), high IMTc (r=0.45, $P<0.05$), but not high 24-hour-SBP (r=0.24, NS).

Table 1

	Baseline		Year 1	
	Atenolol	Losartan	Atenolol	Losartan
No. of patients	20	22	15	14
Lumen (um)	284	276	282	313, $P<0.01$
Media (um)	29	27	31	28
Media/lumen ratio (%)	10.4	10.3	11.3	9.3
Maximal AIR (%)	82	88	87	94
Sensitivity to AIR	7.51	7.44	7.38	7.50
Maximal NIR (%)	92	86	91	96
Sensitivity to NIR	6.45	6.02	6.17	6.35

Conclusion: One year of losartan- vs. atenolol-based anti-hypertensive treatment did not normalize vascular remodeling or significantly improve endothelial function in subcutaneous small arteries in patients with hypertension and left ventricular hypertrophy. However, we observed diverging trends in favor of losartan.

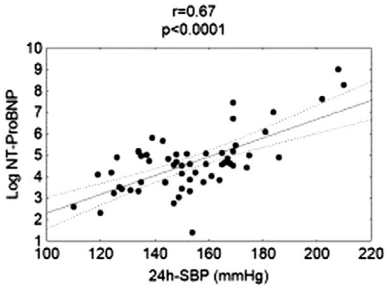
P2207 Systolic blood pressure is a major determinant of plasmatic N-terminal pro-brain natriuretic peptide (NT-ProBNP) concentrations in hypertension

C. Mouly Bertin[1], P. Lantelme[1], M.O. Rial[1], G. Bricca[2], M. Vincent[2], H. Milon[1]. *[1]Hopital de la Croix Rousse, Service de cardiologie, Lyon, France; [2]Université Claude Bernard Lyon 1, Laboratoire de physiologie, UMR MA 103, Lyon, France*

Objectives: Brain Natriuretic Peptide (BNP) and NT-ProBNP are raised in the presence of left ventricular hypertrophy (LVH) and diastolic dysfunction (DD). Thus, it has been suggested that BNP levels could be related to cardiac remodelling in hypertension. However, the respective relationships between BNP, blood pressure, LVH and DD remain unclear. The aim of this study was to identify the determinants of BNP excretion in hypertensive patients.

Methods: We included 65 consecutive patients, referred for hypertension work-up with an ejection fraction $\geq$ 50%. The following parameters were measured: 24-hour blood pressure, echocardiographic left ventricular mass index (LVMI), Doppler indices of diastolic function, and plasma NT-ProBNP (immunoassay).

Results: Values reported are means $\pm$ SD. Mean age was 53 $\pm$ 14 years and 41% of the patients were females. Twenty-four-hour systolic blood pressure (24h-SBP) was 153$\pm$21 mmHg and 24-hour diastolic blood pressure (24h-DBP) was 91$\pm$11 mmHg. LVH was found in 47% and DD in 67% of the patients. NT-ProBNP was on average 369 $\pm$ 1135 pg/ml. It was higher in patients with LVH (p=0.002)



Relation between NT-ProBNP and 24h-SBP

and in patients with DD ($p<0.0001$). NT-ProBNP was strongly correlated with 24h-SBP (r=0.67, $p<0.0001$) who remained the strongest correlate of NT-ProBNP ($p<0.001$), even after adjustment for confounders including LVMI and DD. The relation between 24h-DBP and NT-ProBNP was no more significant in a multivariate analysis.

Conclusion: the present study confirms that, in a group of hypertensives, LVH and DD account in part for plasma NT-ProBNP levels. The new result is the tight correlation between 24h-SBP and NT-ProBNP. This striking finding suggests that NT-ProBNP not only depends on ventricular mass and diastolic stretch but also on systolic wall stress.

P2208 Changes in the extracellular matrix of subcutaneous small resistance arteries of patients with primary aldosteronism

C. De Ciuceis[1], S. Paiardi[1], L. Rodella[2], E. Porteri[1], R. Rezzani[2], R. Bianchi[2], D. Rizzoni[3], E. Agabiti Rosei[1]. *[1]University of Brescia, Dept. of Medical and Surgical Sciences, Brescia, Italy; [2]Chair of Human Anatomy, University of Brescia, Brescia, Italy; [3]Brescia, Italy*

Objective: It has been previously demonstrated that aldosterone may possess a strong profibrotic action in vitro and in animal models of genetic or experimental hypertension both at cardiac and vascular level. However, no direct demonstration of such a profibrotic action in the human microcirculation is presently available. We have investigated 13 patients with primary aldosteronism, 7 patients with essential hypertension and 10 normotensive controls. All subjects were submitted to a biopsy of subcutaneous fat from the gluteal or the anterior abdominal region. Small resistance arteries were dissected and mounted on an isometric myograph, and the tunica media to internal lumen ratio was measured. In addition, the total collagen content within the tunica media was detected (Sirius red staining and image analysis). Collagen subtypes were evaluated using polarized light microscopy; under this condition collagen fibers of different thickness (type I and type III) are differently coloured.

Results: Results are reported in the Table (*$p<0.05$, ***=$p<0.001$ vs Normotensives, #$p<0.01$ vs. Essential hypertension). The media to lumen ratio was significantly increased in primary aldosteronism (0.095±0.02) and in essential hypertension (0.101±0.03) compared with normotensive controls (0.07±0.02, $P<0.05$ at least in any case). Clinic blood pressure values were similar in primary aldosteronism (142/89±10/7) and in essential hypertension (151/86±8/10), and greater than in normotensive controls (115/80±11/6, $P<0.05$ at least in any case). Total collagen and type III vascular collagen was significantly greater in primary aldosteronism than in essential hypertension. Normotensive controls had less total and type III collagen in respect with the two hypertensive groups (see table). Type I collagen was greater in primary aldosteronism than in normotensive controls.

	Total collagen (%)	Type I collagen (%)	Type III collagen (%)
Primary aldosteronism	7.81±2.91 ***#	2.21±1.01*	5.92±1.73 ***#
Essential hypertension	7.00±2.46 ***	2.31±1.06	5.25±1.64 ***
Normotensive controls	3.23±1.63	2.51±1.03	1.60±0.64

Our results indicate that, in small resistance arteries of patients with primary aldosteronisms, a pronounced fibrosis may be detected, even more evident that in blood-pressure matched patients with essential hypertension.

P2209 Arterial stiffness is gradually associated with diverse inflammatory markers in newly diagnosed essential hypertensive subjects: linking pro-inflammatory mechanisms with vascular dysfunction

K. Dimitriadis, C. Tsioufis, M. Toutouza, D. Tousoulis, V. Chatzistamatiou, I. Vlasseros, C. Stefanadis, I. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: Arterial stiffening is a recognised marker of atherosclerosis progression, while low-grade inflammation is associated with adverse cardiovascular outcome. In this study, we examined the plausible correlations between large artery stiffness and, plasma inflammatory markers such as inteurleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and E-selectin in essential hypertensive patients.

Methods: 148 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [98 men, mean age=49 years, office blood pressure (BP)=150/97 mmHg], were divided into three groups according to carotid to femoral pulse wave velocity (PWV) values, by means of a computerized method (Complior SP): Group A (PWV≤7.8 m/sec), group B (PWV=7.9-8.7 m/sec) and group C (PWV>8.7 m/sec). Additionally, venous blood samples were drawn for estimation of lipid profile, IL-6, TNF-a, and E-selectin concentrations.

Results: Patients in group A (n=55) compared to subjects in group B (n=54) and C (n=39) had lower office systolic BP (146.4±11 vs 150.3±14 vs 157.1±14 mmHg, respectively; $p<0.05$ for all cases), while did not differ regarding metabolic profile (p=NS). Moreover, LVMI was more increased in group C than in group B and A (121.7±12 vs 114.7±16 vs 102±16 g/m^2, respectively; $p<0.0001$ for all cases). In the entire population, PWV was correlated with age (r=0.235, $p<0.001$), BMI (r=0.233, $p<0.05$), waist to hip ratio (r=0.261, $p<0.05$), office systolic BP (r=0.221, $p<0.05$), and TNF-a (r=0.189, $p<0.05$), while IL-6 was associated with BMI (r=0.221, $p<0.05$) and office systolic BP (r=0.226, $p<0.005$). Moreover, TNF-a and E-selectin were related to BMI (r=0.214 and r=274, respectively; $p<0.05$ for both cases). Furthermore, patients in group C exhibited higher levels of IL-6 compared to group B and A (0.8±0.3 vs 1.3±0.5 vs 1.8±0.1 pg/ml, respectively; $p<0.005$ for all), greater levels of TNF-a (1.2±0.3 vs 2.5±0.1 vs 3.5±0.07 pg/ml, respectively; $p<0.0001$ for all) and more increased E-selectin concentrations (43.1±1.7 vs 48.7±2.4 vs 55.3±2.1 ng/ml, respectively; $p<0.05$ for all). Analysis of covariance revealed that IL-6, TNF-a and E-selectin values remained significantly different between groups after adjustment for confounding factors ($p<0.05$).

Conclusions: In newly diagnosed essential hypertension, there is an augmentation in IL-6, TNF-a and E-selectin values throughout increasing PWV tertiles. These findings suggest that arterial stiffening is closely related to subclinical inflammatory processes, in this setting.

P2210 Sympathetic activation and baroreflex dysfunction in the metabolic syndrome

G. Grassi[1], G. Seravalle[2], R. Dell'Oro[1], F. Quarti Trevano[1], A. Facchini[1], F. Scopelliti[1], G.B. Bolla[3], G. Mancia[1]. *[1]Universita' Milano-Bicocca in, Dipartimento di Medicina, Monza, Italy; [2]Istitute Auxologico Italiano, Milan, Italy; [3]Centro Interuniversitario Fisiologia, Milan, Italy*

Purpose: Previous studies have shown that vascular, metabolic and inflammatory alterations characterize metabolic syndrome (MS). Whether the alterations include sympathetic hyperactivity is not clearly established. The present study was aimed at clarifying this issue and at determining whether metabolic or reflex mechanisms might be responsible for the possible adrenergic dysfunction.

Methods: In 43 healthy controls (C, age:48.2±1.0 yrs, mean±SEM) and in 48 untreated age-matched subjects with MS (ATP III criteria) we measured, along with anthropometric and metabolic variables (cholesterol, tryglicerides, insulin, glucose and HOMA index), beat-to-beat arterial blood pressure (BP,Finapres), heart rate (HR, ECG), venous plasma norepinephrine and epinephrine (NE and E,HPLC) and efferent postganglionic muscle sympathetic nerve traffic (MSNA, microneurography) at rest and during baroreceptor manipulation (vasoactive drugs infusion technique).

Results: Body mass index, waist circumference, BP, cholesterol, tryglicerides, insulin and HOMA index values were greater in subjects with MS than in C, whereas HDL values were lower. MSNA was significantly greater in subjects with MS than in C both when expressed as bursts incidence over time (43.4±1.6 vs.31.5±1.4 bs/min, $p<0.01$) or when corrected for HR (61.1±2.6 vs. 43.8±2.8 bs/100hb, $p<0.01$). MSNA was greater than in controls also when MS did not include hypertension and mean arterial pressure was superimposable in the 2 groups (C:43.8±2.8 vs. MS:56.3±3.0 bs/100hb). Compared to C, baroreflex-HR and -MSNA sensitivity was significantly impaired in MS, the average reduction amounting to about 32%. MSNA correlated positively with BMI (r=0.42, $p<0.001$), waist circumference (r=0.46, $P<0.001$) and HOMA index (r=0.49, $P<0.001$), negatively with baroreflex sensitivity (r=-0.44, $p<0.001$) but it showed no correlation at all with serum tryglicerides, total cholesterol or HDL-cholesterol values. Plasma NE was slightly but not significantly greater in subjects with MS than in C (264.3± 31 vs. 236.5±26 pg/ml, P=NS), this being the case also for plasma E (22.5±4 vs.19.7±3 pg/ml, P=NS).

Conclusions: These data provide evidence that MS is characterized by sympathetic overactivity. They also show that the sympathetic activation is not limited to individuals in which MS is accompanied by hypertension but is detectable also when BP is normal. They finally suggest that the neuroadrenergic abnormalities depend on insulin resistance as well as on baroreflex alterations.

P2211 Defective nNOS-dependent central control of blood pressure and heart rate in caveolin-1 deficient mice

F. Desjardins, M. Pelat, C. Dessy, O. Feron, J.L. Balligand. *Universite Louvain (UCL), Dept. of Medicine, Pharmacology Unit, Brussels, Belgium*

Endothelial NO synthase (eNOS) is negatively regulated by the caveolar protein, caveolin-1 (cav-1) in endothelial cells. More recently, a similar interaction has been described for the neuronal NOS (nNOS) in vitro. The impact of cav-1 deletion on the central (nNOS-dependent) regulation of blood pressure and heart rate in vivo has however, never been studied.

Using mice genetically deficient in cav-1 (and WT littermate as controls), we recorded systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) with implanted miniaturized telemetry devices. SBP variability (SBPV) and HR variability (HRV) were measured by spectral analysis using fast Fourier transformation, at baseline and in response to pharmacologic agents infused in vivo. Subcellular localization of cav-1 and nNOS was identified by sucrose gradient fractionation in brain tissue extracts.

Cav-1 KO mice had higher DBP (96.9±1.7 vs 89.6±1.1 mmHg) and HR (507±7.2 vs 476±64 bpm; both $p<0.05$) compared to WT (n=6 each). Spectral analysis showed an increase (+30%; $p<0.05$) in their SBPV in the low-frequency band (LF; 0.4-1.5Hz) indicating increased orthosympathetic drive and, accordingly, propranolol induced a more important decrease in HR in cav-1 KO mice (-216±33 vs -100±28 bpm). Conversely, atropine induced less tachycardia (+ 85±8.5 vs 155±6 bpm; $p<0.05$), suggesting a decreased parasympathetic tone. This was due to

defective central mechanisms since the response to carbachol, a direct agonist on muscarinic receptors on cardiomyocytes, was potentiated (+59%; $p<0.05$) in cav-1 KO mice. After selective inhibition of the neuronal isoform of NOS (nNOS) with L-VNIO, the activity of the orthosympathetic system (as reflected by variability in the LF band) increased by 44% ($p<0.05$) in WT mice, but was unchanged in the cav-1 KO mice, which links the hyperadrenergism to a defective pre-synaptic nNOS-dependent control in cav-1 KO mice. This was associated with a translocation of nNOS from lighter, caveolae-enriched membranes to heavier (non-caveolar) fractions in brain extracts of cav1-/-, as analyzed by isopycnic ultracentrifugation.
In conclusion, frequency analysis identifies a sympathovagal imbalance associated with defective central nNOS control in cav-1 KO mice probably due to mislocalization of nNOS. These findings highlight the functional importance of caveolin-1 regulation of NOS isoforms for cardiovascular homeostasis and identify this interaction as a potential therapeutic target in disease states with altered cav-1 abundance.

P2212 Cardiovascular effects of acute and prolonged hypobaric hypoxia in healthy subjects

G. Caldara[1], G. Bilo[1], A. Giglio[1], I. Riva[1], K. Styczkiewicz[2], A. Faini[1], D. Susta[1], G. Parati[3]. *[1]University of Milano-Bicocca, Cardiology, Ospedale S.Luca, IAI, Milano, Italy; [2]Ospedale San Luca, Istituto Auxologico Italiano, Milan, Italy; [3]S. Luca Hospital, Istituto Auxologico Italiano, Milano, Italy*

Hypoxia has important cardiovascular effects, but limited information is available on changes in integrated cardiovascular regulation induced by acute and prolonged hypobaric hypoxia in the same subjects. Aim of our study was to investigate this issue in the experimental lab and at high altitude.
Methods: In 19 healthy subjects (13 M, 6 F, age 40.1±12.6) blood oxygen saturation (pulse oxymetry) beat-by-beat blood pressure (BP, Portapres) and pulse interval (PI) were monitored over 30 min sequentially in supine, sitting and standing position during: 1) normoxia at sea level; 2) acute breathing of a gas mixture with 12% O2; 3) 4 day exposure to hypobaric hypoxia at high altitude (Queen Margherita Hut, QMH, 4559 m, Monte Rosa). Average systolic (S), diastolic (D) BP and PI values, their standard deviations (SD) and spontaneous baroreflex sensitivity (BRS) in the frequency (αLF and αHF coefficients) and in the time domain (slope of SBP and PI sequences, Seq) were computed. 24h ambulatory BP monitoring was performed in all subjects at sea level and at QMH, to assess BP and heart rate (HR) mean values and SD.
Results: see Table. 24h, Day and Night SBP, DBP and HR were higher at QMH than at baseline ($p<0.05$).

Table

N=19	Baseline	Acute	p	QMH Day2	p	QMH Day4	p
SBP (mmHg)	125.8±17.7	129.7±20.3	=0.07	134.6±15.4	N S	140.4±16.6	<0.01
DBP (mmHg)	67.7±10.1	69.5±12.6	NS	75.5±11.8	N S	82.0±15.4	<0.01
PI (msec)	920.9±200.0	820±170	<0.01	770.0±140.0	<0.01	800.0±110.0	<0.01
SBPSD (mmHg)	7.5±1.8	9.2±2.3	<0.05	6.9±1.3	NS	9.8±4.3	NS
PISD (ms)	67.8±37.8	66.4±20.0	<0.05	43.7±20.7	<0.05	55.2±35.7	NS
αLF (ms/mmHg)	9.2±5.5	7.9±4.2	NS	6.4±3.4	NS	8.5±6.3	NS
αHF (ms/mmHg)	13.0±7.1	10.3±5.1	<0.05	9.03±5.8	<0.05	12.1±10.8	NS
Seq (ms/mmHg *	9.85±5.1	8.9±4.7	<0.05	6.5±5.1	NS	8.1±7.25	NS

p values for comparisons vs baseline, * - hypertension/bradycardia sequences

Conclusions: Both acute and prolonged hypoxia induce an increase in BP and HR. In the early phase there is also an increase in BP variability, suggesting an increased sympathetic drive, and a reduced BRS, probably linked to chemoreflex activation, with a return towards baseline values on day 4. These findings may be relevant to the pathophysiology of mountain sickness and of diseases associated with chronic hypoxia.

TECHNICAL ASPECTS OF PCI

P2213 Treatment of long coronary lesions with stenting, cutting balloon and rotational atherectomy, immediate and long-term clinical results: multicenter long coronary lesions registry in Japan

S. Nakamura[1], H. Sato[1], O. Hirashima[1], N. Kurita[1], M. Hirose[1], K. Hozawa[2], S. Nakamura[3], J. Koyama[3]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Chiba Central Medical Center, Department of Cardiology, Chiba, Japan; [3]Secomedic Hospital, Department of Cardiology, Funabashi, Japan*

Background: The optimal percutaneous coronary intervention (PCI) for the treatment of long coronary lesions (more than 30 mm) is still unknown.
Methods: We compared 3 PCI strategies: primary stenting (Stent) (n=506, 588 lesions), Cutting Balloon angioplasty with spot stenting (CB+stent) (n=484, 545 lesions) and rotational atherectomy with spot stenting (Rota+stent) (n=456, 510 lesions) in 1,446 patients. All the stents were bare metal stents. Basic and clinical characteristics were similar among all groups.
Results: See table for immediate and long-term clinical results.

Table

	Stent (n=506)	CB+stent (n=484)	Rota+stent (n=456)
In-hospital			
Procedural success (%)	98.6	99.0	97.6
MACE at 30 days (%)	0	0	0
Lesion length (mean/mm)	33.3	34.5	34.9
Reference diameter (mean/mm)	2.89	2.79	2.81
Post MLD (mean/mm)	2.78	2.72	2.75
Angiographic follow-up at 6 months			
Restenosis (%)	32.5	*24.4	*25.7
TLR (%)	17.5	*17.5	*18.8

*$p<0.05$ vs Stent. MACE: major adverse cardiac event (death/CABG/MI), MLD: minimum lumen diameter, TLR: target lesion revascularization

Conclusion: In long coronary lesions, Cutting Balloon angioplasty with spot stenting and rotational atherectomy with spot stenting provide an advantage in terms of long-term angiographic and clinical outcomes and warrant randomized clinical trial.

P2214 Coronary bifurcation lesion: to stent one branch or both? a meta-analysis

G. Ferrante, G. Niccoli, C. Trani, F. Burzotta, M. Mazzari, A.G. Rebuzzi, R. Mongiardo, F. Crea. *catholic university of sacred heart, cardiovascular dept, rome, Italy*

Objectives: We conducted a meta-analysis of randomized and non randomized trials that addresses the effects of two strategies for the treatment of coronary bifurcation lesions: stent implantation only in the parent vessel with balloon angioplasty of the sidebranch (SA) versus stent implantation in both the parent vessel and the sidebranch (SS).
Background: From previous studies the relative merit of stenting and balloon angioplasty in coronary bifurcations in terms of clinical and angiographic outcomes is not completely known.
Methods: 8 trials (1748 patients) constitute the selected randomized and non randomized experience that compared SA vs SS, in terms of rates of death, myocardial infarction (MI), restenosis of main branch and side branch, target lesion revascularization (TLR) up to a mean follow up of 6-18 months after treatment. Drug eluting stents (DES) were used in 3 trials, bare stents in the other ones.
Results: Follow up death rates were not improved by the use of SS strategy [(0.64% vs 0.36%), fixed odds ratio (OR) 1.34, (95% CI) (0.41 to 4.41), $p < 0.63$] while MI rate was significantly higher in SS strategy group [(3.2% vs 1.21%), fixed OR 2.35, (1.12 to 4.93), $p < 0.02$]. Restenosis rate of the main branch, but not of the side branch, was significanty increased in SS group:[(31% vs 17.7%), random OR 2.02 (1.24 to 3.29), $p < 0.005$] and [(44.7% vs 25.9%), random OR 1.85 (0.8 to 4.28), p 0.15, respectively]. TLR rate was not significanty different between SS and SA groups [(32.6% vs 19.2%), random OR 1.7(0.71 to 4.08), $p < 0.23$]. In a pre-specified subgroup analysis we compared the two strategies when DES and bare stent were used. When considering only bare stent subgroup also restenosis of the side branch and TLR were significantly more common in the SS group: [(53.4% vs 27.2%), fixed OR 3.18 (2.52 to 4.01), $p< 0.00001$, for side branch;(39.7% vs 19.1%), random OR 2.58 (1.61 to 4.12), $p < 0.0001$, for TLR].
Conclusions: This meta-analysis supports the hypothesis that stenting the main branch with balloon angioplasty of the sidebranch in coronary bifurcation lesion is preferable to stenting both branches because of the higher follow up rates of MI and restenosis of the main branch if double stenting is performed. When bare stent is used, also restenosis of side branch and TLR rates are more common in double stenting group. A metaregression will help understand if this finding may depend on the type of the stent used: bare or DES, when more trials with DES comparing the two strategies will be avaible.

P2215 Outcome of PTCA in hospitals with and without on-site cardiac surgery backup

J. Carlsson[1], S. Schneider[2], J. Senges[2], U. Tebbe[3] on behalf of the ALKK study group. *[1]Lanssjukhuset, Medicinsk Klinik, Kalmar, Sweden; [2]Institut fur Herzinfarktforschung, Ludwigshafen, Germany; [3]Klinikum Lippe, Medizinische Klinik II, Detmold, Germany*

The requirement of on-site surgical back-up is a debated issue since the beginning of percutaneous transluminal coronary angioplasty (PTCA). US-american data have shown worse outcome in hospitals without surgical back-up (JAMA 2004;292:1961-68).
The data of a PTCA registry in Germany have been used to investigate the differences in outcome between hospitals with (SB) and without (NOSB) on-site surgical standby. The analysis included a total of 30635 procedures between January and December 2003 (14104 procedures in SB, 16531 in NOSB hospitals). The mean age of the patients was 66.6 (SB) and 66.8 years (NOSB; p=0.016). More patients in SB hospitals had a history of previous CABG (13.3% versus 8.9%; $p<0.0001$) while a third of all patients had undergone a previous PTCA without difference between hospital types. There was a higher percentage of patients with STEMI (22.9% versus 21.5%; $p<0.01$) and NSTEMI (15.9% versus 13.5%; $p< 0.001$) in NOSB hospitals. The percentage of patients with an ejection fraction $< 35\%$ was higher in NOSB than in SB hospitals (5.9% versus 4.5%; $p<0.001$).

Cardiogenic shock was more prevalent in NOSB than in SB hospitals (2.4% versus 1.8%; p<0.001).
Some unadjusted outcome data are listed in the table. After adjustment for differences in baseline risk no significant outcome differences were observable between SB and NOSB hospitals.

PTCA outcome (unadjusted)

	SB hospitals	NOSB hospitals	p-value
Death in connection with intervention	0.7%	0.8%	0.17
Death in-hospital	1.1%	1.6%	<0.001
Infarction (non deadly)	0.6%	0.5%	0.14
TIA/stroke	0.1%	0.1%	0.92
Emergency CABG	0.1%	0.1%	0.20

This analysis could not confirm recently reported differences in PTCA outcome between hospitals with and without on-site surgery backup. This might in part be due to large differences in PTCA volumes between US-american and European hospitals. While 98.3% of the reported US-american NOSB hospitals (22.1% of SB hospitals) performed < 101 PTCA per year, did this analysis not include a single hospital with such a low number of procedures. It does not seem warranted to recommend against PTCA in hospitals without on-site cardiac surgery backup.

P2216 Randomised study on the effectiveness of a filter device for distal protection during direct percutaneous catheter intervention for acute myocardial infarction. PROMISE Study – 6 month follow-up

M. Gick, N. Jander, H.-P. Bestehorn, M. Ferenc, T. Comberg, V. Bassignana, H.J. Buettner, F.-J. Neumann. *Herzzentrum Bad Krozingen, Interventional Cardiology, Bad Krozingen, Germany*

In acute myocardial infarction, distal embolization of debris during primary percutaneous catheter intervention (PCI) may curtail microvascular reperfusion of the infarct region. Our randomised trial investigated whether distal protection with a filter device can improve microvascular perfusion and reduce infarct size after primary PCI. We enrolled 200 patients who had angina within 48 hours after onset of pain plus at least one of three additional criteria: (a) ST-segment elevation, (b) elevated myocardial marker proteins, (c) angiographic evidence of thombotic occlusion. Among the patients included (83% males, mean age 62±12 years) 100 were randomly assigned to the filter-wire group and 100 to the control group. Primary endpoint was the maximal adenosine-induced Doppler flow velocity in the recanalized infarct artery. Secondary endpoint was infarct size, as estimated by the volume of late enhancement on nuclear magnetic resonance imaging. An ST-elevation myocardial infarction was present in 68.5% of the patients, the median time from onset of pain was 6.9 hours. In the filter-wire group maximal adenosine-induced flow velocity was 34±17 cm/s versus 36±20 cm/s in the control group (p=0.46). Infarct size, assessed in 80% of the patients, was 12±9% of the left ventricular mass in the filter-wire group and 11±10% in the control group (p=0.77).
After 6 months, the maximal adenosine-induced flow velocity in the infarct related artery, assessed in 75.5% of the patients, had improved and reached 51 ± 21 cm/s in the filter-wire group versus 52 ± 20 cm/s in the control group (p = 0.69). Infarct size after 6 month was assessed in 66% of the patients. Infarct sizes were smaller than in the acute phase, but did not differ between the two groups (8.7±7.1% of the left ventricular mass in the filter-wire group versus 7.6±7.5% in the control group, p=0.43).
The 180-day incidence of major adverse cardiac events was 13% in the filter-wire group versus 12% in the control group, (p=0.83) with a 3% mortality in both groups, no re-infarctions and a 11% versus 10% rate of reintervention.
Conclusion: our study does not provide a rationale for distal protection with the filter-wire as an adjunct to primary PCI in acute myocardial infarction.

P2217 Impact of thromboaspiration device during primary PCI on left ventricular remodelling in patients with anterior acute myocardial infarction

G. Sardella[1], L. De Luca[2], G. De Persio[1], E. Berardi[1], M. Beraldi[1], T. Tommasone[1], L. Agati[1], F. Fedele[1]. *[1]Policlinico Umberto I, Cardiovascular and Pulmonary Sciences, Rome, Italy; [2]Roma, Italy*

Background: In patients with acute myocardial infarction (AMI), percutaneous coronary intervention (PCI) may cause thrombus dislodgment followed by reduced flow and microvascular dysfunction which is a negative independent predictor of myocardial function recovery and long-term survival. Recent studies demonstrated that thrombectomy devices reduce distal embolization during primary PCI.
We prospectively evaluated the impact of thrombectomy on left ventricular (LV) remodeling after anterior AMI successfully treated with primary PCI.
Methods: Patients with anterior AMI undergoing primary PCI of de novo coronary lesions with angiographic presence of intracoronary thrombus were randomized to a thromboaspiration device (Diver-Invatec®) + stent implantation or conventional coronary stenting. Heparin, Adenosine and Abciximab were administered routinarely in all patients. A complete 2D echocardiography at admission and 6 months after the index intervention was performed.
Results: Sixty-two consecutive patients (65.3±11.2 yrs, 48 males) underwent a primary PCI with (n=28) or without (n=34) thromboaspiration at 6.8±2.3 h from symptoms onset. Patients who underwent thrombectomy were less likely to be male, had a higher prevalence of hypertension (78 vs 55%) and higher levels of creatinine (1.4 vs 1.0 mg/dl). Other baseline clinical characteristics, lesion location, AHA/ACC lesion classification, angiographic measurements and echocardiographic parameters were similar between groups. Patients treated with thrombectomy had an higher rate of post-procedure TIMI 3 flow (86.6 vs 62.5%; p<0.05) and myocardial blush grade 3 (38.2 vs 8.1%; p<0.01).
There was a significant end-diastolic (51.6±2.4 vs 48.6±6.9, p=0.03) and end-sistolic (39.6±4.6 vs 32.4±7.3, p=0.048) diameters increase in conventionally treated patients at 6 months as compared to thrombectomy group.
Conclusion: Compared with conventional stenting, a pretreatment with thrombectomy during primary PCI, seems to be associated with a. significantly lower increase in LV volumes after 6 months in anterior AMI patients.

P2218 Results of angioscopy-guided coronary thrombectomy in acute coronary syndromes

A. Itoh, T. Naruko, Y. Sakanoue, R. Komatsu, K. Shimamura, N. Shirai, K. Fujimoto, K. Haze. *Osaka City General Hospital, Cardiology, Osaka, Japan*

Coronary angioscope can detect the color and surface morphology of atherosclerotic plaque, the presence or absence of thrombi, and the nature of thrombi such as red, white, or mixed. If angioscope can be incorporated into a therapeutic device, technical complexity and device cost will be minimized. Therefore we developed a new imaging and aspiration device for the treatment of acute coronary syndromes (ACS). A 6000-pixel angioscope, VEC-075/M-NF was used in this study. It has 0.75 mm in outer diameter, 3000 mm in total length, and 1700 mm in effective length. Its focal distance is > 2.0 mm and a view angle of 140 degrees. The tip of the angioscope is highly radiopaque, so it is possible to identify the distal tip by fluoroscopy easily. Thrombuster, originally developed solely as an aspiration catheter was used as an inner guiding catheter for the angioscope. After angioscopic observation, angioscopic fiber was withdrawn from a central lumen and aspiration could be performed immediately. Angioscopy-guided coronary thrombectomy was performed in 36 patients with ACS. Thrombi could be seen by angioscope in 30 patients (83%). If thrombi were recognized, repeated aspiration was performed with angiographic and angioscopic guidance. In 2 patients TIMI 3 flow with a residual stenosis less than 50% could be obtained after aspiration. Stent implantation with or without pre-dilation was performed in remaining 34 patients. There was no distal embolization during or after the procedure and final TIMI 3 flow was obtained in 35 pteints (97%). In conclusion, angioscopy-guided coronary thrombectomy is a simple and logical method for revascularization in acute coronary syndromes.

P2219 Effectiveness of distal protection device on the protection of microvascular integrity assessed by myocardial contrast echocardiography in patients with acute myocardial infarction

G.R. Hong, J.H. Kang, J.H. Bae, J.S. Park, D.G. Shin, Y.J. Kim, B.S. Shim. *Yeungnam University, Cardiology Dept., Daegu, Korea, Republic of*

Background: Primary percutaneous coronary intervention (PCI) is a useful method for the treatment of acute myocardial infarction. Primary PCI for in lesions with a large thrombus load increases the procedural complication rate such as no-reflow phenomenon. The GuardWire Plus system (PercuSurge) is a useful adjunctive tool for the protection of distal vascular bed while intervening lesions with a large thrombus load. However, the influence of this system on microvascular integrity of myocardium is not clear. Using myocardial contrast echocardiography (MCE), we can easily quantify the microvascular integrity of myocardium. The purpose of this study is to identify the efficacy of PercuSurge Guardwire system on the microvascular integrity after primary coronary intervention in patients with acute myocardial infarction (AMI) using myocardial contrast echocardiography (MCE).
Methods: Thirty-nine AMI patients (23 men; 62±13 years), with completely occluded infarct-related artery and presented within 12 hours after chest pain onset, were randomly divided into 2 groups: 19 AMI patients who underwent primary PCI using PercuSurge System (group A), and 20 patients who underwent primary PCI without any distal protection device (group B). After successful reperfusion therapy, we performed MCE (real time low mechanical index) within 24 hours with PESDA. Quantitative MCE, with the relation between myocardial signal intensity and time fitted to the exponential equation: $y=A(1-e^{-\beta t})$ has been validated, with "A" representing plateau MCE intensity, "β" representing rate of signal increase, and their product "Aβ" representing myocardial blood flow (MBF).
Results: No differences were found between both groups in demographics, localization of the infarction, and baseline hemodynamic parameters. In patients with distal protection device(group A) the value of A representing myocardial blood volume was significantly higher than patients without distal protection device (group B) (2.15±1.53 vs 1.36±1.07, p<0.01). The β value representing the mean myocardial microbubble velocity was significantly higher in group A (0.40±0.31 vs 0.25±0.19, p<0.01). The MBF determined by MCE(Aβ) was significantly higher in group A(0.85±0.71 vs 0.45±0.37, p<0.05).

Conclusion: GuardWire Plus system (PercuSurge) is a useful protection device for the preservation of microvascular integrity in AMI patients who need primary PCI.

P2220 Effects of stent deployment Vs. POBA alone on regional coronary blood flow in patients with high-risk unstable angina

A. Mongiardo[1], D. Torella[1], C. Spaccarotella[1], F. Achille[1], G. Tagliamonte[1], A. Leone[1], A. Ferraro[1], C. Indolfi[2]. *[1]University Magna Graecia, Cardiology, Catanzaro, Italy; [2]Magna Graecia University, Department of Cardiology, Catanzaro, Italy*

Purpose: Dysfunctional coronary microcirculation is an important determinant of prognosis for patients with acute myocardial infarction after successful reperfusion. However, the effects of plain old balloon angioplasty (POBA) or coronary stenting on regional coronary blood flow in patients with high risk unstable angina (UA) are still unknown.
Methods: In 10 patients with high risk UA (Class II-III B Braunwald), after intracoronary nitroglycerin (NTG, 300 gamma) infusion, pressure gradient between stenosis, mean transit time (MTT) and vessel diameter were measured at the following procedural steps: 1) basal conditions (NTG-Base), 2) after stent-like dilatation with only the balloon catheter (POBA), 3) after stenting deployment (3a: "normal" and 3b: "high " pressure) (STENT) and 4) after final intracoronary NTG administration (NTG-Post). MTT is the parameter used to evaluate coronary blood flow, since it is inversely correlated to the flow according to the formula: flow=volume/MTT, being constant the volume (4 ml cold saline). MTT was measured using a 0.014 inches pressure wire.
Results: Mean MTT decreased from 1,17±0,25 sec (TGG-Base) to 0,73±0,16 sec after POBA, to 0,59±0,14 sec after STENT and to 0,49±0,15 sec after NTG-Post. The arterial blood pressure and heart rate did not change during each step of the study protocol. The mean trans-stenotic pressure gradient at NTG-Base was 0,58±0,08; after balloon dilation, it increased to 0,99±0,04 (POBA); remaining constant (1,00±0,03) after STENT. No further increase in the trans-stenotic pressure gradient was noticed after NTG-Post (1,0±0,04). The vessel diameter distal to successfully dilated stenosis, measured by QCA, compared with NTG-Base changed of -2,1% after POBA, -0,54% post-stenting and +10,6% after NTG-POST. ANOVA one-way analysis did not demonstrate significant differences between any steps of the percutaneous coronary intervention for each of the evaluated parameter.
Conclusions: In high risk patients with UA, stent deployment, after stent-like balloon dilatation, does not influence regional coronary blood flow or decrease vessel diameter distal to the treated lesion. Thus, the consequences of stent deployment in high risk UA might be different from those frequently observed after acute myocardial infarction.

P2221 Acute stent recoil and delivery balloon constraint restrict final stent diameter by 27% irrespective of reference vessel size

S. Aziz, J.L. Morris, R.A. Perry, R.H. Stables. *The Cardiothoracic Centre, Cardiology Department, Liverpool, United Kingdom*

Purpose: Despite using high-pressure stent deployment, coronary stents often fail to reach the expected diameter. Failure of the stent delivery balloon to achieve the expected diameter and stent elastic recoil after balloon deflation are two factors that contribute to stent under deployment. We investigated the incidence and magnitude of this problem.
Methods: We performed a prospective observational angiographic study recruiting consecutive patients undergoing coronary stent implantation between September 2003 and October 2004. Using quantitative coronary angiography (QCA) the minimal lumen diameters of the delivery balloon during stent deployment (MLD1) and following balloon deflation were measured (MLD2). The expected balloon diameter for the deployment pressure according to the manufacturer's chart was also recorded. Delivery balloon deficit was measured by subtracting the MLD1 from the expected balloon size and stent recoil was calculated by subtracting MLD2 from MLD1. The relationship between delivery balloon deficit and stent recoil as a function of reference vessel diameter (RVD) and nominal stent diameter was calculated using analysis of variance.
Results: A total of 499 individual lesions with suitable images for quantitative coronary angiography were recorded. The final stent MLD was a mean (SD) 27.2 (7.2) % less than the predicted diameter. The mean (SD) delivery balloon deficit was 0.65 (0.27) mm and the mean (SD) stent recoil was 0.28 (0.17) mm. The mean (SD) percentage delivery balloon deficit was 18.9 (7.0) % and the mean (SD) percentage stent recoil was 10.0 (5.9) %. Percentage stent recoil and delivery balloon deficit was independent of RVD and nominal stent size.
Conclusion: Failure to achieve predicted final stent diameter is a real problem with contribution from delivery balloon under expansion and stent recoil. On average the final stent MLD is only 73% of the expected diameter irrespective of vessel size.

P2222 Influence of direct stenting to limit the edge effect with the sirolimus coated stent

P. Guerin[1], V. Sauzeau[2], Y. Goueffic[2], M.F. Heymann[3], O. Al Habash[3], D. Crochet[3], P. Pacaud[2], G. Loirand[2]. *[1]CHU Nantes, Loire Atlantique, Nantes Cedex 1, France; [2]Institut du Thorax, Inserm U 533, Nantes, France; [3]CHU Nantes, Loire Atlantique, Nantes cedex 1, France*

The use of sirolimus eluting stent (SES) has strongly limited the incidence of in-stent restenosis, that still remains a problem at the edge of the stent. The aim of this study was to assess the influence of the stent insertion procedure on neointimal thickening in the stented segment of the artery and at the edge of the stent. Both SES (Cypher R, Cordis) and the corresponding bare stent (BS) (BX Velocity R, Cordis) have been used in a model of human mammary artery culture. After 28 days of culture, the "in stent" neointimal thickening was dramatically inhibited in the SES group compared to the BS group whatever the stenting technique (prédilatation: 0,22±0,05 vs 0,30±0,10; p=0,04; direct stenting 0,16±0,04 vs 0,30±0,13; p=0,006). In the BS group, predilatation and direct stenting gave similar 'in-stent" neointimal thickening (0,30±0,10 vs 0,30±0,13; NS). In contract, in the SES group, in stent neointimal thickening was significantly reduced when direct stenting was performed (0,16±0,04% (direct stenting) vs 0,22±0,05 (PD), p=0,03). At the edge of the stent, a similar neointimal thickening was observed with both type of stent when predilatation was performed on the entire segment of mammary artery (BS: 0,16±0,06; SES: 0,19±0,06; NS). Direct stenting significantly reduced the neointimal thickness at the edge when SES where used (0,06±0,01 (direct stenting) vs 0,19±0,06 (predilatation); $p<0,001$) but in the BS group no difference in edge effect was observed between the two technique (0,16±0,06 (predilatation) vs 0,12±0,05 (direct stenting); NS). Smooth muscle cell proliferation, assessed by MIB-1 staining, confirmed these results. Western blot analysis proved that decrease of neointimal thickening with SES was associated with a smallest expression of the small protein G RhoA and an increase of P27 expression. These results show the benefit of direct stenting to limit the edge effect with SES and confirm the effects of rapamycine on RhoA and P27 expression.

P2223 Post dilatation improves stent expansion particularly in cases with a high residual stenosis after coronary stenting

S. Aziz, J.L. Morris, R.A. Perry, R.H. Stables. *The Cardiothoracic Centre, Cardiology Department, Liverpool, United Kingdom*

Introduction: Adjunctive balloon post dilatation following stent deployment is often used to optimise stent expansion. However the benefit of this strategy with modern stent delivery systems using high-pressure stent deployment is not known.
Methods: We performed a prospective observational angiographic study recruiting consecutive patients who underwent stent deployment between September 2003 and October 2004. Quantitative coronary angiography (QCA) was used to measure the minimal lumen diameter (MLD) within the stent before and after post dilatation. The difference between these values was used to calculate the impact of post dilatation. Optimal stent deployment was defined as a stent MLD $\geq$90% of the average reference vessel diameter.
Results: 499 lesions with suitable images for QCA had stent deployment. The mean (SD) stent deployment pressure was 14.6 (1.6) atmospheres. Post dilatation was performed in 40.7% (206/499) of cases, using a non-compliant balloon in 91% (186/206) of cases with a mean (SD) balloon pressure of 15 (1.8) atmospheres. The mean (SD) balloon vessel ratio for the post dilatation balloon was 1.31 (0.17). In those patients that had post dilatation, stent MLD increased from mean (SD) 2.49 (0.40) to 2.70 (0.38), $p<0.0001$. Optimal stent deployment increased from 35.5% (72/203) to 56.5% (115/202). The benefit of post dilatation was most marked in those cases with a high residual stenosis after coronary stenting. A balloon vessel ratio >1.3 was not associated with any further improvement in the proportion of cases with optimal stent deployment. In those cases were post dilatation was not performed, optimal stent deployment was achieved in 64.9% (187/288) of cases.
Conclusion: A significant proportion of patients do not achieve optimal stent deployment with modern stent delivery systems. One third of patients with suboptimal stent deployment did not have post dilatation. When post dilatation was performed with over sized non-compliant balloons, an increase in stent MLD and the proportion of patients with optimal stent deployment was achieved.

P2224 Plaque modification with cutting balloon before left main interventions. The single center experience

A. Erglis, I. Kumsars, I. Narbute, S. Jegere, I. Mintale, I. Zakke. *Latvian Centre of Cardiology, Invasive and Emergency Cardiology Department, Riga, Latvia*

Background: Significant LM (left main) disease has a poor prognosis if treated non-surgically. The role of PCI for LM treatment is not completely clear yet. Plaque modification with cutting balloon (CB) prior to stenting can reduce plaque burden and barotraumas, and may impact the incidence of restenosis.
Purpose: – To achieve maximum acute gain (MSA – minimal square area) with reduced barotrauma using cutting balloons (CB) prior to stenting

– To evaluate the benefit of plaque modification with CB on LM
– To evaluate 6 months clinical, angiographic and IVUS outcome
Methods: This is an on-going prospective study enrolling 138 patients who had undergone elective PCI on unprotected LM from January 2002 with randomization to regular or drug-eluting stent deployment since 2004. The sizes of devices were selected by IVUS measurements following the "media to media" treatment principle. All patients were scheduled for 6-month clinical, angiographic and IVUS follow-up.
Results: The average age of patients were 60.6± 10.7 years. The procedure was successful in 100% of patients. Mean treated segment lengths and average vessel diameter were 7.44±3.34 and 3.27±0.80 respectively. During hospital period we observed: 1 Q-MI, 4 non-Q MI and 1 re-PCI was performed. The in-hospital mortality rate in our study was 0%. At present 70 patients have completed 6-month follow up. During follow-up period we observed 3 TLR (4.3%) – 2 PCI (2.9%) and 1 CABG (1.4%), 1 patients (1.4%) had Q-MI and 2 patient died (one had MI other from lung cancer).
Preliminary IVUS data (n=50).
Neointimal volume (mm^3) at follow-up was 15.7±6.6 mm^3

Preliminary IVUS data (n=50).

	MLD (mm)	MSA (mm^2)	Lumen volume (mm^3)
Pre-intervention	1.71±0.23	3.00±0.75	103.0±15.6
Post intervention	3.17±0.19	9.02±0.79	202.2±22.9
At 6 months f-up	2.88±0.24	7.82±0.90	181.5±26.5
Late loss	0.26±0.12	1.02±0.39	14.2±8.2
Loss index	0.18±0.08	0.17±0.06	0.15±0.10

Conclusions: IVUS guided CB intervention on LM followed by bare-metal stent or DES is safe with excellent acute gain and low 6 months MACE rate. Preliminary IVUS data findings show extremely low neointimal growth 15.7±6.6 mm^3 at six months even in bare-metal stent group.

P2225 1 year results of PCI for acute (3 months) and chronic (3 months) coronary total occlusions-an analysis of 1261 patients

P.R. Kumar[1], G. Dixon[2], A. de Belder[1], S. Holmberg[1], D. Hildick-Smith[1]. *[1]Brighton and Sussex University Hospital, Cardiology, Brighton, United Kingdom; [2]Brighton & Sussex University Hospital, Cardiology Department, Brighton, United Kingdom*

Background: Since June 1999, 1261 patients have undergone PCI for occluded coronary vessels at our institution. We divided this cohort into 2 groups - Group A (occlusion < 3 months duration, n=770) and Group B (occlusion > 3 months duration, n=491) and labelled these groups acute and chronic total occlusions respectively- ATO and CTO. We analysed the 30 day and 1 year outcome dependent on success or otherwise of the index procedure.
Methods: PCI data is prospectively collected on PATS (Dendrite). Follow up was obtained by questionnaire and telephone contact. Mortality tracking was via NHS-net databases. A good PCI result was defined as TIMI 3 flow in the index vessel, a poor result TIMI 0- 2 flow. MACE was defined as death/ Q wave MI/ emergency CABG/ requirement for target vessel revascularisation. Data was analysed with a Chi- Square test-$p<0.05$ was considered statistically significant.
Results: The 2 groups were well matched for age, gender, target vessel and risk factors. Group A were more likely to have had a recent MI(44.7% vs 11.0%), or to be in cardiogenic shock(4.9% vs 1.0%). One year follow up was obtained for 81% (Group A) and 76% (Group B). The 30 day and 1 year MACE is shown in table 1.(*$p<0.05$)

	Gp A good result	Gp A poor result	Gp B good result	Gp B poor result
n	700	70	300	191
30 day Mace	2.71%	18.6% *	0	2.1% *
1 year Mace	10.9%	48.0% *	8.1%	23.8% *
1 year death	4.5%	26.9% *	1.8%	3.4%

Conclusion: The complication rates of CTO PCI are low. Successful PCI for CTOs has excellent 30 day and 1 year outcome. Failure to reopen ATOs however has a poor outcome at 30 days and 1 year.

P2226 Left main stenting vs surgical revascularisation: LE MANS case controlled study

P. Buszman[1], E. Peszek-Przybyla[1], S. Kiesz[2], D. Dudek[3], A. Zurakowski[1], K. Milewski[1], M. Tendera[4]. *[1]Upper-Silesian Heart Center, Coronary Care Unit, Katowice, Poland; [2]University of Texas School of Medicine, San Antonio, TX, United States of America; [3]Jagiellonian University, Collegium Medicus, Krakow, Poland; [4]Upper-Silesian Heart Center, 3rd Department of Cardiology, Katowice, Poland*

Unprotected left main (ULM) stenting is subject of intense investigations as a potential alternative to bypass surgery. The possibility of abrupt vessel closure or restenosis causing death is a main concern of investigators.
Methods: The prospective registry consists of 124 pts (92 males, mean age 61,8 ±10,3 years), who underwent multivessel PCI and ULM stenting with bare metal stents (99 pts) or DES (25pts). Eighteen percent were diabetic and 53% were disqualified from CABG. Unstable angina or non-ST elevation MI was present in 54 (43.5%). Distal LM stenosis was present in 55%, and additionally 1.6±0.5 coronary arteries was severely narrowed. The mean value of Euroscore was 4,4±3,3, indicating moderate surgical risk (predicted in-hospital mortality >5%). In addition to ULM stenting, other vessels were dilated: LAD -82 pts, RCA –60 pts, LCx –52 pts. Follow – up consisted of: stress test and echocardiography after 1, 3, 6, 12 months and coronary angiography: 3-6 months after the procedure.
Results: There were 3 in-hospital deaths (2.4%) and 5 (4%) myocardial infarcts (total in-hospital MACE 8%). The mean follow-up was 13,6±6,0 months. During that time there were another 7 deaths (including 5 non-cardiac). Total number of MACE during observation was 53 (42%), including restenosis and repeat revascularization in 15 vessels other than LM. LM restenosis rate occurred in 21 pts (16,9%). Three of them underwent CABG and 18 had successful re-PCI within LM. There was no cardiac complications related to treatment of ULM in-stent restenosis. The calculated one-year survival according to Kaplan-Meier curve was 92.4% (95% CI: 84,6-100%) while the predicted one-year survival after hypothetical CABG calculated with KUL algorithm was 93,2% (95% CI: 90,5-95,9%) (ns).

CCS, EF and METS results

	Before	1/12	3/12	6/12	12/12	p
CCS	3,2 ±0,9	1,6 ±1,0	1,8 ±0,9	1,6 ±0,8	1,4 ±0,8	<0,0001
EF	49,1 ±13,2	51,3 ±13,7	54,0 ±12,1	54,3 ±12,0	54,6 ±11.7	<0,004
METS	-	8,2 ±3,6	8,9 ±3,5	8,0 ±4,2	9,2 ±3,0	0,305

Conclusions: Multivessel PCI including unprotected LM stenting is feasible and safe alternative to CABG if meticulous follow-up is performed. Percutaneous treatment of LM in-stent restenosis is a safe and efficient procedure. Improved late results would be expected with routine use of drug eluting stents.

ADJUNCTIVE THERAPY DURING AND AFTER 2 PCI

P2227 Antithrombotic therapy with enoxaparin during coronary intervention: is it safe for all?

A. Dana[1], C.M. Nguyen[2], S. Cloutier[3], G.R. Barbeau[2]. *[1]Hopital Laval, Institut de cardiologie de Quebec, Sainte-Foy (Quebec), Canada; [2]Hopital Laval, Institut de cardiologie de Quebec, Sainte-Foy (Quebec), Canada; [3]Hopital Laval, Hematologie, Sainte-Foy, Québec, Canada*

Background: recent evidence suggests that antithrombotic therapy (ATT) with the low molecular weight heparin enoxaparin (Enox) during percutaneous coronary intervention (PCI) may be as safe and effective as unfractionated heparin. Using Enox as the sole ATT at the time of PCI, we encountered intraprocedural macroscopic thrombus formation on PCI equipment in a patient (pt) undergoing rescue PCI.
Aim: we sought to prospectively evaluate the incidence and outcome of periprocedural thrombosis in all pts undergoing PCI on Enox as the sole ATT.
Results: between Apr 2003-Dec 2004, 478 pts underwent coronary angiography who had received Enox. In 253 pts (53%) we proceeded to PCI. Of these, 122 (48%) were within 8 h of the last dose of Enox and did not receive additional ATT. All procedures were performed via the radial route. Patients' ages ranged from 38-90 yrs (mean 61.9) and 83 (68%) were men. All pts received aspirin and clopidogrel prior to PCI unless contraindicated. During this period, 6 pts (5%) were noted to have macroscopically visible large thrombus formation within the PCI equipment (Table). All pts had therapeutic anti-Xa levels (1.02±0.35 IU/mL) at the start of PCI. In all pts PCI equipment needed to be exchanged and the procedure was completed without significant adverse events except pt 6 who had distal embolisation in the LAD artery.

Table

Pt	Age	Sex	Presentation	Procedure	Anti-Xa (IU/mL)
1	52	M	Failed Tx (TNK)	Rescue PCI to LAD	N/A
2	53	M	Failed Tx (TNK)	Rescue PCI to LAD	0.75
3	73	M	Unstable angina	PCI to SVG	1.42
4	52	M	Post-infarct angina	PCI to RCA	0.65
5	74	F	NSTEMI	PCI to LMS after IVUS	0.93
6	74	F	NSTEMI	PCI to LAD after IVUS	1.34

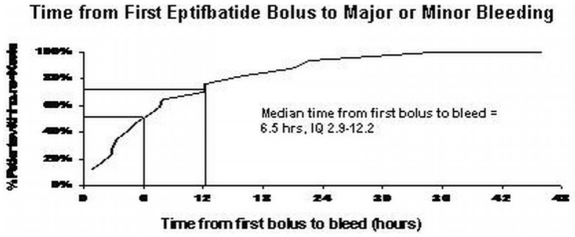
Tx=thrombolysis, TNK=tenecteplase, LMS=left main stem, SVG=saphenous vein graft, LAD= left anterior descending artery, RCA= right coronary artery, NSTEMI=non ST-elevation myocardial infarction, IVUS=intravascular ultrasound.

Conclusion: we report a 5% incidence of periprocedural thrombus formation in pts undergoing PCI following ATT with Enox. The incidence of clinically undetectable microscopic thromboembolism on PCI equipment is possibly higher and may contribute to elevation in troponins. The use of Enox as the sole ATT at the time of PCI warrants further evaluation.

P2228 Correlates of bleeding complications among moderate-high risk ACS patients undergoing contemporary PCI with eptifibatide

A.J. Kirtane[1], S.A. Murphy[2], D.A. Morrow[2], C.H. McCabe[2], E. Braunwald[2], C.M. Gibson[1]. *[1]Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, United States of America; [2]Harvard Medical School, TIMI Study Group, Boston, United States of America*

Background: Identification of bleeding predictors in patients receiving Glycoprotein IIb/IIIa inhibition might identify targets to reduce bleeding risk.
Methods: In the PROTECT-TIMI 30 trial of PCI in patients with moderate-high risk non-ST elevation acute coronary syndromes (NSTEACS), correlates of TIMI major/minor bleeding were identified in 573 patients treated with eptifibatide (EPT).
Results: Increasing age and a failure to dose-adjust the EPT infusion for patients with Creatinine Clearance (CrCl) <50 mL/min were the strongest independent correlates of bleeding events. Failure to reduce the dose of EPT infusion per the dosing instructions, occurring in 17/35 (48.5%) of patients with reduced CrCl, was associated with a 5-fold greater incidence of bleeding events (17.7% vs. 2.7%, p=0.014). While a reduced CrCl alone was associated with higher bleeding rates, this association appeared to be due to the inclusion of age in the Cockroft-Gault formula to calculate CrCl as well as dose-adjusting errors. Patient gender, weight, serum Creatinine, and the peak ACT were not associated with bleeding events. The median time to a bleeding event was 6.5 hrs after the first EPT bolus administered during PCI.



Figure

Conclusions: In PCI patients with moderate-high risk NSTEACS treated with EPT, increased age was the only constituent of CrCl that was associatedwith bleeding events, half of which occurred over 6 hrs after PCI. Dosing errors were common among patients with low CrCl, and were also associated with higher bleeding rates. Consideration should be given to further dosing adjustments in the elderly, to meticulous dosing in patients with renal dysfunction, and to a shorter duration of EPT infusion to potentially reduce later bleeding complications.

P2229 Platelet activation predicts recurrent ischaemic events after percutaneous coronary angioplasty: a 6 months prospective study

J. Gianetti, M.S. Parri, S. Sbrana, U. Paradossi, A. Clerico, S. Berti, A. Biagini. *Hospital "Pasquinucci", Cardiology Dept., Massa, Italy*

Background: An increasing amount of evidence indicates that platelet reactivity, despite a standard anti-thrombotic therapy, is a potential risk factor for recurrent myocardial ischemia in patients with coronary artery disease. We now hypothesize that this condition, measured by collagen-epinephrine (CEPI) or collagen-ADP (CADP) closure times (CT) by Platelet Function Analyzer (PFA-100), may predict the recurrence of coronary events after percutaneous coronary intervention (PCI).
Methods and Results: CEPI and CADP-CT were measured 30 ± 8 hours after PCI in 175 consecutive patients admitted with a diagnosis of stable angina (n=94) or acute coronary syndromes (n=81) and prospectively followed up for a mean period of 6 months. We stratified the patients in accordance to both the CEPI-CT (< or > 190 sec), reflecting the intensity of cycloxygenase inhibition by aspirin and the distribution into quartiles for CADP-CT: CEPI-CT<190 sec as well as CADP-CT <82 sec were associated with a higher rate of clinical recurrence (Hazard ratio 8.5, p<0.001 and 22.9, p<0.001, respectively). Multivariate analysis after adjustment for other risk factors confirmed that the lowest CADP-CT quartile significantly correlates with the risk of recurrent coronary events (Hazard ratio 36.5, p<0.01), whereas the impact of CEPI-CT<190 sec was partially blunted (Hazard ratio 6.7, p=0.01).
Conclusions: An enhanced platelet function after PCI when measured under high shear rates by PFA-100 is an independent predictor of a worst clinical outcome, even during a short term follow-up and may help in patients risk stratification.

P2230 Impact of peri-interventional platelet inhibition after loading with clopidogrel on 30-days clinical outcome of elective coronary stent placement: the excelsior study

W. Hochholzer[1], D. Trenk[2], B. Fischer[2], K. Andris[2], H.-P. Bestehorn[2], H.J. Buettner[2], F.-J. Neumann[2]. *[1]Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany; [2]Bad Krozingen, Germany*

Backgound: Platelet responses after loading with clopidogrel are highly variable. The impact of this variability on the peri-interventional risk of patients undergoing percutaneous catheter intervention (PCI) has not been tested prospectively.
Methods: We designed our study to test the hypothesis that 30-day clinical outcome of patients undergoing elective coronary stent placement differs by quartiles of the level of adenosine diphosphate (ADP)-induced platelet aggregation at the time of PCI. Patients with high risk clinical features such as angina at rest (CCS IV), new ischemic ST-segment changes or acute myocardial infarction were not eligible for the study. Primary endpoint was the 30-day composite (30-day MACE) of death, myocardial infarction (MI) and target lesion revascularization (TLR) on clopidogrel. All patients received a loading dose of 600 mg clopidogrel followed by a daily maintenance dose of 75 mg for at least 4 weeks. Glycoprotein IIb/IIIa inhibitors were not allowed, except for bail-out. We assessed platelet aggregation by optical aggregometry after stimulation with 5 μmol/L ADP before loading and immediately before heparin administration during PCI. For sample size calculation we assumed a 30-day MACE rate of 4.2% based on ISAR-REACT. We intended to have an 80% power to detect an effect size of 0.015 (e.g. 3-fold risk in 4th quartile) at a two-sided p < 0.05. This gave us a minimum sample size of 748 patients.
Results: We enrolled 802 consecutive patients. During 30-day follow-up, 15 patients (1.9%) incurred MACE (3 deaths, 8 MI, 8 TLR). Thirty-day MACE differed significantly (p=0.03) between quartiles of platelet aggregation (see Table). Platelet aggregation above median carried a 6.5-fold risk (p=0.004) of 30-day MACE. Multivariate logistic regression analysis including pertinent covariables confirmed the level of platelet aggregation as a significant (p=0.01) independent predictor of 30-day MACE.

Quartiles of platelet aggregation

Platelet aggregation	1. Quartile (<5%)	2. Quartile (5-14%)	3. Quartile (15-32%)	4. Quartile (>32%)	P
Clinical event rate	1 (0.5%)	1 (0.5%)	6 (3.1%)	7 (3.5%)	0.03

Conclusion: The variability of platelet responses after clopidogrel loading has a major impact on clinical outcome after elective PCI.

P2231 Abciximab reduces in-hospital mortality in patients treated with primary percutaneous coronary intervention for ST elevation myocardial infarction complicated by cardiogenic shock in clinical practice

U. Zeymer[1], R. Zahn[2], A. Gitt[2], R. Winkler[2], B. Mark[2], M. Gottwik[3], J. Senges[2]. *[1]Klinikum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany; [2]Klinikum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany; [3]Klinikum Nürnberg, Medizinische Klinik 8, Nürnberg, Germany*

Background: ST elevation myocardial infarction (STEMI) complicated by cardiogenic shock is associated with a high mortality, even in patients treated with primary percutaneous coronary intervention (PCI). Abciximab has been shown to reduce the rate of ischemic complications during PCI and enhance microvascular perfusion. Therefore we sought to evaluate the impact of abciximab on mortality in patients with cardiogenic shock treated with primary PCI in clinical practice.
Methods: We used the data from two prospective PCI registries, the international SHAKESPEARE Registry performed between 2001 and 2002 and the German ALKK registry from the year 2003. All patients with STEMI complicated by cardiogenic shock and treated with primary PCI within 24 hours after symptom onset were considered for this analysis.
Results: From the ALKK registry 240 patients (120 with and 120 without abciximab) and from SHAKESPEARE 122 (61 with and 61 without abciximab) were included in this analysis. There were no differences between the groups with respect to baseline variables. The rate of TIMI 3 flow after PCI was 70.8% and 68.5% in the ALLK registry and 70.8% and 69.4% in SHAKESPEARE in patients with and without abciximab, respectively. The in-hospital mortality rates are shown in the table. In a multivariate analysis adjusted for confouding variables abciximab remained an independent predictor of survival.

	Abciximab	No GP IIb/IIIa inhibitor	p-value
ALKK	33/120 (27.5%)	48/120 (40%)	0.04
SHAKESPEARE	28/61 (45.9%)	37/61 (60.7%)	0.05
Combined	61/181 (33.7%)	85/181 (47%)	0.01

Conclusion: In clinical practice abciximab is associated with a reduction of in-hospital mortality in patients with primary PCI for STEMI complicated with cardiogenic shock. Since there was no difference in TIMI 3 flow additional effects as improvement of microascular perfusion and anti-inflammatory properties have to be considered for these results.

P2232 Triple therapy with aspirin, warfarin and a thienopyridine in patients undergoing percutaneous coronary intervention is not associated with significant haemorrhagic complications

A. Porter, Y. Konstantino, Z. Iakobishvilli, L. Shachar, A. Battler, D. Hasdai. *Rabin Medical Center, Dept. of Cardiology, Petah Tikva, Israel*

Background: Triple therapy (TT) of warfarin, aspirin and a thienopyridine is strongly discouraged given the potential risk of bleeding complications (BC), although data regarding BC during TT are sparse.
Aim: To assess BC incidence in pts undergoing percutaneous coronary intervention (PCI) with stents and receiving TT.
Methods: All pts undergoing PCI during 2000- 2004 and receiving TT thereafter were retrospectively analyzed. Demographic and clinical data were collected. All cause mortality data determined by census registry. All survivors underwent telephone interview for BC, stratified according to the TIMI bleeding criteria. Continuous variables are presented as median (25th-75th percentiles).
Results: The study group included 180 pts {80% males; age 65 (52, 75.5)}. PCI was done on an urgent basis in 86.6% of pts. The main indications for warfarin use were left ventricular mural thrombus and atrial fibrillation (46.9% and 36.9% respectively). Glycoprotein IIb/IIIa receptor antagonistss were used in 47.7% of pts. Post-PCI TT treatment duration was 30 days (30, 39). Post- TT, 106 pts (58.9%) continued treatment with warfarin and aspirin for 376 days (150, 774). During the TT period, 19 pts developed BC, (mean INR 2.03+ 0.6 @ 7.5 (6, 10.5) days post-PCI): 2 major groin hematoma (initial phase of warfain treatment during overlap with heparin), and 17 minor. During treatment with warfarin and aspirin, 19 pts developed BC: 1 major, and 18 minor. Survival after 21.5 (13.0, 31.3) months of follow-up was 89.4%, with a median interval PCI-death of 60 days (11.5, 426).
Conclusion: TT with aspirin, warfarin and a thienopyridine in pts undergoing PCI is feasible and is not associated with prohibitively high BC rates. The relatively high long-term mortality rates post-PCI in TT-treated pts is probably attributed to their high-risk profile. Thus, TT treatment should be favorably considered in pts with a clear indication for warfarin use.

P2233 Therapeutic strategies after stent placement in chronic anticoagulated patients: effectiveness and safety in daily clinical practice

A. Sambola[1], P. Tornos[2], J. Angel[2], F. Alfonso[3], E. Iraculis[4], V. Mainar[5], J. Zueco[6], O. Rodriguez[7] on behalf of MUSICA STUDY. SPANISH REGISTRY. *[1]University Hospital Vall d'Hebron, Cardiology, Barcelona, Spain; [2]University Hospital Vall d'Hebron, Cardiology, Barcelona, Spain; [3]Hospital Clinico San Carlos, Cardiology, Madrid, Spain; [4]University Hospital Bellvitge, Cardiology, Barcelona, Spain; [5]Hospital General de Alicante, Cardiology, Alicante, Spain; [6]University Hospital M. de Valdecillas, Cardiology, Santander, Spain; [7]University Hospital Germans Trias, Cardiology, Badalona (Barcelona), Spain*

Purpose: Dual antiplatelet therapy with aspirin (AAS) and clopidogrel (CL) after stent coronary placement is mandatory. However, in previously anticoagulated patients there are no recommendations in guidelines.
Methods and Results: A prospective multicentric registry was performed in chronically anticoagulated patients submitted to stenting between November 2003 to January 2005 in order to assess which regimes were used in daily practice and the rate of complications (bleeding, stent thrombosis and thromboembolism) during hospitalization and at 6 months follow-up. One-hundred seventy-two consecutive pts were identified (132 male, 40 female; 71±9 y). Reasons for anticoagulation were: prosthetic valve in 31 pts (18%), atrial fibrillation in 109 pts (63%) and other causes in 32 pts (19%). After stenting 87 pts (51%) were discharged on acenocumarol (AC)+AAS+CL, 20 pts (12%) on low-molecular weight heparin (LMWH)+AAS+CL, 42 pts (24%) on AAS+CL, 21 pts (12%) on AC+CL, 1 pt on AC+AAS and another pt on LMWH+AAS. The choice of therapeutic regimens was influenced by the indication for anticoagulation (33% of patients with atrial fibrillation received only AAS+CL). Bleeding events occurred in 11 pts (6%) (5 major requiring transfusion in pts (3%)). All major bleeding occurred in pts treated with 3 drugs: 3 pts with LMWH+AAS+CL and 2 pts with AC+AAS+CL. One patient on AAS+CL suffered a stent thrombosis at 1 month after self-withdrawal of CL and another one patient with atrial fibrillation on AAS+clopidogrel had a thromboembolic episode at six months after discharge. Three patients died at 3 months of heart failure.
Conclusions: Different therapeutic options are used to treat chronic anticoagulated patients after stent placement. The risk of bleeding is increased in patients treated with either AC or LMWH and AAS+CL. Our results suggest that triple therapy should be restricted to pts with a strong reason for anticoagulation (prosthetic valve, high risk atrial fibrillation).

P2234 Bivalirudin and IIbIIIa inhibitors have similar outcomes in the setting of drug eluting stents

G.J. Mishkel[1], N.J. Goswami[1], R.W. Ligon[1], A. Moore[2]. *[1]Prairie Heart Institute, Springfield, USA; [2]Prairie Education & Research Cooperative, Springfield, USA*

Purpose: drug eluting stent (DES) adoption has dramatically changed the percutaneous treatment of coronary artery disease. Little data are available regarding appropriate anticoagulant/antiplatelet regimens during DES. We sought to provide "real world" data from a high volume cardiac center on the utilisation, outcomes and economics associated with bivalirudin versus IIbIIIa use in DES patients.
Methods: all DES percutaneous coronary interventions (PCI) from 5/1/2003 to 12/31/2004 were included (n=2704). We excluded patients that received a bare metal stent and DES in the same procedure, vein graft interventions, ST segment elevation myocardial infarction, heparin use alone, and combined IIbIIIa/bivalirudin use. Clinical and outcome data were obtained from hospital databases. Economic data were obtained from our hospital accounting system. One year clinical follow up was obtained (95%) via phone call or mailed survey. Major adverse cardiac event (MACE) was defined as death, myocardial infarction (MI), coronary artery bypass (CAB), or target vessel revascularisation.
Results: in our study group, IIbIIIa inhibitor alone was used in 1986 (73.4%) patients and bivalirudin alone used in 718 (26.6%). All patients in the IIbIIIa group received concomitant heparin use. The demographics of the groups were significantly different on several variables. Significantly more patients in the IIbIIIa group had acute coronary syndrome (55.3% vs 39.1%, $p<0.001$), and more patients in the bivalirudin group had a prior MI (29.6% vs 37.9%, $p<0.001$), prior PCI (40.1% vs 47.1%, $p<0.001$), or prior CAB (20.3% vs 25.3%, $p<0.05$). Therefore, propensity analysis was performed to adjust for these differences. In-hospital outcomes were not significantly different [death (IIbIIIa 0.5% vs bivalirudin 0.4%), emergent PCI (0.1% vs 0%), CAB (0.6% vs 0.4%), or vascular bleed (0.6% vs 0.3%)]. At 30 days, MACE was 2.0% in the IIbIIIa group and 1.7% in the bivalirudin group (p=NS). From 30 days to one year, the MACE rate was similar between the groups (10.0% IIbIIIa versus 9.6% bivalirudin, p=NS). The median hospital costs were $10,954 for IIbIIIa and $10,153 for bivalirudin ($p<0.001$). Length of stay was 3.2 days for IIbIIIa, 3.0 days for bivalirudin (P=NS).
Conclusions: bivalirudin use during PCI with DES appears to be as effective as IIb/IIIa inhibitors in regards to in-hospital, short term, and long term outcomes, with statistically significantly lower median hospital costs. These findings are clinically concordant with the results of the REPLACE-2 trial in a real world setting using DES.

TRANSRADIAL APPROACH FOR PCI

P2235 Prevention of arterial spasm during percutaneous coronary interventions through radial artery: the SPASM study

A. Jegou[1], E. Salengro[1], A. Ohanessian[1], R. Cohen[1], S. Walspurger[1], X. Jouven[2], C. Spaulding[1], O. Varenne[1]. *[1]Hopital Cochin, Cardiologie Dept., Paris, France; [2]Hôpital Europeen Georges Pompidou, Cardiology, Paris, France*

Vascular complications at the puncture site are dramatically reduced by transradial interventionnal coronary procedures. However, occurrence of radial artery spasm remains the major limitation of this approach. The aim of the SPASM study was to compare the efficacy of different vasodilatators in the prevention of radial artery spasm during percutaneous coronary interventions.
Methods: Between May and October 2003, 601 consecutive patients were included in this prospective, double-blind study, and were randomized to receive placebo (n=198), molsidomine (1mg; n=203), or verapamil (2.5mg; n=200) intra-arterially after arterial sheath introduction. Only patients with an abnormal Allen test were excluded. Age, sex, wrist and arterial sheath sizes, puncture ability, numbers of catheters used and procedure duration were identical within the three groups. The primary end point was the occurrence of radial spasm defined by the operator as a painful limitation of the catheter movement with or without angiographical confirmation. Secondary end points were the intensity of pain (analogic scale 1-10) and characterization of spasm predictive factors. Statistical analysis included a Student t test (quantitative data) or a Pearson Chi squared test (qualitative data); a $p< 0.05$ was considered significant.
Results: Radial spasm was associated with younger age and female sex ($p<0.0001$ for both). Wrist dimensions, arterial sheath and catheter (5F vs. 6F) sizes did not influence the occurrence of radial spasm. Radial spasm was significantly reduced in patients receiving verapamil (7.5%) and molsidomine (15.3%) compared to placebo (22%), ($p<0.0001$ for both). Pain was reduced and procedures were judged easier and shorter in the absence of arterial spasm ($p<0.001$ and $p<0.0001$ vs spasm respectively). In multivariate analysis, arterial spasm was associated with significant pain (OR=3.3 for pain>2; CI (1.87-5.81)), and a more difficult procedure (OR=2.48; CI (1.37-4.49)). verapamil reduced arterial spasm more efficiently than molsidomine (OR 0.25 (CI(0.13-0.50)) and OR 0.44 (CI(0.24-0.80)) respectively.
Conclusion: This study demonstrates that verapamil is an effective treatment to reduce the occurrence of radial spasm during percutaneous coronary interventions through radial artery approach and should be recommended.

P2236 Safety of cardiac catheterisation by transradial approach in patients with complete and continuous oral coumadin therapy

M. Sanmartin Fernandez[1], B. Pereira[2], J. Esparza[2], M. Valdes[2], J. Moxica[2], V. Argibay[2], M. Gomez[2], A. Iniguez[2]. [1]*Vigo, Spain;* [2]*Hospital Meixoeiro, Interventional Cardiology Unit, Vigo, Spain*

Oral anticoagulants are commonly stopped before elective cardiac procedures. However, withdrawal of coumadin confers a substantial risk of thrombotic or bleeding complications. We assessed the safety of the transradial approach for elective cardiac catheterisation in patients who need continuous coumadin treatment.

Methods: In this prospective study, all consecutive nonhospitalised patients referred for elective catheterisation and taking chronic treatment with coumadin derivatives without interruption were included. Exclusion criteria were as follows: patient's refusal, referral physician preferences, elective percutaneous mitral valvuloplasty, anticipated need for sheaths > 6 French. Arterial sheaths were removed immediately after catheterisation and haemostasia was accomplished with elastic bands.

Results: from march/2004 to january/2005, 2987 consecutive patients underwent a diagnostic catheterisation procedure. A total of 71 patients were selected and included and 23 had at least one exclusion criteria (control group). Mean age was 69 ± 10 years; BMI was 28.4 ± 4.9; 41% were female, diabetes was present in 15 (21%), hypertension in 39 (55%), dyslipemia in 18 (25%). Atrial fibrillation was present in 51% and ischemic heart disease in 39%. Transradial procedure was successful in 65 patients (91.5%). Five patients (7%) needed crossover to transfemoral catheterization and one patient to ulnar access. A femoral closure device was used in only one case. Only 13% (9 patients) required prolonged compression (> 90 min), compared with 8% (2 cases) in control group (p = NS), while a significant haematoma (> 3 cm) at 1-week follow-up was present in only 1 patient (1.4%), compared with 3 patients (12.5%) in control group (p = NS).

Conclusions: in our experience, elective catheterisation by transradial approach in ambulatory patients taking oral anticoagulation is not only safe but is probably the strategy of choice to reduce the inconveniences of stopping oral coumadin therapy.

P2237 Trans Radial approach in Overweight Patients (BMI 35) (TROP study) compared to femoral access for coronary angiogram or PCI

H.B. Benamer[1], I. Narbute[2], I. Ungi[3], P. Garot[4], R.J. Ruiz-Salmeron[5], M. Hamon[6], O. Valsecchi[7], Y. Louvard[8]. [1]*Puteaux, France;* [2]*Latvia, Latvia;* [3]*Hungary, Hungary;* [4]*Quincy, France;* [5]*Barcelona, Spain;* [6]*Caen, France;* [7]*Bergamo, Italy;* [8]*Massy, France*

The incidence of obesity has been increasing in industrialized countries. The rate of cardiovascular disease in this population is higher, as is the reported rate of vascular and groin complications after transfemoral (TF) coronary angiography (CA) or angioplasty (PTCA). The trans-radial approach for CA or PCI may improve the prognosis of overweight patients.

We set up a prospective, multicenter (13 centers), European registry of overweight patients with BMI ≥ 35, undergoing CA and/or PCI in centres with broad experience in the trans radial approach (TR). The vascular approach was left to the operator's discretion.

The primary end point was the occurrence of complications delaying hospital discharge.We also analysed the incidence of all vascular complications and procedural endpoints (contrast, duration...).

Results: (Preliminary results: This registry will be limited to 500 patients)
346 pts: 97 TF (8 with closure device in TF) and 249 TR (CA: 65%, PCI: 11%, CA + PCI: 24%), Age: 61.2±10.9 years, Males: 52.9%, Weight: 108±15 kg, Height: 1.67±0.1 m, BMI: 38.7±3.4 kg/m^2. Extension of Coronary artery disease: No vessel disease (VD): 40%, One VD: 30%, Two VD: 18%, Three VD: 12%.

Results

	TR (n=243)	TF (n=103)	P
Contrast Angio (ml)	117±64	122±70	NS
Contrast PCI (ml)	161±74	205±81	0.03
Angio Duration (min)	26.1±19.0	31.3±17.7	0.03
PCI Duration (min)	29.8±15.7	46.8±22.3	0.003
Xray Exposure Angio (min)	6.8±5.6	7.4±7.6	NS
Xray Exposure PCI (min)	9.0±6.4	13.9±11.1	0.02
Hosp stay (d)	3.7±4.1	4.4±4.6	NS
Hosp stay afterC (d)	1.7±2.2	2.7±4.3	0.02
Primary End Point (%)	3 (1.2)	3 (2.9)	NS
Hematoma (%)	4 (1.6)	9 (8.7)	0.001

TR: Transradial ApproachTF: Transfemral Approach

In conclusion, the high rate of normal coronary angiogram shows that the diagnosis of coronary artery disease in this population is very difficult to make. Obesity is a complication factor in diagnostic angiography and coronary intervention. Use of the radial approach in obese patients reduces the rate of vascular complications.

P2238 Transradial coronary angiography and angioplasty in patients with oral anticoagulation full dose of acenocumarol: a feasibility and safety study

V. Martin, J. Angel, I. Anivarro, E. Domingo, P. Tornos, J. Soler. *Barcelona, Spain*

Aim: transradial coronary angiography+PCI on pat.taking full dose warfarine.

Methods: exclusion criteria: INR>3.5 and abnormal Allen test, or C/D response on plethysmography. Cross over to femoral approach allowed if INR < 2.

Results: Between 27/12/2003-18/11/2004, 1332 coronary angiography procedures were performed, 97 pat taking anticoagulants (7, 28%). Average age: 66, 63±9, 43. Males: 55, 6%. Average INR 2, 41±0, 62.Indication for anticoagulation: FA64, 9%; cardiac metallic valve prosthesis20, 6%;dilated cardiomyopathy 5,15%; stroke4,1%; arterial thrombi 2,06%; antiphospholipid antibody syndrome 1,03%; PE 1,03%; venous thrombosis 1,03%. Indications angiography: preoperatory of cardiac surgery 49, 4%, myocardial ischemia 35%, dilated cardiomyopathy 10%, CHF 2,06%,ventricular arrhythmias 1,03%, prosthetic valve malfunction 1,03%. 2 patients showed bilateral abnormal Allen test results and type C or D responses on plethysmography (2,06%).Cross-over to femoral artery: 6 patients: 2 showed exclusion criteria, 3 very small radial arteries,1 subclavian tortuosity. Access site: right radial artery in78%; left in 20, 8%.5F catheters used in 78%. The most frequent catheter employed for RCA: JR5 (53, 8%) and for LCA: JL 3, 5 (53, 8%). In addition 9, 27%pat.underwent coronary artery bypass graft angiography; 25, 7% aortography;21,6% left ventriculography and 12 PCI (2 balloon angioplasty and 10 coronary stenting).Complications in laboratory room: + common radial spasm(severe in 7, 2%) but the procedure was fully carried out in all pat. Cardiac complication:1 NSVT without aftereffects. There were no local or systemic complications.2 hemostatic devices were employed (Radstad/TR band) 4 hours. Hospitalization period (24 hours) no patient presented any local, cardiac or systemic complication. Telephone follow-up one month after the procedure (92,78%): 1 death (pulmonary alveolitis);1 stroke (INR 2,63) 72 hours after the operation. There were no major local complications. No patient required a blood transfusion, any interruption in the warfarin treatment, or to be admitted as result of a catheterisation complication. Minor local complications: 2 dysaesthesia, 12 small echimoses and 4 haematomas < 5cm. No patient needed specific treatment for these complications.

Conclusions: Radial artery access is feasible and safe in the majority of cases in high risk patients taking full dose of oral anticoagulants with INR < 3, 5. This access does not lead to a prolonged stay in hospital or major acute or subacute local complications and minimizes the risk of systemic emboli.

P2239 Transradial access for cardiac procedures in patients with coronary bypass grafts. Comparison with transfemoral approach

M. Sanmartin Fernandez[1], J. Moxica[2], M. Valdes[2], J. Esparza[2], J.A. Baz[2], A. Ortiz[2], R. Mantilla[2], A. Iniguez[2]. [1]*Vigo, Spain;* [2]*Hospital Meixoeiro, Interventional Cardiology Unit, Vigo, Spain*

Transradial access is a well established technique for coronary angiography. However, its feasibility for diagnostic and intervention procedures in patients with coronary bypass grafts is less well studied. Accordingly, we analysed a consecutive series of patients with bypass grafts referred for catheterisation and compared transradial and transfemoral procedures regarding feasibility, safety and procedural variables.

Methods: retrospective review of 322 cardiac procedures in patients with past surgical revascularization performed in a single centre. Among these, 303 diagnostic procedures were considered eligible for both transradial and transfemoral approach. Fifty patients with angioplasty procedures performed in bypass grafts were also analysed. Selection of the arterial access was individualised according to operator preferences.

Table 1. Procedural data for diagnostic procedures

	Transradial (n = 151)	Transfemoral (n = 152)	p value
Total time (min)	41 ± 22	40 ± 23	0.69
Fluoroscopy (min)	15 ± 9	18 ± 13	0.03
Dye volume (mL)	180 ± 64	195 ± 72	0.14
Catheters	3.2 ± 1.1	3.3 ± 0.9	0.83
Crossover	6 (4.0%)	2 (1.3%)	0.28

Results: radial access was attempted as first choice in 151 cases (left radial in 133) and femoral artery in 152. Total procedural time, fluoroscopy time and dye volume were similar (table). Fifty patients had PCI performed in bypass grafts (15 transradial and 35 transfemoral). Distal protection was used in 44% in transradial and 35% in transfemoral cases (p = 0.8). There were 2 PCI failures in transfemoral group and none in transradial group. Only 2 patients in transradial group needed femoral puncture because of failure to catheterise bypass grafts. One patient in transradial group presented a vascular complication that required prolonged hospitalization.

P2240 Utility of color duplexsonography before repeated percutaneous transradial catheterisation

H.-H. Minden[1], K. Brilla[2], C. Butter[2]. *[1]Berlin, Germany; [2]HZ Bernau, Cardiology, Bernau, Germany*

Introduction: The transradial approach has currently been accepted as an alternative entry method for coronary angiography and angioplasty. The purpose of this study was to evaluate whether color duplexsonography of the forearm arteries can prevent vascular complications in patients before repeated percutaneous transradial catheterisation (RPTC).

Methods and Results: 152 consecutive patients (mean age = 67 years, 110 male) were examined. The mean time to the previous percutaneous coronary intervention (PCI) was 10 month (range 4 – 45 month). The sheath size was 6Fr in all cases. We analyzed the peak systolic and diastolic velocitiy (Vmaxsys, Vmaxdiast) and the pulsatality index (PI) on the access site using a 7,5-MHz linear transducer. The contralateral site served as reference.

Radial arterial occlusions were detected in 5 patients. 4 of these 5 patients were undergoing at least 2 PCI's on the same access site previously. There were no differences evaluable between the access site and the reference site in the Vmaxsys, Vmaxdiast and the PI in the remaining patients. Among the clinical variables of diabetes mellitus (DM), peripheral arterial occlusive disease (PAOD) and renal failure (RF) no significant differences were measured. 7 of 8 patients had normal Doppler flow velocities on the ipsilateral ulnar artery irrespective of negative Allen-testing.

Flow Measurements

radial artery, access site	no risk factors	DM	RF	PAOD	RPTC
PI	3,1±0,9	3,0±0,8	3,4±1,2	3,5±1,0	3,1±1,0
vmaxsys m/s	0,7±0,2	0,7±0,3	0,8±0,4	0,8±0,4	0,7±0,2
vmaxdiast m/s	0,06±0,05	0,06±0,03	0,05±0,03	0,05±0,04	0,06±0,04
Reference					
PI	3,3±1,1	3,2±0,8	3,4±0,8	3,7±1,2	3,3±1,1
vmaxsys m/s	0,7±0,2	0,7±0,3	0,7±0,3	0,8±0,4	0,7±0,2
vmaxdiast m/s	0,07±0,04	0,05±0,04	0,05±0,03	0,05±0,03	0,06±0,05

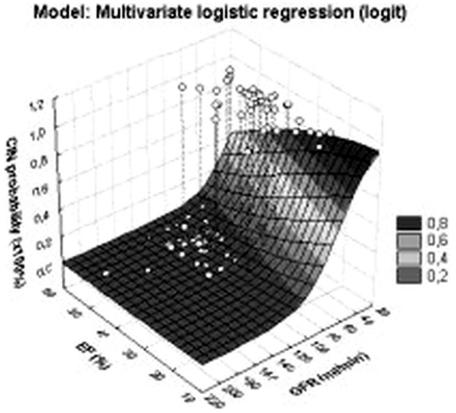
Conclusion: The results suggest that RPTC increases the risk of radial arterial occlusion. Furthermore, no other vascular risk factor affected the measured duplexsonographic parameters. In patients with negative Allen-testing and normal Doppler flow velocity on the ipsilateral ulnar artery transradial approach can be used safely.

HEART AND KIDNEY

P2241 Glomerular filtration rate as a predictor of contrast-induced nephropathy in diabetic patients after myocardial infarction treated invasively

R. Lenarczyk[1], J. Kowalczyk[1], J. Prokopczuk[1], O. Kowalski[1], G. Honisz[1], M. Gasior[2], L. Polonski[2], Z. Kalarus[1]. *[1]Silesian Center for Heart Diseases, 1st Department of Cardiology, Zabrze, Poland; [2]Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland*

Contrast induced nephropathy(CIN)patients(pts)with myocardial infarction(AMI) treated invasively is associated with higher risk of death, especially in pts with diabetes mellitus (DM).Aim of the study:to select CIN-predictors and estimate independent risk factors of CIN among diabetic pts with AMI.Methods: single center study evaluated 320 pts with DM(21,5%)with normal creatinine(SCr)on admission selected from 1486 consecutive AMI pts treated with PCI.Study population was divided into CIN gr(n=45)and nonCIN gr(n=275).CIN was defined by SCr$<$133μmol/L on admission and its 25% increase, with value$>$133μmol/L within 48h after PCI.Glomerular filtration rate(GFR)was estimated using Modification of Diet in Renal Disease Study Equation.Independent CIN predictors were identified using multivariate logistic regression.



CIN probability depending on EFand GFR

Results: CIN pts were older,with more advanced CAD,lower ejection fraction(EF)and lower GFR.Mortality during 29,7 months of follow up was 45,7% in CIN gr vs 15,2% in nonCIN gr, p$<$0,001.Multivatiate analysis identified GFR as the strongest independent predictor of CIN in DM pts.

Independent CIN predictors

	OR/unit (95%CI)	p
Age	1,05 (1,01-1,09)	$<$0,05
EF	0,95 (0,91-0,99)	$<$0,05
GFR	0,96 (0,93-0,99)	$<$0,001

Conclusion: Diabetic pts with AMI prone to CIN have discrete characteristics.GFR is independent and strong predictor of CIN in this group,especially in pts with impaired EF.

P2242 Renal function and choice of myocardial reperfusion modality for ST elevation acute coronary syndrome a substudy of acute coronary syndrome Israeli survey (ACSIS) 2004

R. Dragu[1], S. Behar[2], A. Sandach[2], M. Kapeliovich[3], S. Rispler[3], H. Hammerman[3]. *[1]Rambam Medical Center, Intensive Cardiac Care Unit, Haifa, Israel; [2]Sheba Medical Center, Neufeld Cardiac Institute, Tel Hashomer, Israel; [3]Rambam Medical Center, Intensive Cardiac Care Unit, Haifa, Israel*

Purpose: To assess the preferred modality of myocardial reperfusion, in patients with and without renal failure, suffering from ST elevation acute coronary syndrome (STEACS).

Methods: Out of 1026 patients with STEACS enrolled in ACSIS 2004, we identified 959 patients for whom the glomerular filtration rate (GFR) was estimated by means of Modification of Diet in Renal Disease equation. The study population was grouped according to GFR above and under 60 ml/min/1.73 m^2 body surface area. The outcome (7-day and 30-day mortality) and complications (major bleeding) were compared for patients treated by primary PCI (PPCI) and thrombolysis (TLX) in each group.

Results: In the normal renal function (NRF) group (GFR $>$ 60 ml/min/1.73 m^2), 416 (61.4%) patients received reperfusion therapy. Of them, 66.5% had PPCI, while the rest were treated by TLX. In the renal failure (RF) group ($<$ 60 ml/min/1.73 m^2 BSA), 153 (54.2%) patients received reperfusion therapy, with 67.9% of them having PPCI and the remainder TLX. In both NFR and RF groups, no significant statistical differences were observed between patients treated by PPCI and TLX, regarding age, gender, previous myocardial infarction and stroke, on-admission Killip class and in-hospital ejection fraction.

In NRF group, the 7-day and 30-day mortality of patients treated by PPCI, compared with those receiving TLX, was significantly lower (0.3% vs. 3.5%, P$<$0.02 and 0.3% vs. 4.3%, P$<$0.007 respectively). In the RF group, the outcome of patients treated by PPCI and TLX was similar (11.5% vs. 12.2%, P=0.54 and 17.3% vs. 16.3%, P=0.64).

The myocardial reperfusion modality had not impact on our observations concerning major bleeding, neither in NRF nor in RF group.

Conclusion: The results of our study suggest that, in patients with STEACS and normal renal function, PPCI is the preferred modality of myocardial reperfusion, whereas for those with renal failure PPCI and TLX offer similar results.

P2243 The impact of renal function on long-term clinical outcome after percutaneous coronary intervention

M.I. Papafaklis[1], N.D. Papamichael[1], G. Kollios[2], K.N. Naka[1], L. Sioros[3], V. Sclerou[4], C.S. Katsouras[5], L.K. Michalis[5]. *[1]Michailidion Cardiac Center, Ioannina, Greece; [2]University Hospital of Ioannina, Department of Biochemistry, Ioannina, Greece; [3]General District Hospital of Arta, Department of Cardiology, Arta, Greece; [4]General District Hospital of Preveza, Department of Cardiology, Preveza, Greece; [5]Medical School, University of Ioannina, Department of Cardiology, Ioannina, Greece*

Patients with impaired kidney function undergoing percutaneous coronary intervention (PCI) experience increased in-hospital and 1-year major adverse cardiac events (MACE).

Aim: To investigate the impact of renal function on the extended long-term clinical course of patients after successful PCI.

Methods: Baseline data and follow-up information on MACE (death, Q-wave myocardial infarction, bypass grafting or PCI) and anginal symptoms was obtained for 358 patients not on dialysis who underwent PCI and were discharged alive from June 1995 to June 1999. Glomerular filtration rate (GFR) was estimated using the abbreviated MDRD Study equation and the patients were classified in two groups: A) GFR $<$ 60 ml/min per 1.73m^2 and B) GFR $\geq$ 60 ml/min per 1.73m^2. Survival and MACE-free rates were computed for the two groups and the strength of GFR as an independent predictor for MACE was assessed.

Results: Ninety-one (25.4%) patients had moderate to severe renal insufficiency (GFR $<$60 ml/min per 1.73m^2) and were more likely to be older, female and diabetic and to have a history of previous bypass grafting in comparison to group B. Nine-year all-cause and cardiac mortality rates were significantly higher in the reduced GFR group versus those with GFR $\geq$ 60 ml/min per 1.73m^2 (39.4% vs. 10%, p$<$0.001 and 27.6% vs. 6.4%, p$<$0.001 respectively), while no significant

differences were revealed for all MACE-free survival. Moreover, surviving patients with low GFR had a significantly greater risk for presenting with angina at follow-up compared to surviving patients with GFR $\geq$ 60 ml/min per 1.73m^2 (OR:1.87, p=0.036). Multivariate Cox regression analysis identified GFR $<$ 60 ml/min per 1.73m^2 as an independent predictor of 9-year all-cause and cardiac mortality [HR: 2.68 (1.5-4.7 95% CI), p=0.001 and HR: 2.7 (1.3-5.6 95% CI), p=0.007 respectively].
Conclusion: Moderate to severe impairment of renal function is a strong determinant of long-term all-cause and cardiac mortality after successful PCI.

P2244 Frequency and importance of abnormal renal function in consecutive patients undergoing invasive management of an acute coronary syndrome

A. Cormack[1], C. Berry[2], G. Marshall[1], D. Motherwell[1], J. Rogers[3], J. Christie[3], S.M. Cobbe[1], H. Eteiba[3]. *[1]University of Glasgow, Department of Cardiology, Glasgow, United Kingdom; [2]Western Infirmary, Department of Cardiology, Glasgow, United Kingdom; [3]North Glasgow Hospitals Univ. Trust, Cardiology, Glasgow, United Kingdom*

Background: Renal function influences the prognosis of patients undergoing coronary revascularisation. PCI and CABG are often undertaken in patients with an acute coronary syndrome (ACS), however, the frequency and importance of renal dysfunction in an unselected ACS population are uncertain.
Methods: Consecutive index admissions with a suspected ACS referred for invasive management (31-07-03 to 30-07-04) were prospectively studied. Glomerular filtration rate (GFR) was estimated using the MDRD formula.
Results: Of 1558 admissions with an ACS, 477(31%) were referred for interventional management, which was performed in 455(95%) of these patients (n=147(32%) women). Renal function was available in 447(98%) of these patients. ST-elevation myocardial infarction (MI), NSTEMI or unstable angina occurred in 74(17%), 193(46%) and 188(41%) patients, respectively. Mean(SD) creatinine (C) concentration was 106(52) μmol/L and 63(14%) patients had an elevated C($>$130 μmol/L). Of those with a normal C, 268(70%) and 77(20%) had a GFR 60-89 mL/min/1.73m^2 and GFR 30-59 mL/min/1.73m^2, respectively. A rise in C$\geq$20% occurred in 38(21%), 28(22%) and 19(33%) patients treated with medical therapy, PCI or CABG, respectively (P=0.2; PCI vs CABG P=0.15). Overall, an elevated C or C rise$\geq$20% occurred in 125(28%) patients. Secondary prevention therapy use was similar in with or without stable renal function. Predictors (odds ratio, 95%CI) of an elevated C or C rise$\geq$20% included age (1 year: 1.03(1.01,1.06); P=0.003), anaemia (2.74 (1.64,4.55); P$<$0.0001), valve disease (3.31 (1.45,7.62); P=0.005), vascular disease (3.04 (1.25,7.39); P=0.014), heart failure (3.22 (1.09,9.54); P=0.035) and diabetes (2.19 (1.07,4.48); P=0.032). Duke score and CABG were univariate, but not multivariate, predictors of renal dysfunction.
Admission duration (days) was longer in patients in whom renal function deteriorated compared to in those with stable renal function (13(15) vs 9(9); P=0.0004). Renal dysfunction (GFR$<$60) 3.61(1.28,5.94); P=0.002) and creatinine rise$\geq$20% (3.52 (2.40,4.65); P$<$0.0001) were univariate predictors of admission duration, but after adjustment for other predictors, only a C rise$\geq$20% (not GFR or C) predicted admission duration (4.78 (2.00,7.56); P=0.001). Of those who died in hospital (n=9), 6(67%) experienced a C rise$\geq$20% (P=0.0005)
Conclusions: Renal dysfunction and deterioration in renal function are common in ACS patients undergoing invasive management. Although renal dysfunction is related to hospital outcomes, deterioration in renal function may be a more important prognostic marker.

P2245 Elevated parathyroid hormone is an important risk factor for restenosis after percutaneous coronary intervention in patients with chronic haemodialysis

T. Kubo, T. Hano, M. Obana, Y. Tomobuchi, I. Nishio. *Wakayama Medical University, Department of Cardiovascular Medicine, Wakayama, Japan*

Background: Secondary hyperparathyroidism is prevalent among patients with chronic hemodialysis and influences the calcium metabolism. Excess of parathyroid hormone (PTH) play an important role in the development of coronary calcification and atherosclerosis. However, the influence of secondary hyperparathyroidism on restenosis after percutaneous coronary intervention remains unclear.
Objective: The aim of this study was to evaluate whether serum levels of PTH can predict the risk for restenosis after percutaneous coronary intervention in patients with chronic hemodialysis.
Methods: One hundred and one consecutive patients with hemodialysis who underwent percutaneous coronary intervention were divided into two groups: elevated PTH group (n=42, intact PTH $>$ 300 pg/ml, 477 $\pm$ 239.1 pg/ml, mean $\pm$ SD) and normal PTH group (n=59, intact PTH $<$ or = 300 pg/ml, 136 $\pm$ 104.4 pg/ml). The rates of restenosis (defined as an $>$ 50% diameter stenosis) evaluated by follow-up angiographies at 6 months after percutaneous coronary intervention were compared in two groups.
Results: The baseline clinical and procedural characteristics were not different between two groups. At follow-up angiographies, the minimum lumen diameter in elevated PTH group was significantly lower than that in normal PTH group (1.2 $\pm$ 0.9 mm vs. 2.0 $\pm$ 0.7 mm, p$<$0.001). The late lumen loss during follow-up period in elevated PTH group was significantly higher than that in normal PTH group (1.2 $\pm$ 0.8 mm vs. 0.9 $\pm$ 0.6 mm, p$<$0.05). The rates of restenosis in elevated PTH group was significantly higher than that in normal PTH group (56% vs. 24%, p$<$0.005). Furthermore, multivariate logistic regression analysis demonstrated that secondary hyperparathyroidism was associated with angiographic restenosis after adjusting for conventional risk factors (hazard ratio = 4.4, 95% confidence interval: 1.5 to 12.7, p$<$0.01).
Conclusion: In patients with chronic hemodialysis, the secondary hyperparathyroidism is an independent and strong risk factor for angiographic restenosis after percutaneous coronary intervention.

P2246 Prevalence and predictors of vascular and valvular calcification in patients with chronic kidney disease

S. Dellegrottaglie[1], M. Kiser[2], F. Finkelstein[3], G. Eisele[4], N. Levin[5], M.K. Kuhlmann[5], R. Saran[6], S. Rajagopalan[1]. *[1]Mount Sinai Medical Center, Cardiovascular Insitute, New York, United States of America; [2]University of North Carolina, Division of Nephrology, Chapel Hill, United States of America; [3]Yale University, Yale Medical Group, New Haven, United States of America; [4]Albany Medical College, Division of Nephrology, Albany, United States of America; [5]Renal Research Institute, New York, United States of America; [6]University of Michigan, Division of Nephrology, Ann Arbor, United States of America*

Background: Vascular and valvular calcifications are highly prevalent in patients with end-stage renal disease. The predictors of this process are poorly characterized in the more numerous population of patients with chronic kidney disease (CKD). Since the extent of vascular calcification may influence the high susceptibility of these patients to atherosclerotic events, it is important to understand the variables that may influence these processes. We attempted to describe the prevalence and to identify the major determinants of vascular and valvular calcification in a prospective cohort of CKD patients recruited from four cademic centers in the United States.
Methods: Eighty-five patients (56% men; mean age 59$\pm$15 years) from the Renal Research Institute-CKD Study cohort [mean glomerular filtration rate (GFR) = 23.3$\pm$10 mL/min/m^2) at study entry] underwent a retrospectively-gated 16-slice multi-detector CT (MDCT) imaging for the assessment of calcification at the level of coronary arteries (CA), thoracic aorta (TA), aortic valve (AV) and mitral valve (MV). For each location, Agatston scores were calculated using a dedicated workstation. Calcium scores were log transformed to adjust for skewness of data prior to application of univariate and multivariate regression models.
Results: The prevalence of CA, TA, AV and MV was 66%, 46%, 39% and 16% respectively, while mean scores were 564$\pm$1186, 669$\pm$1564, 158$\pm$433 and 117$\pm$549, respectively. CA score was significantly correlated with TA (r=0.60, p$<$0.0001), AV (r=0.47, p$<$0.0001) and MV (r=0.24, p=0.026) scores. On multivariate analysis (after adjustment for age, gender, race and diabetic status), the extent of CA was positively correlated with a history of coronary artery disease (p=0.001), congestive heart failure (p=0.012) and with serum creatinine (p=0.011), while it was negatively correlated with GFR (p=0.026). Serum levels of calcium, phosphorus, calcium-phosphate product and bio-active parathyroid hormone were not related to vascular or valvular scores.
Conclusion: CKD is associated with high prevalence of vascular and valvular calcification. In this cohort, the extent of calcification does not appear to be related to indices of mineral metabolism, but does correlate with the severity of renal impairment and history of heart disease.

P2247 Impact of renal dysfunction on one year mortality after acute myocardial infarction

F. Schiele, P. Legalery, K. Didier-Petit, N. Meneveau, M.F. Seronde, J.-P. Bassand. *Pole Coeur Poumons, Service de Cardiologie, Besancon Cedex, France*

Background: Survival after acute myocardial infarction is linked to multiple factors, including mild or severe chronic kidney dysfunction. The aim of this study was to determine to what extent a reduction in glomerular filtration rate (GFR) influences one year mortality when risk level at admission and quality of care are taken into account.
Methods: A prospective registry was carried out in a geographically delimited area, including all patients admitted with a diagnosis of acute myocardial infarction (MI) over a 6 month period. The GFR was calculated from serum creatinine levels and patients were stratified into 3 groups: GFR1: $>$59 ml/min/1.73m^2, GFR2: $>$29 and $<$60 ml/min/1.73m^2 and GFR3: $<$30 ml/min/1.73m^2. A risk index based on initial presentation was calculated. In-hospital and discharge treatments were recorded, taking into account possible contra-indications. Patients were followed for one year to assess all-cause mortality rate.
Results: A total of 754 patients were included; 333 ST elevation MI and 421 non ST elevation MI. Overall one year mortality was 11.5%. Patients with impaired GFR were older, with more comorbidities, received fewer effective therapies (less reperfusion, GPIIbIIIa receptors inhibitors, early angiography, betablockers and statins). One year mortality was higher with decreasing GFR: GFR1: 2.3% (5/215), GFR2: 9.4% (31/328) and GFR3: 24.2% (51/211), p$<$ 0.001 for trend. By multivariable logistic regression, a significant association was found between one year mortality and risk index (OR = 1.41 [1.16;1.71] per 10% increase in risk

index), GFR (OR = 0.97 [0.95;0.98] per additional GFR unit), use of beta-blockers (OR = 0.15 [0.05;0.50] for users) and early coronary angiography (OR = 0.26 [0.32;0.66] for patients submitted to angiography).
Conclusions: In patients with acute MI, decreased GFR is associated with higher mortality, and this relation remains strong after adjustment for the level of risk at admission and the effective treatments used.

P2248 Mild to moderate renal failure in patients with chronic heart failure- impact on cardiac function, QRS duration and prognosis

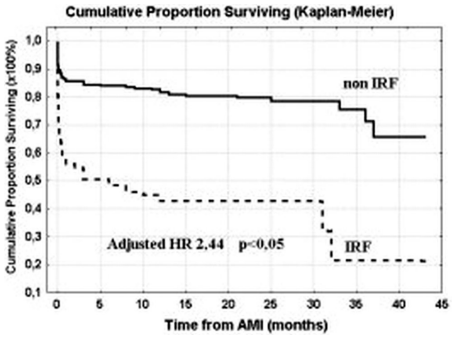
C. Bruch, H. Reinecke, J. Stypmann, L. Eckardt, G. Breithardt, T. Wichter. *WWU Munster, Medizinische Klinik und Poliklinik C, Munster, Germany*

Background/Aim: In patients (pts) with chronic heart failure (CHF), end-stage chronic renal failure (RF) is associated with a poor prognosis. The association of mild to moderate RF with outcome in patients with stable CHF is unclear. The present study was designed to assess the impact of mild to moderate RF on cardiac function, QRS duration and prognosis in subjects with underlying CHF.
Methods: We prospectively enrolled 181 pts with stable CHF (mean age 59±12 years, 114 with ischemic, 67 with non-ischemic cardiomyopathy, mean NYHA functional class 2.7±0.5). RF was defined as a creatinine level = 1.5 mg/dl in men or = 1.3 mg/dl in women. 2-D/Doppler echo measurements included left ventricular (LV) dimensions/volumes, muscle mass index, ejection fraction (EF), mitral E/A ratio, deceleration time and tissue Doppler analysis of mitral annular velocities. The mitral filling pattern was classified as either restrictive or non-restrictive. QRS duration was derived from the 12-lead ECG.
Results: RF was present in 60 pts (35.9% of the study population, two subjects with end-stage RF). Patients with or without RF did not differ significantly with respect to EF (29±10 vs. 30±10%, p=ns), mitral E/A-ratio (1.77±1.80 vs. 1.61±0.97, p=ns), deceleration time (194±84 ms vs. 183±83 ms, p=ns) or mitral annular E' velocity (5.6±1.6 cm vs. 6.0±1.7 cm/s), but RF pts had larger LV volumes, a higher muscle mass index (202 g/m^2 vs. 158 g/m^2, p<0.001) and a longer QRS duration (152±42 ms vs. 130±33 ms, p=0.002). During a follow-up of 412±266 days, 28 pts suffered a cardiac event (cardiac death, n=26; urgent cardiac transplantation, n=2). Stepwise multivariate Cox regression analysis identified the presence of RF (Relative risk: 4.91, 95% CI 2.07-11.6, p<0.001), QRS duration > 147 ms (RR 3.92, CI 1.57-9.24, p=0.002) and a restrictive mitral filling pattern (RR 3.0, CI 1.27-7.04, p=0.009) as the strongest independent predictors of a cardiac event. In pts with RF, the outcome was markedly worse than in patients without RF (event-free survival rate 59% vs. 88%, p=0.0002).
Conclusions: Mild to moderate RF is a strong and independent predictor of poor outcome in patients with stable CHF. Poor outcome is related to prolonged QRS duration predisposing to ventricular arrhythmias and sudden cardiac death.

P2249 Impact of impaired renal function on survival in patients with acute myocardial infarction complicated by heart failure

Z. Kalarus[1], R. Lenarczyk[1], J. Kowalczyk[1], O. Kowalski[1], A. Musialik-Lydka[1], B. Sredniawa[1], M. Gasior[2], L. Polonski[2]. *[1]Silesian Center for Heart Diseases, 1st Department of Cardiology, Zabrze, Poland; [2]Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland*

Symptoms of heart failure (HF) are associated with poor prognosis in patients (pts) with acute myocardial infarction (AMI). Aim of the study was to examine the influence of impaired renal function (IRF) on long-term outcome in AMI pts with HF.
Methods: single center study evaluated 325 pts with HF symptoms on admission (21,9%, NYHA ≥ II) selected from 1486 consecutive AMI pts treated with PCI. Study group was divided into IRF group (serum creatinine during hospitalization >133μmol/L, n=92, 28,3%) and non IRF group (n=233). Cumulative survival during mean follow up of 29,7 months was compared using log-rank, multivariate Cox-regression was used to select independent risk factors.



Survival in studied groups

Results: IRF pts were older, more often hypertensive, diabetic, with lower ejection fraction and higher prevalence of cardiogenic shock. Mortality rate was 59,4% in IRF pts compared to 23,1% in non IRF group (p<0,001). When incorporating significant variables into multivariate analysis, IRF was still an independent risk factor of any-cause death. Separate analysis of functional NYHA classes revealed that IRF influenced survival stronger in NYHA II class (HR 4,38, p<0,001) than III (HR 2,92, p<0,05) or IV (HR 2,87, p<0,05). Presence of IRF was more powerful risk factor (HR 3,3, p<0,001), than NYHA class in the analyzed HF group (HR 1,4, p<0,05).
Conclusions: Impaired renal function has significant and independent influence on remote survival in AMI pts with HF symptoms on admission. Its role is particularly pronounced in moderately advanced HF.

P2250 Gender differences in the relation between mild to moderate renal impairment, angiographic coronary disease and seven-year cardiovascular mortality

R. Chen[1], A. Timmis[2], G. Feder[3], M. Yaqoob[4], H. Hemingway[5]. *[1]University College London Medical School, Epidemiology and Public Health Department, London, United Kingdom; [2]Barts and the London NHS Trust, Cardiology, London, United Kingdom; [3]Barts and the London NHS Trust, General Practice and Primary Care, London, United Kingdom; [4]Barts and the London NHS Trust, Renal Medicine and Transplantation, London, United Kingdom; [5]University College Medical School, Epidemiology and Public Health, London, United Kingdom*

Mild to moderate renal impairment is associated with cardiovascular deaths, but little is known about gender differences in its association with coronary artery disease (CAD) and long-term mortality. We examined 465 female and 1144 male consecutive patients in the Appropriateness of Coronary Revascularization cohort who underwent coronary angiography and had serum creatinine measurement. The presence of CAD related to creatinine of 1.2-1.9 mg/dL (adjusted odds ratio 1.56, 95%CI 1.01-2.41) and glomerular filtration rate (GFR) of 30-59 ml/min/1.73m^2 (1.85, 1.15-2.96) in women, but not in men. Seven-year cardiovascular mortality increased for women in creatinine and GRF (adjusted hazard ratio 1.77, 1.07-2.92 and 5.20, 1.57-17.24) more than men (1.25, 0.88-1.77 and 1.82, 1.32-2.51). Our findings suggest that there may be differences in the association of mild to moderate renal impairment with CAD and cardiovascular morality between genders, and female patients need particular attention on mild to moderate renal impairment.

P2251 Ischaemia-modified albumin for the detection of ischaemia and risk stratification in end stage renal disease

R. Sharma[1], D.C. Gaze[2], D. Pellerin[3], R. Mehtha[4], P.O. Collinson[2], S.J. Brecker[5]. *[1]St George's Hospital, Cardiology, London, United Kingdom; [2]St George's Hospital, Biochemistry, London, United Kingdom; [3]The Heart Hospital, Cardiology, London, United Kingdom; [4]Southampton General Hospital, Statistics, Southampton, United Kingdom; [5]St George's Hospital, Cardiology, London, United Kingdom*

Objective: Ischemia modified albumin (IMA) is a biochemical marker of ischaemia. Cardiac disease is responsible for approximately half of all deaths in end stage renal disease (ESRD) so early diagnosis and treatment is essential. The aim of this study was to assess the prognostic significance of an elevated baseline IMA in ESRD and to determine whether an IMA rise during dobutamine stress can detect myocardial ischaemia in this group of patients.
Methods: 84 patients (mean age 52 ± 12 years, 75 male) referred for renal transplantation (mean creatinine 608 ± 272μmol/L) were prospectively studied over a mean follow - up period of 1.66 ± 0.58 years. All received dobutamine stress echocardiography (DSE). IMA levels were taken at baseline and one hour after cessation of DSE. A positive DSE was defined as the development of a new regional wall motion abnormality with stress or the deterioration in wall motion of baseline hypokinetic segments. Serum IMA was determined on a Cobas MIRA Plus using an indirect colorimetric method. An IMA > 85 kU/L was deemed positive for cardiac ischaemia. The primary end point over the follow up period was all - cause mortality.
Results: 43 (51%) patients had a significantly elevated baseline serum IMA levels. IMA rose with stress in both the DSE positive and negative groups (85.4 ± 28.1 kU/L to 107.9 ± 29.1 kU/L and 86.9 ± 26.7 kU/L to 95.4 ± 26.7 kU/L respectively). The rise in IMA with stress was significantly higher in the DSE positive group compared to those with no inducible ischaemia (22.5 ± 19.9 kU/L vs 8.2 ± 9.6 kU/L, p 0.007). The sensitivity of peak IMA levels to detect inducible ischaemia was 74% but specificity was low at 37%. An elevated baseline IMA was associated with significantly higher mortality (p = 0.02). These patients had significantly impaired mitral annular peak systolic velocity, higher left ventricular (LV) end diastolic diameter and higher LV end systolic diameter (p = 0.02, 0.04 and 0.04 respectively) compared to those without. Age, gender, the proportion of patients with diabetes, inducible ischaemia and on dialysis were similar in the 2 groups.
Conclusions: A significantly elevated baseline IMA level is present in 51% patients with ESRD referred for renal transplantation and is associated with significantly worse survival. These patients have LV dilatation and impaired LV long

axis function compared to those with normal baseline IMA levels. IMA rises during stress and is a sensitive marker of ischaemia in ESRD but specificity is low.

DIABETES/METALOLIC SYNDROME

P2252 Type 2 diabetes mellitus is not a coronary artery disease risk equivalent

C.H. Saely[1], T. Marte[1], S. Aczel[1], L. Koch[2], F. Schmid[2], P. Langer[2], P. Rein[2], H. Drexel[1]. *[1]Landeskrankenhaus Feldkrich, Department of Medicine and VIVIT, Feldkirch, Austria; [2]VIVIT-Institute, Feldkirch, Austria*

An equally high risk to die from a myocardial infarction (MI) has been described for patients with type 2 diabetes mellitus (T2DM) without a history of MI as for non-diabetic patients with a prior MI by one study from Finland, but other studies have not confirmed T2DM as a coronary artery disease (CAD) risk equivalent. Cardiovascular risk among diabetic patients may vary considerably if coronary atherosclerosis is present or absent.
Objective: We therefore aimed at investigating the risk of future vascular events with respect to both T2DM and angiographically diagnosed CAD.
Methods: We assigned 750 consecutive patients according to their coronary angiograms to one of four groups: DM-/CAD- (patients with neither T2DM nor CAD at angiography, n = 244), DM+/CAD- (patients with T2DM but without CAD, n = 50), T2DM-/CAD+ (patients without T2DM but with CAD, n = 342), and DM+/CAD+ (patients with both T2DM and CAD, n = 114). The incidence of fatal and non-fatal vascular events was recorded over 4 years.
Results: The incidence of vascular events averaged 20.1% in the 750 patients and was strongly affected by the angiographic state but not by the diabetic state: the proportion of patients with vascular events was similar in DM-/CAD- (8.9%) and DM+/CAD- (10.0%) patients (p = 0.739), but higher in DM-/CAD+ (23.8%, p <0.001) and DM+/CAD+ patients (40.2%, p <0.001) when compared to DM-/CAD-. Also, the incidence of vascular events was significantly higher in DM+/CAD+ than in DM+/CAD- (p <0.001) or DM-/CAD+ (p <0.001). Most importantly, patients with T2DM only (DM+/CAD-) had a significantly lower event rate than non-diabetic coronary patients (DM-/CAD+, p = 0.034).
Conclusions: Our 4-year prospective study provides strong evidence that T2DM is not a CAD equivalent: patients with T2DM and normal coronary angiography face only half the risk of non-diabetic CAD patients to develop an atherosclerotic event.

P2253 Frequency of angina pectoris in patients with diabetes mellitus compared to non-diabetic patients: clarifying an old myth

R. Zbinden, P. Meier, U. Wenger, S. Windecker, B. Meier, C. Seiler. *University Hospital Bern, Departement of Cardiology, Bern, Switzerland*

Background: According to general believe, diabetic patients have less angina pectoris during myocardial ischemia than non-diabetic patients (silent ischemia). However, this was never investigated systematically under conditions of equal coronary collateral flow.
Methods: 424 patients were included in the study (mean age 64 ± 10; 100 women, 324 men), 106 diabetic patients and 318 non-diabetic patients. Coronary collateral flow was assessed invasively using a pressure guide wire (n=272), Doppler guide wire (n=77) or both (n=75) to calculate pressure- or flow-velocity-derived collateral flow index (CFI). Patients were asked to report any chest pain or discomfort during a one minute balloon occlusion of a coronary artery supplying a non-infarcted myocardial area and an intracoronary ECG (i.c. ECG) (derived from the guidewire) was recorded simultaneously. Silent ischemia was defined as significant ST-segement elevation in the i.c. ECG (defined as ST-elevation >0.1mV) without any chest pain during balloon occlusion.
Each diabetic patient was matched for gender, age and CFI with three non-diabetic control patients (1:3 matching).
Results: The two groups differed significantly for high density lipoprotein (diabetic group: 1.15±0.36mmol/l, non-diabetic group:1.29±0.35 mmol/l; p=0.001) and triglycerides (diabetic group: 2.22±1.67mmol/l, non-diabetic group:1.84±1.32 mmol/l; p=0.02). There was no difference in anti-anginal medication between the two groups.
Coronary collateral flow was identical in the two groups (diabetic patients and non-diabetic patients: 0.21±0.12). In total, 66 (63%) of the diabetic patients and 214 (67%) of the non-diabetic control patients suffered from angina pectoris during the one minute balloon occlusion (p=0.34).
101 patients did not have any ST-segment changes in the i.c. ECG during the one minute balloon occlusion (27(25%) diabetic and 74(23%) non-diabetic patients; p=NS). CFI was significantly higher in patients without i.c. ECG changes compared to patients with i.c. ECG changes (0.34±0.15 vs 0.17±0.08; p<0.0001).
19 (24%) diabetic and 50 (24%) non-diabetic patients had silent ischemia (p=0.50).
Conclusion: Against general believe, diabetic patients do not have less angina pectoris during myocardial ischemia under conditions of equal coronary collateral flow.

P2254 Association between admission hyperglycemia and ST resolution in non diabetic patients after reperfusion therapy for acute myocardial infarction. Data from RICO survey

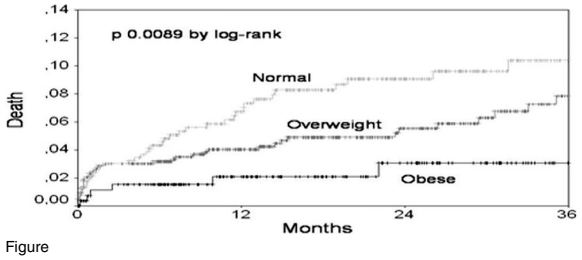
J. Abou Taam[1], L. Lorgis[1], G. Dentan[2], M. Jolak[3], I. L'Huillier[1], M. Vincent-Martin[4], M. Zeller[1], Y. Cottin[1] on behalf of RICO survey working group. *[1]CHU Le Bocage, Cardiology, Dijon, France; [2]Clinique de Fontaine, Cardiology, Fontaine les Dijon, France; [3]Centre hospitalier, Cardiology, Montbard, France; [4]CH, Cardiology, Beaune, France*

Background: After infarct artery recanalization, ST–segment resolution reflects myocardial rather than epicardial flow and hence yields major prognostic information. Recent studies have shown that hyperglycemia measured at admission is associated with worse in-hospital outcome after acute myocardial infarction (MI), even in non-diabetic patients. This is possibly related to impaired micro-vascular function. The present study was conducted to investigate the association between hyperglycemia and ST resolution in patients with acute MI.
Methods: From the French regional RICO survey, a consecutive prospective cohort of non diabetic patients with acute ST segment elevation MI who benefited from primary PCI or lysis < 12 H was analysed. Blood glucose was measured at admission for each patient. The patients were divided according to the degree of ST-segment resolution from the maximal ST-elevation measured on the single worst ECG lead 60 min after reperfusion therapy: group A with <50% ST segment resolution vs group B with ≥ 50% ST-segment resolution.
Results: Among the 458 patients included in the study, 141 (31%) had no ST resolution. Patients from this group had a similar rate of risk factors (age, hypertension, prior MI, smoking and hypercholesterolemia) but worse in-hospital outcome (death or heart failure, 33 vs 22%, p=0.02) than patients with ST resolution. They were also characterized by higher median (interquartile range) levels of glycemia (7.3(6.4-9.0) vs 7.2(6.2-8.7) mmol/l, p=0.02). Moreover, multivariate analysis showed that admission glycemia was an independent prognostic factor for ST segment resolution even after adjustment for potential confounders (age, sex, anterior wall MI and prior MI) (p=0.03).
Conclusion: The present study suggests a strong association between admission glycemia and ST segment evolution in non diabetic patients after reperfusion, and highlights the possible usefulness of early and intensive glycemic control in the setting of reperfusion therapy after acute myocardial infarction.

P2255 The impact of obesity on mortality in patients with unstable angina/non-ST segment elevation myocardial infarction treated with early revascularisation

H.J. Buettner, C. Mueller, M. Gick, M. Ferenc, J. Allgaier, K.D. Werner, T. Comberg, F.J. Neumann. *Herz-Zentrum Bad Krozingen, Kardiologie Abt., Bad Krozingen, Germany*

Background: The impact of obesity on outcome after unstable angina/non-ST segment elevation myocardial infarction (NSTEMI) is unknown.
Methods: In a prospective cohort study of 1676 consecutive patients with unstable angina/NSTEMI, all patients underwent coronary angiography and, if appropriate, subsequent catheter-based revascularization within 24 hours of admission. Patients were divided in three groups according to body-mass index: normal, 18.5 to 24.9 (n=551); overweight, 25 to 30 (n=823), and obese >30 (n=293). The primary endpoint was all-cause mortality.
Results: Obese patients were younger and had a higher incidence of hypertension, diabetes mellitus, elevated troponin T and C-reactive protein levels. The angiographic extent of coronary artery disease as well as in-hospital mortality were similar among the BMI-groups. Cumulative 3-year mortality rates were 9.9 percent in normal, 7.6 percent in overweight and 3.0 percent in obese patients (P=0.009). Figure shows Kaplan-Meier curves. Obese patients had less than half the long-term mortality as compared with normal and overweight patients (hazard ratio, 0.42 [95 percent confidence interval, 0.19 to 0.91]; P=0.028). After adjustment for confounding prognostic factors, the benefit of obesity regarding long-term mortality remained significant (hazard ratio, 0.19 [95 percent confidence interval, 0.05 to 0.80]; P=0.023).



Figure

Conclusions: Obesity is associated with improved outcome after unstable angina/NSTEMI treated with early revascularisation.

P2256 Obesity is associated with shortened telomere DNA in healthy subjects

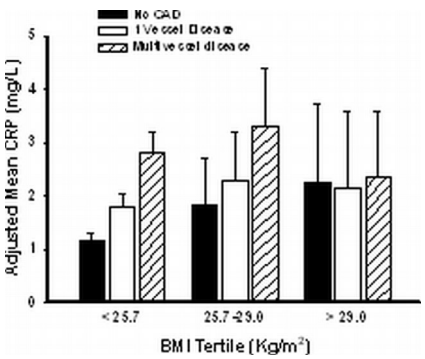
A.G. Stanley, R.A. Hastings, A. Carbone, P.S. Lacy, P.P.R. Swales, M. Dewar, K.E. Herbert, B. Williams. *University of Leicester, Department of Cardiovascular Sciences, Leicester, United Kingdom*

Purpose: Obesity is associated with an increased risk of premature cardiovascular morbidity and mortality. In the Framingham cohort, the life expectancy of forty-year-old obese individuals was reduced by about 7 years in non-smokers and 13 years in smokers. The telomere is a specialised nucleoprotein with a DNA repeat sequence (TTAGGG) that protects the integrity of genomic DNA and is a recognised molecular index of biological age. As a reduction in telomere length is associated with premature cardiovascular morbidity and mortality, this study tested the hypothesis that obesity is associated with shortened telomeres.
Methods: 71 (39 female) healthy volunteers were recruited. Participants were excluded if there was a prior history of significant ill health including cancer, cardiovascular disease, diabetes mellitus. Telomeres were measured from a sample of whole blood: genomic DNA was isolated and digested with HinfI/RsaI, followed by electrophoresis and Southern blotting. The median terminal restriction fragment length (TRF), representing telomere length, was measured after hybridisation with a ^{32}P-labelled telomeric probe and densitometric analysis of the telomere bands.
Results: Baseline demographics were consistent with a normal healthy population. A multiple regression analysis examined the influence of chronological age, mean arterial pressure (MAP), total cholesterol, body mass index (BMI) and gender on leukocyte telomere length (r^2 =0.244). Age (p=0.019) and increasing BMI (p=0.036) were the only significant determinants of telomere shortening. Importantly, the age-related rate of TRF loss was consistent across the age range (Age under 50 years: 30bp per year; age 50 years and over: 32.6bp per year). An obese cohort (BMI $>$30 kg/m^2, n=10) was compared to an identical number of non-obese individuals (BMI $<$21 kg/m^2, n=10); mean age-adjusted TRF values for obese and non-obese cohorts were significantly different (Obese: 6.65$\pm$0.73 kbp; non-obese: 7.65$\pm$0.68 kbp, Mann Whitney p=0.0068).
Conclusions: This data suggests that, independent of other factors, increased body mass is associated with shortened telomere DNA and that a weight gain of 1 kg/m^2 is equivalent to $\sim$3 years of chronological ageing. Obesity is associated with increased levels of systemic oxidative stress and therefore oxidative DNA damage is a likely mechanism to account for the accelerated rate of telomere attrition. Thus, obesity is associated with accelerated telomere attrition, a recognised biomarker of accelerated ageing and a risk indicator for premature mortality from cardiovascular disease.

P2257 Effect of obesity on the relationship between plasma C-reactive protein and coronary artery stenosis in patients with stable angina

D. Aronson[1], A. Goldberg[2], A. Roguin[2], S. Petcherski[2], D. Rimer[2], L. Gruberg[2], W. Markiewicz[2], R. Beyar[2]. *[1]Rambam Medical Center, Cardiology Dept., Haifa, Israel; [2]RAMBAM Medical Center, Cardiology Dept., Haifa, Israel*

Introduction: The association between plasma C-reactive protein (CRP) and the extent of coronary artery disease (CAD) in patients (pts) with stable angina remains controversial. Obesity is strongly associated with elevated CRP, potentially confounding the relationship between CRP and CAD severity.
Methods: We studied the relationship between CRP and the presence and severity of CAD in 830 subjects without known CAD and normal stress test and 218 pts with CAD undergoing elective coronary angiography. Geometric mean CRP were computed in a two-way analysis of covariance (ANCOVA) model in which study participants were stratified into 9 groups according to CAD status (no CAD, single vessel disease or multivessel disease) and tertiles of BMI, adjusting for age, smoking, hypertension, diabetes, and use of aspirin and statins.
Results: There was a significant interaction between CAD and categories of BMI with regard to CRP level (P = 0.003). Pts with CAD in the lower tertile of BMI had markedly higher CRP concentration compared to control subjects (1.16, 1.80, and 2.82 mg/L in subjects without CAD, pts with single vessel disease and pts with multivessel disease, respectively; P = 0.003; Figure). However, the relationship between CRP and CAD became weaker with increasing levels of obesity (P = 0.15 and P = 0.75 in study participants in the middle and upper BMI tertile, respectively; Figure).
Conclusion: The level of obesity is essential to the interpretation of the relationship between CRP and severity of CAD. The production of CRP with increasing levels of obesity becomes the dominant determinant of plasma CRP levels and masks the vascular contribution due to CAD.



Figure

P2258 Metabolic syndrome versus infectious burden on the degree of inflammation and the severity of coronary atherosclerosis

D. Dai[1], J.H. Kao[2], C.N. Hsu[3], F.T. Chiang[3], L.Y. Huang[3], J.L. Lin[3], Y.Z. Tseng[3], J.J. Hwang[3]. *[1]Taipei, Taiwan; [2]National Taiwan University, Graduate Institute of Clinical Medicin, Taipei, Taiwan; [3]National Taiwan University Hospital, Cardiovascular Medicine, Taipei, Taiwan*

Background: The factors responsible for the initiation and maintenance of inflammation in atherosclerosis remain controversial. We carried out a cross-sectional study to compare the effects of metabolic factors and infectious burden on the plasma level of C-reactive protein (CRP), the angiographic severity of coronary atherosclerosis and the lifetime major adverse cardiovascular events (MACEs), including cardiovascular mortality, myocardial infarction and stroke.
Methods: Coronary angiography was performed in 600 patients (400 men, mean age 61.3 $\pm$13 years; 200 women,mean age 64.7$\pm$12 years) with the clinical diagnosis of coronary artery disease (CAD). Gensini score was applied to assess the severity of coronary atherosclerosis. Metabolic score (MS)(0-5) was defined as the number of markers according to the modified criteria of National Cholesterol Education Program Adult Treatment Panel III. Infectious Score (0-7) was defined as the number of positive serology markers to H.pylori, C.pneumonia, herpes simplex virus (1&2), cytomegalovirus, hepatitis A, B and C virus.
Results: Neither the seropositivity to each pathogen nor the infectious score was associated with the plasma CRP level and the Gensini score. Higher MS was significantly associated with higher plasma CRP. Both MS and plasma CRP are independent predictors of Gensini score. MS and plasma CRP are also significantly associated with the risk of lifetime MACEs (for one point increase in MS, OR:1.4, p=0.01).

Regression Model (Gensini; MACEs)

	beta coef. of Gensini Score (95% CI)	OR of MACEs (95% CI)
Ln CRP (mg/L)	7.6 (3.9,11.4)*	1.6(1.3,1.9)*
Metabolic Score	14.3(9.7,18.9)*	1.4(1.1,1.7)*
Infectious Score	-2.2(-8.4,4.0)	1.1(0.8,1.5)
Sex	32.3(18.3,46.3)*	1.5(0.7,2.9)
Age	1.1(0.9,1.2)*	1.0(1.0,1.1)*
Hypercholesterolemia	20.4(8.3,32.4)*	0.8(0.4,1.4)
Smoking	5.1(-8.2,18.4)	0.6(0.3,1.2)

* p$<$0.01

Conclusion: Compared with infectious burden, the metabolic abnormalities have significantly greater contribution to the degree of inflammation, the progression of coronary atherosclerosis and the risk of lifetime MACEs in CAD patients.

P2259 Prognostic implications of fasting plasma glucose level, assessed on admission, in patients with acute myocardial infarction

F. Schiele, K. Didier-Petit, M.F. Seronde, P. Legalery, N. Meneveau, M. Mercier, J.-P. Bassand. *Pole Coeur Poumons, Service de Cardiologie, Besancon Cedex, France*

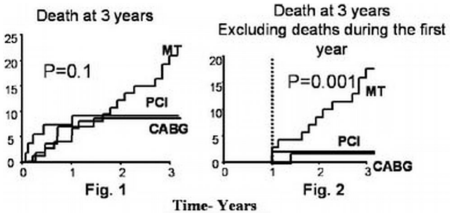
Rationale and Aim: High plasma glucose concentrations at the early phase of myocardial infarction represent a major risk factor for mortality, even in the absence of diabetes. To date, no threshold value for glucose levels to define "stress hyperglycaemia" has been determined and its impact on mortality is poorly documented. The aim of our study was to determine and validate a threshold value for glycaemia that defines "stress hyperglycaemia".
Methods: A prospective observational study including all patients admitted with acute myocardial infarction in 12 cardiology centres. Fasting plasma glucose levels on admission, risk levels (using the Global Registry of Acute Coronary Events risk score), guidelines-recommended treatment use and mortality at 6 months and one year were recorded. The cut-off value of glycaemia to define "stress hyperglycemia" was selected from ROC curves; its incremental predictive value on mortality was assessed by multivariable logistic regression and comparison of c-statistic values.
Results: 320 STEMI and 404 NSTEMI patients were included; the median value for stress glycaemia was 126 mg/dl [104 -167], median GRACE score was 147. Patients with glycaemia $>$140 mg/dl (7.7 mmol/l) were considered as having stress hyperglycaemia, and were generally older, with more frequent history of diabetes and hypertension, as well as worse heamodynamic conditions and a higher GRACE risk score. The use of guidelines-recommended treatments was similar, but mortality was considerably higher in patients with stress hyperglycaemia: 3.7% versus 12.1% (p$<$0.001) at one month. By multivariable logistic regression, three variables were independently related to one month and one year mortality, namely GRACE risk score (OR = 2.3 [1.8;3.0] per 10% increase),

treatment score (OR = 0.7 [0.6;0.8] per 10% increase) and stress hyperglycaemia (OR = 3.2 [1.9;5.6]). Comparison of c-statistic value between different models of logistic regression showed that the addition of "stress hyperglycaemia" in current risk score systems leads to higher discriminatory capacity.
Conclusions: Stress hyperglycaemia, defined as glycaemia > 140 mg/dl, in patients with acute myocardial infarction, represents an independent predictor of mortality, even after stratification for risk score and treatment.

P2260 Invasive coronary treatment (percutaneous and surgical) decreases mortality after 3 years in diabetics with multivessel disease. The Medicine, Angioplasty or Surgery Study (MASS II)

P. Soares, W.A. Hueb, N.H. Lopes, E.E. Martinez, P.A. Lemos, L.A.M. Cesar, S.A. Oliveira, J.A.F. Ramires. *Heart Institute-university Of Sao Paul, Interventional Cardiology, Sao paulo, Brazil*

Introduction: It is currently unknown whether revascularization procedures are associated with an improvement in the prognosis of diabetics, as compared to a more conservative medical treatment.
Patient population: In MASS II, a total of 611 patients (pts) with stable multivessel coronary disease were randomly assigned to medical treatment (203 pts, statins in 68%, betablockers in 68%), surgery (203 pts, mammary grafts in 92%) or angioplasty (205 pts, stent in 72%). From these, 179 patients had diabetes (medical: 74 pts; CABG: 58 pts; angioplasty: 47 pts) and comprised the present study population.
Results: At the end of 3 years of follow-up, patients treated with surgery or angioplasty presented a non-significant trend towards a lower global mortality rate compared to the medical group (Fig. 1). However, when only fatal events occurring between 1 and 3 years of follow-up were computed, both invasive strategies were observed to significantly decrease the death rate compared to patients assigned to medical therapy (with no difference between angioplasty and CABG) (Fig. 2).



Mortality Curves

Conclusion: For diabetics with multivessel disease, coronary revascularization (with either percutaneous intervention or surgery appears to decrease the risk of death in comparison to medical treatment, mainly due to a reduction in deaths after the fisrt year.

P2261 Effect of early ACE-inhibition in patients with acute myocardial infarction and metabolic syndrome

C. Borghi[1], S. Bacchelli[2], D. Degli Esposti[2], G. Mordenti[3], E. Ambrosioni[2]. *[1]Policlinico S. Orsola, Internal Medicine Dept., Bologna, Italy; [2]University of Bologna, St.Orsola Hospital, Internal Medicine, Bologna, Italy; [3]Menarini Research S.p.A., Firenze, Italy*

Background: The early administration of ACE-inhibitors is currently recommended in patients with acute myocardial infarction (MI). Metabolic syndrome (MS) is a risk factor for cardiovascular disease and it is associated with an enhanced activation of tissue renin-angiotensin system (RAS) and increased density of AT1-receptors for angiotensin II.
Objective and methods: The aim the present study is to evaluate the effects of the early admistration of ACE-inhibitor in patients with (MS+, n.686) and without MS (MS-, n.870) and enrolled in the SMILE study. The presence of metabolic syndrome was defined according to NCEP criteria. Patients with an acute anterior MI not undergoing thrombolisis have been randomly allocated within 24 hours from the onset of symptoms to 6-week treatment with zofenopril (30-60 mg/day) or matched placebo according to double-blind study design.
Results: MS+ and MS- patients were matched for demography and baseline characteristics. Blood pressure was higher in MS+ patients who also showed a greater use of antihypertensive drugs. The primary end-point (6-week occurrence of death+severe congestive heart failure) was reduced in MS+ patients treated with zofenoril when compared to placebo (2.5% vs. 7.7%: 2p=0.003). No difference has been observed in MS- patients despite a higher event rate (12.65 vs. 11.2%: 2p=0.61). Kaplan-Meier estimate showed a lesser 6-week cumulative event rate in MS+ patients treated with zofenopril (p=0.017) with an effect that was already evident after 1 week. No significant effect of ACE-inhibition has been observed in MS- patients (2p=0.52). Blood pressure decreases in a similar fashion in response to zofenopril or placebo in both MS+ and MS- patients. A reduced 1-year mortality rate has been observed in zofenopril-treated patients both MS+ (6.6% vs. 9.2%: 2p=0.051) and MS- (14.9% vs. 18.5%: 2p=0.025) even whether RR reduction (RRR) was greater in MS+ patients (RRR: -29% vs. -19.4%).
Conclusions: The results of the present study suggest the primary role of RAS blockade through ACE-inhibition in patients with MS and acute MI.

P2262 Serotonin 5-HT2 receptor antagonist improves vasomotor responses in diabetics with atherosclerosis

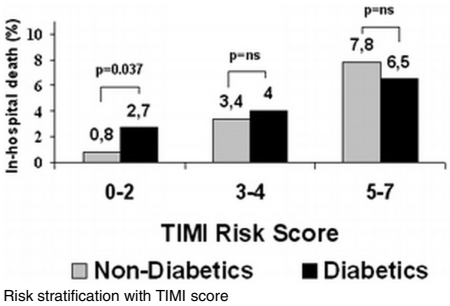
P. Tretjakovs[1], A. Jurka[2], A. Stifts[3], A. Jansone[2], J. Aivars[2], G. Latkovskis[4], A. Erglis[4], V. Pirags[3]. *[1]Latvian Institute of Exp.@Clin.Med., Endocrinology Dept, Riga, Latvia; [2]Latvian Institute of Exp.@Clin.Med., Endocrinology Dept., Riga, Latvia; [3]P. Stradins University Hospital, Endocrinology, Riga, Latvia; [4]P. Stradins University Hospital, Cardiology, Riga, Latvia*

Background: Naftidrofuryl improves the blood supply and ischemic damage of the vessel wall by blocking specifically 5-hydroxytryptamine-2 (5-HT2) receptors without influencing the general circulatory bed and improves glucose aerobic metabolism by an action on succinodehydrogenase.The aim was to evaluate the effect of naftidrofuryl on vasomotor dysfunction in diabetic patients with peripheral arterial occlusive disease (PAOD) and coronary artery disease (CAD).
Patients and Methods: The subjects were 10 type-2 diabetic patients with both PAOD and CAD who received a 600 mg daily dosage of naftidrofuryl orally for 12 weeks. 20 healthy subjects were selected as controls. The patient groups were matched for age, sex, and body mass index. The diagnosis of CAD was substantiated by coronary angiography. All the patients had a decreased ankle brachial index in both legs (0.73 ±0.17). We recorded changes in laser Doppler flux (LDF; PeriFlux 4001, Perimed) induced by a 3 min arterial occlusion on the pulp (apical skin) of the big toe. Basal LDF (b-LDF), postocclusive hyperaemia (m1-LDF), vasoconstrictor response (v-LDF) to deep inspiration (in apical skin), and heat (44?C; PeriTemp 4005) induced hyperaemia (m2-LDF) on the dorsum (non-apical skin) of the big toe were estimated using a PeriSoft programme.
Results: After the therapy the following indices were improved (mean±SD): b-LDF at both locations (apical skin: 48±34 vs 78±42 PU, $p<0.005$; non-apical skin: 14±9 vs 27 ±24 PU, $p<0.05$), v-LDF (13.5±12.4 vs 26.7±15.5%, $p<0.0001$), m1-LDF (100±54 vs 133±60 PU, $p<0.01$) and m2-LDF (61±31 vs 9549 PU, $p<0.01$).
Conclusion: Our results suggest that 12 weeks of naftidrofuryl therapy improves the cutaneous vasomotor response in diabetic patients with CAD and PAOD.

P2263 TIMI risk score is useful for predicting in-hospital mortality in diabetics with non-ST-segment elevation acute coronary syndromes

J. Ferreira Santos[1], J. Ferreira[2] on behalf of Portuguese Society Cardiology Acute Coronary Syndromes Investigators. *[1]Sao Bernardo Hospital, Cardiology, Setubal, Portugal; [2]Santa Cruz Hospital, Cardiology Department, Carnaxide, Portugal*

Background: Diabetes imparts a worse prognosis among patients (pts) with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). The TIMI Risk Score is a well validated tool for risk stratification in NSTE-ACS general population.
Aim: We sought to evaluate the utility of TIMI Risk Score for predicting risk in diabetic pts with NSTE-ACS.
Methods: We studied 6446 pts with NSTE-ACS included in a prospective nationwide clinical registry since 2002. Impact of diabetes in the clinical endpoint of in-hospital death was assessed. Pts were stratified by TIMI Risk Score in low (0 to 2), intermediate (3 and 4) and high risk (5 to 7) and compared according to diabetes status for differences in mortality.



Risk stratification with TIMI score

Results: In-hospital mortality was 3,8%. Diabetes was diagnosed in 1824 pts (28%) and associated with a higher death risk (HR 1.41, 95% CI, 1.08-1.84). Medium TIMI Risk Score was higher in diabetics than in the remaining population (3,99 Vs 3,33, $p<0.001$) and was useful for predicting risk in all pts. Diabetics in the low risk group had a higher mortality than non-diabetics, but there were no differences in the intermediate and high risk groups (Figure).
Conclusions: TIMI Risk Score is useful for stratifying all pts with NSTE-ACS, independently of diabetes status. Diabetic pts in TIMI low-risk group have a more adverse prognosis when compared with non-diabetic NSTE-ACS population.

P2264 Plasma N-terminal pro-B-type natriuretic peptide for pre-operative cardiac risk stratification in patients scheduled for major non-cardiac vascular surgery

H.H.H. Feringa[1], J.J. Bax[2], R. De Jonge[3], O. Schouten[1], A.F.L. Schinkel[4], M.H. Van Sambeek[1], E. Boersma[4], D. Poldermans[5]. *[1]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands; [2]University hospital Leiden, Cardiology, Leiden, Netherlands; [3]Erasmus MC, Clinical Chemistry, Rotterdam, Netherlands; [4]Erasmus Medical Centre, Cardiology Dept., Rotterdam, Netherlands; [5]Erasmus MC - Anesthesiology, Rotterdam, Netherlands*

Background: Peri-operative cardiac events are related to myocardial ischemia and reduced left ventricular function. The utility of plasma N-terminal Pro-B-type natriuretic peptide (NT-proBNP) for pre-operative cardiac risk evaluation has not been evaluated.
Aim: To assess the prognostic value of NT-proBNP for peri-operative cardiac events additional to clinical cardiac risk factors and dobutamine stress echocardiography (DSE) results.
Methods: 170 consecutive patients scheduled for major non-cardiac vascular surgery were evaluated by clinical cardiac risk factors (ischemic heart disease, congestive heart failure, stroke, diabetes mellitus and renal dysfunction), DSE (extend of rest wall motion abnormalities and extend of stress-induced new wall motion abnormalities), and NT-proBNP level. We performed multivariable logistic regression analyses, evaluating the prognostic value of NT-proBNP for the composite end-point of 30-day cardiac death or myocardial infarction, additional to cardiac risk factors and DSE results. NT-proBNP values were dichotomised (positive/negative), and Receiver Operating Characteristic (ROC) analysis was performed to determine the optimal cut-off value.
Results: In this patient cohort (mean age 59±13 years, 70% male, 52% ischemic heart disease, 23% congestive heart failure, 8% stroke, 17% diabetes mellitus and 4% renal dysfunction), the median NT-proBNP level was 13.3 pmol/L (interquartile range: 5.1-46 pmol/L). Cardiac events were observed in 3/149 (2%) patients with NT-proBNP $<$80 pmol/L (i.e. the optimal cut-off value), and in 10/21 (48%) patients with NT-proBNP $\geq$80 pmol/L (unadjusted odds ratio (OR) 49 and 95% CI 11-206, $p<0.0001$). After adjustment for clinical cardiac risk factors and DSE results, NT-proBNP remained significantly associated with peri-operative cardiac events (adjusted OR: 26, 95% CI 6-118, $p<0.0001$).
Conclusion: In patients scheduled for major vascular surgery, elevated plasma NT-proBNP levels were associated with an increased risk of post-operative cardiac events.

P2265 Circulating endothelial progenitor cells predict cardiovascular morbidity and mortality in patients with coronary artery disease

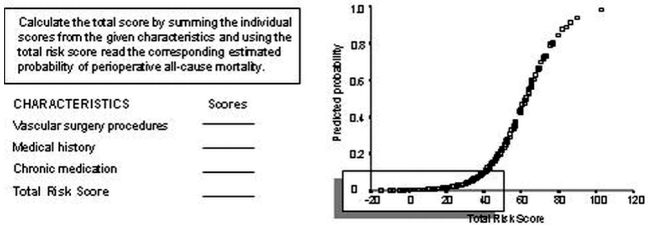
N. Werner[1], S. Kosiol[2], T. Schiegl[2], P. Ahlers[2], K. Walenta[2], A. Link[2], G. Nickenig[2]. *[1]Saarbrücken, Germany; [2]Universitätskliniken des Saarlandes, Innere Medizin III, Homburg-Saar, Germany*

Background: Number and function of endothelial progenitor cells (EPC) negatively correlate with cardiovascular risk factors but the prognostic value of circulating EPC has not been defined.
Methods: The number of CD34+/KDR+ EPC was determined by flow cytometry in 519 patients with angiographically determined coronary artery disease (CAD). The association between EPC baseline levels and cardiovascular mortality, the occurrence of a first major cardiovascular event (myocardial infarction, hospitalization, revascularization, and cardiovascular death), revascularization, hospitalization, and all-cause mortality after 12 months was evaluated.
Results: A total of 43 participants died. 23 patients deceased due to cardiovascular reasons. 214 patients had a first major cardiovascular event. The cumulative event-free survival increased stepwise across tertiles of baseline EPC levels for cardiovascular mortality, first major cardiovascular event, revascularization, and hospitalization. After adjustment for age, gender, vascular risk factors, drug therapy, percutanous coronary intervention, left-ventricular ejection fraction and concomitant disease, decreased EPC levels were associated with a higher risk for cardiovascular death (hazard ratio (HR) 0.31 (95 percent confidence interval (CI) 0.16-0.63, p=0.001), first major cardiovascular event (HR 0.74 (95 percent CI 0.62-0.89, p=0.002), revascularization (HR 0.77 (95 percent CI 0.62-0.95, p=0.017), and hospitalization (HR 0.76 (95 percent CI 0.63-0.94, p=0.012). EPC levels were not predictive for myocardial infarction or all-cause mortality.
Conclusions: The level of circulating CD34+/KDR+ endothelial progenitor cells predicts the risk of cardiovascular events and cardiovascular death. This novel cellular marker of vascular regeneration integrates the complex interactions of cardiovascular risk factors and may help to identify patients at increased cardiovascular risk.

P2266 Optimising the prediction of perioperative mortality in vascular surgery using a customised probability model

M.D. Kertai[1], E. Boersma[2], J. Klein[3], H. van Urk[4], D. Poldermans[3]. *[1]Semmelweis University, Cardiothoracic Surgery, Budapest, Hungary; [2]Erasmus Medical Centre, Cardiology, Rotterdam, Netherlands; [3]Erasmus MC, Anaesthesiology, Rotterdam, Netherlands; [4]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands*

Background: This study aimed to revise and customize the Revised Cardiac Risk (Lee) index to estimate the probability of perioperative all-cause mortality in patients undergoing noncardiac vascular surgery.
Methods: We studied 2,310 patients (mean age, 67.8±11.3 years; males 1,747) who underwent acute or elective major noncardiac vascular surgery between 1991-2000 at the Erasmus MC. In a total of 1,535 patients was assigned for model development, in which the association between predictor variables and mortality occurring within 30 days after surgery were identified to revise and customize the Lee-index, which was then evaluated in a validation cohort of 773 patients.
Results: The perioperative mortality rates were similar in the development (n=103, 6.7%) and validation populations (n=50, 6.1%). The customized risk-prediction model for perioperative mortality identified and allocated scores to type of vascular surgery (acute abdominal aortic aneurysm rupture, +43; thoraco-abdominal and abdominal aortic surgery, +26; infrainguinal bypass, +15; carotid endarterectomy, 0), ischemic heart disease (+13), congestive heart failure (+14), prior stroke (+10), hypertension (+7), renal dysfunction (+16) and chronic pulmonary disease (+7) associated with increased risk, whereas beta-blocker (-15) and statin use (-10) with a lower risk of mortality (Figure).



Figure

Conclusions: The customized index provides more detailed information than the Lee-index about the type of vascular procedure, clinical risk factors and concomitant medication use.

SUDDEN DEATH/RESUSCITATION

P2267 Impact of a professional emergency medical dispatch system on scene response, prehospital management and outcome in patients with suspected acute coronary syndrome and sudden cardiac death

R. Gaillet[1], C. Morger[2], M. von Planta[3], H. Saner[2]. *[1]Prevention and Rehabilitation, Swiss Cardiovascular Center, Bern, Switzerland; [2]Inselspital, Bern, Switzerland; [3]Basel, Switzerland*

Introduction: fast and correct prehospital diagnosis of patients with chest pain and sudden cardiac death (SCD) by an emergency dispatch system is crucial for costs and outcomes of cardiovascular emergencies.
Hypothesis: this study assessed the hypothesis that the introduction of an Emergency medical dispatch (EMD) system reduces the rate of inappropriate scene response of lay defibrillation and EMS-teams in patents with suspected acute coronary syndrome (ACS) thus enabling more accurate identification of patients requiring advanced life support.
Methods: we compared prospectively the identification of patients with suspected myocardial infarction and SCD in a setting of untrained hospital based telephone switchboard (T1) and a professional centralized EMD system (T 2) during 1 year. The EMD system allowed the dispatcher (trained emergency specialist) to question callers using a set of questions whereas the telephone switchboard (trained hospital receptionist) activated the AED/EMD system in a more traditional and less structured way. The outcome measure includes the number of calls categorised as suspicious ACS, the number of inadequate calls for ALS response and the number of correct identification of cardiac arrest by the two dispatching systems. The study was conducted in a mixed suburban and rural county with a population of approximately 90,000 persons.
Results: during T1 there were a total of 118 calls for suspected ACS (T2: 132; p=ns). Compared with the definitive hospital diagnosis, false-positive diagnoses were 21% (T1) and 28% T2, (p=ns). Of the 28 responses designated as SCD calls in T1, 12% were cancelled by EMS team on scene(T2 7%, $p<0.01$). Emergency medical dispatch would have decreased the number of responses initially designed as SCD (13% vs. 6%; $p>0.01$). The percentage of calls originally dispatched as SCD that were transported as initial SCD-survivors increased from 3% to 9%. Finally, we found in T1 a sensitivity of 85% for correctly diagnosing

chest pain from a cardiac (coronary) origin, and a specificity of 56%(T2 87% respectively 65% (p=ns).
Conclusions: with the introduction of a professional EMD dispatcher system inappropriate rate of ALS cancellations significantly decreased and the rate of SCD survivors increased. These results should be taken into consideration when the installation of a professional emergency medical dispatch system is under discussion.

P2268 Causes of sudden death related to sexual activity

Y. Cho[1], S. Lee[2], J. Chae[2]. [1]*Kyungpook National University Hospital, Internal Medicine, Taegu, Korea, Republic of;* [2]*Kyungpook National University, Legal Medicine, Taegu, Korea, Republic of*

Introduction: Sexual activity, combined with organic heart disease, may cause sudden death (SD). However, the causes of SD related to sexual activity are not known well. The aim of this study was to assess the causes of SD related to sexual activity.
Methods: From August 2001 to December 2004, all autopsies performed at Kyungpook National University Hospital were reviewed in search of SD cases related to sexual activity. Since all the autopsies in the Taegu-Kyungpook region of Southeastern Korea were performed by pathologists from the Department of Legal Medicine at Kyungpook National University, we had the opportunity to investigate the causes of SD related to sexual activity.
Results: Eleven cases (45±10 years old, 7 males) with SD related to sexual activity were found. All victims were heterosexual. The toxicologic study was negative in all subjects. Seven cases were witnessed; 5 cases occurred during sexual activity and just after in 2 cases. In 4 unwitnessed cases the victims were found dead in less than 8 hours from their sexual activity. In most cases SD occurred during the sexual act with a prostitute (n=3) or steady extramarital partner (n=7). The causes of the SD were as follows; coronary artery disease in 4 (3 in male), subarachnoid hemorrhage in 4 (3 in female), fibromuscular dysplasia of the AV nodal artery in 1, and unknown in 2.
Conclusions: Coronary artery disease and subarachnoid hemorrhage were the most common causes of SD related to sexual activity.

P2269 Demographic and temporal trends in out-of-hospital sudden cardiac death in Belfast

M. Moore[1], B.M. Glover[2], C.J. McCann[2], N.A. Cromie[2], P. Ferguson[3], D.C. Catney[4], F. Kee[3], A.A.J. Adgey[2]. [1]*Royal Victoria Hospital, Cardiology, Belfast, United Kingdom;* [2]*Royal Victoria Hospital, Cardiology, Belfast, United Kingdom;* [3]*Queen's University of Belfast, Department of Epidemiology, Belfast, United Kingdom;* [4]*Northern Ireland Cancer Registry, Belfast, United Kingdom*

Purpose: There has been a reduction in coronary artery disease mortality over the last 30 years. Any change in the incidence of out-of-hospital sudden cardiac death (OHSCD) is uncertain. In 1966 there were 297 OHSCD's in Belfast. The epidemiology of OHSCD in Belfast from August 2003 to July 2004 was determined.
Methods: The population of Belfast in 1966 and 2001 was obtained from the census office. Prospective data were collected (1st August 2003 to 31st July 2004) for OHSCD in Belfast from 3 sources: Emergency medical services (EMS) report forms, death certificates and autopsy reports. We examined all arrests using the Utstein style including call to response interval (CRI) for the EMS. Sudden cardiac death was defined as witnessed arrest of cardiac aetiology within 1 hour of symptom onset or unwitnessed arrest of cardiac aetiology were the patient was seen alive within 24 hours. Resuscitation was defined as admission alive, and survival defined as discharged alive.
Results: There were 300 OHSCD's, 197 (66%) male: mean age 68 years (± SD14), (range 27-96), mean age of females 72 years (± SD13), and males 65 years (± SD14). Of OHSCD, 234 (78%) occurred at home, 47 (15.7%) in public places and 19 (6.3%) in nursing homes. Two hundred and seventy nine (93%) were attended by the EMS. Rhythm on EMS arrival was asystole 190 (68%), ventricular fibrillation (VF) 75 (27%) and pulseless electrical activity 14 (5%). Mean CRI was 8min (± SD3). In those attended by the EMS, resuscitation was 9.7% and survival 7.2%. Presenting rhythm for all survivors was VF. Mean CRI for survivors was 5 min (± SD2) and non survivors 8 min (± SD3), ($P<0.001$). Ninety one (30%) OHSCD's were witnessed; of these 48 (53%) had VF on EMS arrival. The survival rate for witnessed VF arrests was 20/48 (41.7%). All 20 survivors were witnessed, had VF as presenting rhythm and CRI =7min. The European age-standardised incidence rate for OHSCD was 122/100,000 (95% CI 111-133) for males and 41/100,000 (95% CI 36-46) for females.
Conclusions: Despite a 37% reduction in heart attack mortality in Ireland over the last 20 years, the incidence of OHSCD in Belfast has not fallen over the last 38years. In this study, 78% of OHSCD's occurred at home. The percentage of cases with VF (27%) was low, possibly due to prolonged CRI, confirmed by the higher percentage of VF (53%) among witnessed arrests.

P2270 How long should lay persons for CPR/AED use be trained. A randomised study

D. Andresen[1], R. Kraemer[2], S. Hoffmann[2], R. Arntz[3], S. Osche[4], B. Krause-Dietering[5]. [1]*Klinikum Am Urban, Chefarzt I.Innere Abteilung, Kardiologie, Berlin, Germany;* [2]*Vivantes Klinikum Am Urban, Cardiology, Berlin, Germany;* [3]*Charité Campus Benjamin Franklin, Cardiology, Berlin, Germany;* [4]*DRK, GS, Berlin, Germany;* [5]*Berliner Feuerwehr, FWS, Berlin, Germany*

Early defibrillation has been reported to be the most important intervention in out-of-hospital cardiac arrest (OOHCA) due to ventricular fibrillation. Consequently, automated external defibrillators (AED) have been implemented in first responder systems. Within the next few years an increasing range of laypersons will be trained to combine skills of cardiopulmonary resuscitation (CPR) and AED use. However, so far no data exist as to how long the training course should last.
We performed a prospective trial, in which laypersons were randomly assigned to a 2 hours (group I), 4 hours (group II) and 7 hours (group III) lasting CPR+AED course. All participants received the same curriculum consisting of practice with CPR and AED. At the end of the course skill testing (e.g. assess patient, call 112, place electrodes, etc.) was performed. The test was measured using a scoring system (maximum = 100%).
During the 18 months study period 1096 laypersons were randomized (Group I: 375, group II: 378, group III: 343). Skill evaluation was different being best in group III (97%), followed by group II (94%) and I (91%) (p=0.01). 795/1026 (77%) were retested 6 and 12 months after the initial test. The 6 month test was associated with significantly lower scores (Group III: 75%, group II: 70%, group I: 68%) (p=0.001). However, at the 12 months test there was no further loss of skill and no differences between the groups (Group III: 73%, group II: 73%, group I: 71%) (ns).
Summary: CPR/AED skills of laypersons 1. depend on the duration of the initial course, 2. deteriorate within the first 6 months of follow up and 3. remain stable after a 6 months retraining has been done.
Conclusion: Provided that a retraining after 6 months is performed, a 4 hours lasting initial course is sufficient to enable long-term CPR/AED skills for laypersons.

P2271 Meteorological and geliogeophysical factors and occurrence of sudden cardiac death

G. Kukharchik[1], E.G. Golovina[2], I.V. Reimova[1], K.G. Politov[1], I.V. Konstantinova[1]. [1]*State Medical Academy, Cardiology Department, Saint-Peterburg, Russian Federation;* [2]*Russian State Hydrometeorological Univ, Saint-Peterburg, Russian Federation*

Previous studies have reached different conclusions as to whether geliogeophysical activity, or weather changes are related to the risk of sudden cardiac death (SCD). The purpose of this study was to check for possible associations between mortality, as result of SCD, and geliogeophysical activity and weather changes.
Material and methods: 7485 sudden deaths were analyzed from database of the Saint-Petersburg Regional Bureau of Forensic Medical Examination and compared with data obtained from meteorological database: daily changes of the temperatures, effective temperatures, barometric pressure, wind and others; geliogeophysical factors: solar, geomagnetic and cosmic ray and others.
Results: The total numbers of SCD were 5530. The main causes of the SCD were follow: acute myocardial infarction, acute coronary syndromes, cardiomyopathy, and heart valvular diseases. The number of the SCD was significantly correlated with daily changes of the temperatures ($p<0,01$). There was negative correlation between numbers of SCD and mean daily temperatures ($p<0,05$). Total numbers of SCD increased in winter and the influence was statistically significant for people over 60 years of age. The most important geliogeophysical factors for cases of SCD were noisy storms and radiobursts.
Conclusion: Despite the relatively short study, these findings suggest a significant association between meteorological and geliogeophysical factors and increased SCD incidence.

P2272 Olten AED Study: is the use of semiautomatic defibrillators by minimally trained lay persons in cardiac emergencies safe?

C. Morger[1], R. Gaillet[2], M. von Planta[2], H. Saner[2]. [1]*Swiss Cardiovascular Center Bern, Cardiology, Bern, Switzerland;* [2]*Swiss Cardiovascular Center Bern, Cardiology, Bern, Switzerland*

Purpose: Lay persons get optical and acoustic instructions for the appropriate treatment of the patients when using a automated defibrillator (AED). Are these minimally trained teams able to identify a cardiac arrest reliably and to operate an AED correctly?
Methods: Since July 2000 in a pilot study in the area of Olten (population 82'000) lay persons (more than 400 fire fighters and samaritans) intervened as first responders in cardiac emergencies. The training in cardiopulmonary resuscitation (CPR) and semiautomatic defibrillation lasted 4 hours. The teams are dispatched simultaneously to the ambulances. In this prospective study all emergency medical system (EMS) protocols and event registrations of the automated external defibrillators between January 1st 2001 and December 31 2004 were analyzed.

All actions performed by the lay persons were compared with the evaluations of the professional paramedics and the final diagnosis of the patients.
Results: During the study period 801 interventions were included. In 376 patients (47%) the AED was used for monitoring or defibrillation. 169 patients (21%) were found in cardiac arrest (42 ventricular fibrillation, 15 pulseless electrical activity PEA, 112 asystole). In 130 cases (16%) resuscitation attempts were initiated on site, in 39 cases (5%) the rescuers abstained from starting CPR due to different reasons. This decisions were assessed as appropriate by the later arriving professionals in 36 out of 39 cases. However, 3 of these 39 patients were found with PEA. The first responders didn't start CPR because of misinterpretation of a visible electrical activity on the monitor of the AED. All these 3 patients had a pacemaker and the later arriving paramedics performed a delayed, unsuccessful resuscitation attempt. In contrast to these 3 incorrect assessments, all 42 patients (5%) in ventricular fibrillation or pulseless ventricular tachycardia were defibrillated, 13 successfully. There were no major handling errors with negative effects on the condition of the patients.
Conclusions: A minimal training of first responders during 4 hours allows for a correct identification of a cardiac arrest in 98% of the interventions. In only 3 cases (2%) with PEA the situation was misinterpreted by the lay persons due to ECG-misinterpretation of pacemaker activity and no resuscitation attempt was performed. These results have to be considered in the organisation of duration and contents of early defibrillation courses for lay persons.

P2273 Are automated external defibrillators necessary in swimming baths? Observations in 2.05 Million visitors during three years

M. Nesslinger, H.-J. Trappe. *Herne, Germany*

Background: Automated external defibrillators (AED) save lives when they are used by designated personnel in certain public settings. However, it is still unclear whether AEDs in swimming baths are necessary or not. We performed a three-year prospective study at a big water park (LAGO-Die Therme, Herne, Germany) to assess whether random bystanders witnessing out-of-hospital cardiac arrests would retrieve and successfully use AEDs.
Methods: Eight defibrillators were installed in the water park LAGO-Die Therme. This institution belongs to the biggest facility of its type in Europe and serves approximately 700 000 visitors a year. The locations where AEDs were stored in the water park were chosen to make possible a target interval of 60 seconds or less from collapse to the first defibrillation. Twenty water park security officers were instructed in the use of AEDs. In addition, questionnaires were displayed easy noticeable at the entrance of the park to evaluate the acceptance of the AEDs.
Results: Automated external defibrillators were not used in any patient during a three year period (2002-2004) with 2.05 Million visitors. No patient died in the water park. These two patients had collapsed in the bath not caused by ventricular fibrillation. Therefore, AED did not deliver any shock. Two patients had nonsyncopal sustained ventricular tachycardia (rates 140 and 160 bpm, respectively) terminated by administration of ajmaline (50 mg) after arrival of the emergency-medical-services crew. Questionnaires were completed by 589 visitors (371 males, 218 females, mean age 43+23 years). It showed that 76% of the LAGO visitors (447 of 589 visitors) noticed the AED and 93% (548 of 589) visitors appreciate the existence of the AED around the bath. Seventy-eight percent of the visitors (459 of 589 visitors) feel even more save in the water park and 49% (288 of 589 visitors) attend additional sporting activities because of the adequate medical care in case of emergency.
Conclusions: It is clear that rapid defibrillation by nonmedical personnel using an AED can improve survival after out-of-hospital cardiac arrest (CA). It seems that swimming baths are places with a low incidence of CA. Nevertheless, acceptance and feeling of safety by the visitors were high and visitors even attend to more sporting activities than before because of the possibility of rapid defibrillation. Therefore, installation of AEDs in swimming parks is reasonable.

P2274 Prevention of sudden cardiac death in young patients with long QT syndrome and polymorphic ventricular tachycardia

M. Shkolnikova[1], S. Chuprova[2], V. Beresnitskaya[2], T. Kurileva[2], S. Termosesov[2]. *[1]Moscow Institute for Paediatry&Surgery, Arrhythmia Department, Moscow, Russian Federation; [2]Russian Center for Children Arrhythmia, Moscow, Russian Federation*

Long QT syndrome (LQTS) and polymorphic ventricular tachycardia (PVT) are the most important conditions of the sudden cardiac death (SCD) among young people without ischaemic heart disease. Characteristics of these arrhythmias can be considered as clinical models for identifying markers of SCD risk. This study proposes a method for evaluation of the baseline risk and dynamics of the individual risk factors (RF) among LQTS and PVT patients during treatment for its optimization of antiarrhythmic and ICD therapy.
Patients and Methods: 62 pts with LQTS and syncope (S) and 18 pts with PVT and S aged 3 to 24 years were studied and followed-up during 3 to 15 years. For all pts we monitored: S and pre-syncope episodes, sinus bradycardia, T-alternans, ventricular ectopic activity; for LQTS pts – QTc, EEG pattern, and low ($<$1.2) circadian index, which is calculated as a ratio of day to night HR averages. For PVT we additionally monitored episodes of SVT and high ($>$1.45) circadian index. We constructed the RF scores, based on the set of 14 (for LQTS) or 10 (for PVT) variables. RF score was built on well-established clinical and ECG markers, and family history data.
Results: RF score for LQTS pts varies from 3.5 to 9 (6.2$\pm$2.4). RF score for PVT pts varies from 3.5 to 8 (4.5$\pm$1.8). All pts were treated by beta-blockers. The monitoring of individual risk was based on the dynamics of potentially changeable RF. In 87% of LQTS pts and 56% with PVT the number of individual RF decreases during the follow-up. In 16 pts (8- LQTS and 8 – PVT) the RF scores do not change. 8 of them were treated with ICD (4 – with LQTS and 4 – with PVT) and 3 pts were treated with pacemaker implantation (2 –LQTS and 1-PVT). SCD occurred in 2 pts with LQTS and in 2 pts with PVT. Continuously high level of individual RFs combined with the maximum dozes of beta-blockers should be considered as a reason for the pacemaker or ICD implantation. Since we started the monitoring of individual RFs among LQTS pts, the number of observed cardiac events has decreased from 1.3 to 0.5.
Conclusions: The following RFs are common for LQTS and VT pts: occurrence of 1st S before the age of 6 years, male sex, bradycardia (below 5%o), recurrence of S and aborted SCD under treatment, SCD cases among sibs. Monitoring of individual RFs helps to optimise daily dose of beta-blockers, to reduce the risk of further cardiac events, and to get a better grounds for chosing time when pacemaker or ICD implantation are needed. Higher baseline risk and under-treatment determine worse prognosis in young pts with LQTS and PVT.

P2275 Incidence and characteristics of out-of-hospital cardiac arrest in a French semi-rural population-based study. The DEFI 77 Study

G. Pochmalicki[1], J. Empana[2], L. Guize[3], H. Lardoux[4], J.Y. Le Tarnec[5], J.P. Franchi[6], X. Jouven[3]. *[1]Leon Binet Hospital, Department of Cardiology, Provins, France; [2]INSERM U258, Villejuif, France; [3]European G Pompidou Hospital, Department of Cardiology, Paris, France; [4]Corbeil Essone Hospital, Department of Cardiology, Corbeil Essone, France; [5]Mobile intensive Care Unit, Emergency Department, Fontainebleau, France; [6]Fire Department, Melun, France*

Purpose: Few studies provided incidence rate and circumstances of out-of-hospital cardiac arrest (OHCA) in the population, and most of them were conducted in urban areas. Our aim was to report the incidence, the circumstances and the survival rate of OHCA in the French semi-rural area of "Seine et Marne" of 5.915 km^2 and 1.2 million inhabitants (200 hab/km^2).
Methods: Between January 2001 and February 2004, demographic, medical and prognostic information's of 1256 of OHCA aged 18 years and older were prospectively registered by the fire department teams and the Mobile Intensive Care Units (MICU), and data from these two sources were cross validated. We used the 2000 French population census to estimate the yearly-standardized incidence of OHCA.
Results: The estimated yearly national standardized incidence rate (95% CI) of OHCA was 68.3 for 100 000 person-years (63.8-72.7). The current analysis focused on the 871 OHCA that received advanced medical life support by the MICU. Among these, 69% were men and the mean age (SD) was 65.3 (15.8). Seventy-six percents of the OHCA occurred at home. Although a witness was present in 72% of cases, only 17% provided cardiopulmonary resuscitation (CPR). The mean delay from arrest to the emergency call was 6.1 minutes (8.2); the mean delay between the call and arrival on site of first aid team (firemen) was 9.3 minutes (4.7). Thirty percents of the victims were in ventricular fibrillation or ventricular tachycardia and received electric shock in a mean delay of 9.2 minutes (10.5). Finally, 18.5% were admitted alive at hospital and 3.4% were discharged alive from hospital.
Conclusion: In conclusion, the present data support that OHCA that occurred in a French semi-rural area was characterized by a low rate of witness's CPR and long delays of intervention at each step of the survival chain.

P2276 Bystander CPR in out-of-hospital cardiac arrest: wishful thinking or reality?

C. Morger[1], R. Gaillet[2], M. von Planta[2], H. Saner[2]. *[1]Swiss Cardiovascular Center Bern, Cardiology, Bern, Switzerland; [2]Swiss Cardiovascular Center Bern, Cardiology, Bern, Switzerland*

Purpose: Bystander cardiopulmonary resuscitation (CPR) improves survival in out-of-hospital cardiac arrest. There are no new data concerning frequency, quality and effectiveness of bystander CPR in out-of-hospital cardiac arrest (OHCA) in Switzerland.
Methods: Since July 2000 all out-of-hospital cardiac arrests in the Olten area were prospectively registered and the measures performed by the involved bystanders were analyzed. The data were collected by the emergency medical system (EMS) protocols, the event registration of the automatic external defibrillators (AED), hospital reports and questioning of the involved bystanders/paramedics. The necessary information was evaluated in the context of the Olten AED-study which investigates the pre-hospital aspects of the cardiac emergency and the effects of early lay defibrillation by specially trained fire fighters.
Results: Between January 1st 2001 and December 31 2004 169 out-of-hospital cardiac arrests were registered in the study region. In 130 cases (77%) CPR

was initiated on site, in 39 cases (23%) the bystander abstained from performing CPR due to different reasons. 125 patients (74%) were at home, 44 (26%) in public places. 74 cardiac arrests (44%) were witnessed. In 16 cases (22% of witnessed arrests) bystanders started CPR before the arrival of professional helpers. 11 of these 16 cases happened in public places, 5 at home. The resuscitation efforts were assessed as efficient by the later arriving paramedics/emergency physicians in 9 of these 16 cases. 5 of these 9 patients could be resuscitated successfully and 3 survived to hospital discharge and were in good neurological conditions. These 3 patients were in public places when the cardiac arrest occurred. Bystander CPR was performed more frequently in public places than at home ($p<0.05$).

Conclusions: Despite the fact that half of the out-of-hospital cardiac arrests were witnessed, bystander CPR was performed in only 22% of theses cases. The CPR measures were administered correctly in only half of these cases. The reasons for these poor results are being further evaluated. This gap in the chain of survival should be closed by increased efforts to promote CPR-training in the population.

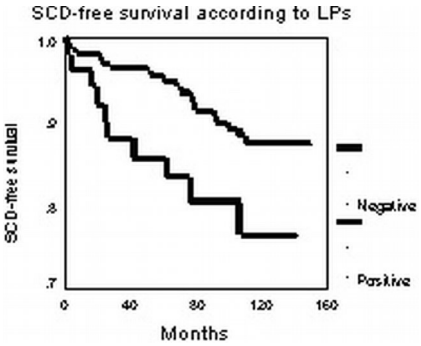
P2277 Predictors of sudden cardiac death in patients with acute myocardial infarction treated with thrombolytic therapy. Ten-year follow-up

B. Stefanovic[1], P. Mitrovic[2], Z. Vasiljevic[2], G. Matic[2], M. Radovanovic[2], N. Radovanovic[2], A. Karadzic[2], A. Milosevic[2].
[1]Belgrade, Serbia and Montenegro; [2]Institute of cardiovascular diseases, Cardiology Clinic, Belgrade, Serbia and Montenegro

Background: Approximately a half of post-myocardial infarction fatalities are sudden cardiac deaths resulting from malignant ventricular tachyarrhythmias. The aim of this study was to estimate predictors of sudden cardiac death (SCD) during long-term follow-up of patients (pts) with acute myocardial infarction treated with thrombolytic therapy.

Method: 320 pts (78% male, mean age 55.4 ± 9.8 years) with acute myocardial infarction treated with streptokinase 1.5 million U/45 min IV. and discharged alive were followed-up to 10 years (mean 6.8 ± 2.9 years). In multivariant Cox proportional hazard model including age, gender, infarct location (anterior vs. inferior), previous infarct (yes vs. no), diabetes (yes vs. no), peak CK (U/L), Killip classes (1-3); left ventricular EF, infarct-related artery TIMI flow (0-3), and late ventricular potentials (LPs) (positive vs. negative) within 1st month; and PCI/CABG within the 1st year of follow-up (yes vs. no), independent predictors of SCD were determined.

Results: During ten-year follow-up 77/320 pts died (24.1%). A half of all deaths were SCD, 39/77 (50.6%). In multivariant model positive LPs and TIMI 0: (OR 2.18, 95%CI 1.12-4.25, p=0.022), (OR 1.96, 95%CI 1.02-3.87, p=0.046), respectively were independent predictors of SCD.



SCD-free survival according to LPs

Conclusion: Positive LPs and occluded infarct-related artery are independent predictors of SCD after 10-year follow-up of pts with acute myocardial infarction treated with thrombolytic therapy.

LIPIDS

P2278 Significant reduction of LDL-cholesterol by addition of ezetimibe (ezetrol) to high dose statin therapy in heterozygous familial hypercholesterolemia patients

C. Masoura[1], J. Skoumas[2], C. Chrysohoou[2], N. Giotsas[2], C. Paliou[2], M. Toutouza[2], C. Pitsavos[2], C. Stefanadis[2]. *[1]Marousi, Greece; [2]Hippokration Hospital, Lipid Clinic, Athens, Greece*

Background: Heterozygous Familial hypercholesterolemia (hFH) is a common inherited disorder of lipoprotein metabolism characterized mainly by elevated levels of low-density lipoprotein cholesterol (LDL-C) and premature cardiovascular disease. Although statins have been shown to be effective in decreasing the incidence of cardiovascular disease in these patients, the cholesterol absorption inhibitor, ezetrol, has been shown to provide significant reductions in LDL-C levels when co-administered with statins. The aim of the present study was to evaluate the efficacy of ezetrol in hFH patients already receiving statin.

Methods: We administered ezetrol in 36 patients (mean age 54 years, 16 men and 20 women) with hFH, already treated with high dose statins at least for one year. The lipid changes between statin – baseline and statin+ezetrol were compared.

Results: Total cholesterol, LDL-C (figure) and triglyceride concentrations were reduced by 33.0%, 41.4% and 22.4% ($p<0.001$), respectively, after statin treatment related to baseline levels, while a further decrease of 17.8% ($p<0.001$), 22.3% ($p<0.001$) and 9.9% ($p<0.02$) respectively was achieved by the combination of statin+ezetrol. HDL cholesterol levels increased by 2.4% (p=0.018) by statin monotherapy, while no further elevation was observed with the co-administration of ezetrol. However, Lp (a) levels were unchanged (41.6 in baseline vs. 41.2 in statins' group vs.39.1 in combination, p=NS)

Conclusion: The co-administration of Ezetrol and high dose statins in patients with hFH produced clinically important reductions of total cholesterol, LDL-C and triglycerides compared with statin monotherapy. Ezetrol seems to provide a new, complementary pharmacological approach for such a high-risk population.

P2279 Early comparative effects of simvastatin versus atorvastatin on oxidative stress and proinflammatory cytokines in hyperlipidemic subjects

M.E. Marketou[1], E.A. Zacharis[1], D. Nikitovic[1], E.S. Ganotakis[2], F.I. Parthenakis[1], D. Arfanakis[1], N.E. Maliaraki[3], P.E. Vardas[4].
[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Dept. of Internal Medicine, Heraklion, Greece; [3]Heraklion University Hospital, Clinical Chemistry - Biochemisty Dept., Heraklion, Greece; [4]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece

Purpose: We investigated the immediate action of atorvastatin and simvastatin as well as their time-dependent effect on oxidative stress and cytokine levels immediately after the start of treatment. These factors play a role in endothelial dysfunction.

Methods: We studied 132 hyperlipidemic patients who were assigned to treatment with either 40 mg atorvastatin, 40 mg simvastatin or placebo. Blood samples were taken before the administration of the drug or placebo and 2 hours, 24 hours, 7 days and 3 weeks after, to evaluate serum levels of total peroxides (TP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-a) and soluble intercellular vascular adhesion molecule 1 (sICAM 1).

Results: An early modulation of TP levels was observed in both the atorvastatin and simvastatin groups, an effect that became obvious within the first 2 hours after treatment was initiated. In the atorvastatin group the TP changes were significantly different at 2 hours and 24 hours (p=0.005), whereas in the simvastatin group we observed a gradual, more or less linear decline of TP until 7 days (p=0.006) and then a plateau. Simvastatin exhibited a faster statistically significant decrease over time on IL-6 and sICAM 1 levels (at 7 days, p=0.014 and p=0.001 respectively). TNF-a demonstrated a faster linear trend in the simvastatin group, but the significant effect appeared late (p=0.006).

Conclusions: Both simvastatin and atorvastatin exert early beneficial effects on oxidative stress, proinflammatory cytokines and endothelial activation in hyperlipidemic subjects. These effects become obvious 2 hours following the initiation of therapy.

P2280 Association between blood lipids and arterial wave reflections in healthy adults

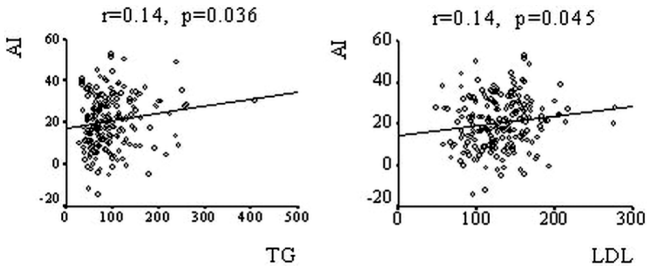
K. Aznaouridis, C. Vlachopoulos, I. Dima, N. Ioakeimidis, T. Gialernios, M. Toutouza, G. Vyssoulis, C. Stefanadis. *Athens Medical School, Hippokration Hospital, 1st Cardiology Department, Athens, Greece*

Purpose: Recent studies have suggested that blood lipids may be important determinants of several indices of arterial elastic properties. Wave reflections (WR), an index of arterial stiffness, is an important predictor of cardiovascular risk. The association of blood lipids with WR has not been investigated.

Methods: This clinical study was performed in 213 healthy subjects (mean age 41 years,141 males) who were not on medications and had not any known cardiovascular risk factor or disease, except for smoking. WR were studied using a validated system (Sphygmocor®) that employs arterial tonometry and pulse wave analysis. Augmentation index (AI) was measured as an estimate of WR. Full biochemical analysis was performed in all participants.

Results: In univariate analysis, a positive relationship between AI and age (r=0.56), male gender (r=0.33), mean blood pressure (r=0.22), pack-years of smoking (r=0.29), LDL-cholesterol (r=0.14, right plot) and triglycerides (r=0.14, left plot), and a negative relationship for heart rate (r=-0.25), ($P < 0.05$ for all) was observed. In a multivariate linear regression model, AI was significantly (p=0.01) associated with triglyceride levels, after controlling for age, gender, body-mass index, heart rate, blood pressure and intensity of smoking (adjusted R2 of model=0.6). On the contrary, the linear relationship between LDL-cholesterol and AI was largely explained when covariates were entered in the model (p=NS).

Conclusion: Our study shows that increased blood triglyceride level is associ-



Correlation plots between lipids and AI

ated with an unfavorable effect on the cardiovascular performance, as expressed by increased WR. This finding provides further insights into the role of hypertriglyceridemia as a potential cardiovascular risk factor.

P2281 Evaluation of lipid lowering therapy and cholesterol goal attainment in Finland

E. Alemao[1], D. Yin[2], H. Sintonen[3], V. Salomaa[4], P. Jousilahti[4]. *[1]Merck and Co, Inc., Outcomes Research, Whitehouse Station, United States of America; [2]Merck and Co., Outcomes Research, Whitehouse Station, United States of America; [3]University of Helsinki, Dept. of Public Health, Helsinki, Finland; [4]National Public Health Institute, Department of Epidemiology and Health, Helsinki, Finland*

Background: clinical trials have demonstrated benefits of aggressively lowering cholesterol among CHD patients and other high-risk subjects. However, many patients in clinical practice do not attain guideline recommended cholesterol (TC <5.0 mmol/l). The study describes treatment patterns for patients receiving lipid-lowering therapy in the Finnish primary care setting and estimates the proportions and determinants of goal attainment.
Materials and Methods: the National FINRISK Study was conducted in 2002 in order to assess the levels of CVD risk factors among the Finnish population. Data on health behavior (including smoking), use of drugs and medical history were obtained using a questionnaire, and blood pressure and serum total cholesterol were measured using a standardised protocol. From the total of 9,581 participants, 622 subjects were on lipid lowering therapy at the time of the survey. 68 subjects were excluded from the present analyses due to missing data on the type or dose of lipid lowering drug. Framingham risk scores were used to determine 10-year risk of a CHD event. Logistic regression analysis was used to estimate factors associated with goal attainment after controlling for covariates.
Results: the average age of the study population was 60.53 (SD 8.2) years and 53% were male. Among the 554 subjects using lipid lowering therapy, 210 (38%) were secondary prevention patients and 51% had 10 year CHD risk $\geq$ 20%. Majority of the patients were prescribed simvastatin (42%) followed by atorvastatin (26%). Around half (51%) of the patients were prescribed low dose statins (simvastatin 10mg or lower equipotent dose). There was no difference in the equipotent dose of statin prescribed for primary and secondary prevention patients. Overall, a majority of the patients (54%) patients failed to attain the guideline recommended cholesterol goals. Secondary prevention patients (OR 3.00; 95% CI 2.07-4.35) and patients prescribed high (4 and higher) equipotent statin dose (OR 1.93; 95% CI 1.35-2.76) had higher odds of attaining goal cholesterol.
Conclusions: in 2002, lipid management in Finland was dominated by low dose statin monotherapy. Majority of secondary prevention patients and other high-risk subjects treated for lipid reduction failed to attain cholesterol goals. More effective therapies are needed to help these patients attain guideline recommended cholesterol goals. In the most recent guidelines the cholesterol goal for high-risk patients is even lower (4.5 mmol/l) than in 2002.

P2282 Statin using have a positive effect on the development of collateral circulation in patients with severe coronary artery disease

S. Dagdelen[1], M. Yuce[1], I. Erdem[1], M. Akcakoyun[1], E. Ekicibasi[1], L. Koroglu Dagdelen[2], N. Eren[1], N. Caglar[1]. *[1]Acibadem Hastanesi, Cardiology Cardiology, Istanbul, Turkey; [2]Kartal Lutfi Kirdar Research Hospital, Clinical Biochemistry, Istanbul, Turkey*

Animal studies have shown that statins can promote angiogenesis in ischemic tissues. Although statins are reported to have a cardioprotective effect, their immediate direct influence on ischemia-reperfusion injury and the underlying mechanisms remain obscure. Clinical studies are still not enough to show that correlation between coronary collaterals and statins. The objective of this study to investigate whether statin therapy is associated with increased coronary collateral formation in patients with severe coronary artery disease.
Method: Among a series of patients who candidate for coronary angioplasty, 218 patient(43 female) having >90% coronary stenosis were intensively investigated. Development of collaterals was classified from 0 to 3 by Rentrop's method, and mean collateral score was defined (sum of the collaterals/the number of the vessels). Patients using statin at least last 3 months were accepted as statin using group.
Results: One hundred twenty four patients were using statin before angioplasty, and 94 patients were not. Baseline homocystein, total/HDLc, LDLc, hsCRP and lactate levels were similar between two groups. Left ventricular ejection fraction was higher in statin group, but this is not statistically significant (p>0.05). The statin-treated group had a significantly higher mean collateral score compared with the patients not using statin (2.17±0.81 vs 0.95±0.69, p<0.001). In statin group, history of myocardial infarction was more than the patients not using statin (43% vs 48%, p=0.019). In the statin using group, Rentrop class 0 and 1 collaterals were significantly lower than the groups not using statin (19% vs 85%, p<0.05), and Rentrop class 2 and 3 collaterals were significantly higher in statin group (81% vs 15%, p<0.05).
Conclusion: Statin therapy is associated with improved coronary collateral formation in patients with severe coronary disease. This may be related with angiogenesis promoter effect of statin, and/or plaque stabilization effect of statin.

P2283 Evaluation of correlation between serum level of lipoprotein(a) and cervical carotid artery stenosis

M.A. Boroumand, S.H. Shirani, N. Maghsoodi, A. Karimi, S. Davoodi, M. Marzban, S.H. Abbasi, N. Fallah. *Tehran Heart Center, Research Department, Tehran, Iran (Islamic Republic of)*

Background: In many studies, Serum lipoprotein(a) [LP(a)] level is considered as an independent risk factor for atherosclerosis. LP(a) level in serum is genetically determined with an autosomal dominant pattern. The aim of this study was to assess the association between LP(a) and cervical carotid artery stenosis in Iranian population.
Material and Methods: Between May 2004 and January 2005, at Tehran Heart Center, 920 patients who were candidate for open heart surgery for any reason, were selected. Carotid Doppler Sonography was performed for all of these patients. Serum levels of LP(a), total cholesterol, triglyceride, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and LDL/HDL ratio of these patients were measured and their correlation with carotid atherosclerosis were assessed.
Results: No correlation was found between high levels of LP(a) (>30mg/dl) and carotid atherosclerosis(P>0.93). Serum levels of cholesterol (P<0.004), triglyceride (P<0.005) and LDL-cholesterol (P<0.001) had meaningful correlation with carotid atherosclerosis. Smoking (p<0.003), female sex (p<0.001), diabetes mellitus (p<0.004) and high level of high sensitivity CRP(C-reactive protein) (P<0.05) were found to be related with carotid atherosclerosis.
Conclusion: In our study, we found no significant correlation between serum LP(a) and carotid atherosclerosis. Further studies need to be done to get a better conclusion in this regard.

NURSING

P2284 Paroxysmal supraventricular tachycardia and driving

U. Walfridsson[1], I. Johansson[2], H. Walfridsson[2]. *[1]University Hospital, Dept. Cardiology, Linkoping, Sweden; [2]University Hospital, Dept. Cardiology, Linköping, Sweden*

Aim: The aim of this study was to evaluate the occurrence of arrhythmia-related symptoms with special focus on driving ability in patients with AV-nodal reentrant tachycardia (AVNRT) or Wolff-Parkinson-Whites syndrome (WPW), referred for radiofrequency catheter ablation (RF-ablation).
Methods and results: The study was an interview study with structured questions and it took part between January 1999 and December 2000. 142 of 201 patients referred for RF-ablation participated in the study, 76 patients with AVNRT and 66 patients with WPW-syndrome, all active drivers
Hemodynamic symptoms frequently occurred during tachycardia, irrespective of driving. In the 142 patients near syncope occurred in 52% and syncope in 13% at least once. Patients with AVNRT reported fatigue more often then patients with WPW-syndrome (p<0.05). Women experienced fatigue (p<0.01), near syncope (p<0.001) and syncope (p<0.01) more often then men. Men reported more often that they were dependent of driving (p<0.05) and they drove longer distances then women (p<0.0001). More than half of the patients had had tachycardia while driving and half of them had had to stop. Twenty-three percent of the patients considered the risk for tachycardia as an obstacle to driving and there was a correlation between having experienced near syncope (p<0.001) or syncope (p<0.05) and considering the risk for tachycardia as an obstacle. One patient was involved in an accident when suffering from syncope probably due to WPW tachycardia.
Conclusions: AVNRT and WPW are often referred to as "benign" tachycardias but half of the patients interviewed had experienced near-syncope and as many as 13% had suffered syncope. Women were more prone to serious symptoms than men.
The risk for such serious tachycardia related symptoms should be considered in these patients, especially in those with a driving licence permitting occupational driving.

P2285 Prevention and non-pharmacologic intervention of delirium in the elderly patients in coronary intensive therapy unit

S. Bartolini[1], R. Piccari[2], C. Tagliabue[2], C. Ludovici[2], F. Fiori[2], A. Giulivi[2], G. Pulignano[2], E. Giovannini[2]. [1]*Roma, Italy;* [2]*San Camillo Hospital, UTIC I Cardiology, Rome, Italy*

Background: Delirium (D) is a common and serious syndrome in the eldelry frail patients, frequently undiagnosed. Its prevalence in hospitalized patients is extimated between 11 and 42% and provocates: lenght of stay increase, mortality increase, more expensive patients care. In our experience, D has been detected in 23% of patients aged >70 years in coronary intensive therapy unit.
Aim: D incidence reduction with the application of a protocol for: a) risk subjects early identification; b) preventive measures; c) in clear cases, precocious and effective treatment.
Methods: D prevention must be based on identification and/or treatment of risk factors (visus reduction, serious systemic diseases, cognitive deficit, dehydration). In patients aged >70 years in first 24-48 hours from coronary intensive therapy unit admission we evalued mental state with Mini Mental State Examination (MMSE), eventually present visus reduction, diseases gravity with APACHE II score and dehydration with urea/creatinine ratio. In high risk patients we employed a prevention protocol including: environment care (calm, natural light with windows where possibile), day-night rhythm preservation, censure sensory with aids well filling and in good repair (hearing aids, glasses, dentures), use of large face clocks and calendars, familiar objects and photos, reassure patient and encourage family presence. For rapid D detecting we used Confusion Assessment Method (CAM). D treatments goals are: 1) etiologic therapy, 2) support therapy, 3) patients safety and injury prevention.
Results: From May to December 2004 we evalued 211 patients aged 76+5,5 years, 33,6% females, mean years of scholarization 7,1+4,1, 36,4% with MMSE <24. 25,1% showed cognitive impairment, 20,3% immobility present before admission, 21,3% poor eiesight, 23,2% poor hearing and 75,3% dehydration. Cardiovascular risk profile was intermediate in 76,7% of patients, in 23,2% high.
Conclusions: D is a serious syndrome needing a multidisciplinary approach with prevalence of non-pharmacologic interventions, usually not included in assistance programs. Elderly patients are frail and comlex: its correct multidimensional evaluation could be particularly useful in preventing D. Spontaneous D resolution is possible if all prevention measures are applied, basing on accurate and precocious detection of causes. In D prevention, early symptoms detection and non-pharmacologic interventions the nurse role could be very important.

P2286 In-hospital information after acute myocardial infarction: what information do patients receive?

K. Oterhals[1], T.A. Hanssen[2], G.E. Eide[2], B.R. Hanestad[3]. [1]*Haukeland University Hospital, Department of Heart Disease, Bergen, Norway;* [2]*Haukeland University Hospital, Centre for Clinical Research, Bergen, Norway;* [3]*University of Bergen, Dept of Public Health and Pr. Health c, Bergen, Norway*

Background: Although patient information and education is increasingly recognised as an important part of treatment and care, several studies indicate that the patients are not satisfied with the information they are provided during hospital stays.
Aim: The aim of the present study was to describe patients perception of the information they receive in hospital after acute myocardial infarction (AMI), and to explore to what extent the results differed with respect to age, gender and length of hospital stay.
Method: In a cross-sectional research design, consecutive patients with main diagnosis AMI, age above twenty years, were approached before discharge and invited to participate in the study. Data was mainly collected through a self-report questionnaire six weeks after discharge. Of the 130 patients consenting to participate 111 (85%) had returned the questionnaire after one reminder.
Results: Patients reported to receive most information on topics such as "what is a myocardial infarction", "causes of myocardial infarction", and "smoking". They reported less information on psychological and personal aspects such as "possible problems after MI", "sexual activity", "employment and lifestyle". Information regarding medication scored low as well. Amount of received information reported was not associated to length of hospital stay. Younger patients reported more information than older patients did (r = -0.24; p = 0.015).
Most patients (62.5%) considered they received the information at the right time, with no significant differences according to age or length of hospital stay. Points of time when most patients missed information were at discharge and after returning to home. It was mostly women that missed information at discharge (p = 0.032). It was the oldest (r = 0.28; p = 0.006) and those with longest hospital stay (r = 0.24; p = 0.020) that mostly missed information after returning home. Women considered the information less satisfactorily than men did (p = 0.001).
Conclusion: Patients want more information about medication and potential future problems that they may face after returning home. Results of this study indicate that it is necessary to examine the current provision of in-hospital information and education to AMI patients, especially in women and older patients.

P2287 Information need on sexual activities of heart failure patients

T. Jaarsma, D.J. van Veldhuisen, A. Koops on behalf of NHS-COACH. *University Medical Center Groningen, Cardiology, Groningen, Netherlands*

Purpose: Sexual function in patients with chronic heart failure (HF) is a very sensitive topic and often ignored in patient education and counselling. Little is known on the importance of sexual function for HF patients and their need for information on this subject.
Method: Data were collected in 107 HF patients (mean age 68 ±12, 56% male, mean Left Ventricular Ejection fraction 32% ± 14) 18 months after a HF hospitalisation. Patients completed a self-report questionnaire on their perceived importance of sexual function in their lives (on a scale from 0 –10) and on their need for information on this subject.
Results: Looking back on the period before their disease patient reported the importance of sexual activity on a 10 point scale as 6,1 ± 2 At the time of the data collection they rated this as 4,6 ± 3 (t=5,0 p<.001). Patients also reported a decrease in satisfaction with their sexual activities due to HF from a score of 6,9 ± 2 (before HF) to 4,6 ± 3 at this moment (t=5,7, p <.001).
In total 8 patients reported to be advised on this topic by a cardiologist (n=4) or a nurse (n=8). Of the total sample, 21% reported that they wanted information on sexual function. This information concerned advice and counselling on possibilities, medication and the consequences of HF for sexual activities. Of the patients who did report impotence (n=29), one third cited medications as reason for their problems and 35% specifically reported that they would have wanted to be treated for these sexual problems.
Conclusion: From this preliminary data we learn that the importance of sexual function changes in the course of the disease. A considerable amount of patients requested more information on sexual function after heart failure regarding possibilities, medication and the consequences of heart failure for sexual activities.

P2288 One day patient education reduces hospitalisations and costs related to heart failure. A community hospital experience

P. Jourdain[1], F. Funck[2], J. Loiret[2], S. Genevelle[2], A. Kern[3], D. Decup[3], M. Bellorini[2]. [1]*Centre Hospitalier Rene Dubos, Service de Cardiologie, Pontoise, France;* [2]*René Dubos Hospital, Cardiology Dept., Pontoise, France;* [3]*Ch dubos, Medical computing, Pontoise, France*

Background: In developed countries, hospitalization costs represent 2/3 of the whole costs induced by heart failure. Hospitalizations become more and more costly every year. Patient education is recommended in European guideline but it's impact on morbidity and costs are still lacking.
Our study's objective was to determine the impact of patient education on Hospitalizations and costs induced by heart failure.
Methods: We have included 412 patients consecutively referred to our center for decompensated heart failure between 2002 and 2004. 350 patients were finally included (Group A) in a "one day" educational program. Education were done by a multidisciplinary team. Educational program includes medical, dietetician and physical training knowledge. Patient's medical therapy was conform to guidelines (ACEI 94%; Beta blockers 72%, diuretics 100%). Patients knowledge was evaluated through a questionnaire before, after the educational program and at 3 and 6 month.
Results: Educational management leads to significant shorter duration of in hospital stay/year (4 vs 9 days/year p<0.001). Hospitalizations due to salt excess or low compliance are reduced by 2/3. All causes hospitalisations are reduced in educated patients group (10% vs 22% p<0.01). Costs induced by heart failure are dramatically reduced by the educational program (-38% p <0,001) during the follow up. Patient's knowledge was increased by educational program and was stable during follow up. Patient compliance was better after the education (92 vs 85%)
Conclusion: A simple "one day" educational program could lead to a dramatic decrease of morbidity and costs related to heart failure.

P2289 Motivational stages to change lifestyle in patients with coronary heart disease

J. Heidrich[1], T. Behrens[1], F. Raspe[1], H. Reinecke[2], A. Loeher[3], U. Keil[1]. [1]*University of Münster, Epidemiology and Social Medicine, Münster, Germany;* [2]*University Hospital Münster, Department of Cardiology, Münster, Germany;* [3]*University Hospital Münster, Thoracic and Cardiovascular Surgery, Münster, Germany*

Purpose: Lifestyle changes are of utmost importance in secondary prevention of coronary heart disease. The motivational stage of change (SOC) according to the transtheoretical model of behaviour change is important to assess readiness for lifestyle changes in individual patients, but information on SOC in coronary patients are currently lacking. Therefore, this study aimed to investigate SOC with respect to smoking cessation, weight reduction and physical activity in coronary patients.
Methods: A cross-sectional questionnaire survey was carried out among 1,339 patients with established coronary heart disease in the region of Münster, Ger-

many, in 2003. The questionnaire aimed at knowledge and attitudes towards cardiovascular risk factors and readiness for lifestyle changes according to the transtheoretical model.
Results: A total of 980 (73.2%) patients participated, 28.3% were female, mean age was 64.7 years. Among smokers, 37% were not considering cessation (precontemplation stage), 47% were thinking about cessation (contemplation stage), and 17% were preparing to stop smoking (preparation stage). Among overweight patients (BMI =25 kg/m^2), 42% claimed to actively loose weight (action and maintenance stage). Among those who did not report weight reduction, however, 51% were in precontemplation, 31% in contemplation and 18% in preparation stage, respectively. Seventy-seven percent of patients reported regular physical activity (action and maintenance stage), but 52% of those who indicated to be physically inactive reported to be in precontemplation, 24% in contemplation and 24% in preparation stage, respectively. Patients with increasing age were more likely to report action/maintenance stage in physical activity ($p<0.05$) but were less likely to report action/maintenance stage in weight reduction ($p<0.05$). Higher education was associated with higher motivational stages in weight reduction ($p<0.05$). Other sociodemographic factors had no significant impact on motivational stages of change in our survey.
Conclusions: About half of coronary patients reporting unhealthy behaviour do not consider lifestyle change and will be difficult to reach with interventions. The other half, however, is actively considering or planning to change behaviour. Identification of these patients and tailoring interventions to their SOC may be a key element to support patients' lifestyle change and to improve secondary prevention of coronary heart disease.

P2290 Increase the level of knowledge in heart failure patients through a multidisciplinary educational programme

J. Roncalli[1], A. Pathak[2], L. Perez[1], L. Spinazze[1], C. Baixas[1], P. Massabuau[1], J.M. Fauvel[1], M. Galinier[1]. *[1]CHU Rangueil, Service de Cardiologie, Toulouse Cedex 9, France; [2]CHU Rangueil, Cardiologie Dept. - INSERM U586, Toulouse, France*

Congestive heart failure (CHF) represents a major and growing public health problem both in terms of incidence, prevalence, morbidity, mortality and economic burden. Hospital activity represents the greatest component of cost. Although some hospitalizations for CHF are central for its management, a large proportion of them is avoidable. As such, there has been increasing interest in the role of multidisciplinary programs that optimize the management of CHF. The main aim of educative sessions is to give better knowledges and some means for self-evaluation of their clinical status going the possibility to the patient to control himself his own health.
A total of 115 patients with the diagnosis of CHF were enrolled in this study. The patients were solicited from the cardiology department of the University Hospital of Rangueil to the CEPIC (Heart failure patient educative center). Using a self-questioning data sheet which we previously presented, we analysed six major topics: knowledge about disease, clinical evaluation (signs and symptoms of deterioration of heart failure), daily physical activity, diet, medical going-on and medical treatment.
Multiple choice questions were used to evaluate knowledge levels for every topic. Each answer was rated with points to obtain a final score from 0 to 20 for each topic. We evaluate as a good score of knowledge if the end score is more than 15 for each topics. In this study, 115 patients (mean age: 56±15 years, 77.8% of male, 26.9% of left ventricular ejection) attended an education session of one day about heart failure. Evaluation was made before, 3 and 12 months after heart failure education session. Before education session we can note that the level of knwoledge is low in south of France. In fact, only 28.7% of patient have a good level in knowledge of disease, 7% in evaluation of clinical signs, 30.4% in knowledge about physical activity, 12.2% in knowledge of medical follow-up, 31.3% in diet and 16.1% in knowledge about medical treatment. We note a significant increase in rate of patients with a good level of knowledge at 3 and 12 months after education program (100%; 66.7%; 81.2%; 79.7%;92.8%; 54.5% respectively; $p<0.5$).
This pilot study confirms that i) a knowledge score is feasible, ii) the level of knowledge about heart failure in patients of South West of France is low, iii) heart failure education program improves significantly knowledge of our patient as assessed by this score and increase the percentage of patient with a good level of knowledge in heart failure and should improve the become of heart failure patient.

P2291 Integrated management of heart failure (HF) patients: a national educational project

G. Cacciatore[1], G. Gigli[1], G. Pulignano[1], F. Oliva[1], G. Ansalone[1], G. Alunni[1], A. Di Lenarda[1], R. De Maria[2]. *[1]Italian Hospital Cardiologist Ass., Working Group on Heart Failure, Firenze, Italy; [2]Fisiologia Clinica CNR Milano, Cardiology Dept., Milano, Italy*

Heart failure (HF) is highly prevalent, costly and may greatly benefit from continuity of care, a goal to be achieved through involvment of all those caring for HF patients.
Methods: The Italian Hospital Cardiologists Association promoted an educational project to disseminate knowledge on HF burden and appropriate process of care and to share opinions on core responsabilities of different health care professionals in HF management. A 10-item questionnaire was administered after 16 regional workshops covering 3 core areas: clinical competence, appropriate process of care and integrated management (Table 1).
Results: 1617 health professionals (980 physicians, 637 nurses) answered the questionnaire. The highest proportion of correct anwers (Table 1) was in the definition of professional roles for integrated HF managment. Agreement was still suboptimal on performance measures for an appropriate HF care process.

Table 1

Proportion of correct anwers	All	Physician	Nurse	p
Epidemiology and clinical competence	85.6	86.8	85.5	.002
Burden of HF admissions, 1996 to 2001	86.6	83.2	92.0	.0001
Treatment of asymptomatic LV dysfunction	90.5	93.7	85.6	.0001
Risk factors for readmissions	89.7	91.4	87.1	.007
Prevalence of renal dysfunction in HF	80.9	79.1	83.7	02
Appropriate process of care	87.1	86.0	85.3	.04
Criteria for HF admission in a medical unit	93.5	1.2	97.0	.0001
Criteria for HF admission in the intensive care unit	93.1	93.7	92.2	NS
Performance measures in HF care	75.0	73.1	78.0	.03
Integrated HF management	95.6	95.7	93.1	.002
Multidisciplinary team, best HF management model	97.0	96.9	97.3	Ns
Role of HF outpatient and day hospital programs	94.6	94.8	94.2	Ns
Role of GPs in HF management	95.5	95.4	95.6	Ns

Conclusion: Integrated HF management is perceived as a hot topic by health care professionals. Concordance on core professional responsabilities and on the tools to achieve continuity of care is high. Improvement is needed in the appreciation of HF burden and comorbidities. Specific efforts should be addressed to implement shared quality performance measures for the optimal management of HF patients in our country.

P2292 Impact of systematic specialised evaluation of hospitalised patients with suspected heart failure

J.M. Meier, G. Girod, X. Jeanrenaud, N. Aebischer, J. Schlaepfer, C. Seydoux. *University Hospital, Dept. of Cardiology, Lausanne, Switzerland*

Background: The increasing proportion of elderly will lead to a higher prevalence of heart failure (HF) in developed countries during the next decades. The emerging concept of pandemia due to heart failure needs a more systematic and structured approach for such a population. The benefit of standardized procedures for evaluation and management of HF in hospitalized as well as out-patients (pts) has been demonstrated by several studies. We sought to define the characteristics of suspected HF pts admitted in our institution in order to improve diagnosis and treatment. We analyzed the efficacy of management of these pts throughout their hospital stay thanks a systematic approach for all of them by a cardiologist specifically involved in the management of HF.
Methods: We prospectively collected data of continuous HF pts hospitalized in our institution during a pilot study of 2 months. HF was defined as an impairment of systolic left ventricular function with an ejection fraction (EF) of 45% or less as defined by transthoracic echocardiography (TTE). For each patient, the attending physician was contacted. Medical evaluation and propositions of management were offered by our HF unit. For the purpose of the study, the screened pts were divided into 2 groups: pts hospitalized in the service of cardiology (Group 1: 24 pts) or in other units (Group 2: 43 pts).
Results: Group 1 and Group 2 were comparable in terms of age (70±10 years vs 70±12 years), EF (34±9% vs 37±7%) and etiology of HF (ischemic 70% vs 65%). Eighty percent of pts (21/26) with newly discovered HF were found in Group 2. A systematic approach in the diagnostic and therapeutic procedures by a cardiologist optimizes the management of pts in Group 2: 22/43 (51%) had a modification of their treatment and 9/43 (21%) a diagnosis initially not evocated.
Conclusion: In our institution, pts hospitalized out of the cardiology unit represent 80% of newly diagnosed HF. Age, severity and etiology of cardiac disease were not different when compared with pts admitted in the cardiology department. Systematic management by a cardiologist may benefit to these pts frequently leading to a modification of their treatment (51%) or to a new diagnosis initially not evocated (21%). Based on this observational study, we decided to develop a computerized algorithm for the diagnosis and management of any patient with suspected HF admitted in our institution during the next 12 months. Following step will be validation of the prospective application of this newly developed computerized algorithm.

P2293 Hospitalisation for heart failure in the real life: health organisation and initial management in the community

L. Fauchier[1], C. Rea[2], A. De Labriolle[3], R. Charlon[2], C. Monpere[4], B. Charbonnier[3]. *[1]Centre Hospitalier Universitaire, Cardiologie, Tours, France; [2]CNAMTS, Service Médical Région Centre, Orleans, France; [3]CHU Trousseau, Cardiologie, Tours, France; [4]Centre de Bois Gibert, Readaptation cardiovasculaire, Ballan Mire, France*

Hospitalisation for congestive heart failure (HCHF) is frequent, but only few data are available that describe the care organisation of HCHF in the community. The

objective of this study was to describe the health channels of HCHF of all cause in unselected patients.
Methods: The study was based on a retrospective analysis of patients with HCHF (defined as main diagnosis after hospital discharge on national registers) during month october 2003. These patients were seen in 27 institutions in the community of the Center region in France (n = 2440329 in 1999).
Results: From systematic analysis of all hospitalisation in the community, 525 were registered as HCHF for 509 patients. Median age was 82 (18-102), 53% were male, 53% had coronary heart disease, 24% had normal systolic function (LVEF $>$ 50%) and 38% already had HCHF in the previous year. Most of the patients were referred by a general practitioner (63%), whereas 18% of the patients came to the institution directly, 7% were referred by a cardiologist and 3% by a geriatric physician. Most of the patients (63%) were seen in the emergency department (ED), whereas only 31% were admitted in a medical department and 5% had a programmed hospitalisation. Patients $>$ 80 yo were more likely to be admitted in the ED (66 vs 57%, $p<0.001$). Initial department of hospitalisation was in cardiology for 36%, internal medicine for 27%, coronary care unit for 14%, ED bed for 14%, pneumology for 4%, geriatric unit for 2% and intensive care unit for 2%. Patients $<$ 75 yo were more likely to be hospitalised in a cardiology department. Hospitalisation was in one department only for 75% but 24% were seen in 2 different departments during HCHF. Length of hospital stay was 11.3 days and was longer for older patients: 9.8 days when age $<$75 vs 11.8 when age $>$75. In hospital mortality was 10.6%. Cardiologist advice was obtained in 78% (88% when age $<$75 vs 75% when age $>$75), geriatric advice for 7%, both for 4% but cardiologist or geriatric advice was not obtained for 11% of the patients during HCHF. On discharge, cardiologist advice influenced the subsequent use of ACE inhibitors (61% vs 37% for geriatric advice), beta blockers 27% vs 7%) and spironolactone (28% vs 18%).
Conclusion: Many HCHF remain initially seen in a emergency unit, particularly for elderly patients. An improvement of the health organisation system and a better application of therapeutic guidelines should probably be obtained. Both education and disease management intervention may result in a better organisation and lower number of emergency HCHF.

P2294 A unique national programme for the development of cardiovascular nurse scientists: the Canadian experience

H. Arthur[1], K.M. King[2] on behalf of The FUTURE Program Mentors. [1]*McMaster University, Health Sciences, Hamilton, Canada;* [2]*University of Calgary, Nursing, Calgary, Canada*

Background: There are approximately 238,000 registered nurses in Canada. Of these, approximately 246 (0.1%) have Doctoral level education, the basic training required for independent investigators. Less than half of those with PhDs are actively engaged in peer-reviewed, competitively funded research, a recognized benchmark of success, and still fewer (an estimated 15-20 in the entire country) specialize in cardiovascular research.
Purpose: The purpose of this 6-year, nationally funded program is to strategically advance the training of cardiovascular nurse-scientists, provide collaborative training and learning opportunities, provide flexibility for students and supervisors, enrich the students' learning and increase research productivity in the cardiovascular area. The FUTURE Program will formally link nurse-scientists from across Canada and will define a new national standard for nursing research training.
Design: The hub of the curriculum for the FUTURE Program is formed by integrated courses related to research designs (e.g. clinical trials), research methods (both quantitative and qualitative), scientific manuscript and grant writing, evidence-based practice and knowledge translation. The 5 curriculum elements of the Program are: 1) a web-based distance education course in Evidence Based Health Care, 2) a monthly web-conferenced seminar series with presentations from funded nurse scientists, 3) a 2-week Trainee Research Interchange Program (TRIP), where students visit a nurse scientist in another part of the country, 4) a 1-week summer institute which focuses on research methods and 5) an annual scientific meeting which is held in conjunction with the Canadian Cardiovascular Congress. At the annual meeting students present their developing research and network with nurse scientists from across Canada. We are currently entering the third year of the program and, to date, have admitted 10 nurses who are doing PhD study and 2 Post-Doctoral Fellows. Experiences of the first two years will be presented.
Implications: The FUTURE Program has the potential to make an immediate and significant impact on both knowledge and research capacity. Graduates of the Program will establish programs of research and contribute importantly to the national and international community of scholarship.

P2295 Primary care direct access to a hospital based heart failure disease management programme is associated with reduced hospitalisation: 3 year follow up of 524 patients

C. Conlon, C. O'Loughlin, C. Ryan, C. Traynor, R. Martos, M. Ledwidge, K. McDonald. *St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland*

Background: It has been shown that a 3 month, multidisciplinary, hospital-based disease management programme (DMP), comprising of intensive patient education, close clinical follow-up in addition to optimal medical care, can significantly reduce short term emergency hospitalisations. Although extension of this intensive programme from 3 to 6 months has been shown to provide no clinical benefit on longer term follow-up, ongoing primary care direct access (PCDA) to the heart failure (HF) service may be critical in reducing longer term morbidity.
Aim: To examine if a PCDA facility reduces the incidence of hospitalisations in a HF DMP.
Methods: For patients surviving admission with NYHA class IV HF our DMP consisted of intensive in-hospital education followed by scheduled clinic visits at 2, 6 and 12 weeks and weekly phone calls throughout the first 3 months on non-clinic weeks. Subsequently, patients were reviewed annually at the clinic. Patients were advised to contact the clinic directly in the event of suspected early clinical deterioration (PCDA). We evaluated mortality, emergency HF hospitalisations, emergency non-HF hospitalisations and episodes of PCDA in 477 patients who were enrolled onto the intensive DMP over the initial 3 month post discharge period and compared them to a control group of 47 patients initially randomised to Routine Care (RC) and subsequently followed up as part of the DMP. All patients were followed for 3 years.
Results: At 3 years, 79% of DMP patients (age 69.5 $\pm$11.9 years, 64.8% male, 83.2% systolic dysfunction, 67.9% ischaemic) and 51% of RC patients (age 70.8 $\pm$10.7 years, 70.2% male, 68.1% systolic dysfunction, 48.9% ischaemic) had initiated PCDA visits to the HF service for suspected clinical deterioration (p=0.0001). The RC group had significantly more emergency HF hospitalisations (unadjusted hazard ratio (HR) 2.7, 95% CI 1.6-4.4, $p<0.0001$) and significantly less PCDA clinic visits (unadjusted HR 0.32, 95% CI 0.19-0.37, $p<0.001$) than DMP patients. Multivariable analysis demonstrated that DMP care was independently associated with reduced hospitalisation ($p<0.0001$). There were no significant differences in mortality observed between the groups (p=0.699), or the composite endpoint of mortality and/or all-cause emergency hospitalisation (p=0.253).
Conclusions: Although we have shown that extending the intensive 3-month Hospital based DMP to 6 months yields no morbidity or mortality benefit, these data support the role of direct access for patients to a hospital-based HF service in reducing HF hospitalisations over an extended follow up period.

P2296 The effect of early education plus bi-weekly telephone nursing consultation on anxiety and health related quality of life in patients waiting for elective cardiac catheterisation

H. Arthur, K.M. Smith, K. Harkness. *McMaster University, Health Sciences, Hamilton, Canada*

Background: Waiting lists for cardiac catheterization (CATH) exist in many countries. Waiting for CATH is a stressful experience that can increase risk. There is little information about the effect of specific interventions during the waiting time.
Purpose: To examine the combined effect of early education plus bi-weekly telephone nursing consultation throughout the waiting period, on anxiety and health related quality of life (HRQL) in patients waiting for elective CATH.
Methods: This was a two-group randomized controlled trial, with stratification for previous CATH. The primary outcome was patient anxiety, as measured by Spielberger's State-Trait Anxiety Inventory and a 10-point verbal anxiety rating. Secondary outcomes were both general and disease-specific HRQL, as measured by the Medical Outcomes Study SF-36 and Seattle Angina Questionnaire respectively.
Results: A total of 246 patients were randomly assigned to one of the two study groups; 65 had undergone previous CATH and 181 were having a first CATH. There were no differences between groups at baselines. Significant main effects for anxiety were: 1) a main effect for time (p=0.002) where both groups demonstrated higher levels of anxiety at the end of the waiting time compared to baseline, and 2) a main effect for CATH (p = 0.003), where "previous CATH" patients had lower state anxiety than "first CATH" patients throughout the study. There was a significant time-by-previous CATH interaction (p = 0.004); "previous CATH" patients showed no significant change in state anxiety but the "first CATH" patients had a significant rise in anxiety. General HRQL deteriorated over the waiting time, however, there was a 3-way interaction where "previous CATH" patients in the intervention group had significantly improved physical HRQL compared to patients in the "first CATH" group by the end of the waiting period (p=0.029).
Conclusion: Anxiety rises and HRQL deteriorates among patients who are on a waiting list for their first CATH. An educational intervention, combined with ongoing telephone support throughout the wait, has a significant impact among patients who have had a previous CATH.

COST-EFFECTIVENESS

P2297 Cost-effectiveness of perindopril compared to placebo to prevent cardio-vascular events in stable coronary heart disease

L.W. Niessen[1], W.K. Redekop[1], J.W. Deckers[2], F.F.H. Rutten[1] on behalf of EUROPA trial investigators. *[1]Erasmus MC, Erasmus U, iMTA/iBMG, Rotterdam, Netherlands; [2]Erasmus MC, Erasmus U, Department of Cardiology, Rotterdam, Netherlands*

The EUROPA study showed that treatment with perindopril, 8 mg, in patients with proven coronary artery disease (CAD) causes a significant 20% relative risk reduction in cardio-vascular death, non fatal MI and cardiac arrest compared to placebo. This study estimates medical costs for cardiovascular disease per patient, and costs per life year gained per patient in The Netherlands, France, Italy and Poland.

All data from the four-year randomized trial of 12,218 patients in 24 countries are used. A Monte Carlo analysis estimates total life-years lived in each arm, using a country-specific life table corrected for excess age-specific cardiovascular risk observed in the control arm. Costs are computed using individual data on length of hospital stay, procedures, type and number of events and country-specific unit prices, from country-specific datasets,using sampling with replacement. Uncertainties regarding the incremental cost-effectiveness ratio (ICER) are presented as a confidence ellipse on the cost-effectiveness plane.

The outcomes for each country (Table) vary from 0.182 to 0.208 life years gained per patient lifetime and from 462 to 1,861 euros in medical costs per patient, at a 3% discount rate (large SEs). Country point estimates for the ICER range from 2,536 to 8,904 euros per life-year gained. The probability that the ICER for a country falls below the threshold value of 20,000 euros varies from 73% to 92%; at a threshold of 30,000 euros this range is between 80% to 94%. Outcomes are sensitive to the discount rate for life years.

Table. Cost-effectiveness of perindopril

	Netherlands	France	Italy	Poland
Health gain per patient (life years)	0.194	0.207	0.209	0.182
SE	(0.152)	(0.158)	(0.159)	(0.120)
Change in medical costs per patient (euros)	1,121	1,537	1,861	462
SE	(142)	(78)	(62)	(25)
Cost-effectiveness ratio (euros/life year)	5,778	7,425	8,904	2,630
Proability that ICER < 30.000 euros	84	80%	83%	94%
Probability that ICER < 20,000 euros	80%	73%	77%	92%

Costs are in 2003 euros, discounted at 3%. SE: standard error.

Given prevailing ICER thresholds, perindopril very likely is cost-effective.

P2298 Projected benefits and cost effectiveness of switching to dual inhibition therapy (ezetimibe/simvastatin) in Germany for patients not at goal on statin monotherapy

K.J. Krobot[1], G.M. Davies[2], E. Alemao[3], D.D. Yin[3], J.R. Cook[2]. *[1]MSD Sharp & Dohme GmbH, Outcomes Research, Haar, Germany; [2]Merck&Co, Inc., CBARDS/Health Economics, Blue Bell, PA, United States of America; [3]Merck&Co, Inc., Outcomes Research, Whitehouse Station, NJ, United States of America*

Purpose: Many CHD patients remain above recommended LDL-C goals (100 mg/dL) despite lipid-lowering therapy. Clinical trials have demonstrated higher cholesterol goal attainment rates with dual inhibition of cholesterol synthesis and absorption than with statin monotherapy. We therefore estimated life-years gained and the cost effectiveness of switching CHD patients not at goal with statin monotherapy in Germany to dual inhibition therapy with Ezetimibe/Simvastatin.

Methods: The Markov model used changes in lipid parameters from clinical trials. The risk of fatal and nonfatal recurrent CHD events was estimated by Framingham risk equations, and national mortality statistics were used to estimate non-CHD death. Patients not at goal on their current statin were either switched to equipotent simvastatin doses or maintained on their current statin with or without subsequent titration to goal. Titration to goal was defined as doubling of the statin dose in both arms of the model until either maximum approved statin dose or LDL-C goal is attained. Predictions are based on patient level data from a published observational study from Germany.

Results: Characteristics of patients (SD) currently prescribed statins who failed to reach lipid goal: 63.2 (9.8) years of age, females 34%, mean LDL-C 148.5 (34.0) mg/dL, mean HDL-C 47.9 (14.3) mg/dL, mean total cholesterol 227.4 (43.7) mg/dL, and diabetes mellitus 34%. Treatment costs are based on pharmacy retail prices (ICER-1) or reference prices (ICER-2). Results are given in Table 1 for each strategy.

Table 1

	LYG	ICER-1	ICER-2
Switch of patients on Atorvastatin or Simvastatin to Ezetimibe/Simvastatin vs.			
Switch to Generic Simvastatin with no titration	0.78	12,817	12,397
Switch to Generic Simvastatin with titration to goal	0.46	15,415	17,061
Switch of patients on Atorvastatin to Ezetimibe/Simvastatin vs.			
Continue on Atorvastatin with no titration	0.81	7,929	11,630
Titrate on Atorvastatin to attain goal	0.54	cost saving (390 € p.a.)	cost saving (64 € p.a.)

LYG = Life-years gained; ICER = incremental cost per life-year gained

Conclusion: Switching secondary prevention patients not at LDL-C goal on their current statin to Ezetimibe/Simvastatin is projected to increase life expectancy and is cost effective compared to generic simvastatin, and cost effective to cost saving compared to atorvastatin.

P2299 Cost-effectiveness of aldosterone blockade with eplerenone in patients with heart failure after acute myocardial infarction: results from EPHESUS applied to four European countries

W.S. Weintraub[1], Z. Zhang[1], M. Kvasz[2], R. Willke[2]. *[1]Emory Center For Outcomes Research, Emory West, Atlanta, United States of America; [2]Pfizer, Inc., New York, United States of America*

Objective: EPHESUS showed efficacy of selective aldosterone blockade (eplerenone) in heart failure (HF) post MI, with reductions in all-cause death and cardiovascular (CV) death or hospitalisations. This study determines cost-effectiveness of eplerenone with unit costs from France and Spain.

Methods: 6,632 patients in 37 countries with HF post-MI were randomised to eplerenone 25-50 mg/day vs placebo and followed 16 months. Overall efficacy and resource utilisation were used, including all-cause rehospitalisations, medications, outpatient procedures, and emergency room visits. To estimate life years gained (LYG) with eplerenone, data from Framingham, Saskatchewan Health and Worcester MI databases were used to estimate life expectancy. Costs and life years were discounted 3%. The cost of eplerenone used was €2.00 a day (may not be the final marketed price).

Results: there were 478 deaths in the eplerenone group and 554 in the placebo group (relative risk 0.85, 95%CI 0.75 to 0.96). Eplerenone reduced both CV (13% risk reduction, p=0.03) and HF rehospitalisations (23% risk reduction, p=0.002). Costs of both CV and HF rehospitalisations were significantly lower in the eplerenone group showing that adding eplerenone will result in less in-patient resource use. Efficacy is expressed as LYG with eplerenone and the incremental cost-effectiveness ratio (ICER) in cost/LYG (see table).

Cost-Effectiveness of Eplerenone

	Cost, Placbo	Cost, Eplerenone	Added Cost of Eplerenone	LYG with Eplerenone	ICER (€/LYG)	% <50,000 (€/LGY)
France						
Framingham	4,745	5,471	726	0.101	7,164	99
Saskatechewasn	4,745	5,471	726	0.0636	11,423	99
Worcester	4,745	5,471	726	0.134	5,432	99
Spain						
Framingham	5,029	5,762	733	0.101	7,230	99
Saskatchewan	5,029	5,762	733	0.0636	11,530	98
Worcester	5,029	5,762	733	0.134	5,483	99

Conclusions: in both France and Spain, selective aldosterone blockade with eplerenone in the setting of HF post-MI prevents events, prolongs life, and is cost-effective. Adding eplerenone to standard therapy will result in less in-patient resource use.

P2300 The cost-effectiveness of clopidogrel based on three trials

P. Lindgren[1], A. Ringborg[2], B. Jonsson[3]. *[1]Institute of Environmental Medicine, Health Economics, Stockholm, Sweden; [2]Stockholm Health Economics, Stockholm, Sweden; [3]Stockholm School of Economics, Stockholm, Sweden*

Purpose: The purpose of the study was to compare three models for assessing the cost-effectiveness of the use of clopidogrel to prevent ischemic events in patients with acute coronary syndromes in a Swedish setting based on the CURE, PCI-CURE and CREDO studies.

Methods: Three Markov models with similar definitions of the disease were used to simulate the long-term effect of treating patients during one year. The same set of costs (based on published sources) was used in the three models. The perspective was that of society as a whole, including both direct costs of care and costs due to lost production. Events included were those included in the primary end-point of the trials (cardiovascular death and non-fatal MI in all three models and stroke in the CURE and CREDO models). The risk of an event was estimated based on different sources: the inpatient register (CURE model), the RIKS-HIA register (PCI-CURE) and the trial itself (CREDO).

Results: All three models predicted an increased cost in the clopidogrel arm: 149 € in the CURE model, 332 € in the PCI-CURE model and 168 € in the CREDO model. The incremental cost-effectiveness ratios were 1009 €, 8127 € and 2338 € per gained year of life in the three models.

Conclusion: The difference between the studies is explained by two factors: A lower risk of events in the PCI population and a very conservative event definition in the PCI-CURE model. In all cases, the incremental cost-effectiveness ratios fall well below what is generally considered cost-effective.

P2301 Cost saving anticoagulation with enoxaparin in patients undergoing cardioversion of nonvalvular atrial fibrillation – results from the Anticoagulation in Cardioversion using Enoxaparin (ACE) Study

P.K. Schaedlich[1], C. Schmidt-Lucke[2], E. Huppertz[3], W. Lehmacher[4], U. Nixdorff[5], C. Stellbrink[6], J.G. Brecht[1] on behalf of the ACE Study Group. *[1]InForMed GmbH, Ingolstadt, Germany; [2]University Hospital, Molecular Cardiology, Frankfurt am Main, Germany; [3]Aventis Pharma Deutschland GmbH, Bad Soden am Taunus, Germany; [4]University of Cologne, Institute for Medical Statistics, Cologne, Germany; [5]University Hospital, Medical Clinic II, Erlangen, Germany; [6]University Hospital, Medical Clinic I, Aachen, Germany*

Purpose: In the ACE study, anticoagulation with the sc low-molecular weight heparin enoxaparin (ENOX) was shown to be noninferior to iv unfractionated heparin followed by oral phenprocoumon (UFH/PPC) in preventing deaths and ischemic, thromboembolic, and hemorrhagic events. Opposed to UFH/PPC, initiation of anticoagulation with ENOX is not necessarily inpatient based, sc injection by the patient himself or a relative is well-accepted and safe, and coagulation control is less frequent except for patients with renal impairment. The purpose therefore was to estimate – from the perspective of Statutory Health Insurance (SHI, third-party payer) in Germany – the economic consequences of using ENOX instead of UFH/PPC for anticoagulation in transesophageal echocardiography (TEE) guided early electrocardioversion (ECV) of persisting nonvalvular atrial fibrillation (AF) without intracardiac clot. Savings or incremental expenses of SHI for ENOX versus UFH/PPC were chosen as the target variable.
Methods: The target variable was quantified using a decision-analytic model considering the in- and outpatient sectors. The analysis encompassed 28 (26–30) treatment days, according to the ACE study. Phase I with 5 (3–12) days comprised diagnostics, initiation of anticoagulation, and ECV. Phase II with the remaining days comprised continued anticoagulation. Resource use during in- and outpatient treatment was valuated in monetary terms, according to German healthcare regulations (reference period 2003/2004).
Results: The base-case analysis considered patients with any comorbidity and complication level (all patients). In phase I, in 38% and 62% of the ENOX patients and in 100% and 0% of the UFH/PPC patients in- and outpatient ECV, respectively, was assumed. There were savings for SHI of EUR 338 per patient with ENOX (EUR 1357) instead of UFH/PPC (EUR 1695). The subgroup analysis with low-risk patients (low comorbidity and complications expected only in rare cases) was based on 1-day inpatient ECV (phase I) in 1% of the ENOX patients and revealed savings for SHI of EUR 579 per patient with ENOX (EUR 892) instead of UFH/PPC (EUR 1471). Comprehensive deterministic and stochastic sensitivity analyses showed the robustness of the results.
Conclusions: Using ENOX instead of UFH/PPC for anticoagulation in patients undergoing TEE-guided ECV of AF without intracardiac clot offers SHI in Germany a considerable saving potential.

P2302 Cost-effectiveness of atorvastatin (10mg) among patients with type 2 diabetes without coronary heart disease: CARDS trial analysis

A.J. McGuire[1], M. Raikou[2]. *[1]London School of Economics, LSE Health and Social Care, London, United Kingdom; [2]London School of Economics, LSE Health and Social Care, London WC2A 2AE, United Kingdom*

Purpose: To investigate the cost-effectiveness of lipid-lowering therapy with atorvastatin 10mg in the primary prevention of CVD in patients with type 2 diabetes using data from the Collaborative Atorvastatin Collaboration Study (CARDS) trial.
Methods: An incremental cost-effectiveness analysis was undertaken on the 2838 patients, from the 132 treatment centres in the UK and Eire, with type 2 diabetes at risk of CVD as part of CARDS trial. The statistic calculated was an incremental cost per cardiovascular event free year based on the pre-defined primary and secondary trial outcomes for the ITT population. The primary efficacy parameters used for the economic evaluation were acute CHD death; non-fatal MI including silent MI; hospitalised unstable angina; resuscitated cardiac arrest; coronary revascularization; and stroke. The secondary endpoints were total mortality and any other cardiovascular endpoint. The incremental cost-effectiveness analysis was undertaken for the within trial ITT population - median follow-up of 3.9 years - where the number randomised to atorvastatin was 1428 and to placebo was 1410. Patients had to have one of the following risk factors on entry: hypertension, retinopathy, microalbuminuria or macroalbuminuria or be a current smoker. Event free life year was calculated as the Area under the defined survival to endpoint curve.Costs were calculated using individual patient data based on within trial resource use and unit costs from various UK published sources at 2003/04 prices.
Results: Treatment with atorvastatin 10mg raised net treatment costs by £521 per patient over the study period (discounting at 3.5% per year). The cost per CVD event averted over the trial period, using the definition of primary endpoints averted was £16,196. Discounting costs and outcomes at 3.5% per year, the incremental cost per event free year, based on an endpoint definition of all fatal CHD and non-fatal MI events, was £7,608 per event free-year, while the incremental cost per event free year based on any cardiovascular endpoint, was £4,896 per event free year, and £4,119 per event free year when events were defined as all study endpoints over the study period.
Conclusion: Administering atorvastatin 10mg in the primary prevention of CVD in patients with type 2 diabetes is concluded to be cost-effective when compared to a range of other interventions in similar patient populations and compares favourably to the calculated cost-effectiveness ratios reported by the UKPDS and Heart Protection Study.

P2303 The cost-effectiveness of drug-eluting stents in elective percutanous coronary interventions

L. Golan[1], L. Simek[2], M. Skvarilova[2], J. Horak[2], J.C. Lubanda[2], A. Kovarik[2], A. Linhart[2], M. Aschermann[2]. *[1]The Charles University Hospital, IInd Department of Internal Medicine, Prague 2, Czech Republic; [2]The Charles University Hospital, IInd Department of Internal Medicine, Prague, Czech Republic*

Aims: Drug-eluting coronary stents can significantly reduce the rate of restenosis, decrease the cost of rehospitalisation and increase the quality of life. However the widespread use is limited by high cost. We were interested in the cost-effectiveness of implantation drug-eluting stents in all elective percutanous coronary interventions.
Methods: We constructed a decision analysis model (programme DATA 3.5, TreeAge Software) to compare the strategy of implantation drug-eluting stents in all elective percutanous coronary interventions vs. the strategy of implantation uncoated stents. Probabilities of clinical outcomes were derived from a clinical trial (SIRIUS) after a 1-year follow-up. Costs of percutaneous coronary interventions were estimated from costs of cathetrization laboratory and charges to health insurance companies. The quality of life was obtained from literature.
Results: In the base case we found that the strategy of implantation drug-eluting stents is more expensive (4740.– vs. 4120.– EUR), but provides greater effect (0,9899 vs. 0,9743 quality-adjusted life year-QALY). The cost of additional quality-adjusted life year in the base case was 40 000.– EUR. The disease specific cost-effectiveness ratio – the cost of repeat revascularization avoided was 4230.– EUR. In the sensitivity analysis of the model the cost-effectiveness improved significantly with decreasing cost difference between drug eluting and uncoated stents. The cost-effectiveness was better in patients with higher risk of restenosis.
Conclusions: Since the mortality benefit of drug eluting stents is unknown and the cost high, the cost effectiveness of implantation drug eluting stents in all patients is borderline. Before the introduction of this perspective strategy we need more information from long-term clinical trials and drug-eluting stents should be implanted in patients with higher risk of restenosis.

P2304 Effect of a primary angioplasty programme for myocardial infarction on length of hospital stay

A. Patil[1], P.A. MacCarthy[2], S. Wheatcroft[2], P. Thompson[3], A.M. Shah[2], R.J. Wainwright[2], M.R. Thomas[2]. *[1]Kings College Hospital, Department of Cardiology, London, United Kingdom; [2]Kings College Hospital, Department of Cardiology, London, United Kingdom; [3]Kings College Hospital, Department of Accident and Emergency, London, United Kingdom*

Background: Primary angioplasty for myocardial infarction (PAMI) has improved outcomes compared to the delivery of thrombolysis. The effect of such a change of strategy on length of stay (LOS) in hospital is less clear.
Aim: We assessed the effect of a change of treatment strategy (from thrombolysis to PAMI) for acute myocardial infarction on LOS. In addition, the clinical outcomes of the patients were measured to ensure any reduction in LOS did not result in increased cardiac events.
Methods: From September 1st 2003 to November 2004 a total of 117 sequential patients were treated within a PAMI programme at Kings College Hospital, London UK. Clinical outcomes and LOS were compared with a historical control group submitted to the myocardial infarction national audit project (MINAP) between Sep 2002 and August 2003.
Results: Of the 117 patients in the PAMI programme, 109 patients had a coronary angiogram, and 95 patients had an primary angioplasty. Clinical outcome was better in the PAMI group. Mortality and stroke at mean follow up of 8.3 months was 9.4% (in-hospital 6.3%) and 1.05% in the PAMI group, and 23.8% (in-hospital 16.6%) and 4.7% respectively in the MINAP group. The median length of stay was 9.2 days in the MINAP group and 4 days in the PAMI group.
Conclusion: A switch from a thrombolysis to a PAMI strategy is accompanied by an impressive reduction in LOS with associated improvement in clinical outcomes. This is likely to offset the cost implications of the strategy change and should contribute to the cost effectiveness of primary angioplasty for acute MI.

P2305 Risk factor management in patients with premature coronary artery disease

H. Voeller[1], K. Bestehorn[2], H. Benecke[2], H. Renner[3], K. Wegscheider[4]. *[1]Klinik am See, Cardiology Dpt., Rudersdorf, Germany; [2]MSD Sharp & Dohme, Haar, Germany; [3]Staufenburg Klinik, Durbach, Germany; [4]University Hamburg, Institut for Statistics & Econometrics, Hamburg, Germany*

Usually atherosclerosis is seen as an age dependent process where risk factors like dyslipidemia play a major role. However, it is not known whether the risk

profile of patients with CAD at an early age is comparable to the older patients with CAD. Therefore we started a registry to address this question.
Methods: From April 2003 to March 2004 in Germany 15.381 consecutive patients were included prospectively from 101 cardiovascular rehab centres. To be included in the registry patients had to be either younger than 55 (men) or 65 (women) when they had their cardiovascular event (group 1) or - if they were older - to have an LDL-Cholesterol > 2.6 mmol/l (group 2). Besides family history of premature atherosclerosis the conventional risk factors smoking, diabetes mellitus, dyslipidemia and hypertension were recorded. Additionally the emerging risk factors lipoprotein a, homocysteine and impaired glucose tolerance were assessed. Lipid levels and blood pressure as well as medication were recorded on admission and at discharge. Statistical analysis was performed by Chi-square testing.
Results: Patients of group 1 (n = 5725) had a mean age of 50.0 ± 7.2, patients of group 2 (n = 9656) 69.3 ± 7.3 (p = 0.0001). Diabetes mellitus (30.1% vs 23.5%) and hypertension (87.0% vs 71.4%) were more frequent in the older group (p = 0,0001). Dyslipidemia (92.7% vs 91.8%), smoking (31.5% vs 9.4%), a positive family history of premature atherosclerosis (43.6% vs 26.4%) were more frequent in the younger group (p=0.00001) and impaired glucose tolerance (20.8% vs. 14.8%, p < 0.05). Increased homocysteine levels were seen in 51.2% of the older patients vs 39.8% in the younger patient group (p = 0.0027). Elevated levels of Lipoprotein (a) were seen equally often in both groups (8.0%). LDL-cholesterol levels < 100 mg/dl at discharge were more frequent in the younger patients (38.8% vs 33.7%, p < 0.00001), whereas blood pressure (systolic > 140 mmHg) was higher in the older group (15.4% vs 7.8%, p < 0.00001). There were no significant differences in the medication between the two groups.
Conclusion: Whereas it might be expected that older patients have more frequently diabetes mellitus and hypertension it is surprising that dyslipidemia and impaired glucose tolerance were more frequent in younger patients. For them smoking cessation as well as controlling the other modifiable cardiovascular risk factors is even more important because of their genetic background.

P2306 Implementation of antithrombotic management in atrial fibrillation. Audit in outpatient clinic

L. Morcillo[1], J.J. Gomez-Doblas[2], A. Perez-Cabeza[1], F. Valencia[1], M. Ramirez[1], M. Jimenez[1], F. Cabrera[1], E. De Teresa[1]. *[1]University Hospital Virgen de la Victoria, Cardiology Department, Malaga, Spain; [2]University Hospital Virgen de la Victoria, Cardiology Department, Malaga, Spain*

Atrial fibrillation (AF) greatly increases the risk of stroke. Long-term oral therapy with oral anticoagulation (OA) reduces the risk of AF-related stroke, and guidelines now call for anticoagulant therapy in most patients without specific contraindications to anticoagulation. The aim of the study was to assess the extent to which published recommendations had been adopted into clinical practice in a outpatient clinic
Methods: Retrospective chart review of 351 patients with AF between March 2003- January 2004.
Results: In a retrospective study (and audit), we examined 351 cases of AF (persistent, paroxysmal non-sustained and chronic sustained) admitted to an outpatient clinic. We analysed specifically 232 patients with chronic AF. 54,7% were women with mean age of 71,2 ± 8 years old. 67,7% received OA, 24,1% were on aspirin, 3% other antiplatelet drugs and the remaining 5,2% received neither OA or antiplatelet. 46 patients (19,8%) with absolute indication of OA received aspirin or nothing without contraindications for it. After univariate analysis neither age, gender or any other clinical variable could be identified as determinant factors for starting anticoagulation prophylaxis.
Conclusions: More awareness is needed among physicians managing AF particularly in relation to anticoagulation. Despite broad consensus in recent publications, antithrombotic management of AF remains imperfect, with many patients exposed to unnecessarily high risk of stroke.

P2307 Trans-thoracic echocardiography in suspected endocarditis – the reality!!

A. Rao[1], K. Booker[2], K.W. Clarke[2], P. Wong[2], E.R. Rodrigues[2]. *[1]QMC University Hospital, Cardiology Dept., Nottingham, United Kingdom; [2]University Hospital Aintree, Cardiology, Liverpool, United Kingdom*

Infective endocarditis (IE) is a diagnostic challenge. Trans-thoracic echocardiography (TTE) in patients with suspected IE is recommended, however systematic usage in clinical practice remains ill defined.
Purpose: To assess characteristics of patients referred for a TTE to exclude IE and their impact on resources. To examine if clinical criteria may aid decision making with respect to the use of TTE in patients with suspected endocarditis.
Methods: Patients referred for a TTE to exclude IE between Oct 2003 and May 2004 in a University Hospital were identified. Retrospective case note audit was undertaken. Pre-determined risk factors that predispose to endocarditis and modified Dukes criteria were assessed.
Results: 164 requests for TTE to exclude IE were received. 110 (67%) notes were audited. The majority of requests were from General Medicine and Intensive Care (76%). 11% of requests were from Cardiology.
Mean age of patients was 58(20) years, 61(56%) male. The mean length of hospital stay was 30 (32) days. 18% of patients had intravenous antibiotic therapy, 54% had oral therapy and 8% had both; with a mean length of therapy of 17(16) days. No patients had their antibiotics stopped, despite a normal echocardiogram.
The common risk factors were intravenous drug use- 24%; prosthetic valves - 11%; recent surgery or instrumentation -10% and the presence of a pacemaker -9%.
Vegetations were reported on 13 (12%) echoes, one of who had old endocarditis and was an out- patient. The rest were diagnosed with IE; all of who fulfilled a minimum of 1 major and 2 minor modified Dukes criteria.
65 (59%) patients fulfilled < 2 modified Dukes minor criteria and none of them had endocarditis.
The common alternative diagnosis was Chest infection (14.3%); skin infections-cellulitis/abscess (12.5%) and urinary tract infection (8%).
Conclusions: The use of TTE to exclude IE is common but diagnostic yield is poor in patients with low clinical suspicion and does not appear to influence management.
These patients have a significant impact on resources due to prolonged hospitalisation, antibiotic use and requests for TTEs.
The modified Dukes criteria were sensitive in identifying patients with IE.

P2308 Opportunities of improvement in treatment of heart failure. A multicenter study

J.J. Gomez-Doblas[1], M. Anguita[2], J.L. Lopez Sendon[3], A. Castro[4], E. De Teresa[5] on behalf of ATIICA Study. *[1]University Hospital Virgen de la Victoria, Cardiology Department, Malaga, Spain; [2]Hospital Univ Reina Sofia, Cardiology, Cordoba, Spain; [3]Hospital Gregorio Marañon, Cardiology, Madrid, Spain; [4]Hospital Juan Canalejo, Cardiology, La Coruña, Spain; [5]University Hospital Virgen de la Victoria, Cardiology Department, Malaga, Spain*

Effective therapy for chronic heart failure is underutilized despite a broad consensus regarding treatment recommendations. The aim of this study was to assess the treatment and recommendations at discharge in heart failure patients.
Patients AND Method: 27 hospitals participated. We studied consecutive patients with diagnosis of heart failure at discharge. All the patients were managed by cardiologist. Quality indicators were defined previously as proportion of patients in whom ejection fraction were evaluated, treatment at discharge (ACEI, betablockers, espironolactone) and hygienic or dietary recommendations (diet, exercise, weight, etc.) referred to all patients in whom these measures should have been used ("ideal patients"). Every hospital were compared with each other using Achievable Benchmarks of Care (ABC) procedure.
Results: 932 patients were included. Mean age was 69,2 ± 2 years, higher percentage of men (61,8%) The most frequent aetiology was ischaemic (40%) and hypertensive (28%). Ejection fraction was evaluated in 88,2%.The quality indicators of this ideal cohort referred to treatment prescribed and diet at discharged are showed in the following table.

Recommendations	%	Treatment	%
Diet without salt	79,1	Diuretics	98,1
Exercise	53,3	ACE inhibitors	91
Ideal weight	28,9	Betablockers	84,4
Diuretics autodosification	29,9	Espironolactone	87,9
Recommended ACEI dose	51	Anticoagulation	97,3
Recommended Betablockers dose	49,9	Digoxin	92,3

Conclusions: For patients with heart failure who are discharged there is an adequate use of the recommended treatment by guidelines although is susceptible to improve. Improvement is necessary about recommendations of diet, recommended dose of drugs and hygienic measures. Quality improvement efforts therefore need to be focused on both discharge planning and outpatient care.

P2309 Quality of hospital and outpatient care after stroke or TIA: insights from a stroke survey

W.J.M. Scholte op Reimer[1], D.W.J. Dippel[2], C.L. Franke[3], R.J. Oostenbrugge[4], G.J. de Jong[5], S. Hoeks[6], M.L. Simoons[1]. *[1]Erasmus Medical Centre Rotterdam, Thoraxcentre, Dept. of Cardiology, Rotterdam, Netherlands; [2]Erasmus Medical Center, Dept. of Neurology, Rotterdam, Netherlands; [3]Atrium Medical Center, Dept. of Neurology, Heerlen, Netherlands; [4]University Hospital, Dept. of Neurology, Maastricht, Netherlands; [5]ISALA Klinieken, Neurology, Zwolle, Netherlands; [6]Erasmus Medical Centre Rotterdam, Thoraxcentre, Dept. of Cardiology, Rotterdam, Netherlands*

Background and Purpose: Limited data are available on stroke management of outpatients and clinicians' reasons to withhold procedures recommended by guidelines. We assessed to what extent guidelines are appropriately applied after ischemic stroke or TIA, in admitted patients as well as outpatients.
Methods: A survey was conducted in 11 centers in the Netherlands, who prospectively enrolled 579 admitted patients and 393 outpatients. Data were collected by trained research assistants. Duplicate assessment in 10% of patients showed good agreement with neurologists (median kappa=0.86). Treating neurol-

ogists were asked to provide reasons for withholding recommended procedures in eligible patients, if this was not documented in the patient's hospital chart.
Results: Recommended acute procedures were provided in the majority of admitted eligible patients, but less often in eligible outpatients: brain imaging (98% and 93%, respectively), 12-lead ECG (96% and 81%), laboratory tests (97% and 86%), aspirin within 48 hours (90% and 68% of eligible patients). Secondary preventive measures were not always taken in both eligible inpatients and eligible outpatients: carotid endarterectomy (31% and 47%), antiplatelet agents (93% and 90%), oral anticoagulants (60% and 48%), antihypertensive agents (57% and 44%), and cholesterol lowering therapy (71% and 52%). Reasons for withholding recommended procedures were plausible for almost all admitted patients, but were unclear in the majority of outpatients.
Conclusion: Compared to other national surveys, we found high-quality acute care in admitted ischemic stroke patients, while secondary prevention was comparably poor. Although the majority of our centers have rapid access TIA clinics, there is still room for substantial improvement of quality of stroke care in outpatients.

P2310 Are we using low molecular weight heparin safely in acute coronary syndromes?

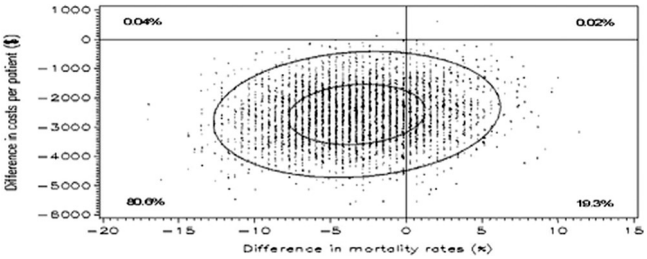
L.E. Hudsmith[1], S. Haldar[2], S. Bull[2], N. Chahal[2], C.J. McKenna[2], W.P. Orr[2]. [1]*Oxford, United Kingdom;* [2]*Battle Hospital, Department of Cardiology, Reading, United Kingdom*

Introduction: The use of Low Molecular Weight Heparin (LMWH) has revolutionised the treatment of acute coronary syndromes (ACS). These patients represent a large number of high-risk medical admissions. LMWH can be administered subcutaneously without the need for laboratory monitoring of anticoagulation. LMWH has an improved side-effect profile and a more predictable and consistent anticoagulant response compared to unfractionated heparin.
The FRISC study showed a 65% relative reduction of death or myocardial infarction in ACS patients with the use of LMWH compared to placebo.
With the addition of potent antiplatelet therapies such as glycoprotein IIb/IIIa, clopidogrel and aspirin, it is imperative that appropriate doses are prescribed to avoid exposing patients to unnecessary risks of bleeding.
We investigated the accuracy of LMWH dosing of patients admitted with an acute coronary syndrome (ACS).
Methods: 64 inpatients (36 male) admitted with an acute coronary syndrome (ACS) were identified and weighed. Patient demographics and the dose of dalteparin (fragmin) prescribed were noted. Weight adjusted doses for patients were calculated and compared to doses received.
After a 2 month period of education of all medical professionals including doctors, nurses and pharmacists, a further 25 (17 male) inpatients with ACS were identified and weighed.
Results: 64 inpatients (36 male, age range 30-90 years, weight range 53-96 kg) were receiving doses between 6000-10000 units/12 hours.
53% were receiving an inappropriate dose of LMWH: 19% (12) overtherapeutic and 34%(22) undertherapeutic. 47% (30) patients were receiving therapeutic LMWH.
A further 25 inpatients (17 male, age range 38-91 years, weight range 58-130kg) were receiving doses between 5500-10000 units/12 hours. 72% (18) patients were receiving therapeutic LMWH. 28% were receiving an inappropriate dose of LMWH: 8% (2) were receiving overtherapeutic and 20% (5) undertherapeutic doses of LMWH.
Conclusion: Even within the acute hospital setting, patient weights are often "guessed" initially leading to a significant proportion (>50%) of patients being prescribed potentially unsafe doses. These inaccuracies are likely to be of major importance in other clinical settings, particularly in older patients including the safe use of pre-hospital thrombolysis/anticoagulation and GPIIb/IIIa antagonists in primary angioplasty.
After a 2 month period of education, we showed a significant improvement in the accuracy and safety of LMWH dosing in 25 ACS inpatients, closing the audit loop.

P2311 Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnoea

C. Mueller[1], K. Laule-Kilian[2], C. Schindler[2], B. Frana[2], D. Rodriguez[2], A. Perruchoud[2]. [1]*Medizinische Klinik A Kantonsspital Basel, Department of Internal Medicine, Basel, Switzerland;* [2]*University Hospital Basel, Internal Medicine, Basel, Switzerland*

Background: B-type natriuretic peptide (BNP) is a quantitative marker of heart failure that seems to be very helpful in its diagnosis. It was the aim of this study to estimate the cost-effectiveness of BNP-guidance.
Methods: We performed a prospective randomized study (BASEL) including 452 patients who presented to the emergency department with acute dyspnea. Non-parametric bootstrapping was used to estimate the distribution of incremental costs and effects on the cost-effectiveness plane for the in-hospital period, as well as at 90 days and 180 days follow-up. Data on survival and use of health care resources were obtained for all 452 BASEL participants.
Cost-effectiveness was analysed with a time horizon of 180 days from the third-party payer perspective. Participants were randomly assigned to a diagnostic strategy involving the measurement of BNP levels (n=225) or assessment in a standard manner (n=227). Outcome measures included survival, total treatment cost, and cost-effectiveness.
Results: At 180 days, all-cause mortality was 20% in the BNP group and 23% in the control group (P=0.422). Total treatment cost was significantly reduced in the BNP group ($7,930 versus $10,503 in the control group; P=0.004). Analysis of incremental 180-day cost-effectiveness showed that BNP guidance resulted in lower mortality and lower cost in 80.6%, in higher mortality and lower cost in 19.3%, and in higher or lower mortality and higher cost in both below 0.1%.
Sensitivity analysis showed that results were robust to changes in most variables, but sensitive to changes in re-hospitalization with BNP guidance.



BASEL: Cost-effectiveness at 180 days

Conclusion: BNP testing is cost-effective in patients with acute dyspnea.

P2312 Incremental cost-effectiveness of Mediterranean diet on cardiovascular disease risk; the ATTICA study

M. Sitara[1], D.B. Panagiotakos[2], C. Pitsavos[3], C. Chrysohoou[3], C. Stefanadis[3]. [1]*Harokopio University, Department of Nutrition and Dietetics, Athens, Greece;* [2]*Glyfada, Greece;* [3]*University of Athens, Hippokration Hospital, Athens, Greece*

Background: Adherence to the Mediterranean diet has long been associated with longevity and a better health status. In this study cost-effectiveness of this traditional diet compared to a more "westernized" diet was assessed in relation to cardiovascular risk.
Methods: From May 2001 to December 2002 we randomly enrolled 1514 adult men and 1528 women, without any clinical evidence of cardiovascular disease, stratified by age – gender, from the greater area of Athens, Greece. Adherence to the Mediterranean diet was ascertained through a food frequency questionnaire and a special diet score (range 0–55) that incorporates the inherent characteristics of this dietary pattern. People with values above the median were considered to be "closer" to the Mediterranean dietary pattern. Then the incremental cost-effectiveness ratio was calculated, as the additional cost required adding one extra life-year without developing a cardiovascular event (i.e. <10% absolute risk) on a "westernized" diet versus Mediterranean diet. Health care cost of life years gained was estimated in 2002 Euros for western Europe, and effectiveness was estimated using a 10-year risk model that incorporates the Framingham equation in order to obtain the life years gained during a the specific period according to age, sex and cholesterol concentration.
Results: The incremental cost of health care between "westernized" and Mediterranean dietary patterns was, on average, 315 Euros per participant. The incremental life expectancy between the Mediterranean and the "westernized" diet group was 0.004 years of life per participant. Therefore, the incremental cost-effectiveness ratio for the Mediterranean diet versus westernized diet was 78,750 Euros per year of life saved.
Conclusion: We provide the first detailed economic analysis of Mediterranean diet in cardiovascular disease risk. Many investigators asses the threshold of a cost-effectiveness ratio of a "therapy tool" which provides significant medical benefit in relation to its incremental costs to be more than 65,000 Euros per life-year added. On that basis the cost per life-year added with adherence to the Mediterranean diet falls in the economically attractive range over a wide spectrum of starting parameters and assumptions.

P2313 Cost-effectiveness of transoesophageal echocardiography guided direct current cardioversion for acute atrial fibrillation

R. Mitra[1], H. Gage[2], E.W. Leatham[3]. [1]*Swansea, United Kingdom;* [2]*University of Surrey, Guildford, United Kingdom;* [3]*Royal Surrey County Hospital, Department of Cardiology, Guildford, United Kingdom*

Background: Admissions to hospitals with acute Atrial Fibrillation (AF) of greater than 48 hour duration or of unknown onset time are usually treated with rate control and anticoagulation with a view to future Direct Current Cardioversion (DCCV)if appropriate. This amounts to significant cost to the health care system. The use of trans-oesophageal echocardiography (TOE) has enabled prompt treatment of AF by means of early DCCV.
Hypothesis: TOE guided DCCV is cost-effective treatment for acute AF in comparison to conventional treatment.
Methods: Prospective, 2 armed, randomised controlled trial of two equal groups

involving conventional treatment (rate control, anticoagulation, outpatient DCCV in 4 weeks, fololow-up at 8 weeks) or fast-track (TOE-guided DCCV, low-molecular weight heparin + warfarin, follow-up at 4 weeks). All patients had AF for at least 48 hours or of unknown onset and were not anticoagulated beforehand. Those failing fast-track treatment were allowed to crossover. Data were collected over a period of 14 months starting August 2001. Rhythm outcomes, length of stay and costs to the health care system and the patient were recorded. An intention to treat analysis was performed.

Results: 25 cases were randomised (mean age 69 years; 84% male), 13 to fast track treatment and 12 to the conventional arm. Groups were similar at baseline. All were seen within 16 hours. Only 2 failed TOE-guided DCCV; 1 patient crossed over due to finding of clot; one patient had slipped back into AF at outpatient review compared to 5 in the conventional arm (p = 0.2). There was a significant reduction in length of stay in hospital in the fast-track arm (49 hours vs. 112 hours p = 0.011). The fast-track arm was more cost-effective with an average saving of £205 to the health care system despite a small crossover rate.

Conclusion: The results suggest that fast-track treatment is cost-effective. It is less costly to the health care system than conventional care (mostly due to reduced length of hospital stay) and it may increase patients' chances of a sustained return to sinus rhythm at one month (75% vs 50%).

MECHANISMES OF ARRHYTHMIAS

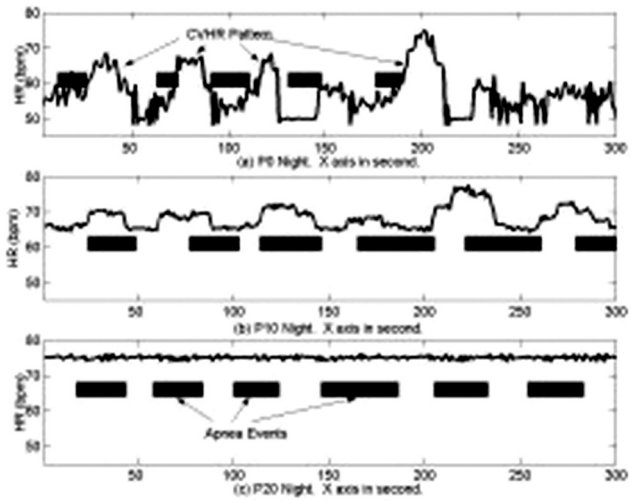
P2314 Effect of atrial overdrive pacing on cyclic heart rate variations in patients with sleep disordered breathing

C. Hansen[1], R. Freedman[2], A. Shalaby[3], M. Cramer-Bornemann[4], Y. Pu[5], A. Doelger[6], A. Koenig[6], J. Neuzner[1]. *[1]Klinikum Kassel, Kassel, Germany; [2]Univ. of Utah, Salt Lake City, UT, United States of America; [3]Pittsburgh VA Healthcare System, Pittsburgh, PA, United States of America; [4]Hennipin County Medical Center, Minneapolis, MN, United States of America; [5]Guidant CRM, Research, St. Paul, MN, United States of America; [6]Guidant Europe, Clinical Research, Diegem, Belgium*

Background: Cyclic variation of heart rate (CVHR) is associated with sleep apnea (SA) in patients (pts) with normal sinus function. CVHR reflects increased cardiac vagal tone during apnea followed by rebound tachycardia. Atrial overdrive pacing (AOP) was proposed to reduce SA by preventing SA onset bradycardia. We studied the presence of CVHR in pacemaker (PM) patients with sick sinus syndrome (SSS) and the effect of AOP on CVHR and SA.

Methods: PM pts (Guidant PULSAR Max I/II or INSIGNIA) were screened for SA by sleep study. Pts with apnea/hypopnea index (AHI)$\geq$15 and baseline heart rate (BHR)$<$ =70bpm were randomized to 3 nocturnal pacing modes: 50bpm (P0), AOP at BHR+10bpm (P10), and BHR+20bpm (P20). CVHR was defined as =5 consecutive brady-tachycardia cycles (=5bpm) during concurrent SA. CVHR amplitude was defined as the peak to trough difference of the brady-tachycardia cycle.

Results: During screening, 9/13 pts (69%) demonstrated CVHR. CVHR amplitude correlated with AHI (r2=0.72), 7/13 pts had SA(AHI$>$15) and were randomized to AOP. Six (89%) of these pts demonstrated CVHR with an amplitude of 12.2$\pm$2.2 bpm during P0, 2.7$\pm$4.3 bpm during P10 and 0.0$\pm$0.0 bpm during P20. At P20, AOP completely suppressed CVHR in all pts, yet SA patterns remained. Compared to P0, CVHR was significantly reduced both during P10 ($p<0.01$) and P20 ($p<0.001$), while AHI was unchanged (p=0.84, p=0.97, respectively).



CVHR Example

Conclusion: CVHR was seen in PM pts with SSS and its amplitude correlated with SA severity. CVHR amplitude was reduced when the AOP rate was above the minimum CVHR rate, and completely suppressed when the AOP rate was above the maximum CVHR rate. Suppression or elimination of CVHR, however, is not a plausible explanation for previously reported beneficial effects of AOP on SA.

P2315 Temporal variations in microvolt T-wave alternans testing after acute myocardial infarction

M.J.M. Oliveira[1], A. Fiarresga[2], N. Pelicano[2], N. da Silva[2], A.T. Timoteo[2], I. Carlos[2], S. Silva[2], J. Quininha[2]. *[1]Hospital Santa Marta, Department of Cardiology, Lisbon, Portugal; [2]Hospital Santa Marta, Cardiology Dept., Lisbon, Portugal*

Microvolt T-wave alternans (TWA) has been accepted as a new tool for assessing vulnerability to malignant ventricular tachyarrhythmias (VT/VF) after acute myocardial infarction (AMI). There is lack of data concerning prospective temporal variations in TWA measurements after AMI. Moreover, the relationship between left ventricular dysfunction and TWA changes remains unknown.

Aim: to analyse prospectively the temporal patterns of TWA in pts with an AMI and assess whether left ventricular dysfunction can influence TWA measurements.

Methods: TWA tests were performed $<$1 month (TWA1) and 6 months (TWA2) after AMI in 51 pts (35 men; 57,5$\pm$11 years) treated with successful PTCA. Twenty seven pts (53%) had anterior wall infarctions and 24 pts (47%) inferior/lateral wall infarctions. TWA was measured using the HearTwave System (Cambridge Heart, Inc.) and recorded during a treadmill manual exercise protocol to increase heart rate to 110 beats/min. TWA was defined as positive if the sustained alternans microvoltage was $>$1,9mV at heart rates $>$100 bpm, negative if the criteria for positivity were not met while maintaining heart rate at a level $>$105 bpm and indeterminate if it could not be classified as either positive or negative. Pts were excluded if they had atrial fibrillation, $>$10 extrasystoles/min, bradycardia $<$40 beats/min, wide QRS complex, congestive heart failure, implanted pacemaker or use of antiarrhythmics (beta-blockers were held for 24h prior to TWA testing). TWA "non negative" (TWA positive or indeterminate) was considered a risk marker for the occurrence of VT/VF. Group A included pts with TWA negative in both tests and Group B included pts with TWA "non negative" at first or second determinations.

Results: TWA1 was negative in 38 pts (74,5%) and "non-negative" in 13 pts (24,5%) - positive in 15,6% and indeterminate in 8,9% -. At TWA2, 10 pts (19,6%) changed from TWA negative to TWA "non negative" and 4 pts (7,8%) from TWA "non negative" to TWA negative. After serially TWA assessments (TWA1+TWA2), 45% of the pts had 1 test classified as "non-negative". Left ventricular ejection fraction was $<$50% in 6 pts (22%) of Group A and 12 pts (52%) of Group B (p=0,037).

Conclusions: In a population of AMI survivors: a) significant temporal changes in TWA may occur during the first 6 months causing an increase of TWA "non negative" pts despite successful PTCA. b) the results of TWA might be closely associated with left ventricule dysfunction.

P2316 Patients with hypertensive heart disease and nonsustained ventricular tachycardia – do they need an EP study?

M. Vater, T. Kleemann, T. Becker, K. Doenges, O. Yildiz, J. Senges, K. Seidl. *Herzzentrum Ludwigshafen, Cardiology, Ludwigshafen, Germany*

Background: Little is known about the prognostic value of nonsustained ventricular tachycardia (nsusVT) in patients (pts) with hypertensive heart disease.

Methods: From 1995 until 2001, 42 pts with exclusive hypertensive heart disease (HHD = LV hypertrophy because of arterial hypertension and diastolic LV dysfunction with normal coronary angiography) undergoing EP study for nsusVT were included in a prospective consecutive registry. The mean follow up was 3 years.

Results: The mean age was 65 $\pm$ 8 years, 27 pts (64%) were male. The mean left ventricular ejection fraction was 54 $\pm$ 12% (median 60; 50-60%). 8 pts had a syncope before EP study.

37 pts had no inducible susVT (88%), 4 pts had an unspecific EPS result (10%; inducible fast polymorphic VT, ventricular fibrillation) and only one pt had an inducible susVT (2%).

The results during follow up are shown in table 1.

3 pts died, all of them without ICD and with a negative EPS result. The cause of death was progressive heart failure in 2 pts and carcinoma in 1 patient.

Results during follow up

	EPS positive (1 pt)	EPS unspecific (4 pts)	EPS negative (37 pts)
ICD implantation	1	0	1
VT/VF episodes	1	0	0
Death	0	3	0

Conclusion: 1) 42 pts with HHD underwent EP study for nsusVT, most of them (88%) with a negative EPS result. 2) 2 pts received an ICD, one pt with positive EPS result, and one with negative EPS result but indication for biventricular pacing. The pt with positive EPS result had ICD episodes during follow up. 3) 3 pts (7%) died but none of them for sudden cardiac death – so EP study is of low value in pts with hypertensive heart disease.

P2317 Cardiac autonomic activity in patients with transient left ventricular apical ballooning: a case control study

J. Ortak[1], U.K. Wiegand[1], V. Kurowski[1], I.K. Wilke[1], F. Bode[1], F. Hartmann[1], H. Schunkert[1], H. Bonnemeier[2]. [1]*Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany;* [2]*University Lubeck, Medical KLinik II, Luebeck, Germany*

Objectives: even though recent findings strongly suggest myocardial stunning due to enhanced sympathetic outflow, cardiac autonomic nervous activity has not yet been investigated in patients with transient left ventricular apical ballooning (AB).
Background: transient left ventricular AB, a syndrome that mimics acute ST-segment elevation myocardial infarction (MI), is characterized by reversible left ventricular wall motion abnormalities in the absence of obstructive coronary heart disease (CHD). Even though various underlying pathophysiological mechanisms have been discussed, the cause of this syndrome is not yet known.
Methods: we prospectively enrolled 11 consecutive patients (9 women, median age 64, range 35 to 80 years) with transient left ventricular AB. A total of 11 age-, gender-, body mass index- and left ventricular function-matched patients with acute anterior ST-segment elevation MI undergoing successful direct percutaneous coronary intervention for a proximal total occlusion of the LAD served as a control group. Time and frequency domain heart rate variability (HRV) and heart rate turbulence (HRT) 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, Thrombolysis in Myocardial Infarction (TIMI) frame counts and TIMI risk scores between AB and MI groups, except higher peak enzyme release in MI patients. Vagus associated parameters of HRV were significantly higher in patients with AB (SDNN 112.0±15ms vs. 95.6±13ms, $p<0.05$; High frequency 286.3±163ms2 vs. 143.3±80ms2, $p<0.05$). AB patients also exhibited higher values for HRT (turbulence slope 8.99±2.7 ms/beat vs. 5.75±2.8ms/beat, $p<0.01$). Parameters of cardiac sympathovagal balance revealed a shift towards sympathetic predominance in MI patients (LF/HF-ratio 1.24±0.6 vs. 1.94±0.5, $p<0.01$). Mean RR-intervals tended to be higher in AB patients, without reaching statistical significance (871±86ms vs. 826±78ms, NS).
Conclusion: the present study is the first to demonstrate significant differences of cardiac autonomic modulation in patients with acute ST-segment elevation myocardial infarction with and without obstructive CHD. Even after successful early reperfusion therapy and concomitant medical treatment, there is a delayed recovery of tonic and reflex autonomic nervous modulation in MI patients compared to patients with transient left ventricular AB. The rapid restoration of parasympathetic function may in part explain the favourable prognosis of AB patients.

P2318 Relationship of autonomic tone to early recurrences following cardioversion of persistent atrial fibrillation

H.E. Mavrakis[1], E.M. Kanoupakis[1], P. Kafarakis[1], M.H. Melessanakis[1], S. Anagnostopoulos[1], E.G. Manios[1], P.E. Vardas[2]. [1]*Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece;* [2]*Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: The autonomic nervous system activity after persistent atrial fibrillation (AF) cardioversion (crdv) and its possible relation to arrhythmia recurrence remains largely unknown. We analyzed heart rate variability to explore changes in autonomic tone preceding the recurrence of AF following successful internal crdv.
Methods: We evaluated holter recordings of 123 successfully converted patients, the first day after crdv. Twenty-four episodes of AF recurrence were recorded and submitted to frequency-domain heart rate variability analyses. We studied 60 minutes, divided into twelve 5-minute periods, before AF recurrence.
Results: There were no significant differences in age, sex and the other clinical parameters studied between relapsed and non-relapsed patients. During the last 30 minutes before AF recurrence a significant increase in high-frequency (HF) component, index of vagal modulation ($P<0.01$) and a progressive decrease in low-frequency (LF) component ($P<0.05$) were observed. The LF/HF frequency ratio showed a linear increase before AF suggesting a significant increase of vagal tone.
Conclusions: AF recurrence the first day following cardioversion of persistent AF, depends on variations of the autonomic nervous system activity. Those patients who maintain enhanced vagal tone are more vulnerable for recurrence.

P2319 The effect of levosimendan on QT variability, QT dynamicity and complex ventricular arrhythmias in patients with decompensated heart failure

P. Flevari[1], I. Parissis[1], D. Leftheriotis[1], F. Panou[1], K. Kourea[1], G. Theodorakis[2], D.T. Kremastinos[1]. [1]*Attikon University Hospital, 2nd University Cardiac Clinic, Athens, Greece;* [2]*Onassis Cardiac Surgery Center, 2nd Cardiology Clinic, Athens, Greece*

Levosimendan, a novel calcium sensitizer, improves cardiac contractility without increasing myocardial oxygen demand. A recent study has shown that levosimendan shows no tendency to increase cardiac arrhythmias. A slight prolongation of the corrected QT interval has also been reported. QT variability and QT dynamicity - as expressed by the 24-hour standard deviation of QT interval (SDQT) and QT/RR slope respectively - provide direct insight into abnormal dynamics of repolarization potentially leading to arrhythmic events.
Aim: To assess the effect of levosimendan on QT/RR slope and ventricular arrhythmias in patients with decompensated heart failure.
Methods: We studied 24 patients (pts), mean aged 67 + 1.5 years, with heart failure refractory to conventional therapy, left ventricular ejection fraction 22 ± 1.6%, BNP levels at study entry 817±88 ng/ml. All were in sinus rhythm. Sixteen patients were randomized to levosimendan, while 8 received placebo. Following a 24-hour Holter ECG recording for baseline assessment, levosimendan or placebo was infused for 24 hours (levosimendan at a dose of 0.2 μg/kg/min). During this period, a second 24-hour ECG recording was performed, to assess possible changes in QT dynamicity or complex ventricular arrhythmogenesis. Complex ventricular arrhythmias were assessed by the episodes of ventricular tachycardia (VT) during the recordings (events/24 h). BNP levels were assessed again at the end of levosimendan infusion.
Results: Following levosimendan, a decrease was observed in BNP levels (levosimendan vs baseline: 396±78 vs 814±84, $p<0.05$). This improvement was not associated with changes in QT/RR slope (0.19±0.09 vs 0.18±0.09, p: NS). A decrease was observed in SDQT (54.3±6.7 vs 74±6.7, $p<0.05$), while the number of VT episodes/24 h increased (1.17 ±0.3 vs 0.08±0.3 at baseline, $p<0.05$). In patients receiving placebo, no changes were observed in the assessed parameters.
Conclusion: Short-term levosimendan therapy of patients with heart failure improves cardiac function and shows no tendency to alter QT/RR slope. However, it decreases QT variability and increases complex ventricular arrhythmias.

P2320 The Poincare-lesson: usefulness of the true phase-plots for heart rate analysis in the risk stratification of sudden cardiac death

S. Khoor[1], E. Kail[2], K. Fugedi[3], I. Kovacs[4], J. Nieberl[5]. [1]*Budapest, Hungary;* [2]*Artintell Ltd, Budapest, Hungary;* [3]*Szent István Hosp., Cardiology, Budapest, Hungary;* [4]*Szent István Hospital, 3rd Chr. Int. Med., Budapest, Hungary;* [5]*BION Ltd., Budapest, Hungary*

The Poincaré plot graphically represents the relation of the R-R intervals (first and the next), and the calculated parameters of the ellipsoid were used for the non-linear analysis of heart rate variability. Unfortunately, the relation of these values is linear and not suitable for non-linear analysis. Up to now, we had not good indicators for the prediction of sudden cardiac death (SCD).
The data collections were performed from our internet ECG database, where the mobile, GPRS ECG recordings were stored. During the past 5 years 234, 24 hour ECG recordings were registered, where frequent (> 4000/24 hours) ventricular ectopic beats were found.
The mean follow-up was 3.6 months. Nineteen SCD events were observed in this patient population. The studied population (age 64.5±8.2) consists of 67 postinfarction patients, 116 of known coronary artery disease without myocardial infarction, and 51 chronic heart failure (NYHA III., IV.) patients.
Two phase plots were constructed from the beat-to-beat heart rate data. The first phase-plot was constructed from the normal-to-normal beats with two "dimensions": the normalized R-R interval, and the normalized change of this interval. We used these two values such as the angle phi and the angular velocity omega = dphi/dt in the nonlinear analysis of a pendulum.
The second phase plot represents the same parameters from the interectopic intervals derived from the ventricular ectopic beats. The two phase-plots were represented in one phase space. The interrelation of the plots was qualitatively analyzed. The narrowing of a segment of the normal-to-normal loop atthe intersection of the normal-to-normal and interectopic loops (orbits) were observed in 14 of the 19 patients with SCD, and 6 of the 215 patients without SCD. The sensitivity was 0.73, the specificity 0.97 ($p>0.01$). The above mentioned method was implemented in our telemedicine system, where the results were used in our wireless GPRS ECG monitoring for alarming purpose. It is combined with our other SCD prediction method, where the application of Piecewise Aggregate Approximation (PAA) of the data mining made possible for indexing the patient's data (finding the most similar above mentioned two time series in the database given a query time series Q, and some similarity/dissimilarity measure D(Q,C)) into the two clusters (SCD or not).

P2321 Histologic exploration of the connections between the coronary sinus musculature and left atrium in humans

T. Matsuyama[1], S. Inoue[2], G. Ogawa[2], M. Makino[1], T. Sakai[3], Y. Kobayashi[3], T. Katagiri[3], H. Ota[1]. [1]*Showa University School of Medicine, 2nd Department of Pathology, Tokyo, Japan;* [2]*Showa University Toyosu Hospital, Department of Internal Medicine, Tokyo, Japan;* [3]*Showa University School of Medicine, 3rd Department of Internal Medicine, Tokyo, Japan*

Background: The area between the coronary sinus (CS) and left atrial free wall have been demonstrated as the source of the atrial arrhythmias. Although recent histologic observations revealed the various degree of the myocardial connection between the CS and left atrium, the analysis of the age-related alternation has not been fully detailed.

Methods: Twenty-one autopsied hearts were studied; mean age 67.4 years ranging from 43 to 82, 10 females. We divided the hearts into two age groups (<70 years and >70 years). Three cases in elder group were documented atrial arrhythmias. After fixation in formalin, left inferior atrioventricular junction was excised together with left atrial posterior wall and the opening of CS. The removed tissue blocks were cut into 5mm thick slices perpendicular to the atrioventricular ring. Each tissue sample was sectioned and stained with azan-Mallory. We observed the manner of the myocardial connection and measured percent area of the musculature at proximal and distal CS area using computer digital analyzer (WINROOF, MITANI).
Results: The myocardial connection between the CS and left atrium were divided into three groups; the tight connection, loose connection, and the complete isolation concomitantly with the fatty infiltration.
At the proximal CS, isolated pattern was 2 cases in the <70 years group and 3 cases in the >70 years group. At the distal CS, isolated pattern was 4 cases in the <70 years group and 6 cases in the > 70 years group (Table 1). Percent muscular area of the proximal CS was 27.5% in the <70 years group and 20.3%, in the >70 years group. That of the distal CS was 17.3% and 18.9%, respectively.

Table 1

	Proximal CS	Proximal CS	Distal CS	Distal CS
Age (y.o.)	<70	>70	<70	>70
Tight pattern	3	3	0	2
Loose pattern	5	5	6	3
Isolated pattern	2	3	4	6

Conclusion: The myocardial connection between the CS and left atrium was tight in the proximal CS especially in younger group. The muscular diversity and area reduction in the proximal CS due to aging change seem to influence the conduction deterioration between the CS and left atrium and hence related to arrhythmogenisity in this area.

P2322 A simple algorithm for defining the mechanism and the chamber of origin in atrial tachycardias

T. Shalganov[1], R. Vatasescu[1], D. Paprika[1], L. Kornyei[1], J. Vanyi[1], L. Geller[2], S. Szilagyi[2], T. Szili-Torok[1]. *[1]GOKI, Dept. of pacing & clinical electrophysiology, Budapest, Hungary; [2]SOTE, Er es Szivsebeszeti Klinika, CVC, Budapest, Hungary*

Introduction: Although macroreentrant and focal atrial tachycardias can be successfully cured by catheter ablation, the proper diagnosis and treatment of these arrhythmias can still be challenging. The surface ECG has sometimes low predictive accuracy or can even be misleading.
Aim: To develop an algorithm allowing rapid diagnosis of the mechanism and the chamber of origin of atrial tachycardias, based on bipolar intracardiac catheter recordings from 20-polar halo catheter deployed in the right atrium and 8-polar catheter in the coronary sinus.
Methods: A self-developed 2-stepped algorithm was used: 1: The time of biatrial activation measured from the beginning of the earliest atrial potential to the beginning of the latest atrial potential was expressed as a percentage of the tachycardia cycle length (TCL). If the derived value was <40% we assumed that the tachycardia had focal origin. In case of biatrial activation ≥ 40% of TCL the tachycardia was considered to be macroreentrant. 2: In focal tachycardias the earliest activation recorded by 1 of the 2 diagnostic catheters was used to define the chamber of origin. In macroreentrant tachycardias if the typical activation sequence of the isthmus-dependent atrial flutter was not present, the time of the right atrial activation was determined or entrainment was used at different sites. If the right atrial activation occupied <40% of the tachycardia cycle length or entrainment was unsuccessful we assumed that the tachycardia was of left atrial origin. 16 intracardiac recordings with the above mentioned configuration were distributed between four fully trained electrophysiologists blinded to the mechanism and the chamber of origin. They reviewed the recordings following the algorithm described above. The results of the analysis of the electrophysiologists were compared to the intraoperative diagnosis justified by successful ablation using CARTO (Biosence-Webster) electroanatomical mapping system. Results: The algorithm correctly identified all focal atrial tachycardias (100%) and 11 of 13 macroreentrant tachycardias (84,6%). The site of origin was correctly identified only in 33% focal and in 12 out of 13 (92,3%) macroreentrant atrial tachycardias.
Conclusions: 1. This algorithm allows rapid discrimination between focal and macroreentrant atrial tachycardias with a hundred percent accuracy. 2. The chamber of origin is detected with a high accuracy in macroreentrant tachycardias. 3. The earliest atrial activation recorded as described above is not a good predictor for the chamber origin in focal tachycardias.

P2323 Differential diagnosis between idiopathic right ventricular outflow tract tachycardia and arrhythmogenic right ventricular cardiomyopathy/ dysplasia by 3-D electroanatomic voltage mapping

D. Corrado[1], B. Tokajuk[1], L. Leoni[1], A. Pavei[1], A. Nava[1], G. Thiene[2], G. Buja[1], S. Iliceto[1]. *[1]Division of Cardiology, University of Padova, Padova, Italy; [2]University of Padova, Cardiovascular Pathology, Padova, Italy*

Background: Differential diagnosis between idiopathic right ventricular outflow tract (RVOT) tachycardia and minor and/or early form of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is challenging. We assessed whether 3-D electroanatomic mapping, because its ability to detect low-voltage areas that correspond to regions of RV fibrofatty replacement, can differentiate between the two conditions.
Methods: The study population comprised 24 consecutive patients (13 males and 11 females, mean age 34±11 years) with recurrent ventricular tachycardia (VT) originating from the RVOT, and without echocardiographic evidence of RV dilatation/dysfunction. 3-D geometry of the RV depicting the peak-to-peak amplitude of the bipolar electrograms recorded at multiple endocardial sites was constructed in real-time.
Results: Activation mapping showed that all VTs arose from the RVOT: anteroseptally in 11, anterolaterally in 9, posterolaterally in 3, and close to the His bundle in one. Voltage mapping was normal in 17 of 24 patients (70%, Group A), with electrogram voltage > 1.5 mV throughout the RV. The other 7 patients (30%, Group B), had abnormal voltage mapping showing 2±1.4 areas with bipolar electrogram amplitude <0.5 mV (scar). Two patients from Group B had abnormalities limited to the RVOT, whereas in the other 5 the disease also involved the anterior (4 patients), the inferobasal (3 patients), and the apical (2 patients) regions. Independent predictors of electroanatomic scars were right precordial QRS prolongation (p<0.001) and inducibility at programmed ventricular stimulation (p <0.01). Catheter ablation successfully eliminated VT in 13 of 15 patients. During a follow-up of 26±9 months, 3 out of 7 patients (57%) from Group B received an ICD after having experienced syncope or cardiac arrest, whereas all patients from Group A had an uneventful outcome (p=0.02).
Conclusions: Electroanatomic RV scars were detected in nearly 30% of patients with RVOT tachycardia, suggesting an underlying early/minor form of ARVC/D at risk of lifethreatening arrhythmic events.

P2324 Comparison of epicardial breakthrough of fibrillation waves between patients with acute and chronic atrial fibrillation

N.M.S. De Groot[1], M.J. Schalij[2], M.A. Allessie[3]. *[1]Leiden University Medical Centre, Cardiology Dept., Leiden, Netherlands; [2]Leiden University Medical Center, Cardiology, Leiden, Netherlands; [3]Cardiovascular research institute, Electrophysiology, Maastricht, Netherlands*

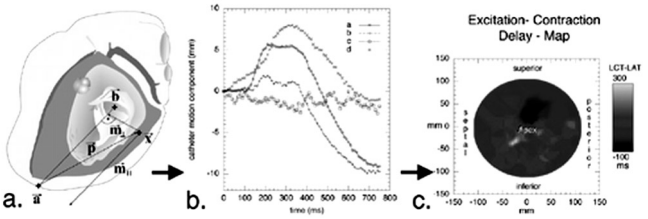
Introduction: Epicardial breakthroughs (EB) during atrial fibrillation (AF) are thought to be the result of transmural conduction of fibrillation waves. In this study, characteristics of EB during induced (AAF) and chronic AF (CAF) were compared and the impact of EB on conduction of fibrillation waves in the epicardial plane was examined.
Methods: Epicardial mapping during cardiac surgery (244 electrode-array, interelectrode distance 2.25 mm) of the right right atrial free wall was performed during AAF in patients (n=20, age 31±12 yrs) with normal atria and no history of AF and during CAF in patients with valve disease (n=12, age 66±9 yrs). Episodes of 8 seconds of AF were analysed. An EB was defined as a de novo arising wavefront in the mapping area which could not be explained by fibrillation waves propagating in the epicardial plane. For each patient, the incidence, the spatial distribution and repetitiveness EB was determined. Also, the degree of premature activation, the incidence of conduction block at the EB origin was assessed.
Results: The incidence of EB during CAF was higher than during AAF (1.49±0.82[0.33-3.41]/cycle versus 0.24±0.25 [0-0.77]/cycle, p<0.00). EB in all pts were non-repetitive and randomly distributed. The majority of electrograms recorded at the site of the site of origin of an EB consisted of fractionated potentials (AAF: 64±32%, CAF: 62±18%). Fractionated potentials were associated with shorter EB coupling intervals (AAF: R=-0.14, p<0.04, CAF: R=-0.10, p<0.04). EB coupling intervals (AAF: 128±27 ms, CAF: 171±26 ms) were shorter than the median AFCL (AAF: 157±26 ms CAF: 185±28 ms), indicating premature activation of the epicardium (p<0.001). The incidence of conduction block at the EB origin was higher in the CAF patients (AAF: 77±11%, CAF: 86±12%, p<0.03).
Conclusion: In humans with AF, EB frequently occur at the right atrial free wall; they appear as solitary events and are randomly distributed across the mapping area. EB are high dominant frequency sources giving rise to premature activation of the epicardium. The findings of this study are most supportive for 3-dimensional conduction of fibrillation waves during human AF.

P2325 Excitation-contraction mapping in the ischaemic heart: a novel application of electro-anatomic mapping

H.U. Klemm[1], R. Ventura[2], O. Franzen[2], K. Mortensen[2], T. Risius[2], T. Rostock[2], B. Lutomsky[2], S. Willems[2]. *[1]University Hospital Eppendorf, Dept. of Cardiology, Hamburg, Germany; [2]University Hospital Eppendorf, Dept. of Cardiology, Hamburg, Germany*

Background: In the era of cardiac resynchronization therapy interest has focused on cardiac contraction in the diseased heart. Purpose of this study was to delineate the influence of ischemic tissue on cardiac excitation-contraction (EC) spread and to demonstrate the feasibility of a novel mapping technique.
Methods and Results: 5 pts with remote myocardial infarction referred for ablation of monomorphic ventricular tachycardia (VT) and 2 control pts presenting

idiopathic VT were studied during sinus rhythm using CARTO. In addition to sampling intracardiac signals, real time catheter position is retrieved every 10ms. Trajectory data, currently not accessible via CARTO, were extracted from backup files using a custom-made software. Detailed maps of the left ventricle were obtained via the retrograde aortic approach. Points not fulfilling conditions of stable heart rate, depolarization and catheter position were excluded. Catheter motion was analyzed along a line connecting the catheter tip with the apex (fig. a). The local contraction (LCT) and activation times (LAT) were set to the onsets of the fast inward motion and the major bipolar electrogram, respectively.
4 shapes of catheter motion curves were identified (fig. b): (a) atrial preloading and contraction – healthy tissue (b) contraction with limited preloading – apical healthy tissue (c) no motion - scar (d) dominant outward motion – aneurysm. An analysis of the EC-delay (fig c) revealed areas of passive contraction, e.g. the LAT > LCT (black), and slowly contracting myocardium with up to 300ms EC-delay (yellow).



Construction of an EC-map

Conclusion: Slow conduction as well as long EC-intervals are responsible for delayed contraction that can be differentiated with the described mapping technique.

P2326 The incidence of fractionated electrograms decreases with increasing distance from the origin of focal atrial tachycardias

N.M.S. De Groot[1], W.K. Chan[1], P. de Leeuw[2], M.J. Schalij[1]. [1]*Leiden University Medical Centre, Cardiology Dept., Leiden, Netherlands;* [2]*Leiden University Medical Center, Cardiology, Leiden, Netherlands*

Background: Based on the observation that successful ablation sites of focal atrial tachycardias (FAT) are characterized by low amplitude, fragmented electrograms, it was hypothesized that cellular uncoupling is a pre-requisite for the development of FAT. Cellular uncoupling results in a diminished electrotonic inhibition thereby allowing a rapid discharging focus to become manifest. This study analysed characteristics of atrial potentials in relation to its distance to the site of earliest activity during FAT.
Methods: 3-D electro-anatomical activation maps obtained from patients (n=15, 6 male, 41±16 yrs) referred for catheter ablation of a FAT were analysed. All bipolar potentials (BP) were categorized according to the number of deflections. Fractionated potentials were defined as atrial potentials consisting of 2 or more deflections. The time interval between the first and last deflection (fractionation delay) of each BP was measured. The BP with the earliest local activation time with respect to the surface p wave was defined as the site of origin of the focus. The distance to this site of earliest activity was measured for all BP in the activation map in order to study the occurrence of fractionated potentials in relation to its distance to the site of earliest activity during FAT.
Results: Seventeen different FAT (CL 340±110[190-550] ms) were mapped and successfully ablated. All FAT originated from the right atrium. Activation maps consisted of 121±67 BP. The incidence of fractionated potentials ranged from 19 to 75 [48±16]%.
The occurrence of fractionated BP within a distance of less than 2 cm of the site of earliest activity ('focal area') was higher compared to the remainder of the atria (71±23% versus 31±15%, p<0.001). Fractionation delays of BP recorded from the 'focal area' were longer than from the remainder of the atria (BP focal area: P50: 41 ms, [P0: 7- P100: 154 ms], remainder: P50:27 [P0:2-P112 ms], p<0.002).
Conclusion: Significant differences in fractionation and fractionation delay of BP between the 'focal area' and the remainder of the atria exist. The results of this study support the hypothesis that a certain degree of cellular uncoupling is required for the development of a FAT thereby providing further insight into the aetiology of FAT.

P2327 Relationship between inflammation and cardiac autonomic dysfunction in patients with unstable angina

F. Infusino[1], G.A. Lanza[1], D. Cianflone[2], A.G. Rebuzzi[1], G. Angeloni[1], A. Sestito[1], F. Crea[1], A. Maseri[2] on behalf of SPAI (Stratificazione Prognostica dell'Angina Instabile) Study Group.
[1]*Policlinico A. Gemelli, Istituto di Cardiologia, Rome, Italy;* [2]*Università Vita e Salute, Istituto di Cardiologia, Milano, Italy*

Background: Heart rate variability (HRV) and markers of inflammation have both been shown to be of prognostic value in patients with acute coronary syndromes. However, no previous study investigated whether any relationship does exist between HRV parameters and indices of inflammation in this clinical context.
Methods: To address this topic we reviewed the ECG Holter recordings of 532 patients with UA (age 63±10 years, 356 men), enrolled in the multicenter prospective Italian study "Stratificazione Prognostica dell'Angina Instabile" (SPAI), who underwent 24-hour Holter monitoring within 24 hours of hospital admission and who also had C-reactive protein (CRP) serum levels, measured at admission using a high-sensitivity assay. As an inclusion criterion, all patients had a left ventricle ejection fraction >40%.
Results: Patients were divided into 4 groups according to quartiles of CRP levels. Statistically significant differences in HRV parameters among quartiles of CRP serum concentrations were found, with the lowest HRV values being in the upper CRP quartile (Table). A significant, although mild, negative correlation between CRP serum levels and all HRV variables was also found, with the best correlation being between CRP levels and very low frequency (VLF) amplitude (r=-0.21, p<0.0001).

Table

	CRP <2.0	CRP 2.0-4.5	CRP 4.5-10.7	CRP >10.7	P
RR interval	967±148	961±157	949±139	904±146	0.002
SDNN	108±31	106±33	103±37	93±33	0.0006
SDANN	90±42	82±26	86±43	74±28	0.006
SDNNi	58±23	59±29	55±32	50±25	0.014
VLF	47±21	46±19	43±22	39±24	0.0014
LF	26±12	27±17	26±19	21±12	0.002
HF	20±11	20±13	20±18	18±12	0.03
LF/HF ratio	1.4±0.4	1.4±0.4	1.4±0.5	1.3±0.4	0.048

CRP values are expressed as mg/L

Conclusions: Our data show that, in patients with unstable angina, high levels of serum CRP levels are significantly associated with decreased HRV. The pathophysiological meaning and clinical implications of such correlation deserve further investigation.

P2328 Influence of left bundle branch block in QT interval dispersion and clinical evolution of patients with chronic heart failure treated with carvedilol

D.C. Albuquerque, R. Mourilhe Rocha, R. Esporcatte, E.P. Gouvea, B.R. Tura, F.M. Albanesi Filho. *State University of Rio de Janeiro, Cardiology Dept., Rio de Janeiro, Brazil*

Background: The role of QT interval dispersion (QTD) in heart failure (HF) remains poorly defined and controversial.
Objective: Evaluate the impact of QTD in the clinical evolution of chronic HF patients compensated due to the use of carvedilol (CVD).
Methods: A total of 108 patients (22-82 y/o), male=65.7%, caucasians=72.2%, with stable chronic HF and NYHA functional class (FC) II, III and IV on optimized treatment, with an left ventricle ejection fraction (EF) of < 0.40 were selected for therapy with CVD. All patients had complete history and physical exam performed, as well as, laboratorial evaluation, ECG, echocardiogram and followed-up at the HF clinic (average period = 38.2 months). All used CVD at the maximum tolerated dose. The evaluated parameters were: general characteristics, etiology of HF, concomitant medications, NYHA FC, maximum CVD dose, EF and QTD before and 6 months after CVD, presence of left bundle branch blockade (LBBB), hospitalizations, complications and deaths.
Results: A QTD reduction and an increase in the EF were found after 6 months of therapy with CVD (p<0.001). The general characteristics of the population (p>0.05), concomitant medications (p>0.05), CVD dose (p=0.80), cardiomyopathy etiology (p=0.959), presence of complications (p=0.851) and of LBBB (p=0.161) did not influence in the QTD reduction. This reduction was related to the patients with worse FC pre-CVD (p=0.007), with FC improvement (p=0.028) and with fewer admissions per year of follow-up (p=0.047). A pre-CVD QTD of ≤90ms was predictive of admissions (AUC = 0.636; sens. = 43.1%; spec. = 82%; positive likelihood ratio = 2,39; negative likelihood ratio = 0,69). The presence of LBBB (p=0.002; OR=4.606) and post-CVD QTD > 90ms were mortality predictors (p=0.034; OR=3.912) (AUC = 0.061; sens. = 29.2%; spec. = 90.5%; positive likelihood ratio = 3.06; negative likelihood ratio = 0.78). The independent predictors of survival found were LBBB (p=0.007; OR=0.293), the presence of complications during follow-up (p=0.006; OR=0.133) and the QTD reduction (p=0.004; OR=5.48).
Conclusions: CVD use reduced the QTD and increased the EF in patients with chronic HF. The QTD reduction was positively related to the HF improvement and less hospital admissions. The presence of LBB and QTD > 90ms post-CVD, were mortality predictors. The independent survival predictors were the presence of LBBB and the occurrence of complications, determining a reduced survival and the QTD reduction related to an increased survival.

P2329 Effect of sildenafil sitrate on heart rate variability and QT dynamicity indices

A. Kirilmaz[1], S. Altunkan[2], M. Uzun[3]. *[1]GATA Haydarpasa Egitim Hastanesi, Kardiyoloji Servisi, Istanbul, Turkey; [2]Metropol Hipertansiyon Klinigi, Ankara, Turkey; [3]GATA ve Askeri Tip Fakultesi, Kardiyoloji AD, Ankara, Turkey*

Purpose: Sildenafil sitrate is a commonly used medication to treat erectile dysfunction (ED) in men. Although cardiovascular complications including sudden cardiac death have been reported anecdotally, there is no clear correlation between sildenafil and lethal side effects. Mechanisms are also unclear.
Methods: To assess the effects of sildenafil on heart rate variability and QT dynamicity, 46 patients (mean age 53?13, range 22-76 years) with ED without known heart disease received 24-hour Holter monitor before and during sildenafil usage (50 mg QD for the last 4 days following 3-month of treatment). QT dynamicity was assessed by plotting the mean hourly QTend and QTpeak (QTp) against the mean RR over the entire 24 hours, day and night hours of recording for each individual and linear regression model was used to reveal QT/RR and QTp/RR slope.
Results: Statistically significant difference was found in the following time and frequency domain parameters (Table 1). Comparison of QT dynamicity parameters before and during sildenafil usage did not reveal any significant difference.

Table 1

	HRV parameters	Before sildenafil	During sildenafil	P value
Total (day+night)	Mean RR interval (ms)	776±95	752±82	0.005
	r-MSSD	39±19	48±30	0.038
	pNN50	10±8	13±10	0.023
	Balance (LF/HF)	3.0±1.6	2.6±1.3	0.057
Night (23:00-07:00)	SDNNi	59±23	67±33	0.049
	rMSSD	41±23	59±45	0.023
	pNN50	13±12	18±17	0.010

*rMSSD: Square root of the mean of the sum of squares of differences between adjacent filtered RR intervals. PNN50: Percentage of differences between adjacent filtered RR intervals that are greater than 50ms. SDNNi: Standart derivation of normal NN intervals

Conclusions: Sildenafil increased the mean heart rate most probably because of reflex response to vasodilation. Increased parasympathetic activity was characterized by a decrease in LF/HF balance and an increase in r-MSSD and pNN50. The drug had no effect on QT dynamicity. With the exception of a small increment in heart rate, sildenafil does not elucidate any adverse outcome on HRV and QT dynamicity, instead may have beneficial effects by increasing HRV.

P2330 The clinical characteristics of patients with congestive heart failure are significantly influenced by gender. Data from the ALPHA study registry

M.V. Tritto[1], G. Pettinati[2], E. Adamo[3], G. Mascioli[4], M. Revera[5], S. Sarzi Braga[6], L. Sallusti[7], J.A. Salerno-Uriarte[8]. *[1]University of Insubria - Varese, Clinical Institute Mater Domini, Castellanza, Italy; [2]F.Ferrari Hospital, Casarano (LE), Italy; [3]Sacro Cuore Hospital, Negrar (VR), Italy; [4]University of Brescia, Spedali Civili, Brescia, Italy; [5]IRCCS S. Matteo, University of Pavia, Pavia, Italy; [6]IRCCS S.Maugeri Foundation, Tradate (VA), Italy; [7]Guidant Italia, Milano, Italy; [8]Fond. Macchi, University of Insubria, Dept. Cardiovasc. Sci., H Circolo, Varese, Italy*

Few information are available about gender-related differences among patients affected by congestive heart failure (CHF). In addition, data about this topic are usually derivedfrom clinical trials and not from routine daily practice. The aim of the present analysis is to assess the influence of gender on the main clinical and demographic characteristics of patients with CHF, evaluated in 9 centers in Italy and included in the registry of the ALPHA (T-wave Alternans in Patients with Heart fAilure) study, a trial aimed to analyze the prognostic value of T-wave alternans in CHF of non ischemic etiology.
Patients and Methods: The ALPHA study registry included 3513 consecutive outpatients: 29% females; age 67±13 years; left ventricular ejection fraction (LVEF): 34±10%; QRS duration >120 ms: 47%. NYHA class I-IV were 9, 56, 29 and 6%, respectively; 46% of pts had coronary artery disease, 26% dilated cardiomyopathy, 15% hypertensive cardiomyopathy, 10% valvular heart disease, and 11% had CHF of different etiologies. The main clinical and demographic characteristics of women and men have been compared.
Results: The results are summarized in table 1.

Table 1

	Women (n=1025)	Men (n=2488)	P value
Age (mean ± SD)	72 ± 13	66 ± 12	< 0.0001
Nonischemic etiology	633 (61%)	1272 (51%)	< 0.0001
NYHA class III-IV	414 (40%)	805 (32%)	< 0.0001
LVEF (mean ± SD)	40 ± 15%	35 ± 14%	< 0.0001
LVEF < 40%	504 (62%)	389 (80%)	< 0.0001
QRS dur > 120 msec	590 (42%)	435 (46%)	0.036
Atrial fibrillation	268 (26%)	484 (19%)	< 0.0001
Implanted devices (PM or ICD)	102 (10%)	334 (13%)	0.045

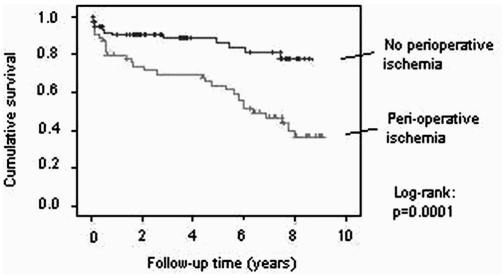
PM: pace-maker; ICD: implanted cardioverter defibrillator

Conclusions: In this outpatient population, which is representative of CHF pts in routine daily practice, significant differences were related to gender: women were older than men, presented more frequently a nonischemic etiology of CHF, and had a greater functional impairment according to NYHA class. Moreover, LVEF was better preserved in women, suggesting an higher proportion of CHF related to left ventricular diastolic dysfunction. These differences may have relevant clinical implications in prognostic and therapeutic scenarios of CHF.

P2331 Perioperative myocardial ischaemia assessed by continuous 12-lead electrocardiographic monitoring predicts long-term survival after vascular surgery

H.H.H. Feringa[1], J.J. Bax[2], M.D. Kertai[3], S.H. Meij[4], M.H. Van Sambeek[1], H. Boersma[4], J. Klein[3], D. Poldermans[5]. *[1]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands; [2]University hospital Leiden, Cardiology, Leiden, Netherlands; [3]Erasmus MC, Anaesthesiolgy, Rotterdam, Netherlands; [4]Erasmus Medical Centre, Cardiology Dept., Rotterdam, Netherlands; [5]Erasmus MC - Anesthesiology, Rotterdam, Netherlands*

Background: Continuous 12-lead electrocardiographic monitoring (12-lead ECG) may identify patients (pts) at risk for perioperative cardiac events, however, its long-term prognosis remains ill-defined.
Aim: To assess the long-term prognostic value of perioperative myocardial ischemia assessed by 12-lead ECG in relation to cardiac risk factors, dobutamine stress echocardiography (DSE) results and beta-blocker therapy.
Methods: 142 pts undergoing major vascular surgery were screened for risk factors and beta-blocker use. Before surgery, DSE was performed to detect new wall motion abnormalities (NWMA) as a marker of myocardial ischemia. 12-lead ECG started 12 hours before surgery and continued for three days after. Mean follow-up time was 4.5 years (±3 years).
Results: During follow-up, cardiac death occurred in 43 (30%) pts. The incidence of cardiac death was significantly higher in pts with myocardial ischemia detected by 12-lead ECG, compared to pts without ischemia (54% vs 17%, p<0.0001) and was significantly lower in pts using beta-blockers, compared to pts who did not (16% vs 84%, p=0.007).
Using stepwise multivariable Cox-regression analysis, NWMA during DSE (HR: 2.3, 95% CI: 1.3 - 4.3) and myocardial ischemia detected by 12-lead ECG (HR: 2.1, 95% CI: 1.1 - 4.1), were identified as significant predictors for postoperative cardiac death. Importantly, beta-blocker therapy was associated with a significant reduction in cardiac death (HR: 0.35, 95% CI: 0.1 - 0.8).



Kaplan Meijer curve

Conclusion: In patients undergoing major vascular surgery, continuous 12-lead ECG monitoring identifies patients at risk for late cardiac events who respond favourably to beta-blocker treatment.

P2332 Cardiac dysrhythmias in hyperthyroidism before, during and after effective antithyroid therapy

F. Osman[1], J.A. Franklyn[2], M.C. Sheppard[2], M.D. Gammage[3]. *[1]Queen Elizabeth Hospital, Cardiovascular Medicine, Birmingham, United Kingdom; [2]Queen Elizabeth Hospital, Department of Medicine, Birmingham, United Kingdom; [3]Queen Elizabeth Hospital, Cardiovascular Medicine Dept., Birmingham, United Kingdom*

Hyperthyroidism induces many cardiovascular effects including dysrhythmias and is associated with significant vascular morbidity and mortality. The prevalence and outcome of dysrhythmias in hyperthyroidism are unknown.
Aim: To evaluate dysrhythmia risk in overt hyperthyroidism before, during and after effective antithyroid therapy.
Methods: 408 consecutive unselected patients with hyperthyroidism were recruited with 408 age/sex-matched euthyroid controls for comparisons; all had 12-lead ECG and 24-hr Holter monitoring. Patients were reassessed during and after antithyroid therapy. Comparisons were made between patients exhibiting the biochemistry of subclinical hyperthyroidism (normal serum thyroid hormones with suppressed thyrotrophin {TSH}) and controls, as well as those rendered biochemically euthyroid and controls.
Results: Median age of both cohorts was 50yrs (IQR 37-65); 320 females and 88 males in each. Cohorts were matched with respect to past history and family history of vascular disease (20% vs 18% and 68% vs 70%, p=ns). Median presentation serum free thyroxine (T4) and tri-iodothyronine (T3) concentrations in patients were 37.5pmol/L (IQR 27-52) and 11.4pmol/L (IQR 8-18); serum TSH

was undetectable in all. Serum free T4, T3 and TSH were normal in controls. Persistent and paroxysmal atrial fibrillation (AF) was more prevalent in patients than controls (8% vs 1%, p<0.0001) as were atrial salvoes (>3 consecutive atrial ectopics, 24% vs 14%, p<0.002). Ventricular salvoes (>3 consecutive ventricular ectopics) and non-sustained VT (>5 consecutive ventricular beats lasting <30sec) were no different (4% vs 1%, p=0.1 and 2% vs 0%, p=0.3). Significant atrial or ventricular premature beats (>240/24hr) were no different (7% vs 5%, p=0.8 and 7% vs 8%, p=0.7) but dropped beats were more prevalent in patients (14% vs 3%, p<0.0001). 110 patients exhibited the biochemistry of subclinical hyperthyroidism (mean±SE 27.1±2.1wks); AF and nsVT were more prevalent in patients compared with controls (6% vs 1%, p<0.04 and 4.5% vs 0.2%, p<0.0001). 219 were rendered biochemically euthyroid (mean follow-up 36.9±1.6wks); AF was still more prevalent in patients than controls (6% vs 1%, p<0.0001); all other rhythm disturbances were no longer different.
Conclusions: Hyperthyroidism is associated with rhythm abnormalities at presentation, especially supraventricular. This may account, in part, for our previously reported early vascular mortality in subjects with hyperthyroidism. Arrhythmias persist during antithyroid therapy but all except AF correct after restoration of biochemical euthyroidism.

P2333 Role of late potentials in the assessment of the effect of non-pharmacological treatment of ventricular tachyarrhythmias

K. Lefflerova[1], J. Bytesnik[1], J. Kautzner[1], J. Pirk[2], P. Peichl[1], V. Vancura[1]. [1]*Institute for Clin.and Exp.Medicine, Department of Cardiology, Prague 4, Czech Republic;* [2]*Institute for Clin. and Exp. Medicine, Department of Cardiovascular Surgery, Prague 4, Czech Republic*

Survivors of myocardial infarction (MI) are at risk of developing malignant ventricular tachyarrhythmias (VTA) that reflect the presence of arrhythmogenic substrate within myocardium. Ventricular late potentials (LP) have been identified as a prognostic factor in the prediction of VTA. Despite high efficacy of implantable cardioverter-defibrillator in termination of VTA, ablative techniques either catheter or surgical carry a substantial potential to prevent and possibly cure substrate-related VTA.
The aim of this study was to assess the effect of successful non-pharmacological treatment of VTA following MI on parameters of LP.
Patients and methods: Study population consisted of two groups of patients with clinical VTA after MI. Group A:17 pts (1 female, mean age 62±9 years, mean left ventricular ejection fraction 31±9%) who underwent successful surgical ablation (cryoablation, subendocardial resection, aneurysmectomy). Group B:15 men (mean age 64±9 years, mean left ventricular ejection fraction 28±9%) who underwent successful catheter ablation using three-dimensional electroanatomical mapping. Complete success was defined in both groups as noninducibility of any VTA except polymorphic and/or ventricular fibrillation. During a mean follow-up period of 10±6 months, patients have remained free of recurrences of any VTA. Late potentials were analyzed by means of MAC 5000 (Marquette Electronics, Milwaukee, WI, USA), 250 QRS complexes were avereged in time domain analysis, quantitative variables were processed at 40 to 250 Hz, level of noise < 0,50 uV. The measurements were performed before and within one week after procedure in both groups.
Results: In group A the value of filtered QRS duration (ms) was before surgical procedure 167±33, after successful procedure 143±32. Pair - t- test was used to examine the results, there was significant shortening of QRS complex: p < 0.001. In group B the value of filtered QRS duration (ms) was before catheter ablation 170±32, after procedure 170±25. There was no significant statistical difference in analyzed parameters.
Conclusions: The role of late potentials in the assessment of the effect of non-pharmacological treatment of VTA may differ in surgical and in catheter procedure despite success in both methods. Significant changes in duration of filtered QRS complex after the successful surgery are in concordance with the concept of more extensive substrate modification.

P2334 Prediction of atrial fibrillation by signal-averaged P wave ECG; long-term prospective study

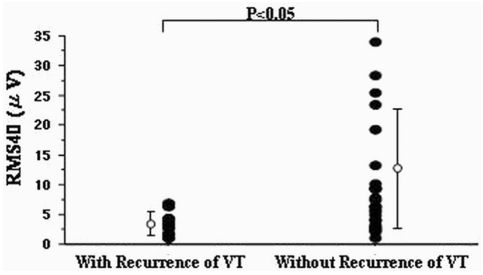
T.S. Kang[1], H.M. Kwon[2], Y.W. Yoon[2], S.J. Lee[2], S.W. Kwon[2], J.K. Park[2], S.J. Yoon[2], B.K. Hong[2]. [1]*Yonsei University College of Medicine, Division of Cardiology, Seoul, Korea, Republic of;* [2]*Yongdong Severance Hospital Yonsei University, Cardiology Department, Seoul, Korea, Republic of*

Background: Paroxysmal atrial fibrillation(PAF) is a very common cardiac arrhythmia that cause electro-physiologic and hemodynamic changes in the atrioventricular myocardium. The present study was designed to evaluate prospectively the accuracy of defined signal-averaged P wave ECG(SAECG) for prediction of PAF and AF after coronary artery bypass graft surgery(CABG).
Methods: The study groups are divided into 4 subgroups: normal control(Group 1, n=45),PAF patients(Group 2, n=66),patients who have not AF after CABG(Group 3, n=32), and patients who have AF after CABG(Group 4, n=30). We compared with four groups for clinical characteristics, echocardiographic and SAECG parameters. Furthermore, we evaluated the long-term prediction of CAF from PAF in group 2 and 4.
Results: There was positive correlation between left atrial dimension and total filtered P wave duration (tFPd) (r2=0.169, p<0.05). There were significant difference of tFPd between the group 2 and group 1(122.4±11.8 versus 146.2±22.8 ms, p<0.01), the group 4 and group 3(117.4±11.0 versus 136.8±17.2 ms, p<0.01). A cutoff value of tFPd over 130 ms predicted PAF with 77.0% sensitivity, 73.0% specificity, 74.0% positive predictive value and 76.0% negative predictive value in group 1 and 2 (p<0.001), post-operative AF with 69.0% sensitivity, 84.0% specificity, 81.1% positive predictive value and 73.0% negative predictive value (p<0.001). During the follow-up period (mean, 28±12 months), 36 patients (39%) in group 2 and 4 acquired CAF, whereas the transition to CAF was observed in only 3 patients (3%) in group 1 and 3 (log-rank test, P<.0001). The Cox regression model identified that the variables most significantly associated with the transition to CAF was tFPd(>130ms) [2.516 (1.08-5.84), p<0.01] was observed.
Conclusions: A prolonged tFPd as measured by SAECG may be a noninvasive independent predictor for the development of PAF and transition to CAF in patients with PAF or even in patients with bypass surgery.

P2335 Prediction of long-term efficacy of catheter ablation by time-domain signal-averaged electrocardiogram in patients with arrhythmogenic right ventricular cardiomyopathy

K. Obayashi, K. Kajimoto, D. Yumino, K. Takeuchi, T. Manaka, K. Tanizaki, M. Shoda, H. Kasanuki. *Tokyo Women's Medical University, Department of Cardiology, Tokyo, Japan*

Recently, it is suggested that catheter ablation (CA) therapy provides long-term VT control in patients (pts) with arrhythmogenic right ventricular cardiomyopathy (ARVC). However, there is a subgroup of pts with ARVC who do not response to CA therapy. The purpose of this study is to determine whether the long-term efficacy of CA therapy for pts with ARVC can be predicted by time-domain signal-averaged electrocardiogram (SAECG).
Methods: Among consecutive 74 pts with ARVC in our hospital, 41 pts who underwent direct current or radiofrequency CA were investigated. A time-domain SAECG was measured before CA therapy, and three variables were quantitatively evaluated: total filtered QRS duration (f-QRS), duration of low amplitude signal <40μV (LAS), and root mean square voltage for the last 40ms (RMS). In the retrospective study, these three variables were compared between pts with and without recurrence of VT during a mean follow-up of 8.1± 6.0 years.
Results: In this retrospective study, there were no significant difference in f-QRS and LAS between pts with (N=14) and without (N=27) recurrence of VT (173± 37 vs. 153± 45 msec and 97± 32 vs. 75± 43 msec, respectively). However, regarding RMS, there was a significant difference between pts with and without recurrence of VT (3.3± 1.8 vs. 12.6± 16.1 μV, p<0.05; Figure).
In these 41 pts, a criteria of RMS > 5.0 μV, which was calculated by the ROC curve analysis, gave a sensitivity of 87%, a specificity of 77%, a positive predictive value of 67%, and a negative predictive value of 91% for predicting the long-term efficacy of CA therapy for pts with ARVC.



Plots of the RMS40

Conclusions: The quantitative analysis of SAECG is useful in predicting the long-term efficacy of catheter ablation for patients with ARVC.

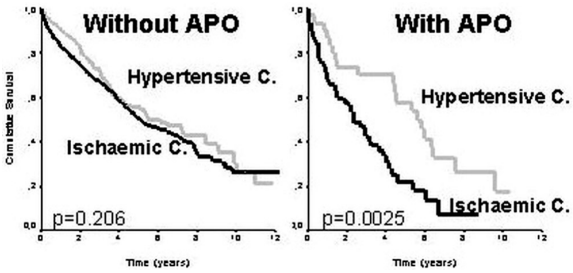
PROGNOSIS

P2336 The influence of aetiology on the prognosis of patients with and without acute pulmonary oedema

A. Varela Roman, L. Grigorian, P. Regueiro Veloso, A. Virgos Lamela, J.R. Gonzalez-Juanatey. *Santiago de Compostela, Spain*

Aims: to investigate the impact of acute pulmonary oedema (APO) on the prognosis of patients hospitalized with congestive heart failure (CHF) and if the underlying cardiopathy influence the survival of this clinically severe group of patients.
Method and Results: All patients admitted to the Cardiology Department of a tertiary hospital with CHF between 1991 and 2002 were included in the present study. APO was diagnosed in 176 of 1659 patients. 60.2% of them were of ischaemic aetiology, 48.6% and 42.9% of hypertensive and valvular origin, respec-

tively. Survival analysis carried out in April 2003 has shown that APO patients have higher mortality rates, with a median survival of 3.1 years as against 4.8 years. This difference was due only to the behaviour of patients with ischaemic CHF as among patients with non-ischaemic CHF, the difference in median survival survival between patients with and without APO was insignificant. Within the APO group the survival of ischaemic patients was lower than that of non-ischaemic (median survival of 2.3 years vs 4.5 years, respectively). The difference was more pronounced between APO patients with CHF of ischaemic and hypertensive origin (median survival of 5.6 years for the latter). Among patients without APO, there was no significant difference between different aetiologycal groups.



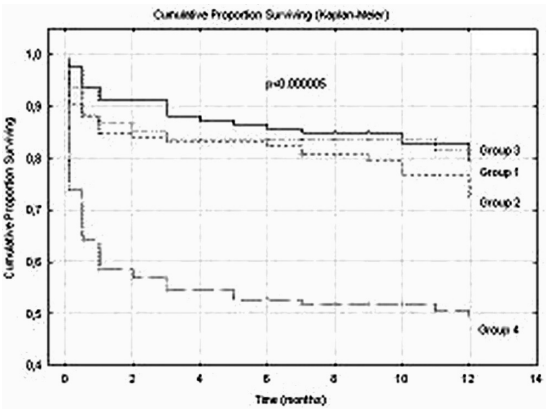
Kaplan-Meier survival curves.

Conclusion: in this study we found that the survival time of CHF patients is significantly shortened by the concurrence of APO and ischaemic aetiology but not by either of these factors without the other.

P2337 Relationship between admission white blood count and one-year mortality in patients with chronic heart failure

M. Roik, S. Stawicki, M.H. Starczewska, A. Solarska-Pochlopek, D. Kosior, G. Horszczaruk, R. Rodzoch, G. Opolski. *University Hopsital, 1 st Department of Cardiology, Warsaw, Poland*

Background: Recent studies have established that systemic inflammation is important in prognosis in patients with coronary artery disease. In pts with chronic heart failure (HF) inflammation may play a prognostic role not only in ischemic but also in non-ischemic etiology.
Aim: We evaluated the relationship between white blood count (WBC) count on admission and survival during one-year follow-up in HF pts.
Methods: A total of 501 consecutive pts with CHF hospitalized in Dept. of Cardiology between 2002-2003 were enrolled to study. Baseline clinical parameters were measured immediately after the admission. The WBC count were divided into the quartiles (1st quartile < 7.24, n=126, 2nd quartiles 7.24-9.22, n=125, 3rd quartiles 9.22-12.4, n=128, 4th quartiles > 12.4,n=123).
Results; Age, gender, non-ischemic etiology, comorbidities (hypertension, diabets meliitus), ejection fraction, renal dysfunction did not differ between quratiles. During one-year folow-up 19%, 16%, 19% and 50% death occurred in the first, second, third and fourth quartile ($p < 0.0005$). Kaplan-Meier curves showed lower survival with higher level of WBC count. A multivariate logistic regression analysis were performed adjusting for age, eetiology of HF, NYHA status, ejection fraction and medical therapy (ACE-inhibitors, beta-blockers, combination of both and statins). The risk of death increase continuously with quartiles of WBC count and showed that WBC count over 11,000 is strong independent predictor of mortality (OR: 1.48, CI: 1.21 – 1.80, $p < 0.001$).



The Kaplan-Meier curve

Conclusion: 1) Admission WBC is an independent predictor of mortality in pts with CHF.
2) WBC appears to be a simple marker and provides useful prognostic information.

P2338 C34T AMPD1 gene polymorphism is a survival factor in male chronic heart failure with preserved left ventricular function

B. Andersson[1], B. Norman[2], C. Sylvén[3]. *[1]Sahlgrenska University Hospital, Dept. of Cardiology, Gothenburg (Goteborg), Sweden; [2]Karolinska Inst, Karolinska Univ Hosp, Div of Clinical Physiology, Stockholm, Sweden; [3]Karolinska Inst, Karolinska Univ Hosp, Div of Cardiology, Stockholm, Sweden*

Background: AMPD1 encodes the muscle specific isoform of AMP deaminase. Individuals who are carriers of the T-allele at C34T polymorphism in AMPD1 have decreased levels of AMP deaminase. A reduced level of this enzyme leads to increased production of adenosine, which may have a cardioprotective effect.
Hypothesis: The mutant allele can be associated with preserved left ventricular function and improved survival in chronic heart failure.
Materials and Methods: Chronic heart failure with unknown etiology including dilated cardiomyopathy was identified in 194 population-based patients. Left ventricular function was determined by echocardiography. Survival data was obtained during 10 years of follow-up. The patients and 77 healthy controls were genotyped with TaqMan fluorogenic probes for the identification of a common C34T mutation in the AMPD1 gene.
Results: The prevalence of the mutated allele was not significantly different in the heart failure and control groups (13.1 vs. 13.0%). There was a tendency for better survival in male patients (n=144) with the mutated allele than in those with the normal allele, hazard's ratio 1.55 (0.95 to 2.56), p=0.08, but not in female patients (p=0.71). In the male group, the tendency to improved survival was pronounced in patients with preserved systolic function (ejection fraction >0.40), HR 5.51 (1.27 to 23.8), p=0.02.
Conclusions: The C34T mutation that results in reduced AMP deaminase levels and increased adenosine production was associated with a 50% improved survival in male patients with chronic heart failure and preserved systolic function. The AMPD1 C34T polymorphism might be cardioprotective and influence development of systolic failure and thereby be a reason for the decreased mortality observed in this group of patients.

P2339 Low pulse pressure independently predicts mortality and morbidity in patients with chronic heart failure: results from the second Cardiac Insuffiency Bisoprolol (CIBIS-2) trial

C.J. Petrie[1], A.A. Voors[2], H.J. Dargie[3], D.J. van Veldhuisen[2], J.J.V. McMurray[3], P. Lechat[4] on behalf of CIBIS-2 Investigators. *[1]Clinical Research Initiative, Cardiology Department, Glasgow, United Kingdom; [2]University Hospital, Department Cardiology, Thoraxcenter, Groningen, Netherlands; [3]Western Infirmary, Dept. Cardiology, Glasgow, United Kingdom; [4]Hopital Pitie-Salpetriere, Service de Pharmacologie, Paris, France*

Low pulse pressure independently predicts mortality and morbidity in patients with chronic heart failure: results from the second Cardiac Insuffiency Bisoprolol (CIBIS-2) trial.
Introduction: After myocardial infarction and in mild chronic heart failure (HF) an elevated pulse pressure (PP) has been consistently and independently associated with increased (cardiovascular) mortality. By contrast, in acute decompensated heart failure, a lower PP predicted an increased risk of death. The prognostic importance of PP in advanced HF has not been well described.
Aim: To assess the relationship between PP and morbidity and mortality in patients with advanced CHF.
Methods: We evaluated the relationship between manually determined PP at baseline, and mortality and hospitalisation for heart failure in the 2647 patients enrolled in CIBIS 2. The effects of both PP and MAP were assessed in a multivariate Cox regression model that adjusted for potential confounders, including mean arterial pressure (MAP), ejection fraction, renal function, age and medication (bisoprolol or placebo).
Results: Overall, the mean age of enrolled subjects was 61 years, 80.5% were male, 83% NYHA class III and 17% NYHA class IV, 55% had a history of prior myocardial infarction and the mean ejection fraction was 27.4%. Mean baseline creatinine was 103.9 mmol/L and 67% had an estimated creatinine clearance $>$60ml/min. Both a lower MAP and a lower PP were consistently found to be independent predictors of mortality and morbidity. A low pulse pressure and MAP predicted the combined end point of death or hospitalisation for heart failure independently of each other. For PP-HR 0.94/10mmHg (P= 0.044) and MAP- HR 0.88/10mmHg ($P<0.001$).
Conclusion: Whilst a low MAP is recognised as an independent predictor of outcome in CHF, a low pulse pressure, readily obtainable by simple clinical measurement, is also an independent predictor of death or hospitalisation for heart failure, in patients with advanced CHF. This appears to be incremental to other well established markers of adverse outcome in this population and is in contrast to milder heart failure, where an elevated pulse pressure predicts adverse cardiovascular events.

P2340 Multimarker approach to risk stratification in stable advanced congestive heart failure; simultaneous measurement of Troponin I, c-reactive protein, and b-type natriuretic peptide

M. Chandavimol[1], A.P. Ignaszewski[2], M.R. Pudek[2], L.P. Straatman[2], C.A. Davies[2], T.L. Sedlak[2], K.G. Gin[2]. *[1]Vancouver, Canada; [2]Vancouver, Canada*

Background: B-Type natriuretic peptide (BNP) is well established as an independent predictor of prognosis in patients with congestive heart failure (CHF). However, little is known about its prognostic ability in stable advanced CHF in an out-patient setting. Data concerning prognostic ability of Troponin I (Tn) and high sensitive C-reactive protein (CRP) are also very limited. The purpose of this study was to examine the usefulness of simultaneous measurement of BNP, CRP and Tn for prognostic information in stable advanced CHF patients.
Methods and Results: We prospectively studied 85 consecutive patients with stable advanced CHF followed in an out-patient multidisciplinary Heart Failure clinic. Baseline measurements of BNP, Tn, and CRP were sampled and patients followed up for a median of 659 days. The primary endpoint of death or heart transplantation (OHT) was reached in 21 (24.7%) patients. Of these patients, median BNP level was 460 pg/ml (inter-quartile range; 211, 917), 14.0% (N=12) had positive Tn and 41.2% (N=35) had positive CRP. Analyzing the three markers individually, BNP concentration above median was the only independent predictor of primary endpoint (OR = 2.56 (1.10- 5.97), P=0.02) [Figure 1]. There was no difference in age, gender, functional class, left ventricular ejection fraction, peak exercise oxygen consumption, sodium level, creatinine level, as well as number of positive CRP or Tn in patients with elevated BNP, as compared to those without elevation.

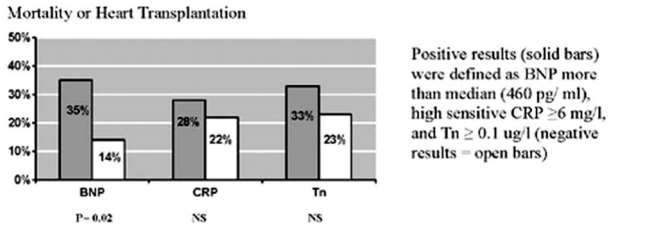


Figure 1

Conclusion: In patients with stable advanced CHF, BNP was the only independent prognostic marker of death or heart transplantation. High sensitive CRP and Tn failed to reach statistic significance as a prognostic marker.

P2341 Long-term follow up of left ventricular reverse remodelling and relation with mortality in chronic heart failure

N. Nyolczas[1], M. Dekany[1], T. Borsanyi[1], B. Szabo[1], I. Preda[2]. *[1]National Health Service Centre, Department of Cardiology, Budapest, Hungary; [2]Hungarian Academy of Sciences, Cardiovascular Research Group, Budapest, Hungary*

Background: Adequate therapy improves the function of the failing left ventricle, prevents or reverses progressive left ventricular dilatation; consequently having a positive effect on cardiac remodelling in chronic heart failure (CHF). The process has become increasingly recognised, however limited amount of long-term data is available.
Aim: The investigation of frequency and course in time of left ventricular reverse remodelling as well as the relation with mortality during optimal drug therapy of CHF.
Methods: Left ventricular ejection fraction (LVEF), end-systolic diameter (ESD) and end-diastolic diameter (EDD) were measured annually for 5 years follow up by 2D-echocardiography in 150 patients (126 men; age: 55.7±14.1 years, NYHA: 3.07±0.81; ischaemic: 51, non-ischaemic: 99 patients). The therapy, that patients received, resulted in optimal left ventricular unloading and neurohormonal blockade. They were treated with diuretics (95%), ACE inhibitors (94%), ARBs (10%), beta blockers (94%), spironolactone (64%), direct vasodilators (70%) and digoxin (60%).
Results: During the five years follow-up the LVEF (30.7 ± 8.6; 37.6 ± 10.7; 39.7 ± 7.9; 40.7 ± 7.7; 38.6 ± 9.6; 39.5 ± 11.1%) improved significantly already in the first year, while significant decrease in EDD (70.3 ± 10.4; 70.8 ± 11.1; 63.4 ± 11.0; 64.5 ± 6.6; 65.6 ± 8.3; 65.1 ± 11.1 mm) and ESD (59.4 ± 11.1; 57.3 ± 12.2; 50.0 ± 11.7; 50.8 ± 7.6; 51.4 ± 9.4; 52.3 ± 12.3 mm) occurred from the second year only. These favourable changes maintained in the entire period of the follow-up. By the end of the second year the LVEF was improved in 118 (78.7%) and deteriorated or unchanged in 32 (21.3%) patients. The improvement of LVEF was accompanied by the decrease in EDD and ESD (complete reverse remodeling - CRR) in 86 patients (57.3%). The five years mortality in the group of patients with deteriorated or unchanged LVEF was 21.9%; in the patients with improved LVEF but increased EDD proved to be 18.8%; while in the group of patients with CRR was found 5.8%.
Conclusions: Optimal therapy causing left ventricular unloading and neurohormonal blockade has resulted in long-term CRR in the majority of patients (60-65%) with CHF. Mortality rate of patients with CRR proved to be low. The lack of CRR in spite of increasing LVEF can prognosticate less favourable long-term outcome of the disease.

P2342 In-hospital mortality predictors in patients with heart failure and preserved left ventricular ejection fraction

L. Perez de Isla, J. Zamorano, L. Contreras, C. Almeria, J.L. Rodrigo, L. Mataix, D. Herrera, C. Macaya. *Hosp.Clinico San Carlos, Istituto Cardiovasc., Unidad de Imagen Cardiovascular, Madrid, Spain*

To date, in-hospital mortality predictors of patients with heart failure (HF) and depressed systolic left ventricular ejection fraction (LVEF) are well known. Nevertheless, this is not the case of patients suffering from HF with preserved LVEF. Our aim is to describe the predictors of in-hospital mortality in patients during the first admission due to HF with preserved LVEF.
Methods: 771 consecutive patients with a first admission to hospital because of HF with preserved LVEF (LVEF>50%) between January 2002 and September 2003 comprised our study group. Cardiovascular risk factors, clinical, electrical and echocardiographic variables were studied. Uni and multivariate logistic regression analysis was performed.
Results: Mean age was 82.6±43.6 (551 patients–66.3%-women). Variables in both groups were similar except for the history of ischemic heart disease, dilated cardiomiopathy and the presence of normal sinus rhythm. The results of the multivariate logistic regression analysis are shown in the table below.

Table 1. Multivariate logistic regressiona analysis results

	Relative risk	95% CI	p
Ischemic heart disease	2.5	1.15-5.5	0.021
History of dilated cardiomyopathy	5.9	1.46-23.5	0.013
Sinus rythm	0.4	0.18-0.9	0.03

Conclusions: Antecedents of ischemic heart disease or dilated cardiomiopathy are independent predictors of in-hospital mortality in patients with HF and preserved LVEF. On the other hand, the presence of normal sinus rhythm is an independent protective factor in these patients. These factors must be especially considered during admission of this kind of patients.

P2343 Atrial fibrillation carries similar risks in heart failure irrespective of ejection fraction-results from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)

L.G. Olsson[1], K. Swedberg[2], C.B. Granger[3], E. Michelson[4], J.J.V. McMurray[5], M. Puuh[6], S. Yusuf[7], M.A. Pfeffer[8]. *[1]Sahlgrenska University Hospital/Östra, Medicine, Göteborg, Sweden; [2]Sahlgrenska University Hospital/ostra, Department of Medicine, Goteborg, Sweden; [3]Duke University, Cardiology, Durham, United States of America; [4]Astrazeneca, Wilmington, United States of America; [5]University of Glasgow, Cardiology, Glasgow, Scotland, United Kingdom; [6]Astrazeneca, Mölndal, Sweden; [7]McMaster University, Hamilton ON, Canada; [8]Brigham and Women Hospital, Cardiology, Boston, United States of America*

Background: atrial fibrillation (AF) is associated with increased risk of adverse cardiovascular (CV) outcomes in low EF chronic heart failure (HF). Patients with HF and preserved ejection fraction (PEF) i.e. >40% and reduced LVEF differ. The risk of AF in PEF is unknown. CHARM enrolled symptomatic patients with HF and a broad range of EF. We estimated the risk associated with AF in patients with preserved and reduced EF in CHARM.
Methods: among 7601 patients randomized in CHARM, 1148 patients had AF at baseline: 670 in low EF (58%) and 478 in PEF (42%). Compared with patients in sinus rhythm (SR), patients with AF at baseline were older and had more often a previous hospitalisation for heart failure. Heart failure was more often of hypertensive or idiopathic origin and they were more often treated with diuretics and spironolactone and less often with a beta-blocker.
The risk associated with baseline AF was similar in low EF and PEF patients. In a multivariate analysis baseline atrial fibrillation remained of independent importance for cardiovascular death or hospitalisation for heart failure HR 1.19; (95% CI 1.09, 1.30) p=0.045. New onset AF among patients with SR at baseline (n=392) was associated with significant increased risk for CV outcomes. The risk was similar in low EF and PEF patients (data not shown). The beneficial effects of candesartan were similar in patients with AF and SR at baseline.

CV Outcomes	Reduced EF N=4576 HR (95% CI)	Preserved EF N=3023 HR (95% CI)	P for interaction
CV Death or CHF hospitalisation	1.287 (1.136, 1.458) No of events=1761	1.724 (1.446, 2.056) No of events=699	0.12
CV death	1.368 (1.175, 1.592) No of events=1120	1.803 (1.408, 2.309) No of events=340	0.93
Hospitalisation due to CHF	1.304 (1.119, 1.519) No of events=1158	1.639(1.332,2.017) No of events=517	0.07
Fatal or non-fatal stroke	1.920 (1.340, 2.749) No of events=166	1.453 (0.935, 2.256) No of events=121	0.61

Conclusions: AF is associated with a significantly and similarly increased risk of adverse CV outcome in patients with HF and both reduced and preserved EF. Candesartan reduced CV outcomes similarly in both groups. New AF is also associated with an increase in risk in both types of HF.

P2344 Assessment of left and right ventricular diastolic function and its relation to prognosis in congestive heart failure patients with and without comorbid diabetes mellitus

K.G. Adamyan, L.R. Tumasyan, A.B. Nargizyan. *Institute of Cardiology, Yerevan, Armenia*

Background: Co-existence of diabetes mellitus (DM), reported in about of one third of patients (pts) with chronic heart failure (CHF), can affect myocardial systolic and diastolic function and worsen prognosis, especially in pts with CHF of ischemic origin. The aim of study was to evaluate left (LV) and right ventricular (RV) diastolic functions and its relation to prognosis in pts with NYHA III-IV functional class CHF of ischemic etiology with and without type II DM.
Methods: 98 consecutive pts (mean age 58.1±0.4 years) in sinus rhythm who had an echocardiographic diagnosis of dilated cardiomyopathy (LV end-diastolic dimension>60mm and ejection fraction<35%) were randomly assigned to groups with (Group A, n=50) and without DM (Group B, n=48). The groups of pts were not significantly different for age, sex, NYHA functional class, LV and RV ejection fraction. Peak early (E) and late (A) filling velocities, E/A ratios, acceleration (AT) and deceleration (DT) times of E-waves of transmitral and transtricuspid flow, LV and RV isovolumic relaxation (IVRT) and overall filling (OFT) times (msec) were obtained using Doppler-echocardiography.
Results: The 3-year mortality [48% vs. 33.3%; relative risk (RR)=0.77, $p<0.05$], hospitalization rate (82% vs. 64.6%; RR=0.83, $p<0.05$) and combined end point of mortality or hospitalization (94% vs. 77.1%; RR=0.86, $p<0.05$) were higher in diabetic compared with non-diabetic pts. Restrictive transmitral and transtricuspid filling patterns were revealed in both group, but the E/A ratio (2.8±0.21 vs. 2.2±0.15, $p<0.05$) of transmitral filling was significantly higher and DT (112.2±2.2 vs. 120.5±2.8, $p<0.05$), AT (72.2±2.1 vs. 79.5±2.7, $p<0.05$) of E wave, LV IVRT (42.2±1.4 vs. 48.5±2.5, $p<0.05$), and LV OFT (332.2±4.8 vs. 353.5±9.1, $p<0.05$) were significantly less in Group A compared to Group B. Similarly, in Group A DT (113.2±2.1 vs. 122.4±3.6, $p<0.05$) and AT (71.5±2.2 vs. 78.2±2.3, $p<0.05$) of early transtricuspid flow, RV IVRT (43.3±1.4 vs. 49.5±2.3, $p<0.05$) and RV OFT (329.2±5.1 vs. 348.5±7.3, $p<0.05$) were significantly shorter, and E/A ratio significantly higher (2.7±0.19 vs. 2.1±0.16, $p<0.05$) than in Group B.
In conclusion, the worse prognosis of pts with CHF and ischemic dilated cardiomyopathy with type II DM seems to be related to more impaired LV and RV diastolic dysfunction compared to their nondiabetic counterparts. Therefore these pts need more aggressive therapeutic strategies in order to correct diastolic dysfunction and improve prognosis.

P2345 Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure

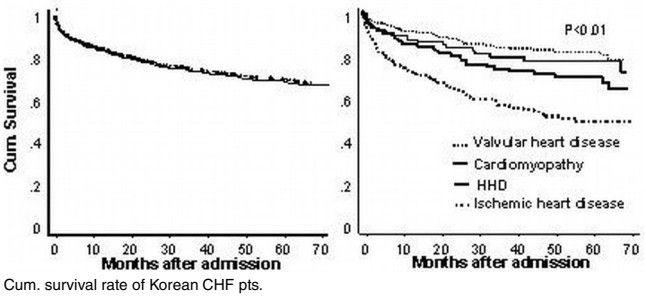
J. Meluzin, L. Spinarová, P. Hude, J. Krejèí, V. Kincl, R. Panovský. *St. Anna Hospital, 1st. Department of Internal Medicine, Brno, Czech Republic*

Background: little is known about the prognostic importance of the right ventricular (RV) systolic and diastolic function. The purpose of this study was to determine the prognostic power of systolic and diastolic RV functional parameters derived from Doppler tissue imaging (DTI) of the tricuspid annular motion and to assess whether their combination may improve the risk stratification of patients with heart failure.
Methods: one hundred and forty patients with symptomatic heart failure and left ventricular ejection fraction $\leq$ 40% underwent standard echocardiography, DTI of the tricuspid annular motion, and the right heart catheterization. They were followed up for a mean period of 17 months for cardiac related death and non-fatal cardiac events including the implantation of a cardioverter-defibrillator and the hospitalization for heart failure decompensation.
Results: forty-eight cardiac events occurred: 19 patients died, 26 were hospitalized for heart failure decompensation, and 3 because of the need for implantation of a cardioverter-defibrillator. The peak systolic tricuspid annular velocity (Sa) $\leq$ 10.8 cm/s, the peak early diastolic tricuspid annular velocity (Ea) $\leq$ 8.9 cm/s, the tricuspid annular acceleration during isovolumic contraction (IVA) $\leq$ 2.52 m/s2, and the Doppler RV index (Tei index) $\geq$ 1.20 were found to significantly worsen survival or event-free survival. However, their combinations significantly exceeded the predictive potential of individual parameters. The worst survival was predicted by the combination of Sa $\leq$ 10.8 cm/s + Ea $\leq$ 8.9 cm/s + IVA $\leq$ 2.52 m/s2 (relative risk 6.17, $p < 0.001$), while the worst event-free survival was identified by the combination Sa $\leq$ 10.8 cm/s + Ea $\leq$ 8.9 cm/s + Tei index $\geq$ 1.20 (relative risk 3.62, $p < 0.001$).
Conclusion: the combination of RV systolic and diastolic functional parameters represents a very powerful tool for risk stratification of patients with symptomatic heart failure.

P2346 Clinical characteristics and prognostic factors of congestive heart failure in hospitalised patients

K.H. Ryu[1], B.H. Oh[2], S.C. Chae[3], M.C. Cho[4], E.S. Cheon[5], J.J. Kim[6], D.J. Choi[7], Y.G. Ahn[8]. *[1]Konkuk university hospital, Cardiology Department, Seoul, Korea, Republic of; [2]Seoul national Univ Hospital, Cardiology, Seoul, Korea, Republic of; [3]Kyungbuk national Univ Hospital, Cardiology, Daegu, Korea, Republic of; [4]Chungbuk national Univ Hospital, Cardilogy, Cheongju, Korea, Republic of; [5]Sungkyunkwan university, Cardilogy, Seoul, Korea, Republic of; [6]Ulsan university hospital, Cardiology, Seoul, Korea, Republic of; [7]Seoul national Univ Bundang Hosp, Cardiology, Seongnam, Korea, Republic of; [8]Chonnam national Univ Hospital, Cardiology, Gwangju, Korea, Republic of*

Congestive heart failure(CHF) is a leading cause of morbidity and mortality in developed countries, and is also a growing health problem. Racial aspects and public health care system may be important factors for outcome of patients with CHF. So survey participating 6 university hospitals in Korea have been performed since 1998.
Methods: the presented data are from 6 university hospitals during the period from Jan 1998 to Aug 2003, clinical data of 1,829 patients with CHF were collected. Clinical feature including etiology, associated medical illness and survival data were obtained from medical records and Korea National Statistical Office. The duration of observation was 37.0±20.7(0.1-68.2) months.



Cum. survival rate of Korean CHF pts.

Results: 923 were male (50.5%) and the mean age of overall patients was 64.1±14.3 years (male 61.5±12.9, female 67.3±16.4 years). Thiry-one percent of patients had history of hypertension and these for diabetes in 28.6% of patients. Ischaemic heart disease was the most prevalent cause of CHF(38.3%) and cardiomyopathy, majority of them was idiopathic dilated cardiomyopathy was 21.7% of patients. Hypertensive heart disease was 18.5% and the valvular heart disease was reported in 16.5% of patients. Cumulative survival rate at 6 months, 1 year and 2 year were 0.875, 0.829 and 0.770 respectively. Ischaemic heart disease as underlying disease showed most unfavorable outcome. The survival rate of those at 6 months, 1 year and 2 year were 0.794, 0.702 and 0.612 respectively. Low serum concentration of sodium at admission was most unfavorable feature of patients with CHF and previous history of myocardial infarction, history of diabetes and azotemia were independent unfavorable prognostic factors.

P2347 Do BNP changes during therapeutic unloading in patients with chronic heart failure have a prognostic impact?

E. Aiolfi[1], S. Capomolla[1], M. Ceresa[2], A. Nori[1], O. Febo[1], M.T. La Rovere[1], A. Rossi[1], F. Cobelli[1]. *[1]Istituto scientifico Montescano, Fondazione "S Maugeri" IRCCS Pavia, Montescano, Italy; [2]Fondazione "S.Maugeri", IRCCS, Cardiology Dept., Montescano, Italy*

Background: Brain Natriuretic Peptide (BNP) is a useful marker for Chronic Heart Failure (CHF) stratification. However, the prognostic value of BNP changes during therapeutic unloading is still poorly defined.
Aim: To address the relationship between BNP changes during therapeutic unloading and short-term outcome in patients with CHF.
Methods: Forty-two consecutive CHF patients (age 57±11 years, LVEF 26±7%) underwent BNP (TRIAGE, Biosite) and clinical evaluation both at hospital admission and at discharge. During a mean hospital stay of 23±15 days optimal medical treatment according to guidelines has been provided. BNP changes have been described as percentage of admission values. A change of 30% (median value) has been used as a cut-off value. Major clinical events including deaths and re-hospitalizations have been recorded.
Results: Twenty-four out of 42 pts (57%) have been managed with iv infusion of

Table 1

	Admission	Discharge	p
BNP(pg/dl)	1147± 987	778±1067	0.007
ACE – Long-ac. (mg/day)	12 ± 7	12.7±7	ns
ACE – Short-ac. (mg/day)	91±46	114±48	.01
Beta-blockers (mg/day)	18±9	22±9	0.08
Nitrate (mg/day)	37±45	64±57	0.004
Diuretics (mg/day)	81±68	84±62	ns
Aldost. Antag. (mg/day)	47±38	39±34	ns

diuretics and nitroprusside. Changes in oral drugs are reported in the Table 1. As compared to admission, at discharge 29/42 patients (69%) showed a decrease in BNP ≥30%.During a mean follow-up of 91± 61 days, 15 major clinical events occurred in 11/42 patients (26%): 12 (80%) rehospitalizations due to worsening heart failure and 3 (20%) cardiac deaths. Among patients with a ≥30% reduction of baseline BNP values, the number of patients with events (4/29, 14%) was significantly lower as compared to patients with a < 30% BNP reduction (7/13, 54%) (logRank p<.01). BNP change ≥30% identified patients with risk reduction of major cardiac events(RR 0.35 (IC 95% 0.30 – 0.41).
Conclusions: BNP changes during therapeutic unloading are significantly related to short-term clinical outcome in patients with CHF.

P2348 Which are the markers of long-term mortality in patients with heart failure and preserved left ventricular ejection fraction?

L. Perez de Isla, J. Zamorano, L. Contreras, C. Almeria, J.L. Rodrigo, D. Herrera, L. Mataix, C. Macaya. *Hosp.Clinico San Carlos, Istituto Cardiovasc., Unidad de Imagen Cardiovascular, Madrid, Spain*

Background and aim: More than 15 million people around the world suffer from heart failure (HF). To date, prognostic factors concerning those patients with depressed systolic left ventricular ejection fraction (LVEF) are well known. Nevertheless, prognostic factors regarding HF with preserved LVEF are still not well described. Our aim is to show the predictors of increased long-term mortality after a first admission due to HF with preserved LVEF.
Methods: 771 consecutive patients with a first admission to hospital because of HF with preserved LVEF between January 2002 and September 2003 comprised our study group. Cardiovascular risk factors, clinical, electrical and echocardiographic variables were studied. In all patients, long-term follow-up was performed by means of clinical revisions and telephone contact. Death was the primary endpoint. Uni and multivariate Cox regression analysis was performed.
Results: Mean age was 82.6±43.6 (551 patients – 66.3%- women). Mean follow up was 564.5±298.3 days. Age, the presence of hypertension, renal failure, history of ischemic heart disease, left atrium diameter, aortic regurgitation and the pulmonary artery systolic pressure were found as predictors of increased mortality in the univariate analysis. Nevertheless only age and pulmonary artery systolic pressure were found to be independent markers of increased mortality in the multivariate analysis (table).

Table

	Relative Risk	5% CI	p
Age	1.09	1.043-1.131	<0.001
Pulmonary artery systolic pressure	1.023	1.006-1.04	0.009

Results of the Cox regression multivariate analysis.

Conclusions: Age and the degree of pulmonary hypertension are independent markers of increased mortality in those patients with a first admission due to heart failure with preserved LVEF.

P2349 Prognostic role of chronic obstructive pulmonary disease in congestive heart failure. Data from the IN-CHF registry

G.M.T. Fabbri[1], F. Orso[2], M.C. Albanese[2], M. Floresta[2], L. Gonzini[2], G. Lepera[2], E. Zanelli[2], A.P. Maggioni[2] on behalf of IN-CHF Investigators. *[1]ANMCO Research Center, Florence, Italy; [2]ANMCO Research Center, Florence, Italy*

Background: Non cardiac comorbidities such as chronic obstructive pulmonary disease (COPD) are highly prevalent in patients (pts) with heart failure (HF) but the association with the outcome is still scarcely investigated. We examined whether the presence of COPD influences one year outcome of outpts with HF.
Methods: Data concern 8267 outpts enrolled in the IN CHF Registry. Diagnosis of HF was clinical, based on the ESC criteria. Diagnosis of COPD was obtained from records of specific (inhalation and/or oral) treatments and from patient history. Multivariable analysis was performed to identify the independent predictors of one year outcome.
Results: A history of COPD was present in 1238 (14.3%) of the pts. Pts with COPD were significantly older, more likely to be in advanced NYHA class and obese than those without COPD. No differences were found between the two groups regarding the etiology (ischemic or not), systolic blood pressure values, left ventricular function, renal dysfunction and the presence of diabetes and atrial fibrillation. Pts with COPD had a higher 1-year all cause mortality than those without COPD (13.5%, vs 10.8%, p=0.0047). Also cardiovascular mortality was higher in pts with COPD (11.5% vs 9.2%, p=0.0084 respectively). All cause-hospitalization rate was 26.4% for pts with COPD vs 21.8%, p=0.0003 but no significant differences were found in the rate of hospitalization for cardiovascular reasons (18.9% vs 17.0%, p=ns). Multivariable analysis did not confirm the association between COPD and the risk of death (HR 1.02, 95% CI 0.86-1.21) or hospitalization rate (HR 1.13, 95% CI 0.99-1.27). After adjustment, the presence of COPD was not associated with the combined end-point of total mortality or hospitalizations for any cause (HR 1.09, 95% CI 0.98-1.22).
Conclusions: Pts with COPD appeared to be more symptomatic despite a similar ventricular function. However, in this unselected population of pts with HF, the presence of COPD does not seem to increase the risk of one year all cause death and hospitalization, when the possible counfounding factors are taken into account.

P2350 Presence of desmin in cardiomyocytes and long-term prognosis in patients with heart failure

R. Gil[1], A. Pawlak[1], E. Walczak[2], H. Rdzanek[1], T. Niemirka[1], J. Rzezak[1], P. Seweryniak[1]. *[1]Central Hospital of Internal Affairs and, Department of Invasive Cardiology, Warsaw, Poland; [2]Institute of Rheumatology, Department of Patomorphology, Warsaw, Poland*

Background: Desmin is the protein which is responsible for stability of muscular filaments and it improves their systolic function. The abnormality of accumulation of desmin deposits in cardiac muscle cells plays a vital role in progression of congestive heart failure (HF).
Material and methods: Diagnostic endomyocardial biopsy (DMB) was performed in 100 patients (85 males, mean age 48.1±12.6 years) with clinical symptoms of HF (LVFE <40%). Four specimens were taken from right ventricle. Desmin was detected with immunohistochemical reactions in cardiomyocytes. Study population was divided into three groups: I group – 21 patients without desmin, II group – 23 patients with abnormal accumulation of desmin, III group – 56 patients with normal expresion of desmin in cardiomyocytes.
Results: The duration of follow- up was 38.2?14.6 (from 10 to 60) months. Cardiac death was affirmed in 28.6% of the cases in group I, 8.6% in group II and 5.4% in group III. There were relatively more patients with transplanted heart in group I than in group II and III (11.1% vs. 4.3% vs. 0.0%). Additionally, in the first group we found lower degree NYHA class than in the other groups (2.25±0.9 vs 1.8±0.7 vs 1.5±0.6) in the long-term observation. There were more patients with implanted pacemakers and cardioverter-defibrilator devices in group II rather then in group I (17.4%, 13.0%).
Conclusions: Our results suggest that the presence of desmin in cardiomyocytes has its direct links with long-term prognosis for patients with HF. The lack of desmin in cardiomyocytes in immunohistochemical assay is associated with very strong prognostic parameter of HF development.

P2351 Long-term follow-up of patients with heart failure with preserved left ventricular ejection fraction: prognostic determinants

L. Perez de Isla, J. Zamorano, L. Contreras, C. Almeria, J.L. Rodrigo, A. Aubele, M. Quezada, C. Macaya. *Hosp.Clinico San Carlos, Istituto Cardiovasc., Unidad de Imagen Cardiovascular, Madrid, Spain*

More than 15 million people around the world suffer from heart failure (HF). To date, prognostic factors concerning those patients with depressed systolic left ventricular ejection fraction (LVEF) are well known. Nevertheless, prognostic factors regarding HF with preserved LVEF are still not well described. Our aim is to show the prognostic determinants of long-term bad outcome after a first admission because of HF with preserved LVEF.
Methods: 771 consecutive patients with a first admission to hospital because of HF with preserved LVEF between January 2002 and September 2003 comprised our study group. Cardiovascular risk factors, clinical, electrical and echocardiographic variables were studied. In all patients, long-term follow-up was performed by means of clinical revisions and telephone contact. Death or a new admission to hospital because of heart failure was the primary composite endpoint. Uni and multivariate Cox regression analysis were performed.
Results: Mean age was 82.6±43.6 (551 patients – 66.3%- women). Mean follow up was 457±311.7 days. Age, the presence of diabetes, history of ischemic heart disease and the pulmonary artery systolic pressure were found as predictors of poor long-term outcome and the presence of normal sinus rhythm as a predictor of good outcome in the univariate analysis. Nevertheless only age and pulmonary artery systolic pressure were found as independent markers of poor long-term outcome in the multivariate analysis (table).

Table

	Relative risk	95%CI	p
Age	1.04	1.015-1.064	0.001
Pulmonary artery systolic pressure	1.014	1.003-1.025	0.013

Multivariate Cox regression analysis results

Conclusions: The age and the degree of pulmonary hypertension are independent markers of bad long-term outcome in those patients after a first admission due to heart failure with preserved LVEF.

P2352 Restrictive filling pattern is a powerful prognostic indicator in patients with heart failure: a meta-analysis

G.A. Whalley[1], G.D. Gamble[2], R.N. Doughty[2]. [1]*University of Auckland, Medicine Dept, Auckland, New Zealand;* [2]*University of AUckland, Medicine, AUckland, New Zealand*

Background: Several studies have reported that the presence of a restrictive filling pattern is associated with poor outcome in patients with heart failure. These studies, of variable sample size, have involved different heart failure patient groups with variable associated mortality rates and follow-up time and while powered for effects on combined end-points such as death or hospital admission, many were under-powered to reliably determine the overall effect of the restrictive filling pattern on total mortality. Consequently, we performed a meta-analysis to determine the prognostic power of the restrictive filling pattern with regard to total mortality in patients with heart failure.
Methods: We searched several online medial databases for prospective studies of patients with heart failure. All authors were contacted to seek confirmation of their data. We compared all-cause mortality in groups with restrictive filling pattern compared to non-restrictive filling patterns. Reference manager version 4.2.7 software was used for the analysis.
Results: 2671 patients in 27 studies were identified (425 idiopathic cardiomyopathy, 2246 mixed aetiology heart failure). Average follow-up was between 3 months and 5 years: 10 studies had longer than 2 years follow-up. 600 events occurred (death and/or transplantation) and the overall odds ratio for death was 4.19 (95% CI 3.41, 5.15); idiopathic group: 6.41 (95% CI 3.74, 11.01); mixed group: 3.88 (95% CI 3.11, 4.85). The overall odds ratio for death/transplantation was 4.95 (95% CI 4.06, 6.02); idiopathic group: 9.31 (95% CI 5.54, 15.6); mixed group: 4.95 (95% CI 4.06, 6.02).
Conclusions: Restrictive filling pattern is associated with a four-fold increase in mortality in patients with heart failure and thus should be an important part of the echocardiographic assessment of patients with heart failure.

P2353 Intra-ventricular dysynchrony: an important determinant of long-term outcome in patients with known or suspected coronary disease

M.I. Burgess[1], J. Chan[2], E. Rozis[2], T.H. Marwick[2]. [1]*Brisbane, Australia;* [2]*University of Queensland, Department of Medicine, Brisbane, Australia*

Background: Improvement of intra-ventricular dysynchrony (IVD) in pts undergoing bi-ventricular pacing is associated with clinical improvement but little is known about the relationship between IVD and prognosis. We sought whether IVD influences long-term outcome in pts with known or suspected coronary disease (CAD).
Methods: Tissue Doppler imaging was performed at baseline in 184 pts (aged 61+10 years, 67% male) prior to dobutamine stress echo (DSE). From regional myocardial velocity curves the interval between QRS onset and maximal systolic tissue velocity (Ts) was measured in the basal myocardium of the septal, lateral, inferior and anterior segments. The maximal difference in Ts between the 4 segments (TsMax) was calculated as a measure of IVD. The standard deviation in Ts (TsSD) between all segments and the septal to lateral difference in Ts (TsSL) were also calculated. Patients were followed up for a median interval of 5.4 years and a Cox model was used to assess the effect of each parameter on survival.
Results: The median wall motion score index (WMSI) was 1.3 (IQR 1.0-1.8) at rest and 1.4 (IQR 1.3-1.9) at peak stress. 23 (13%) pts had wide QRS (>120msec). When defined as TsSD>32msec, 56 (30%) pts had IVD. Pts with wide QRS had more IVD than those with narrow QRS (TsSD 48±24msec vs 22±20msec, TsMax 98±47msec vs 46±42msec and TsSL 71±54msec vs 31±39msec respectively; $p<0.01$ for each). There were 41 deaths during follow-up. Deceased pts, compared to survivors, showed greater IVD (TsSD 33±22msec vs 23±21msec, TsMax 69±49msec vs 50±44msec and TsSL 50±48msec vs 34±42msec respectively; $p<0.05$ for each). Although WMSI both at rest (p=0.03) and peak stress (p=0.02), TsSD (p=0.06), TsSL (p=0.02) and TsMax (p=0.05) but not QRS duration were univariate predictors of mortality, TsSL was the only independent predictor of death (p=0.01).
Conclusion: IVD is common in pts with known or suspected CAD even in patients with QRS<120msecs. Pts with higher degrees of IVD have a reduced long-term survival, independent of WMS.

P2354 Bundle branch block is associated with worse clinical outcomes in heart failure, especially with reduced systolic function: evidence from the CHARM programme

N.M. Hawkins[1], D. Wang[2], J.J.V. McMurray[3], M.A. Pfeffer[4], K. Swedberg[5], C.B. Granger[6], S. Yusuf[7], F.G. Dunn[1] on behalf of CHARM Investigators and Committees. [1]*Stobhill Hospital, Cardiology Department, Glasgow, United Kingdom;* [2]*School of Hygiene & Tropical Medicine, Medical Statistics Unit, London, United Kingdom;* [3]*University of Glasgow, Cardiovascular and Medical Sciences, Glasgow, United Kingdom;* [4]*Brigham & Women's Hospital, Cardiovascular Division, Boston, United States of America;* [5]*Sahlgrenska University Hospital, Department of Medicine, Göteborg, Sweden;* [6]*Duke University Medical Center, Durham, United States of America;* [7]*McMaster University, Cardiology Division, Hamilton, Canada*

Background: Bundle branch block (BBB) is a powerful independent predictor of cardiovascular mortality in patients with symptomatic chronic heart failure (HF) and reduced left ventricular ejection fraction (LVEF). However, the prognostic implications in heart failure with preserved systolic function (HF-PSF) are unknown.
Methods: The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme randomized patients with symptomatic HF into one of three parallel clinical trials according to LVEF and angiotensin converting enzyme inhibitor (ACE-I) treatment: CHARM-Preserved LVEF > 0.40; CHARM-Alternative LVEF = 0.40 and ACE-I intolerant; and CHARM-Added LVEF = 0.40 and ACE-I treated. The primary outcome comprised cardiovascular death or hospital admission for worsening HF. Secondary endpoints included cardiovascular death, hospital admission for HF, and composites of the primary outcome with non-fatal myocardial infarction and stroke. The median follow-up was 37.7 months. Investigators completed a structured report on electrocardiographic findings on all patients at baseline. The relative risk conveyed by BBB compared to the normal ECG was examined in a Cox model, adjusting for up to 33 co-variates of prognostic importance.
Results: The prevalence of BBB was significantly lower in patients with preserved compared with reduced systolic function (Preserved 14.4%, Alternative 29.6%, Added 30.5%), $p<0.0001$. In the overall CHARM programme, BBB was an independent predictor of worse prognosis. The adjusted hazard ratio (HR) for the primary outcome was: 1.50 (95% confidence interval 1.23-1.83), $p<0.0001$; cardiovascular death 1.81 (1.36-2.42), $p<0.0001$; CHF hospitalisation 1.43 (1.13-1.80), p=0.0029. This reflected increased risk in patients with reduced LVEF: HR for primary outcome 1.80 (1.34-2.43), $p<0.0001$; cardiovascular death 2.23 (1.46-3.39), p=0.0002; CHF hospitalisation 1.69 (1.19-2.42), p=0.0035. The point estimate for increased risk among patients with HF-PSF was modest: HR for primary outcome 1.12 (0.83-1.51).
Conclusion: The simple clinical finding of BBB was a powerful independent predictor of worse clinical outcomes in patients with HF and reduced left ventricular systolic function.

P2355 High incidence of adverse events in patients with idiopathic dilated cardiomyopathy and inducible tachyarrhythmias

B. Brembilla-Perrot, F. Chometon, O. Marcon, C. Suty-Selton, Y. Juilliere. *CHU de Brabois, Département de Cardiologie, Vandoeuvre les Nancy, France*

The management of arrhythmias in idiopathic dilated cardiomyopathy (DCM) remains debatable. These patients are prone to ventricular and supraventricular arrhythmias; the treatment of the last arrhythmias frequently is difficult. The purpose of the study was to evaluate the clinical significance of inducible atrial tachyarrhythmias in patients with DCM.
Methods: Electrophysiological study including atrial and ventricular programmed stimulation was performed in 319 patients with DCM; all patients had a left ventricular ejection fraction < 40% (mean 30±6%); 41 patients had spontaneous ventricular tachycardia (VT); 85 patients had unexplained syncope and 126 were asymptomatic and were studied because they had nonsustained VT on Holter monitoring. Coronary angiography was normal. Programmed atrial stimulation was systematic using 1 and 2 extrastimuli delivered on 2 cycle lengths. Patients were followed 3±2 years.
Results: sustained ATA was induced in 110 patients (34%): atrial fibrillation or tachycardia in 81 patients, atrial flutter in 19 patients and paroxysmal junctional tachycardia in 10 patients. Sustained ventricular tachyarrhythmia (VTA) was induced in 94 patients (29%). The induction of ATA was the only electrophysiological finding in 28 patients with syncope. Among the patients with VTA, 34 had a bitachycardia (36%). In 48 patients induced ATA was considered as no significant, but 2 of them developed a stroke during the follow-up and 10 developed a permanent AF with occurrence of heart failure (grade III or IV of NYHA). Among the 15 patients who died of heart failure, 9 were in AF. Among the 8 patients in whom heart transplantation was performed. Among 10 sudden deaths, 5 were in AF.
Conclusion: inducible atrial tachyarrhythmia in idiopathic dilated cardiomyopathy is frequently associated with adverse events as syncope, ventricular tachyarrhythma (bitachycardia), stroke or heart failure.

VALVULAR HEART DISEASE AND SURGERY

P2356 Mitral valve surgery: the need for pacemaker implantation because of sinus node dysfunction depends on the surgical approach

P. Lukac[1], V. Hjortdal[2], A.K. Pedersen[3], P.T. Mortensen[3], H.K. Jensen[3], P.S. Hansen[3]. *[1]Slovak Cardiovascular Institute, Arrhythmia Department, Bratislava, Slovakia; [2]Aarhus University Hospital at Skejby, Department of Thoracic Surgery, Aarhus, Denmark; [3]Aarhus University Hospital at Skejby, Department of Cardiology, Aarhus, Denmark*

Purpose: To compare the need for pacemaker after mitral valve surgery using the superior transseptal and left atrial approaches.
Methods: The subjects of the study were consecutive patients (pts) who had surgery for mitral valve (MV) disease or left atrial myxoma from November 16, 1994 through January 26, 2004. The surgeons used either the superior transseptal (group A) or left atrial (group B) approaches. Pts who had a pacemaker implanted before the operation were excluded. The Danish Pacemaker and ICD Register provided information on pacemaker implantation during follow-up, the date of the implantation and the indication (sinus node dysfunction or atrioventricular conduction disturbances). Follow-up was terminated May 31, 2004. The data were analyzed as time from the operation until pacemaker implantation using the log-rank test and Cox regression analysis.
Results: Of 607 pts included, 167 were in group A and 440 in group B. Twenty-three patients had a pacemaker implanted because of sinus node dysfunction, 12 (7.2%) in group A and 11 (2.5%) in group B. The only significant univariate predictor of pacemaker implantation because of sinus node dysfunction was group A (p=0.0036). This remained the only significant predictor after adjustment for age at operation, gender and intervention performed (MV replacement, MV repair, extirpation of myxoma). Twenty-five patients had a pacemaker implanted because of atrioventricular conduction disturbances, 7 (4.2%) in group A and 18 (4.1%) in group B. The only significant univariate predictor of pacemaker implantation because of atrioventricular conduction disturbances was age>60 years (p=0.0314). This remained the only significant predictor after adjustment for surgical approach used, gender and intervention performed.
Conclusions: The superior transseptal approach is associated with a higher need for pacemaker implantation because of sinus node dysfunction, but not atrioventricular conduction disturbances.

P2357 Improvement of cardiac haemodynamics with inhaled nitric oxide after surgery in patients with mitral stenosis and severe pulmonary hypertension

J. Fernandes[1], R.O. Sampaio[2], C.M. Brandao[2], L.F. Cardoso[2], F. Tarasoutchi[2], P. Pomerantzeff[2], J.O. Auler Jr[2], M. Grinberg[2]. *[1]Campinas, Brazil; [2]Heart Institute (InCor), Sao Paulo, Brazil*

Background: Mitral stenosis is frequently associated with increased pulmonary vascular resistance (PVR), pulmonary hypertension and right ventricular dysfunction that persist even after surgery. Inhaled nitric oxide (NO) has been shown to selectively reduce PVR in patients with pulmonary hypertension. We tested the hypothesis that NO would improve the hemodynamic effects and short term clinical outcomes of patients with mitral stenosis and severe pulmonary hypertension undergoing cardiac surgery.
Methods: Twenty seven patients (3 male, 24 female) with a mean age of 46.9±12.9 years with mitral stenosis and elevated pulmonary artery systolic pressure (PASP) were randomly allocated to receive continuously inhaled NO at 10 parts per million (NO group) or oxygen therapy (control) for 48 hours immediately after surgery. Hemodynamic data, number and doses of vasoactive drugs, duration of stay in the intensive care unit (ICU) and short term complications (infections, respiratory and/or renal failure, and death) were assessed.
Results: The mean mitral valve area, gradient and PASP were 0.88±0.20cm^2, 15.7±5.0mmHg and 70.9±10.3mmHg respectively for all patients. After 48 hours patients receiving NO showed an increased cardiac index compared to patients receiving oxygen therapy with a reduction in the number of vasoactive drugs used. There was a significant reduction in PASP in both groups compared to preoperative levels but no differences were observed between the groups. A tendency towards a reduction in pulmonary vascular resistance, ICU stay and acute complications was observed in the NO group but did not reach statistical significance.

Table 1

Group (n=27)	NO (n=14)	Oxygen (n=13)	p
Cardiac Index (L.min-1.m-2)	3.93±0.9	2.65±1.3	0.03
PVR (mmHg.mL-1.min-1)	236±182	295±108	0.15
PASP (mmHg)	60±11.5	57±13.2	0.88
Vasoactive drugs (n)	2.15±0.15	2.57±0.17	0.05
ICU stay (days)	5.88±3.0	6.85±2.3	0.4
Complications (%)	29	54	0.36

Conclusions: Use of inhaled NO immediately after surgery in patients with mitral stenosis and severe pulmonary hypertension improves cardiac hemodynamics and may have clinical benefits in short term outcomes.

P2358 Correlation of tissue selectin expression and haemodynamic parameters in rheumatic mitral valve disease

L. Tokgozoglu[1], I. Can[2], P. Korkusuz[3], E. Asan[3], N. Ozer[4], M. Demircin[5]. *[1]Ankara, Turkey; [2]Selcuk University, Cardiology Department, Konya, Turkey; [3]Hacettepe University, Department of Histology and Embryology, Ankara, Turkey; [4]Hacettepe University, Cardiology Department, Ankara, Turkey; [5]Hacettepe University, Department of Thoracic Surgery, Ankara, Turkey*

Aim: The aim of this study was to examine the tissue expression of the adhesion molecules E-selectin and P-selectin on atrial and valvular endothelium of the patients with rheumatic mitral stenosis before they underwent mitral valve replacement surgery. We also investigated wether adhesion molecule expression was correlated with hemodynamics.
Methods: 13 patients (8 women, 5 men, mean age 51±10 years) with severe rheumatic mitral stenosis who underwent mitral valve replacement surgery were examined on the day before operation by cardiac catheterization and echocardiography. Specimens from mitral valve and left atrium of each patient were evaluated for CD 62E and CD 62P expression using indirect immunoperoxidase and immunofluorescent techniques
Results: A great majority of the patients presented E and/or P selectin expression of variable intensity on atrial and valvular endothelium. A more diffuse and stronger reaction for CD 62P was noted comparing to that of CD 62E. End-diastolic left ventricular diameter was positively correlated with endocardial CD 62P (r=0.85, p=0.001) and both vascular (r= 0.84, p= 0.001) and endocardial (r=0.75, p= 0.003) CD 62E expression. End-systolic left ventricular diameter was strong positively correlated with endocardial (r=0.63, p=0.02) and vascular (r=0.74, p=0.004) endothelial CD 62E expression. Left atrial diameter was positively correlated with endocardial CD 62P (r=0.74, p=0.04) and both vascular (r=0.625, p=0.02) and endocardial (r=0.74, p=0.004) CD 62E expression. Right atrial pressure presented strong positive correlation with both CD 62E (r=0.80, p=0.03) and CD 62P (r=0.8, p=0.03) endocardial expression.
Conclusion: This study presented marked tissue expression CD 62E and CD 62P on vascular, atrial and valvular endothelium and the degree of expression of adhesion molecules were significantly correlated with the left atrial and the left ventricular chamber diameters, as well as right atrial pressure. This is the first study in humans to show the correlation of hemodynamic parameters with the expression of adhesion molecules on atrial and valvular endothelium.

P2359 What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery?

M. Mirabel[1], B. Iung[2], D. Messika-Zeitoun[1], A. Cachier[1], E. Butchart[3], G. Baron[4], F. Vermeer[5], A. Vahanian[1] on behalf of the Scientific Committee. *[1]Bichat Hospital, Cardiology, Paris, France; [2]Hopital Bichat, Service de Cardiologie A, Paris Cedex 18, France; [3]University Hospital, Cardiac Surgery, Cardiff, Wales, United Kingdom; [4]Bichat Hospital, Epidemiology and Biostatistic, Paris, France; [5]Laurentius Ziekenhuis, Cardiology, Roermond, Netherlands*

Purpose: Guidelines recommend surgery in patients who present with severe, symptomatic mitral regurgitation (MR). However, little is known regarding decision for surgery in current practice. We used the data from the Euro Heart Survey on valvular heart disease to identify the proportion and characteristics of patients with severe, symptomatic, MR who were denied surgery.
Methods: Among the 5001 pts included in the Euro Heart Survey on valvular heart disease between April and July 2001, 877 had isolated MR, of whom 546 had severe MR defined as MR grade ≥ 3/4, and 437 had severe MR and symptoms, i.e. dyspnea NYHA class II or greater and/or angina.
Results: Mean age of the 437 patients was 66±12 years, 201 (46%) being aged ≥70. 39% of patients were in NYHA class I-II, 46% in class III, and 15% in class IV; 35% patients had signs of congestive heart failure at admission. Atrial fibrillation was present in 141 patients (32%). Etiology was degenerative in 238 (56%), rheumatic in 66 (15%), ischaemic in 40 (9%) endocarditis in 13 (3%), and other in 80 (18%). Left ventricular ejection fraction (LVEF) was 52±15%, it was <60% in 62% of patients and <30% in 7%. At least one comorbidity was present in 179 patients (41%). Coronary angiography was performed in 245 patients (56%) and showed significant coronary artery disease in 112 patients (46%).
It was decided against surgery in 226 patients (52%). In multivariate analysis, age ≥ 70 years (p=0.0001), LVEF < 60% (p=0.0002), congestive heart failure (p=0.0007), NYHA class II (p=0.01), and the presence of at least one comorbidity (p=0.01) were associated with the decision not to operate.
Conclusion: In this contemporary survey 1) Surgery was denied in as much as a half of patients with severe, symptomatic MR. 2) Older age and comorbidity might be valid grounds for deciding against surgery in certain cases. 3) Conversely, moderately decreased LVEF, congestive heart failure, and moderate symptoms (NYHA class II) should not lead to deny surgery according to current guidelines.

P2360 Aortic regurgitation complicated with extreme dilated left ventricle or severe depressed ejection fraction. Long-term outcome after surgery

A. Sambola[1], P. Tornos[2], A. Evangelista[2], Z. Gomez[2], A. Martin[2], G. Permanyer-Miralda[2], J. Soler-Soler[2]. *[1]University Hospital Vall d'Hebron, Cardiology, Barcelona, Spain; [2]University Hospital Vall d'Hebron, Cardiology, Barcelona, Spain*

Purpose: The long-term outcome of patients submitted to surgery for aortic regurgitation (AR) with extremely dilated left ventricle (LV) or severe depressed ejection fraction is uncertain. We assessed the outcome for AR complicated by end-diastolic dimension (EDD>or=80 mm) or EF<35%.
Methods and results: Two-hundred ten patients underwent surgical correction for pure severe AR between 1982 and 2002. One-hundred seventy patients (135 m, 35 f; age 50±14 y) underwent preoperative echocardiography. Among these pts we identified 63 pts (27%) with a preoperative EDD>or=80 mm (30 pts) or EF<35% (33 pts), (52 male/11 female; age 51±13 y). Regarding to the NYHA CF: 34 pts (54%) were in CF III-IV. Preoperative echo dimensions were: EDD 84±5; ESD 64±9; EF 41±13 y in pts with EDD>or=80 mm and EDD 75±10; ESD 60±12; EF 32±9 in pts with EF<35%. Perioperative mortality was 4 pts (6%). Follow-up was 10±6 y and no pt was lost. Overall mortality during follow-up was 24 pts (41%): (non-cardiac 2 pts and cardiac mortality was 22 pts). Causes of cardiovascular death during follow-up were: 18 pts (82%) heart failure or sudden death; 2 pts (9%) stroke; 1 pt (4.5%) aortic dissection and another pt (4.5%) infectious endocarditis. Survival rates by actuarial analysis were: 60±7% at 10 y and 42±9 at 20 y. At the end of follow-up: 24 pts (69%) were in CFI; 8 pts (23%) in CFII and 3 pt (9%) in CF III. Final echocardiographic dimensions were: EDD 58±12 mm; ESD 43±12 mm; EF 52±11% in pts with EDD>or=80 mm and EDD 62±11; ESD 44±13; EF 44±13% in pts with EF<35%.
Conclusions: Our data demonstrate that pts with AR complicated with extremely dilated LV or severely depressed EF have an increased operative risk but an acceptable long-term survival. Therefore our data suggest that surgery should not be denied on the basis of bad preoperative LV function in pts with AR.

BASIC MECHANISMS IN VALVE DISEASE

P2361 A role for mast cell-derived cathepsin G in the adverse remodelling of stenotic aortic valves

S. Helske[1], S. Aalto[2], M. Kupari[3], J. Lappalainen[1], M. Laine[3], J. Lommi[3], P.T. Kovanen[2], K.A. Lindstedt[2]. *[1]Wihuri Research Institute, Helsinki, Finland; [2]Wihuri Research Institute, Helsinki, Finland; [3]Helsinki University Central Hospital, Department of Cardiology, Helsinki, Finland*

Purpose: The pathogenesis of aortic stenosis (AS) is characterized by extensive adverse remodeling of the valves, including infiltration of inflammatory cells, extracellular matrix degradation, and fibrosis. Angiotensin II (Ang II), a powerful mediator of inflammation and fibrosis, is generated locally in the valves and may participate in the remodeling process. However, the molecular mechanisms responsible for Ang II-generation and collagen deposition in stenotic valves are poorly understood. Here we analyze whether cathepsin G, an Ang II-forming enzyme with a potent elastolytic activity, is present in aortic valves and may contribute to AS progression.
Methods: Stenotic aortic valves (n=86) were obtained from patients undergoing valve replacement surgery and control valves (n=17) from cardiac transplantations. Cathepsin G, transforming growth factor-β (TGF-β), collagens I and III, and the valvular collagen/elastin ratio were analyzed by RT-PCR, immunohistochemistry or histochemistry. Colocalization of mast cells and cathepsin G was studied with double immunofluorescence and confocal microscopy. Cultured human mast cells were stimulated with cigarette smoke and histamine release of the cells was determined by fluorometry.
Results: Cathepsin G was present in mast cells and showed an increased expression ($p<0.001$) in stenotic aortic valves. Moreover, TGF-β, collagens I and III mRNA levels were upregulated ($p<0.001$), and correlated positively with cathepsin G expression. TGF-β protein was found particularly in mast cell-rich areas of the stenotic valves. The collagen/elastin-ratio was increased in stenotic valves ($p<0.001$), and correlated positively with smoking ($p<0.05$). Cigarette smoke directly activated cultured human mast cells. A striking pattern of elastin degradation was observed in stenotic valves containing activated, cathepsin G-secreting mast cells, and in normal valves treated with cathepsin G in vitro.
Conclusions: In stenotic aortic valves, activated mast cells show increased expression and secretion of cathepsin G in parallel with increased TGF-β expression, collagen synthesis, and elastin degradation. An increased collagen/elastin-ratio in stenotic valves associated with smoking, a trigger of mast cell activation. Thus, cathepsin G secreted by activated mast cells may induce adverse valve remodeling in AS.

P2362 The association of the vitamin D receptor polymorphism and calcific aortic and mitral valve stenosis

M.M.A.M. Salama[1], E. Mashhour[2], M. Abou Freikha[3], H. Kassem[4], S. Atia[4]. *[1]Tanta, Egypt; [2]tanta university, Clinical pathology, tanta, Egypt; [3]tanta university, internal medicine, tanta, Egypt; [4]Tanta University Hospital, Cardiology Dept., Tanta, Egypt*

Background: Vitamin D receptor (VDR) polymorphism is a markerof linkage distribution with another gene involved in calcium metabolism. This as yet unknown gene might be important for osseous and extraosseous calcification.
Objective: To detect the hypothesis that vitamin D receptor polymorphism is associated with calcific aortic valve stenosis and whether such polymorphism may have impact of calcific rheumatic mitral valve disease.
Methods: The study included 68 subjects divided into 3 groups:group I(20 healthy controls); group IIA (9 patients with calcific mitral stenosis); group IIB(7 patients with calcific mitral restenosis) and group III(32 patients with calcific aortic stenosis). All patients and controls were subjected to full history taking and clinical examination, ECG, X ray chest, echocardiography and cardiac catheterization (when indicated) Vitamin D receptor polymorphism was also assessed for all subjects using polymerase chain reaction.
Results: Vitamin D receptor B allele showed significantly higher prevelance in group IIA and IIB than controls ($p<0.05$); while the BB genotype reported higher, yet nonsignificant,frequency compared with controls($p>0.05$). In group III, both Vitamin D receptor B allele and BB genotype were significantly higher than controls ($p<0.05$).
Conclusions: Vitamin D receptor polymorphism is associated with calcific aortic valve and mitral valve stenosis. The B allele of vitamin D receptor was significantly more common in patients with calcific aortic valve stenosis and calcific mitral stenosis and restenosis.
The difference was significant in genotype BB in patients with aortic stenosis yet non significant in the calcific mitral stenosis and restenosis group.

P2363 Heart type fatty acid protein (H-FABP) predicts the progression of left ventricular hypertrophy in mild aortic stenosis

M. Iida[1], K. Kamiya[2], H. Honjo[2], I. Kodama[2]. *[1]Mitsubishi Nagoya Hospital, Cardiology, Nagoya, Japan; [2]School of Medicine, Nagoya University, Department of Circulation, RIEM, Nagoya, Japan*

[Purpose] Heart type fatty acid binding protein (H-FABP), a soluble cytoplasmic protein abundant in cardiac myocytes, has been recognized as a marker of ongoing myocardial damage even in non-ischemic heart failure. The protein may leak into the blood circulation following myocardial injury or remodeling process in pressure overloaded hearts. The aim of this study is to evaluate the predictive value of H-FABP for the progression of left ventricular (LV) hypertrophy overtime in patients with aortic stenosis. [Methods] H-FABP, troponin T, brain natriuretic peptide (BNP), LV wall thickness (LVWT) and aortic jet velocity were measured in mild aortic stenosis (AS, n=62), healthy subjects (control, n=25). We prospectively followed up the patients for 2 years, and re-examined echocardiography to assess the progression of LVWT and aortic jet velocity. [Results] At initial assessments, troponin T levels were below cut-off levels in all the participants. H-FABP levels were significantly ($p<0.05$) greater in AS (4.8±3 ng/ml) than in control (2.7±1) as well as BNP (77±81 pg/ml vs. 14±8). H-FABP levels were significantly correlated with BNP levels in AS (r=0.35), but not in control. Follow-up assessments revealed that LVWT increased in 23 patients (23%, from 1.0±0.1 to 1.2±0.1 cm), and aortic jet velocity increased in 17 patients (27%, from 2.25±0.59 to 2.55±0.74 m/s). The predictors of these increments overtime were examined using a multivariate logistic regression model including age, gender, the initial values of BNP, H-FABP, and aortic jet velocity. The strongest independent predictor of LVWT increments was H-FABP (chi-square= 4.11, p=0.04), in contrast, the strongest predictor of aortic jet velocity increment was BNP (chi-square= 9.4, p=0.001). [Conclusion] H-FABP, associated with BNP, predicted the progression of LV hypertrophy in patients with mild aortic stenosis.

P2364 Direct enumeration of endothelial progenitor cells in patients with heart valve disease

J. Terrovitis[1], P. Batten[2], F. De Robertis[3], A. Khaghani[3], A. Chester[1], P. Taylor[1], M. Yacoub[1]. *[1]Imperial College, London, United Kingdom; [2]Imperial College, London, United Kingdom; [3]Royal Brompton and Harefield NHS Trust, London, United Kingdom*

Endothelial progenitor cells (EPCs) circulating in the peripheral blood are thought to participate in reparative mechanisms after tissue injury. Their numbers increase after coronary artery revascularization; however enumeration of these cells up to now have been indirect, derived from their percentage in relation to the total white blood cell counts, therefore introducing multiple potential sources of errors.
Purpose: In the present study we have determined direct absolute counts of EPCs using the FACSAria flow cytometer in patients undergoing cardiac surgery for heart valve disease (HVD) without concomitant coronary artery disease (CAD) and for patients with CAD.
Methods: 25 consecutive patients (65±11yrs) were enrolled (18 with CAD and 7

with HVD). 200μl of whole blood, obtained at baseline, 6h, 24h and 5d after sternotomy, were stained with anti-CD45-APC, CD34-PerCPCy5 and CD133-PE directly conjugated antibodies. Direct absolute numbers of EPCs (CD34+/CD133+) were obtained using TruCount flow cytometry method.
Results: HVD patients had consistently higher numbers at all time points, although the difference was statistically significant only at baseline (p=0.004). Baseline EPC numbers were negatively correlated with age (Pearson correlation=-0.386, p=0.057). A significant increase in EPC numbers was found at 6h and 5d after sternotomy (p<0.01), with a transient decrease at 24h (Table). Both HVD and CAD patients (67±8 yrs vs 64±12 yrs respectively, p=0.487) demonstrated this pattern of response and the magnitude of change was comparable. The use of cardiopulmonary bypass was associated with higher EPC numbers at 6 hours (1.20±0.67/μl vs 0.66±0.24/μl, p=0.026).

Table

	Age (yrs)	EPC baseline (/ul)	EPC 6hr (/ul)	EPC 24hr (/ul)	EPC 5d (ul)
Whole cohort (n=25)	65±11	0.65±0.40	0.97±0.59*	0.62±0.45	1.04±0.60*
CAD (n=18)	64±12	0.51±0.29	0.85±0.50*	0.61±0.50	0.89±0.46*
HVD (n=7)	67±8	1.00±0.46	1.33±0.74	0.63±0.33	1.38±0.76

*p<0.05 vs baseline

Conclusion: This study documents for the first time the markedly elevated number of EPCs in patients with valve disease, which could have important implications for pathogenesis and possibly therapy.

P2365 The 5A/5A polymorphic allele MMP-3 gene is associated with increased left ventricular remodelling in patients with severe degenerative mitral regurgitation

M.R. Yusoff[1], D. Oceandy[2], L. Neyses[2]. [1]*University Hospital of South Manchester, Cardiology Dept., Manchester, United Kingdom;* [2]*University of Manchester, Division of Cardiology, Rm 1.302, Manchester, United Kingdom*

Matrix metalloproteinases (MMP's) play an important role in the process of left ventricular remodelling in heart failure through degradation of a wide range of extracellular matrix proteins. However, their role in determining ventricular and mitral annulus dilatation in mitral valve prolapse (MVP) is unclear. We therefore studied the role of MMP1 and MMP3 polymorphisms in left ventricular remodelling in patients with MVP.
48 patients with MVP had a full 2D echo and measurements were made according to the recommendations of the American Society of Echocardiography. Left ventricular mass and left atrial volume were indexed to body surface area. Polymorphisms in the promoter regions of MMP1 (-1607 1G/2G) and MMP3 (-1171 5A/6A) were determined by PCR and restriction enzyme digestion.
All patients had severe mitral regurgitation (regurgitant fraction >50%), 75% were in NYHA I/II and 25% in NYHA III. There was no association between polymorphism in the MMP1 gene and cardiac phenotype. In contrast, we found that the MMP3 (-1171 5A/6A) polymorphism was associated with left ventricular remodelling. 5A/5A homozygote patients had a larger end-diastolic dimension (P<0.01), left ventricular mass index (P<0.01), left atrial volume (P<0.01) and mitral annulus (P<0.01). These patients also had larger regurgitant volumes (P<0.05).
Thus, the 5A/5A polymorphic allele, which is associated with a more active promoter of MMP3 gene, is associated with more extensive left ventricular remodelling, mitral annular dilation and increased mitral regurgitation. This data identifies the 5A/5A MMP3 polymorphism as a possible novel marker of an adverse disease course in MVP.

P2366 Effects of statins on soluble CD40 ligand, high-sensitive C-reactive protein and interleukin-6 levels in patients with aortic stenosis: establishing a cause-effect relationship

L. Moura[1], J. Zamorano[2], L. Mataix[2], S. Ramos[3], L.F. Azevedo[3], L. Perez de Isla[2], F. Monteiro[3], F. Rocha Goncalves[3]. [1]*Oporto, Portugal;* [2]*Madrid, Spain;* [3]*Oporto, Portugal*

Background: Several large-clinical studies demonstrated that markers of inflammation, such as high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and soluble CD40 ligand (sCD40L), are potent and independent predictors of vascular risk. The aim of the present study was to assess prospectively the effect of statin therapy on the hemodynamic progression of AS and to evaluate the impact of this treatment on prothrombotic and inflammatory markers from baseline to 6 months follow-up.
Methods: Open-label, observational, prospective study. 82 consecutive patients with asymptomatic AS (age 73,1±9,4 years; 42 men). Patients (pts) required normal LVF, peak velocity > 2,5 m/s with an echo performed every 6 months. 42 pts (51%) received rosuvastatin 20 mg according to NCEP-ATPIII guidelines; 40 (49%) did not. Cholesterol profile, hsCRP, IL-6, sCD40L, NTF and BNP serum levels were obtained.
Results: In treated pts, the annualized change in peak post valve velocity was 0,05±0,25m/s vs 0,18 ± 0,27m/s for non-statin pts (p=0,025). During follow-up, statin therapy reduced sCD40L levels by 24% while a small decrease of 1,3% was observed among non-statin pts (p=0,023). No correlation was observed between change in LDL-cholesterol and change in sCD40L levels (p>0,101). There was a weak correlation between change in peak post valve velocity and change in sCD40L levels (r=-0,240; p=0,032). In stepwise multiple linear regression the independent predictors of change in sCD40L were statintherapy and change in peak post valve velocity.A reduction in median IL-6 levels by 51,9% was observed in statin treated pts and a median decrease of 46,2% in non-statin pts (p=0,888). There was no correlation between change in peak post valve velocity and change in IL-6 levels (r=0,031; p=0,785). Statin therapy reduced median hsCRP levels by 28% while a small decrease of 19% was observed among non-statin pts (p=0,523). No significant association was observed between baseline hsPCR and baseline LDL-C levels over time (r=0,118; p=0,281) or between change in hsCRP levels and change in LDL levels (p=0.13). There was no correlation between change in post valve velocity and change in hsCRP levels (r=-0,114; p=0,312).
Conclusions: In this short-term prospective study, we found an association between the rate of AS progression and statin use independent of changes in cholesterol serum levels and inflammatory markers (hsCRP,IL-6), that may be related with reduced thrombogenesis (reduced sCD40L)).

P2367 Proinflamatory cytokines are elevated in rheumatic chronic severe aortic regurgitation, and not correlated with symptoms

G.S. Spina[1], F. Tarasoutchi[2], R.O. Sampaio[2], M. Katz[2], L. Guilherme[2], A.C. Pereira[2], M. Grinberg[2]. [1]*Heart Institute(InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil;* [2]*Heart Institute(InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil*

Background: Proinflamatory cytokines has been implied in the physiopathology of heart failure. We determined for the first time behaivour of proinflamatory cytokines and their antagonists in patients with chronic severe aortic regurgitation (AR).
Methods: We analised 89 patients with AR mean age 33±11y, 84.6% male, 60% asymptomatic, all of rheumatic etiology and 12 healthy controls. Patients were evaluated clinically and by ecocardiography. Mean values were: left ventricular (LV) diastolic diameter (DD) 71.9±8.3mm, LV systolic diameter (SD) 50.4±9.3mm and LV ejection fraction 0.64±0.11. We mesured the plasma levels of tumor necrosis factor-alpha (TNF), its soluble receptors type I and II (sTNFRI and sTNFR II), Interleukin 6 (IL-6), its antagonists, Interleukin 1-beta receptor antagonist and endothelin-1.
Results: Plasma TNF levels were significantly increased in AR patients in relation to normal controls (92.65±110.24 pg/ml vs 1.67±1.21 pg/ml, p<0.001), similar to IL-6 (7.17±7.78pg/ml vs 0.81±0.38pg/ml, p=0.0001) and sTNFRI (894.75±348.87pg/ml vs 521.42±395.13pg/ml, p=0.007). There was a significant correlation between sTNFRII and LVDD (r=-0,329, p=0,038) and LVSD (r=-0,352, p=0,027). Levels of cytokines were similar in asymptomatic and sympromatic AR patients (table 1)

Cytokine levels in AR patients

	Asymptomatic	Symptomatic	p
TNF (pg/ml)	86.9±85.2	103.5±141.4	0.21
sTNFRI (pg/ml)	906.8±299.6	881.4±404.5	0.52
sTNFRII (pg/ml)	1868.7±530.5	1891.7±675.9	0.99
IL-6 (pg/ml)	6.5±7.4	8.3±8.4	0.26
IL6-R(ng/ml)	33.6±12.5	34.5±6.9	0.42
IL1-RA(pg/ml)	134.1±230.2	19.8±60.1	0.10
ET-1 (pg/ml)	7.0±5.1	7.6±8.3	0.44

TNF = tumor necrosis factor alpha, sTNFRI = soluble TNF receptor type I, sTNFRII = soluble TNF receptor type II, IL-6 = Interleukin-6, sIL6R = Soluble interleukin-6 receptor, IL1-RA = Interleukin1 receptor antagonist, ET-1 = Endothelin-1.

Conclusion: AR patients have increased plasma levels of proinflamatory cytokines in relation to normal controls, regardless of symptoms. In patients with severe AR, sTNFRII levels were negatively correlated with an increase in ventricular diameters.

P2368 Absence of cytomegalovirus, Helicobacter pylori and Chlamydium pneumoniae DNA in human aortic valves

G. Latsios[1], N. Michalopoulos[1], A. Saetta[2], E. Agapitos[2], E. Patsouris[2], C. Stefanadis[3]. [1]*Athens, Greece;* [2]*University of Athens, Pathology, Medical School, Athens, Greece;* [3]*Ippokration General Hospital of Athens, Cardiology, Athens, Greece*

Background: Inflammation and immune mechanisms are considered important mechanisms for the pathogenesis non-rheumatic aortic valve stenosis (AVS). In seroepidemiological studies various micro-organisms have been associated with human atherosclerosis, including Cytomegalovirus (CMV), Helicobacter pylori (HP) and mainly Chlamydium pneumoniae (CP). By means of immunohistochemistry, in-situ hybridization or polymerase chain reaction, all of these organisms have been demonstrated in atherosclerotic lesions.
In the present study we tried to detect the presence of genetic material of CMV, HP or CP in samples of atherosclerotic plaques with the sensitive method of the polymerase chain reaction –PCR

Methods: We studied twenty-two samples of aortic valves, all derived from aortic valve replacement due to valve stenosis. For the detection of CMV, HP and CP the reliable and exceptionally sensitive method of polymerase chain reaction – PCR was used, with primers specific for the CMV, HP and CP genome.
Results: Despite the fact that the positive control reactions for CMV, HP and CP always resulted in strongly positive PCR products we failed to detect DNA of these organisms in the aortic valve specimens that we studied.
Conclusions: In our material we failed to demonstrate the presence of Cytomegalovirus (CMV), Helicobacter pylori (HP) and Chlamydium pneumoniae (CP) in aortic valve specimens. We believe that more extensive studies should be undertaken in order to further shed light on these results.

P2369 Gene-profilling: statins reduce inflammation on calcified stenosed aortic valves

T. Anger[1], F.K. Pohle[2], T. Barthel[2], T. Fischlein[3], W.G. Daniel[2], S. Achenbach[2], C.D. Garlichs[2]. *[1]Friedrich- Alexander Universitaet, Medizinische Klinik II - Kardiologie, Erlangen, Germany; [2]Friedrich-Alexander Universitaet, Medizinische Klinik II - Kardiologie, Erlangen, Germany; [3]Friedrich- Alexander Universitaet, Department for cardiac surgery, Erlangen, Germany*

Sclerotic calcification of the aortic valve is a common disease in advanced age. However, pathophysiologic processes leading to valve calcifications are poorly understood and therapeutic interventions other than valve replacement in advanced disease are unknown. In previous studies, we performed gene-profiling on calcified stenotic aortic valves (CSAV) and compared gene expression with the typical pattern found in atherosclerotic lesions in order to define inflammation as a main trigger for calcification in CSAV. Since statins are known to inhibit inflammation and the progression of atherosclerotic lesions we tested the hypothesis that statins reduce inflammation on CSAV seen in gene expression using microarray technique. We investigated three groups of valves: CSAV of patients with (AS+; n=4) and without (AS-; n=4) statin therapy prior to valve replacement, and non-calcified, non-stenotic valves of patients with aortic regurgitation as controls (AR; n=4). We performed gene-profiling using microarray technique and real-time PCR for transcriptional verification. Fluorescence intensity changes between two groups on one microarray- slide were brought to significance when ratio was below 0.5 or above 2.0. Immunohistochemistry staining of valves was used to confirm translational markers for inflammation. In comparison to the control, analysis of AS- explored several markers of inflammation significantly altered in gene expression. However, statins therapy in the history prior to valve replacement influenced found gene expression markedly. Significantly upregulated genes in AS-/AR were neutralised in AS+/AR, i.e. Monokine induced by gamma Interferon (AS-/AR: 2.8 vs. AS+/AR: 0.8), Interferon Receptors (2.4 vs. 1.1), Chemokine Eotaxin3 (2.6 vs. 0.2), Interleukin 16 (2.8 vs. 1.8), Vascular Adhesion Protein 1 (3.4 vs. 1.2), Complement c5 (2.6 vs. 1.7), Complement c1 (3.3 vs. 1.6) or Peroxisome proliferative activated Receptor alpha (2,1 vs. 1,1). In contrast, significantly downregulated genes in AS- were neutralised in AS+ as well, i.e. Vascular Cell Adhesion Molecule-1 (0.4 vs. 1.2), Interleukin 4 (0.3 vs. 1.2), Tissue Inhibitor of Metalloproteinase 3 (0.4 vs. 0.8) or Caspase 8 (0.3 vs. 0.6). Apparently, statins play a major role as effectors of inflammation on calcified stenotic aortic valves demonstrating significant reduction of markers of inflammation on CSAV in-vivo. Therapeutic use of statins could inhibit inflammation on valves, reduce progression of calcifications, prolong survival and reduce mortality.

HYPERTROPIC CARDIOMYOPATHY

P2370 Inducibility in electrophysiologic study does not predict appropriate interventions of implantable cardioverter/defibrillators in patients with hypertrophic cardiomyopathy

H. Buschler, L. Faber, J. Vogt, J. Heintze, C. Hoppe, B. Lamp, D. Horstkotte. *Heart Center NRW, Ruhr Univ Bochum, Department of Cardiology, Bad Oeynhausen, Germany*

Background: Sudden cardiac death (SCD) is a feared complication of hypertrophic cardiomyopathy (HCM). Due to the fact that nearly all patients (pts.) fail to survive their first episode of ventricular fibrillation (VF), risk stratification is important. A family history of SCD, recurrent syncopes, nonsustained ventricular tachycardia (VT) on Holter monitoring, severe left ventricular hypertrophy, and abnormal blood pressure response to exercise have been identified as main risk factors (RFs). The purpose of this study was to investigate the impact of VT/VF inducibility during electrophysiologic study (EPS) on the frequency of adequate ICD interventions in HCM pts. implanted for primary prevention.
Methods: Since 2001 27 pts. with at least two main RF received an ICD for primary SCD prevention. Before implantation, EPS was performed with a cycle length of 500 ms with up to 3 extrastimuli at the right ventricular apex and outflow tract. The decision to implant the ICD was independent of the EPS result. After implantation the ICDs were interrogated at 3 to 6 months intervals.
Results: Sustained polymorphic VT or VF was induced in 14 pts. (group A). Group B consists of 13 pts. with negative EPS. Clinical characteristics are shown in Table 1. The distribution of RFs was comparable in both groups.

Table 1

	Group A	Group B	P value
Age (years)	40.7±14.5	42.4±15.9	n.s.
NYHA class	1.5±0.6	1.5±0.5	n.s.
Number of RFs	2.3±0.5	2.3±0.6	n.s.
LVEF (%)	78.6±12.5	78.2±10.3	n.s.
Duration of follow-up (months)	16.1±10.1	17.3±11.5	n.s.
Adequate ICD interventions (number/pts)	7/3	7/4	n.s.

Conclusions: In our cohort of pts. with HCM and ICD implantation for primary prevention the inducibility of VT or VF during EPS did not correlate with the frequency of adequate ICD intervention during follow-up.

P2371 Hypertrophic cardiomyopathy: abnormal blood pressure response in exercise is not a consistent finding

A. Anastasakis[1], C. Kotsiopoulou[2], A. Theopistou[2], E. Sevdalis[2], N. Mammalis[2], N. Protonotarios[2], C. Stefanadis[2]. *[1]University of Athens, Cardiology Department, Athens, Greece; [2]University of Athens, Cardiology Department, Athens, Greece*

Introduction: Abnormal blood pressure response (ABPR) during exercise, defined as hypotension or failed blood pressure increase (<20 mmHg) with exercise, is common in young hypertrophic cardiomyopathy (HCM) patients and has been associated with an increased risk of sudden cardiac death. The aim of the present study was to identify, in a series of exercise tests, the consistency of this valuable risk factor for young, HCM patients.
Methods: 60 young patients (age: 24.8±11.1years, 37 males and 23 females, left ventricular wall thickness: 19.2±3mm) with an ABPR at their first exercise test, were selected to further undergo a series of 4 cardiopulmonary exercise tests with 3-months interval between tests. All patients were subjectively asymptomatic (peak oxygen consumption (pVO2): 68±11% predicted VO2), with no obstructive HCM. They had no indications for symptomatic treatment and no other risk factors. All patients exercised to the point of exhaustion using a maximum symptom-limited ramp cycle ergometer exercise test with simultaneous gas exchange analysis and ECG monitoring. Blood pressure was recorded by the same physician at 1-minute intervals during the exercise and the recovery periods with a mercury sphygmomanometer.
Results: The results show that ABPR was consistently detected at all 4 exercise tests in only 6 out of 60 patients (10%), whereas 13%, 57%, and 20% of the patients had 3, 2 and 1 abnormal blood pressure responses, respectively, in the series of the 4 exercise tests that performed (Table 1).

Table 1

No. of ABPRs	No. of Patients (%)
1	12/60 (20%)
2	34/60 (57%)
3	8/60 (13%)
4	6/60 (10%)

Conclusion: Abnormal blood pressure response in exercise is not a consistent finding. Therefore, it could be wise to risk stratify the patient, considering the blood pressure response, in less than a year intervals.

P2372 A screening strategy based on the analysis of beta-myosin heavy chain, cardiac myosin binding protein C and cardiac troponin T in a large consecutive cohort with hypertrophic cardiomyopathy

F. Girolami[1], I. Olivotto[2], I. Passerini[1], D. Vargiu[3], F. Torricelli[1], F. Cecchi[3]. *[1]Az Ospedaliera Universitaria Careggi, Cytogenetics Unit, Firenze, Italy; [2]Firenze, Italy; [3]Azienda Ospedaliera Careggi, Cardiology Unit II S. Luca, Florence, Italy*

Background: Mutations causing hypertrophic cardiomyopathy (HCM) have been described in ten different genes of the sarcomere. However, most known mutations have been found in three genes: the Beta-Myosin Heavy Chain (MYH; MIM#160760), the Cardiac Myosin Binding Protein C (MYBPC3; MIM#600958), and the Cardiac Troponin T (TNNT2; MIM#191045). An initial approach to genetic screening of HCM based on the analysis of these 3 genes has been advocated. Thus, we prospectively assessed a screening strategy based on the comprehensive evaluation of MYBPC3, MYH7 and TNNT2 in a consecutive population with HCM.
Methods: A total of 163 unrelated HCM patients were screened in the exons and splice sites of MYBPC3, MYH7 and TNNT2 by DHPLC followed by automatic sequencing.
Results: We identified 54 mutations in 82 index patients (50% of the study cohort); 37 were novel. The prevalence rates for MYBPC3, MYH7 and TNNT2 were 34%, 12% and 4%, respectively. MYBPC3 mutations were 35, including 7 frameshift, 7 splice-site and 3 nonsense. The 35 mutations clustered more commonly within three specific domains, i.e. the C3, the C6 and the MyBP-C motif.All were "private" except E542Q, IVS24-2 A>G, insC1065, R502Q, M555T, and IVS12+1G>A, which were present in 2-5 unrelated patients. Moreover, E258K

was found in 12% of the patients, suggesting a founder effect. One patient was homozygous for a MYBPC3 mutation. MYH7 mutations were 13, all missense; 8 were novel. In TNNT2, only 5 missense mutations and one codon deletion were found. Ten patients carried a double mutation within the MYBPC3 gene (n=6), or were double heterozygous for a MYBPC3 mutation associated with a mutation in MYH7(n=3) or TNNT2 (n=1).
Conclusions: Mutations of MYH7, MYBPC3 and TNNT2 accounted for 50% of patients in a consecutive Italian HCM cohort. Thus, the combined analysis of these 3 genes represents a rational and cost-effective initial approach to genetic screening of HCM.

P2373 Investigations in the clinical value of endomyocardial biopsy (EMCB) in patients with hypertrophic non obstructive cardiomyopathy (HNCM)

G. Beer[1], N. Stoevesandt[2], C. Strunk-Mueller[2], T. Lawrenz[2], H. Kuhn[2]. *[1]The Bielefeld Klinikum, Department of Cardiology, Bielefeld, Germany; [2]The Bielefeld Klinikum, Department of Cardiology, Bielefeld, Germany*

In pts with HNCM there is debate about the clinical value of EMCB. Systematic studies employing EMCB in consecutive pts with HNCM and additional "blinded evaluation" are lacking.
Methods: We performed for the first time a systematic study in 100 consecutive pts with HNCM (62 men and 38 women; mean age 56 years) by right ventricular EMCB. Additionally we investigated in a blinded prospective study a group of 100 consecutive symptomatic pts with 7 different cardiac disorders (for example pts with dilated cardiomyopathy, hypertensive heart disease, valvular aortic stenosis, coronary heart disease, hypertrophic cardiomyopathy (HCM)) by EMCB. In these pts the pathologist performed a "blinded evaluation" of the EMCB (i. e. the final written report of the pathologist was performed without any clinical information). If the pathologist regarded an EMCB finding as characteristic for HNCM, he stated a diagnosis of HCM on the basis of morphological alterations. In all pts EMCB (4 to 5 EMCB per pt) was performed during the diagnostic coronary angiogram and ventricular angiogram. All EMCB were evaluated by electron (EM) and light (LM) microscopy.
Results: LM alterations in the 100 pts with HNCM showed the unspecific findings of interstitial fibrosis and myocyte hypertrophy. The frequency and extent ofthese alterations differed not from the 100 pts with different cardiac disorders who were evaluated in a "blinded fashion". In 3/100 pts (3%) with HNCM the surprising result of EMCB revealed Amyloid heart disease and in 7/100 (7%) pts the diagnosis of concealed cardiac Fabry disease. In 10/100 pts of the "blinded study", the pathologist stated a diagnosis of HCM on the basis of EMCB because he suspected the morphological alterations to be characteristic for HCM. However in none of this 10 pts (0%) the diagnosis was correct.
Conclusion: The clinical value of EMCB in HNCM is to exclude or diagnose concealed cardiac storage disease, mostly on the basis of EM evaluation. In 10% of consecutive pts with HNCM, EMCB revealed the surprising result of concealed cardiac storage disease with important prognostic and therapeutic consequences for the individual pt (enzyme replacement therapy in Fabry disease, chemotherapy in Amyloid heart disease). In a subgroup of pts with HNCM, a causal therapy is initiated on the basis of EMCB. Considering the small risk of EMCB additional to the diagnostic invasive coronary angiography and ventricular angiogram, EMCB with additional EM seems to be indicated in all symptomatic pts with HNCM to exclude or diagnose concealed storage disease.

P2374 MYBPC3 gene mutations are associated with high risk of arrhythmic events in patients with hypertrophic cardiomyopathy

M. Pasotti[1], M. Tagliani[2], C. Lucchelli[2], M. Grasso[2], E. Porcu[2], N. Marziliano[2], L. Tavazzi[3], E. Arbustini[2]. *[1]Pavia, Italy; [2]I.R.C.C.S. Policlinico San Matteo, Cardiovascular genetics, Pavia, Italy; [3]San Matteo Hospital, Cardiology, Pavia, Italy*

Background: Preliminary data on genotype-phenotype correlations in patients diagnosed with hypertrophic cardiomyopathy (HCM) showed that myosin-binding protein C (MYBPC3) gene mutations are associated with late-onset disease characterized by mild hypertrophy and relatively good prognosis. Beta myosin heavy chain (MYH7) gene mutations have been originally associated with early-onset disease characterized by severe hypertrophy and bad prognosis while HCM caused by troponin T (TNNT2) gene mutations by high arrhythmogenic risk.
Aim: Aim of the present study was to record events [all deaths, heart transplant (HTx), congestive heart failure (CHF) evolution, implantable cardioverter-defibrillator (ICD) implantation] in genotyped patients diagnosed with HCM according to WHO criteria.
Methods and Results: One hundred sixty-eight unrelated probands (107 males, mean age 41±24 years) diagnosed with HCM and 342 relatives underwent clinical evaluation and molecular genetic analysis. We identified 38 carriers of MYH7, 94 of MYBPC3, 6 of TNNT2 gene mutations and 10 carriers of double heterozigosity (n=6) and compound heterozigosity (n=4)(mean age 36±13, 40±15, 43±17, 43±15 years respectively, p=NS). After 60±21 months from diagnosis, 29/38 carriers of MYH7 gene mutations (76%) are affected: among them we recorded 10 events (34%): one sudden cardiac death (SCD); 6 HTx, one ICD implantation for ventricular arrhythmias and 2 CHF evolution. The remaining 19 (66%) patients are in stable clinical conditions, 10 in NYHA class I and 9 in NYHA class II. Of 94 carriers of MYBPC3 gene mutations, 62 (66%) are affected: among them we recorded 28 (45%) events: 10 SCD, 2 CHF deaths, 13 ICD implantation and 3 CHF evolution. The remaining 34 (55%) patients are in stable clinical conditions, 23 in NYHA class I and 11 in NYHA class II. Of 6 carriers of TNNT2 gene mutations, one underwent ICD implantation while the remaining 5 are stable in NYHA class I. Of the 10 carriers of double mutations, we recorded 7 (70%) events: one CHF death, 2 CHF evolution, 3 HTx and 1 ICD implantation. The remaining three patients are stable, in NYHA class I.
Conclusions: Our data suggest that MYBPC3 gene carriers are at high risk to develop arrhythmic events (23/62, 37%), at least analogously to other disease-gene mutations. However, the evaluation of larger series of genotyped patients is necessary before reliable genotype-phenotype correlation data can be used for prognostic stratification and genetic counseling.

P2375 Is myocardial bridging a determinant of sudden death in hypertrophic cardiomyopathy?

C. Basso[1], B.J. Maron[2], D. Corrado[3], J.L. Titus[4], G. Thiene[1]. *[1]University of Padua (Padova) Medical School, Institute of Pathological Anatomy, Padua, Italy; [2]Minneapolis Heart Institute Foundation, Minneapolis, United States of America; [3]Cardiology, University of Padua, Padova, Italy; [4]Jesse Edwards Cardiovascular Registry, St Paul, United States of America*

Background: Although myocardial bridging (MB) of the left anterior descending (LAD) coronary artery has been associated with myocardial ischemia and sudden death (SD) in young patients with hypertrophic cardiomyopathy (HCM), its prevalence in different age groups is unresolved and its overall significance remains controversial.
Methods: The files of two pathology cardiac registries were searched for diagnosed cases of HCM. A total of 105 hearts were enrolled (32 female and 73 male, ages ranging 1 day-90 yrs, mean 30 ± 21). Hearth weight and septal thickness were 465±208 g and 19±6 mm, respectively. Mode of death/failure was SD in 67 (64%), heart failure (HF) in 27 (27%) (14 with heart transplantation), early postsurgical death in 2 (myectomy), infective endocarditis in 1 and extracardiac causes in 6.
Results: A MB of the LAD was present in 40 (38%) of 105 HCM pts, compared to 21 (21%) of 100 consecutive controls who died of causes unrelated to HCM (p= 0.01). MB was present in 39% of SD cases, 41% of HF, and 33% of pts who died of extracardiac causes p=NS). The prevalence of MB in different age groups was ranging from 20% in pts aged <10 yrs to 57% in pts aged 20-30 yrs. A higher prevalence was found among pts aged >20 yrs (46%) than pts <20 yrs (26%, p=.05), whereas no difference was found specifically among SD pts aged >20 (41%) as compared to those <20 yrs (38%,p=NS). No correlation was found between the presence of MB and either septal thickness or heart weight. MB had a mean length of 14.8±6.6 mm and a mean thickness of 2.0±1.5 mm. No correlation was found between MB thickness and heart weight and septal thickness, whereas the longer the MB the greater the MB thickness. At histology, MB more frequently consisted of a sheath of myocardial fibers totally encircling the coronary vessel (71%) than of a few superficial fibers transversally oriented (29%).
Conclusions: In HCM, MB was present at postmortem in a sizeable minority of pts (i.e., more than one-third). However, MB prevalence in HCM did not differ between HCM pts with sudden or other modes of death, nor with respect to age and gender. Our preliminary findings do not support the hypothesis that MB represents "per se" a prognostic marker for sudden death in young HCM pts.

P2376 MRI study of contractile function, perfusion and delayed contrast enhancement in 52 patients with hypertrophic cardiomyopathy

J. Garcia de Lara[1], R. Soler[2], E. Rodriguez[2], J. Peteiro[3], P. Pinon[1], B. Bouzas[1], A. Castro-Beiras[3], L. Monserrat[4]. *[1]CHU Juan Canalejo, Cardiology Department, A Coruña, Spain; [2]CHU Juan Canalejo, Radiology Department, A Coruña, Spain; [3]RECAVA, Cardiovascular research network, A Coruña, Spain; [4]CHU Juan Canalejo, A Coruna, Spain*

Background: MRI provides detailed infomation about morphology and function in hypertrophic cardiomyopathy (HCM), including myocardial perfusion and fibrosis.
Objective: To analyze the relation between contractile function, first-pass perfusion and delayed contrast enhancement with clinical, morphological and functional findings in HCM.
Methods: We studied wall thickness, first pass perfusion, motility (by tissue tagging) and delayed contrast enhancement by MR in 884 myocardial segments of 52 HCM patients. Clinical, echocardiographic, exercise test, Holter and follow up data were collected in a prospectively designed data base.
Results: Delayed enhancement was present in 77 segments (9%) of 29 patients (56%), with higher wall thickness (25 vs 22 mm, p=0.03), lower resting (26 vs 54 mmHg, p=0.02) and post exercise gradients (26 vs 94 mmHg, p<0.001) and less mitral regurgitation. The number of segments with enhancement was directly associated with thickness (r=.4, p=0.002) and inversely with METs on exercise test (r=-0.03, p=0.04) and gradient (r=-0.3, p=0.04). First pass perfusion defects

were found in 22 segments of 12 patients, associated with lower stroke volume (62 vs 74 ml, p=0.03) and end diastolic volume (87 vs 101 ml, p=0.04), younger age at diagnosis (38 vs 49, p=0.01) and lower gradients (at rest 13 vs 34 mmHg, p=0.035, postexercise 24 vs 58, p=0.005). 18 of the 22 segments had also delayed enhancement, that was found in the 12 patients with first pass perfusion defects(p<0.001). Hypokinesia was detected in 62 segments of 16 patients, who were younger (45 vs 56, p=0.02), had higher wall thickness (27 vs 22, p=0.045) and had more segments with perfusion defects and delayed enhancement. Only 3 of these 16 patients did not had delayed enhancement (p=0.02). We found a possitive correlation between number of sudden death risk factors and presence of hypokinetic segments (p=0.04).
Conclusions: MR frequently detects areas of impaired contractility, perfusion defects and delayed enhancement in patients with HCM, mostly in hypertrophic segments. Delayed enhancement is associated with non-obstructive HCM with severe hypertrophy. Resting perfusion defects correspond to areas of fibrosis. Hypokinetic segments are associated with younger age, more hypertrophy, lower exercise capacity and number of risk factors for sudden death. Further studies are neccesary to clarify the role of myocardial tagging, first pass perfusion and delayed enhancement in HCM risk stratification.

P2377 Myocardial gene expression profiling in Fabry cardiomyopathy

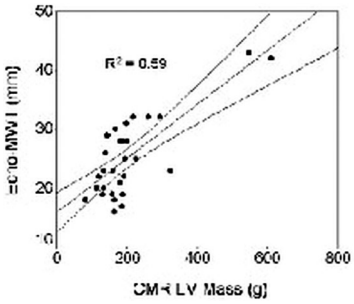
M. Pieroni[1], L. Nanni[2], C. Chimenti[1], M. Bellin[3], A. Maseri[4], G. Lanfranchi[3], A. Frustaci[1]. *[1]Catholic University, Cardiology Department, Rome, Italy; [2]Vita-Salute University S. Raffaele, Cardio-Thoracic-Vascular Department, Milan, Italy; [3]Padua University, Department of Genetics, CRIBI, Padua, Italy; [4]San Raffaele Hospital, Cardio-Thoracic-Vascular Department, Milan, Italy*

Background: Fabry cardiomyopathy (FC) is characterized by cardiac walls thickening with increased ECG voltages. Whether this is sustained by a real hypertrophy with enhanced cardiac myofibrillar content or by an electrical effect of glycolipids accumulation, is still unclear.
Methods: We studied frozen endomyocardial biopsies from 5 patients (pts) with FC and 5 pts with hypertrophic cardiomyopathy (HCM) presenting the same degree of LV hypertrophy at echocardiographic evaluation. Ten myocardial samples obtained at necropsy from normal hearts were used as controls. Total RNA was extracted, subjected to 2 rounds of linear amplification and used as target for hybridizations. The platform used was a tissue-specific microarray containing 5000 different 3'-end cDNA tags from skeletal and cardiac muscles, and bone marrow.
Results: A total of 53 deregulated transcripts were identified. We observed the reduced expression of some ribosomal proteins, alpha-actinin-2-associated LIM protein (ALP), whose down regulation may blunt the protein synthesis, cell size, and sarcomere organization; under-expression of the tumor suppressor gene PTEN and of the inositol polyphosphate-5-phosphatase leading to cardiomyocyte hypertrophy with increased protein synthesis; the down-regulation of the fatty acid binding protein 4 mRNA producing changes in the fatty-acid binding capacity previously associated to the development of hypertensive myocardial hypertrophy. The low levels of calpain 7 and of Na/K-ATPase transcripts observed are consistent with most models of cardiac hypertrophy. Instead we found over expression of titin suggesting an increased demand for re-assembling sarcomeric structural components.
Conclusions: Deregulation of genes involved in the development of myocardial hypertrophy is observed in FC along with HCM. These findings are relevant with regard to treatment, as regression of wall thickening should require not only glycolipids removal through enzyme-replacement therapy, but also hypertrophic processes deactivation.

P2378 Relationship of echocardiographic maximum left ventricular wall thickness to cardiac mass assessed by magnetic resonance in hypertrophic cardiomyopathy

G. Casolo[1], I. Olivotto[2], R. Manta[1], L. Rega[1], S. Nistri[3], P. Petrone[1], G.F. Gensini[1]. *[1]Careggi Teaching hospital, Cardiology Department, Florence, Italy; [2]Firenze, Italy; [3]CMSR Veneto Medica, Altavilla Vicentina, Italy*

Background: Echocardiographic maximum left ventricular (LV) wall thickness (Echo-MWT) is considered a convenient estimate of the degree of hypertrophy in patients with hypertrophic cardiomyopathy (HCM) and is routinely employed for assessment of risk. However, the correlation of Echo-MWT to the true LV mass remains to be established. We analyzed the relationship of Echo-MWT to LV mass measured by cardiovascular magnetic resonance (CMR), as the gold standard.
Methods: Thirty HCM patients (age 48±17 years, 23male, 5 with resting LV outflow obstruction, 7 in NYHA functional class III-IV) were imaged blindly by conventional 2D- echocardiography and CMR. LV mass was calculated using a modified Simpson method, and repeated steady state cine-series covering the whole LV.
Results: Average Echo-MWT was 25±7 mm (range 16-43). LV mass was 203±112 g (range 81-609). There was a significant but less than optimal correlation between Echo-MWT and LV mass (Figure); R2 was 0.59, SE 4.36, p<0.0001. The correlation of MWT by CMR and LV mass provided similar results (R2=0.46, SE 4.5, p<0.001). LV mass values below the study group average were associated with a wide range of Echo-MWT (range 16-31 mm). Conversely, Echo-MWT values =30 mm, an established predictor of sudden death, were associated with LV mass values ranging from 167 to 609 g.



Figure

Conclusions: Maximum LV wall thickness assessed by echocardiography is not an accurate estimate of the degree of hypertrophy in HCM patients. Hypertrophy considered as "extreme" may be associated with only moderate increases in true LV mass. These findings may have important implications for assessment of risk and sudden death prevention.

P2379 How are patients with hypertrophic cardiomyopathy treated in Europe? Insight from Eurogene Heart Failure Study

H. Madeira[1], R. Isnard[2], C. Hengstenberg[3], L. Tavazzi[4], J. Cleland[5], M.C. Aumont[6], O. Dubourg[7], M. Komajda[2] on behalf of On behalf of the "Eurogene Heart Failure Study" Group (Leducq Foundati. *[1]Hospital de Santa Maria, Lisboa, Portugal; [2]Hopital Pitie-Salpetriere, Service de Cardiologie, Paris Cedex 13, France; [3]Universitatklinikum Regensburg, Regensburg, Germany; [4]IRCCS Policlinico San Matteo, Pavia, Italy; [5]University of Hull, Hull, United Kingdom; [6]Hôpital Bichat, Paris, France; [7]Hôpital Ambroise Paré, Boulogne, France*

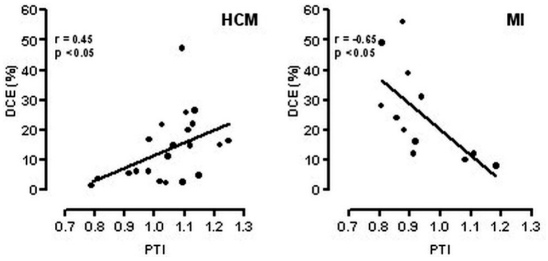
Background: the clinical spectrum of hypertrophic cardiomyopathy (HCM) is heterogeneous, ranging from asymptomatic forms to severe complications such as heart failure and sudden death. So far the treatment is not well codified. The aim of this study was to evaluate how patients with HCM are treated in Europe.
Methods: a large population of unrelated index patients with HCM was prospectively enrolled in 11 centres in seven different countries in Europe (June 2001-December 2004). Clinical features and treatment of these patients were analysed.
Results: we studied 423 patients with HCM (mean age 50±17 years, male 60%, familial form known at inclusion 37%). Most of the patients were asymptomatic or mildly symptomatic (NYHA class I: 57%, class II: 31%; class III or IV: 12%). Only 33 (8%) had had a previous episode of decompensated heart failure, 6 (1.4%) a resuscitated cardiac arrest, 14 (3.3%) a thromboembolic complication and 53 (13%) a familial history of sudden death.
At inclusion, the most common medication was beta blockers (46%), followed by calcium blockers (24%) and anticoagulant (14%). Thirty five (8%) had a dual chamber pace-maker (PM), 13 (3%) had received an internal cardiac defibrillator (ICD), 13 (3%) had undergone a septal myectomy, and 5 (1, 1%) an alcohol septal ablation. Differences in the therapeutic management according to the country of the patients will be analysed.
Conclusions: in this large European population of unrelated index patients with HCM, we observed that 1) a large majority of patients had a benign form of disease with few complications and only mild or no symptoms, 2) the most common non medical treatment remains the dual chamber PM, 3) ICD implantation, septal myectomy or alcohol septal ablation are rarely performed (< 5%).

P2380 Delayed contrast enhancement and perfusable tissue index in hypertrophic cardiomyopathy

P. Knaapen[1], W.G. van Dockum[1], O. Bondarenko[1], M.J. Gotte[2], C.A. Visser[1], A.C. van Rossum[1], A.A. Lammertsma[3], F.C. Visser[1]. *[1]VU University Medical Centre, Cardiology dept, Amsterdam, Netherlands; [2]University Hospital, Cardiology, Groningen, Netherlands; [3]VU University Medical Center, Nuclear Medicine and PET Research, Amsterdam, Netherlands*

Delayed contrast enhancement (DCE) visualized by cardiac magnetic resonance imaging (CMR) is a common feature in patients with hypertrophic cardiomyopathy (HCM), presumed to be related to myocardial fibrosis. The pathophysiological basis of hyperenhancement in this patient group, however, remains unclear as limited histologic comparisons are available. The present study compares the perfusable tissue index (PTI), an alternative marker of myocardial fibrosis obtained by positron emission tomography (PET), with DCE-CMR in HCM.
Methods: Twenty-one patients with asymmetrical septal HCM, 12 chronic myocardial infarction (MI) patients, and 6 age matched healthy control subjects were studied with DCE-CMR and PET. PET was performed using oxygen-15-labeled water and carbonmonoxide to obtain the PTI.

Results: No hyperenhancement was observed in controls and PTI was within normal limits (1.10±0.07). In MI patients the extent of hyperenhancement (25±16%) was inversely related to the decrease in PTI (0.94± 0.12, r=-0.65, p<0.05). Average hyperenhancement in HCM was 14±12%, predominantly located in the interventricular septum. PTI in the hypertrophied interventricular septum, however, was not reduced (1.12±0.13). Furthermore, in contrast to MI patients, there was a modest positive correlation between the extent of DCE and PTI in HCM (r=0.45, p<0.05).



DCE vs PTI in HCM and MI

Conclusion: DCE in the hypertrophied septum of HCM patients is not accompanied by a decline in PTI, and there is a positive correlation between the extent of DCE and PTI. These results suggest that hyperenhancement may not be caused solely by fibrotic replacement scarring in this patient group. Other pathological changes associated with HCM may also cause Gd-DTPA hyperenhancement.

P2381 Septal ablation for hypertrophic obstructive cardiomyopathy in clinical routine 2000-2004

L. Faber, D. Welge, D. Hering, D. Fassbender, N. Bogunovic, F. van Buuren, D. Horstkotte. *Heart Center North Rhine-Westphalia, Cardiology Dept., Bad Oeynhausen, Germany*

Background and introduction: In 1/1996, percutaneous septal ablation (PTSMA) was introduced in our institution as an alternative to myectomy for drug-refractory hypertrophic obstructive cardiomyopathy (HOCM). Until 1999, several modifications of the protocol have been implemented (routine echo monitoring [EM], reduced dose of ethanol [Eth; 1 ml/cm septum thickness], score system to pre-check for pacemaker [PM-] dependency after PTSMA). We now report on 103 consecutive patients (pat.) treated between 1/2000 and 7/2004.
Results: In-hospital and follow-up (3 months) data were available in all cases. In 15 pat. (15%) PTSMA was aborted: due technical problems in 4 pat. (4%; among these: 1 LAD dissection, 1 septal branch dissection), and driven by EM (no adequate target vessel) in 11 pat. (11%). In 18 additional pat., EM led to a target vessel change, thus the overall impact of EM on the interventional strategy was 28%. Following an Eth dose of 2.0±0.5 ml, peak CK rise was 473±184 U/l (normal range <80 U/l). The PM rate was 7% (6 pat.). No death occurred in hospital or during 3 months of follow-up.
After 3 months, 84 out of the 88 pat. (96%) with completed PTSMA reported clinical improvement; mean NYHA functional class decreased from 2.8±0.4 to 1.6±0.6 consistent with the data detailed in table 1.

Table 1

	Baseline	Follow-up	P value
Max. watt (bicycle exercise test)	96±42	114±42	<0.001
Peak VO2 (ml/kg/min)	17±5	20±6	<0.01
Septum thickness (mm)	20±4	17±4	<0.001
LA diameter (mm)	48±6	45±7	<0.001
Echo gradient at rest (mmHg)	60±31	11±19	<0.001
Echo gradient provoked (mmHg)	121±26	43±40	<0.001

Conclusions: Clinical and hemodynamic results of echo-guided, low-Eth-dose-PTSMA are comparable to the reference standard of myectomy. Our standardized peri-interventional approach has a very low complication rate, however, the rate of aborted procedures has increased.

P2382 Long-term prognosis in patients with mid-cavity obstructive hypertrophic cardiomyopathy

Y. Terajima, K. Kajimoto, N. Kawashiro, B. Yashiro, N. Hagiwara, H. Kasanuki. *Tokyo Women's Medical University, Cardiology Dept., Tokyo, Japan*

Background: It is of clinical importance to distinguish between the obstructive and non-obstructive forms of Hypertrophic Cardiomyopathy (HCM), based on the presence or absence of a left ventricular outflow tract pressure-gradient (LVOT-PG). Recently, management strategies and prognosis in outflow-tract obstructive HCM have been evaluated until now. However, diagnostic criteria, clinical profiles, or prognosis in patients with mid-cavity obstructive HCM (MO-HCM) is not clear. Therefore, the purpose of this study was to describe clinical profiles and long-term prognosis in patients with MO-HCM.
Methods: A retrospective study of 455 patients with HCM (mean age at diagnosis was 43±16 years), who were diagnosed and followed-up in our hospital, was analyzed. MO-HCM was defined as having PG > 20mmHg across the LV mid-cavity, measured by under basal condition at echocardiography. Moreover, patients with LVOT-PG > 30mmHg at rest were excluded. We analyzed the incidence, clinical profiles, HCM-related morbidity (stroke, syncope, or heart failure), and HCM-related mortality (stroke related death, heart failure related death, or sudden cardiac death) in patients with MO-HCM during a mean follow-up of 11±6 years.
Results: In 455 patients with HCM, 46 pts (10.1%) were diagnosed as MO-HCM (mean age at diagnosis was 52±15 years, 27 males, mean PG across the LV mid-cavity = 41 ± 22 mmHg) during a mean follow-up of 11±6 years. In these 46 pts, the incidence of familial HCM and familial history of sudden death were 13% and 6.5%, respectively. During a 11 year follow-up period, the probability of stroke, syncope, and heart failure were 8 patients (17.4%), 11 patients (23.9%), and 1 patient (2.2%), respectively. Furthermore, HCM-related death occurred in 3 of 46 patients (6.5%). Among these 3 patients, two patients had non-fatal cardiac arrest and one patient had appropriate implantable cardioverter-defibrillator interventions.
Conclusions: This study demonstrates that patients with MO-HCM have a high incidence of HCM-related morbid events and sudden death. Therefore, in patients with MO-HCM, an aggressive prevention for stroke and sudden cardiac death should be considered.

P2383 Mechanisms of exercise limitation in hypertrophic cardiomyopathy

F. Re[1], E. Zachara[1], F. Albi[1], D. Cartoni[1], A. Avella[2], P. Tanzi[1]. *[1]S. Camillo Hospital, Central Cardiological Unit, Rome, Italy; [2]S. Camillo Hospital, II Cardiological Division, Rome, Italy*

Background: diastolic functional abnormalities, often responsible for exercise limitation in patients (pts) with hypertrophic cardiomiopathy (HCM), can be detected by tissue Doppler imaging (TDI). Particularly, left ventricular (LV) filling pressure can be effectively estimated by the ratio of transmitralic early LV filling velocity (E) to early diastolic TDI septal velocity of mitral annulus (transmitral E/Ea ratio). An E/Ea ratio > 10 is considered to express increased LV filling pressure (capillary pulmonary wedge pressure > 15 mmHg). Aim of our study was the analysis of potential correlations between end diastolic pressure TDI profile and exercise tolerance assessed by cardiopulmonary test.
Materials and methods: 77 HCM pts (47 males, age 48 ± 14) were enrolled. 37 pts were in NYHA I functional class, 33 in II class and 7 in III class. All pts underwent conventional and TDI echocardiography and cardiopulmonary test. The following measurements were made: early (Ea) and late (Aa) diastolic velocities, septal and lateral transmitral E/Ea ratio. The study population was divided in two groups: Group A with E/Ea ratio > 10 (54 pts) and Group B with E/Ea ratio < 10 (23 pts). The following cardiopulmonary indexes were measured at the end of a symptom limited exercise: peak oxygen consumption volume (pVo2), anaerobic threshold (AT),Vo2 to work rate ratio (Vo2slope) and the respiratory minute volume to carbon dioxide production ratio (VE/Vco2).
Results: 75 pts (97%) had pVo2 < 80% of the predicted value. GrA pts presented significantly reduced (P < 0.05) oxigen consumption indexes:
pVo2 GrA 19.6 ± 7.3 vs GrB 16.7 ± 5.8 (ml/kg/min)
Vo2% GrA 61 ± 13 vs GrB 55 ± 14
In both groups pVo2 appeared not correlated with echo conventional diastolic indexes, while a significant correlation was evidenced with all TDI velocites (with the exception Aa velocity) as well as with E/Ea ratio. GrA pts presented a significant reduction of the following parameters: Ea septal (P < 0.001), Aa septal (P < 0.05), E lateral (P < 0.001), S septal (P<0.001) S lateral (p<0.001). In the same pts E and A velocities appeared significantly increased (P < 0.05)
Conclusion: our study confirms TDI as a usefull non invasive method to assess end diastolic LV pressure. An E/Ea ratio > 10 can identify a subgroup of HCM pts characterized by a greater diastolic disfunction and a reduced exercise tolerance. Our data seem to identify a significant correlation between increased end diastolic LV pressure and riduced exercise tolerance.

P2384 Diagnostic accuracy of a new 2D echographic hypertrophy score for the screening of familial hypertrophic cardiomyopathy

P. Charron[1], J.F. Forissier[2], S. Tezenas[3], M. Desnos[4], J.B. Bouhour[5], K. Schwartz[6], M. Komajda[1], O. Dubourg[2]. *[1]CHU Pitie Salpetriere, Service de Cardiologie, Paris, France; [2]A. Pare Hospital, Service de Cardiologie, Boulogne, France; [3]Hôpital Pitié-Salpêtrière, Service de Biostatistiques, Paris, France; [4]Hopital Europeen G. Pompidou, Cardiology Dept., Paris, France; [5]Hôpital Laennec, Service de Cardiologie, Nantes, France; [6]Inserm U582, Paris, France*

Aims: to study the diagnostic value of a new 2D echographic hypertrophy score (2D LVH) in families with HCM, in comparison to the conventional wall thickness measurement (MWT) (>13 mm in adults), which is limited by a low sensitivity in relatives.
Methods and results: the study was performed in 237 adults from genotyped families with HCM. Population A (derivation sample) comprised 109 adults, and population B (validation sample) 128 adults. MWT and 2D LVH score (sum of

thicknesses of four segments) were determined by echocardiography. Genetic status was the gold standard for diagnosis. In population A, a theoretical value for LVH score was determined in the healthy population by a multiple linear regression model including age, sex and body surface area. An abnormal cut-off value was defined as a score > maximum theoretical value according to a ROC analysis. Sensitivity and specificity were respectively 62.5% and 100% for MWT, and 73% and 96% for 2D LVH score. Improvement of sensitivity was particularly important in adults < 50 years (54% versus 69% respectively, p<0.04). These results were validated in population B: sensitivity and specificity of LVH score were 75% and 96% in this sample, and sensitivity of LVH score in adults < 50 years was better than that of MWT (67% versus 53%, p<0.03).
Conclusions: the LVH score has a higher diagnostic value for HCM than the conventional criterion of MWT, particularly in young adults. This echographic parameter may be proposed as an alternative diagnostic criterion for familial screening.

P2385 Is HCM different in men and women? Impact of gender on clinical presentation and outcome

I. Olivotto[1], M.S. Maron[2], A.S. Adabag[3], D. Vargiu[4], M.S. Link[2], J.E. Udelson[2], F. Cecchi[4], B.J. Maron[3]. *[1]Firenze, Italy; [2]Tufts-New England Medical Center, Hypertrophic Cardiomyopathy Center, Boston, United States of America; [3]Minneapolis Heart Institute Foundation, Minneapolis MN, United States of America; [4]Azienda Ospedaliera Careggi, Cardiology Unit II S. Luca, Florence, Italy*

Background: Little is known regarding the impact of gender on the clinical expression of hypertrophic cardiomyopathy (HCM). We have assessed gender-related differences in a multicenter HCM patient population from Italy and the US.
Methods: A total of 969 consecutive HCM patients were studied over 6.2±O6.1 years.
Results: Males had a 3:2 predominance (59%), similar in Italy and the U.S. (p=0.24). At initial evaluation, females were older and more symptomatic than males (47±23 vs. 38±18 years; p<0.001; mean NYHA functional class 1.8±0.8 vs. 1.4±0.6; p<0.001), suggesting a delay in diagnosis, and also more frequently showed left ventricular outflow obstruction at rest (37% vs. 23%; p<0.001). Moreover, females were less often diagnosed fortuitously by routine medical examination (23%, versus 41% in males, p<0.001). Female gender was independently associated with the risk of symptom progression to NYHA classes III or IV or death from heart failure or stroke (independent relative hazard 1.5; p<0.001), particularly in patients >50 years old and with outflow obstruction (p<0.005). HCM-related mortality and risk of sudden death was similar in the two genders.
Conclusions: Women with HCM were under-represented, older, and had more advanced heart failure symptoms than did men, suggesting potential biases against timely clinical diagnosis. Women also showed greater susceptibility for symptom progression to NYHA classes III or IV or death from heart failure or stroke, often associated with outflow obstruction. Gender-specific differences in diagnosis and disease complications underscore the importance of heightened clinical suspicion for HCM in women, which will allow for earlier diagnosis and implementation of appropriate treatment strategies, including relief of outflow obstruction.

P2386 Obstruction in hypertrophic cardiomyopathy impairs primary haemostasis (type IIa von Willebrand syndrome): close correlation with the peak outflow gradient

T. Le Tourneau[1], S. Susen[1], A. Millaire[2], C. Caron[1], N. Lamblin[2], G. Deklunder[3], C. Bauters[2], B. Jude[1]. *[1]INSERM ERI-9, University of Lille, Lille Cedex, France; [2]Hopital Cardiologique, Cardiologie C, Lille, France; [3]Hopital Cardiologique, Service d'EFCV, Lille, France*

Background: We previously demonstrated an impairment of von Willebrand factor (VWF) with abnormal bleeding in aortic stenosis. As the main determinant of VWF alteration is shear stress, we sought to evaluate the frequency of such abnormalities in obstructive cardiomyopathy.
Methods: We prospectively enrolled 50 patients (44±16 yrs, 32 males) with either obstructive (HOCM, 19) or non obstructive (HCM, 31) hypertrophic cardiomyopathy. Cardiomyopathy was considered as obstructive in the presence of an outflow peak gradient ≥ 30 mmHg at rest. History of bleeding events was recorded and severity of obstruction was evaluated in echocardiography. Selected parameters of primary hemostasis reflecting VWF abnormalities were evaluated.
Results: Mean septal thickness was 19±6 mm and LV EF was 65±12%. The mean value of peak gradient was 36±31 mmHg (3 to 130 mmHg). Peak gradient was higher in HOCM compared withHCM (60±21 vs 6±5 mmHg, p<0.0001). In HOCM, 21% (4/19) of patients presented an history of abnormal spontaneous bleeding (epistaxis, menorrhagia, severe intestinal bleeding). Shear-induced platelet adhesion (PFA 100®) was prolonged in HOCM (257±61 vs 150±55 s, p< 0.0001). VWF antigen was in the normal range and did not differ between the 2 groups. VWF-collagen binding activity and the percentage of high molecular weight multimers (%HMW) of VWF were reduced in HOCM compared with HCM (55±18 vs 113±49%, and 4.8±1.5 vs 11.0±1.9% respectively, p<0.001). Moreover, there was a close correlation (Fig) between %HMW and the peak gradient (r=0.75, p<0.001).
Conclusion: HOCM impairs primary hemostasis related to type IIa Von Willebrand acquired syndrome. The degree of VWF alteration is closely correlated to the peak gradient. These abnormalities might favor abnormal bleeding in HOCM.

P2387 Plasma B-type natriuretic peptide measurement is not useful as a screening method for carriers of familial hypertrophic cardiomyopathy

D. Brito[1], E. Infante de Oliveira[1], P. Richard[2], M. Komajda[3], H. Madeira[1]. *[1]Faculdade de Medicina de Lisboa, Clínica Universitária de Cardiologia, Lisboa, Portugal; [2]GH Pitié Salpêtrière, UF Cardiogenétique et Myogenétique, Paris, France; [3]Pitié Salpêtrière, CHU, Paris, France*

Background: In hypertrophic cardiomyopathy, plasma B-Type natriuretic peptide (BNP) levels rise in response to abnormal left ventricular wall stress and are a marker of left ventricular dysfunction. However, in this disease, sub-clinical ventricular dysfunction may be present before conventional ECG and echocardiographic (echo) changes are evident.
Aim: The possible diagnostic value of plasma NT-proBNP levels for screening for familial HCM in the absence of clinical disease expression.
Methods: 45 genotyped individuals from 5 unrelated families with HCM (5 different mutations, 2 genes involved) were characterised genetically and clinically (ECG and echo) and divided in 3 groups (Gr): Gr1, genetically and phenotipically affected (G+Ph+), 12 pts with HCM; Gr 2 (G+Ph-), 11 asymptomatic carriers; and Gr 3 (G-Ph-), 22 normal individuals). The clinical diagnosis of HCM relied on classical ECG and echo criteria. Plasma levels of NT-proBNP were measured (ECLIA - Elecsys-proBNP) in all individuals. Groups were compared in relation to age, sex, echo parameters, Doppler indices (mitral and pulmonary flow study) and NT-proBNP plasma levels.
Results: Gr 1 pts (all with an hypertrophied non-dilated well contracting left ventricle) differed significantly - p<0.0001 - from Groups 2 and 3 in relation to age (mean age 51 ± 15 y), most echo and Doppler parameters and NT-proBNP levels (mean: 697 ± 562 pg/ml). Groups 2 and 3 were identical in relation to all analysed variables - see table for some data.

Comparison between groups 2 and 3

	Age (y)	NT-proBNP (pg/ml)	ST (mm)	LAD (mm)	LVDD (mm)	LAFS (%)
Gr 2 (n=11)	20±15	64±78	8±2	31±7	40±7	36±10
Gr 3 (n=22)	19±12	34±28	9±2	32±5	44±5	40±10
p	NS	NS	NS	NS	NS	NS

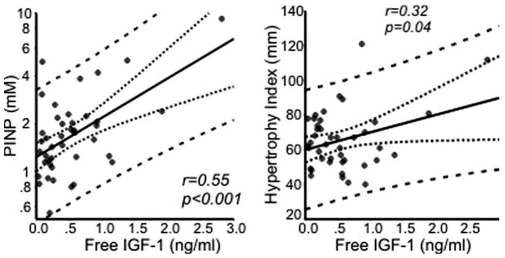
ST=septal thickness; LAD=left atrial dimension; LVDD=left ventricle diastolic dimension; LAFS=LA fractional shortening

Conclusions: Plasma levels of NT-proBNP in genetically affected individuals with familial HCM but with no phenotypic disease expression were identical to those of normal individuals. Peptide levels do not seem to be useful as a screening tool for a pre-clinical diagnosis of HCM. However, larger numbers of asymptomatic carriers are needed to confirm this finding.

P2388 Insulin-like growth factor-1 influences collagen turnover in hypertrophic cardiomyopathy

R. Lombardi, S. Betocchi, C. Esposito, M.A. Losi, G. D'Alessandro, M. Miranda, A. Cacace, M. Chiariello. *Federico II University of Naples, Dept of Clin. Med, Cardio and Immun. Sciences, Naples, Italy*

Purpose: We have demonstrated that collagen accumulation impairs passive diastolic function in patients with hypertrophic cardiomyopathy (HCM). Insulin-like Growth Factor-1 (IGF-1) has been reported to stimulate hypertrophy and interstitial fibrosis in secondary LV hypertrophy. This study aims at evaluating IGF-1 influence on collagen turnover in HCM.
Methods: We studied 46 HCM patients (35 men; age 34±10 years). Diagnosis was based on echocardiographic evidence of unexplained LV hypertrophy; an estimate of hypertrophy was provided by the sum of maximal thickness in 4 short axis segments at either of 2 levels (Hypertrophy Index). Collagen turnover was assessed by radioimmunoassay measurement of serum levels of peptides resulting from collagen I synthesis (PINP) and degradation (ICTP), and by ELISA assay of collagenases (matrix metalloproteinases: MMP-1 and MMP-9). As an estimate of



Figure

collagen I build-up, the molar difference between PINP and ICTP was calculated. Free IGF-1 serum levels were assayed by ELISA.
Results: Levels of [PINP] and [ICTP] and their molar difference were not normally distributed; hence, we expressed them as natural logarithm. Free IGF-1 was directly related to [PINP] (Figure, left panel), [ICTP] (r=0.54, p< 0.001), and [PINP-ICTP] (r=0.52, p<0.001). These correlations held also after correction for age, which affects all these variables. Furthermore, IGF-1 was directly related to Hypertrophy Index (Figure, right panel). There was no correlation between free IGF-1 and MMPs.
Conclusions: Higher serum levels of IGF-1 are associated to higher degrees of LV hypertrophy and interstitial fibrosis, assessed as a prevalence of collagen synthesis over degradation in HCM.

P2389 Long-term follow up of a Spanish regional cohort of 351 patients with hypertrophic cardiomyopathy

L. Monserrat[1], X. Fernandez[2], J. Peteiro[3], M. Pineiro[3], C. Dumont[3], R. Rios[3], R. Marzoa[3], A. Castro-Beiras[3]. [1]*CHU Juan Canalejo, A Coruna, Spain;* [2]*RECAVA, Cardiovascular research network, A Coruña, Spain;* [3]*CHU Juan Canalejo, Cardiology Department, A Coruña, Spain*

Background: Growing experience and favourable results of interventional procedures in patients with HCM and the increasing availability of ICDs seem to invite us to extend their indications. The evaluation of the natural history of the disease with a less aggressive approach may help us to weight their potential benefits in unselected populations.
Objective: To describe the clinical characteristics, management and prognosis of a Spanish regional cohort of patients with HCM.
Methods: Patients prospectively followed up in a monographic HCM clinic since 1995. Clinical, echocardiographic, Holter and exercise test data, therapies and events were registered. Status at last follow up was confirmed by direct clinical visits, phone calls and mortality registries in 2004.
Results: We analysed 351 patients (63% males). Mean follow up was 5.6±3.4 years. Age at diagnosis was 50±17 years, 54% were in NYHA I, 39.5% in II and 6.5% in III or IV. Maximal LV wall thickness was 20±6 mm, 27% had a gradient>30 mmHg and 5% had a LV fractional shortening lower than 25%. Risk factors for sudden death were: family history of sudden death (3.1%), non sustained ventricular tachycardia (20%), abnormal blood pressure response (24%), syncope (17%), severe hypertrophy (8%) and severe obstruction (>90 mmHg)(10%). Two patients (0.6%) had 4 risk factors, 9 (2.6%) had 3, 48 (13.7%) had 2, 100 (28.5%) had 1, and 192 (54.7%) had no risk factors. During follow up 26% were at least once in NYHA III or IV and 37% had exertional chest pain. There was AF in 113 (32%). Patients received beta blockers (66%), calcium antagonists (40%), amiodarone (29%), oral anticoagulation (30%), low doses of diuretics (24%), ACE inhibitors (21%), and dysopiramide (4%). Forty-one (10%) received a pacemaker, 5 (1.3%) alcohol septal ablation, 2 (0.5%) myectomy, and 12 (3.2%) an ICD. There were 33 deaths (9.4%: 1.7% per year): 4 sudden deaths and 1 appropriate ICD discharge (1.1%: 0.2% per year), 5 heart failure deaths, 8 other cardiovascular deaths (3 strokes), 13 non cardiovascular or unknown cause deaths, and 3 patients lost for follow up (considered as possible deaths). Two patients were transplanted. Patients who died were 13 years older than survivors (62 vs. 49 years, p<0.001)and had more atrial fibrillation (55% vs 30%, p=0.006).
Conclusion: Our patients, representative of a Spanish non-selected population, have presented a very low incidence of sudden death and all cause mortality, even though the rate of interventional procedures and ICD implantation has been low. Medical treatment seems to be appropriate in most patients

P2390 First experience with transcoronary ablation of septum hypertrophy with microspheres in patients with hypertrophic obstructive cardiomypoathy

T. Konorza[1], M. Haude[2], H. Kaelsch[2], U. Neudorf[2], M. Katz[2], D. Boese[2], R. Erbel[2]. [1]*University of Essen, Cardiology, Essen, Germany;* [2]*Universitaet GH Dusburg Essen, Department of Cardiology, Essen, Germany*

Background: In hypertrophic obstructive cardiomyopathy (HOCM) therapy, surgical myectomy and DDD pacemaker implantation are considered in patients with refractory symptoms for reducing left ventricular outflow track gradient (LVOTG). Also percutaneous transluminal septal myocardial ablation (PTSMA) by alcohol-induced septal branch occlusion has become an established technique. Ablation with chemically inert microspheres offers theoretical advantages and is currently in clinical evaluation.
Methods: Eight patients who were symptomatic despite adequate drug therapy with clinical and echocardiographic diagnosis of HOCM (5 men, 3 women) and leading dyspnea (N.Y.H.A. III) were treated by PTSMA with microspheres. The target vessel was determined by probatory balloon occlusion (PBO) and myocardial contrast echocardiography (MCE). 3-5 ml microspheres (Contour®, size: 45 – 150 μm, Boston Scientific) were injected over the balloon catheter in the septal branch.The left ventricular outflow track gradient (LVOTG) was documented with simultanous pressure registration in the aorta and the left ventricle.
Results: The invasively determined LVOTG could be reduced with a mean reduction from 135 ± 43 to 27 ± 26 mm Hg post extrasystole (p < 0.0001). Peri- and postinterventional, no arrhythmias were documented, and there was no serve chest pain.
Conclusion: PTSMA in HOCM with micospheres is a promising additional non-surgical technique for septal myocardial ablation, avoiding for significant reduction of the LVOTG. Possible long- term activity of alcohol and the acute pain associated withits use are avoided. Prospective long- term observations of larger populations and a comparison with the established forms of therapy are necessary in order to determine the definitive value of PTSMA with microspheres.

P2391 Clinical features and long-term outcome of hypertrophic cardiomyopathy in Taiwan

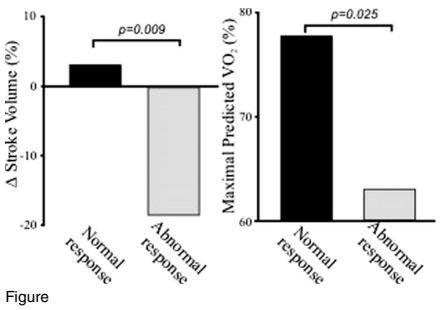
C.H. Lee, P.Y. Liu, L.M. Tsai, L.J. Lin, J.H. Chen. *Tainan, Taiwan*

Background & Objectives: Hypertrophic cardiomyopathy (HCM) has a great heterogeneity of morphologic, functional, and clinical features. Most information has derived from Western countries. The aim of this study was to describe clinical characteristics and outcome in Taiwanese patients with HCM.
Methods: A retrospective cohort study with HCM diagnosed at a tertiary referral center locted in Taiwan, from 1990 through 2004 was performed. Diagnosis was based on the demonstration of left ventricular hypertrophy (maximal wall thickness≥15mm during diastole) using transthoracic echocardiography. 163 patients (84 male, 79 female, diagnosed age 60.9±12.7 years) with HCM have been evaluated for a mean period of 5.3±4.1 years. Initial presentations, diagnosed age, clinical findings, cardiovascular morbidity and mortality were compared between male and female patients. Clinical predictors of major cardiovascular events related to HCM were evaluated with univariate and multivariate methods.
Results: Among 163 patients, asymmetric septal HCM (58.9%) predominates, and the percentage of pure apical HCM was up to 16.0%. The male patients had obviously earlier onset of presentation than females (mean age ± SD, 57.2±12.9 vs 64.8±11.3 years, p<0.001). The male patients had near 3-fold incidence of pure apical HCM (22.6% vs 8.9%, p=0.03), higher percentage of giant T wave inversion (28.6% vs 8.9%, p=0.001), and less percentage of hypertrophic obstructive cardiomyopathy (33.3% vs 63.3%, p=<0.001). Twenty-three patients (4 males, 19 females) died and 8 of these deaths were directly related to HCM. Overall HCM annual mortality rate was 2.7% and annual cardiovascular mortality rate was 1.0%. In multivariate analysis, beta-blocker was the only independent negative predictor of all-cause mortality (OR: 0.2, CI 0.04-0.88, p=0.034). Female in gender(OR: 4.69, CI 1.13-19.43, p=0.033), existences of left ventricular outflow obstruction(OR: 1.13, CI 1.12-1.15, p<0.001), paroxysmal atrial fibrillation(OR: 5.62, CI 1.43-22.22, p=0.036), and left bundle branch block(OR: 11.49, CI 2.89-45.45, p=0.003) were the independent positive predictors of all-cause mortality.
Conclusions: Even in this tertiary referral center-based Oriental patient population, HCM did not significantly increase the rate of mortality or adversely influence overall life expectancy. High incidence of apical HCM in Taiwan was very similar as in Japan. Adult male patients clinically presented different from females. These features suggest an adverse phenotypic expression and clinical course than in white patients

P2392 Abnormal blood pressure response to exercise and oxygen consumption in patients with hypertrophic cardiomyopathy

Q. Ciampi[1], S. Betocchi[2], M.A. Losi[3], L. Lombardi[3], E. Celentano[3], G. Barbati[3], B. Villari[1], M. Chiariello[3]. [1]*Fatebenefratelli Hospital, Division of Cardiology, Benevento, Italy;* [2]*Federico II University of Naples, Dept of Clin. Med, Cardio and Immun. Sciences, Naples, Italy;* [3]*Federico II University, Medicine & Cardiovascular Sciences, Naples, Italy*

Background: Exercise-induced abnormal blood pressure response is a risk factor for sudden death in patients with hypertrophic cardiomyopathy (HCM). We assess the hemodynamics of exercise by ambulatory radionuclide monitoring of LV function (VEST)and exercise tolerance by oxygen consumption.
Methods: 21 HCM patients exercised on a treadmill during VEST monitoring and, a few days apart, underwent cardiopulmonary exercise test with expired gas measurement. VEST data were averaged for 1 min and analyzed at baseline, at 3 min, and at peak exercise. Stroke volume, cardiac output and systemic vascular



Figure

resistance were expressed as % of baseline. Exercise tolerance was assessed as maximal oxygen consumption as % of predicted value (according to age, sex, and height).
Results: In 8 HCM patients (38%) with exercise-induced abnormal blood pressure response, ejection fraction (-30±16% vs -16±20%, p=.032) and stroke volume fell more than in 13 patients with normal blood pressure response (Figure). Cardiac output increased less in the former patients (51±41 vs 96±47%, p=.002). Systemic vascular resistance decreased similarly irrespective of blood pressure response. Percent of maximal predicted oxygen consumption was lower in HCM patients with abnormal blood pressure response (Figure).
Conclusions: Exercise-induced abnormal blood pressure response was associated with exercise-induced LV systolic dysfunction and impairment in oxygen consumption. This may cause hemodynamic instability, associated with a high risk of sudden cardiac death.

P2393 Interaction between autonomic activity and BNP release in hypertrophic cardiomyopathy

M. Revera[1], F. Mori[2], C. Campana[1], S. Ghio[1], M. Pasotti[1], E. Vanoli[2]. *[1]Policlinic S Matteo IRCCS, Cardiology Dept., Pavia, Italy; [2]Univ. of Pavia, Policlinico San Matteo IRCCS, Department of Cardiology, Pavia, Italy*

Background: The cardiac autonomic activity in hypertrophic cardiomyopathy (HCM) is not fully understood and contrasting data exist also about brain natriuretic peptide (BNP) levels, especially in low functional classes.
Aim: To study autonomic function and BNP release at rest and in conditions associated with sympathetic activation in HCM patients (pts).
Methods: So far, 61 pts with HCM entered the study. Autonomic study included the analysis of baroreflex sensitivity (BRS) and tilt test; BRS was assessed in 16 pts by using the phenylephrine (PHE) and nitrates (TNT) method. HRV was calculated, by autoregressive method, at rest and toward the end of 10 minute 70° tilt. BNP levels were assessed before and at the end of an exercise test.
Results: Mean age of the study population was 40±14 years. In most pts hypertrophy involved the septum (maximal thickening of 21±5 mm). All pts were in 1st functional class. Mean BNP levels were 184±197 pg/ml at rest and increased ($p<0.01$) to 251±236 pg/ml after exercise. Two distinctive responses to tilt were observed: in 22 pts mean RR did not change (936±137 ms at rest, 922±142 ms during tilt) while in the other pts decreased from 1023±166 to 817±147 ms ($p<0.01$). Pts with no heart rate response to tilt had a lower LF/HF ratio during tilt (3±4 vs. 6.6±6.8 p=0.03) and higher BNP plasma levels both at rest and after exercise (299±230 vs 76±88 pg/ml, p=0.003 and 370±255 vs 109±151 pg/ml, p=0.004). Mean BRS was 9.7±5 ms/mmHg with PHE and 5.2±3.2 ms/mmHg with TNT. We found an inverse correlation between BRS and both basal BNP (r=0.66, p=0.008 for PHE and 0.53, p=0.03 for TNT) and post-exercise BNP (r=0.72, p=0.008 for PHE, and 0.58, p=0.03 for TNT).
Conclusion: In this population pts with high BNP levels are associated with depressed autonomic response to tilt and an inverse correlation exists between BRS and BNP. This evidence of an altered control of circulation in HCM suggest that at least some of the syncopal events observed in HCM might be of vagal origin. This finding may carry important implication for risk stratification in HCM.

P2394 Diverse profiles and determinants of progressive heart failure and death in hypertrophic cardiomyopathy

P. Melacini[1], B.J. Maron[2], A. Angelini[3], F. Bobbo[4], C. Basso[3], B. Tokajuk[4], S. Iliceto[4], G. Thiene[3]. *[1]University of Padua, Experimental and Internal Medicine, Padua, Italy; [2]Minneapolis Heart Institute Foundation, Minneapolis, United States of America; [3]Cardiovascular Pathology, Padua, Italy; [4]Cardiology, Experimental and Internal Medicine, Padua, Italy*

Background: Hypertrophic cardiomyopathy (HCM) is an important cause of heart failure-related disability at any age. Profile and determinants of severe and progressive heart failure (HF) leading to NYHA class III and IV or often to death or transplantation have not yet been adequately defined in a large consecutive HCM population.
Methods: The clinical and morphologic determinants of HF were assessed in 293 consecutive HCM patients (pts) with a follow-up of 6.9±5.7 years. Gross and histologic features were assessed semiquantitatively in 12 pts in which the heart was available due to transplant or death.
Results: Fifty of 293 pts (17%) developed severe HF, including 10 who died and 8 who had heart transplantation. Five distinctive profiles of HF were defined associated with: 1) AF in 15 (30%); 2) end-stage systolic dysfunction (EF<50%) in 14 (28%); 3) left ventricular outflow obstruction (LVOTO) in 11 (22%); 4) restrictive due to diastolic dysfunction (mild-moderate left ventricular wall thickening, left atrial diameter>45 mm, left ventricular end-diastolic diameter <55 mm, EF>50%, and deceleration time <150 msec) in 7 (14%); and 5) a rare form with no LVOTO and at sinus rhythm in 3 (6%). The probability of reaching HF at 7 years follow-up was 16% in pts with either left atrium >45 mm or with AF, and 29% in the presence of both (long-rank <0.0001). Pathologic analysis of cases in which the heart was available showed extensive replacement fibrosis in all end-stage pts, in 60% of HF secondary to AF, but in none of the other forms.
Conclusions: Progression to severe HF in HCM is due to a variety of pathophysiologic mechanisms in keeping with the heterogeneous nature of this disease, occurring with and without left ventricular outflow obstruction. These include end-stage systolic dysfunction and AF associated with substantial myocardial scarring, left ventricular outflow obstruction, and restrictive form unassociated with obstruction and replacement fibrosis. Awareness of these diverse forms is imperative, given the diverse management strategies required.

P2395 Morbidity and mortality during follow-up of patients with hypertrophic cardiomyopathy in the ISAAC registry

A. Keren[1], M. Potekhin[1], Z. Khoury[1], G. Levin[1], S.A. Reisner[2], A. Katz[2], J. Shaheen[2], J.M. Dreyfus[1] on behalf of ISAAC investigators. *[1]Bikur Cholim Hospital, Department of Cardiology, Jerusalem, Israel; [2]For the ISAAC investigators, Israel*

Methods and Patients: The ISAAC registry (Israeli Shared Action for Advancement of Cardiomyopathies) includes clinical hemodynamic and morphologic data of 135 pts with Hypertrophic Cardiomyopathy (HCM) enrolled by several Cardiology Centers in Israel. There were 94 (70%) males, mean age was 50±17(1-84) years and mean follow-up was 44±20 (1-84) months. The disease was non-obstructive in 65% of cases.
Results: There was no significant change in symptoms and NYHA class during follow-up. NYHA class 1 and 2 were found in 78% of cases at enrollment and in 73% at the end of follow-up (p=ns). The major reasons for 96 hospitalizations in 58(43%) pts were: coronary angiography (16 of 96, 17%), ICD (13%) and pacemaker (10%)implantatiopn, alcohol ablation (11%), chest pain (10%), cardiac surgery (9%), atrial fibrillation (9%) and heart failure (8%). Of the 13 pts who received an ICD, one had one risk factor, 7 had 2 risk factors and 5 had >3 risk factors for sudden death. Two pts had aborted sudden death and 8 (6%) died: 4 had sudden death, 2 died of heart failure, one after heart transplantation and one after CVA. None of the patients who received an ICD died. Of the 6 pts with sudden death (2 of them aborted), 3 had 2 or more risk factors but 3 had only one known conventional risk factor for sudden death: either family history of sudden death or non-sustained VT on Holter.
Conclusions: During a mean follow-up of 3,7 years of 135 pts with HCM, there was no significant change in symptoms and functional class, 43% of pts were hospitalized, 60% of the hospitalizations were for cardiological or surgical interventions and 6% of pts died. Only one conventional risk factor for sudden death was known in three of the six pts with sudden death. None of the 13 pts who had an ICD implanted died.

P2396 Lower than expected mutation frequency in MYH7 gene in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy

R. Laredo-Vazquez[1], L. Monserrat[2], M. Hermida[3], M. Medin[3], I. Rodriguez[3], X. Fernandez[2], J. Muniz[3], A. Castro-Beiras[3]. *[1]University Institute of Health Science, Department of Molecular Cardiology, A Corunha, Spain; [2]Juan Canalejo University Hospital, Cardiology, A Coruña, Spain; [3]University Institute of Health Science, Molecular Cardiology, A Corunha, Spain*

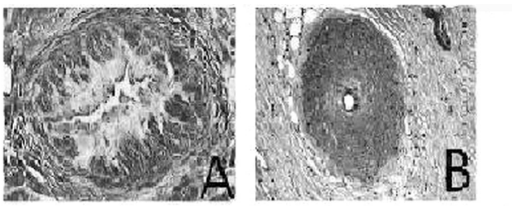
Objetives: The aim of this study was the analysis of the mutation spectrum in the gene encoding the cardiac myosin heavy chain (MYH7) in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy.
Background: Over 180 missense mutations have been identified in the gene encoding the cardiac myosin heavy chain (MYH7) and it is estimated that the 25-30% of all the cases of Hypertrophic Cardiomyopathy (HCM) are due to mutations in this gene. Greater disease penetrance, more severe hypertrophy, and high risk of SCD have been associated with mutations in MYH7 versus other sarcomeric genes. However, these data are only rough estimates, because the selection of families is somewhat arbitrary, over representing the poor prognosis and negative screening results are usually not reported.
Methods: We screened 142 unrelated consecutive patients with HCM (83 male/59 female; mean age of diagnosis, 45± 21 years; mean maximal left ventricular wall thickness 22 ± 8 mm) from the Juan Canalejo University Hospital area for variants in the coding regions of the MYH7 gene. The screening of mutations was done with a DNA single-strand conformation polymorphism analysis of each exon and flanking intronic regions, followed by sequencing each abnormal pattern on a capillary DNA. A variant was considered a mutation on the basis of the following 3 criteria: cosegregation with affected members in the family, absence of the mutation in 200 unrelated chromosomes of healthy adult controls, and the conservation of the mutated residue among species and isoforms. The mutation were confirmed by RFLP or by ARMS.
Results: 12 patients (8.5%) harboured 10 different mutations in MYH7. Only one disease-causing mutations was identified in the rod region of myosin. Three of this mutations were novel (M388T, R442C and A797P), but in the R442 and A797codons were described other mutation before. Three families had the I736T mutation, one of them with a second mutations (R787H) in heterozigosity.
Conclusion: The frequency of mutation in the MYH7 gene in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy is lower than expected. With the analysis of the codons in where mutation have been published

the detection rate of the allelic variant is over 90%. Due to the low frequency of mutations founded, the systematic analysis of the rod domain of the myosin is not profitable.

P2397 Myocardial fibrosis and progression to dilatation of the left ventricle in patients with hypertrophic cardiomyopathy

A. Fernandez[1], C. Vigliano[2], J.H. Casabe[2], L. Favaloro[2], M. Diez[2], E. Guevara[2], R.R. Favaloro[2], R. Laguens[2]. *[1]Favaloro Foundation, Cardiology, Buenos Aires, Argentina; [2]Favaloro Foundation, Cardiology, Buenos Aires, Argentina*

Objetive: To investigate the pathogenesis of dilation in patients (p) with hypertrophic cardiomyopathy (HCM) who progressed to the dilated phase of HCM (DHCM) and were submitted to heart transplantation.
Methods: Diagnosis of HCM was based on ecocardiographic findings and presence of fiber disarray in endomyocardial biopsy. In explanted hearts from 7 p with DHCM the extent of arteriolar dysplasia and fibrosis were determined in Masson trichrome-stained tissue sections involving the whole left ventricle (LV) wall at the mid-zone between the apex and the mitral annulus. The amount of fibrosis and proportion of intramural dysplasic arterioles were determined with a digital analysis system.
Results: Age 40.6 ± 10 (32 - 56 years), 5 males, diastolic LV diameter 61.3 ± 11.8 mm. The hearts weighed 393 (260-755 g). The epicardial coronary arteries had a patent lumen. Replacement patchy fibrosis was distributed in 37.6 ± 12.6% of the LV wall and 87.5 ± 14.6% of the intramural arterioles were dysplasic (figure). Many arterioles, especially within the fibrosis areas presented complete luminal occlusion. All hearts presented areas with fiber disarray and myocyte hypertrophy



Lumen narrowing (A) and periarteriolar fibrosis (B)

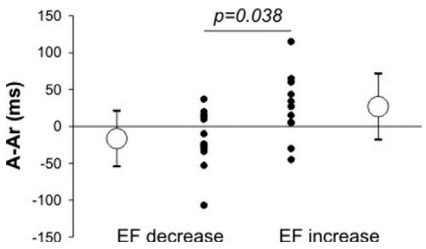
Figure

Conclusions: All p with DHCM presented a severe arteriolar disease and replacement of more than 1/3 of the LV mass by fibrous tissue, it can be hypothesized that dilation leading to heart failure is the consequence of a remodeling process secondary to chronic ischemia and myocyte death. This observation confirming other published reports pose the possibility that the new strategies for increasing the heart microcirculation, either by gene therapy or cell transplant, may be beneficial for preventing or ameliorating dilation and heart failure in HCM

P2398 Diastolic dysfunction is related to haemodynamic instability during isometric exercise in patients with nonobstructive hypertrophic cardiomyopathy

Q. Ciampi[1], S. Betocchi[2], R. Lombardi[2], M.A. Losi[2], A. Cacace[2], G. D'Alessandro[2], B. Villari[1], M. Chiariello[2]. *[1]Fatebenefratelli Hospital, Division of Cardiology, Benevento, Italy; [2]Federico II University of Naples, Dept of Clin. Med, Cardio and Immun. Sciences, Naples, Italy*

Background: Isometric exercise is deemed harmful in hypertrophic cardiomyopathy (HCM). We assessed the hemodynamic adaptation to isometric exercise in HCM by ambulatory radionuclide monitoring (VEST) of LV function.
Methods: During VEST monitoring, 27 nonobstructive HCM patients gripped a dynamometer at 75% of their maximal strength for up to 5 min. End-diastolic, end-systolic and stroke volumes, cardiac output, and systemic vascular resistance were expressed as % of baseline.
Results: We divided the HCM patients in 2 groups: 13 HCM patients in whom ejection fraction (EF) increased during exercise and 14 patients in whom it decreased. In patients in whom EF decreased, handgrip led to no differences in end-diastolic volume and systemic vascular resistance, whereas end-systolic volume rose (22±4% vs -14±22%; p<.001). Patients with EF decrease showed: a) higher incidence of history of syncope (7/14 vs 1/13; p=.021); b) smaller left ventricular diameter (42.3±2.6 mm vs 46.3±6.1 mm; p=.035); c) larger left atrial diameter (46.3±3.0 mm vs 40.6±6.3 mm; p=.020): d) impaired diastolic function, assessed by peak filling rate (2.6±0.8 SV/s vs 3.5±1.1 SV/s; p=.034) and by the difference in duration between transmitral A wave and retrograde pulmonary venous flow (Ar) (figure).



Conclusions: Handgrip-induced impairment in systolic function occurs in HCM patients with active and passive diastolic dysfunction. This may lay grounds for syncope. In this subset of patients isometric exercise is contraindicated.

P2399 Novel mutations in cardiac MYBPC3 and early onset malignant hypertrophic cardiomyopathy

S. Carballo, E. Blair, H. Watkins. *Department of Cardiovascular Medicine, Oxford, United Kingdom*

A molecular diagnosis is made in 50-60% of individuals affected by hypertrophic cardiomyopathy (HCM), and variants in genes encoding sarcomeric proteins account for the majority of these. Mutations in cardiac myosin-binding protein-C (MYBPC3) are found in 20-25% of cases. Initial genotype-phenotype studies, as well as recent and large surveys, have associated this gene with late onset disease. A similar clinical course and mortality rate is observed once hypertrophy is manifest. As part of a systematic study, DNA was obtained from 34 consecutive families with HCM and coding exons of MYBPC3 were screened by temperature-modulated heteroduplex analysis. Exons with aberrant profiles were sequenced and variants confirmed by restriction digestion, segregation analysis and study of normal controls. Three novel mutations were found that appear to produce an early malignant phenotype in 5 unrelated families. A missense mutation, Arg502Trp, was found in 3 probands; in all 3 families there was symptomatic disease and/or sudden death under 16 years of age. Severe heart failure required heart transplant in 1 individual. A novel Tyr749X mutation was identified in a family with disease onset as young as 12 years and sudden death in 1 individual aged 23. A novel delC2096 mutation was identified in an individual with a family history of young onset disease and 2 instances of sudden death amongst 5 affected (20 and 27 years). These new data indicate that mutations in MYBPC3 can sometimes produce symptomatic HCM in the young, associated with a severe phenotype. We suggest that even where genotype-phenotype correlations in HCM are robust, and have generally been replicated, exceptions are not rare. The frequent occurrence of private mutations further confounds derivation of reliable genotype-phenotype correlations. Although clinical findings may guide molecular investigations, targeted screening of only a subset of genes cannot be justified on clinical grounds.

P2400 Long-term efficacy of a combined therapy with beta-blocker and class I antiarrhythmic drug in hypertrophic obstructive cardiomyopathy

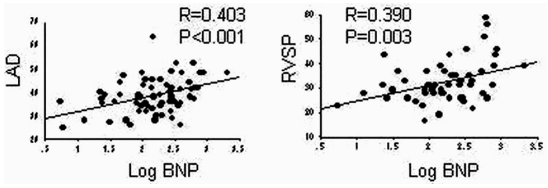
K. Kajimoto[1], Y. Minami[2], H. Kasanuki[2]. *[1]Tokyo Women's Medical University, Department of Cardiology, Tokyo, Japan; [2]Tokyo Women's Medical University, Department of Cardiology, Tokyo, Japan*

It has been suggested that pharmacologic agents with negative inotropic effect, such as beta-blockers (BB), class-I antiarrhythmic drugs (I-AD), or calcium blockers (Ca-B), are widely administered and have produced reduction of left ventricular outflow tract pressure gradient (LVOT-PG) in patients (pts) with hypertrophic obstructive cardiomyopathy (HOCM). Further, a combined therapy with these drugs is commonly administered in patients with HOCM refractory to each drug. However, few studies deal with an efficacy of their combined drug therapy in pts with HOCM who do not experience improvement of symptoms with each drug therapy. Therefore, the purpose of this study was to evaluate a long-term efficacy of a combined therapy with BB and I-AD (Combined-therapy) for reduction of LVOT-PG in pts with HOCM in comparison to a mono therapy with BB, I-AD, or Ca-B alone (Mono-therapy).
Methods: Among 108 pts with HOCM (LVOT-PG>30mmHg at rest; mean LVOT-PG=75 mmHg), 37 pts (34%) who had severe symptoms refractory to maximal medications were treated with therapeutic interventions. Therefore, in the remaining71 pts (66%), we compared the long-term efficacy, such as an improvement of both LVOT-PG and New York Heart Association (NYHA)-class and cardiovascular morbidity (arrhythmia, heart failure, or stroke), between pts with Combined-therapy (n=40) and Mono-therapy (n=31), retrospectively. Follow-up duration was 7.2±5.0 years.
Results: The improvement of LVOT-PG in patients with Combined-therapy was significantly better than those with Mono-therapy (83 to 37 mmHg, p<0.0001 and 65 to 54 mmHg, p=NS, respectively). Also, the improvement of NYHA-class with Combined-therapy was significantly better than those with Mono-therapy (2.8 to 1.9, p<0.0001 and 2.2 to 2.1, p=NS, respectively). Furthermore, the cardiovascular morbidity in patients with Combined-therapy was significantly better than those with Mono-therapy (7.5% vs. 25.8%, p<0.05).
Conclusion: This study demonstrates that the combined therapy with BB and I-AD leads to significant improvements in LVOT-PG, NYHA-class, and morbidity in comparison to the mono therapy in patients with HOCM. Therefore, it is suggested that the combined therapy with BB and I-AD shows beneficial long-term effects in patients with HOCM.

P2401 Elevated plasma brain natriuretic peptide is associated with pressure overload in right ventricle in patients with hypertrophic cardiomyopathy

M. Mizuno[1], K. Kajimoto[2], D. Yumino[2], N. Hagiwara[2], H. Kasanuki[2].
[1]Tokyo Women's Medical University, Cardiology, Tokyo, Japan; [2]Tokyo Women's Medical University, Cardiology, Tokyo, Japan

Background: It is suggested that brain natriuretic peptide (BNP) levels are elevated due to diastolic dysfunction, pressure gradient, or silent myocardial ischemia in left ventricle (LV) in patients with hypertrophic cardiomyopathy (HCM). However, mechanisms of BNP secretion due to these phenomenons in HCM are still unclear. In this study, we evaluated the relationship between plasma BNP levels and various echocardiographic parameters in patients with HCM
Methods: We prospectively assessed plasma BNP levels in consecutive 72 patients with HCM (non-obstructive HCM; n=45, obstructive HCM; n=27) who were performed echocardiography. Left atrial dimension (LAD), LV diastolic dimension, maximum LV wall thickness, LV ejection fraction, E wave/A wave ratio, deceleration time (DcT), and right ventricular systolic pressure (RVSP) were evaluated. Patients with reduced LV contraction were excluded from the study.
Results: In 72 patients with HCM, plasma BNP levels did not show any significant correlation with LV diastolic dimension, maximum LV wall thickness, LV ejection fraction, DcT, and E wave/A wave ratio. However, plasma BNP levels had a significant correlation to both LAD and RVSP (R=0.403; p<0.001, and R=0.390; p=0.003, respectively, Figure).



Correlation between log BNP and LAD, RVSP

Conclusions: In patients with HCM, plasma BNP levels correlate with both LAD and RVSP. Therefore, these results could illustrate that elevated plasma BNP values are associated with both left and right ventricle in patients with HCM.

P2402 Metabolism extracellular matrix in intraventricular septum from patients with idiopathic obstructive hypertrophic cardiomyopathy

Y. Gudkova[1], L.? Bokeria[2], S.? Sozin[3], ?N. Semernin[3], ?V. Borisov[2], ?B. Chukhlovin[4], ?? Totolyan[4], ?V. Shlyakhto[3].
[1]St-Petersburg Medical University, Internal Medicine I. Clinic, St. Petersburg, Russian Federation; [2]Bakoulev Cardiovascular Surgery Center, Department of cardiosurgery, Moscow, Russian Federation; [3]Sr.Petersburg Pavlov Medical Universit, Facullthy Therapy, St.Petersburg, Russian Federation; [4]Pavlov State Medical Univeversity, Res. Center for Molecular Medicine, St. Petersburg, Russian Federation

Purpose: To estimate matrix metalloproteinase 1 (MMP-1), tissue inhibitor of matrix metalloproteinases type 1 (TIMP-1), collagen I and collagen III genes expression in intraventricular septum (IVS) from patients with obstructive hypertrophic cardiomyopathy (OHCM).
Materials and methods: We examined 22 patients with OHCM. The mean age was 33,0±14,4; male/female ratio was 1/1. We used 8 patients with essential hypertension (EH) stage III as controls. We used myocardial samples obtained as a result of cardiosurgery in OHCM group and as a result of express-autopsy in EH group for RNA isolation with subsequent RT-PCR.
Results: We did not reveal any significant differences in collagen I gene expression between OHCM and EH groups. Collagen III gene expression in IVS area of hypertrophy was significantly higher in OHCM group (0,21±0,05) to compare with EH group (0,10±0,06), ?<0,05. MMP-1 gene expression in IVS area of hypertrophy was 5,6 times higher in OHCM group (0,8±0,22) to compare with EH group (0,14±0,08), ?<0,05. We revealed a negative correlation between MMP-1 and TIMP-1 genes expression in OHCM group(R=-0,48;p<0,01).
Conclusion: We revealed a disproportional increase of collagen III and TIMP-1 genes expression in the area of asymmetrical IVS hypertrophy in patients with OHCM.

P2403 Increased intraventricular septum thickness and alpha-galactosidase activity

S. Pankuweit[1], A.C. Sewell[2], B. Maisch[3], H. Boehles[2]. *[1]Philipps-University, Department of Internal Medicine - Cardiology, Marburg, Germany; [2]University Children's Hospital, Frankfurt am Main, Germany; [3]Marburg, Germany*

Fabry disease is caused by a deficient activity of the enzyme a-galactosidase A (a-gal), leading to the intracellular accumulation of globotriaosylceramide (Gb3). Cardiac involvement is frequent with Gb3 accumulation leading to an increase in ventricular and interventricular septal wall thickness which mimicks hypertrophic cardiomyopathy. We therefore investigated 78 male patients with suspected hypertrophic cardiomyopathy and increased systolic intraventricular septal thickness (IST >12mm on echocardiography) for the presence of Fabry disease.
Methods & Patients: Sera of 78 male patients (age range 17–82 years) were investigated by enzyme analysis for a-gal activity. Endomyocardial biopsies (EMB) of these patients were investigated by immunohistochemistry and conventional histopathology to diagnose a storage disease or inflammatory heart disease. PCR was carried out for viral (entero-, cytomegalo-, herpes, influenza, Ebstein Barr) or bacterial (chlamydia, borrelia) etiologies.
Results: a-Gal activities in sera of all patients ranged from 1.60 nmol/ml/h to 26.3 nmol/ml/h (reference range 6.0—26.0 nmol/ml/h). 16/78 patients (20.5%) had an activity <6.0 nmol/ml/h and 2 of them an activity <2nmol/ml/h. The endomyocardial biopsies of these 16 patients showed a normal histology in 12 cases. In 4 patients we diagnosed focal infiltrates compatible with inflammatory heart disease. Viral or bacterial PCR was negative in all 16 patients. All patients with decreased a-gal activity had a significant increased IST (14.21mm versus 15.75mm) with p< 0.039.
Conclusions: Patients with low a-Gal activity are first line candidates of Fabry disease despite of a non conforming histology. They will be investigated for mutations and EMBs will be re-examined for intracellular accumulation of Gb3.

P2404 Common carotid artery intima media thickness correlates strongly with left ventricular hypertrophy in patients with Fabry disease

N. Brakch[1], F. Barbey[2], A. Linhard[3], X. Jeanrenaud[4], D. Hayoz[1].
[1]University Hospital Lausanne, Angiology and vascular medicine, Lausanne, Switzerland; [2]University Hospital, Nephrology, Lausanne, Switzerland; [3]Charles University, Second Department of Internal Medicine, Prague, Czech Republic; [4]University Hospital, Cardiology, Lausanne, Switzerland

Background: Fabry disease is an X-linked disorder due to deficiency of the enzyme alpha-galactosidase A. This defect leads to accumulation of neutral glycosphingolipids – primarily globotriaosylceramide – in tissues throughout the body. The most common cardiac manifestation of the disease is progressive left ventricular hypertrophy (LVH). The undelying mechanism resulting in LVH, however, remains unclear, as lysosomal glycosphingolipid deposits represent less than 2% of the left ventricular (LV) mass. Patients with LVH also show a marked increase in common carotid artery (CCA) intima–media thickness (IMT). The present study set out to determine whether there is a correlation between LV mass and CCA IMT in male and female patients with Fabry disease. In addition, plasma from patients was tested for any proliferative effect on vascular smooth muscle cells (VSMC) in vitro.
Methods and Results: Thirty hemizygous males and 38 heterozygous females with Fabry disease were enrolled in the study. Ultrasound methods were used to measure LV mass and CCA IMT. LVH was present in 60% of men and 39% of women in the study. An increased CCA IMT was also observed, which was comparable in male and female patients. There was a strong positive correlation between LV mass and CCA IMT (r^2 =0.56 p<0.0001, r^2 =0.16 p<0.05 for men and women respectively). The observed VSMC proliferative index correlated with CCA IMT and interventricular septum (r^2 = 0.39 p<0.0004 and r^2 = 0.41 p<0.0001 respectively).
Conclusions: Hypertrophy of the left ventricle and intima–media of the wall of the CCA occurs concomitantly in patients with Fabry disease. An abnormal CCA IMT occurs to the same degree in men and women. This study is the first in which comparable penetrance of a systemic manifestation of Fabry disease has been demonstrated in hemizygotes and heterozygotes of comparable age. The correlation between LV mass and CCA IMT suggests a common hypertrophic mechanism in the cardiovascular pathology of Fabry disease. In-vitro experiments indicate the presence of putative circulating growth-promoting factors that may be responsible for the IMT and LV abnormalities.

P2405 Asynchrony of the left ventricular (LV) activation and origin of systolic pressure gradient and mitral regurgitation in obstructive hypertrophic cardiomyopathy

O. Rasputniak. *Institute of Cardiovascular Surgery, Valvular Heart Deseases, Kiev, Ukraine*

Background: The LV outflow tract (OT) systolic pressure gradient (SPG) and dysfunction of the mitral valve (MV) are classical features of hypertrophic obstructive cardiomyopathy (HOCM).Such type of cardiohaemodynamics in the case of subaortic obstruction is characteristic only of HOCM and is not observed in organic subaortic stenosis in which the LVOT narrowing is present as well. The physiological substantiation of the SPG and mitral regurgitation (MR) origin in HOCM is insufficient. While with surgery the reduction of SPG in LV OT and of MR are achieved with the help of myocardial trauma, the DDD pacing has the same effect changing nothing in heart but the ventricular contraction pattern. The present study is intended to determine whether the LV OT obstruction and MR in HOCM can be conditioned by the LV activation asynchrony.
Methods: 55 consequtive HOCM pts (mean age 31.7±3.2 yrs) were evaluated by M-mode, 2D and Doppler echocardiography with SPG determination, mitral regurgitation assessment, and short distance (h, cm) between interventricular septum

(IVS) and MV anterior leaflet in systole measurement; this was followed by angiography with direct LV OT SPG measurement and by LV endocardial mapping in relation to His potential registered in the AV node region. We compared the LV apex (LVA) His-V interval with the same for the hypertrophied part of IVS and calculated t-index- the difference in ms between the His-V in LVA and the His-V in LV OT. The appearance of the "–" sign before t-index shows the LVA excitation delay as compared to its OT excitation.SPG on LVOT in 36 pts was 72.8±9.0 mmHg, in 19 pts it was < 30 mmHg (mean 13.0±3.3mmHg)
Results: LV apex excites later than the hypertrophied zone of IVS (t-index ranged from -40 to -5 ms)in 28(78%)of obstructive pts and in 3(18%)nonobstructive pts. Systolic anterior motion of MV and MR were found in all 36 obstructive pts and in 3 (18%)nonobstructive pts.
The linear regression analyses established: 1)negative relations between h, distance between IVS and anterior MV leaflet in systole and SPG on LV OT (r = -0,4, p<0, 001), 2) negative relation between the t-index and SPG value (r=-0.32, p<0.001), and 3) positive relation between t and h, (r =0.3, p =0.001).
Conclusion: The LV outflow tract systolic pressure gradient and MR in HOCM pts are conditioned by LV apex and papillary muscles activation delay relatively to the hypertrophied part of IVS.

P2406 Hypertrophic cardiomyopathy in adolesence: mode of presentation, gender differences and disease progression

M.T. Tome Esteban[1], D. Ward[2], E. Sevedalis[2], J. Shah[2], R. Thaman[2], J. Deanfield[3], P.M. Elliott[2], W.J. Mckenna[2]. *[1]The Heart Hospital, Cardiology, London, United Kingdom; [2]The Heart Hospital, Cardiology, London, United Kingdom; [3]Great Ormont Street Hospital, Cardiology, London, United Kingdom*

Background: Hypertrophic cardiomyopathy (HCM) is reported to develop through adolescence; however this age group is underrepresented in the literature.
Aim: to describe mode of presentation of HCM in childhood and adolescence from a centre with active family screening.
Methods: 212 consecutive patients diagnosed with HCM were studied. All of them underwent comprehensive cardiac examination, ECG and echocardiogram. Holter monitoring and cardiopulmonary exercise test (CPET) was performed in accordance with minimum age for a meaningful test. All of them were followed every 6 months, yearly or as required clinically.
Results: The mean age at the time of diagnosis (TD) was 10.8 ± 5.6 years, 107 were male (64.3%). 155 (73.1%) fulfilled conventional diagnostic criteria for HCM, 28 (13.2%) fulfilled extended diagnostic criteria for relatives, 4 (1.9%) presented HCM with restrictive pattern and 25 (11.8%) were diagnosed as gene carriers. Only 77 of them (36.3%) presented with symptoms at the time of diagnosis. 72% of the females aged (13.5 to 18 years) vs males 36.2% presented with symptoms with statistically significant difference (p 0,001). Chest pain was infrequently reported in those aged ≤4 years old 4%, vs 20, 17 and 22% for ages (4.5 to 9),(9 to 13.5) and (13.5 to 18) respectively, p. 0.048. Syncope was present in 15% of those older than 9.5 years old. Dyspnoea class III-IV was present in 5 patients at the TD,1 aged <4.5 y and 4 of them older than 9 y. Palpitations were reported 12.1% in those older than 9 y. 13% of them presented severe left ventricular hypertrophy (SLVH) (≥30 mm) at TD and up to 20% developed SLVH during follow up. 45 patients had an increase ≥ 5mm of the maximal left ventricle wall thickness (MLVWTH) during follow up. Chest pain was associated with greater MLVWTH significantly (23mm ± 5 vs 17mm± 8, 0.0001).Significant left ventricular outflow tract obstruction (≥ 30 mm Hg) was found in 20% at the TD and during follow up it was notice in 30% of them.
Conclusion: Most of the patients with hypertrophic cardiomyopathy develop before the age of 18 are asymptomatic. Pubertal females are more symptomatic than the males. Those with greater maximal wall thickness are more likely to present with chest pain.

MYOCARDIAL AND PERICARDIAL DISEASE

P2407 Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-center all-case analysis

G. Artom[1], N. Koren-Morag[2], D.H. Spodic[3], A. Brucato[4], J. Guindo[5], A. Bayes-Genis[5], E. Schwammenthal[6], Y. Adler[6]. *[1]Tel Aviv, Israel; [2]Tel Aviv University, Sackler school of Medicine, Tel Aviv, Israel; [3]St Vincent Hospital, Worchester, Massachusetts, United States of America; [4]Niguarda Ca'Granda Hospital, Department of Medicine Brera, Rheumato, Milan, Italy; [5]Hospital de la Santa Creu i Sant Pau, Service of Cardiology, Barcelona, Spain; [6]Sheba Medical Center, Cardiac Rehabilitation Institute, Tel-Hashomer, Israel*

Aims: Effective prevention of recurrent pericarditis remains an important yet elusive goal. Corticosteroid therapy often needs to be continued for a prolonged period and causes severe side effects. We performed a multi-centre all-case analysis to investigate the efficacy of colchicine in preventing subsequent relapses of pericarditis, and addressed the hypothesis that pretreatment with corticosteroids may attenuate the beneficial effect of colchicine.
Methods and Results: One hundred forty published and unpublished cases of patients treated with colchicine after at least two relapses of pericarditis were aggregated from European centers. Of those, 119 were included in the study group. Only 18% of the patients had relapses under colchicine therapy, and 30% after its discontinuation. There were significantly more relapses among male patients after colchicine treatment (36% versus 17%, P=0.046), and those with previous corticosteroid treatment (43% versus 13%, P=0.02). Multivariable logistic regression analysis identified previous corticosteroid therapy (OR 6.68, 95% CI: 1.65 to 27.02) and male gender (OR 4.20, 95% CI: 1.16 to 15.21) as independent risk factors for recurrence following colchicine therapy.

Predicted relapses after colchicine tx

Variable	OR	95% C.I.	P
Male gender	4.20	1.16-15.21	0.029
Age (5 years)	0.90	0.76-1.11	0.237
Previous Corticosteroids treatment	6.68	1.65-27.02	0.008
Treatment duration (6 months)	1.13	0.91-1.39	0.278
Follow-up after colchicines treatment (3 months)	0.96	0.91-1.01	0.174

Conclusions: Treatment with colchicine is highly effective in preventing recurrent pericarditis, while pre-treatment with corticosteroids exacerbates and extends the course of recurrent pericarditis.

P2408 Neoplastic pericarditis: comparison of different therapeutic approaches

C. Lestuzzi[1], E. Bidoli[2], E. Viel[1], F. Macor[3], A. Buonadonna[4], G.L. Nicolosi[3], A. Veronesi[4], N. Meneguzzo[1]. *[1]Centro di Riferimento Oncologico, Cardiology, Aviano, Italy; [2]Centro di Riferimento Oncologico, Epidemiology, Aviano (PN), Italy; [3]A.O. S.Maria d. Angeli, Cardiology, ARC, Pordenone, Italy; [4]Centro di Riferimento Oncologico, Oncology C, Aviano (PN), Italy*

Introduction: several methods have been used to treat neoplastic pericarditis (NP): extended pericardial drainage (ED), i.v. chemotherapy (IVC), intrapericardial chemotherapy (IPC), sclerosing therapy (S), but there are no data comparing these methods. We reviewed all the cases of NP treated in our Institutions during 24 years that had an echocardiographic follow-up of at least one month.
Methods: all the echocardiographic and clinical records of patients (pts) with evidence of NP were reviewed. Data of pts who died shortly thereafter and those with incomplete clinical data were excluded from further analysis. We selected then 104 pts (58 males, age 22 to 84, mean 53) with lung (44 pts) or breast (18 pts) carcinoma, lymphoma (16 pts) other tumors (24 pts). Among the 104, 25 had a relapsing pericarditis months after recovery from a first episode, or underwent different therapies after failure of one approach: totally we could analyze 140 events. The outcome of each event was based on the last echocardiogram available or on the time when worsening required a different therapy, and classified as: complete or partial recovery if both the effusion and the pericardial metastases disappeared at all (CR) or were significantly reduced (PR); unchanged (U) if effusion and masses were stable; worsening if pericardial fluid reaccumulated after drainage or if pericardial metastases grew.
Results: in 104 cases a pericardial catheter was inserted (in 36 the amount of fluid was insufficient): the catheter was left in site up to 134 days (mean 14), without any infection. IVC only was used in 51 cases, IPC alone in 23, IVC+IPC in 54 and ED with or without S, or no therapy in 12. The mean follow-up was 266 days (9 days to 20 years, median 200 days); 13 pts are still alive. For IPC we used more often platinum, bleomycin, methothrexate. At last follow-up CR was observed in 37.3% of the pts treated with IVC, 69.6% of those treated with IPC, 61.1% of those on IPC+IVC and 8.3% of those without specific therapy; PR was found in 27.5% of IVC group, 4.3% of IPC group, 14.8% of IVC+IPC group and 8.3% of ED/S group. Considering altogether CR and PR, the best result was obtained in the IVC+IPC (75.9%), followed by IPC (73.9%) and IVC (64.7%) group. Worsening was observed in 25.5% of the IVC group, 13% of the IPC group, 7.4% of IVC+IPC group and 66.7% of ED/S/no therapy group.
Conclusions: in treating neoplastic pericarditis local IPC is more effective than systemic IVC; the best results are obtained combining both treatment. Simple drainage or sclerotherapy are useful for short-term palliation only.

P2409 Infectious etiology of pericardial effusion: impact of diagnostic techniques on treatment selection

B. Maisch[1], S. Pankuweit[2], A.D. Ristic[3]. *[1]Marburg, Germany; [2]Philipps-University, Department of Internal Medicine - Cardiology, Marburg, Germany; [3]Belgrade, Serbia and Montenegro*

Confirmation of the infectious etiology of pericardial effusion (PE) in contrast to autoreactive and neoplastic disease has important therapeutic implications. The aim of the present study was to investigate impact of various diagnostic techniques on identification of infectious agents causing pericarditis and PE.
Methods: The patient population included 234 consecutive patients undergoing pericardiocentesis, pericardioscopy and pericardial/epicardial biopsy (56.8% males, mean age 56.3±14.2 years). In all pts pericardial effusion analyses for neoplastic and inflammatory cells, cytokines, conventional lab analysis and epicardial/pericardial biopsy histology, immunohistochemistry and PCR analysis of

microbial agents were performed. The presence of the following infectious agents was specifically considered: RNA of enteroviruses (EV), the DNA of adeno- (ADV), cytomegalo- (CMV), Ebstein Barr-(EBV), herpes simplex (HSV, influenza virus (IV), borrelia burgdorferi (BD), chlamydia pneumoniae (CP), mycobacterium tuberculosis (TBC) in addition to bacterial and viral cultures from the effusion and serological assessment for HIV, hepatitis C, B, A.

Results: 64.9% of investigated patients had non malignant PE. The following etiologies could be assessed: ADV 17/234 (7.2%); EV 7/234 (3.0%), CMV 30/234 (12.8%), Influenza 1 (2,2%), hepatitis B 1 (2,2%), HSV 1 (2,2%), TBC 3 (6,6%), other bacteria 3 (6,6%), uremia 3 (6,6%). No etiological agents were identified 26/45 (58%). These were termed autoreactive when lymphocytes and/or anti-cardiac antibodies were detected (21/45) and idiopathic if only serous fluid was isolated (3/45).

Conclusions: The identification of viral and bacterial etiology has obvious implications for the treatment regimens: Only patients with virus- and bacteria-negative effusions should be considered for corticoid or immunosuppressive therapy. Therefore a careful microbiological and molecular PCR analysis is mandatory for the treatment of pericarditis.

P2410 T lymphocyte subpopulations CD4+/CD45RA+ and DR+/CD8+ predict recurrence of acute idiopathic pericarditis

A. Zacharoulis[1], D. Korres[2], A. Karavidas[2], N. Michelekakis[2], V. Vigklis[2], S. Boti[2], A. Zacharoulis[2]. *[1]Athens, Greece; [2]Athens, Greece*

Acute pericarditis (PR) is a common, self-limited inflammation of the pericardium. Its major complication is recurrence that can reach up to 30%. T Lymphocytes have a central role in the inflammatory process, and stimulation of different subpopulations may predict the severity of the disease.

Aim: To investigate the role of different T lymphocytes subpopulations in predicting recurrence of PR.

Methods: During the acute phase of PR, we studied the T lymphocyte subpopulations in 28 patients and 5 healthy subjects (controls). Peripheral blood T lymphocyte subpopulation analysis was performed, using monoclonal antibodies (Becton-Dickinson) and laser flow cytometry. The T lymphocyte subpopulations investigated were, CD3, CD4 (CD45/RA+ and CD45/RO+), CD8, CD19, NK, CD8+/CD38+, CD4+/CD25+ and DR+/CD8+. Patients were followed every six months clinically and by echocardiography for a mean follow up period of 26 + 36,5 months and recurrence was reported. Patients were allocated into two groups; group I, patients with recurrence; group II, patients without recurrence. All patients received the same medical treatment i.e. Ibuprofen 600mg three times daily until symptoms were relieved.

Results: Group I consisted of 11 patients with mean percentage(±Standard Deviation)of CD4+/CD45RA+ subpopulation 10.45±9.84%, group II had 17 patients with mean CD4+/CD45RA+ subpopulation percentage 18.31±9.24%; the control group had 12.8± 6.18% CD4+/CD45RA+ T lymphocytes. Using analysis of variance the difference in the percentage of CD4+/CD45RA+ T lymphocytes is significant among all groups and controls (p= 0.04). The percentage of DR+/CD8+ subpopulation also presented significant differences among all groups with 8.27±6.43% in group I, 2.18±2.04% in group II, and 1.6±1.02% for the controls (p=0.006). All other T lymphocyte subpopulation percentages were similar.

Conclusion: During the acute phase of idiopathic PR the percentage of CD4+/CD45RA+ and DR+/CD8+ T lymphocyte subpopulation may predict recurrence of the disease.

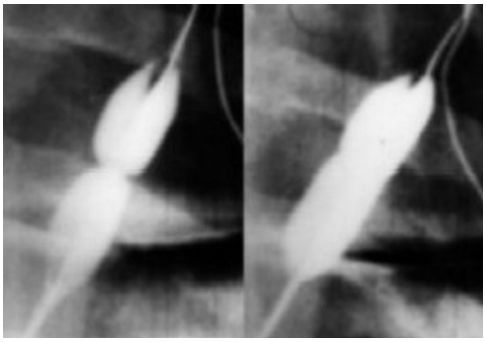
P2411 Triangular percutaneous balloon pericardiotomy: reduction of pericardial effusion recurrence rate and mortality due to tamponade in malignant pericardial disease

P.M. Seferovic, A.D. Ristic, D.S. Simeunovic, R. Maksimovic, V. Kanjuh, M. Ostojic. *Univ. Institute for Cardiovascular Diseases, Cardiology Department, Belgrade, Serbia and Montenegro*

Background: Neoplastic pericardial effusion frequently relapses after pericardiocentesis. The aim of the study was to investigate efficacy of triangular percutaneous balloon pericardiotomy (PBP) in prevention of the recurrences.

Methods: Thirty-six patients with recurrent pericardial effusion >2 cm or cardiac tamponade underwent pericardiocentesis and were subsequently randomly assigned to PBP or prolonged pericardial drainage. PBP was performed using Schneider Trefoil-Meier triple balloon catheter (Figure), 3x5 mm (Group 1: 60% males, age 54.8±8.6 years, 10 lung cancers, 7 breast cancers, 2 Hodgkin diseases, 1 sinoviosarcoma). Pericardial drainage was performed for 3.6±1.7 days, using 7F pigtail catheter (Group 2, 62.5% males, age 56.9±11.3 years, 9 lung cancers, 6 breast cancers, 1 mesothelioma). Pericardial effusion relapses were calculated per patient/per month of follow-up.

Results: Triangular PBP was effective in 90% of the patients and reduced pericardial effusion recurrences in comparison to the pre-procedural history (0.032 vs. 0.673; $p<0.01$) as well as in comparison to Group 2 (0.032 vs. 0.638; $p<0.01$). No major complications occurred. Minor complications included pain during the balloon inflation (12/22), and transient fever (8/22 in Group 1 and 3/16 in Group 2). During the follow-up (mean 142±119 days) 14/20 patients from Group 1 and 10/16 patients from Group 2 died due to the progression of the neoplastic disease. There was no mortality due to cardiac tamponade in Group 1 in contrast to 3/16 patients in Group 2 ($p<0.05$).



Percutaneous balloon pericardiotomy

Conclusion: Triangular PBP significantly reduced pericardial effusion recurrence rate in patients with malignant pericardial disease and prevented mortality due to cardiac tamponade.

P2412 Is there any relationship between serum cardiac troponin I levels on admission and relapses in patients with acute idiopathic pericarditis?

A. Karavidas[1], G. Lazaros[2], D. Korres[1], A.C.H. Zachaoulis[1], I. Fotiadis[1], E. Matsakas[1], M. Foukarakis[1], A.P. Zacharoulis[1]. *[1]Athens General Hospital, Cardiology Department, Athens, Greece; [2]Athens, Greece*

Purpose: The prognostic value of serum cardiac Troponin I (cTnI) elevation in acute coronary syndromes is well established. In this study, we have prospectively assessed whether serum cTnI positivity on admission could predict the relapse of pericarditis in a one-year follow-up period, in patients (pts) with idiopathic acute pericarditis (IAP).

Methods: Our study population consisted of 88 consecutive pts (age 53±12 years, 42 men), with the diagnosis of IAP. The final diagnosis of pericarditis was established by the association of history with the typical clinical findings (i.e. positional chest pain, fever, and pericardial friction rub), electrocardiographic criteria (serial compatible ST-Tchanges), and echocardiographic criteria (i.e. presence of pericardial effusion). Pts with secondary etiologies of pericarditis and those with acute coronary syndromes were excluded. In all pts serum cTnI levels were measured on admission by a highly sensitive enzymoimmunofluorometric method.

Results: The total number of relapses during the follow up period was 24 (27%). The mean time to relapse was 189±96 days (range 35-356). CTnI on admission was detectable in the sera of 32 pts (36% - mean values±Std 8±14ng/ml). C-TnI positivity was associated with ST-segment elevation ($p<0.001$) and pericardial effusion ($p<0.01$). CTn-I values above the threshold for myocardial infarction detection (i.e.>2ng/ml) were found in 9 of them (28%). In the group of pts with detectable CTnI, pericarditis relapse was observed in 10 of them (i.e. 31%) whereas in the group of 56 pts with undetectable cTnI, relapse was observed in 14 ones (i.e. 25% p=0.042).

Conclusions: In this investigation pts with IAP and detectable cTnI on admission were more likely to have a relapse at 12 months follow-up. CTnI elevation in the above pts seems to have a prognostic significance.

P2413 Gene silencing of the coxsackievirus-adenovirus-receptor leads to a decreased pathogenic effect after a CVB 3 infection in HeLa-cells

V. Ruppert, S. Pankuweit, B. Maisch. *Philipps-University, Cardiology Department, Marburg, Germany*

Group B coxsackieviruses (CVBs) are a common etiologic agent of viral myocarditis and dilated cardiomyopathy. The expression of specific viral receptors, such as the coxsackie-adenovirus receptor (CAR), may be the primary determinant of host susceptibility and organ tropism. Differences of CAR expression or density in the membrane of the hearts of different mouse strains may account for the different clinical phenotypes of CVB 3 infection. In this study, we wanted to examine the effect of a CVB 3 infection in HeLa-cells, after gene silencing of CAR by RNA interference (RNAi).

Methods: HeLa-cells were grown up in 96-well plates as well as in 6-well plates. Double-stranded siRNA molecules against human CAR with a length of 21nt had been designed. The cells were transfected with siRNA. 10h after transfection, the cells were infected with CVB 3 and incubated for another 48 hours. CAR mRNA expression was measured by real-time rtPCR. The cytopathic effect of CVB 3 was measured by a MTT assay.

Results: The cellular siRNA transfection for Gene silencing of CAR led to a decreased proliferation of HeLa-cells. The mRNA expression of CAR was decreased

by siRNA transfection at about 60%. The pathogenic effect of CVB 3 infection was reduced in the transfected cells from 30% viable cells to more than 80% (Fig. 1).

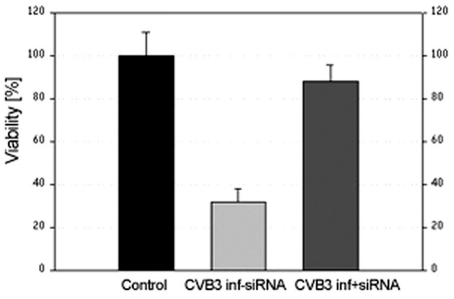


Figure 1

Conclusion: In this study we could shown the direct effect of the CAR expression after a CVB 3 infection. RNA-interference of the CAR led to a significant reduction of the pathogenic effect of CVB 3 in HeLa cells. These results support the thesis that a different CAR expression may be one reason for CVB 3 resistance or susceptibility. RNAi-based gene therapies, especially in viral diseases will become more and more interesting and promising.

P2414 Cardiovascular magnet resonance assessment of human myocarditis using a standardised combined right and left ventricular endomyocardial biopsy protocol

M. Mangin[1], H. Mahrholdt[2], S. Hager[1], C. Deluigi[1], H. Vogelsberg[1], A. Wagner[3], R. Kandolf[4], U. Sechtem[1]. *[1]Robert Bosch Med. Ctr., Cardiology, Stuttgart, Germany; [2]Robert Bosch Krankenhaus, Abteilung Kardiologie, Stuttgart, Germany; [3]Cardiology, Duke Cardiovascular MR Center, Durham, NC, United States of America; [4]Universityhospital, Pathology, Tuebingen, Germany*

CMR provides insight in morphology and distribution of myocarditis that was only available by necropsy before. Recent data suggests that the low sensitivity of RV endomyocardial biopsy (EMB) might be due to sampling error caused by focal distribution of myocarditic lesions. Thus we evaluated a CMR guided EMB approach versus the established RV EMB using a standardized combined RV and LV protocol.

We evaluated 40 pts presenting for workup of myocarditis. All pts underwent CMR followed by RV and LV EMB. CAD was ruled out by cath. RV biopsy was taken from the right side of the IVS, whereas the LV biopsy was directed towards the region of contrast enhancement (CE).

CE was present in 29 of the 40 pts and was distributed subepicardial or intramural in the LV. Myocarditis was diagnosed histologically by LV and/or RV EMB in 26 pts resulting in a sensitivity of 81% for the diagnosis of myocarditis by CMR. Interestingly in all pts with exclusively left lateral CE (n=11) CMR guided LV EMB was positive in 8 cases, whereas RV EMB was positive in 3 cases ($p<0.01$). Therefore the sensitivity of guided EMB in the setting of left lateral CE is 72% compared to 27% for the RV EMB. However, in pts presenting with septal affection by CE (n=13) 10 pts had positive RV and 9 positive LV biopsy, suggesting a more diffuse distribution of myocarditis in the setting of septal affection. Using CMR as the gold standard, sensitivity for the guided EMB was 72% compared to 55% for the unguided standard septal RV EMB.

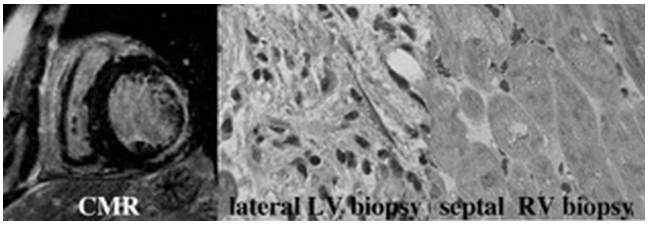


Figure 1

CMR imaging is capable of detecting biopsy proven myocarditis with high sensitivity (81%) in vivo. Septal affection by CE seems to be associated with a more diffuse distribution of myocarditis. The CMR guided EMB seems to improve sensitivity of EMB in the setting of myocarditis.

P2415 The influence of inferferon and herb huangqi on tumour necrosis factor in murine viral myocarditis

B. Han, X.J. Yao, X.Z. Han on behalf of the Pediatric Cardiology Team in Shandong Provincial Hospital. *Shandong Provincial Hospital,Jinan, P.R.China, Pediatric Cardiology, Jinan, China*

In both the preliminary virus induced inflammation and the subsequent immunological responses, cytokine such as TNF-amight play an important role in the development of VM.

Aim: To investigate the mechanism of treatment of IFN and huangqi on VM.

Methods: Eighty five-week-old Balb/c male mice were randomly divided into four groups (each group including 20 mice): group A, B, C, D. Each mouse in group B,C and D was inoculated with 0.1ml CVB3 (TCID50 108/ml) intraperitoneally, while group A was given 0.1ml normal saline. The mice in Group C were injected with IFN 10,000μ/g.d intraperitoneally from day 2 to day 7. The mice in group D were given huangqi 30mg/g.d to their stomach by gastric catheter, and mice in group A and B were simply given normal saline intraperitoneally in the same way. Five mice in each group were sacrificed on day 7, 14, and 21 post inoculation. The TNF-a level of each mouse was measured by biantibody ELISA. Formalin-fixed hearts were embedded in paraffin, and stained with HE for histopathology under microscopic examination, and the pathologic score were determined.

Results: The pathological damage in mice of group C and group D were alleviated to some degree. On day 7 and 14, the pathological scores in both group C and group D were significantly lower than that in group B($P<0.01$). On day 14, the pathological score in group C was significantly lower than that in group D. The average TNF-a levels in group B on day 7, 14, and 21 were significantly higher than those in group A ($P<0.01$). On day 7, 14 and 21, the TNF-a levels in group C and D were significantly lower than that in group B. On day 7, the TNF-a level in group C were significantly lower than that in group D($P<0.01$). The pathological score of the myocardium on day 7, 14 and 21 were positively correlated with the TNF-a dynamic levels in serum ($r=0.75$, $p<0.05$)

Conclusions: TNF-a might play an important role in the development of VM. Both of IFN and huangqi can reduce the TNF-a level in serum and alleviate the myocardial injury and IFN is better.

P2416 Investigation of endomyocardial biopsies from 3345 patients over 10 years. A retrospective analysis by immunohistology and molecular biology

S. Pankuweit[1], V. Ruppert[2], B. Maisch[2]. *[1]Philipps-University Marburg, Dept. of Internal Medicine/Cardiology, Marburg, Germany; [2]Philipps-University Marburg, Dept. Internal Medicine - Cardiology, Marburg, Germany*

Immunohistological and molecular biological investigations of endomyocardial biopsies (EMB) have been demonstrated as important tool for the diagnosis of inflammatory heart muscle diseases with or without viral persistence. From 1993 until 2003 we investigated 3345 EMB from patients with clinically suspected inflammatory heart disease. We used immunohistochemical methods (IHC) for the demonstration of infiltrating cells according to the WHF-criteria and polymerase chain reaction (PCR) for the detection of viral or bacterial genomes, which may have pathogenic importance. (Parvovirus PB 19=PVB 19, Cytomegalovirus =CMV, Adenovirus=ADV, Enterovirus=EV)

Results of IHC and PCR investigations:

	Inflammation 1) EF>45%	Inflammation 2) EF<45%	No inflammation 3) EF>45%	No inflammation 4) EF<45%
n =	816	282	1663	584
LVEDD (mm)	54±10	65±7	51±9	66±11
Virus pos (%)				
Influenza A	1.3	0	0	0.1
Parvovirus B 19	20.4*	33.3**	23.9*	17.6
Enterovirus	1.5	2.8	1.1	0.5
Adenovirus	1.5	2.1	1.4	1.2
Cytomegalovirus	3.1	3.9	2.0*	0.8
Borrelia burgdorferi	0	0	0.1	0

*$p<0.05$ (group1 versus 2 or group 3 versus 4). **$p<0.05$ (group 2 versus 4)

Summary: Inflammatory heart disease was diagnosed by immunohistochemistry in 32.8% of all investigated patients. Parvovirus B 19 was the most often detected virus in all patient's subgroups. Detection of PVB 19 genome was significantly correlated with an inflammatory heart disease and reduced ejection fraction (** $p<0.05$ group 2 versus 4). In contrast, the high prevalence of PVB 19 in group 3 reflects the patients with dilated cardiomyopathy without inflammation, in whom prevalence of PVB 19 is about 17%. However, the role of PVB 19 in inflammatory heart disease has to be further evaluated.

P2417 Systolic and diastolic function in cardiac Fabry disease – investigations in the definition of the clinical phenotype

G. Beer[1], O.A. Breithardt[2], H. Kuhn[3]. *[1]The Bielefeld Klinikum, Department of Cardiology, Bielefeld, Germany; [2]University Mannheim, Department of Cardiology, Mannheim, Germany; [3]The Bielefeld Klinikum, Department of Cardiology, Bielefeld, Germany*

Fabry disease (FD) is an X - linked recessive lysosomal storage disorder characterized by the progressive intracellular accumulation of glycospingolipids in various tissues, especially in the cardiovascular system. Preliminary data indicate that in a substantial part of pts with FD cardiac involvement can be the sole manifestation of the disease mimicking the clinical features of hypertrophic non obstructive (HNCM) or obstructive (HOCM)cardiomyopathy. Based on recent re-

ported progress in enzyme replacement therapy of FD major attention has been focused on cardiac FD. Systematic clinical and echocardiographic studies in pts with unequivocal cardiac Fabry disease based on morphological evaluation of cardiac biopsy tissue are lacking and the phenotype of cardiac variant FD has still to be defined precisely. Furthermore there is debate about diastolic and systolic dysfunction in the course of the disease.
Methods: Therefore, we investigated in a systematic study 30 consecutive non related symptomatic pts with cardiac FD (23 male and 7 female pts; age 56 years, range 19 to 77 years). In all pts light and electron microscopic evaluation of cardiac biopsy tissue revealed cardiac FD. In all pts transthoracic echocardiography (TTE) were performed for the evaluation left ventricular hypertrophy (LVH), diastolic and systolic dysfunction and correlated to morphological and clinical data.
Results: TTE revealed in all pts pronounced LVH mimicking hypertrophic cardiomyopathy (HCM). In 1 pt TTE revealed a dynamic left ventricular outflow tract gradient (95 mmHg). In this pt FD mimicked the clinical features of HOCM; in 25 pts FD mimicked the clinical features of HNCM (septum 18 mm, range 13 to 35 mm; posterior wall 14 mm, range 11 to 20 mm). Diastolic dysfunction was present in 9/25 pts. In 15/25 pts (64%) left ventricular diastolic and systolic function were well preserved. In 4 male pts global systolic dysfunction was present together with pronounced LVH (23 mm).
Conclusion: In the majority of pts cardiac FD mimicks the clinical features of HNCM, in single pts that of HOCM. Diastolic dysfunction is present in a larger part of pts. In some pts global systolic dysfunction and LVH are present, mimicking the rare clinical picture of "burned-out HCM". One can speculate that in a subset of pts cardiac FD leads first to diastolic dysfunction and then to progressive global systolic dysfunction resulting in end stage heart failure. The correct diagnosis of cardiac FD is mandatory because enzyme replacement therapy seems to offer a specific therapeutic option in a subgroup of pts with HCM.

P2418 Iron overload by multislice multiecho T2* and biventricular function by cine dynamic imaging for the evaluation of efficacy of oral deferiprone in beta thalassemia major

A. Pepe[1], M. Lombardi[1], F. Sorrentino[2], M. Capra[3], R. Malizia[4], D. De Marchi[1], M. Midiri[2], A. Maggio[5]. *[1]CNR, Clinical Physiology Institute, Cardiology Department, MRI Lab, Pisa, Italy; [2]University of Palermo, Radiology Department, Palermo, Italy; [3]G. Di Cristina ARNAS Hospital, Pediatrics Department, Palermo, Italy; [4]Villa Sofia Hospital, Pediatrics Department, Palermo, Italy; [5]V. Cervello Hospital, Haematology Department, Palermo, Italy*

Purpose: Heart failure is the major cause of death in beta thalassemia major (TM) and cardiac siderosis is considered the leading determinant. Conventional treatment with parenteral iron chelator desferrioxamine (DSF) improves mortality, but prognosis remains poor. Oral deferiprone(L1)appears to be promising. T2* magnetic resonance imaging (MRI) with a single measurement in the mid-ventricular septum, was validated as quantitative evaluation of myocardial iron overload. However, postmortem studies have demonstrated that there is a marked heterogeneity of iron distribution. We set-up a multislice multiecho T2* MRI approach for detection of the heterogeneous distribution of myocardial iron overload. Aim of our study was to investigate differences between L1 vs DSF -treated patients using this new approach and correlate heart T2* values with biventricular function parameters.
Methods: 36 beta TM patients (16 men; age 29±8 years) underwent MRI scanning. 18 patients received long-term L1 alone and 18 patients, matched for age and sex, received DFS. In order to evaluate the heterogeneity of iron distribution, T2*multiecho sequences on three short axis views of left ventricle were obtained and analyzed with homemade software. The myocardium was automatically segmented into twelve segments. T2* value on each segment as well as the global T2* value were calculated. Cine dynamic images in short axis were also obtained to evaluate biventricular function by quantitative analysis.
Results: On T2* global value the coefficient of variation for intra- and inter-observer reproducibility was 3.9% and 5.5%, respectively. There was a correlation between the global T2* value and the T2* value in the mid-ventricular septum (r=0.94, $p<0.0001$). The global heart T2* value was significantly higher in L1 vs DSF group (35±7 ms vs 27±12 ms; p= 0.02). The number of segments with normal T2* value (> 20ms) is significantly higher in L1 vs DF group (11±1 vs 8±5; p=0.03). There was not correlation between global heart T2* and left ejection fraction (EF)(r=0.2; p=0.2). We did not detect significant differences between L1 vs DSF group in left and right EF, in left ventricular mass index and in left and right end-diastolic and end-systolic volume indexes.
Conclusions: The segmental approach provides a reproducible way for assessing myocardial iron distribution and confirms that L1 seems to be more effective than DSF in removal of myocardial iron. Global heart T2* did not correlate with left ejection fraction and L1 vs DSF group did not showed significant differences in biventricular function parameters.

P2419 Prevalence of ECG abnormalities in patients with left ventricular non-compaction

S.K. Kohli, S.P. Page, H. Jones, J. Shah, D.J. Ward, M.T. Tome, P.M. Elliott. *NHS Hospital, Cardiomyopathy Unit, London, United Kingdom*

Background: Left Ventricular Non-Compaction (LVNC) is a disorder characterised by excessive and prominent trabeculation of the left ventricle. The prevalence and spectrum of electrocardiographic (ECG) abnormalities are poorly characterised. The aim of this study is to determine the prevalence and characteristics of ECG abnormalities within a cohort of patients diagnosed with LVNC.
Methods: Using two diagnostic criteria (Chin et al and Jenni et al) we identified a cohort of 50 patients (age = 37.2±17.6 years; 13-90; 28 male) referred to The Heart Hospital. Each patient had a clinical examination, ECG and echocardiogram. Quantitative analysis was performed by two independent observers.
Results: Eighteen patients (36%) reported a family history of cardiomyopathy or sudden cardiac death. Twenty patients(40%) had two or more cardiac symptoms and 11 (22%) gave a history of heart failure at presentation. Echocardiographically, the mean left ventricular end diastolic diameter (LVed), end systolic diameter (LVes) and fractional shortening (FS) were 5.8±1.2cm, 4.5±1.5cm and 24.8±9.5% respectively. One patient (2%) had atrial fibrillation and 4 (8%) had a permanent pacemaker implanted at first evaluation. The mean PR interval, QRS duration and corrected QT interval were 163.6+30.6ms, 105.9+25.6ms and 407.9+42.9ms respectively. Three (6%) patients had PR intervals < 120ms and 4 (8%) it was > 200ms. The prevalence of left bundle branch block (QRS duration > 120ms) was 20% (10/50), and inter-ventricular conduction delay was 40% of patients. The prevalence of pathological Q-waves in two or more contiguous leads was 36% (18/50). T-wave inversion was present in two or more contiguous leads in 19 (38%) of patients. Peaked T-waves were seen in 18 (36%) patients and only seen in the precordial leads. There was a correlation between the QRS duration and age, LVed, LVes and FS (r = 0.4, r = 0.6, r = 0.5 and r = -0.4; $p < 0.01$ respectively). The prevalence of left bundle branch block increased with age (none in lowest tertile and 46.7% in the highest, Chi squared = 10.2, p = 0.006).
Conclusions: This study shows that conduction abnormalities are common in LVNC, and parallel disease severity assessed by echocardiography. The clinical implication of the high prevalence of conduction disease remains to be ascertained.

P2420 Outcome of patients with arrhythmogenic right ventricular cardiomyopathy after cardioverter defibrillator implant: relevance of lead-related complications

G. Boriani, P. Artale, C. Valzania, M. Biffi, C. Martignani, D. Saporito, M. Ziacchi, A. Branzi. *Institute of Cardiology, Cardiology Dept., Bologna, Italy*

Aim: to investigate the outcome of patients (pts) with arrhythmogenic right ventricular cardiomyopathy (ARVC) after implant of a cardioverter defibrillator (ICD), focusing on rate of arrhythmic events, electrophysiological parameters and rate of adverse events related to ICD-system.
Patients: we examined 15 pts with ARVC (mean age 55±15 yrs, range 18-74), implanted with an ICD for primary (n=6) or secondary (n=9) prevention of sudden death. As control population, we identified 30 pts with coronary artery disease (CAD) (mean age 60±10 yrs, range 39-79) with a similar duration of follow up (65±42 months, median 41 in ARVC pts vs 62±40 months, median 41 in CAD pts), implanted with an ICD for primary (n=6) or secondary (n=24) prevention of sudden death.
Methods: at ICD implant R-wave amplitude, pacing and defibrillation threshold were evaluated for each patient; during follow up ICD interventions, sensing and pacing threshold were also analysed.
Results: mean R-wave amplitude was significantly lower in ARVC pts than in CAD pts both at implant (11.5±4.8 mV vs 16.7±5.6 mV, p=0.004) and at each follow up evaluation. Moreover, in ARVC pts mean R-wave amplitude significantly decreased during follow-up (7.3±4.3 mV after 5 yr, P=0.003). Mean pacing threshold was significantly higher in ARVC pts than in CAD pts both at implant (0.9±0.5 V vs 0.6±0.4 V, p=0.02) and during early follow up. At implant, no significant difference in mean defibrillation threshold was observed between ARVC and CAD pts (16.8±6.1 J vs 13.4±6.0 J, P=ns). During follow up, 8 of ARVC pts (53%) and 15 of CAD pts (50%) received appropriate ICD therapies. Ventricular tachyarrhythmias >240/min occurred in 6 of ARVC pts (40%) and in 1 of CAD pts (3%). Inappropriate ICD interventions, determined by supraventricular tachycardias or lead failure, occurred in 5 of ARVC pts (33%) and in 10 of CAD pts (33%). The incidence of lead-related adverse events requiring surgical revision was significantly higher (P=0.02) in ARVC pts (n=6, 40%) than in CAD pts (n=4, 13%).
Conclusion: in ARVC pts the rate of appropriate ICD interventions is around 50% in a mean 5-year follow-up, with a high percentage of interventions for fast ventricular tachyarrhythmias. However, treatment with ICD in ARVC is characterized by more difficult lead positioning at implant and by an higher incidence of lead-related adverse events than in conventional ICD recipients with CAD. These complications and the changes in electrophysiological parameters related to right ventricular sensing and pacing might be related to progression of ARVC disease.

P2421 Extracellular matrix turnover in patients with Anderson-Fabry disease

J.S. Shah[1], D. Hughes[2], M.H. Tayebjee[3], R. MacFadyen[3], A. Mehta[4], P.M. Elliott[1]. *[1]The Heart Hospital, University College London, Cardiology, London, United Kingdom; [2]The Royal Free Hospital, The Lysosomal Storage Disorders Unit, London, United Kingdom; [3]City Hospital, University Department of Medicine, Birmingham, United Kingdom; [4]The Royal Free Hospital, The Lysosomal Disorders Unit, London, United Kingdom*

Background: Anderson-Fabry Disease (AFD) is an inherited X-linked lysosomal disorder associated with premature death. Studies suggest that patients with AFD develop progressive left ventricular (LV) remodelling and heart failure. We hypothesized that altered extracellular matrix turnover (ECM) is important in the pathophysiology of AFD.
Methods: twenty-nine (15 male, aged 44.1±11.7 years) consecutive patients with a confirmed diagnosis of AFD and 21 age and gender matched normal controls (10 male, aged 39.7±11.3 years) had serum analysed for matrix metalloproteinase (MMP) -9, MMP-2, tissue inhibitor of matrix metalloproteinase (TIMP)-1 and TIMP-2 levels. Patients were assessed clinically, with echocardiography and using the Mainz Severity Score Index measurement (MSSI, a validated score for disease severity).
Results: MMP-9 levels were significantly higher in patients than controls (mean=427.1 ng/ml, 95%CI=252.1-602.2 ng/ml, p<0.001, Figure 1). There were no differences in MMP-2 or TIMP levels between patients and controls. There was no correlation between MMP-9 levels and LV mass or maximal LV wall thickness. There was a negative correlation between MMP-9 and fractional shortening (FS, r=-0.5, p=0.01). There was a positive correlation between MMP-9 levels and MSSI (r=0.5, p=0.01). These relations were independent of age and gender using stepwise linear regression analysis.

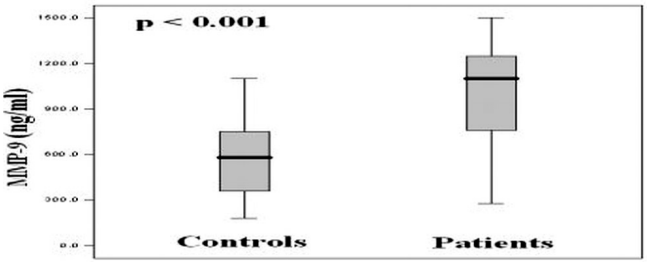


Figure 1

Conclusions: patients with AFD have abnormal ECM turnover compared to normal controls. The correlation between MMP-9 levels, disease severity and FS suggests that altered ECM turnover is a central component in the pathogenesis of this disease, and that circulating levels of MMP-9 may provide a useful marker for disease severity and response to enzyme replacement treatment.

P2422 Association between amyloid myocardial involvement and cardiac cachexia

R. Caccialanza[1], G. Palladini[2], S. Perlini[3], M. Vezzoli[3], H. Cena[1], C. Vagia[1], C. Roggi[1], G. Merlini[2]. *[1]University of Pavia, Human Nutrition Unit, Pavia, Italy; [2]IRCCS S.Matteo, University of Pavia, Amyloid Center, Biotech. Res. Lab., Pavia, Italy; [3]University of Pavia, Clinica Medica 2, IRCCS San Matteo, Pavia, Italy*

Maintenance of a good nutritional status is associated with prolonged survival and better quality of life in many diseases, and in heart failure patients the presence of cardiac cachexia has been recognized as a marker of poor outcome. Cardiac involvement is diagnosed in approximatively 50% patients presenting systemic light-chain amyloidosis (AL), representing an ominuos sign associated with a worse prognosis. Aim of the present study was to investigate the nutritional status of AL outpatients in relationships with different clinical features of the disease, including cardiac involvement. Over a 6-month period, in 106 consecutive AL outpatients several anthropometric (body mass index, BMI; mid-arm muscle circumference, MAMC), biochemical (serum transthyretin, albumin and transferrin) and clinical (presence of anorexia, dysphagia, dysgeusia, vomiting, diarrhoea and degree of unintentional weight loss) variables were measured. Cardiac involvment was assessed relying on clinical, electrocardiographic and echocardiographic parameters. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) definition.
Results: Unintentional weight loss was reported by 58 (54.7%) patients (median 11.3%, range 2.6-34% of usual body weight) within the previous 2-72 months (median 12 months). In 31 patients (29.2%), 26 of whom had cardiac involvement, unintentional weight loss was greater than 7,5% of usual unedematous body weight, and occurred over a time period longer that 6 months, configurating a clinical picture resembling cardiac cachexia. Median BMI was 24.5 (range 17.5-33.7); BMI was >30 in 8 (7.5%), >25 and <30 in 38 (35.8%) and < 20 in 9 (8.5%) patients, respectively. MAMC was below the 10th age-sex matched centile in 29 (27.3%) patients. Mean percentage weight loss was higher among patients with cardiac involvement (9.7%), heart failure (12.4%), ECOG Performance Status >2 (14.1%) and distinctly different among NYHA and ECOG Performance Status classes (P < 0.001). Percentage weight loss was significantly higher among patients with serum prealbumin below 200 mg/L (lower reference limit) (P < 0.05), which was the best indicator of undernutrition among the biochemical markers.
Conclusions: Unintentional weight loss was the only nutritional variable with prognostic significance, being precisely related to the severity of the disease. The much higher prevalence of weight loss in patients with cardiac involvement suggests that systemic AL amyloidosis represents a clinical condition at a very high risk to develop cardiac cachexia.

P2423 Diagnosing of arrhythmogenic right ventricular cardiomyopathy: value of electrocardiographic versus imaging abnormalities

P. Kies, J.J. Bax, M. Bootsma, E.E. van der Wall, M.J. Schalij. *Leiden University Medical Center, Cardiology, Leiden, Netherlands*

Introduction: Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is based on a set of criteria proposed by the International Task Force (TF) for Cardiomyopathies in 1994. To fulfil these criteria, presence of both electrocardiographic- and anatomical abnormalities must be assessed with ECG and imaging techniques respectively. Not all patients have both abnormalities. Since ARVD/C has a progressive nature, serial evaluation may demonstrate that ECG abnormalities precede anatomical abnormalities.
Methods and Results: Sixty consecutive patients (41 men, mean age 40±15 yrs) were evaluated by the TF criteria for possible ARVD/C because of presentation with a left bundle branch block (LBBB) ventricular tachycardia (VT), representing 1 minor criterium. The presence on the ECG of a T-wave inversion beyond V2 (1 minor) and the presence of right precordial QRS prolongation (1 major) or an epsilon wave (1 major) were scored together with the visualization of severe regional/global RV dysfunction (1 major) or mild segmental dilatation/regional hypokinesia (1 minor) by imaging techniques. Initially 21 (35%) patients were TF positive. After 47±39 (range 6-146) months, 23 TF negative patients were re-evaluated because of recurrent VT with 12 (52%) additional patients now meeting the TF criteria. 11 of 12 (92%) patients presented initially with ECG abnormalities only, but had developed anatomical abnormalities on imaging at late follow-up.
Conclusion: These results suggest that ECG abnormalities precede anatomical abnormalities; serial re-evaluation of ARVD/C may therefore specifically be indicated in TF negative patients with evidence for abnormalities on the ECG.

P2424 Lack of Wnt-1 signalling and high expression of PPARgamma in some cardiomyocytes in arrhythmogenic right ventricular cardiomyopathy

E. Czarnowska[1], B. Cukrowska[1], M. Brudek[1], E.K. Wlodarska[2], A. Turska-Kmiec[3], B. Wozniewicz[1]. *[1]The Children Memorial Health Institute, Dept. Pathology, Warsaw, Poland; [2]Insitute of Cardiology, Congenital Heart Diseases, Warsaw, Poland; [3]The Children Memorial Health Institute, Cardiology Dept, Warsaw, Poland*

Background: Loss of cardiomyocytes accompanied by expansion of fibro-fatty tissue within the myocardium in an unknown mechanism is a histopathologic feature of arrhythmogenic right ventricular cardiomyopathy (ARVC). Studies on adipogenesis revealed that Wnt signalling factors function as adipogenic switches and also play a role in reprogramming myoblasts to the adipocyte lineage by regulating ?-catenin intercellular levels and inducing PPARgamma. The aim of this study was to determine whether the same mechanisms are involved in the process of fatty tissue expansion in ARVC and transdifferentiaton of cardiomyocytes or fibroblasts into adipocytes.
Material and methods: RV samples obtained by endomyocardial biopsy from 10 patients (4M and 6F, mean age 23.7±18.6) with ARVC diagnosed according to the task force criteria were examined immunohistochemically using anti-Wnt-1, beta-catenin and PPARgamma antibodies. EMBs from pts with myocarditis (4 pts) and dilated cardiomyopathy (3 pts) with mean age-matched ARVC patients served as controls. Relations between distribution and expression of Wnt-1, PPARgamma and beta-catenin were analysed in serial sections and correlated with localization of fibro-fatty tissue in Azan-stained sections.
Results: Wnt-1 expression was low in ARVC in contrast to control hearts. Additionally in ARVC, Wnt-1 failed to localise in the extracellular space and on cardiomyocyte membranes, which exhibited marked loss of beta-catenin.Wnt-1 was strongly expressed in areas of fibrous tissue in ARVC. Positive expression of PPARgamma was observed in nuclei of typical adipose cells and in some cardiomyocytes in samples obtained from ARVC pts except one. In control samples Wnt-1 and beta-catenin were regularly expressed while PPARgamma was negative.
Conclusions: The results provide evidence for participation of Wnt-1, beta-catenin and PPARgamma in the biological mechanisms underlying transdifferentiation of cardiomyocytes into adipose tissue in ARVC. These proteins could be the targets of a future therapeutic approach. However, further investigations are necessary to evaluate this process on a larger number of hearts and to elucidate the mechanism of low Wnt expression in the myocardium of pts with ARVC.
Acknowledgements. This work was supported by project QLG1-CT-2000-0191 financed by the UE.

P2425 Non-fat diet ameliorates lipotoxic cardiomyopathy due to impaired fatty acid oxidation in a murine model of systemic carnitine deficiency

T. Asai, R. Takahashi, H. Murakami, R. Murakami, Y. Numaguchi, H. Matsui, K. Okumura, T. Murohara. *Nagoya University, Department of Cardiology, Nagoya, Japan*

Background: Excess lipid accumulation in cardiomyocytes due to an imbalance between fatty acid uptake and utilization may promote cardiac hypertrophy and dysfunction, referred to as lipotoxic cardiomyopathy. The juvenile visceral steotosis (JVS) mouse, a murine model of systemic carnitine deficiency, develops pathological cardiac hypertrophy with lipid accumulation due to impaired fatty acid oxidation. Dietary fat cessation may exert beneficial effects on lipotoxic cardiomyopathy in JVS mice. To test this, we investigated the effects of non-fat diet on the hearts in JVS mice.
Methods: Both wild-type mice and JVS mice were fed a non-fat diet or a normal diet from 4 weeks of age.
Results: At 6 weeks of age, the ventricular weight-to-body weight ratio in JVS mice was higher than that in wild-type mice and was significantly reduced by non-fat diet (Table 1). The myocardial triglyceride levels in JVS mice were markedly elevated compared with those in wild-type mice and were significantly reduced by non-fat diet. At 8 weeks of age, echocardiography revealed LV dilatation and reduced LV fractional shortening in JVS mice compared with wild-type mice; non-fat diet significantly attenuated LV dilatation and improved LV fractional shortening in JVS mice. Furthermore, the high mortality in JVS mice was significantly suppressed by non-fat diet.

Table 1

	Wild-type mice		JVS mice	
	normal diet	non-fat diet	normal diet	non-fat diet
Ventricular weight/body weight (mg/g) (6wk)	3.6±0.1	3.8±0.1	8.3±0.2*	6.6±0.1*,‡
LV end-diastolic dimension (mm) (6 wk)	1.94±0.05	1.97±0.03	2.28±0.06†	2.30±0.06†
LV end-diastolic dimension (mm) (8 wk)	2.27±0.08	2.37±0.03	3.36±0.13*	2.63±0.06‡
LV fractional shortening (%) (6wk)	55.5±1.7	54.2±0.9	41.4±1.6*	46.3±1.1†
LV fractional shortening (%) (8wk)	53.2±0.7	52.8±0.5	28.0±2.0*	41.3±1.3*,‡
Myocardial triglyceride levels (6wk) (mg/mg dry ventricular wt)	4.4±0.3	6.0±1.1	109.5±12.5*	32.8±8.1†,‡
Survival rate at 16weeks of age (%)	100	100	10.3*	77.3‡

Values are mean±SEM. *P<0.01, †P<0.05 vs. Wild-type mice – normal diet; ‡P<0.01 vs. JVS mice – normal diet.

Conclusions: Dietary fat cessation attenuates cardiac hypertrophy and improves cardiac function and survival with reduction of lipid accumulation in the hearts of JVS mice. These results suggest that excess myocardial lipid accumulation plays a crucial role in the pathogenesis of lipotoxic cardiomyopathy due to impaired fatty acid oxidation.

P2426 Myocardial fibrosis in beta thalassemia major by late gadolinium-enhanced magnetic resonance imaging: correlation with ECG-changes, biventricular function parameters and myocardial iron overload

A. Pepe[1], F. Sorrentino[2], V. Positano[1], M. Capra[3], R. Malizia[4], A. Maggio[5], M. Midiri[2], M. Lombardi[1]. *[1]CNR, Clinical Physiology Institute, Cardiology Department, MRI Lab, Pisa, Italy; [2]University of Palermo, Radiology Department, Palermo, Italy; [3]G. Di Cristina ARNAS Hospital, Pediatrics Department, Palermo, Italy; [4]Villa Sofia Hospital, Pediatrics Department, Palermo, Italy; [5]V. Cervello Hospital, Haematology Department, Palermo, Italy*

Purpose: In beta thalassemia major (TM) cardiac disorders are the leading cause of mortality. Myocardial fibrosis has been shown in autopsy. Magnetic Resonance Imaging Delayed Enhancement (MRI-DE) after Gadolinium has been proven to allow visualization of fibrosis, but no dedicated studies are available in TM. Aim of this study was a) to determine in patients with TM whether myocardial fibrosis can be detected by MRI-DE; b) to correlate the presence of myocardial fibrosis with ECG-changes, biventricular function parameters and myocardial iron overload.
Methods: 53 beta TM pts (17 male; 29±9 years) were enrolled. Each patient performed an ECG before the MRI study. MRI studies were performed on a 1.5 T scanner (GE, USA). Myocardial fibrosis was determined by MRI-DE. Images were evaluated by a visual assessment of two independent observers and by a semi-automatic software tool for objective pixel quantification. Iron overload was determined by a T2* multi-echo sequence on three parallel short axis views of left ventricle. Cine dynamic images in short axis of the left ventricle were also obtained to evaluate biventricular function by quantitative analysis.
Results: Fibrosis was present in 20 patients (38%), irrespectively of age and sex. Contrast to noise ratio resulted 2.0. The fibrosis was predominantly patchy. Out of the 20 pts with scar, 13 (65%) had two or more foci of fibrosis. Out of the 46 areas of fibrosis, 25 (54%) involved the interventricular septum. Fibrosis did not followed coronary distribution. No asynergic segments were detectable. There were no significant difference between fibrosis group vs no-fibrosis group in left and right ejection fraction, in left ventricular mass index and in left and right end-diastolic and end-systolic volume indexes. Myocardial fibrosis did not significantly affect the T2* value (fibrosis group 27±13 ms vs no-fibrosis group 27±11, p= 0.8). A significant correlation was found between the presence of myocardial scarring and ECG changes (chi-square 9.0; p = 0.001). In pts with hyperenhanced tissue, the commonest findings were a T wave inversion, ST depression and right bundle-branch block. The sensitivity, specificity, negative predictive value and positive predictive value of ECG in detecting myocardial scarring were 81%, 72%, 86% and 65%, respectively.
Conclusions: Myocardial fibrosis is detectable in a significant percentage of patients with beta TM. Myocardial scarring did not correlate with biventricular function parameters and myocardial iron overload. ECG-changes showed a significant accuracy to predict myocardial fibrosis.

P2427 Serial change in left ventricular diastolic function and longitudinal axis systolic function as early manifestation of doxorubicin cardiotoxicity

M.C. Choi, K.L. Tsui, T.K. Yau, W.C. Ko, T.S. Tse, C.K. Chan, K.K. Chan, S.K. Li. *Hong Kong SAR, China*

Purpose: Doxorubicin (Dox) is an useful chemotherapeutic agent but its use is limited by its cardiotoxicity. Our previous data showed that left ventricular (LV) diastolic dysfunction occurred early after Dox use and may be an early marker of Dox cardiotoxicity. This study was performed to evaluate the progressive change in diastolic and systolic function after Dox therapy.
Methods: Baseline LV systolic and diastolic function was assessed in consecutive patients receiving or just before the beginning of Dox-containing chemotherapy. Follow-up echocardiography (Echo) was performed at around 2.5 years after last dose of Dox.
Results: There were 64 patients (M:F=1:63) with age 49±7 years. Follow-up Echo was done at 30.8±5.6 months after last dose of Dox, with a mean accumulated Dox dose of 229mg/m^2. 38 patients had normal diastolic function on first Echo. They showed a significant decrease in E:A ratio (1.40 to 1.18, p<0.001), increase in mitral A (0.58 to 0.69m/s, p<0.001) and decrease in mitral annular early diastolic velocity (Ea) (125 to 90mm/s, p<0.001). In the 26 patients showing impaired relaxation on first Echo, there were significant increase in mitral E (0.60 to 0.73m/s, p<0.001), increase in E:A ratio (0.79 to 0.96, p=0.008), decrease in Ea (86 to 75mm/s, p=0.005) and mitral annular systolic velocity (Sm) (88 to 74mm/s, p=0.001). 13 patients had baseline Echo before beginning of chemotherapy (group A). 51 patients had baseline Echo in early Dox course after a mean accumulated dose of 102mg/m^2 (Group B). Decrease in Ea was greater in group A than in group B (35% vs 17%, p=0.025). Patients with normal diastolic function on first Echo showed greater drop in Ea when compared to those with impaired relaxation on first Echo (25% vs 12%, p=0.019). In group B, patients with impaired relaxation on first Echo showed greater drop in Sm when compared to those with normal diastolic function on first Echo (13% vs 1%, p=0.031).
Conclusions: There was progressive LV diastolic dysfunction & subclinical LV systolic dysfunction after Dox therapy. Diastolic dysfunction may occur earlier than subclinical systolic dysfunction, both of which precede impairment in LV ejection fraction.

THE HEART IN HYPERTENSION. HYPERTENSION, VASCULAR EFFECT

P2428 Myocardial tissue characterisation by acoustic densitometry in patients with hyperaldosteronism. Effect of treatment

M. Salvetti[1], M.L. Muiesan[2], A. Paini[2], C. Monteduro[2], B. Bonzi[2], E. Porteri[2], D. Rizzoni[2], E. Agabiti Rosei[2]. *[1]University of Brescia, Internal Medicine, Brescia, Italy; [2]University of Brescia, Internal Medicine, Brescia, Italy*

In patients with primary aldosteronism(PA)aldosterone may promote the development left ventricular hypertrophy and the deposition of myocardial collagen.
Aim: Aim of this study was to evaluate the effect of treatment on cardiac structural changes in patients with primary aldosteronism.
In 22 patients with PA(14 with adrenal hyperplasia (AH), 8 with aldosterone producing adenoma (APA) (12 M,10 F, mean age 50±10 years)left ventricular anatomy and function were evaluated by conventional echocardiography at baseline and after treatment(surgery for patients with APA and an aldosterone receptor blocker in AH).Mean follow up was 14.6±6months.In all subjects integrated backscatter signal was analyzed by acoustic densitometry(IBS).The signal was sampled with a R.O.I. placed in the mid portion of the interventricular septum(IVS)and of the posterior wall(PW).Analysis of IBS mean amplitude and of systo-diastolic variation(CV)of IBS were considered.Left atrial dimensions (LA), LV mass index(LVMI),relative wall thickness(RWT),endocardial and midwall fractional shortening(mid FS) were calculated.Transmitral flow velocities, E wave deceleration time and IVRT were measured for diastolic filling evaluation.
Results: A significant reduction of blood pressure values, of LVMI, of LA dimensions as well as of the prevalence of diastolic dysfunction was observed during treatment.Furthermore a significant increase of IBS CV was observed, both at the IVS and at the PW (table).
Conclusions: In patients with APA or AH surgery or pharmacological treatment with an aldosterone receptor blocker is associated with an improvement of structural and functional properties of the left ventricle, possibly related to a reduction

Table 1. Results

	Basal	Follow up
BP mmHgBP	155±24/94.5±13	140±14*/89±7
LVMI gr/m^2	48±10	40±9.5*
RWT	0.363±0.36	0.345±0.34
LA	3.82±0.85	3.55±0.43*
Diast dysf	41%	18%#
CV IBS septum dB	4.6±1.4	7.4±2.5*
CV IBS post wall	6.5±2.3	9.1±4.5*

* p at least 0.05 vs basal,T test; # p<0.05,Mc Nemar Test

of myocardial collagen content, as suggested by ultrasound tissue characterization.

P2429 Diastolic function at rest and during dobutamine stress echocardiography in women with hypertension – comparison with assessment of coronary microcirculation by cardiovascular magnetic resonance

D. Czarnecka[1], K. Kawecka-Jaszcz[1], A. Kwiecien-Sobstel[1], A. Olszanecka[2], M. Pasowicz[3], P. Klimeczek[3], R. Banys[3], A. Klecha[1]. *[1]Jagiellonian University, I Cardiac Department, Kraków, Poland; [2]Jagiellonian University, I Cardiac Department, Krakow, Poland; [3]John Paul the 2nd Hospital, Krakow, Poland*

The aim of the study was to asses left ventricle diastolic function in women with arterial hypertension, history of chest pain and normal coronary angiograms and to compare the results with parameters of myocardial perfusion detected by cardiovascular magnetic resonance imaging (CMR).

Material and methods: The study included 26 women (age 56.4±8.4 years) with hypertension and normal coronary angiograms. In all women echocardiographic examination was performed to evaluate diastolic function: peak velocity of E wave (E); A wave (A) and E/A ratio. In all women dobutamine stress echocardiography was performed. Using pulsed wave tissue Doppler echocardiography (TDE) peak velocities of basal segments of interventricular septum (IVS) and lateral wall (LW): early diastolic (E') and late diastolic (A') were measured at rest, during low and high dose of dobutamine. Each women underwent myocardial first pass perfusion CMR imaging both at rest and during infusion of adenosine 140 μg/kg/min. Signal intensity vs time curves were constructed for each patient. Quantitative perfusion analysis was performed by using upslope of myocardial signal enhancement to derive the myocardial perfusion index and the myocardial perfusion reserve index (MPRI) defined as the ratio of perfusion index during stress to the index at rest for each of the myocardial regions of interest.

Results: The study group was divided according to the presence of diastolic dysfunction (E/A < 1). There were no differences in myocardial velocities measured by TDE at rest and during infusion of dobutamine according to parameters of diastolic function. Neither at rest, nor during stress we could observe any differences in the parameters of myocardial perfusion between women with and without diastolic dysfunction (table).

Results

	n	MPRI		IVS rest		LW rest		IVS high dose		LW high dose	
		IVS	LW	E'	A'	E'	A'	E'	A'	E'	A'
Group 1											
(E/A >1)	12	0.99	1.04	7.4	8.5	11.3	8.8	7.9	11.1	12.6	10.2
Group 2											
(E/A <1)	14	0.93	1.00	6.0	9.0	9.43	9.75	6.9	11.4	11.0	11.6

Conclusion: In the examined group of women with arterial hypertension the presence of diastolic dysfunction did not affect the parameters of diastolic function during dobutamine stress echocardiography measured by pulsed wave TDE and did not affect coronary microcirculation assessed by perfusion CMR imaging.

P2430 Nonhaemodynamic factors determing prognosis in hypertensive patients with left ventricular hypertrophy

O.M. Moiseeva[1], S. Villevalde[2], I. Emelyanov[2], E. Shlyachkto[2]. *[1]Research Institute of Cardiology, Heart Failure Departmen, St-Petersburg, Russian Federation; [2]Research Institute of Cardiology, Noncoronary disease, St-Petersburg, Russian Federation*

Objective: Left ventricular hypertrophy (LVH) is a powerful and independent predictor of cardiovascular complications and death in subjects with essential hypertension. However, the mechanisms of association LVH with cardiac and cerebrovascular morbidity are unclear. The present study was designed to investigate change of nonhemodynamic factors which are able to promote cardiovascular risk in hypertensive patients with LVH.

Design and Methods: We examined 60 untreated hypertensive men (age 46.9±7.1 yrs) and 15 normotensive healthy volunteers (age 45.7±6.5 yrs). In all subjects 24-hour ABP monitoring, echocardiograms, evaluation of carotid intima-media thickness, flow-mediated dilatation (FMD) of radial artery were performed. Plasma concentrations of von Willebrand factor (vWf), soluble intercellular adhesion molecule-1 (sICAM-1) and vascular endothelial growth factor (VEGF) were measured by ELISA method. Flow cytometric analysis was carried out to measure expression of CD3, HLA-DR, CD25, CD11b, and CD69. Neutrophils' (PMN) adherence to ECV304 cell line was quantificated. Hemorheologic parameters (platelets' aggregation, red blood cell (RBC) aggregation and rigidity) were assessed.

Results: vWf, sICAM-1 and VEGF levels were elevated in hypertensive patients with essential hypertension comparing with control group. Concentrations of these factors correlated with duration of hypertension, clinic and 24-hour average BP. In hypertensive patients with the echocardiographic signs of LVH vWf (94.2±2.2% and 77.2±4.9%, p<0.01) sICAM-1 (425.8±11.8 ng/ml and 347.5±18.5 ng/ml, p<0.01) and VEGF (156.5±18.4 pg/ml and 91.7±7.6 pg/ml, p<0.01) concentrations were statistically higher. Increased left ventricular mass index was accompanied by increased platelets' (r=0,444; p<0,001) and RBC aggregation(r=0,370; p<0,01), and decreased RBC rigidity (r=0,367; p<0,01). Maximal increase of these factors was found in patients with concentric LVH. Decrease of FMD in hypertensive patients was associated with increased sICAM-1 (beta = -0.549; p<0.01) and VEGF level (beta = -0.532; p<0.01). sICAM-1 level (beta=0.442; p=0.002) correlated with increased intima-media thickness of carotid arteries. In hypertensive patients with LVH we revealed increased PMN adherence (p<0,001), the number of circulating CD11b+-lymphocytes and monocytes (p<0,001), CD3+DR+-lymphocytes (p<0,05).

Conclusion: Increased risk of cardiovascular events in hypertensive patients related with endothelial dysfunction, abnormal angiogenesis, and development of protrombotic condition and atherogenesis progression.

P2431 Impact of the rate of blood pressure changes on left ventricular mass

E. Manios[1], G. Tsivgoulis[2], K. Spengos[2], G. Barlas[3], I. Ikonomidis[3], K. Dolianitis[3], K. Vemmos[3], N. Zakopoulos[3]. *[1]Athens, Greece; [2]University of Athens, Department of Neurology, Athens, Greece; [3]University of Athens, Department of Clinical Therapeutics, Athens, Greece*

The extent of target-organ damage has been positively related to the magnitude of blood pressure (BP) variability in essential hypertension. However, the clinical implications of the rate of BP changes have never been investigated.

Aim: We evaluated the potential association between the 24-hour time rate of systolic blood pressure (SBP) variation derived from computerized analysis of ambulatory BP monitoring (ABPM) data and the left ventricular mass (LVM) in normotensive (n=658) and in uncomplicated hypertensive subjects (n=428).

Methods: No antihypertensive treatment had ever been administered in any of the 1086 subjects who underwent ABPM on a usual working day and M-mode echocardiography. The time rate of SBP variation was computed as the first derivative of the SBP values against time. The degree of nocturnal BP dip was calculated as: [(mean daytime values- mean nightime values)/mean daytime values] x 100. Echocardiographic measurements were made according to the Penn Convention protocol to measure LVM, which was calculated by the formula according to Devereux and expressed as LVM index (LVMI). Statistical analyses were performed by means of ANCOVA, simple and multiple linear regression analyses.

Results: The daytime and night-time rate of SBP variation were significantly (p<0.01) higher in hypertensive (0.622mmHg/min, 95%CI:0.610-0.624 and 0.533mmHg/min, 95%CI:0.519-0.547 respectively) than in normotensive individuals (0.596mmHg/min, 95%CI:0.586-0.606 and 0.514mmHg/min, 95%CI:0.503-0.525 respectively) even after adjusting for baseline characteristics, daytime and night-time heart rate (HR), SBP- and HR variability. In the entire group of patients multiple linear regression models revealed independent determinants of LVMI the following ABPM parameters even after adjusting for baseline characteristics: daytime HR (standardized linear regression coefficient: β= −0.226, p<0.001), nocturnal SBP dipping (β= −0.169, p<0.001), daytime SBP (β= +0.151, p<0.001), night-time heart rate variability (β= −0.090, p=0.003) and night-time rate of SBP variation (β= +0.073, p=0.018). A 0.1mmHg/min increase in the night-time rate of SBP variation was associated to an increment of 1.205 kg/m^2 (95%CI:0.209-2.201) in LVMI independent of baseline characteristics BP- and HR levels, BP- and HR variability and dipping status.

Conclusions: The rate of BP fluctuations is greater in hypertensive patients and is associated to early hypertensive target-organ damage. This relationship is independent of traditional cardiovascular risk factors and of ambulatory BP levels.

P2432 Mechanisms underlying the nebivolol-induced eNOS-activation in human umbilical venous endothelial cells

K. Brixius. *Clinic III of Internal Medicine,Cologne Univ., Lab. of Muscle Res. & Mol. Cardiology, Cologne (Koln), Germany*

Nebivolol (NEB) has been shown to be a selective blocker of the β1-adrenoceptors with additional vasodilating properties which are mediated -at least partly- by an endothelial-dependent liberation of nitric oxide (NO). The present study investigated the underlying mechanisms. Immunohistochemical stainings of the endothelial NO-synthase (eNOS) were performed in the absence and presence of NEB in human umbilical venous endothelial cells (HUVEC). In addition, we measured the release of NO using diaminofluorescein. Metoprolol (MET) and Carvedilol (CAR) were measured for comparison.

NEB, but not CAR or MET (each 10 μM), time-dependently increased NO-release

from HUVEC (increase in DAF-fluorescence 1 vs. 10 min, NEB: +234±7%basal, CAR: +71±3%basal, MET: 55±22%basal). Blockade of the β3-adrenoceptors by SR 59230A (1 μM) partly reduced the Nebivolol-induced DAF-fluorescence. A complete blockade of NEB-induced NO-liberation was achieved after simultaneous β3-adrenoceptor- and estrogen receptor blockade. Application of NEB significantly increased eNOS-translocation and SER1177 phosphorylation of eNOS. The latter was paralleled by an increased phosphorylation/activation of Akt/protein kinase B. Nebivolol did not alter eNOS-phosphorylation at Ser114 and was free of generation of oxygen derived free radicals

Conclusion: The endothelium-dependent NO-liberation induced by Nebivolol is due to a stimulation of β3-adrenoceptors and estrogen receptors and goes along with an eNOS-translocation and a phosphorylation at eNOS SER1177. Nebivolol is free of the generation of radical oxygen/nitrogen species. These characteristics of Nebivolol may be not only beneficial when treating patients suffering from cardiovascular disease but may also prevent a further deterioration of endothelial dysfunction.

P2433 Antihypertensive efficacy of zofenopril plus hydrochlorothiazide fixed combination is superior to that of single components

E. Malacco[1], S. Omboni[2] on behalf of the Study Group. *[1]L. Sacco Hospital, Internal Medicine III, Milano, Italy; [2]Docleader S.r.l., Somma Lombardo, Italy*

Aim: to compare the antihypertensive effect and safety of a fixed combination of Zofenopril (Z) and Hydrochlorothiazide (HCTZ) vs. the single components in essential hypertensive patients.

Design: two international, multicentre, double-blind, randomized, parallel group studies were performed. Study 1 (S1) included 463 mild-moderate essential hypertensive patients (95≤DBP≤115 mm Hg) aged 18-75 years (56% males) randomized 2:1:1 to Z 30 mg + HCTZ 12.5 mg, Z 30 mg or HCTZ 12.5 mg od for 36 weeks, following 4 weeks of placebo wash-out. Efficacy was evaluated in the first 12 weeks; safety over the whole study period. In study 2 (S2) 369 mild-moderate essential hypertensive patients (90≤DBP≤109 mm Hg) aged 18-70 years (46% males), after 4 weeks of placebo, were treated with Z 30 mg od (single-blind). Non responder patients after 4 weeks of T were randomized (double-blind) to Z 30 mg + HCTZ 12.5 mg or Z 30 mg od for 8 weeks. Intention-to-treat (ITT) and per-protocol (PP) analyses were performed.

Methods: at baseline and at the end of T, BP was measured by mercury sphygmomanometry 24h after last dosing. DBP and SBP changes with T and rate of DBP and SBP responders were calculated.

Results: DBP and SBP reductions with T (S1) were significantly greater under combination T (14±9/19±16 mm Hg, n=235) than under Z (10±9/11±16 mm Hg, n=115) or HCTZ alone (10±8/16±13 mm Hg, n=113). Rate of DBP responders (DBP ≤90 mm Hg or reduction =>10 mm Hg) was also greater under Z + HCTZ than under single drug T ($p<0.01$). In the patients of S2 non responders to T after 4 weeks (SBP =>130 and DBP =>85 and/or SBP reduction <20 and/or DBP reduction <10 mm Hg: 77%), a further BP decrease was observed with Z (5±7/8±12 mm Hg, n=184), but this was less consistent than that observed under Z + HCTZ (7±6/10±10 mm Hg; $p<0.05$ for DBP and $p<0.001$ for SBP, n=185). BP reached a plateau with Z at week 8, while kept decreasing with the combination. Rate of responder patients (DBP<85 mm Hg or reduction =>10 mm Hg) was greater under Z + HCTZ (43%) than under Z alone (30%). Results of PP analysis (S1: 342 subjects; S2: 282 subjects) were in line with those of ITT population. HR was not modified by T. Safety was better or comparable under Z + HCTZ and single drug T (6% of patients withdrawn for adverse events vs. 12% under Z and 11% under HCTZ in S1; 2% vs. 2% under Z in S2).

Conclusions: the fixed combination of Z + HCTZ improved the efficacy of either component alone, with a good tolerability profile. The advantage of this combination was particularly evident in non-responders to single drug T with Z.

P2434 Carvedilol blood pressure antihypertensive effect is modulated by Arg389Gly beta1-adrenergic receptor polymorphism

K. Lucarelli[1], S. Sorrentino[1], P. Guida[1], C. Forleo[1], E. De Tommasi[1], R. Romito[2], M. Iacoviello[1], M.V. Pitzalis[1]. *[1]University of Bari, Institute of Cardiology, Bari, Italy; [2]S. Maugeri Foundation, Cardiology Dept., Cassano M, Italy*

Genetic polymorphisms in adrenergic receptors (AR) may contribute to interindividual differences in antihypertensive therapy response. Since carvedilol is a non-selective betablocker, we sought to evaluate whether its blood pressure lowering effect is related to functionally relevant alpha- and beta-AR polymorphisms in the genes coding for these receptors.To test this hypothesis, 54 never treated hypertensive patients (46±10 years, 43 men) underwent baseline examinations including 24-hour ambulatory blood pressure monitoring (ABPM). After four weeks at stable dose of carvedilol (25 mg/die), ABPM was repeated. Patients were genotyped for the following polymorphisms: Ser49Gly and Arg389Gly of the beta1-AR; Arg19Cys in the promoter region, Arg16Gly and Gln27Glu in the coding region of the beta2-AR; Arg492Cys of the alpha1A-AR.

At baseline, patients carrying homozygosity for Arg389 variant of the beta1-AR (Homo Arg389: 26 pts) had a significantly higher 24-hour (140±8 mm Hg vs 133±7 mm Hg, $p<0.01$), daytime (dt) (145±9 mm Hg vs 138±7 mm Hg, $p<0.01$) and night-time (nt) (126±10 mm Hg vs 120±10 mm Hg, $p<0.05$) systolic (S) BP in comparison with those carrying at least one copy of Gly389 allele (Hetero Arg389Gly: 22 pts and Homo Gly389: 6 pts). After carvedilol administration, patients who were homozygous for Arg389 allele had a significantly greater reduction in 24-hour, daytime BP and night-time diastolic (D) BP values compared with the others (Table).

Table

	Homo Arg389	Not Homo Arg389	p
	n= 26	n=28	
24-h SBP (mm Hg)	-14 ± 9	-9 ± 6	<0.05
24-h DBP (mm Hg)	-9 ± 6	-6 ± 4	<0.01
dtSBP (mm Hg)	-14 ± 10	-9 ± 7	<0.05
dtDBP (mm Hg)	-9 ± 7	-6 ± 4	<0.05
ntSBP (mm Hg)	-12 ± 12	-8 ± 7	NS
ntDBP (mm Hg)	-9 ± 6	-5 ± 5	<0.05

Mean blood pressure changes according to Arg389Gly polymorphism of the beta1-AR after carvedilol

In conclusion, beta1-AR Arg389Gly polymorphism is both a modulating factor of blood pressure evaluated at baseline conditions and a relevant determinat of carvedilol blood pressure antihypertensive effect in patients with essential hypertension.

P2435 Ascending aortic blood pressure waveform is related to the risk of coronary artery disease also in normotensive subjects

P. Jankowski[1], D. Czarnecka[2], M. Brzozowska-Kiszka[2], B. Kiec-Wilk[2], M. Loster[2], A. Posnik-Urbanska[2], K. Styczkiewcz[2], K. Kawecka-Jaszcz[2]. *[1]Krakow, Poland; [2]Jagiellonian University, I Department of Cardiology, Kraków, Poland*

Background: Aortic blood pressure (BP)-derived indices were shown to be related to the extent of coronary atherosclerosis. However, the blood pressure-derived indices – coronary atherosclerosis relationship in subjects without hypertension (HT) is still unknown. Therefore, the aim of the present study was to evaluate relation between ascending aortic BP waveform and the incidence of coronary artery disease (CAD) in patients with and without HT.

Methods: The study group consisted of 626 consecutive patients (438 men and 188 women; 491 hypertensives and 135 normotensives; mean age: 57.3±10.2 years) with preserved left ventricular systolic function, undergoing coronary angiography. Invasive ascending aortic BP during catheterization and conventional sphygmomanometer measurements were taken.

Results: Out of 626 participants CAD was diagnosed in 436 (69.8%) patients. The adjusted means (for age and gender) of aortic BP-derived indices according to CAD and HT status are given in the table. In multivariate logistic regression analysis only aortic pulsatility (the ratio of pulse pressure to mean blood pressure) and aortic pulsatility index (the ratio of pulse pressure to diastolic blood pressure) were independently related to the presence of CAD: pulsatility per 0.1 OR 1.22 (95%CI 1.03-1.45) and 1.91 (1.09-3.32); pulsatility index per 0.1 OR 1.12 (95%CI 1.02-1.24) and 1.48 (1.03-2.12) for hypertensives and normotensives, respectively. None of brachial blood pressure-derived indices was related to CAD.

Mean values of aortic BP-derived indices

	Hypertensives		Normotensives	
	CAD (-) N = 146	CAD (+) N = 345	CAD (-) N = 44	CAD (+) N = 91
SBP (mmHg)	141.1 (± 22.3)	141.4 (± 23.1)	123.3 (± 19.3)	128.3 (± 20.7)
DBP (mmHg)	74.5 (± 10.6) *	72.0 (± 10.9)	69.8 (± 10.9)	69.4 (± 11.7)
MBP (mmHg)	96.7 (± 13.2)	95.1 (± 13.7)	87.6 (± 13.0)	89.0 (± 14.0)
PP (mmHg)	66.6 (± 17.3)	69.4 (± 17.9)	53.5 (± 12.5) *	58.9 (± 13.4)
Pulsatility	0.69 (± 0.14) *	0.73 (± 0.14)	0.61 (± 0.11) *	0.66 (± 0.12)
Pulsatility index	0.91 (± 0.25) *	0.98 (± 0.26)	0.77 (± 0.18)	0.85 (± 0.19)

* $p < 0.05$ vs CAD (+); SBP–systolic blood pressure, DBP–diastolic blood pressure, MBP–mean blood pressure, PP–pulse pressure

Conclusion: Aortic pulsatility is related to the risk of coronary artery disease in hypertensive and normotensive subjects.

P2436 Brachial artery vasoreactivity in patients after myocardial infarction: possible correction of endothelial dysfunction using trimetazidine

A. Parkhomenko[1], I. Goncharova[1], S. Kozhukhov[2]. *[1]Institute of Cardiology, Coronary care unit, Kiev, Ukraine; [2]Institute of Cardiology, Coronary care unit, Kiev, Ukraine*

Aims: Endothelial dysfunction (ED) had been identified as a predictor of unfavorable outcomes in patients (pts) with CAD. We aimed to examine vasoreactivity in patients after acute myocardial infarction (AMI).

Methods: Current study was a substudy within open-label randomized trial of atenonol, trimetazidine or both in pts 6 or more months after AMI with angina on exertion. Non-diabetic pts were randomized to atenolol (n=15), trimetazidine (n=15) or both (n=15). Diabetic pts received both atenolol and trimetazi-

dine (n=15). Vasoreactivity was studied by duplex sonography of brachial arteries using Celermajer's protocol. All pts underwent reactive hyperemia cuff-test for endothelium-dependent (EDVd) and nitroglycerin test for endothelium-independent vasodilatation (EIDVd). Increase in vascular diameter after occlusion by >10% and increase after nitroglycerin by >20% were considered normal.
Results: Study groups were comparable in terms of baseline characteristics. ED was present in 86.7% of patients. After 3wks of treatment with trimetazidine or it's combination with atenolol EDVd increased (by 78.8% and 59.2% respectively, $p<0.05$) and EIVDd remained unchanged, whereas time of blood flow recovery (TBFR) increased (by 29.1% and 21.4% respectively), PI3 increased by 23.3% only in trimetazidine group ($p<0.05$). Most prominent increase in EDVd was observed in diabetics (by 81.2%), who also demonstrated longer TBFR after treatment with study drugs (by 21.4%, $p<0.05$). In atenolol group after 3 wks of therapy vasoreactivity did not differ from the baseline.

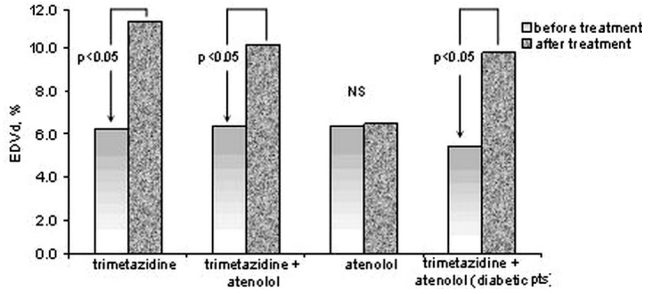


Figure 1.

Conclusion: Atenolol does not impact vasoreactivity. Use of trimetazidine alone or in combination with atenolol is associated with regression of ED, although exact mechanism of action of trimetazidine remains unclear.

P2437 Graded relationship between adiponectin levels and arterial stiffness in newly diagnosed essential hypertensive subjects: a promising marker of diffuse atherosclerosis?

K. Dimitriadis, C. Tsioufis, D. Chatzis, M. Toutouza, E. Taxiarchou, G. Chartzoulakis, C. Stefanadis, I. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: Adiponectin is emerging as a marker of atherosclerosis progression, while increased arterial stiffness is associated with adverse cardiovascular outcome. In this study, we examined whether plasma adiponectin levels are associated with large artery stiffening in essential hypertensive patients.
Methods: 148 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [98 men, mean age=49 years, office blood pressure (BP)=150/97 mmHg], were divided into three groups according to carotid to femoral pulse wave velocity (PWV) values, by means of a computerized method (Complior SP): Group A (PWV$\leq$7.8 m/sec), group B (PWV=7.9-8.7 m/sec) and group C (PWV>8.7 m/sec). Additionally, venous blood samples were drawn for estimation of lipid profile and adiponectin concentrations.
Results: For the pooled population, body mass index (BMI) was 27.17$\pm$3.6 kg/m^2, total cholesterol was 226$\pm$34 mg/dl, adiponectin levels were 8.4$\pm$4.7 μg/ml, left ventricular mass index (LVMI) was 107.4$\pm$23 g/m^2, relative wall thickness was 0.42$\pm$0.05 and PWV was 8.2$\pm$1.3 m/sec. In the entire population, plasma adiponectin levels were negatively related with BMI ($r=-0.168$, $p<0.05$), waist to hip ratio, ($r=-0.421$, $p<0.0001$), office systolic BP ($r=-0.285$, $p<0.0001$), total cholesterol ($r=-0.220$, $p<0.005$) and PWV ($r=-0.280$, $p=0.001$). Additionally, PWV was associated with age ($r=0.294$, $p<0.001$), BMI ($r=0.233$, $p<0.05$), waist to hip ratio ($r=0.261$, $p<0.05$) and office systolic BP ($r=0.221$, $p<0.05$). Patients in group A (n=55) compared to subjects in group B (n=54) and C (n=39) had lower office systolic BP (146.4$\pm$11 vs 150.3$\pm$14 vs 157.1$\pm$14 mmHg, respectively; $p<0.05$ for all cases) and lower office diastolic BP levels (94.2$\pm$8 vs 97.5$\pm$4 vs 101.3$\pm$5 mmHg, respectively; $p<0.05$ for all cases), while did not differ regarding metabolic profile (p=NS). Moreover, LVMI was more increased in group C than in group B and A (121.7$\pm$12 vs 114.7$\pm$16 vs 102$\pm$16 g/m^2, respectively; $p<0.0001$ for all cases). Furthermore, patients in group C exhibited lower levels of adiponectin compared to group B and A (6.7$\pm$3.2 vs 8.2$\pm$4.1 vs 9.8$\pm$3.6 μg/ml, respectively; $p<0.05$ for all cases). Analysis of covariance revealed that adiponectin values remained significantly different between groups after adjustment for confounding factors ($p<0.05$).
Conclusions: In newly diagnosed essential hypertension, there is a decrease in adiponectin values throughout augmenting PWV tertiles. These findings further denote the interrelationships of hypoadiponectinemia with diffuse vascular dysfunction, in this setting.