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ABSTRACT

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AUTONOMIC FAILURE

Poster #1

Locus coeruleus degeneration is associated with orthostatic responses in Parkinson disease and multiple system atrophy

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Background: Locus coeruleus (LC) is a central autonomic regulator affected early and progressively in Parkinson disease (PD) and multiple system atrophy (MSA). Its role in PD/MSA-related autonomic failure is unresolved.
Study purpose: Compare LC volumes (LCv) between PD and MSA patients with neuromelanin-sensitive MRI (NM-MRI) and explore how LC integrity correlates with orthostatic vital signs (OVS).
Hypothesis/prediction: MSA causes centrally mediated autonomic failure, whereas PD involves central and peripheral pathology. We predicted lower LCv to be better associated with OVS in MSA, compared to PD.
Methods: Patients (PD = 73, MSA = 16) had supine and OVS measured at 1 min of active standing; a subset of PD (N = 47), and all MSA, also had 3 min OVS. Orthostatic hypotension (OH) was defined as a systolic BP drop $\geq$ 20 mmHg within 3 min of standing. NM-MRI data were acquired using two Siemens 3 T-MRI scanners (Trio/Prisma-fit) with a 2D gradient-echo sequence with magnetization transfer preparation pulse. LCv (mm^3) were measured using a highly reproducible approach robust to scanner type. One-way ANCOVA compared between-group LCv (controlling age, disease duration, levodopa equivalent daily doses). Two-tailed Spearman correlations were calculated between LCv and OVS. These analyses were repeated after OH-presence stratification (PD + OH = 15; MSA + OH = 9).
Results: LCv were lower in MSA than PD (F = 7.1, p = 0.009). In PD, LCv correlated negatively with 1 min-HR response (r = − 0.34, p = 0.003); in MSA, LCv tended to correlate positively with HR responses (1 min r = 0.49, p = 0.06; 3 min r = 0.45, p = 0.08). No LCv-OVS correlations were significant for OH-negative PD or MSA. In contrast, LCv negatively correlated with 1 min-HR response (r = − 0.79, p < 0.001) in PD + OH, whereas LCv correlated positively with HR response in MSA + OH (1 min r = 0.68, p = 0.04; 3 min r = 0.66, p = 0.05). Systolic BP responses also strongly correlated with LCv in MSA + OH (1 min r = 0.70, p = 0.04; 3 min r = 0.85, p = 0.003).
Conclusions: LCv were lower in MSA than PD, indicating greater LC pathology in MSA. LC integrity correlated with orthostatic HR response with a diagnosis-specific directionality, and a significant positive correlation was observed between LCv and systolic BP response in MSA + OH. These findings support a role for LC neurodegeneration in OH, particularly for MSA, but also suggest differences in OH mechanism between PD and MSA.
Funding: Dr. Huddleston has received support from The Michael J. Fox Foundation (MJFF-10854, MJFF-010556), National Institutes of Health (NINDS 1K23NS105944, NIA 1R34AG056639-02S1, NIA 1U19AG071754), the American Parkinson's Disease Association Center for Advanced Research (Emory University), and the Lewy Body Dementia Association Research Center of Excellence (Emory University), and the McMahon Family.

Poster #2

Multiple system atrophy and breast cancer

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Objective: To assess whether breast cancer is more frequent in multiple system atrophy (MSA) than in the population.
Background: The pathological hallmark of MSA are glial cytoplasmic inclusions containing aggregated alpha-synuclein (α-syn). The functions of the other synucleins (β-syn and γ-syn) are poorly understood. Although not known to be implicated in MSA, γ-syn appears to have a complex relationship with α-syn. γ-Syn colocalizes with α-syn in inclusion bodies in human pathological and transgenic models, inhibits α-syn aggregation in vitro, but in its oxidized form has been shown to initiate α-syn aggregation. When secreted from neuronal cell cultures, γ-syn is internalized by glial cells. As γ-syn is highly expressed in advanced breast carcinomas, we hypothesized that breast cancer might occur more frequently in MSA patients or their families.
Methods: Medical records were queried for personal and family histories of breast cancer in 56 autopsy-proven cases of MSA and compared with 93 sex-matched cases of progressive supranuclear palsy (PSP) and with population cancer data. Categorical variables were compared to population prevalence data by a one-sample test of proportions and between groups by Fisher's exact test with significance set at $p < 0.05$.
Results: Of 27 women with MSA and 46 women with PSP, 5 (19%) and 1 (2%), respectively, had a history of breast cancer ($p = 0.024$). The frequency of breast cancer in MSA exceeded the 1.4 cases expected from population data (Z score 3.11, $p = 0.002$). Breast cancer diagnoses postdated the onset of MSA symptoms in all cases (mean 3.4 years). Of all the 56 MSA and 93 PSP cases, 10 and 7 had a mother (p = 0.066, NS), and 6 and 1 had a sister (p = 0.012) with breast cancer. No significant differences were seen for other types of cancer.
Conclusions: MSA was associated with an increased frequency of a prior history or sibling history of breast cancer. Overexpression of γ-syn or an unknown shared genetic, epigenetic, or environmental factor affecting both α-syn and γ-syn may play a role in the pathogenesis of both breast cancer and MSA. Also, patients with MSA or their families may be at increased risk for breast cancer.

Poster #3

Neurogenic orthostatic hypotension is common in isolated REM sleep behavior disorder

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Introduction: Rapid eye movement (REM) sleep behavior disorder (RBD) is a prodromal synucleinopathy, as the majority of individuals with isolated RBD (iRBD) will phenoconvert to clinically manifest synucleinopathy within a decade. Autonomic dysfunction is common in iRBD, however the prevalence of neurogenic orthostatic hypotension (nOH) in iRBD is unknown. We aimed to prospectively evaluate the prevalence of nOH in a large multicenter cohort of participants with iRBD.
Methods: Participants > 18 years of age with overnight polysomnogram-confirmed iRBD were enrolled from the North American Prodromal Synucleinopathy (NAPS) Consortium. Participants were excluded if they were on antihypertensives or other medications that might contribute to OH. All participants underwent orthostatic stand testing with supine blood pressure (BP) and heart rate (HR) measured after 5-min of supine rest and after 3-min of standing. The ΔHR/Δ systolic BP ratio was calculated for all participants. OH was defined as a SBP and/or diastolic blood pressure (DBP) drop of ≥ 20 mm Hg and/or ≥ 10 mm Hg, respectively. nOH was defined as OH with a ΔHR/ΔSBP ratio of < 0.5. All participants also completed a battery of questionnaires including the Scales for Outcomes in Parkinson's Disease—Autonomic Dysfunction (SCOPA-AUT), as well as neurologic testing across cognitive, motor, psychiatric and sensory domains.
Results: 334 iRBD participants met eligibility criteria. OH was identified in 87 (26%) participants, of which 69 (21%) met criteria for nOH (ΔHR/ΔSBP 0.31 ± 0.24) and 18 (5%) met criteria non-neurogenic OH (ΔHR/ΔSBP 0.70 ± 0.27). There was no difference in participant age, age of RBD onset, or years of education across groups. The rate of supine hypertension was similar in nOH and non-neurogenic OH (71% vs. 67%, respectively), which were both ~ twofold higher than those without OH (34%). Pupillary and sexual dysfunction as measured by SCOPA-AUT subdomain scores, as well as olfaction, were all significantly worse in those with nOH and non-neurogenic OH compared to those without OH. There was no difference in cognitive, motor, or psychiatric outcomes across groups.
Conclusions: nOH is common in those with RBD. These data support the rationale to routinely include orthostatic stand testing in the evaluation of patients with iRBD.
Funding: NIH R34 AG056639.

Poster #4

Longitudinal analysis of ampreloxetine for the treatment of symptomatic neurogenic orthostatic hypotension in subset of patients with multiple system atrophy

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Background: Ampreloxetine, a selective norepinephrine reuptake inhibitor, was investigated in a Phase 3 program for the treatment of neurogenic orthostatic hypotension (nOH) in patients with pure autonomic failure, Parkinson's disease and multiple system atrophy (MSA). Here we assess the efficacy and tolerability of ampreloxetine in the subgroup of patients with multiple system atrophy across the program.
Methods: The Phase 3 program comprised a 4-week randomized double blind placebo controlled study (SEQUOIA), a randomized withdrawal (RW) study containing a 16 week open label (OL) treatment period and a 6 week RW period (REDWOOD) and an OL long term safety study (OAK). Although the Phase 3 program comprised 3 separate studies, patients were allowed to roll over from SEQUOIA into REDWOOD and subsequently into OAK. Efficacy was assessed using the Orthostatic Hypotension Questionnaire (OHQ) and the orthostatic standing test. Safety and tolerability were also examined.
Results: 68 MSA patients received ampreloxetine across the three studies with a combined exposure to ampreloxetine of 45.8 years. Over the 20 weeks from the start of the SEQUOIA study to the end of the OL treatment period in the REDWOOD study, patients experienced a reduction in signs and symptoms as measured by Orthostatic Hypotension Symptom Assessment (OHSA) composite score (mean change, − 2.6 points) and OHSA item 1 "dizziness/lightheadedness" (mean change, − 3.6 points). During the RW period of the REDWOOD study, ampreloxetine patients observed a benefit over placebo across numerous endpoints including the OHSA composite score (LS mean difference, − 1.6 points; 95 percent confidence interval, − 2.7 to − 0.5), OHSA item 1 (LS mean difference, − 1.5 points; 95 percent confidence interval, − 3.2 to 0.2) and 3-min standing systolic blood pressure (LS mean difference, 15.7 mmHg; 95% confidence interval, 3.2 to 28.1). Ampreloxetine was well tolerated in MSA patients across all studies with the proportion of patients experiencing adverse events similar to placebo during each of the placebo-controlled periods.
Conclusion: Longitudinal analysis of the ampreloxetine phase 3 program supports the durability of ampreloxetine as a potential treatment of symptomatic nOH in patients with MSA.

Poster #5

Cutaneous alpha-synuclein deposition: a biomarker in multiple system atrophy

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Objective: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder caused by the abnormal accumulation of alpha-synuclein in the nervous system. Clinical features include autonomic and motor dysfunction, which overlap with those of Parkinson disease (PD), particularly at early disease stages. There is an unmet need for accurate diagnostic and prognostic biomarkers for MSA, and, specifically, a critical need to distinguish MSA from the other synucleinopathies, particularly PD.
Methods: We studied 31 patients with MSA and 54 patients with PD diagnosed according to current clinical consensus criteria. We also included 24 matched controls. All participants underwent neurologic examinations, autonomic testing, and skin biopsies at three locations. The density of intra-epidermal, sudomotor and pilomotor nerve fibers was measured and the ratio of total alpha-synuclein to nerve fiber density was calculated. The deposition of phosphorylated alpha-synuclein was also quantified. Results were compared to clinical ratings assessments and autonomic function test results.
Results: Patients with PD had reduced nerve fiber densities compared to patients with MSA ($P < 0.05$, all fiber types). All patients with MSA and 51/54 with PD had evidence of phosphorylated alpha-synuclein in at least one skin biopsy, with no phosphorylated alpha-synuclein in controls. Patients with MSA had greater and more widespread distribution of phosphorylated alpha-synuclein than patients with PD ($P < 0.0001$). Quantitation of synuclein deposition and distribution provided > 90% accuracy in distinguishing MSA from PD and correlated with disease severity.
Classification of Evidence: This cohort study provide Class II Evidence for skin biopsy quantitation of phosphorylated alpha-synuclein in differentiating patients with MSA from PD.
Discussion: Alpha-synuclein is present in peripheral autonomic nerves of MSA patients, and combined with synuclein distribution, accurately distinguishes MSA from PD.
Funding: This work was supported by National Institutes of Health [NIH U54 NS065736]; the Langer Family Foundation (to R.F.); the MSA Coalition (to R.F.) and University of Colorado Skin Disease Research Center (to DSK).

Poster #6

Tilt-evoked, breathing-related blood pressure oscillations despite baroreflex-sympathoneural failure

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Background: Orthostasis increases blood pressure (BP) variability. Reports about tilt-induced BP oscillations have dwelled on relatively low-frequency "Mayer waves", which are linked to sympathoneural modulation. Orthostatic BP oscillations can also occur at the relatively higher frequency of breathing. Whether these also depend on baroreflex-sympathoneural modulation has been unclear. We report large tilt-evoked, breathing-driven BP oscillations in a patient with post-neurosurgical orthostatic hypotension who had severe baroreflex-sympathoneural failure.
Methods: Autonomic medical consultation was requested for a patient who had undergone posterior fossa neurosurgery for medullary hemangioblastoma associated with von Hippel-Lindau disease and had developed severe, disabling orthostatic hypotension post-operatively. Neurogenic orthostatic hypotension (nOH) was demonstrated by a progressive decline in BP in Phase II of the Valsalva maneuver, a markedly prolonged pressure recovery time of about 60 s (normal $\leq$ 4 s) after release of the maneuver, and an attenuated orthostatic increment in the plasma norepinephrine concentration. We opined that nOH in this case reflected a lesion at the level of the nucleus of the solitary tract (NTS), which is located bilaterally in the dorsal medulla and is the site of initial synapse formation of baroreflex afferents to the brain.
Results: Unexpectedly, the patient had normal baroreflex-cardiovagal function; this excluded an NTS lesion. Nevertheless, both upon initial evaluation and after symptomatic improvement about 2 weeks later, the patient had clearly seen, tilt-evoked, breathing-driven BP oscillations (about 10–20 mmHg systolic).
Conclusions: The findings in this case suggest that, in contrast with Mayer waves, respiration-driven BP oscillations during orthostasis can occur independently of baroreflex-sympathoneural modulation. The oscillations may represent unbuffered mechanical effects of respiration on ventricular filling.
Funding: Supported by the Division of Intramural Research, NIH, NINDS.

Poster #7

Baroreflex-sympathoneural dysfunction predicts central Lewy body diseases in at-risk individuals

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Background: In central Lewy body diseases (LBDs) such as Parkinson's disease (PD), by the time catecholaminergic neurodegeneration manifests clinically substantial neuronal loss has already occurred. It is crucial to identify biomarkers that can detect central LBDs in a preclinical phase. Cardiac sympathetic neuroimaging and cerebrospinal fluid neurochemistry have this capability but are impractical. We asked whether more readily available physiological biomarkers predict central LBDs during long-term follow-up in individuals with multiple risk factors for PD. Highlighted here are data about the log of the pressure recovery time after release of the Valsalva maneuver (LogPRT), an index of baroreflex-sympathoneural dysfunction.
Methods: In a prospective, longitudinal cohort study individuals provided information about family history of PD, olfactory dysfunction, dream enactment behavior, and orthostatic hypotension at a protocol-specific website. Of these, 28 had at least 3 confirmed risk factors at the NIH Clinical Center and then underwent comprehensive inpatient testing every 18 months until a diagnosis of PD or dementia with Lewy bodies or until 7.5 follow-up years. LogPRT data in individuals developing a central LBD (PDRisk + , N = 7) were compared to those in risk-matched individuals who did not develop a central LBD (PDRisk-, N = 21). Data were also analyzed for screen failures with < 3 confirmed risk factors (N = 24) and healthy volunteers (HVs, N = 33).
Results: The PDRisk + group had greater mean LogPRT at baseline than did the PDRisk-group (p = 0.0054), screen failures (p = 0.0030),

and HVs (p = 0.0003). All PDRisk + and 33% of PDRisk-individuals had baseline PRT ≥ 4 s (sensitivity 100% at specificity 67%).
Conclusions: In at-risk individuals, prolonged LogPRT sensitively identifies those who go on to be diagnosed with a central LBD during long-term follow-up.
Funding: Supported by the Division of Intramural Research, NIH, NINDS.

Poster #8

Evaluating phenoconversion from pure autonomic failure to Parkinson's disease using ^{18}F-dihydroxyphenylalanine (DOPA) PET imaging

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Background: Individuals diagnosed with pure autonomic failure (PAF) have a high-risk for phenoconversion to a central alpha-synucleinopathy including multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and Parkinson's disease (PD). PD specifically is characterized by lack of striatal dopamine. ^{18}F-dihydroxyphenylalanine (DOPA) is a positron emission tomography (PET) radiotracer used to measure dopamine integrity in the brain. The purpose of this study is aiming to evaluate 18F-DOPA uptake in patients with PAF and PD.
Methods: Ten participants (aged 59–73, 4 females, 6 males) with PAF (n = 6) and idiopathic PD (n = 4) completed a baseline 18F-DOPA scan and 5 participants completed a follow-up scan after 1 year. 30 min prior to the scan, participants were administered an oral dose of entacapone (400 mg) and carbidopa (200 mg) to inhibit peripheral aromatic amino acid decarboxylase and increase tracer availability in the striatum. Parametric influx constant (K_i^{cer}; unit: min^{-1}) maps were calculated using the graphical Patlak reference model with the cerebellum used as the reference region. Of the follow-up participants, 2 phenoconverted and met clinical criteria for PD. Kruskal–Wallis rank sum tests were used for statistical comparisons.
Results: At baseline, PD participants had reductions in mean K_i^{cer} localized to the globus pallidus (PD mean = 0.0042, PAF mean = 0.0063; p = 0.02) and putamen (PD mean = 0.0053, PAF mean = 0.0097; p = 0.02). In follow-up scans (n = 5), there appeared to be reductions in the caudate (mean change = − 14.69%; p = 0.06) and putamen (mean change = − 15.35%; p = 0.06). We did not see significant differences in PD patients at baseline compared to phenoconverted PD patients after 1 year.
Conclusions: Findings support the use of 18F-DOPA PET imaging to characterize presynaptic monoamine changes in key striatal regions that help identify the progression and phenotype of patients who convert to central synucleinopathies. Ongoing investigations to evaluate 18F-DOPA uptake correlations with noninvasive methods, such as neuromelanin, are warranted.
Funding: This study was supported by the National Institutes of Health (5K24AG064114-02 to D.O.C.).

Poster #9

Urinary symptom profile in early multiple system atrophy

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Objective: Evaluate the Urinary Symptom Profile (USP) in a cohort of patients with early multiple system atrophy (MSA).
Background: Multiple system atrophy is a progressive neurodegenerative disease that presents with motor and autonomic symptoms. Urinary symptoms can occur at any time along the disease process; however, no study has carefully characterized patient reported urinary symptoms in MSA. The Urinary Symptom Profile (USP; https://doi.org/10.1016/j.urology.2007.11.100) is a validated, 13 item patient-reported scale that assesses stress urinary incontinence (SUI), over active bladder (OAB), and low stream (LS). The USP was applied to a cohort of early MSA patients from the bioMUSE Natural history study.
Design/Methods: This early MSA population included 16 participants, 8 females and 8 males, mean age 62 (range 49–79), with a mean symptom duration of 3.25 years. One participant had a bladder stimulator and 3 were taking medications for urinary symptoms. All completed a neurologic examination, the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I, the Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus scale (PPS), and the Urinary Symptom Profile (USP) questionnaire. The PPS and UMSARS total urinary symptom scores were correlated with the total USP score using a t-distribution and the Spearman's rank correlation.
Results: The mean USP score was 14.06, range 4 to 30. The total USP scores positively correlated with total urinary symptom scores from the UMSARS (p = 0.075, r^2 = 0.458) and PPS (p = 0.002, r^2 = 0.713). Across this cohort, the most severe complaints were related to urinary urgency (OAB avg = 8.4), and reduced amount of time to hold urine (SUI avg = 2.63). Subscale analysis of the USP indicates that the most common symptoms relate to OAB, and least common were SUI.
Conclusions: In early MSA, urinary symptoms are greatest in relation to overactive bladder, specifically urgency and frequency. These results suggest that the USP can be used for comprehensive evaluation of urinary complaints and give important insights to the concerns of patients early in disease.
Funding: Alterity Therapeutics.

Poster #10

Cutaneous phosphorylated synuclein as a diagnostic biomarker in potential pure autonomic failure

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Background: Pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are neurodegenerative diseases characterised by abnormal α-synuclein deposition. 12–34% with PAF later develop other neurological symptoms consistent with MSA, PD or DLB. Subacute disabling autonomic failure and other atypical features may suggest

underlying autoimmune rather than degenerative aetiology, even without known auto-antibodies. Early biomarkers to confirm an underlying synucleinopathy could aid prognostication and help tailor treatment strategies.
Methods: We present preliminary results from a cohort study of patients with possible PAF, MSA and PD and disease controls with non-synuclein pathology from a national autonomic centre between April 2018-June 2021. All patients had comprehensive autonomic testing and distal leg skin biopsies and were re-evaluated up to June 2022 for possible phenoconversion. 4 potential PAF patients with atypical features received a trial of immunotherapy from treating clinicians for possible autoimmune disease without improvement. Skin biopsies were analysed using indirect immunofluorescence to measure intraepidermal and pilomotor innervation and evaluate for phosphorylated synuclein (p-synuclein) on nerves supplying sweat glands, piloerector muscles, vessels, and subepidermal nerves, deeper cutaneous nerves and nerve bundles giving a semiquantitative p-synuclein score out of 6.
Results: 39 patients (14 female, median age 60) were studied: 27 with synucleinopathies, including 11 with potential PAF (9 retained diagnosis by last review, 1 developed PD, 1 developed DLB), 13 with MSA, 3 with PD, and 12 with non-synuclein pathology, including autoimmune autonomic ganglionopathy (8), progressive supranuclear palsy (2), toxic and inherited neuropathies (2). Cutaneous p-synuclein was present in 24/27 synucleinopathy patients: 11/11 with potential PAF, 12/13 with MSA, and 1/3 with PD and 0/12 non-synuclein controls. Average p-synuclein score was significantly higher in patients recruited with PAF (median 4.5, IQR 3.75–4.75) vs. MSA (1, 0.5–1.5) and PD (0, 0–0.75), $P < 0.01$. Intraepidermal and pilomotor innervation did not differ between groups.
Discussion: Cutaneous p-synuclein is a valuable diagnostic biomarker in patients with potential PAF and appears to be more abundant in PAF vs. MSA and PD, consistent with predominant peripheral synuclein deposition. Further larger studies are needed to evaluate if synuclein deposition patterns can predict later phenoconversion.
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Poster #11

Diagnostic value of ambulatory blood pressure monitoring across the spectrum of orthostatic intolerance

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Background: Accurate recognition of syndromes of different orthostatic intolerance is indispensable for optimal management and counseling of patients. We aimed to study the diagnostic value of 24-h ambulatory blood pressure monitoring (ABPM) in identifying patients with autonomic failure.
Methods: We retrospectively analyzed consecutive autonomic reflex screens and ABPM performed at Mayo Clinic in Rochester, MN between 2000 and 2020 in patients with syndromes of orthostatic intolerance. We analyzed average values and standard deviation of systolic blood pressure (SD-SBP) and heart rate (SD-HR) on ABPM, indices of baroreflex function, and hemodynamic responses to tilt. This study was reviewed and approved by the Mayo Clinic institutional review board and included patients who provided consent for use of their medical records for research purposes.
Results: We identified 216 patients (129 men [59.7%]). Orthostatic intolerance was secondary to autonomic failure in multiple system atrophy (MSA, N = 30), pure autonomic failure (PAF, N = 30), afferent baroreflex failure (ABF, N = 77), and autonomic neuropathy (N = 20), whereas other causes of orthostatic intolerance included syncope (N = 29), and postural tachycardia syndrome (POTS, N = 30). There were significant correlations between individual ABPM parameters and autonomic function tests. Patients in the POTS and syncope groups had lower ambulatory SD-SBP compared to all other groups. In contrast daytime SD-HR was lower in patients with autonomic failure compared to syncope and POTS. A daytime SD-SBP/SD-HR ratio > 1.25 mmHg.min^{-1} efficiently distinguished patients with autonomic failure from others with a sensitivity and specificity of 97.2% and 89.7%, respectively.
Conclusion: Parameters derived from ABPM reflect autonomic function across syndromes of orthostatic intolerance. Analysis of the SD-HR and SD-SBP on ABPM allows for accurate identification of patients with autonomic failure. This approach may lead to early identification of patients with autonomic failure.
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Poster #12

Longitudinal follow-up data by cardiac and brain PET scanning fit with "brain-first/body-first" progression of Lewy body diseases

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Background: A recently proposed "brain-first/body-first" dichotomy model of disease progression in Parkinson's disease (PD) claims that Lewy body (LB) pathologies can begin either in the brain or in the body and progress in opposite rostro-caudal or caudal-rostral directions. Testing this model requires longitudinal follow-up of patients using objective biomarkers. The goal of this study was to analyze the spatio-temporal pattern of disease progression by serial striatal dopaminergic and cardiac noradrenergic neuroimaging in patients with LB diseases (PD or the LB form of pure autonomic failure (LB PAF)).
Methods: We conducted an observational, retrospective, longitudinal case series. Data were reviewed from all PD or LB PAF patients who had been evaluated 2003–2022 by the Autonomic Medicine Section (formerly Clinical Neurocardiology Section) and had undergone serial putamen ^{18}F-DOPA and cardiac ^{18}F-dopamine positron emission tomographic (PET) scanning. Putamen dopaminergic deficiency preceding cardiac noradrenergic deficiency would indicate brain-first; cardiac noradrenergic deficiency preceding putamen dopaminergic deficiency would indicate body-first.
Results: In 3 patients diagnosed clinically with PD, decreased putamen/occipital cortex (PUT/OCC) ratios of ^{18}F-DOPA-derived radioactivity preceded decreased cardiac ^{18}F-dopamine derived radioactivity by 2, 6, and 8 years. In 2 patients with LB PAF, decreased cardiac ^{18}F-dopamine-derived radioactivity preceded decreased putamen PUT/OCC ratios and a clinical diagnosis of PD or DLB by 3 and 8 years. In 2 other patients with LB PAF, PUT/OCC ratios remained normal without a diagnosis of PD or DLB after 18 years.
Conclusions: Longitudinal clinical and neuroimaging data from this case series fit with the brain-first/body-first dichotomy and extend the

concept to DLB and to "body-only" LB PAF. The results highlight the need for prospective, longitudinal studies to test the brain-first/-body first model.
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Poster #13

Continuous positive airway pressure for the treatment of nocturnal supine hypertension and orthostatic hypotension in autonomic failure

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The clinical picture of autonomic failure (AF) patients is dominated by orthostatic hypotension (OH), but most of these patients also have supine hypertension. This complicates the management of OH and there is a reluctance of treating supine hypertension for fear of worsening OH. Current literature argues that the short-term risks of OH justify prioritizing its treatment over the management of supine hypertension. Supine hypertension, however, not only causes end-organ damage but also promotes pressure diuresis during the night, resulting in nocturnal volume depletion and worsening of daytime OH. Finding a treatment for supine hypertension that would also improve daytime OH would resolve the controversy about whether supine hypertension should be treated. We previously showed, in awake AF patients with supine hypertension, that increasing levels of continuous positive airway pressure (CPAP 4, 8, 12 and 16 cm H_2O, each for 3 min) had an acute, dose-dependent, blood pressure (BP)-lowering effect (maximal systolic BP [SBP] drop of 22 ± 4 mmHg with CPAP 16), driven by reductions in stroke volume (− 16 + 3%) and cardiac output (− 14 ± 3%), suggesting a Valsalva-like effect. In this proof-of-concept study, we hypothesized that overnight CPAP therapy can improve nocturnal supine hypertension, nocturia and daytime OH. Eleven AF patients with supine hypertension (age 74 ± 2 years, 8 men, supine SBP 179 ± 7 mmHg) had placebo or CPAP (8–12 cm H_2O) applied for 8 h (10 pm–6 am) on 2 separate nights. Supine BP was measured every 2 h from 8 pm–8 am. Morning orthostatic tolerance was assessed at 8 am. SBP significantly decreased during overnight CPAP therapy compared to placebo (P = 0.044 by mixed-effects model) with a maximal reduction of 25 ± 5 mmHg at 4 h of CPAP (versus − 1 ± 7 mmHg for placebo; P = 0.023). This BP effect was associated with lower nighttime diuresis (609 ± 84 vs. placebo 1004 ± 160 mL; P = 0.004) and improved morning orthostatic tolerance ($AUC_{upright\ SBP}$ 642 ± 121 vs. placebo 410 ± 109 mmHg*min; P = 0.014). In conclusion, CPAP is potentially a novel non-pharmacologic approach to treat the supine hypertension of AF that can also improve nocturia and daytime OH.
Funding support: This work was supported by the National Institutes of Health (NIH) Grants R01 HL144568, R01 HL161095, PO1 HL56693, U54 NS065736, R01 HL122847, and UL1 TR000445 (National Center for Advancing Translational Sciences). Additional support was provided by the American Heart Association Grant 14CRP20380211 (L.E.O.), the Overton and Jeannette Smith Fund and NIH R01 HL142583 (A.D.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the NIH.

Poster #14

Do cold hands and feet support a diagnosis of multiple system atrophy?

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Background: The presence of cold hands and feet has been described as a common finding in multiple system atrophy (MSA). This is reflected in the MSA Diagnostic Consensus Criteria which list cold hands and feet as "supportive feature" which has been maintained in the most recent criteria revision. A systematic evaluation and objective exploration of this presumed marker of MSA is lacking.
Objective: To systematically quantify limb skin temperatures in patients with MSA and explore differences compared to healthy and diseased control groups.
Methods: As part of a prospective, longitudinal study of synucleinopathies, we enrolled patients with early MSA (n = 28, UMSARS I ≤ 17, 14 MSA-C and 14 MSA-P), Parkinson's disease (PD, n = 14), Pure Autonomic Failure (PAF, n = 37), and healthy controls (CON, n = 15), and measured skin temperatures at 12 standardized sites per limb using a digital infrared temperature scanner with high spatial resolution under controlled ambient temperature. Patients were followed for up to 3 years and measurements were obtained annually. Proximal and distal measurement sites were averaged and proximal to distal temperature gradients calculated. Subjects were also asked about symptoms of cold hands/feet.
Results: At baseline, the average proximal skin temperature in both upper and lower extremities was mildly but significantly higher in MSA and PD compared to CON. There were no significant temperature differences at distal sites between these groups, and no difference in proximal to distal temperature gradients. In contrast, patients with PAF had significantly higher distal skin temperatures and significantly lower proximal to distal temperature gradients compared to the other groups. These findings were virtually identical at last follow-up. In contrast, 71% of MSA vs. 38% of CON, 35% of PAF and 40% of PD patients reported symptoms of cold hands OR feet, while 59% of MSA vs. 23% of CON, 19% of PAF and 10% of PD patients reported cold hands AND feet.
Conclusion: While a larger percentage of MSA patients reports symptoms of cold hands and feet, measurements of skin temperatures do not reveal any difference in distal temperatures or proximal to distal temperature gradients compared to control groups. Symptoms of cold hands and feet may therefore be either merely subjective, triggered only under certain circumstances, or limited to the advanced disease stage. These findings raise concern about using this feature to support a diagnosis of MSA.
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Poster #15

An interdisciplinary care model for multiple system atrophy at the University of North Carolina at Chapel Hill

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Background: Multiple system atrophy (MSA) is a progressive neurodegenerative disease that causes many symptoms including parkinsonism, cerebellar ataxia, autonomic failure, vocal cord dysfunction, dysphagia, and sleep disturbances. No single medical discipline is equipped to address all care needs of this patient population, though literature exploring interdisciplinary care models for MSA is lacking. Recently, there has been a call for interdisciplinary care approaches to manage the diverse symptoms of this life-limiting disease.
Objective: To describe the UNC atypical parkinsonism clinic, to present results of patient-reported benefits, and to describe the clinical features of the MSA patients who have come through this clinic. To promote the replication of similar care models at other centers, we also share lessons learned from experience at UNC.
Methods: We critically evaluated our interdisciplinary clinic model. Descriptive statistics (N, mean, standard deviation, range, percentages as appropriate) describing demographics, clinical data, and responses from satisfaction surveys of this MSA cohort will be presented.
Results: 20 people with MSA (12 women, 8 men) were evaluated in the UNC atypical parkinsonism interdisciplinary clinic between November 2017-December 2021. Each patient is evaluated by physical, occupational, speech, and pelvic therapy, a movement disorders neurologist with training in autonomic neurology, and is evaluated by a clinical social worker days prior to the clinic date. After the clinic visits, the team meets to discuss each case, including patient goals, exam findings, and an individualized recommended plan of care. A comprehensive assessment with recommendations is reviewed with the patient and tailored referrals to local therapies and other resources are provided. Patients are asynchronously referred to ENT, neuro-ophthalmology, sleep neurology, and/or palliative care. The satisfaction surveys indicate a high level of satisfaction with the clinic. MSA patients are able to tolerate the 5-h clinic duration. Due to the complex needs of this population, we found that each specialty required one hour for their evaluations.
Conclusions: An interdisciplinary team approach in the management of MSA is possible and beneficial for patients. We present one successful model here, and hope to encourage the development of specialized interdisciplinary care models at other centers.

AUTONOMIC PHYSIOLOGY AND PATHOPHYSIOLOGY: BASIC SCIENCE & ANIMAL STUDIES

Poster #19

TRPV1 on the endings of thin fiber muscle afferents is not needed to evoke the exercise pressor reflex

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The role played by the transient receptor potential vallinoid-1 (TRPV1) on the endings of thin fiber muscle afferents in evoking the exercise pressor reflex is controversial. To shed light on this controversy, we used TRPV1-/- rats that were made by a CRISPR-Cas9 deletion to introduce a 26-bp frameshift deletion in exon 3. We compared the magnitude of the reflex between TRPV1 + / + wild-type rats (WT), TRPV1 ± heterozygous rats (HET), and TRPV1-/- knockout rats (KO). The exercise pressor reflex was evoked by stimulating the tibial nerve (40 Hz, 0.01 ms, 1.5 times motor threshold) in precollicular decerebrated unanesthetized rats with freely perfused hindlimbs. We found that there was no difference ($p = 0.61$) between the magnitude of the reflex in the three groups of rats. Specifically, the exercise pressor reflex in the WT rats (n = 9) averaged 12.7 ± 2 mmHg, 13 ± 1.5 mmHg in HET rats (n = 5), and 15.8 ± 3.3 mmHg in KO rats (n = 6). Stimulation of the tibial nerve after paralysis of the rats with pancuronium (iv) had trivial effects on arterial pressure (WT: − 0.2 ± 0.7 mmHg; HET: 2.4 ± 0.9 mmHg; KO: 1.3 ± 0.8 mmHg). These findings with pancuronium indicated that the pressor responses to contraction were not caused by electrical stimulation within the axon of the tibial nerve. Intra-carotid arterial injection of the TRPV1 agonist, capsaicin (0.5 ug), evoked a significant pressor response in the WT rats (27.6 ± 6.9 mmHg) and in the HET rats (30.5 ± 5.1 mmHg), but not in the KO rats (5 ± 2.1 mmHg). In electrophysiological studies of dorsal root ganglion cells innervating the gastrocnemius muscles, capsaicin evoked inward currents in the WT and HET rats, but not in the KO rats. Moreover, immunofluorescence revealed the presence of TRPV1 in the DRG of WT, but not in the DRG of KO rats. We conclude that TRPV1 is not needed to evoke the exercise pressor reflex in rats with freely perfused contracting hindlimb muscles. This result is consistent with our previous finding that pharmacological antagonism of TRPV1 has no effect on the exercise pressor reflex.
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Poster #20

Herpes simplex virus and SARS-CoV-2 infection of autonomic neurons

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Autonomic neurons are largely disregarded in viral pathogenesis studies. However, sympathetic and parasympathetic neurons respond to and regulate viral infections differently than other types of neurons. Herpes simplex viruses (HSV-1 and HSV-2) establish latent infections in sensory neurons following orofacial or genital infection and reactivate from latency to cause recurrent disease episodes throughout the life of the host. The viruses are also found in autonomic ganglia in humans and animal models, although the contribution of latent viral reservoirs in autonomic neurons has not been determined. Chemical ablation of sympathetic axons with 6-hydroxydopamine (6-OHDA) in adult guinea pigs, followed by HSV-1 or HSV-2 infections, significantly reduced disease severity ($p = 0.004$) and neurological involvement ($p = 0.049$) during acute disease for HSV-1 but not HSV-2. 6-OHDA treatment also significantly reduced clinical recurrences 74% for HSV-1 and 49% for HSV-2 ($p \leq 0.001$). Thus, sympathetic pathways play a significant role in acute disease severity and neurological involvement of HSV1, but not HSV2, and are

responsible for a significant portion of both HSV1 and HSV2 recurrences, with a greater impact on HSV1 than HSV2. Exogenous factors known to trigger HSV recurrences, such as stress hormones or nerve injury, selectively induce HSV1 or HSV2 reactivation from latency in autonomic and sensory neurons, demonstrating that different types of peripheral neurons have alternative mechanisms to respond to and control neurotropic virus infections. Similarly, SARS-CoV-2, the virus that causes COVID-19, is able to infect peripheral neurons, producing divergent pathological outcomes in sensory and sympathetic ganglia, which may contribute to some of the symptoms experienced by COVID-19 patients. SARS-CoV-2 replicates to high titers (10^5–10^7 virus copies/200 ng total RNA by RT-qPCR) in sensory and sympathetic ganglia following intranasal inoculation of mice. While infection is evident in most sensory neurons of the trigeminal and dorsal root ganglia by 6 days post inoculation, neuron and ganglion integrity is maintained. In sympathetic superior cervical ganglia, SARS-CoV-2 causes neuronal vacuolization and loss of ganglionic architecture. Taken together, our studies show that autonomic neurons respond differently to neurotropic virus infections compared to other types of neurons, with particular sensitivity to HSV and SARS-CoV-2.

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Poster #21

Purinergic 2X receptors subtypes 3 and 4 contribute to the exaggerated mechanoreflex in rats with simulated peripheral artery disease

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The stimulation of mechanically activated channels on group III/IV skeletal muscle afferents during skeletal muscle contraction evokes reflex increases in sympathetic nerve activity and blood pressure (i.e., the mechanoreflex) and facilitates exercise performance. In peripheral artery disease (PAD), these mechanically activated channels may become sensitized by the stimulation of neighboring ATP-sensitive purinergic 2X (P2X) receptors. This results in a sensitization and exaggeration of the mechanoreflex during exercise which augments sympathetic nerve activity and the blood pressure response to exercise and elevates the risk of ischemic cardiovascular events such as fibrillation and/or stroke. However, the specific P2X subtype(s) involved in the mechanoreflex sensitization in PAD remains unknown. Accordingly, the purpose of the present investigation was to determine the role played by $P2X_3$ and $P2X_4$ in the P2X-mediated mechanoreflex sensitization in PAD. We hypothesized that, in rats with simulated PAD hindlimb arterial injection of either the selective $P2X_3$ receptor antagonist NF-110 (20 μg) or the selective $P2X_4$ antagonist 5-BDBD (8 μg) would reduce the reflex increase in mean arterial blood pressure (MAP) evoked during 30 s of 1 Hz dynamic hindlimb muscle stretch (a model of mechanoreflex activation isolated from contraction-induced metabolite production). Experiments were performed on ~ 12-week-old male and female Sprague–Dawley rats subjected to femoral artery ligation ~ 72 h before the final experimental protocol. In rats with simulated PAD (n = 6 M/2F), we found that hindlimb arterial injection of the $P2X_3$ antagonist NF-110 reduced the peak pressor (control: 36 ± 5; NF-110: 26 ± 6 mmHg; P = 0.001) but not the integral of the blood pressure response (i.e., BPI) to hindlimb muscle stretch (control: 479 ± 89; NF-110: 415 ± 125 mmHg·s; P = 0.078). Additionally, in a different cohort of rats with simulated PAD (n = 1 M/3F), we found that hindlimb arterial injection of the $P2X_4$ antagonist 5-BDBD had no effect on the peak pressor (control: 34 ± 7; 5-BDBD: 31 ± 10 mmHg; P = 0.280) but reduced the BPI response to hindlimb muscle stretch (control: 529 ± 97; 5-BDBD: 385 ± 187 mmHg·s; P = 0.047). Tension-time-index of the stretch maneuvers were not different before and after hindlimb arterial injection of NF-110 (control: 14.0 ± 0.4; NF-110: 14.5 ± 0.4 kg·s; P = 0.306) or 5-BDBD (control: 12.6 ± 1.7; 5-BDBD: 12.6 ± 1.3 kg·s; P = 0.974). Our data suggest that both $P2X_3$ and $P2X_4$ receptors contribute to the P2X-mediated mechanoreflex sensitization in PAD.

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Poster #22

Central inhibition of proinflammatory cytokines attenuates exaggerated stress-mediated neurohumoral excitation and sympathetic activity in mice with dilated cardiomyopathy

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Emotional stress activates the hypothalamic-pituitary axis (HPA) to cause neurohumoral excitation and increases in sympathetic activity and proinflammatory cytokines (PIC). Increased sympathetic drive and neurohumoral excitation in heart failure and dilated cardiomyopathy (DCM) is strongly associated with ventricular remodeling and cardiac arrhythmias. However, the fundamental molecular mechanisms within the brain that cause these adverse outcomes remain largely unknown. Recently, we have generated a unique mouse model of DCM by targeted deletion of *Sgcd* gene (sarcoglycan-delta) in the cardiomyocytes *[FASEB J, 2022].* We find that stress leads to homeostatic failure in cardiac-specific Sgcd-deficient mice (cSgcd-KO). Thus, we hypothesized that stress-mediated increase in PIC (TNF, IL-1b) within the cardiovascular regulating areas of the brain evokes adverse outcomes in DCM. cSgcd-KO and littermate control (WT) mice (n = 4–10 per genotype) were implanted with radiotelemeters (DSI) at ~ 35 weeks of age. Changes in mean blood pressure (BP), heart rate (HR), and locomotor activity were measured before and during stress challenge (20 min exposure to predator odor). Autonomic indices including baroreflex sensitivity (BRS, sequence technique), and resting cardiac vagal and sympathetic tone (HR responses to 1 mg/kg of atropine and 1 mg/kg propranolol, respectively) were calculated. After baseline measurements, PIC inhibitor pentoxifylline (10 μg/kg/h, ICV) was administrated for a week. At 36 ± 1 weeks of age, cSgcd-KO mice exhibit 62% increase in left ventricular (LV) end-diastolic volume and 58% decrease in LV ejection fraction. cSgcd-KO mice exhibit BRS impairment (0.72 ± 0.08 vs. 2.01 ± 0.05 ms/mmHg), reduced vagal tone (ΔHR = + 32 ± 6 vs. + 151 ± 18 bpm), and increased sympathetic tone (ΔHR = − 212 ± 12 vs. − 123 ± 10 bpm) at baseline ($p < 0.05$ vs. WT). As expected, stress increased BP, sympathetic activity and release of HPA neurohormones in the WT mice; whereas in the cSgcd-KO mice stress triggered marked increase in PIC within the LV and brainstem, severe hypotension, excessive neurohumoral excitation, LV dysfunction and arrhythmias ($P < 0.05$ vs. WT). Importantly, centrally administered pentoxifylline improved autonomic function, and prevented stress-induced homeostatic failure in cSgcd-KO mice ($p < 0.05$ vs. WT). Our results implicate that inhibition of central proinflammatory cytokines with pentoxifylline is a promising treatment strategy that improves autonomic/cardiovascular function and prevents stress-evoked adverse outcomes in dilated cardiomyopathy.

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Poster #23

Mechanosensitive renal sensory responses are attenuated in DOCA-salt hypertension

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Introduction: Elevated renal afferent nerve (ARNA) activity or dysfunctional reno-renal reflexes contribute to hypertension. Renal sensory nerves respond to changes in intrarenal pressures and chemokines to reflexively alter sympathetic nerve activity, renal function, and blood pressure. The spontaneously hypertensive and 2-kidney-1-clip rat models of hypertension exhibit attenuated ARNA responses to mechano- and chemosensory stimuli. The present study evaluated the extent by which ARNA responses to increased pelvic pressure or intrarenal infusion of chemokines (i.e., bradykinin and capsaicin) are also attenuated in deoxycorticosterone-salt (DOCA) hypertension.
Methods: Uninephrectomized male and female Sprague–Dawley rats (250–400 g) received 100-mg DOCA (SC) and 0.9% saline for 21 days and were assessed by multifiber nerve recordings. Using Inactin anesthetized preparations, baseline ARNA was not different between DOCA versus sham-operated rats (6 ± 2 Hz; n = 11 vs. 5 ± 1 Hz, n = 8, respectively).
Results: Stepwise increases in renal pelvic pressure (0–30 mmHg, 30 s) via a ureteral catheter increased ARNA in all groups. Mechanosensitive ARNA responses were significantly attenuated in DOCA versus control rats at 20 mmHg (7 ± 1 Hz, n = 5 M, 6 F vs. 24 ± 9 Hz, n = 4 M, 4 F; $p < 0.05$) and 30 mmHg (12 ± 4 Hz, n = 5 M, 6 F vs. 25 ± 7 Hz, n = 4 M, 4 F; $p < 0.05$). The threshold sensitivity within each group was defined as the lowest pressure step to produce a statistically significantly response from 0 mmHg. The threshold pressure was 20 mmHg for DOCA and 10 mmHg for control rats ($p < 0.05$). No significant sex differences were observed for ARNA responses within groups. In marked contrast, chemosensitive responses to intrarenal infusion of bradykinin [0–10 μM] produced a concentration-dependent increase in ARNA in all groups. ARNA responses to bradykinin were not significantly different between DOCA and control rats (10 μM: 22 ± 5 Hz, n = 5 M, 5 F vs. 30 ± 5 Hz, n = 3 M, 3 F, respectively). As a second chemokine stimulus, intrarenal infusion of capsaicin [0–10 μM] also produced a concentration-dependent increase in ARNA in all groups. ARNA responses were not significantly different between DOCA and control rats (10 μM: 20 ± 7 Hz, n = 5 M, 5 F vs. 41 ± 13 Hz, n = 3 M, 3 F, respectively). No significant sex differences were observed for ARNA responses to intrarenal bradykinin or capsaicin with groups.
Conclusion: In conclusion, ARNA responses to increased renal pelvic pressure, but not intrarenal chemokines, are attenuated in DOCA-salt hypertension.
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Poster #24

Effects of chronic intermittent hypoxia on cognitive function in rats

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Obstructive sleep apnea (OSA) affects approximately 2.2 million people worldwide and is characterized by frequent bouts of hypoxia during sleep, a loss of autonomic balance and increased risk of cardiovascular diseases. Recent work has shown OSA is also strongly linked with cognitive impairments. In this study we tested whether chronic intermittent hypoxia (CIH), an animal model of OSA, elicits anxiety and impaired learning and memory. Eight adult female Sprague Dawley rats were exposed to CIH (74 cycles of 3.5 min at 6% and 3 min at 21% O_2) for eight hours a day during their sleep cycle. Age matched controls were maintained under similar noise and manipulation conditions, but at room air. After six months of CIH, learning skills were assessed. Animals were trained to find a visible platform in a circular pool using a Morris water maze protocol. During the training animals went under six daily trials for five consecutive days. After training, the CIH regime continued for two more months. At month eight, animals were tested again for spatial memory by repeating the Morris water maze test with a hidden platform. In conjunction, anxiety levels were assessed using an open field maze test to quantify the duration of time an animal explores open regions on a platform. Animals exposed to CIH displayed significantly longer learning times and lower levels of spatial recognition (memory). These animals also demonstrated significantly more anxiety than control animals. Our results show, in an animal model of OSA, CIH impairs cognitive function and increases anxiety. Future work will test if new treatment paradigms for OSA, such as oxytocin network activation, blunts decreases in cognitive abilities and increases in anxiety.

Poster #26

Intravenous vagal nerve stimulation catheter, JOHAKU, rapidly controls heart rate without exacerbating hemodynamics in a dog model of acute heart failure

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Background: In heart failure condition, excessive tachycardia increases myocardial oxygen consumption (MVO_2) and worsens cardiac function. However, an inappropriate heart rate (HR) reduction, in turn, worsens hemodynamics. HR reduction is the one of the evident physiological responses of vagal nerve stimulation (VNS). We repeatedly reported the dynamic characteristics of HR reduction of VNS. Recently, we have developed an intravenous VNS catheter, JOHAKU, which can stimulate right vagal nerve via the basket catheter placed in the superior vena cava (SVC).
Purpose: We examined the impact of JOHAKU on HR, MVO_2, and hemodynamics in the acute heart failure condition.
Methods: We used five beagle dogs with acute heart failure. The myocardial damage was induced by the direct ethanol injection (0.5–2 ml/kg) to myocardium. The catheter was inserted through the right femoral vein and the basket shaped electrode was placed at the SVC. VNS intensity was adjusted to reduce HR by 10–20% (20 Hz, 10–22 V). We simultaneously recorded HR, blood pressure (BP), cardiac output (CO), and left circumflex artery blood flow (CF). MVO_2 was calculated by the product of hemoglobin concentration, CF, and the difference of oxygen saturation between coronary artery and coronary sinus vein. We compared HR, MVO_2, and hemodynamics between baseline and 5 min after stimulation.
Results: The direct ethanol injection reduced CO (Before ethanol: 2.0 ± 0.4 vs. After ethanol 1.5 ± 0.2 l/min) and BP (86 ± 6 vs. 75 ± 15 mmHg) and increased left ventricular end-diastolic pressure

(12 ± 6 vs. 16 ± 7 mmHg). VNS rapidly and dose-dependently reduced HR. In the acute heart failure dog model, JOHAKU significantly reduced HR (Baseline: 122 ± 7 vs. 5 min after VNS: 108 ± 14 bpm, $p < 0.05$) and MVO_2 (3.3 ± 0.4 vs. 2.8 ± 0.6 mlO_2/min/100 g), while did not affect mean BP (73 ± 8 vs. 72 ± 2 mmHg, $p = 0.56$).
Conclusion: Intravenous VNS catheter could attenuate HR and MVO_2 without exacerbating hemodynamics in the acute heart failure model dogs. The device may contribute to the control of excessive cardiac load in unstable hemodynamics.

Poster #27

SK channel blockade in the paraventricular nucleus alters frequency components of renal and splanchnic sympathetic nerve activity in rats

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The hypothalamic paraventricular nucleus (PVN) is a prominent regulatory center for sympathetic nerve activity (SNA). We have previously demonstrated that blockade of small conductance calcium-activated potassium (SK) channels in the PVN significantly increases splanchnic and renal SNA, and dysfunction of SK channels contributes to the pathogenesis of hypertension. However, the influence of PVN SK channel blockade on the SNA firing pattern remains unclear. We hypothesized that SK channel blockade would shift the SNA burst pattern towards lower frequencies. All experiments were performed in ventilated, anesthetized (urethane 800 mg/kg and α-chloralose 80 mg/kg) male Sprague–Dawley rats (n = 5) with the approval of the Michigan Technological University IACUC. Splanchnic and renal SNA signals were band pass filtered (10–1000 Hz) with a 60 Hz notch filter, digitized at 5000 Hz and integrated with a 10-ms time constant. Bilateral microinjection of the SK channel blocker apamin (12.5 pmol, 50 μL) into the PVN significantly ($p < 0.05$) increased splanchnic SNA (Δ253 ± 61%), renal SNA (Δ216 ± 48%), and mean arterial pressure (MAP; Δ28.7 ± 7.6 mmHg) compared to baseline. Power spectral density was calculated using Welch's method on 10-min segments of SNA during baseline, and during the maximum response to apamin. Data were normalized and expressed as a percentage of total power from 0–15 Hz. PVN SK channel blockade with apamin resulted in a significant increase in power in the 0–2 Hz frequency band for both splanchnic (68.0 ± 6.3% vs. 45.7 ± 7.4%, $p < 0.01$), and renal (64.6 ± 7.9% vs. 33.2 ± 5.7%, $p < 0.01$) SNA compared to baseline. In contrast, PVN apamin did not significantly alter power in the 5–7 Hz frequency band (cardiac related) for splanchnic (10.4 ± 2% vs. 9.3 ± 2.8%) and renal (19.9 ± 3.8% vs. 12.3 ± 4.7%) SNA when compared to baseline. In conclusion, PVN SK channel blockade with apamin significantly increases renal and splanchnic SNA, and shifts the SNA burst pattern towards lower frequencies.
Funding: Michigan Technological University (Larson); NIH 1R15HL145655(Chen).

Poster #29

Exaggerated blood pressure response to static exercise in peripheral artery disease: Role of acid sensing ion channel following limb muscle ischemia–reperfusion

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Significance and Hypothesis: In patients with peripheral artery disease (PAD), responses of the sympathetic nerve activity and blood pressure (BP) are exaggerated during leg exercise, and evidence suggests that the exercise pressor reflex (EPR) is a key determinant of why amplified BP occurs in PAD. Notably, an elevated BP response by the EPR is a risk factor for cardiovascular diseases. Thus, it is clinically significant to identify the mechanisms for the exaggerated BP response to exercise in PAD and explore interventions alleviating BP and increasing exercise tolerance. Utilizing animal studies, we hypothesized that ischemia–reperfusion (IR) stress in PAD increases the EPR and IR-induced acidic products and acid sensing ion channels subtype 3 (ASIC3) are involved in the amplified EPR.
Methods: The hindlimb muscle IR was induced in rats with femoral artery ligation (6 h) followed by re-opening the ligation (18 h). BP response was evoked by static contraction of the hindlimb muscle. Western blot analysis and whole cell patch clamp were used to determine the protein levels of ASIC3 in the dorsal root ganglion (DRG) and the activities of ASIC current.
Results: Response of mean arterial pressure to muscle contraction was 19 ± 3 mmHg in control rats/n = 6 and 29 ± 9 mmHg in IR rats/n = 8 ($P < 0.05$ *vs.* control) and no significant difference was observed in the peak tension during contraction between the two groups (543 ± 101 g in control and 520 ± 28 g in IR rats; $P > 0.05$). Response of mean arterial pressure to lactic acid (4 μmol/kg) administered into the hindlimb muscle was 25 ± 6 mmHg in control rats/n = 9 and 37 ± 10 mmHg in IR rats/n = 15 ($P < 0.05$ *vs.* control). The optical density of ASIC3 expression in IR18h rats/n = 10 was 1.42-fold greater than that in control rats/n = 8 ($P < 0.05$ *vs.* control). With application of a solution with pH 6.7, ASIC3-like current density in muscle DRG neurons of control rats/n = 15 was 193.4 ± 51.8 pA/pF and 295.1 ± 56.3 pA/pF in IR rats/n = 21 ($P < 0.05$ *vs.* control).
Conclusion: IR significantly increases the EPR and ASIC3 is likely a part of signaling pathways responsible for the exaggerated BP response. A blockade of ASIC3 would improve the EPR and enhance walking distance in PAD patients.
Funding: This study is supported by American Heart Association Grant #940567, NIH P01 HL134609 and R01 HL141198.

Poster #30

Exposure to a diet rich in linoleic acid promotes nociceptive hypersensitivity and elevated systemic blood pressure in both spinal-intact and spinalized rats

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Pain is associated with the development of cardiovascular disease and nociceptive hypersensitivity may contribute to increased systemic blood pressure. Various fatty acyl lipid mediators (e.g., oxylipins) are derived from dietary polyunsaturated fatty acids (PUFAs) and modulate nociception. The modern diet is rich in the omega-6 PUFA, linoleic acid (LA), which may present a risk factor for developing pain conditions and associated risk for development of cardiovascular disease. In this study rats were randomized, at the time of weaning, to receive one of two modified AIN-76A diets each containing 5.1% fat. The standard corn oil was replaced with a custom triglyceride blend rich in either LA or oleic acid (OA; 18:1n-9), a monounsaturated fatty acid that is not metabolized to form oxylipin lipid mediators. The average body weight at 9 weeks of age in rats fed the LA-rich diet was not different than that of rats fed the OA-rich diet. In general, rats maintained on the LA-rich diet displayed greater plasma accumulation of pro-nociceptive oxylipin lipid mediators when compared to rats maintained on the OA-rich diet. The accumulation of pro-nociceptive oxylipin lipid mediators was associated with a significant increase in thermal nociceptive hypersensitivity. Using an unanesthetized, decerebrate preparation, splanchnic sympathetic nerve activity (sSNA), arterial blood pressure and heart rate were measured at baseline and in response to ganglionic blockade. Rats maintained on the LA-rich diet displayed higher baseline mean arterial pressure (MAP) compared to littermates maintained on the OA-rich diet (94 ± 16 vs. 78 ± 14 mmHg; $p < 0.02$), while baseline heart rate was not influenced by diet. Ganglionic blockade with hexamethonium (20 mg/kg, i.v.) produced a larger fall in baseline in MAP in rats maintained on the LA-rich diet compared to littermates maintained on the OA-rich diet (-54 ± 15 vs. -41 ± 12 mmHg, respectively; $P < 0.05$). Moreover, the effects of diet on nociceptive hypersensitivity and baseline MAP were preserved in chronic spinalized (T2 transection) rats. These findings illustrate the potential of intraspinal circuits to modulate systemic blood pressure and support the notion that elevated systemic blood pressure associated with chronic pain may involve intraspinal circuitry. All animal protocols were reviewed and approved by the Wayne State University Institutional Animal Care and Use Committee (IACUC).

Poster #31

Does renal denervation restore sodium-glucose cotransporter 2 (SGLT2) expression and function in heart failure?

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Various clinical studies demonstrate that sodium-glucose cotransporter 2 (SGLT2) inhibitors ameliorate heart failure (HF). It is also well documented that there is enhanced sympatho-excitation particularly to the kidneys in HF. The present study was conducted to assess the contribution of enhanced renal sympathetic tone in influencing the effects of SGLT2 inhibitors in HF. HF was induced by left coronary ligation surgery for 4 weeks and rats were surgically renal denervated (RDN) for 2 weeks. RDN resulted in reduced levels of urinary norepinephrine excretion in rats with HF compared with sham-operated control rats. RDN resulted in reduced levels of SGLT2 staining in the kidneys of rats with HF. RDN also resulted in restoration of diuretic and natriuretic responses to SGLT2 inhibition in rats with HF. In vitro studies using human embryonic kidney cells demonstrated that norepinephrine promoted translocation of SGLT2 to the cell membrane. These results indicate that intact renal nerves contribute to the enhanced effects of SGLT2 in HF. RDN restores SGLT2 levels and thus attenuates the enhanced sodium retentive state commonly observed in HF.
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Poster #32

Comparison of heart rate variability, blood pressure variability and metabolic parameters in different phases of hemorrhagic shock in normal and vagotomized conscious male rats

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Introduction: Hemorrhagic shock (HS) is one of the life-threatening complications of traumatic injury. The diagnosis and treatment of hemorrhagic shock is primarily based on clinical parameters, which are only able to detect the late stages of HS. Changes in autonomic nervous system (ANS) activity are an initial response to HS. Measurement of ANS may be a useful method to detect the early stages of HS and allow rapid implementation of life-saving measures at the point of care.
Aim: An animal model of hemorrhagic shock of different classes with and without sub-diaphragmatic vagotomy is used to investigate the covariation of heart rate variability (HRV), blood pressure variability (BPV), and blood gas biomarkers. The sub-diaphragmatic vagotomy blunts the cardiac vagal tone surge in response to severe HS.
Methods: Conscious male rats were randomly divided into HS 0%, HS 20%, and HS 50% classes; based on the percentage of shed blood volume had been returned to maintain shock. A multimodal analysis was performed using the autonomic regulation of hemodynamics and cardiovascular variations at three time points of the protocol.
Results: HS 20% and 50% groups have significant differences in between vagotomized and non-vagotomized category interaction in the low frequency band for HRV and BPV from steady state to after resuscitation state. Within the combined groups of HS 20% and 50%, a significant difference in correlation between the changes in high and low frequency HRV, from steady state to nadir, is related to the sub-diaphragmatic vagotomy. The correlation between the two HRV change scores is positive for the vagotomized animals and negative for the intact animals in these groups ($r = 0.740$, $N = 15$, $p = 0.002$, vagotomized; $r = -0.532$, $N = 16$, $p = 0.034$, non-vagotomized). This contrast is significant using the Fisher's r to z transformation (difference of Z's = 3.855, $p < 0.001$).
Conclusion: The combination of heart rate and HRV, blood pressure and BPV gives unique information about the patient's condition in terms of cessation or persistence of hemorrhage, degree of HS, and transition to de-compensatory phase. Sub-group differences will be discussed with respect to informing clinical management of HS.

Poster #33

Adipose tissue catecholamine resistance correlates with differential sympathetic outflow onto visceral and subcutaneous fat

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The sympathetic nervous system controls energy homeostasis, in part, by regulating adipose tissue lipolysis. However, adipose tissue from both patients and murine models of metabolic syndrome exhibits catecholamine resistance, defined as impaired lipolytic responses to b2/3 adrenergic receptor (b-AR) stimulation. Mechanistic studies have largely focused on endocrine and inflammatory causes of catecholamine resistance, with comparatively less attention to the antecedent neural circuit; i.e., the sympathetic nerves themselves. This gap is important because increased norepinephrine release could cause downregulation of adrenergic receptors, impaired adrenergic signaling, and catecholamine resistance. The objective of our study was to examine the relationship between sympathetic nerve activity and catecholamine resistance in visceral mesenteric (mWAT) and inguinal subcutaneous fat (iWAT) under high fat diet (HFD) feeding. 16 weeks of 60% HFD feeding induces weight gain and expansion of both mWAT and iWAT in male mice. To measure catecholamine induced lipolysis, acute fat explants were stimulated with isoproterenol (10 uM) for one hour, followed by measurement of media glycerol (a lipolytic product). HFD feeding blunted lipolysis in mWAT by 50% as compared to control diet mice; no such difference was observed in iWAT ($p < 0.005$; Welch's t-test). B3-AR mRNA was downregulated in both tissues, though to a greater extent in mesenteric fat (mWAT ddCT 0.450 ± 0.17 vs. iWAT 0.16 ± 0.09, $p < 0.05$, Welch's t-test). These data suggest tissue specific mechanisms induce catecholamine resistance. We postulated that differential sympathetic nerve outflow onto visceral and subcutaneous fat could precede development of catecholamine resistance. To test this hypothesis, we performed norepinephrine turnover studies (NETO; using the a-methyl-p-tyrosine method) after 8 weeks of HFD. In mice on chow diet, mWAT and iWAT exhibited similar NETO rates ($p = 0.57$; simple linear regression). However, subcutaneous fat from mice on HFD demonstrated markedly reduced norepinephrine turnover as compared to mesenteric fat ($p < 0.05$; simple linear regression). Differential sympathetic outflow onto mWAT matches predictions made from functional lipolysis deficits and b3-AR mRNA downregulation. These data suggest that the sympathetic nervous system could play a causative role in the development of visceral adipose tissue catecholamine resistance and may constitute a novel therapeutic target.

Poster #37

The impact of vericiguat on baroreflex-mediated sympathetic circulatory regulation: an open-loop analysis

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Background: We examined the effects of vericiguat, a stimulator of soluble guanylate cyclase, on baroreflex-mediated sympathetic circulatory regulation. As a reference, we also examined the effects of sodium nitroprusside (SNP), a nitric oxide doner, on the baroreflex-mediated sympathetic circulatory regulation.

Methods: Carotid sinus baroreceptor regions were isolated from the systemic circulation in anesthetized rats (n = 7 each). We changed the carotid sinus pressure (CSP) stepwise from 60 to 180 mmHg, while measuring splanchnic sympathetic nerve activity (SNA), arterial pressure (AP), and aortic flow (AoF). The baroreflex-mediated changes in SNA and AP were quantified using a four-parameter logistic function. The parameters were compared before and during the administration of vericiguat or SNP at 10 μg/kg/min.
Results: The stepwise increase of CSP reduced AP and SNA in a sigmoidal manner. Both vericiguat and SNP shifted the CSP-AP relationship downwards and decreased the response range of AP significantly (vericiguat: 62.2 ± 5.3 vs. 34.8 ± 4.1 mmHg, $P < 0.05$; SNP: 50.6 ± 3.4 vs. 32.0 ± 4.1 mmHg, $P < 0.05$). Meanwhile, neither vericiguat nor SNP significantly changed the CSP-SNA relationship. Vericiguat increased mean AoF from 60.3 ± 9.8 to 70.4 ± 10.9 mL/min ($P < 0.05$), while SNP did not significantly alter mean AoF (48.4 ± 3.1 vs. 49.4 ± 2.3 mL/min, NS).
Conclusion: Vericiguat and SNP reduced AP mainly through their peripheral cardiovascular effect without significantly affecting the SNA regulation. The cardiovascular effects of vericiguat and SNP may be different in that vericiguat increased mean AoF possibly due to the preservation of the preload to the heart.

AUTONOMIC PHYSIOLOGY AND PATHOPHYSIOLOGY: HUMAN STUDIES

Poster #38

Resting sympathetic nerve activity differentially influences cold-pressor reactivity in older men and women

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Background: The cold pressor test (CPT) is a sympathoexcitatory stimulus used to evaluate autonomic function in health and disease. Previous literature demonstrates heightened sympathetic reactivity in older women vs. older men during the CPT, yet the impact of baseline muscle sympathetic nerve activity (MSNA) remains unknown. Therefore, we hypothesized that elevated baseline MSNA would influence CPT reactivity in older men and women differently.
Methods: Sixty older (mean ± SD; 68 ± 6 y) participants were divided by sex (men and women) and terciled by baseline MSNA (high, medium, low; n = 10/group). Subsequent analyses were conducted on high baseline men (HM), low baseline men (LM), high baseline women (HW), and low baseline women (LW). Systolic (SBP) and diastolic (DBP) blood pressures (SunTech/Nexfin), heart rate (HR; lead II electrocardiogram), and MSNA (microneurography) were collected during supine baseline, a 2-min CPT (~ 4 °C), and a 3-min recovery.
Results: By design, HM and HW, relative to LM and LW, had greater baseline MSNA burst frequency (37 ± 5 and 38 ± 3 vs. 9 ± 4 and 15 ± 5 bursts/min), burst incidence (59 ± 14 and 60 ± 8 vs. 16 ± 10 and 23 ± 7 bursts/100 hbs), and total activity (521 ± 111 and 537 ± 80 vs. 159 ± 75 and 244 ± 69 AU/min; all $P < 0.001$). Despite these MSNA differences, baseline SBP, DBP, and HR were not different (all $P > 0.05$). During the CPT, there were no group differences in ΔSBP, ΔDBP, or ΔHR (all $P > 0.05$). Conversely, ΔMSNA burst frequency was lower in HW vs. LW (8 ± 9 vs. 22 ± 12 bursts/min; $P = 0.012$) yet was similar in HM vs. LM (17 ± 12 vs. 19 ± 10 bursts/min, $P = 0.994$). Further, ΔMSNA burst

incidence was significantly lower in HW vs. LW (9 ± 13 vs. 28 ± 16 bursts/100 hbs; $P = 0.020$), while there were no differences between HM and LM (21 ± 17 vs. 31 ± 17 bursts/100 hbs; $P = 0.455$). There were also no differences between groups for ΔMSNA total activity (HM: 617 ± 458; LM: 622 ± 622; HW: 319 ± 254; LW: 577 ± 387 AU/min; $P = 0.313$).
Conclusion: These data suggest that heightened baseline activity attenuates the typical increase in MSNA burst frequency and incidence during the CPT in older women, but not older men, despite similar cardiovascular responses between groups. While the underlying mechanisms remain unknown, these sex differences in CPT reactivity may derive from altered sympathetic neural recruitment and/or neurovascular transduction.
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Poster #39

Cardiovascular and sympathetic reactivity during a stressor in early-menopausal females

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Introduction: Menopause is associated with an increased risk of hypertension (HTN) and cardiovascular disease, and early menopause (EM; age < 46 yrs) substantially increases this risk. Stressors such as the cold pressor test (CPT) can be used to predict HTN risk, but it is unknown if females who experience EM demonstrate greater blood pressure (BP) and sympathetic neural reactivity compared with typical-age menopausal (TAM) females (age > 46 yrs). We hypothesized that females who experienced EM would have greater BP and sympathetic reactivity to a CPT compared with TAM females.
Methods: Eighteen postmenopausal females completed two study visits. Participants were divided into two age-matched groups: EM (n = 9) and TAM (n = 9). Visit 1 consisted of consent and health questionnaires. Visit 2 included measurements of heart rate (HR), BP and muscle sympathetic nerve activity (MSNA) during a 10 min rest and 2 min CPT.
Results: Groups were similar in age (TAM: 63 ± 1; EM: 64 ± 1 yrs; p = 0.78) and body mass index (TAM: 25 ± 1; EM: 26 ± 2 kg/m^2; p = 0.93), but different in time from menopause (TAM: 11 ± 2; EM: 21 ± 1 yrs; p < 0.001). While there were no differences between groups in resting systolic BP (TAM: 133 ± 5; EM: 120 ± 7 mmHg), diastolic BP (TAM: 81 ± 4; EM: 81 ± 5 mmHg), mean BP (TAM: 98 ± 4; EM: 96 ± 6 mmHg), or HR (TAM: 56 ± 2; PEM: 59 ± 3 bpm; p > 0.05 for all), TAM had higher resting MSNA burst incidence (TAM: 60 ± 4; EM: 34 ± 7 bursts/100 heartbeats; p = 0.02, n = 10) and burst frequency (TAM: 35 ± 7; EM: 20 ± 3 bursts/min; p = 0.02, n = 10). During the CPT, BP, HR, MSNA burst incidence, and MSNA burst frequency increased similarly in both groups (p > 0.05 for all). However, absolute MSNA burst incidence (group effect, p = 0.007) and burst frequency (group effect, p = 0.02) were overall lower in EM compared with TAM.
Conclusion: Contrary to our hypothesis, females who experienced EM did not demonstrate greater BP and sympathetic reactivity compared with TAM. Although sample sizes were small, MSNA was lower overall in the EM group compared with the TAM group. This suggests other mechanisms may be involved in the greater cardiovascular risk in EM females.
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Poster #40

Muscle sympathetic nerve reactivity to anticipatory stress predicts reactivity to subsequent mental stress tasks

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Cardiovascular reactivity to mental stress is predictive of future health outcomes. Although the sympathetic nervous system plays a key role in the stress response, muscle sympathetic nerve activity (MSNA) responses to laboratory mental stress are highly variable. The purpose of the present study was to assess MSNA reactivity to anticipatory, public speaking, and mental arithmetic phases of the Trier Social Stress Test (TSST), an ecologically valid psychosocial stressor. We hypothesized that MSNA reactivity to the anticipatory phase of the TSST would predict subsequent responsiveness to the remainder of the protocol. 26 healthy adults (11 men, 15 women, 25 ± 6 years, 24 ± 3 kg/m^2) participated in a morning autonomic function test consisting of simultaneous recordings of heart rate (HR, electrocardiogram), beat-to-beat blood pressure (finger plethysmography), and MSNA (microneurography; n = 20) The TSST consisted of a resting baseline (10 min), speech preparation/anticipation (5 min), socially evaluated speech (5 min), and mental arithmetic (5 min) in front of two laboratory judges and video recording. Compared to baseline, mean arterial pressure and heart rate was increased throughout all stress tasks ($P < 0.001$). While MSNA burst frequency (BF) was significantly reduced compared to baseline during the preparatory ($\Delta -5 \pm 1$, $P < 0.001$) and math ($\Delta -4 \pm 2$, $P = 0.037$) phases, it remained unchanged during the speech task ($P = 0.919$). Regression assessing changes in MSNA BF during speech preparation on changes in MSNA BF during the speech task was significant ($R^2 = 0.548$, $F(1,18) = 21.842$, $P < 0.001$), with changes in MSNA BF during the preparation period significantly predicting MSNA BF reactivity during the speech task ($\beta = 0.740$, $P < 0.001$). Similarly, regression assessing changes in MSNA BF during preparation on changes during the math task was significant ($R^2 = 0.440$, $F(1,18) = 14.138$, $P = 0.001$) with changes in MSNA BF during the preparation period significantly predicting BF reactivity during the math task ($\beta = 0.663$, $P = 0.001$). The current findings indicate that anticipatory MSNA responses to stress accurately predict an individual's sympathetic response to subsequent laboratory mental stress. Anticipatory stress may offer a more reliable assessment of inter-individual differences in stress reactivity, along with key physiological mechanisms underpinning the variability observed in MSNA responses to mental stress.
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Poster #41

Relative amplitude of muscle sympathetic nerve activity: physiological or methodological?

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Muscle sympathetic nerve activity (MSNA) has high intraindividual reliability when quantified as burst frequency (bursts/min) or incidence (bursts per 100 heart beats). In contrast, there remain conflicting opinions and practices for various analyses involving burst amplitude, including the reliability of relative burst amplitude across sessions and between-subjects. The purpose of the present study was to assess the relationship between relative burst amplitude and resting burst frequency within a representative cohort of men and women of varying ages. Given our general observations that individuals with elevated burst frequency exhibit greater variability in burst sizes, we hypothesized that higher resting MSNA would be associated with reductions in relative amplitude due to the greater prevalence of smaller bursts. 132 adults between (66 men, 66 women, 29 ± 1 years, 25 ± 1 kg/m^2) participated in an autonomic testing session consisting of simultaneous recordings of 5–10 min of resting heart rate (HR, electrocardiogram), beat-to-beat blood pressure (finger plethysmography), and MSNA (microneurography). Prior to the autonomic test, mean arterial pressure (MAP) was determined using three resting brachial blood pressures. MSNA relative burst amplitude was calculated by assigning a value of 100 to the largest burst observed during the baseline period and expressing all other burst amplitudes as a percentage of the maximum burst. Both average (AAmp) and median (MAmp) relative burst amplitudes were determined. MSNA burst frequency was inversely correlated to AAmp ($R = -0.464$, $p < 0.001$) and MAmp ($R = -0.428$, $p < 0.001$). MSNA burst frequency was positively associated with resting MAP ($R = 0.488$, $p < 0.001$). Conversely, AAmp ($R = -0.179$, $p = 0.041$) and MAmp ($R = -0.153$, $p = 0.080$) tended to be negatively associated with resting MAP. The current findings suggest that relative MSNA amplitude is partially dependent upon burst frequency, whereby individuals with higher resting burst frequency exhibit lower relative burst amplitude. This supports the concept that caution should be practiced when interpreting relative MSNA amplitude given paradoxical and inverse relationship with burst frequency. Future studies assessing whether the observed inverse relationship between burst frequency and relative burst amplitude is due to differing sympathetic recruitment patterns, or perhaps methodological considerations, is necessary prior to further use of relative MSNA amplitude in between-subject comparisons.
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Poster #42

Orthostatic responses and excessive daytime Sleepiness

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Frequently described as an indication of obstructive sleep apnea (OSA), excessive daytime sleepiness (EDS) is an emerging marker of cardiovascular risk. While the mechanism(s) linking EDS to cardiovascular risk remain unclear, sympathetic activation is implicated. Hemodynamic responses to an orthostatic challenge are sympathetically modulated and predict cardiovascular events; thus, we examined whether EDS is associated with abnormal orthostatic responses in patients with and without OSA. Sixty relatively healthy individuals completed overnight polysomnography to identify OSA (AHI ≥ 5 events/hr) and an Epworth Sleepiness Scale (ESS, ≥ 11 indicating EDS). Autonomic function was quantified as the change (Δ) in BP and HR (assessed via brachial cuff) from rest (10 min supine) to 60 s post-standing. Mayo Clinic's IRB approved this protocol. The following groups were compared: OSA$^+$/EDS$^+$ (n = 12, 2F, AHI = 26 ± 16 events/hr, 46 ± 9 yrs, 33.7 ± 3.8 kg/m^2), OSA$^+$/EDS$^-$ (n = 21, 4F, AHI = 28 ± 22 events/hr, 40 ± 10 yrs, 33.7 ± 3.9 kg/m^2), OSA$^-$/EDS$^+$ (n = 11, 6F, AHI = 2 ± 2 events/hr, 39 ± 9 yrs, 31.7 ± 5.4 kg/m^2), OSA$^-$/EDS$^-$ (n = 16, 10F, AHI = 2 ± 2 events/hr, 37 ± 12 yrs, 28.6 ± 4.3 kg/m^2). OSA$^+$/EDS$^+$ and OSA$^+$/EDS$^-$ had fewer females (%) relative to OSA$^-$/EDS$^+$ ($p = 0.06$ and 0.04) and OSA$^-$/EDS$^-$ ($p = 0.04$ and 0.02, respectively) There were no between-group differences in age ($p = 0.13$) although BMI was lower in OSA$^-$/EDS$^-$ relative to OSA$^+$/EDS$^+$ and OSA$^+$/EDS$^-$ ($p < 0.05$ for both). A one-way ANOVA showed ΔSBP (mean ± SD: 4 ± 9, 0 ± 7, 3 ± 7, 4 ± 11 mmHg; $p = 0.48$), ΔDBP (10 ± 9, 8 ± 7, 8 ± 6, 10 ± 7 mmHg; $p = 0.71$), and ΔHR (13 ± 14, 17 ± 11, 12 ± 10, 10 ± 6 beats/min, respectively; $p = 0.25$) did not differ between groups. Using sex ($p = 0.16$ to 0.43), BMI ($p = 0.29$ to 0.64), and AHI ($p = 0.21$ to 0.55) in analyses of covariance did not change these results. Univariate regressions showed no associations between ESS scores and ΔSBP ($R^2 = 0.03$, $p = 0.38$; $R^2 = 0.00$, $p = 0.92$), ΔDBP ($R^2 = 0.01$, $p = 0.65$; $R^2 = 0.19$, $p = 0.49$), nor ΔHR ($R^2 = 0.03$, $p = 0.76$; $R^2 = 0.07$, $p = 0.18$) in patients with or without OSA, respectively. The lack of significant associations remained after adjusting the models for sex (adjusted $R^2 = -0.43$ to 0.46; $p = 0.07$ to 0.95), BMI (adjusted $R^2 = -0.32$ to 0.32; $p = 0.11$ to 0.89), and AHI (adjusted $R^2 = -0.25$ to 0.32; $p = 0.12$ to 0.83). These data suggest that the responses to an orthostatic challenge do not differ between sleepy and non-sleepy individuals with and without OSA.
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Poster #43

Autonomic dysfunction in postoperative patients of unilateral head and neck paragangliomas

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Background: Paragangliomas are rare neuroendocrine tumors that arise from structures associated with the central nervous system and the extra-adrenal autonomic paraganglia. They are usually benign, slow growing and only a minority (20–30%) produces catecholamines. Their location in close of nerves and vascular structures often causes symptoms such as hearing loss, tinnitus, dysphagia and cranial nerve palsy. Paragangliomas can be divided into 2 groups: sympathetic and parasympathetic tumors. Nearly all head and neck paragangliomas arise from the parasympathetic nervous system. Approximately 90% of tumors occur in the adrenal paraganglia and in terms of extra-adrenal tumors, 85% occur in the abdomen, 12% in the thorax and 3% in the head and neck. Carotid body paragangliomas are

the most common tumors in the head and neck and the management involved surgical extirpation.
Objective: To determine the autonomic alterations before and after surgical resection of unilateral paragangliomas.
Material and Methods: Autonomic studies, including HRDB, Valsalva, and Tilt tests, were performed to assess the autonomic function of patients before and after neck surgery.
Results: We analyzed the autonomic studies of 15 patients before and after neck surgery (1 month). All of the patients were women with an average age of 56 years (± 15.1). Before surgery, five patients (33.3%) presented parasympathetic failure (HRDB and Valsalva test), six patients (40%) with adrenergic failure (Valsalva), and six patients (40%) with a drop more significant than 20 mmHg were recorded in the Tilt test. After surgery, three patients (20%) presented parasympathetic failure (HRDB and Valsalva test), three patients (20%) with adrenergic failure (Valsalva), and two patients (13%) with a drop more significant than 20 mmHg in the Tilt test.
Summary and Conclusion: We found improvement in autonomic alterations after one month of neck surgery for unilateral paragangliomas in our group of patients.

Poster #44

Autonomic dysregulation in a multisystem phenotype with high-risk for developing temporomandibular disorders: results from the OPPERA dataset

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Introduction: Temporomandibular disorders (TMD) affect approximately 5–10% of the adult population and are major contributors to chronic pain. Altered autonomic functions (ANS) are well documented in chronic TMD and related comorbidities, such as in pain in other parts of the body, in anxiety and depression, and in sleep disorders. However, ANS abnormalities prior to developing TMD are less clear. In a recent study, we identified a multisystem phenotype with self-reported diagnosis or symptoms from 3 categories (the Triad) of pain-related issues, psychological issues, and sleep-related issues. This Triad phenotype was found to have an eightfold risk for developing initial onset of TMD pain in the multicenter Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) dataset. In the current study, we hypothesized that the Triad phenotype will have reduced cardiovascular ANS regulation as compared to non-Triad phenotype.
Methods: Secondary analysis was performed on 1199 non-Triad and 154 Triad TMD-free OPPERA enrollees at baseline. Resting heart rate variability (HRV), heart rate (HR), and blood pressure (SBP, DBP, MAP) were compared between Triad and non-Triad groups. Bivariate analyses were performed via Chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Non-parametric tests were used for all measures due to non-normal distribution. All comparisons were adjusted for demographic (age, gender, race) and study site (site ID) differences. All analyses were performed using R version 4.0.0.
Results: The Triad group was older (median age 30 vs. 23) and consisted of more females (63% vs. 48%) than the non-Triad group. Overall, significantly lower resting HRV in both time and frequency domains, and higher resting HR emerged in the Triad group compared to the non-Triad group ($p < 0.05$). In the blood pressure measures, the resting DBP was higher in the Triad group in bivariate analysis ($p = 0.003$), but no group difference in any blood pressure measures was found after adjusting for demographics and study site differences (p's > 0.05).
Conclusion: The presence or absence of multisystem issues may carry critical information when searching for disease pathophysiology and developing prevention strategies for TMD. Cardiovascular autonomic functions should be further studied in those with multisystem presentations prior to developing TMD.
Funding: This study was supported in part by the University of Iowa, College of Dentistry. Phenotypes were collected in studies supported by Grants U01DE017018, P01NS045685, and R01DE016558 from the National Institutes of Health. Additional resources were provided by Battelle Memorial Institute; University at Buffalo, State University of New York; University of Florida; University of Maryland; and University of North Carolina at Chapel Hill.

Poster #45

Is the cardiac autonomic profile of remote working office employees with and without kids different?

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Background: Remote work is a novel job condition characterized by an overlap between working and domestic demands. The stress-related impact of this modality has been mainly evaluated qualitatively but not quantitatively.
Aim: Therefore, the aim of the study was to compare the cardiac autonomic profile of office employees with and without kids during a day of remote work.
Methods: We acquired the 24-h Holter ECG of 23 workers with at least one child (KID group, age 48 ± 8 yrs, 9 males) and 27 without (NO_KID group, age 32 ± 6 yrs, 16 males). Visual analogue scale (VAS) was applied to measure the perceived level of stress. Long-term power spectral analysis was performed on the RR interval (RR) series during daytime (DAY) and nighttime (NIGHT). RR variance (σ^2_{RR}) was calculated and the power in high frequency (HF, 0.15–0.4 Hz) band (HF_{RR}) was considered as an index of the cardiac vagal modulation directed to the sinus node.
Results: We found that the VAS was not significantly different in KID and NO_KID. HFRR did not change between DAY and NIGHT in KID group (297 ± 39 vs. 568 ± 474 ms^2), while it was higher during NIGHT compared to DAY in NO_KID group (1584 ± 2289 vs. 599 ± 1029 ms^2). During NIGHT, HF_{RR} was greater in NO_KID than in KID group (1584 ± 2289 vs. 568 ± 474 ms^2). σ^2_{RR} did not differ between groups and experimental conditions.
Conclusion: Our results suggest that during remote working, KID group was characterized by a reduced nocturnal vagal modulation compared to NO_KID one. This finding introduces the need of a careful evaluation of the home social environment in order to correctly consider new factors that could potentially contribute to the risk

to develop work-related complications including cardiovascular diseases.

Poster #47

Autonomic manifestations in neuroendocrine tumors

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Introduction: Neuroendocrine tumors (NET) are a heterogeneous group of malignancies; the term "neuro" is based on the identification of dense core granules which store monoamines, the "endocrine" property refers to the synthesis and secretion of these monoamines. NETs have been described in the central nervous system, respiratory tract, larynx, gastrointestinal tract, thyroid, skin, breast, and urogenital system. NETs account for about 0.5% of all newly diagnosed malignancies, have a female preponderance of around 2.5:1. The most frequent primary sites are the gastrointestinal tract. The presence of carcinoid syndrome (CS) that results from the hypersecretion of amines and peptides facilitates diagnosis of NETs. The classical CS with watery diarrhea, flushing, bronchospasm, hypotension, and right-sided heart disease. These findings correlate with high seric serotonin levels. Confirmation of diagnosis require urinary 5-hydroxyndole acetic acid, a serotonin metabolite, and plasma chromogranin A.
Methods: We present a series of 4 patients with autonomic symptoms and neuroendocrine tumor. All underwent autonomic evaluation with sympathetic and parasympathetic tests.
Results: We followed four women, age 53–67 years, 3 patients with episodes of flushing, dizziness, and hypo or hypertension, 2 of these also with watery diarrhea. These patients were referred to our center because they all presented symptoms related to autonomic alteration. After the autonomic evaluation we required plasmatic serotonin and chromogranin A levels. All patients had elevated plasmatic serotonin. PET-CT with GaDOTANOC was performed, tumors from all patients expressed somatostatin receptors. Two patients presented bilateral serotonin-producing paragangliomas, one patient had a carcinoid tumor of terminal ileum and one patient had pancreatic tumor. Autonomic evaluation showed that all patients had labile blood pressure, one patient had cardiovagal regulation failure, and one patient had sympathetic adrenergic dysfunction.
Conclusion: Neuroendocrine tumors should be suspected in patients with episodes of flushing and labile blood pressure, the PET-CT with GaDOTANOC is useful in diagnosing patients with tumors that express somatostatin receptors although they do not have the classical clinical presentation of carcinoid syndrome.

Poster #48

Evaluation of cardiac autonomic functions in patients with endometriosis

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Background: Cardiac autonomic dysfunction was found to be associated with endometriosis in previous animal studies. Sympathetic nerves through β2 adrenergic receptors accelerate the progression of endometriosis and the reduced vagal activity reported in endometriosis patients indicates the disrupted autonomic balance in these patients. The non-invasive measurement of heart rate variability (HRV) and Ewing's battery of tests are the sensitive, reproducible and reliable markers for the quantitative assessment of the parasympathetic and sympathetic innervation of the autonomic nervous system. The study aimed to evaluate the cardiac autonomic function using short-term HRV analysis and Ewing's battery of reactivity tests in patients with endometriosis.
Methods: This is a retrospective case–control study, which included 44 endometriosis patients (Age: 30.27 ± 7.59) and 25 healthy females (Age: 34.6 ± 10.59). Short-term HRV was assessed by recording 5-min of lead II ECG signal during supine rest followed by autonomic reactivity tests which included deep breathing test (DBT), cold pressor test (CPT), and tilt table test. Changes in heart rate and blood pressure were recorded in response to different stimuli.
Results: Systolic blood pressure (SBP) and heart rate (HR) were significantly higher in patient group compared to control [{SBP:113 (109.5–120) vs. 110 (103.8–114.5), p = 0.03}; {HR: 85 ± 12.52 vs. 71.79 ± 10.72, p = 0.001}]. Both, frequency and time domain indices of parasympathetic activity were significantly decreased in patients with endometriosis compared to healthy control [{high frequency power: 2.34 ± 0.64 vs. 2.71 ± 0.65, p = 0.04}; {SDSD: 25.09 (14.64–39.86) vs. 38.96 (23.33–64.24), p = 0.01}; {RMSSD: 25.06 (14.63–39.81) vs. 38.11 (22.56–55.55), p = 0.02}; {pNN50 = 2.09 (0.04–9.73) vs. 6.69 (1.61–22.68); p = 0.0445}. Overall variability of HRV represented by total power (TP) and SDNN were also significantly lower in patients compared to control [T.P: {2.91 ± 0.42 vs. 3.15 ± 0.51, p = 0.04}; {SDNN: 30.06 (23.44–39.91) vs. 41.29 (25.81–54.49), p = 0.01}]. However, no statistically significant difference was observed in sympathetic activity of HRV (low frequency power: 2.3 ± 0.44 vs. 2.5 ± 0.47, p = 0.07). The results of parasympathetic and sympathetic reactivity tests were comparable between endometriosis patients and healthy control group.
Conclusion: The current study indicated that the patients with endometriosis have dampened parasympathetic activity and overall HRV compared to healthy control suggesting dysfunction in resting cardiac autonomic activity in endometriosis.

Poster #49

Does 18F-DOPA PET scanning provide a valid biomarker of cardiac sympathetic innervation?

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Background: Brain 18F-DOPA positron emission tomographic (PET) scanning is approved in the United States to aid the diagnostic evaluation of parkinsonism. Since 18F-DOPA is converted to 18F-dopamine in organs such as the heart that express L-aromatic-amino-acid decarboxylase, 18F-DOPA might also be useful for imaging cardiac sympathetic innervation. 18F-dopamine is well established for this purpose but is available only as an investigational drug. We compared 18F-DOPA with 18F-dopamine cardiac scanning in the same patients who either had or did not have low myocardial 18F-dopamine-derived radioactivity.
Methods: In a prospective, observational, within-subjects study brain and cardiac 18F-DOPA PET scanning and, on a different day, cardiac 18F-dopamine PET scanning were done in patient groups with neurogenic orthostatic hypotension, parkinsonism, or both abnormalities. The cutoff for myocardial 18F-dopamine-derived radioactivity was 6000 nCi-kg/cc-mCi) and for the the putamen/occipital cortex (PUT/OCC) ratio of 18F-DOPA-derived radioactivity was 2.70. We also examined inter-relationships of these indices with scores on the

Unified Parkinson Disease Rating Scale (UPDRS) in patients with vs. without parkinsonism.
Results: A group of 12 subjects had decreased cardiac 18F-dopamine-derived radioactivity, and a group of 8 subjects had normal radioactivity ($p < 0.0001$). Cardiac 18F-DOPA-derived radioactivity did not differentiate the groups. PUT/OCC ratios of 18F-DOPA-derived radioactivity were negatively correlated with UPDRS scores ($r = -0.67$, $p = 0.0015$) but were unrelated to either cardiac 18F-DOPA-derived radioactivity or cardiac 18F-dopamine-derived radioactivity.
Conclusions: Brain 18F-DOPA scanning provides a clinical laboratory biomarker of parkinsonism, but cardiac 18F-DOPA scanning does not provide a biomarker of myocardial sympathetic innervation.
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Poster #50

Nocturnal heart rate variability following evening binge alcohol consumption: sex differences

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Recent work from our laboratory has demonstrated decreased HRV in stage II (N2) sleep, slow wave sleep (SWS), and rapid eye movement (REM) sleep after evening binge alcohol consumption. Despite evidence that sex (i.e., male vs. female) impacts the relationship between alcohol consumption and sleep, it remains unknown if nocturnal HRV differs between men and women after binge alcohol consumption during key polysomnographic sleep stages. We hypothesized that women would exhibit a more dramatic decrease in HRV due to higher prevalence of alcohol-mediated sleep disturbances after alcohol consumption. Utilizing a randomized, crossover design, thirty-one participants (15 M, 16 F; age: 26 ± 2 years; BMI: 27 ± 1 kg/m^2) enrolled in the study and were tested after both alcohol and fluid control beverage conditions ($\sim$ 1 month apart to control for menstrual phase). The alcohol condition simulated a binge-drinking episode via a 4–5 drink equivalent (1 g/kg men, 0.85 g/kg women) within two hours. Overnight polysomnography and two-lead electrocardiogram (ECG) were recorded during 8-h in-laboratory sleep acquisition. Five-to-ten-minute periods of stable sleep were selected for each participant in each sleep stage free of scorable arousals and apneic events. The nocturnal ECG was imported into custom software (WinCPRS, Absolute Aliens, Finland) for HRV analysis. Cardiovagal activity was assessed via time- and frequency-domain HRV. The proportion of R-R intervals that varied by more than 50 ms (pNN50) and root mean squared of successive R-R interval differences (RMSSD) were reduced similarly between men and women after evening binge alcohol consumption in N2 (condition: $p = 0.002$, 0.007) and SWS (condition: $p < 0.001$ for both). REM sleep pNN50 was reduced following alcohol consumption in both men and women (condition: $p = 0.033$), but not RMSSD (condition: $p = 0.288$). High-frequency (HF) HRV was reduced in N2 sleep following binge alcohol consumption in both sexes (condition: $p = 0.039$), but not REM sleep (condition: $p = 0.405$). HF HRV was reduced in SWS in both sexes (condition: $p < 0.001$, with a more robust reduction in men [1931 (626–2874) vs. 540 (208–1558)] compared to women [857 (393–2038) vs. 649 (160–1358); condition $\times$ sex: $p = 0.014$]. Contrary to our initial hypothesis, men exhibited greater cardiac vagal tone dysregulation during SWS after binge alcohol consumption when compared to women.
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Poster #52

Altered autonomic responses to happy and fearful music in patients with a history of mild traumatic brain injury

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Background: Even after mild traumatic brain injury (mTBI) there may be long-lasting changes in autonomic responses to emotional stimuli. Happy or fearful music triggers emotional perception and autonomic responses. So far, these responses have not been evaluated in patients with a history of mTBI (post-mTBI-patients).
Objective: To assess cardiovascular autonomic responses to happy and fearful music in post-mTBI-patients.
Methods: In 24 post-mTBI-patients (35.3 ± 2.7 years; 6 women, interval since mTBI 33.6 ± 5.8 months) and in 26 healthy persons (30.4 ± 2.3 years; 10 women), we monitored respiration, RR-intervals (RRIs), systolic and diastolic blood pressure (BPsys, BPdia) at rest and during the presentation of 3-min excerpts of "happy" music (Marriage of Figaro, Overture, K. 492) and "fearful" music (The miraculous Mandarin, Suite, Op. 19). Participants rated "happiness" and "fear" on Likert scales from 1 to 5.
Results: Likert scores assigned to happy and fearful music were similar in patients and controls. "Happy" music accelerated respiration only in controls (14.1 ± 0.7 vs. 16.0 ± 0.7 bpm), increased BPsys in controls (134.0 ± 3.5 vs. 137.7 ± 3.5 mmHg) and patients (129.0 ± 3.1 vs. 133.7 ± 3.3 mmHg) but did not change BPdia and RRIs. "Fearful" music increased respiration only in controls (15.0 ± 0.5 vs. 16.1 ± 0.6 bpm), increased BPsys in controls (130.9 ± 3.1 vs. 135.1 ± 3.3 mmHg) and patients (128.9 ± 3.6 vs. 133.4 ± 3.7 mmHg), and BPdia in controls (67.4 ± 1.9 vs. 68.8 ± 2.1 mmHg) and patients (64.7 ± 1.5 vs. 65.9 ± 1.7 mmHg), while RRIs did not change in both groups.
Conclusion: The similar emotional ratings of the musical stimuli in patients and controls suggest that the patients' emotional perception of "happy" and "fearful" music was not significantly compromised at the time of the study, 33.6 ± 5.8 months after the mTBI. In contrast, lack of respiration-acceleration with both happy and fearful music in the patients indicates the persistence of subtle changes in sympathetic processing of musical stimuli even months to years after mild TBI. The findings suggest that central autonomic regulation might be more vulnerable to mTBI than is the perception of emotional stimuli.
Funding: The study was partially funded by the International Brain Research Foundation Inc. (IBRF), Secaucus, NJ, USA.

Poster #53

Cardiovascular autonomic dysfunction in patients referred for autonomic testing

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Background: Patients referred for cardiovascular autonomic (CV-Aut) tests include a wide range of symptoms and/or presumptive diagnosis. Autonomic symptoms can be objectified and measured using questionnaires.
Objectives: To describe the presence of CV-Aut symptoms and of CV-Aut function tests in patients referred for autonomic evaluation.
Methods: 47 consecutive patients (33 women), symptoms and/or presumptive diagnosis: orthostatic intolerance (OI) without postural tachycardia n = 19, small fiber neuropathy (SFN) n = 9, Parkinsonism (PAR) n = 7, OI/vasovagal syncope n = 5, OI/postural orthostatic tachycardia syndrome (POTS) n = 4, OI/pure autonomic failure (PAF) n = 1, OI/autoimmune autonomic ganglionopathy (AAG) n = 1, gastrointestinal autonomic neuropathy n = 1. Autonomic symptoms questionnaires: Composite autonomic symptoms scale (COMPASS-31) and Scale for Outcomes in Parkinson's Disease Autonomic Dysfunction (SCOPA-aut). CV function tests: orthostatic blood pressure (BP) change on standing, BP during isometric exercise, Valsalva ratio, heart rate (HR) change during deep breathing and HR change on standing. Ewing battery total scores: 0–0.5 = normal CV function, 2 or more = CV autonomic dysfunction.
Results: 1. CV Symptoms: Neither COMPASS 31 nor SCOPA-aut scores did show correlation with the Ewing scores. Mean scores of both questionnaires did not show difference in patients with normal CV-Aut function, while in patients with CV-Aut dysfunction COMPASS 31 was higher than the SCOPA-Aut. 2. CV autonomic tests: neurogenic orthostatic hypotension and a CV-Aut dysfunction was found in PAF and AAG cases. Patients with OI without postural tachycardia, OI/vasovagal and OI/POTS showed normal CV-Aut function, as did with presumptive Parkinsonism and small fiber neuropathy without OI.
Conclusions: In the majority of patients referred for autonomic function evaluation there is no association between OI symptoms and the presence of CV-Aut dysfunction.

Poster #54

Oscillatory LBNP induced vasoconstriction does not cause baroreflex activation: causality based approach

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Background: Oscillatory lower body negative pressure (LBNP) in the range of − 10 to − 20 mmHg is a non-invasive tool for simulating non-hypotensive hypovolemia. Despite no change in blood pressure, an increase in total peripheral vascular resistance (TPVR) is observed. Due to mechanical stiffening of vessels, there is a disjuncture of mechano-neural coupling at the level of arterial baroreceptors which has not been investigated. Therefore the present study was designed to quantify both cardiac and vascular arms of baroreflex using partial directed coherence (PDC)—spectral granger causality method.
Methodology: 33 healthy human volunteers were recruited. Continuous heart rate and blood pressure—systolic, diastolic and mean blood pressure (measured as the area under curve of the pulse waveform) were recorded. The measurements were taken in resting state (0 mmHg), at − 10 mmHg and − 15 mmHg. Spectral causality—PDC was estimated from the MVAR model in the low frequency band using GMAC matlab toolbox. Causality from blood pressure (SBP and MBP) to RR interval and TPVR was calculated. Statistical analysis was performed using Graphpad Prism.
Results: There was a significant increase in TPVR from baseline at both − 10 mmHg (p value < 0.0001) and − 15 mmHg (p value $<$ 0.0001). PDC from mean blood pressure (MBP) to RR interval showed no change at − 10 mmHg (p value 0.073) and − 15 mmHg (p value 0.740). PDC from mean blood pressure to TPVR also showed no change at − 10 mmHg (p value 0.232) and − 15 mmHg (p value 0.365). Similar results were seen for PDC estimation using systolic blood pressure (SBP) as input.
Conclusion: There is no statistically significant change in the spectral causality quantified by PDC from MBP to RR interval and PDC from MBP to TPVR. This implies that the arterial baroreflex does not get activated by vasoconstriction at − 10 and − 15 mm Hg of oscillatory LBNP.

Poster #55

The physiology of the caffeine hit

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Background: The role of the sympathetic nervous system in the transient hypertensive response to coffee is controversial. Caffeine, the active component, blocks adenosine resulting in central stimulation of sympathetic activity (SNA) and direct vasoconstriction of peripheral vessels. We monitored total peripheral resistance with muscle sympathetic nerve activity (MSNA) in response to increased plasma caffeine levels.
Methods: Using a double-blind cross-over method, we monitored hemodynamics and MSNA for a study period of 120 min after consumption of espresso coffee, water or decaffeinated coffee (decaff) in healthy adults (n = 16). At 15 min intervals we measured: plasma caffeine levels, mean arterial pressure (MAP), heart rate (HR) stroke volume (SV), cardiac output (CO) total peripheral resistance (TPR) and muscle sympathetic activity (MSNA). Baroreflex activity was assessed using burst incidence and RR interval changes to spontaneous blood pressure fluctuations.
Results: Mean age was 34.4 ± 2 years, 7/16 were women; and mean coffee intake 2 ± 0.3 cups per day. During the study period plasma caffeine levels increased from 2.4 ± 0.8 at baseline to 21.0 ± 4 μmol/L, and MAP from 96 ± 3 to 103 ± 3 mmHg. Percent baseline MAP after coffee was 108 ± 1% compared to water 106 ± 1% (p = 0.1) and decaff 104 ± 1% (p = 0.002). Heart rate decreased only after coffee and decaff: 98 ± 1% (p = 0.01) and 99 ± 1% (p = 0.02) and there was no correlation with plasma caffeine levels. After coffee, TPR increased to 120 ± 4% baseline versus water 107 ± 4% (p = 0.01) and decaff 109 ± 4% (p = 0.02). However, MSNA levels decreased: manually assessed burst frequency 96 ± 3% versus water 106 ± 3% (p = 0.04) and decaff 112 ± 3%

(p = 0.001) and automated burst frequency 88 ± 8% versus 128 ± 11% (p = 0.001) and 132 ± 11% (p = 0.001). Simultaneously, sympathetic baroreflex activity fell at 60 min from − 2.2 ± 0.1 to − 1.8 ± 0.1 bursts/100 beats/mmHg, compared to water (p = 0.009) and decaff (p = 0.004). Cardio-vagal baroreflex activity remained constant.
Conclusions: The hypertensive response to coffee is secondary to peripheral vasoconstriction but this is not mediated by MSNA. Instead there is appropriate baroreflex-mediated inhibition of MSNA and slowing of heart rate. Therefore vasoconstriction is more likely secondary to direct caffeine blockade of vascular adenosine receptors than SNA-mediated vasoconstriction in muscle. However, caffeine may dampen baroreflex inhibition of MSNA by blocking adenosine receptors in the brainstem.

Poster #56

Effects of obstructive sleep apnea on baroreflex sensitivity in hypertrophic cardiomyopathy

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Introduction: Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy associated with impaired systolic and diastolic function. Prior, oximetry-based studies have suggested a high prevalence of obstructive sleep apnea (OSA) in patients with HCM. HCM and OSA are independently associated with impaired baroreflex sensitivity (BRS). Thus, we sought to determine the prevalence of OSA in HCM using gold-standard polysomnographic assessment and the impact of concurrent OSA on baroreflex sensitivity in HCM.
Methods: In this prospective observational study, 152 HCM participants and no prior history of OSA underwent assessment of BRS during spontaneous breathing as well as overnight polysomnography. Individuals had to be in sinus rhythm at the time of BRS testing where changes in RR interval per mmHg fluctuation in blood pressure (BP) were evaluated using non-invasive beat-to-beat monitoring. An Apnea Hypopnea Index (AHI) > 5/Hr was considered diagnostic for OSA (5–14 mild, 15–29 moderate, ≥ 30 severe). An assessment of mean office BP was also undertaken.
Results: Of the 152 subjects, (age 59.6 ± 19 years, 99 (65.1%) male), 74 (48.9%) were diagnosed with OSA (36 mild, 17 moderate, and 21 severe) with mean AHI scores of 9.3, 22.4, and 53.4, respectively. Cardiovagal baroreflex sensitivity measured during spontaneous breathing was significantly lower in the OSA group (10.66 ± 6.6 vs 11.94 ± 9.9 ms/mmHg, p = 0.01). When compared to HCM patients without OSA, those with OSA were more likely to be male (73.0% vs. 57.7%, p = 0.048), were older (median 61.1 vs. 53.0 years, p = 0.001) had higher BMIs (32.6 vs. 29.6, p < 0.001) and higher average office systolic BP (122.1 vs. 115.8 mmHg, p = 0.008), with a higher prevalence of dyslipidemia (75.3% vs. 53.4%, p = 0.006), smoking (54.1% vs. 32.4%, p = 0.008), coronary artery disease (24.3% vs. 8.1%, p = 0.007), and mitral regurgitation (73.8% vs. 52.9%, p = 0.039). Ventricular septal thickness and outflow tract velocity remained similar between both groups as did the prevalence of hypertension and history of atrial fibrillation.
Conclusion: There is a high prevalence of OSA in HCM. BRS is impaired in HCM with concurrent OSA. Whether the impaired BRS is due to OSA per se, or due to older age, obesity or higher SBP remains to be determined.
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Poster #58

Impact of altered breathing frequency on cardiorespiratory interactions: examining the relationships between paced breathing, heart rate, and blood pressure

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Background: Individuals with spinal cord injury (SCI) often experience autonomic dysfunction, with abnormal control of heart rate (HR), blood pressure (BP), and breathing. These functions are intrinsically linked, and impairments are often further provoked under orthostatic stress. Analyses of HR and BP variability show promise for the quantitative assessment of autonomic function after SCI. However, methodological considerations at the time of assessment may influence the results of these analyses. We aimed to evaluate the impacts of (i) paced vs. spontaneous breathing and (ii) the seated vs. supine posture on baroreflex and respiratory interactions.
Methods: We tested 9 able-bodied controls (5 female, aged 26 ± 5.5 years) during: supine spontaneous breathing; supine paced breathing (0.25 Hz); and seated spontaneous breathing. Beat-to-beat BP and HR were recorded continuously. Power spectral analysis of low frequency (LF; 0.05–0.15 Hz) and high frequency (HF; 0.20–0.30 Hz) systolic arterial pressure (SAP) and R-R intervals (RRI) were used to measure autonomic function. Cross spectral analysis was performed between SAP and RRI to quantify the frequency-related coherence, phase shift, and gain (sensitivity) within the LF (to assess cardiac baroreflex control) and HF (to assess the impact of respiration on SAP and RRI) ranges.
Results: When supine, paced breathing reduced LF RRI (12.4 ± 1.8% vs. 34.0 ± 4.6%; p = 0.001), and increased both HF SAP (22.6 ± 4.9% vs. 5.6 ± 0.7%; p = 0.01) and HF RRI (41.4 ± 5.62% vs. 17.03 ± 3.31%; p = 0.001). In the LF range, paced breathing produced more negative phase (− 53.5 ± 12.0° vs. − 32.4 ± 8.9°; p = 0.0073) with longer baroreflex time delay (1.7 ± 0.5 s vs. 0.8 ± 0.2 s; p = 0.012). In the HF range, paced breathing increased coherence (0.94 ± 0.02 vs. 0.71 ± 0.09; p = 0.021). The transition to a seated position increased LF SAP (34.5 ± 4.3% vs. 19.6 ± 4.4%; p = 0.002), and decreased HF RRI (12.3 ± 3.1% vs. 17.0 ± 3.3%; p = 0.03), with no effect on LF RRI (p = 0.715), or any cross-spectral parameter (p > 0.05).
Conclusion: In healthy controls, both paced breathing and the seated posture significantly impact HR and BP variability analyses. Further research is needed to ascertain whether these findings are translatable to individuals with SCI, who may respond differently to these orthostatic and respiratory challenges. These data will guide methodology for cardiovascular autonomic function testing post-SCI and improve understanding of the high cardiorespiratory morbidity and mortality of those living with SCI.

Poster #59

Cardiovascular and cerebrovascular responses to urodynamics testing after spinal cord injury: the influence of autonomic injury

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Background: Autonomic dysfunction is a prominent concern following spinal cord injury (SCI). In particular, autonomic dysreflexia (AD; paroxysmal hypertension in response to sensory stimuli below the level of injury that is often associated with bradycardia) is common in autonomically complete injuries at or above T6. AD is currently defined as a > 20 mmHg increase in systolic arterial pressure (SAP) from baseline, without specific heart rate (HR) criteria. Urodynamics testing (UDS) is performed routinely after SCI to monitor urological sequelae, often provoking AD in high-level SCI. We, therefore, aimed to assess the impact of autonomic injury on cardiovascular and cerebrovascular responses during UDS in individuals with chronic (> 1 year) SCI.
Methods: Following blood draw (plasma norepinephrine [NE]), continuous SAP, HR, and cerebral blood flow (CBF) were recorded at baseline (10-min supine), during standard clinical UDS, and recovery (10-min supine) ($n = 22$). Low frequency variability in systolic arterial pressure (LFSAP; a marker of sympathetic modulation of blood pressure) and cerebral resistance were determined. High-level injury ($\geq$ T6) with blunted/absent LFSAP (< 1.0 mmHg^2) and/or low plasma NE (< 0.56 nmol•L^{-1}) indicated autonomically-complete injury. Known electrocardiographic markers of atrial (p-wave duration variability) and ventricular arrhythmia (T-peak—T-end variability) were evaluated at baseline and during UDS.
Results: Nine participants were determined as autonomically-complete, yet 20 participants had increased SAP > 20 mmHg during UDS. Of these 20 participants, 10 experienced bradycardia (HR $<$ 60 bpm) during UDS, 7 of which were considered autonomically-complete based on criteria. Maximum SAP was higher in autonomically-complete injuries (207.1 ± 12.3 mmHg) compared to autonomically-incomplete injuries (165.9 ± 5.3 mmHg) during UDS ($p < 0.001$). HR during UDS was reduced compared to baseline ($p = 0.056$) and recovery ($p = 0.048$) only in autonomically-complete lesions. CBF was not different between groups or phases (all $p > 0.05$). However, cerebrovascular resistance was increased during UDS in autonomically-complete injuries compared to baseline ($p < 0.001$) and recovery ($p < 0.001$). Risk for both atrial and ventricular arrhythmia increased during UDS compared to baseline ($p < 0.05$), particularly in autonomically-complete injuries ($p < 0.05$).
Conclusion: UDS is recommended yearly in chronic SCI but is associated with profound AD and an increased risk of arrhythmia, highlighting the need for continued monitoring during UDS. Our data also highlight the need for HR criteria in the definition of AD.
Funding: Heart and Stroke Foundation of Canada.

Poster #60

Rapid sympathetically-mediated increases in circulating leukocytes during experimental muscle pain

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Work from our lab has shown that long-lasting muscle pain causes a sustained increase in muscle sympathetic nerve activity (MSNA), blood pressure (BP) and heart rate (HR) in some individuals (Responders) but not in others (Non-Responders). Given the interaction between the sympathetic and immune systems, we hypothesised that there will be a sympathetically mediated inflammatory response in the Responder group, as evidenced by release of leukocytes into the circulation. MSNA was recorded from 14 participants via tungsten microelectrodes inserted percutaneously into the common peroneal nerve. Blood samples were taken via an intravenous cannula in the arm every 5 min during 15 min of baseline, during muscle pain induced by infusion of 5% hypertonic saline into the tibialis anterior muscle for 40 min, and during 20 min of recovery. Eight participants (57%) showed significant increases in MSNA burst amplitude during pain (119.1 ± 8.8% above baseline), while six (43%) showed no response (96.2 ± 7.9%). There were significant differences between the Responder and Non-Responder groups ($P < 0.0058$), but no significant differences in peak pain ratings between the two groups (6.3 ± 1.1 vs 5.5 ± 2.2 out of 10, $p = 0.3091$). In the Responder group leukocyte count increased within the first 5 min of pain and remained elevated for the duration of muscle pain, showing significant positive correlations with MSNA burst amplitude ($r = 0.6857$, $p = 0.0061$), systolic BP ($r = 0.6179$, $p = 0.0162$), diastolic BP ($r = 0.5464$, $p = 0.0377$) and HR ($r = 0.7637$, $p = 0.0009$). There were no changes in leukocyte count in the Non-Responder group. We have shown, for the first time, that long-lasting muscle pain causes an increase in circulating leukocytes in individuals in whom MSNA, BP and HR increased. We conclude that the increase in leukocytes was mediated by the increase in sympathetic outflow during muscle pain.

Poster #61

Paradoxical respiratory arrhythmia in patients after transplantation is a simulation of vagal regulation of the heart rhythm

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Background and Objective: After heart transplantation (HT), the neurogenic regulation of the heart rhythm disappears. While the possibility of sympathetic reinnervation in some patients has a convincing evidence base, the restoration of vagal control is not so obvious. The respiratory arrhythmia associated with the parasympathetic heart regulation. The aim of our study was to clarify the characteristics of respiratory arrhythmia evaluation in patients at different times after HT.
Materials and Methods: We examined 27 patients with terminal heart failure aged 47.6 ± 13.2 years and 20 healthy volunteers of comparable age. The examination of autonomous regulation was carried out before, and 3–6, 9–12 and 21–24 months after the HT. All participants were assessed for Valsalva index (VI) and respiratory sinus arrhythmia (RSA) during a deep breathing test (6 breaths per minute). Hemodynamics was recorded by the Finometer-pro (Nederland)

monitor. During the tests, the interaction of heart rate (HR) and cardiac output (CO) were analyzed.
Results: It was found that patients with heart failure initially had a significant decrease in both VI (1.43 ± 0.26 vs. 1.80 ± 0.38; $p < 0.005$) and RSA (10.7 ± 2.9 vs. 17.4 ± 3.1; $p < 0.001$) compared with the control group. Changes in HR and CO were in the counterphase with an average delay of 2.1 ± 0.3 beats/min. Inversion of IV (0.97 ± 0.02) and sharp decrease in RSA (3.8 ± 0.8) were observed 3–6 months after HT (both $p < 0.001$). With deep breathing, the arrhythmia was non-respiratory in 11 patients, while in the remaining 16 cases there was a change in the interaction of phase parameters in the form of a positive correlation between the dynamics of HR and CO with a delay of 1.7 ± 0.7 beats/min. On re-examination, there was a tendency to reduce the paradoxical reaction of the VI: 0.97 ± 0.02, 0.98 ± 0.03, and 0.99 ± 0.02 ($p = 0.09$), and RSA: 3.8 ± 0.8, 3.1 ± 0.7, and 2.7 ± 0.7 ($p = 0.06$) while maintaining common-mode dynamics HR and CO.
Conclusion: Paradoxical respiratory arrhythmia appeared in a number of patients after HT, which is most likely not associated with vagal regulation of the heart rhythm, the magnitude of which is greater immediately after surgery. Given the absence of vagal arrhythmia two years after HT, the likelihood of vagal reinnervation is doubtful.
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Poster #62

Hypothalamic nuclei activity and connectivity changes following a glucose challenge: a single subject fMRI study

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Introduction: Hypothalamic neural circuits, which adjust efferent autonomic activity in the face of altered nutrient supply, have been implicated in the pathogenesis of obesity, obesity-associated hypertension, and type 2 diabetes mellitus. Recent advances in functional magnetic resonance imaging (fMRI) permit to capture hypothalamic activity changes in groups of subjects. Because the approach obscures interindividual variability in hypothalamic regulation, we studied individual hypothalamic activity and functional connectivity in a single subject during multiple glucose challenges in the MRI scanner.
Methods: We conducted ten oral glucose tolerance tests at different days in the same healthy man (56 years, 64 kg, 1.77 m). We acquired functional images using a 3 T scanner before, and 10 and 45 min after glucose ingestion. Moreover, we measured plasma glucose and insulin levels at seven time points in three of the tests. Activity and functional connectivity changes were calculated using independent component analysis followed by a dual regression using an F-test and post-hoc two-sample t-tests. All analyses were corrected for multiple comparisons.
Results: Plasma glucose (147.5 ± 8.4 mg/dl) peaked 30 min after glucose intake followed by an insulin maximum 15 min thereafter (45.7 ± 7.0 mU/l). We observed significant activity increases 45 min after glucose intake in the arcuate, paraventricular, and dorsomedial nuclei, as well as in the posterior hypothalamic area, infundibulum, and mamillary bodies. Moreover, the mamillary bodies increased their functional connectivity to the ventromedial, dorsomedial, and periventricular nuclei.
Conclusion: Our results, which are consistent with previous animal experiments, show that fMRI can capture individual activity and connectivity changes in specific hypothalamic nuclei during a glucose challenge. Individual hypothalamic fMRI holds promise in delineating disease mechanisms in single patients.

Poster #63

Forebrain responses to handgrip exercise in premenopausal and postmenopausal women

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Introduction: Postmenopausal women (POST) have increased muscle sympathetic nerve activity (MSNA) at rest compared to premenopausal women (PRE). While MSNA is generated by nuclei in the medulla oblongata, several forebrain regions can influence the generation of sympathetic activity. Still, functional differences in autonomic forebrain regions have yet to be compared between PRE and POST.
Purpose: We tested the hypothesis that blood oxygen level dependent (BOLD) functional MRI signal intensity change in supramedullary regions which promote sympathetic activity occur at a larger magnitude in POST relative to PRE during handgrip exercise.
Methods: We examined BOLD signal intensity changes in response to 3 trials of 2-min isometric handgrip exercise at 30% of maximal voluntary contraction in 3 PRE (23 ± 2 yr, 22 ± 2 kg/m^2) and 5 POST (54 ± 4 yr, 24 ± 3 kg/m^2). A voxel-based analysis was performed using FSL with corrected voxel threshold of $P < 0.05$. Region of interest analyses on bilateral forebrain areas including the amygdala, insula, and medial prefrontal cortex were then performed. BOLD signal intensity change was calculated in 30-s bins as a percent change from the first volume. Statistical analyses were performed using unpaired t-tests and 2-way repeated measures ANOVAs. Data are presented as mean ± SD.
Results: Resting systolic BP (PRE: 107 ± 12 vs. POST: 118 ± 15 mmHg, $P = 0.34$) and diastolic BP (PRE: 70 ± 6 vs. POST: 81 ± 10 mmHg, $P = 0.15$) were not different between PRE and POST. Robust increases in BOLD signal intensity were observed in the contralateral primary motor cortex which were similar between groups (Time: $P < 0.01$, Group: $P = 0.28$, Interaction: $P = 0.55$). The increases in BOLD signal intensity in the insula (Time: $P < 0.01$, Group: $P = 0.15$, Interaction: $P = 0.08$) and amygdala (Time: $P < 0.01$, Group: $P = 0.62$, Interaction: $P = 0.82$) did not differ between groups. Conversely, a significant reduction in BOLD signal intensity was found in the medial prefrontal cortex (Time: $P < 0.05$, Group: $P = 0.26$, Interaction: $P < 0.43$) which did not differ between groups. *Conclusions:* Consistent with the existing literature, these preliminary data demonstrate that the insula, amygdala, and medial prefrontal cortex are responsive to an autonomic stimulus such as handgrip exercise. While these data are preliminary, they suggest that autonomic forebrain responses to handgrip exercise may not differ between PRE and POST.
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Poster #65

Acoustic stimulation during slow wave sleep improves heart rate variability in an afternoon nap

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Adequate sleep is essential for proper autonomic function. Recent studies have reported that acoustic stimulation (AS) during overnight sleep can improve sleep quality. However, there is a paucity of research regarding the impact of AS on daytime napping and/or autonomic function. In the present study, we hypothesized that AS during an afternoon nap would improve heart rate variability (HRV) during stage 2 (N2) and slow wave sleep (SWS) when compared to a control (C) nap without AS. Nineteen healthy adults (10 female, 24 ± 1 years, 24 ± 1 kg/m^2) with habitual sleep time of < 8 h per night participated in two, 90-min afternoon naps with or without AS (0.8 Hz monaural beats at 30 decibels; Deep Sleep Boost, Hibernate device) using a randomized, crossover design (minimum 1-day washout). Polysomnographic sleep was recorded throughout each nap with continuous five-lead electrocardiography (ECG). ECG recordings were imported into a custom software (WinCPRS, Absolute Aliens, Finland) for time- and frequency-domain HRV analysis. Paired t-tests, or Wilcoxon Signed Rank tests for nonnormally distributed data, were performed to assess sleep time and HRV during N2 (n = 17) and SWS (n = 13) within individuals who experienced a minimum of 5 min of N2 or SWS during both naps. Total nap times were not different between the control (74 ± 4 min) and AS (77 ± 3 min) conditions ($p > 0.05$). Similarly, the time spent in N2 (C:35 ± 4 vs. AS:34 ± 3 min, $p > 0.05$) and SWS (C: 24 ± 3 vs. AS: 27 ± 3 min, $p > 0.05$) were not different between conditions. AS did not significantly alter HRV during N2 sleep ($p > 0.05$ for all HRV indices). AS improved key HRV indices during SWS, including increased root mean squared of successive differences (RMSSD; 83 ± 10 vs. 103 ± 12 ms, $p = 0.021$), proportion of consecutive R-R intervals that differ more than 50 ms (pNN50; 53 ± 6 vs. 62 ± 5%, $p = 0.030$), and high frequency (HF; 1535 ± 298 vs. 2534 ± 644 ms^2, $p = 0.044$) compared to the control. Our findings indicate AS during an afternoon nap significantly improved SWS HRV in healthy adults, suggesting improved parasympathetic control during AS. Future research is necessary to replicate these findings, and to assess whether AS during napping improves HRV within unhealthy populations that might have impaired parasympathetic control.

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Poster #66

Risk prediction of major adverse cardiac events in post-infarction patients based on combination of autonomic reactivity and ejection fraction parameters

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Background: A compromised cardiac autonomic reactivity with an impaired left ventricular ejection fraction (LVEF) leads to increased mortality and morbidity in post myocardial infarction (MI) patients. We examined the combination of autonomic profile parameters with LVEF for prediction of major adverse cardiac events (MACE) in post-MI patients.
Hypothesis: The combination of compromised autonomic reactivity and low LVEF predicts cardiovascular events in post-MI patients.
Methods: A retrospective cross-sectional observational study in 203 diagnosed post-MI patients was conducted with MACE as the primary endpoint, including all-cause-mortality, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and late revascularization. The combination of autonomic reactivity (Ewing's battery of tests) and low (LVEF 50%) or preserved (LVEF > 50%) EF as a predictor-model for MACE were assessed. Patients were classified into three categories based on autonomic reactivity: no autonomic neuropathy (CAN = 0–1), early autonomic neuropathy (CAN = 2–3), and definite autonomic neuropathy (CAN = 4–6) using the Cardiac Autonomic Neuropathy (CAN) score system. Patients with low CAN (both early and definite CAN) were further divided into two groups of low EF and preserved EF. Multivariable logistic regression and area under receiver operating characteristic (ROC) curves (AUC) of low autonomic reactivity measures and LVEF were used to create the final MACE predictive model.
Results: 76 (37.4%) of 203 post-MI patients had MACE throughout the 9-year follow-up period (n = 14, all-cause death; n = 22, non-fatal MI; n = 10, non-fatal stroke; n = 18, unstable angina; and n = 12, late revascularization). Compromised autonomic parameters were found in 122 (60.09%) of the 203 post-MI patients (n = 76, CAN = 2–3; n = 46, CAN = 4–6). Out of 122 post-MI patients with poor autonomic profile 51 (41.8%) had low EF (LVEF < 50%) and 71 (58.18%) had preserved EF (LVEF > 50%). Compromised autonomic parameters with low EF or preserved EF predictive models had AUCs of 0.8873 (95% CI 0.798–0.976), 83.87% positive predictive value (PPV) and 80.00% negative predictive value (NPV) and 0.790 (95% CI 0.687–0.893), PPV 68.89% and NPV 57.69%, respectively ($p < 0.0001$).
Conclusion: MACE in post-MI patients is well predicted by a combination of poor autonomic reactivity measures and low ejection fraction. An integrated prediction model may be developed to prevent MACE in post-MI patients.

Poster #67

Orthostatic tolerance following heat acclimation: a single blinded randomised controlled trial

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Introduction: Plasma volume (PV) is correlated with orthostatic tolerance. Heat acclimation (HA) is known to increase plasma volume (PV) however exercise training itself produces similar effects. Moderate exercise is known to increase orthostatic tolerance. The primary aim of this study was to investigate if active HA improved OT compared to temperate exercise.
Methods: 20 (15 male, 5 female) endurance trained cyclists were randomised, in a single-blind fashion, to either 8 days of mixed passive and active heat acclimation (HEAT) or 8 days of controlled

temperate exercise (CONTROL). Prior to, and after, intervention participants in both groups underwent a head-up tilt test with graded lower body negative pressure in the heat (32.0 ± 0.3 °C, 20 ± 3% relative humidity) with the time to presyncope recorded (OT) as well as heat stress testing (HST) to ascertain the physiological effects of the intervention. Measures included HR, rectal temperature, PV and perceptual ratings of heat and exertion.
Results: There was a significant increase in OT in the HEAT group (28 ± 9 to 40 ± 7 min) in comparison to the CONTROL group (30 ± 9 to 33 ± 4 min, p = 0.0116). During HST, in the HEAT group, there was a significant reduction (p = 0.0033) in peak heart rate (HEAT-pre; 165 ± 18, HEAT-post 152 ± 18, CONTROL-pre; 166 ± 16, CONTROL-post 168 ± 16) as well as mean exertional heart rate (p = 0.0026) compared to CONTROL. There was also a significant reduction (p = 00,063) in resting rectal temperature (HEAT-pre; 37.1 °C ± 0.2, HEAT-post; 36.8 °C ± 0.3, CONTROL-pre; 37.1 °C ± 0.2, CONTROL-post°C; 37.1 ± 0.2) as well as mean temperature (p = 0.0007). Perceptually there was a significant reduction (0.0049) in thermal comfort (HEAT-pre; 2.9 ± 1.0, HEAT-post; 1.7 ± 1.0, CONTROL-pre; 3.3 ± 0.8, CONTROL-post; 2.7 ± 0.8). There was a significant increase in PV in HEAT (9.6% ± 7.3) compared to CONTROL (− 0.3% ± 11.1).
Discussion: These data suggest that the improvements in orthostatic tolerance, following a mixed heat adaptation regimen, are above that conferred by exercise. Heat adaptation is protective against posturally mediated syncope exacerbated by heat stress.
Funding: This study was supported by the Ministry of Defence.

Poster #68

Baroreflex sensitivity during rapid changes in head positioning in patients with acute ischaemic stroke and healthy controls

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Background: Patients with acute ischaemic stroke (AIS) have been shown to have blunted blood pressure (BP) variability (BPV) responses to rapid head positioning (RHP), a maneuver designed specifically to enhance BPV to improve BP signal-to-noise ratio and reliability of dynamic cerebral autoregulation (dCA) assessment (Lam et al*., Am J Physiol Heart Circ Physiol*, 2019). We aimed to assess the frequency dependent BP responses and baroreflex sensitivity (BRS) in AIS and healthy controls to understand possible explanation for the different responses.
Methods: Two 5-min recordings of continuous beat-to-beat blood pressure and ECG in 15 AIS patients (69 ± 7.5 years) and 15 healthy controls (57 ± 16 years) was performed. For the first 5-min at rest with lying flat (0°) head-position, and a second 5-min RHP paradigm comprising of a 2-min of 0° head-position followed by four rapid changes from 0° to 30° head-position, then back to 0° over 15 s, and finally 2-min with 0° head-position. low frequency (LF) systolic blood pressure (SBP) power (measure of BPV), LF pulse-interval (PI) power, and alpha-index (measure of spontaneous baroreflex sensitivity-BRS) were calculated from the BP and ECG signals.
Results: In healthy controls there was significant increase in the LF-PI {9.28 (3.20, 21.15) ms^2 vs. 14.04 (10.14, 22.41) ms^2; p-value = 0.04*} and LF-SBP {0.19 ± 0.12 $mmHg^2$ vs. 0.34 ± 0.28 $mmHg^2$; p-value = 0.02*} during the RHP, however, there was no significant change in the LF-PI {5.33 (2.43, 13.89) ms^2 vs 6.96 (4.69, 13.16) ms^2; p-value = 0.11} and LF-SBP (0.37 ± 0.31 $mmHg^2$ vs. 0.63 ± 0.68 $mmHg^2$; p-value = 0.14) in AIS. The alpha-index was significantly higher in controls than AIS at baseline {10.30 (6.79, 15.10) vs. 4.7 (3.02, 7.56); p-value = 0.04*} and during RHP {9.85 (7.34, 16.28) vs. 4.62 (3.21, 8.69); p-value = 0.002*).
Conclusion: Patients with AIS when compared with healthy controls, have a low baseline BRS which does not change with RHP. The reduced BRS in AIS patients could explain the lack of increase in BPV with RHP. This finding has considerable implications for the choice of protocols for assessment of dCA in stroke patients.

Poster #69

Lower urinary tract symptoms in myasthenia gravis

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Objective: It remains uncertain to what extent lower urinary tract (LUT) symptom (LUTS) is a comorbidity of myasthenia gravis (MG). We prospectively administered a LUTS questionnaire devised for detecting neurogenic pelvic organ dysfunction (not validated) in an MG group and healthy control group and compared the results.
Methods: The MG group comprised 21 patients: 15 women, 6 men, age range 22–73 (mean 47) years, illness duration range 0.2–8 (mean 3.5) years, median MGFA grade 2, all walking independently. Therapies included thymectomy in 17, predonisolone 5–20 mg/day in 10, and pyridostigmine bromide 60–180 mg/day in 9. The control group, who were undergoing an annual health survey, comprised 235 consecutive subjects: 120 women, 115 men, age range 30–69 (mean 48) years. The questionnaire had 9 questions. Each question was scored from 0 (none) to 3 (severe) with an additional quality of life (QOL) index scored from 0 (satisfied) to 3 (extremely dissatisfied). Statistical analysis was made using Student's t-test.
Results: Compared with the control subjects, the frequency of LUTS in the MG patients was significantly higher for daytime frequency (43%; $p < 0.01$), nocturia (24%; $p < 0.01$) and urinary incontinence (43%; $p < 0.05$). The LUTS-related QOL index for the MG patients was significantly higher for MG patients as a whole than for all control patients (29%) ($p < 0.05$).
Conclusions: Our study results showed that MG patients had significantly more LUTS (overactive bladder) than healthy control subjects and had worse LUTS-related QOL; therefore amelioration of LUTS in MG is important.

Poster #70

Faster gastric peristalsis and meal emptying during transcutaneous auricular vagus nerve stimulation in functional dyspepsia: a 4D cine-MRI study

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Background: The vagus nerve controls both sensory and motor aspects of gastric physiology, thus vagal neuromodulation may be promising to regulate gastric function in disorders of gut-brain interaction such as functional dyspepsia (FD). Transcutaneous auricular vagus nerve stimulation (taVNS) targets the nucleus tractus solitarii (NTS) in the brainstem, and we showed that NTS response is enhanced by stimulating during exhalation, via Respiratory-gated Auricular Vagal Afferent Nerve Stimulation (RAVANS). Here, we use abdominal 4D cine-Magnetic Resonance Imaging (MRI) to assess the effect of RAVANS taVNS on velocity of gastric peristalsis and meal emptying in FD subjects and controls.
Methods: We enrolled 15 FD patients (13 F, 29.1 ± 13.2 y/o) and 15 healthy controls (10 F, 32.1 ± 7.7 y/o). MRI followed ingestion of a food-based contrast meal (pineapple-based for high manganese content). Each subject was scanned 15, 45 and 70 min post-meal (T0, T1, T2), while experiencing active RAVANS ("A", 1.5 s stimulation trains delivered at 100 Hz in left cymba concha) or Sham ("S", no current) on two separate visits (randomized order). MRI images were semi-automatically segmented to isolate gastric meal content, and peristaltic propagation velocity in the antrum was calculated using cross-sectional area time series. Effects of RAVANS were assessed using mixed-effects linear models.
Results; RAVANS taVNS did not modulate gastric function in healthy controls. In FD, peristaltic velocity was on average 0.7 mm/s faster during RAVANS compared to sham ($\widehat{\beta}$=0.67, SE = 0.28, t = 2.39). Follow-up comparison on data averaged across post-meal time points confirmed significantly higher velocity during active RAVANS (A: 5.1 ± 0.3 mm/s (mean ± SEM); S: 3.7 ± 0.4 mm/s; p = 0.017). The increase in peristaltic velocity was accompanied by a trend towards faster meal emptying during RAVANS ($\widehat{\beta}$=− 4.15, SE = 1.94, t = − 2.14). Post-hoc tests using Tukey correction for multiple comparisons suggested faster emptying during active RAVANS at T1/T0 (A: − 17.8 ± 3.4%; S: − 9.5 ± 3.6%; p = 0.032) and at T2/T0 (A: − 30.7 ± 3.4%; S: − 22.4 ± 3.6%; p = 0.032).
Conclusion: Our analysis found that RAVANS taVNS can successfully modulate gastric function in FD patients, suggesting therapeutic applicability in disorders of gut-brain interaction. Further, our 4D cine MRI approach allowed for a fully non-invasive evaluation of gastric function. Future work focusing on the central circuitry underlying gastric response to RAVANS taVNS will inform applicability of this therapy for FD patients.
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Poster #71

Barriers and facilitators encountered by health care practitioners when supporting individuals with SCI to change their bowel care

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Individuals with spinal cord injury (SCI) can experience severe autonomic dysfunction that impacts various autonomic processes, including continence and bowel function. Improving bowel care has been identified as a priority by individuals living with SCI, for whom bowel care is associated with high levels of dissatisfaction and impaired quality of life. However, despite bowel care being identified as problematic by 78% of people with SCI, most (71%) individuals with SCI have not changed their bowel management approaches with the goal of improving their quality of life for at least 5 years. We recently evaluated this disconnect, finding that lack of access to resources and knowledge about bowels and bowel care options were barriers to changing bowel care routines, while workplace flexibility, opportunity or circumstance, and peer mentorship were all facilitators to making change. Of note, individuals with SCI often turn to healthcare providers (HCP) for support in navigating and treating their bowel dysfunction, highlighting the important role of HCP perspectives in facilitating effective bowel care. Using an integrated knowledge translation approach, we aimed to explore the barriers and facilitators encountered by health care practitioners when discussing options and supporting individuals with SCI to change their bowel care. Our approach was guided by the Behaviour Change Wheel and used the Theoretical Domains Framework (TDF). Semi-structured interviews were conducted with HCP who worked with individuals with SCI (n = 3, mean age 45.7 ± 24 years, 2 female) and transcribed verbatim (duration 39 ± 23 min). Barriers and facilitators were extracted, deductively coded using TDF domains and inductively analysed for themes within domains. Preliminary results suggest that cost of intervention and impact on independence can be barriers to implementing a change in bowel care routines. Understanding these barriers and facilitators is vital to develop targeted and relevant interventions that will reduce barriers and enhance facilitators to changing care routines, empowering individuals with SCI to make changes to their bowel care, potentially decreasing the effects of autonomic dysfunction, with the goal of improving their quality of life in this priority area.

Poster #72

Comparing responses of Valsalva's maneuver to ischemic handgrip following spinal cord injury

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Introduction: Individuals with spinal cord injury (SCI) commonly have impaired sympathetic control below the level of injury. However, partial sympathetic regulation may remain and may not be appreciated if different regulatory pathways are not engaged. Valsalva's maneuver engenders a rapid reduction in baroreflex sympathoinhibition whereas ischemic handgrip exercise engenders a progressive increase in group III/IV afferent sympathoexcitation. Therefore, we characterized responses to these two different pathways and patterns of sympathetic recruitment in individuals with SCI (SCI, N = 8) and uninjured controls (CON, N = 10).
Methods: The electrocardiogram and beat-by-beat blood pressure were recorded during three 15-s Valsalva's maneuvers at expiratory pressure of 30 mmHg and during a three-minute isometric handgrip exercise at 40% maximal force. Forearm ischemia was induced in the final two minutes, with two additional minutes of ischemia after handgrip release (four minutes total of ischemia). Presence of phase 2 stabilization during Valsalva was interpreted as increased sympathetic

outflow to the lower extremities. Sustained systolic blood pressure (SBP) following release of handgrip during ongoing ischemia was similarly interpreted. Individuals with SCI were dichotomized based upon presence or absence of phase 2 stabilization during Valsalva (SCI + or SCI-) and their ischemic handgrip responses were each compared to controls.
Results: Phase 2 of Valsalva's maneuver was present in three of eight individuals with SCI (SCI +) and all CON. Peak increase in SBP during hand grip were similar between SCI and CON (53 ± 21 mmHg in SCI + ; 46 ± 3 mmHg in SCI-; 57 ± 5 mmHg in CON). In the five SCI-individuals, magnitude of peak SBP increases during handgrip were interspersed between the upper and lower bounds of the responses of SCI + individuals, showing no obvious differentiation. In the final minute of post-handgrip ischemia, with central command absent, SBP fell 0 ± 8 mmHg in SCI + , 14 ± 7 mmHg in SCI-, and 16 ± 6 mmHg in CON. Notably, there were no differences in tachycardia responses across testing components.
Conclusions: Individuals with SCI who are unable to generate rapid sympathetic engagement may still generate sympathetic responses with prolonged sympathetic engagement, though these may be blunted.
Funding: K23HD102663, Foundation for Physical Medicine & Rehabilitation.

Poster #73

Effects of transcutaneous spinal cord stimulation on autonomic testing following spinal cord injury

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Introduction: Prior work has suggested that spinal cord stimulation stabilizes/increases systolic blood pressure in those with spinal cord injury (SCI) during orthostatic challenge. However, it is unclear if this reflects improved dynamic autonomic regulation or increase in basal sympathetic tone.
Methods: The electrocardiogram, beat-by-beat blood pressure, and whole limb blood flow were recorded both at rest and during three, 15-s Valsalva's maneuvers at expiratory pressure of 30 mmHg. Individuals fasted, abstained from exercise/caffeine, and had morning recordings both at baseline and with transcutaneous spinal cord stimulation, separated by at least seven days. Stimulation occurred at T10-T11 at 120 Hz and 80% of tested motor threshold, with anodes placed at bilateral iliac crests.
Results: Two individuals with SCI and two uninjured age/gender matched peers participated (CON). SCI cohort was composed of individuals aged 23 and 27, with T3 and T5 neurological levels of injury, both with American Spinal Injury Association Impairment Scale A injuries. Resting blood pressures and heart rates were similar for all four individuals. During 2 min of spinal cord stimulation while at rest, mean blood pressure changed by + 9/− 1 mmHg and + 6/ + 1 mmHg (SBP/DBP) in CON. In those with SCI, mean blood pressure changed by + 8/ + 7 mmHg and − 2/− 8 mmHg. Change in heart rate with stimulation was − 1 and + 3 bpm in CON and + 1 and − 11 bmp in SCI. Mean relative limb blood flow decreased by 8.3% and 1.6% for CON. In individuals with SCI relative limb blood flow decreased 19.6% in one individual and increased of 1.5% in another with stimulation. Both CON were able to maintain phase II of Valsalva on trials without/with stimulation, with no significant change. Without stimulation, both individuals with SCI had absent phase II of Valsalva stabilization and a precipitous fall in blood pressure. With stimulation, despite sustained Valsalva's maneuver at target expiratory pressure, no clear phase II fall occurred.
Conclusions: Transcutaneous spinal cord stimulation may induce variable tonic sympathetic activity below the level of injury.
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Poster #75

Central sodium sensing in the human brain: acute hypernatremia increases functional connectivity within the circumventricular organs

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Introduction: Rodent studies have identified specialized sodium chloride (NaCl)-sensing neurons in the circumventricular organs, which mediate NaCl-induced changes in sympathetic nerve activity, arginine vasopressin, thirst, and blood pressure. Few human studies have investigated the network of NaCl-sensing regions of the brain using functional magnetic resonance imaging (fMRI).
Objective: To determine how the functional connectivity of sodium sensing regions change during an acute hypernatremic stimulus.
Methods: Resting-state fMRI was performed on 13 healthy adults (29 ± 6 yrs, 6 males) at baseline and during a 30-min 3% NaCl intravenous infusion delivered at a rate of 0.15 ml/kg/min. Time control experiments were also performed in 5 adults (29 ± 9 yrs, 1 male): fMRI was performed at baseline and during a 30-min control period (no infusion). Electrolytes, plasma osmolality, hematocrit, hemoglobin, and perceived thirst (Likert scale, cm) were assessed pre- and post-infusion/control period. Seed-based voxel-wise functional connectivity analysis was performed in AFNI using spherical seeds placed in the subfornical organ (SFO) and the organum vasculosum lamina terminalis (OVLT). A 2 × 2 (group by time) mixed models ANOVA was performed to compare functional connectivity of the SFO and OVLT between the 3% NaCl infusion and time control groups at baseline and late phase (min 16–30). A 2 × 2 (group by time) mixed models ANOVA was also performed to compared blood biochemistry and thirst.
Results: Plasma osmolality, serum sodium and thirst all increased in the 3% NaCl infusion group ($p < 0.05$) but not the time control group ($p > 0.13$). There was a group by time interaction ($p = 0.02$) whereby functional connectivity between the SFO and OVLT increased from baseline to late phase in the 3% NaCl infusion group (Z score baseline = 0.01 ± 0.07 vs. 0.14 ± 0.09, $p < 0.001$) but not the time control group (0.05 ± 0.11 vs. 0.05 ± 0.04, $p = 0.99$). Head motion was minimal and did not change from baseline to late phase (mean motion = 0.09 ± 0.02 vs. 0.09 ± 0.02 mm, $p = 0.81$).
Conclusion: Acute hypernatremia increases local functional connectivity within the circumventricular organs of the brain.
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Poster #76

Autonomic response to a stressor in postmenopausal females with vasomotor symptoms

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Introduction: Vasomotor symptoms (VMS, hot flashes and night sweats) associated with menopause are linked to cardiovascular disease (CVD) risk, and 70% of females experience VMS. Hypertension is a major contributor to CVD and stressors, such as the cold pressor test (CPT), can be used to predict hypertension. Postmenopausal females, compared with age-matched males, demonstrate greater sympathetic reactivity to a CPT. However, it remains unknown if postmenopausal females with VMS demonstrate greater reactivity to a CPT than those without VMS. We hypothesize that blood pressure (BP) and sympathetic reactivity to CPT will be greater in females with VMS than females without VMS.
Methods: Forty-one postmenopausal females completed two study visits. Visit 1: Participants completed an informed consent and were screened for eligibility. Using the Menopause-Specific Quality of Life Questionnaire, participants were divided into VMS (n = 23) and No VMS (NVMS; n = 18) groups. Visit 2: Participants reported to the laboratory after fasting and abstaining from caffeine, exercise, and alcohol for a minimum of 12 h. Heart rate (HR, electrocardiography), BP (finger plethysmography) and muscle sympathetic nerve activity (MSNA, microneurography [VMS: n = 18; NVMS: n = 12]) were monitored during a 10-min rest and two-min CPT.
Results: Groups were similar in age (VMS: 63 ± 4; NVMS: 62 ± 4 yrs), age of menopause (VMS: 51 ± 4; NVMS: 50 ± 5 yrs), and body mass index (VMS: 24 ± 3; NVMS: 26 ± 5 kg/m^2) ($p > 0.05$). While there were no group differences in baseline mean arterial pressure (MAP) (VMS: 95 ± 8; NVMS: 95 ± 14 mmHg; p = 0.83) or MSNA burst incidence (VMS: 55 ± 17; NVMS: 51 ± 16 bursts/100 hb; p = 0.48), HR was similar at baseline (VMS 55 ± 7; NVMS 59 ± 8 bpm, p = 0.08 bpm), but was overall attenuated throughout the CPT in the VMS group compared with the NVMS group (group effect, p = 0.04). Further, MAP (group × time, p = 0.26) and MSNA burst incidence (group × time, p = 0.86) increased similarly during the CPT.
Conclusion: Contrary to our hypothesis, females who experience VMS did not demonstrate greater BP and sympathetic reactivity a CPT, but did demonstrate lower HR, suggesting alternative mechanisms may be involved in the greater CVD risk in women with VMS.
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Poster #77

Autonomic control of blood pressure in chronic fatigue syndrome

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Background: Autonomic dysfunction has been observed in patients with chronic fatigue syndrome (CFS), with potential implications for beat-to-beat blood pressure control. However, direct measurements of muscle sympathetic nerve activity (MSNA) in this population are lacking.
Aim: To examine baroreflex control of blood pressure and sympathetic neurovascular transduction in patients with CFS.
Methods: In 16 participants (8 CFS, 8 controls), blood pressure (BP), ECG and muscle sympathetic nerve activity (MSNA via microneurography) were recorded at rest. Sympathetic baroreflex sensitivity (sBRS) was calculated by plotting MSNA burst incidence against diastolic BP. Cardiovagal baroreflex sensitivity (cBRS) was calculated via the sequence method. Vascular transduction of MSNA was defined as the average peak in mean arterial pressure following bursts of MSNA.
Results: Sympathetic BRS was − 1.6 ± 1.5 bursts/100 hb/mmHg in patients with CFS, compared with − 3.1 ± 1.6 bursts/100 hb/mmHg in healthy controls, although this did not reach significance (P = 0.07). Cardiovagal BRS in response to rising pressures was 15.6 ± 8.7 ms/mmHg in patients with CFS, compared with 41.5 ± 36.5 ms/mmHg in healthy controls, but did not reach significance (P = 0.07). Cardiovagal BRS in response to falling pressures was not significantly different between groups (P = 0.28). There was no significant difference in vascular transduction of MSNA bursts between patients with CFS (1.6 ± 0.6 mmHg) and healthy controls (2.5 ± 1.8 mmHg, P = 0.21).
Conclusions: Additional participants are required to confirm the attenuation of the baroreflex control of blood pressure in patients with CFS. Preliminary data indicate comparable neurovascular transduction in patients with CFS and healthy controls.
Funding: The Mason Foundation.

Poster #78

Autonomic function in AChR antibody-positive generalized myasthenia gravis

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Objective: To characterize autonomic function in patients with AChR seropositive generalized myasthenia gravis (MG) and to characterize the autonomic effects, if any, of chronic pyridostigmine therapy.
Introduction: Patients with MG report symptoms of dysautonomia that are often neglected. Cardiac parasympathetic dysfunction may be present, especially in the setting of thymoma. Chronic pyridostigmine use may also affect autonomic function in these patients. A careful assessment of autonomic function in MG patients is needed. We performed a small pilot project to assess feasibility and performance of standard autonomic testing in this population.
Methods: Five patients with generalized AChR seropositive MG taking at least 180 mg daily pyridostigmine for at least 1 year were recruited. Study was IRB-approved, and patients provided informed consent. Participants underwent standard autonomic function testing after holding their pyridostigmine for 24 h. Testing was then repeated one hour after taking pyridostigmine 60 mg orally. Participants also completed the myasthenia gravis symptom scale (MG-ADL), autonomic symptom scale (COMPASS-31) and the general quality of life

scale (SF-36). The Composite Autonomic Severity Score (CASS) was calculated for each patient from autonomic data.
Results: Five participants (4 male, age 41–72) had median COMPASS-31 score of 19.5. One patient (who also had diabetic neuropathy) had a high score (total 50). Patients with higher autonomic symptom scores had higher MG-ADL scores, suggesting a correlation. Testing was limited in one patient because of facial weakness. Two (one with diabetes) had impaired cardiovagal function and QSART responses. Autonomic testing was normal in the other three. Results did not change significantly after pyridostigmine in any patient. Quantitative pupillometry showed slowed constriction velocities in 4 patients (one with diabetes). After pyridostigmine, pupil constriction velocity improved in 3 (with a marked improvement in one) and worsened in one.
Discussion: Autonomic function may be impaired in MG patients, but routine autonomic testing is generally normal (unless affected by other conditions). Quantitative pupillometry may be more sensitive in detecting mild cholinergic autonomic impairment in MG that may be related to chronic cholinesterase inhibition. This pilot study suggests that major autonomic deficits are not common in MG, but further studies which control for the effects of pyridostigmine are warranted.

Poster #79

Autonomic reflex resting confirms autonomic disturbances in a cohort of patients with idiopathic hypersomnia

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Introduction: Symptoms suggestive of autonomic nervous system (ANS) dysfunction have been previously described in patients with idiopathic hypersomnia (IH), however, objective ANS reflex testing data have not been reported. We aimed to better quantify symptoms of ANS dysfunction in a cohort of patients with IH through the use of standardized ANS reflex testing.
Methods: Patients diagnosed with IH based on ICSD-3 criteria using overnight video polysomnography and multiple sleep latency testing (MSLT) were consecutively enrolled in our study, regardless of ANS symptoms. All patients underwent ANS reflex testing, including measures of parasympathetic (heart rate variability with deep breathing and Valsalva ratio) and sympathetic adrenergic function (Valsalva blood pressure response and 10-min head-up tilt at an angle of 70 degrees) with continuous blood pressure and heart rate monitoring. Eleven patients also underwent measures of sympathetic cholinergic function (quantitative sudomotor axon reflex testing). All medications that affect ANS function were held prior to ANS testing, including wake-promoting medications and sodium oxybate.
Results: Seventeen patients with IH were enrolled. Seven were long sleepers (> 11 h). Mean sleep onset latency and number of sleep onset REM periods (SOREMs) on MSLT were 6.6 (± 3.1) mins and 0.2 (± 0.4), respectively. Mean duration of IH symptoms prior to the date of ANS testing was 4.9 (± 5.3) yrs. Eighty-two percent (14/17) of patients had abnormal ANS testing. Of these, 65% (11/17) had sympathetic adrenergic impairment, 64% (7/11) had sympathetic cholinergic impairment, and 6% (1/16) had parasympathetic impairment. Forty-seven percent (8/17) of patients were diagnosed with postural tachycardia syndrome (POTS), 45% (5/11) with small fiber neuropathy, 6% (1/17) with inappropriate sinus tachycardia and 6% (1/16) with neurally-mediated syncope. Seventy-six percent (13/17) of patients reported orthostatic intolerance regardless of autonomic diagnosis.
Conclusions: ANS dysfunction was common and severe in our cohort of IH patients, and affected all domains of ANS reflex testing, with more prominent impairment in sympathetic domains. POTS was the most common comorbid diagnosis, and most patients reported orthostatic intolerance. There was no association with IH disease duration, though our sample size was limited. Future studies will focus on ANS testing in larger cohorts of IH patients, specifically on shared pathophysiological mechanisms of hypersomnia and ANS dysfunction.

DIABETIC, AUTOIMMUNE & OTHER AUTONOMIC NEUROPATHIES

Poster #80

Mortality risk factors in patients with (symptomatic) diabetic cardiac autonomic neuropathy: insights from a structured clinical documentation toolkit

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Purpose: The purpose of this study was to identify mortality risk factors in patients with diabetic autonomic neuropathy.
Methods: 77 patients were followed for up to 281 weeks after a diagnosis of symptomatic diabetic autonomic neuropathy based on clinical evaluation and autonomic testing. Autonomic testing results and clinical data obtained close to the time of testing from a customized electronic-medical-record based, structured clinical documentation toolkit that longitudinally captures standardized somatic and autonomic polyneuropathy patient information were retrospectively analyzed to identify characteristics differing between surviving (N = 59) and non-surviving (N = 18) patients. Kaplan–Meier and Cox proportional hazards analyses were used to identify mortality risk factors.
Results: The time from autonomic testing to death in non-survivors was shorter than the time to the last follow-up in survivors (99.7 ± 62.4 vs. 160.6 ± 75.1 weeks, $p = 0.002$). Non-survivors had lower body mass index ($p = 0.0009$) and more distal-foot ulcerations ($p = 0.009$), conduction abnormalities (ventricular/supraventricular tachycardia and/or atrial fibrillation) ($p = 0.049$), and neurogenic orthostatic hypotension ($p = 0.002$). Clinically, survivors and non-survivors often were similarly affected, having $< 5^{th}$ percentile scores on autonomic tests, somatic diabetic neuropathy, abnormal glycosylated hemoglobin (HbA1c) and creatinine levels. In unadjusted analyses, DAN diagnosis age [hazard ratio (95% confidence interval): 1.052 (1.009–1.097), $p = 0.017$], history of stroke [3.278 (1.219–8.811), $p = 0.019$], and neurogenic orthostatic hypotension [4.494 (1.477–13.681), $p = 0.008$] significantly increased mortality risk. In adjusted analyses, DAN diagnosis age [1.049 (1.007–1.093), $p = 0.023$] and neurogenic orthostatic hypotension [4.308 (1.408–13.181), $p = 0.010$] remained significant.

Conclusion: These findings can inform guidelines for multifactorial risk control to reduce mortality in patients with diabetic autonomic neuropathy.
Funding: This work was supported by the Agency for Healthcare Research and Quality (R01HS024057).

Poster #81

Autoimmune autonomic ganglionopathy: three cases, three different scenarios

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Introduction: Autoimmune autonomic ganglionopathy (AAG) is a clinical entity with a broad spectrum; it has etiological correlations with antibodies directed against the ganglionic acetylcholine receptor (gAChR) in the autonomic ganglia. Patients demonstrated widespread and severe autonomic failure that includes sympathetic and parasympathetic. The seropositive AAG is associated with systemic autoimmune diseases such as Sjögren's syndrome and with tumors as a paraneoplastic syndrome, but these are infrequent. We aim to report three patients with clinical autonomic failure, positive antibodies against gAChR but different clinical scenarios.
Case 1: A 52-year-old female started with a 2-year history of severe constipation, significant weight loss, syncope, and orthostatic intolerance; autonomic testing demonstrated low score in heart rate deep breathing (HRDB) and Valsalva index (VI), tilt test showed neurogenic orthostatic hypotension (nOH) with a drop of 80 mmHg of SBP. By SUDOSCAN test hypohidrosis was found in hands and feet. Antibody testing showed gAChR levels of 312 pmol/L. Tumor screening confirmed chronic myeloid leukemia. Symptoms improved considerably after cancer treatment.
Case 2: A 63-year-old male was referred for orthostatic intolerance and recurrent syncope that began five years before evaluation. Autonomic testing showed low HRDB and VI, nOH with a 79 mmHg SBP drop in tilt testing, and hands and feet hypohidrosis by SUDOSCAN. GAChR antibody levels were 78.8 pmol/L. Cancer assessment and rheumatologic panel turned out negative. He now completed his first cycle of IVIG.
Case 3: A 39-year-old male was evaluated for an 11-month complaint of orthostatic intolerance, syncope, dry mouth, and chronic diarrhea. The tilt test demonstrated nOH with a 67 mmHg drop of SBP. Hypohidrosis was confirmed only in hands with the SUDOSCAN test. GAChR antibody levels were 15 pmol/L. Rheumatologic panels showed positivity for SSA and SSB antibodies, and salivary gland biopsy reported a focus score of 3. He is about to start IVIG and Rituximab.
Conclusion: These 3 AAG patients had similar clinical characteristics but different and rare associated triggers. The coexistence of cancer and Sjögren syndrome in AAG patients is reported in 15% and 23%, respectively, encouraging us to broaden the assessment of these patients, because the outcome could change.

Poster #82

Occurrence and impact of dysautonomia on quality of life in Sjögren's: results of a Sjögren's Foundation patient survey

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Background: Sjögren's is a serious and systemic autoimmune disease that affects the entire body, including the autonomic nervous system. This analysis aimed to better understand the occurrence of dysautonomia and its impact on quality of life (QoL) in Sjögren's.
Methods: A QoL survey covering all aspects of Sjogren's, including dysautonomia, was administered online to U.S.-based Sjogren's patients aged $\geq$ 18 years by The Harris Poll between Oct. 13, 2021 and Nov. 8, 2021. The survey was reviewed by the Western Clinical Group IRB and determined to be exempt under 45 CFR § 46.104(d)(2).
Results: A total of 3,622 eligible responses were received. Respondents were asked to report on frequency and impact of their symptoms, with a response of "daily or weekly" being defined as "frequent" and "major or moderate" defined as "severe." Symptoms related to dysautonomia included brain fog (n = 2,896; frequency = 72%; severity = 68%), trouble sleeping (n = 2,650; frequency = 88%; severity = 88%), trouble swallowing (n = 2,080; frequency = 61%; severity = 50%), headache (n = 2,028; frequency = 65%; severity = 58%), feeling faint or dizzy (n = 1,837; frequency = 62%; severity = 58%), shortness of breath (n = 1,393; frequency = 70%; severity = 67%); sweating irregularities (n = 1,343; frequency = 85%; severity = 62%), migraine (n = 1,075; frequency = 40%; severity = 70%) and POTS (n = 263; frequency = 78%; severity = 81%). When asked to choose the symptom with the greatest negative impact, dysautonomia-related symptoms accounted for 16% of the total response (range = 1–4%). When compared to those not experiencing symptoms of dysautonomia, respondents who perceive their dysautonomia symptoms as having a major impact on their life were up to 9.52 times more likely to state that they did not feel they were living a fulfilling life (all, $p < 0.0001$). New therapies to address dysautonomia symptoms were identified as a critical need by a majority of respondents (symptom range: 55–77%).
Conclusion: Dysautonomia is commonly experienced in Sjögren's patients and greatly impacts quality of life. Patient-reported symptoms of dysautonomia frequently include trouble sleeping and brain fog and there is a need for new therapies to manage and treat related issues. Because of its multifactorial nature, fatigue was not included in this analysis, though it remains one of the biggest issues impacting QoL in Sjögren's patients. Further study is needed to better understand dysautonomia in Sjögren's and inform approaches to optimal care.

Poster #83

Sympathetic activity in patients with type 2 diabetes mellitus treated with empagliflozin or hydrochlorothiazide

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Reductions in sympathetic nervous system activity may contribute to beneficial effects of sodium glucose transporter (SGLT2) inhibition on cardiovascular outcomes. We hypothesized that SGLT2 inhibition with empagliflozin (Empa) lowers sympathetic activity compared with hydrochlorothiazide (HCT). The active comparator HCT was chosen to discern SGLT2-specific actions from non-specific responses to increased natriuresis. In this double-blind, randomized study, patients with type 2 diabetes mellitus on metformin monotherapy received either 25 mg/day Empa (n = 20) or 25 mg/day HCT

(n = 21) for 6 weeks. Muscle sympathetic nerve activity (MSNA), blood pressure, cardiovascular, and metabolic biomarkers were assessed at baseline and at the end of treatment. Empa increased urinary glucose excretion (difference in change from baseline 47.4 mmol/l vs. HCT), reduced fasting plasma glucose, HbA1c, and body weight (all $p < 0.05$). Office systolic blood pressure decreased with both treatments. MSNA, baroreflex heart rate control, and plasma catecholamines did not change significantly with either treatment. MSNA increased with higher body weight loss with both treatments, presumably related to intravasal volume depletion because of increased natriuresis. The relationship was shifted to lower MSNA with Empa as compared to HCT. In conclusion, neither Empa nor HCT treatment led to clinically relevant changes in sympathetic activity. Given the important role of the sympathetic nervous system in the progression of cardiovascular disease, mechanisms attenuating sympathetic activity in the face of increased sodium excretion deserve further attention.
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Poster #84

Anti-nociceptive properties of cardiopulmonary baroreceptors in patients with chronic pain

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Reduced pain perception following a persistent noxious stimulus within a study session (short-term habituation) is mediated, in part, by descending inhibitory mechanisms, although not all have been identified. We examined the hypothesis that cardiopulmonary baroreceptor unloading via lower body negative pressure (LBNP), which reduces central venous pressure, would significantly increase short-term habituation in chronic back pain (CBP) patients. A short-term habituation protocol was utilized that involved 1-s pulses ($\times$ 10) at 105% heat pain threshold on the anterior forearm at 0.5 Hz. Short-term habituation was observed in young, healthy participants (n = 11), as indicated by a reduction in subjective pain ratings across the 10 repetitive heat pulses ($-$ 42% $\pm$ 29, $P < 0.01$, n = 11), and demonstrated good reliability between visits (ICC:0.83, 95%CI:0.49–0.95). Short-term habituation was also observed in CBP patients ($-$ 32% $\pm$ 30, $P < 0.01$, n = 12). Cardiopulmonary baroreceptor unloading via LBNP significantly reduced pain ratings across the 10 repetitive heat pulses in CBP patients compared with supine control and upright sitting conditions, as indicated by a more negative area under the curve index (LBNP: $-$ 16.3 $\pm$ 4.1; Control: $-$ 14.4 $\pm$ 2.6; Upright sitting: $-$ 15.1 $\pm$ 4.1, $P = 0.02$). However, LBNP-mediated reductions in pain ratings were selective to CBP patients with more severe symptoms, i.e., neuropathic pain (LBNP: $-$ 14.7 $\pm$ 2.1; Control: $-$ 12.8 $\pm$ 1.4; Upright sitting: $-$ 12.1 $\pm$ 1.2, $P = 0.04$), whereas no effect of LBNP was observed in young, healthy participants ($P = 0.83$). In support, LBNP elicited significantly elevated mechanical pressure pain threshold in CBP patients with neuropathic pain ($P = 0.04$). Together, these findings demonstrate that pain perception during repetitive noxious stimuli is attenuated by cardiopulmonary baroreceptor unloading in CBP patients with greater pain severity.
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Poster #85

Profile of vascular dysfunctions in type 2 diabetes mellitus (T2DM) patients

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Background and Aims: Type 2 diabetes mellitus (T2DM) is an emerging global pandemic which is associated with lots of co-morbidities and reported vascular dysfunctions. T2DM associated vascular dysfunction leads to vasculopathy in the form of altered peripheral vascular dynamics. Cold stress test (CST) is a reliable sympathetic reactivity test used for assessing vascular dysfunction. In this study we are trying to quantify vascular dysfunction in T2DM patients non-invasively by various parameters of photoplethysmography (PPG) of cold stress test.
Methods: Parameters are recorded by Finger-PPG before, during and after CST (1 min) in 2 groups, control (20 healthy volunteers) and case (20 diagnosed T2DM patients).
Results: Due to cold stress, PPG parameters like amplitude were significantly decreased in both control and T2DM groups ($P < 0.0198$ and $P < 0.006$, respectively). However, recovery trend of amplitude was significantly slow in T2DM compared to healthy subjects. Another PPG parameter, peak to peak interval (PPI), was significantly higher in control compared to T2DM patients.
Conclusion: This study showed that T2DM patients has significant deranged pulse volume parameters like amplitude and PTT and can be used to objectively quantify the vasculopathy in T2DM patients by using sympathetic reactivity to cold stress.

Poster #86

Sweat gland nerve fiber density and association to sudomotor function, symptoms/signs and risk factors in adolescents with type 1 diabetes in the T1(D)ANES study

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Aim: To quantify sweat gland nerve fiber density (SGNFD) in adolescents with type 1 diabetes (T1D). In addition, to investigate associations between SGNFD, quantitative sudomotor axon reflex test (QSART), and possible risk factors for abnormalities indicating sudomotor neuropathy.

Methods: This study was a part of the T1(D)ANES study including 60 adolescents with T1D and 23 control subjects. Clinical data, biochemical data, QSART, and skin biopsies from the distal leg were obtained. Skin tissue was immunostained and imaged by confocal microscopy. Quantification of the sweat gland volume and 3D reconstruction of the nerve fibers was performed using a recently described quantitative, unbiassed technique.
Results: In total, 452 sweat glands (SG) were analyzed with a mean of 5.5 SG per individual. The adolescents with T1D had significant reduction of maximum and mean values of total nerve fiber length (NFL) and SGNFD compared to controls (NFL $p = 0.002$, $p = 0.03$; SGNFD $p = 0.002$, $p = 0.02$). The sweat gland volume (SGv) was non-significantly reduced ($p = 0.243$). Higher NFL was associated to higher SGv and SGNFD, and a trend of higher NFL leading to higher sweat response was found. In cases with reduced SGNFD, a higher occurrence of abnormal sweat response was observed, when all three parameters; NFL, SGv and SGNFD were affected. Higher height, systolic blood pressure, total daily insulin dose, basal/total insulin dose, and lower low-density lipoprotein, and HbA1c (mean last 5 yrs) was associated to higher sweat response. Age, other microvascular complications, and cholesterol increased the relative risk for reduced SGNFD.
Conclusion: Adolescents with T1D had significant reduction in NFL and SGNFD compared to control subjects. Evaluating all three parameters; NFL, SGv, and SGNFD was important for understanding the association to sweat response obtained by QSART. 3D reconstruction of sudomotor innervation adds important information about the distribution of structural nerve damage and allows for distinguishing between structural and functional changes indicating sudomotor autonomic dysfunction.
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Poster #87

Isolating autonomic dyspnea: expanding the clinical spectrum of anti-MAG neuropathy

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Background: IgM paraproteins can bind myelin-associated glycoprotein (MAG) in peripheral nerves. Classically, anti-MAG antibody neuropathy presents with symmetrical distal sensory-predominant demyelinating polyneuropathy. Autonomic neuropathy can occasionally accompany somatic neuropathy. Here we describe a patient with anti-MAG autonomic neuropathy manifesting as exercise intolerance and dyspnea without somatic nerve involvement.
Case: A 61-year-old man was initially seen in July 2018 for episodic positional dizziness, dyspnea and headache. He was an avid cyclist now experiencing dyspnea with only brief, mild exertion, and exertional syncope. Initial pulmonology evaluation with chest xray and pulmonary function tests was unremarkable. Cardiology evaluation including stress test, electrocardiogram, and echocardiogram showed hyperdynamic function without other abnormalities. Electrodiagnostic studies for paresthesia of his left hand showed left median neuropathy at the wrist without generalized large-fiber polyneuropathy. For continued symptoms he underwent autonomic reflex testing in March 2021, including 10 min active stand, QSART, heart rate variability and beat-to-beat blood pressure recording with deep breathing and Valsalva, all of which was normal. In July 2021, for ongoing unexplained dyspnea, he underwent advanced cardiopulmonary exercise testing (CPET) with right heart catheterization. He had excellent exercise capacity (7.9 metabolic equivalents) but exercise was limited by lightheadedness and minor ST depression. Low right atrial filling pressure was noted while upright, but not supine, suggesting a cardiac limit due to dysautonomia. Skin punch biopsy for evaluation of small fiber neuropathy was normal. Serum protein electrophoresis with immunofixation electrophoresis was positive for IgM gammopathy, which was determined to be anti-MAG antibody, with glycolipid sulfoglucuronyl paraglobiside (MAG-GSPG) antibody titre 1:3200 (normal < 1:1600). He was tried on pyridostigmine without improvement. Salt tabs, fluids, and nortriptyline were also ineffective. He is now trialing propranolol, while pursuing insurance approval for immunomodulating therapy.
Discussion: Here we describe a patient with exertional dyspnea and exercise intolerance without abnormalities on routine testing who was found with limited autonomic dysfunction, characterized by poor right atrial filling pressure while upright during advanced CPET. Work-up subsequently identified an anti-MAG IgM gammopathy. To our knowledge this is the first such case of isolated autonomic neuropathy reported with MAG antibodie and expands the clinical spectrum of anti-MAG neuropathy.

Poster #88

Global anhidrosis associated with focal chronic inflammatory demyelinating polyradiculoneuropathy

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Introduction: Classic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disease of large, myelinated fibers and has been demonstrated to have little to no autonomic involvement. On the other hand, focal and multifocal forms of CIDP are increasingly recognized to be distinct in terms of electrodiagnostic findings, type of autoimmunity, and degree of autonomic/small fiber involvement.
Case description/Methods/Results: A 46-year-old woman with history of Grave's disease developed slowly progressive right foot drop, mild burning, and numbness. The patient also reported progressive heat intolerance over the same period prompting a move to colder climate. NCS/EMG showed electrophysiologic evidence of a right common peroneal mononeuropathy. Thermoregulatory sweat test (TST) showed 82.6% global anhidrosis and autonomic reflex screen showed cardiovagal impairment suggestive of a cholinergic autonomic ganglioneuropathy. Superficial peroneal nerve biopsy showed an unequivocal neuropathic process characterized by multifocal decrease in myelinated fiber density, mixed onion-bulbs formations, and moderate epineurial inflammation diagnostic of focal CIDP. Laboratory testing for paraneoplastic, inflammatory/immune mediated, and genetic neuropathies was unrevealing. The patient was treated with intravenous immunoglobulin (IVIG) leading to improvement of her foot drop and heat intolerance evaluated on four months follow up. Repeat NCS/EMG showed improved summated compound muscle

action potential (CMAP) and repeat TST showed improvement of anhidrosis to 66.5%. The patient later had COVID-19 infection and her IVIG treatment was interrupted for two months leading to worsening of all findings to pre-treatment levels.
Conclusions: Focal CIDP may have distinctive feature compared to classic CIDP including potentially significant associated autonomic impairment. We report a case of focal CIDP associated with autonomic ganglioneuropathy manifested with global anhidrosis. Adequate autonomic history taking, appropriate testing, and treatment provides great service for these patients. Additional research characterizing the autonomic involvement in focal CIDP and investigating the potential pathophysiology, including type of autoimmunity, of such involvement is warranted.

Poster #89

A novel bioluminescent assay to detect functional immunomodulating autoantibodies against native ganglionic acetylcholine receptor in autoimmune autonomic ganglionopathy

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Autoimmune autonomic ganglionopathy (AAG) is a rare disorder resulting in immune mediated autonomic failure. Autoantibodies against the ganglionic acetylcholine receptor (gnAChR) are associated with AAG and exert their effects via immunomodulation, with receptor crosslinking and internalisation. Immunoassays for gnAChR antibody detection are, however, not widely available and have significant limitations. We developed a novel bioluminescent assay for the detection of immunomodulating gnAChR antibodies following the presentation of a 57-year-old male with acute pandysautonomia characterized by severe orthostatic hypotension, constipation, urinary retention, erectile dysfunction and complex pupillary dysfunction. Autonomic studies demonstrated severe adrenergic, cardiovagal and sudomotor impairment. gnAChR antibodies were initially detected using a previously published flow cytometric assay, consistent with a diagnosis of AAG. To establish our novel assay, the patient's serum was incubated overnight with IMR-32 cells, a neuroblastoma cell line which expresses fully formed, conformational gnAChR on its surface. Cells were then fixed in 1% paraformaldehyde, with remaining surface gnAChR detected via a NanoLuc luciferase generated bioluminescent signal. Our patient's serum demonstrated a significant reduction in light signal compared to non-AAG controls, consistent with the effect of immunomodulating gnAChR antibodies. These results agreed with those obtained from a validated functional flow cytometric assay for the detection of gnAChR antibodies via immunomodulation. We therefore describe a novel bioluminescent luciferase-based assay to detect autoantibody mediated gnAChR immunomodulation. The use of a bioluminescent detection system allows rapid non-radioactive signal acquisition, with ultra-high throughput workflow and may overcome the limitations of existing flow cytometric and radioimmunoprecipitation assays. Further assessment and validation of the assay will be performed with a number of established AAG and non-AAG controls.

GENETIC AUTONOMIC DISORDERS

Poster #90

Effect of RNAi therapeutics patisiran and vutrisiran on orthostatic hypotension due to dysautonomia in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy

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Background: Hereditary transthyretin-mediated (hATTR) amyloidosis is a rapidly progressive, multisystem disease, in which orthostatic hypotension (OH) due to autonomic neuropathy is a common yet hard-to-treat manifestation. Here, we present the quantitative effect of the RNAi therapeutics patisiran and vutrisiran on OH in patients with hATTR amyloidosis with polyneuropathy, from a sub-analysis of the APOLLO (NCT01960348), Global Open-Label Extension (OLE) (NCT02510261), and HELIOS-A (NCT03759379) studies.
Methods: In APOLLO, patients were randomised 2:1 to patisiran 0.3 mg/kg or placebo, IV q3w. Patients who completed APOLLO (APOLLO-placebo, APOLLO-patisiran) could enroll into the ongoing Global OLE (patisiran 0.3 mg/kg IV q3w). In HELIOS-A, patients were randomised 3:1 to vutrisiran (25 mg SC q3m) or patisiran (0.3 mg/kg IV q3w; reference group). OH was evaluated using the postural blood pressure (PBP) component of the modified Neuropathy Impairment Score (mNIS + 7; primary endpoint of APOLLO [M18] and HELIOS-A [M9]). PBP was calculated as mean of 2 supine readings of systolic BP (SBP, mmHg) taken 15 min apart minus the lowest SBP upon standing at 1, 3, and 5 min. Smaller reductions in observed SBP between supine and upright readings indicated improved PBP.
Results: APOLLO enrolled 225 patients (placebo, n = 77; patisiran, n = 148), Global OLE 211 and HELIOS-A 164 (vutrisiran, n = 122; patisiran, n = 42). Baseline OH severity was similar between within-study treatment arms in APOLLO and HELIOS-A. In APOLLO, patisiran improved or stabilized PBP from baseline to M18 (mean change in SBP: baseline, − 17.6; M18, − 13.5), with this effect maintained at Global OLE M36 (− 13.4). In contrast, the placebo arm had an increased change in PBP to M18 (baseline, − 17.5; M18, − 20.4); their PBP improved after patisiran initiation (Global OLE M36, − 16.6). In HELIOS-A, PBP stabilized in the vutrisiran arm (baseline, − 11.2, M18, − 11.7). In the smaller patisiran arm, while the change in PBP increased, the value remained within normal range (baseline, − 11.6; M18, − 14.2). Patisiran and vutrisiran have acceptable safety profiles.
Conclusions: PBP analyses quantify the benefits of patisiran and vutrisiran on autonomic function in patients with hATTR amyloidosis with polyneuropathy. The increase in change in PBP to a symptomatic range without treatment indicates the importance of early intervention.
Funding: Alnylam Pharmaceuticals.

Poster #91

Autonomic failure is a frequent and early prognostic marker of disease progression in hereditary transthyretin amyloidosis: a single centre experience

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Objective: Hereditary transthyretin amyloidosis (ATTRh amyloidosis) is a rapidly progressive proteinopathy resulting in deposits of extracellular fibrillary misfolded β-sheets in the heart, gastrointestinal tract, and peripheral nerves. We aimed to describe the autonomic features and quantitative cardiovascular autonomic function testing (AFT) in a population of ATTRh amyloidosis, and to assess whether autonomic dysfunction at disease onset could serve as a prognostic marker of disease progression.
Methods: A cohort of 94 patients with a confirmed diagnosis of ATTRh amyloidosis underwent AFT (head-up tilt table testing, standing test, Valsalva manoeuvre, pressor stimuli, and deep breathing). The severity of autonomic impairment was stratified according to 3 stages: Autonomic Stage 0—no cardiovascular dysfunction; Autonomic stage 1—isolated parasympathetic or mild mixed sympathetic and parasympathetic autonomic dysfunction; Autonomic stage 2—widespread autonomic cardiovascular dysfunction. Clinical autonomic features (orthostatic intolerance, gastrointestinal, genitourinary dysfunction, and sweating abnormalities) were collected both at disease onset and at the time of autonomic assessment. The polyneuropathy disability (PND) staging was used to stratify the severity of peripheral neuropathy and its progression rate (time to reach PND stages 1–2 and further progression to stages 3–4).
Results: Autonomic failure was present in 51/67 (76.1%) patients on AFT. 27/67 (40.2%) had parasympathetic or mild mixed parasympathetic and sympathetic autonomic dysfunction, 24/67 (35.8%) showed a widespread autonomic cardiovascular dysfunction. A clear clinical onset could not be collected retrospectively in 8/94 patients. Autonomic symptoms at onset were present in 29/86 (33.7%) patients. Within a mean disease duration of 5.16 ± 5.19 (years ± SD, time of autonomic assessment), 82/94 (87.2%) patients reported involvement in all autonomic domains. Gastrointestinal dysfunction was the most common feature (63/94, 67.0%), followed by orthostatic intolerance (43/94, 45.7%) and genitourinary dysfunction (27/94, 28.7%). Progression rate to reach PND stages 3–4 was available for a subset of 34 patients, and it was significantly shorter for patients with autonomic symptoms at onset (median time 3 years; range 2–4 years), compared to patients without autonomic onset (median time 6 years; range 4–8 years).
Conclusion: Autonomic dysfunction is an early, underestimated and progressive feature in ATTRh amyloidosis, and it is associated with faster disease progression.

Poster #92

Severe autonomic failure in a patient compound heterozygous for a frame shift mutation and deletion of the ganglionic acetylcholine receptor alpha-3 subunit

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The alpha-3 subunit is a crucial component of the ganglionic acetylcholine receptor. Indeed, pharmacological ganglionic blockade or antagonistic antibodies against the alpha-3 subunit virtually abolish postganglionic sympathetic and parasympathetic traffic in human beings. Mutations of the CHRNA3 gene encoding the alpha-3 subunit appear to be a rare cause of autonomic failure. We encountered an 18-year-old woman who had exhibited a fixed heart rate in utero and a rocky clinical course with repeated hypoglycemic episodes following birth. She presented with warm skin, hypohidrosis, pupillary rigidity, accommodation disorder, severe orthostatic hypotension, gastrointestinal dysmotility with a megacolon, and suprapubic catheter for urinary drainage. Intraneural nerve recordings from skin and muscle fascicles showed normal afferent but missing sympathetic activity. Isometric handgrip did not increase blood pressure. Axon reflex sweating and respiratory sinus arrhythmia were minimal. Very low supine and upright plasma norepinephrine but normal levels of related precursors and metabolites as well as skin biopsy suggested the presence of biochemically intact postganglionic neurons yet defective ganglionic neurotransmission. We performed trio whole exome sequencing using the Agilent SureSelect Human All Exon v8 enrichment chemistry on an Illumina NovaSeq6000 platform. Variant calling and copy number variant detection was done using the QIAGEN CLC Genomics Workbench, variant annotation and filtering with in-house developed software. We detected the hemizygous frameshift variant c.907_908delCT (p.Lys303Asnfs*115) in trans with a heterozygous deletion of exons 5–6 in the CHRNA3 (NM_000743.5) gene in the index patient. The frameshift variant was inherited paternally, the deletion maternally. Both variants were classified as pathogenic. We describe the first case of a patient compound heterozygous for previously described frame shift mutation and a deletion of the gene encoding the alpha-3 subunit of the ganglionic acetylcholine receptor. Clinically, the condition is associated with life-long autonomic failure with severe cardiovascular, gastrointestinal, and urogenital involvement.

Poster #93

Autonomic dysfunction in V142I transthyretin inherited amyloidosis patients

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Introduction: Autonomic dysfunction is a prominent feature of transthyretin (TTR) inherited amyloidosis. The V142I mutation has been previously described as incompletely penetrant, a mainly cardiomyopathic phenotype. It is the most common mutation in the United States, with up to 3% of African Americans carrying the mutation. We have demonstrated a higher prevalence of polyneuropathy in our V142I cohort and hypothesize that autonomic dysfunction is also more common than previously thought.
Methods: Patients with V142I TTR mutations were evaluated at three sites and data collected for neurological examination, nerve conduction studies, autonomic symptoms and orthostatic blood pressures.
Results: 35 V142I patients were studied, 32 were African American, 12 were women, in 3 centers. 29 patients had carpal tunnel syndrome. 29 patients had abnormal nerve conduction studies consistent with polyneuropathy (PN). The remaining patients had abnormal skin biopsy. Eight patients had orthostatic hypotension or abnormal AFT. 13 patients had GI symptoms complaining of diarrhea, early satiety, constipation (alternating). Men had erectile dysfunction.
Conclusion: Autonomic dysfunction is more common in V142I patients than previously described in cardiac literature. Patients with polyneuropathy, carpal tunnel syndrome and autonomic dysfunction should be screened for TTR mutations.

Poster #94

Norepinephrine transporter defects cause sympathetic hyperactivity in stem cell and mouse models of familial dysautonomia

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Familial dysautonomia (FD) is a rare neurodevelopmental and neurodegenerative disorder that affects the sympathetic nervous system. Patients harbor a mutation in *ELP1*, yet how loss of Elp1 affects the function of symNs remains unresolved. Such an understanding is critical since the most debilitating hallmarks of the disease include cardiovascular instability, dysautonomic crises and renal failure, all of which result from dysregulated sympathetic activity. We have employed the human pluripotent stem cell (hPSC) technology as a modeling system to understand human, sympathetic neuron (symN)-specific disease mechanisms and provide a platform for drug testing and discovery. We found that FD symNs are intrinsically hyperactive in vitro, in co-cultures with cardiomyocyte target tissue and in FD animal models. We showed that *ELP1*-rescued isogenic lines remain hyperactive, which suggests a different/additional disease mechanism beyond the classic FD *ELP1* mutation. Accordingly, we report decreased intracellular norepinephrine (NE) levels, decreased NE reuptake via NET and excessive extracellular NE in FD symNs. Lastly, we performed a small drug screen showing that current and new candidate drugs were able to lower the spontaneous hyperactivity. Our findings may have implications for other peripheral nervous system disorders and our drug screening platform may allow future drug testing and discovery for such disorders.
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NEW TECHNOLOGIES

Poster #95

Quantification of visually-rated anhydrosis in thermoregulatory sweat testing by using a hygrometer

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Background: Uneven powder thickness spread over different body parts during a TST can affect its interpretation, leading to false conclusions of anhydrosis. The volume of sweat output (SO) needed to change powder color is unknown.
Objective: To quantify sweat output during TST and correlate it with the visual impression of raters.
Methods: Two autonomic specialists independently reviewed pictures of patients who underwent a TST. Raters had to decide whether the patient had normal or reduced sweating or anhydrosis over the foot, calf, dorsum of the hand and forearm, around a hygrometer capsule placed over these areas. 3 groups were obtained. Group 1: raters agreed on anhydrosis. Group 2: raters disagreed on anhydrosis. Group 3: raters agreed on normal or reduced sweating. SO was measured in microliters/cm^2, using a 0.79 cm^2 hygrometer capsule. The Kruskal–Wallis test was used to compare means.
Results: 308 pictures representing 77 patients were reviewed. SO in each group (microliters/cm^2): G1: Interquartile range (IR): foot 0.25–0.78; calf 0.36–1.28; hand 0.25–2.74; forearm 0.15–0.49. G2: IR: foot: 0.89–2.35; calf: 0.68–2.21; hand: 0.39–3.98; forearm: 0.52–1.91. G3: IR: foot: 0.99–4.99; calf: 2.73–6.70; hand: 3.14–10.10; forearm: 3.2–7.88. SO was significantly different between group 3 and the other two groups at the calf, hand and forearm, and between group 1 and the other two groups at the foot (all $p < 0.004$). Only 10% of cases in the anhydrosis group (G1) had no measured SO while 90% had a measured SO that did not result in color change.
Conclusions: Based on the 25th percentile of sweat output in G3, we estimate the minimum amount of SO required for color change to be 2.7–3.3 µl for calf, hand and forearm and 1 µl for foot. This difference may be due to the powder falling off the feet in the supine position, leading to a thinner layer that could turn purple with a smaller amount of sweat. 90% of visually-rated "anhydrosis" cases showed a detectable SO by the hygrometer. Adding an objective measurement of SO to the current binary (present or absent) interpretation system of TST may help improve the accuracy of the test.

Poster #96

Teaching autonomic medicine virtually: initial experience from the AAS Lecture Program

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Objective: To describe the initial results of a virtual lecture program in autonomic medicine.
Background: Disorders of the autonomic nervous system are relatively common, yet exposure to autonomic medicine is limited in graduate and undergraduate medical education. Many academic medical centers do not have physicians qualified in autonomic medicine who are able to provide high quality instruction.
Methods: The Education Committee of the American Autonomic Society (AAS) established a lecture program targeting residency and fellowship training programs. A speaker panel of selected, active AAS members was created. The Committee advertised the opportunity for the lectures on listservs targeting neurology and neurophysiology training program leadership. This report reviews the initial progress of this lecture program.
Results: Twenty-four programs responded to the initial round of advertisement in February 2022. Respondents were primarily based in the United States, with one program from eastern Africa and one from the Middle East. Twenty-one lectures have been delivered by twelve lecturers as of June 15, 2022. Two other lectures are scheduled. The majority of lectures have focused on introductory clinical topics, but other lectures have addressed more advanced and detailed topics. Respondents to a post-lecture survey indicated uniformly outstanding satisfaction with the lecture quality and process (mean 5.0/5.0). This lecture program is now being advertised to family practice, pediatrics, internal medicine, and cardiology training programs. Future lectures will focus on increased audience participation through use of audience response systems and participant presentation of cases for discussion.
Conclusions: There is tremendous interest in autonomic lectures among neurology training programs. This may arise from the mismatch between the availability of trained autonomic physicians who are able to provide high quality education and abundance of autonomic problems faced in clinical practice. Centralizing autonomic education within the AAS allows for greater access for medical training programs. Additional educational outreach is indicated to improve physician competency in autonomic medicine and meet the needs of patients with autonomic disorders.

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Poster #97

Effect of a passive cycling wheelchair attachment on cardiovascular function in able-bodied controls

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Background/Aims: Individuals with spinal cord injury (SCI) may have autonomic impairment that adversely affects cardiovascular control, resulting in resting and orthostatic hypotension with decreased stroke volume (SV) and cardiac output (CO). Previous work indicates that passive cycling (PC) may augment cardiovascular control, and is positively correlated with cycling cadences; however, accessibility is a barrier. We aimed to establish the safety, efficacy, and acceptability of an accessible prototype PC wheelchair attachment on blood pressure (BP), heart rate (HR), SV, CO, cerebral blood flow (CBF), and user ratings of comfort and satisfaction.
Methods: In this analysis-blinded study, able-bodied controls (n = 16, 9 females, aged 27 ± 6 years) participated in lower extremity PC, seated in a wheelchair while an attachment pedaled their legs in 10-min intervals at 3 randomized speeds (0.3, 0.6, and 0.9 $m{\cdot}sec^{-1}$). Intervals were separated by a 5-min rest period. Cardiovascular parameters were continuously measured using beat-to-beat finger plethysmography. CBF was derived via Doppler ultrasound. After the protocol, two questionnaires were completed (Comfort Rating and QUEST).
Results: Systolic BP was increased during PC at 0.6 $m.sec^{-1}$ (+ 8 ± 10 mmHg, p = 0.038) and 0.9 $m.sec^{-1}$ (+ 10 ± 14 mmHg, p = 0.003). CO was increased at these same speeds (+ 0.5 ± 0.5 $L{\cdot}min^{-1}$, p = 0.036; + 0.6 ± 0.4 $L{\cdot}min^{-1}$ p = 0.004, respectively), driven by an increase in SV (p = 0.013, main effect for treatment). User comfort and satisfaction ratings were high, particularly for safety and tolerance.
Conclusion: This study provides evidence that upright PC using this prototype attachment improves cardiac indices in healthy controls, with high degrees of safety and tolerance. Individuals with SCI may experience greater cardiovascular benefits from PC through activation of the skeletal muscle pump, mitigating the increased blood pooling seen in this population and further augmenting SV and CO. Based on

these results, recruitment and testing is underway for individuals with SCI.

Poster #99

Evaluation of stroke volume estimation during orthostatic stress: the utility of Modelflow™

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Background: One common method to non-invasively estimate stroke volume (SV) is through the use of Modelflow™ (FinometerPro, Finapres Medical Systems). However, the accuracy of Modelflow™ estimates during profound reductions in SV is unclear, particularly in the absence of calibration to a gold standard (a common approach during routine research and clinical application). We aimed to evaluate the accuracy of SV estimation by Modelflow™, in comparison to echocardiography, at rest and during orthostatic challenge.
Methods: Orthostatic stress was induced in 13 individuals (age 24 ± 2 years; 7 female) using combined head up tilt and lower body negative pressure, continued until pre-syncope. We assessed SV derived by both Modelflow™ and echocardiography (CX50 ultrasound machine, Phillips; left ventricular outflow tract velocity–time integral multiplied by cross-sectional area) on multiple occasions while supine, during orthostatic stress, and at pre-syncope. SV index (SVI) was determined by normalising SV for body surface area (Du Bois method). Bias and limits of agreement were determined using Bland–Altman analyses. Two one-sided tests (TOST) were used to validate equivalency within 10% equivalency bounds of echocardiography values.
Results: Across all timepoints, Modelflow™ estimates of SV (67.4 ± 1.6 mL) were strongly correlated with echocardiography estimates (63.4 ± 1.2 mL) ($r = 0.6$, $p < 0.001$) with a bias of 6.1 ± 21.8 mL. TOST evaluation revealed that Modelflow™ responses were equivalent to echocardiography, with minimal bias ($p = 0.02$). Bias was larger in the supine phase (13.3 ± 22.7 mL) and improved during orthostatic stress (5.4 ± 21.7 mL). Accounting for body size with SVI further improved bias (2.2 ± 11.8 mL). Likewise, when assessing percentage change from baseline, Modelflow™ estimates of SV (− 30.2 ± 1.5%) were strongly correlated with echocardiography estimates (− 22.7 ± 1.3%) ($r = 0.8$, $p < 0.001$), with minimal bias (− 6.1 ± 14.7%), suggesting that normalization of SV responses relative to supine further increased the accuracy of Modelflow™.
Conclusion: These investigations demonstrate that Modelflow™ accurately tracks changes in SV during profound orthostatic stress, and that accuracy can be further enhanced with correction relative to supine values or body size. These data support the use of Modelflow™ estimates of SV for autonomic function testing.
Funding: Natural Sciences and Engineering Research Council (NSERC) of Canada.

Poster #100

Validation study of metachromatic clothes in thermoregulatory sweat test

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Introduction: The thermoregulatory sweat test can evaluate the presence or absence of abnormalities in the central or peripheral sweat pathway through sweat secretion. It evaluates sweating by applying an indicator powder to the area of interest that changes color to purple when sweat is found. Some ingredients of the index powder used may irritate the skin or mucous membranes, and those may not be easily removed because they are adapted for the skin. To compensate for these shortcomings of the indicator powder, metachromatic clothes that change color when sweating were used. In this study, we tried to check whether the evaluation of the degree of perspiration through discolored clothing was different from that when using indicator powder, and to check what form it appeared in healthy controls.
Methods: Thirty healthy male (n = 15) and female (n = 15) participants were enrolled. Each test was performed twice. First the indicator powder test was performed, and then the sweat test was performed while wearing metachromatic clothes at a similar time period. The test results using the indicator powder were photographed and compared with the test using metachromatic clothes.
Results: There was no difference in the amount of perspiration seen when using the indicator powder or metachromatic clothes. Advantages of metachromatic clothes are: (1) the degree of sweating occurring on both the front and back sides can be checked at the same time, and (2) unlike with the indicator powder, where sweat flows down from the original sweat source, sweating can be checked only in the source area, so it can be confirmed more accurately. There were no skin problems in all subjects who wore metachromatic clothes. Regarding the disadvantages of discolored clothing, it was difficult to detect sweat on the distal extremities, i.e., the hands and feet, and sweat could not be accurately confirmed when the clothing was floating, such as under a woman's breast.
Conclusions: If some additions are made, we think that metachromatic clothes are suitable to replace the indicator powder, eliminating the discomfort of patients with having skin discoloration or the requirement to take off all their clothes for examination.

Poster #103

The SPARC Portal promotes collaborative, sustainable, and FAIR neuroscience in bioelectronic medicine

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Stimulating the autonomic nervous system (ANS) to modulate organ physiological function holds enormous therapeutic promise, but the underlying mechanisms are poorly understood. The NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) program aims to improve targeted therapies by providing public access on the SPARC Portal (https://sparc.science) to high value datasets, maps, tools, and predictive simulations to support the development of new, safe, and effective neuromodulation devices. To date, over 100 SPARC teams world-wide have contributed nearly 200 data and computational studies on ANS mapping, manipulation/observation tools, and thera peutic translation, which can be found through knowledge-base and map-driven search, viewed, downloaded, or executed. To assure an integrative approach and facilitate collaborative open science, SPARC has established the Data and Resource Center (DRC) to develop key technologies for the SPARC Portal so that datasets are scientifically interpretable, FAIR (Findable, Accessible, Interoperable and Reusable), and compliant with the 2023 NIH Data Management and Sharing Policy. Within the SPARC DRC, multifunctional teams work with investigators to disseminate high-quality, structured and well-documented data and integrate the knowledge uncovered onto the SPARC Portal. The data core provides access to Pennsieve, a cloud-based data management platform to manage, curate, and pub lish large scientific datasets with citable DOIs. The knowledge management core aggregates and exposes information associated with datasets that facilitates advanced search functionality. They have also created a unique knowledge base representing connectivity in the ANS permitting query, search and reasoning over these connections. The mapping core integrates experimental data into sophisticated multi-scale 2D and 3D connectivity maps and data viewers so that the full experience of data products can be explored. The simulation core provides access to o^2S^2PARC, a cloud-based, open, extensible com putational platform so that the effects of ANS neuromodulation on organ function can be predicted. Surfaced relationships and connec tions bridge organs and experimental approaches and serve to bring the autonomic nervous system into the forefront. This integration of SPARC platform resources will accelerate progress in the field of bioelectronic medicine, the wider life-sciences and beyond as data contribution from the wider ANS community expands.

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Poster #104

Stimulating peripheral activity to relieve conditions (SPARC)

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The NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) program seeks to accelerate development of therapeutic devices that modulate electrical activity in peripheral nerves to improve organ function. SPARC is generating data, knowledge, maps, and tools to identify and influence therapeutic targets that exist within the neural circuitry of a wide range of organs and tissues. This therapeutic strategy, also known as bioelectronic medicine, could offer new treatment options for diverse diseases and conditions, especially those related to the autonomic nervous system such as hypertension, heart failure, gastrointestinal disorders, type II diabetes, inflammatory disorders, and more. In the first phase of SPARC, significant progress was made in these areas, and results are being disseminated widely through publications and the SPARC Portal (https://sparc.science/). The SPARC Portal aims to accelerate bio electronic medicine research and development by providing access to digital resources that can be shared, cited, visualized, computed, and used for virtual experimentation. Phase 2 of the SPARC program is currently ramping up and contains the following initiatives: the Reconstructing Vagal Anatomy (REVA) and VNS Endpoints from Standardized Parameters (VESPA) initiatives are examining the anatomy and functional connectivity of the human vagus nerve, respectively; the Human Open Research Neural Engineering Tech nologies (HORNET) initiative is building a new ecosystem of neuromodulation systems comprised of open-source hardware, soft ware, and firmware for exploratory and clinical neuromodulation studies; the Neuromod Prize challenges the innovator community to demonstrate peripheral nerve stimulation that can independently reg ulate two or more desired autonomic functions without unintended effects on non-target organs. Through these complementary initia tives, SPARC expects to facilitate the development of new best-in-class bioelectronic medicine therapies.

ORTHOSTATIC HYPOTENSION, SUPINE HYPERTENSION & SYNCOPE

Poster #105

Wearable multimodal cardiovascular monitoring and machine learning can detect episodes of cardiovascular dysautonomia in patients with Parkinson's and multiple system atrophy

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Background: Detecting occurrences of cardiovascular dysautonomia (CVDA), such as orthostatic hypotension (OH), in patients with Parkinson's disease (PD) or multiple system atrophy (MSA) is challenging considering poor symptom recognition in patients and suboptimal long-term monitoring methods. Wearable sensing of cardiovascular reactivity is a promising solution. We tested whether OH could be sensitively detected through the fusion of machine learning and a novel chest wearable capturing electrical (electrocardiogram, ECG), cardiomechanical (seismocardiogram, SCG), and hemodynamical (photoplethysmogram, PPG) activity of the heart.
Methods: Our wearable patch was placed on participants with PD (n = 6; mean ± SD: 65 ± 11 years; 1 female) and MSA (n = 2; 64 ± 3 years; 1 female) concurrent with a finger-cuff beat-to-beat blood pressure (BP) system (ccNexfin) during supine rest, controlled breathing (six breaths/minute), and active standing. OH was defined through BP comparisons of supine rest versus standing. Eight physiologic features were derived from each cardiac cycle, including heart rate (HR), heart rate variability (HRV), systolic timing intervals, and pulse transit time (PTT). Standing-based features were normalized separately by the feature-means of the controlled breathing task before entry into a Logistic Regression classifier with leave-one-subject-out cross-validation. Each cycle across all subjects during active standing (n = 5970) was classified as 'normal' or as occurring during a CVDA (OH) event.

Results: The model identified cardiac cycles occurring in episodes of OH with high accuracy (96%), sensitivity (96%), and specificity (97%). It also correctly differentiated participants with OH (n = 4) from those without. Feature weightings indicated that pre-ejection period (PEP), an indicator of sympathetic activity, and PTT, a correlate of BP, alongside frequency domain HRV were the most discriminate features. This complete feature set outperformed classification using only HR and HRV features, which exhibited reduced accuracy (60%), sensitivity (23%), and specificity (85%).
Conclusion: Our pilot findings support use of wearable technologies and machine learning models to improve detection of OH in PD and MSA patients. Features correlated with sympathetic function and BP enabled better differentiation of 'normal' from CVDA (OH) events. Further validation with larger numbers of participants, and under long-term monitoring conditions could lead to advancements in the detection of CVDA events and more optimized patient care.
Funding: Supported by the McCamish Parkinson's Disease Innovation Program at Georgia Tech and American Parkinson Disease Association (APDA) Center for Advanced Research in Parkinson's Disease at Emory University.

Poster #106

A phase 3, 22-week, multi-center, randomized withdrawal study of ampreloxetine in treating symptomatic neurogenic orthostatic hypotension

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Introduction: Ampreloxetine is a selective norepinephrine reuptake inhibitor being evaluated for durability of effect and safety and tolerability in patients with neurogenic orthostatic hypotension (OH) associated with Parkinson's disease (PD), multiple system atrophy (MSA) and pure autonomic failure (PAF).
Methods: The study included 16-week open-label period (OLP) followed by 6-week double-blind randomized withdrawal period (RWP). Randomization was 1:1 ampreloxetine (10 mg QD):placebo stratified by disease type. Primary endpoint was treatment failure at Week 6 of RWP: worsening in both OH Symptom Assessment (OHSA) item#1 and Patient Global Impression of Severity (PGI-S). Secondary endpoints included OHSA#1 and OHSA composite score. Primary endpoint was analyzed using logistic regression adjusting for treatment, disease type and baseline OHSA item#1 and PGI-S. Secondary endpoints were analyzed using mixed model for repeated measures. A prespecified subgroup analysis was by disease type.
Results: 203 subjects were enrolled in OLP and 128 participated in RWP (64:64 ampreloxetine:placebo). The study was terminated early because of negative results from a prior phase 3 study (NCT03750552). Subjects in RWP were mainly male (71.1%), white (96.9%), with mean age of 67.9 years, mean BMI of 25.65 kg/m^2; sample sizes for PD, MSA, PAF were 68, 40 and 20. The study failed to meet its primary endpoint but showed a trend favoring ampreloxetine: least squares (LS) failure rate ampreloxetine:placebo = 30%:42%; odds ratio = 0.6 (p = 0.2). The MSA group showed a stronger trend: LS failure rate ampreloxetine:placebo = 15%:38%, odds ratio = 0.28 (p = 0.105); reduction in LS mean change OHSA item#1: 1.5 points (p = 0.086); reduction in OHSA composite: 1.57 points (p = 0.0056). During RWP, TEAEs, laboratory values, ECG intervals and ambulatory blood pressure were similar between groups. In the ampreloxetine arm, 2 of 4 SAEs were related/unknown; 2 deaths (1 unrelated, 1 unknown and imputed as related). In the control arm, 1 of 2 SAEs was reported as related.
Conclusion: Overall, ampreloxetine was generally safe and well tolerated. It demonstrated durability of treatment effect up to 22 weeks in the MSA population.
Funding: Theravance Biopharma.

Poster #107

Long-term outcomes in patients with hyperadrenergic orthostatic hypotension

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Background: We previously reported a distinct sub-phenotype of orthostatic hypotension associated with an exaggerated increase in norepinephrine levels upon standing, known as hyperadrenergic orthostatic hypotension (hyperOH). Since patients with neurogenic orthostatic hypotension (nOH) usually have lower upright norepinephrine levels due to impaired sympathetic tone, we hypothesized that these hyperOH patients could represent an early-stage autonomic neuropathy with a distinct pathophysiology and prognosis. Hence, the purpose of this study was to determine the 10-year incidence of phenoconversion to neurodegenerative autonomic disorders and all-cause mortality for patients with hyperOH.
Methods: Prospective observational study, the cohort was comprised of 26 patients (69.7 $\pm$ 7 years, 52% male) who were evaluated at the Vanderbilt Autonomic Dysfunction Center and met the criteria for hyperOH (upright norepinephrine $>$ 600 pg/mL). These patients were followed for up to 10 years after their initial visit to our center, when autonomic function tests (AFTs) were performed. Patients were contacted by phone, and health records were reviewed to assess for changes in the diagnosis, related morbidity, and causes of death. The cumulative incidence of phenoconversion to autonomic neuropathies and the cumulative mortality were estimated using life tables which accounted for loss of follow-up.
Results: As expected, hyperOH patients showed an exaggerated increase in norepinephrine upon standing (948 $\pm$ 51 pg/mL) despite having impaired autonomic reflexes and neurogenic OH; systolic blood pressure decreased from 144 $\pm$ 4.3 mmHg supine to 106 $\pm$ 4.8 mmHg standing. The 10-year cumulative incidence of phenoconversion to multiple system atrophy (MSA) was 19% after adjusting for loss of follow-up. In addition, death was frequent in this cohort with a mortality incidence of 38%. Among the patients who were deceased, deaths were caused by MSA (n = 3) and malignancies (n = 4), including amyloid.
Conclusions: Hyperadrenergic orthostatic hypotension is not a benign condition; it has a mortality incidence of 38% within 10 years after diagnosis. Furthermore, 19% of hyperOH patients develop MSA.

Patients with hyperOH may require careful monitoring during follow up given that this condition is associated with negative outcomes.

Poster #108

Analgesics in the pre-hospital setting: effects of low-dose ketamine, fentanyl, and morphine on tolerance to simulated hemorrhage in conscious humans

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Introduction: Hemorrhage is a leading cause of battlefield and civilian trauma deaths. It is paramount that the administered analgesic does not disrupt autonomic mechanisms necessary to maintain blood pressure during a hemorrhagic insult. Current guidelines from the US Army's Committee on Tactical Combat Casualty Care (TCCC) for the selection of pain medications administered to a hemorrhaging soldier are based upon limited scientific evidence. These TCCC guidelines state that morphine and fentanyl should only be administered if the casualty is "not in hemorrhagic shock or respiratory distress and are not at significant risk for developing either condition," while ketamine is recommended if the casualty is experiencing these symptoms. However, the effect of analgesic doses of these drugs on hemorrhagic tolerance in humans is unknown.
Purpose: We tested the hypothesis that intravenous administration of fentanyl (75 μg; N = 28) and morphine (5 mg; N = 30), but not ketamine (20 mg; N = 30), would reduce tolerance to simulated hemorrhage in conscious humans.
Methods: Each analgesic was evaluated independently among different cohorts of healthy adults (aged 18–45 years) in a randomized, crossover, placebo-controlled fashion using doses derived from TCCC guidelines. One minute after an intravenous infusion of the analgesic or placebo (saline), simulated hemorrhagic tolerance was assessed via a pre-syncopal limited progressive lower-body negative pressure (LBNP) protocol. Hemorrhagic tolerance was quantified as a cumulative stress index (CSI), which is the sum of products of the LBNP stage and the duration at that stage (e.g., [40 mmHg × 3 min] + [50 mmHg × 3 min] …) until LBNP termination.
Results: Neither ketamine (CSI: drug 635 ± 391, placebo 652 ± 360 mmHg•min; mean ± SD, $p = 0.77$) nor fentanyl (CSI: drug 647 ± 386; placebo 676 ± 295 mmHg•min; mean ± SD, $p = 0.61$) administration reduced hemorrhagic tolerance. In contrast, morphine (CSI: drug 385 [251–728]; placebo 692 [473–997] mmHg•min; median [IQR], $p < 0.001$) administration reduced median hemorrhagic tolerance by ∼ 45%.
Conclusions: These experimental data demonstrate that median simulated hemorrhage tolerance is reduced by ∼ 45% with morphine. Thus, morphine should not be administered to a hemorrhaging individual in the prehospital setting, while fentanyl may be an appropriate analgesic for a casualty in hemorrhagic shock or expected to develop such a condition.
Funding: Department of Defense—US Army, W81XWH1820012 (CGC); NIH F32HL154559 (JCW).

Poster #109

The percentages of cardiac baroreflex sequences calculated over positive and negative arterial blood pressure variations are different in Parkinson's disease patients with orthostatic hypotension

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Background: The sequence (SEQ) method can be exploited to differentiate the patterns of cardiac baroreflex origin according to the sign of systolic arterial pressure (SAP) variations. Indeed, SEQ method allows the calculation of the percentages of sequences of cardiac baroreflex origin derived by contemporaneous increase of heart period (HP) and systolic arterial pressure (SAP) (%SEQ + +) or contemporaneous decrease of HP and SAP (%SEQ–). It is well known that %SEQ + + and %SEQ– are balanced in healthy subjects, independently from age, but no data are available in patients with autonomic dysfunction. Therefore, the aim of this study was to calculate and compare %SEQ + + and %SEQ– in Parkinson's disease (PD) patients with and without orthostatic hypotension (OH).
Methods: We studied a group of 20 PD patients while supine (REST) and during 70° head-up tilt test (TILT). Five patients (2 males, 72.8 ± 8.23 yrs) experienced OH during TILT, while the other 15 patients (11 males, age 66.53 ± 6.32 yrs) did not.
Results: We found that %SEQ + + and %SEQ– were balanced in patients without OH both at REST (1.58 ± 3.33 vs. 1.18 ± 2.56) and during TILT (0.89 ± 2.23 vs. 1.04 ± 2.46). On the contrary, in the group of patients with OH %SEQ + + and %SEQ– were unbalanced at REST (0.65 ± 0.84 vs. 2.34 ± 3.08) and during TILT (0.28 ± 0.44 vs. 2.29 ± 1.95), reaching the statistical significance only during TILT. In this group, %SEQ– was higher than %SEQ + + . Our results suggest that in presence of OH, the sequences of cardiac baroreflex origin in response to negative arterial blood pressure changes are higher than those in response to increases, probably suggesting a tentative of the cardiovascular system to cope the OH.
Conclusion: We conclude that the study of the baroreflex asymmetry, i.e., different response of the baroreflex to arterial blood pressure increase or decrease, could provide important insight in the study of postural disturbances in patients with autonomic disfunction.

Poster #110

The epidemiology and risk factors of reflex syncope in the UK Armed Forces

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Introduction: Reflex syncope in the military is anecdotally common but the extent in the UK Armed Forces (UKAF) is unknown. The aim of this study was to assess the incidence and prevalence of reflex syncope in the UKAF and to investigate individual susceptibility factors for syncope in soldiers.
Method: A retrospective search of UKAF electronic primary healthcare record, was performed over a 1 year period. Data were obtained on 76,103 service personnel (SP) (53% of the UKAF). A further retrospective cohort study was performed on 200 soldiers. A questionnaire was undertaken reviewing the soldier's medical history and circumstances of any fainting episodes. A consented detailed review of the participant's healthcare medical record was also performed. Participants were divided into two groups (SYNCOPE [n = 80) and CONTROL (n = 120) based on whether they had previously fainted.
Results: The syncope case rate for the UKAF was 10.5 per 1000 person-years (p-yrs). In comparing services there was a significantly increased risk of syncope in the British Army (10.7 per 1000 p-yrs) compared with the Royal Air Force (8.6 per 1000 p-yrs) ($p = 0.0365$), SP who served overseas (16.7 per 1000 p-yrs) in comparison with UK medical centres (10.3 per 1000 p-yrs) ($p < 0.0001$), and British Army units that regularly took part in State Ceremonial and Public Duties (15.8 per 1000 p-yrs vs. 10.2 per 1000 p-yrs) ($p = 0.0035$). Army training units conferred a significantly reduced risk of syncope ($p < 0.0001$). In the SYNCOPE group orthostasis (61%) and heat (35%) were the most common precipitating factors. A history of migraines/headaches was found to increase risk of reflex syncope ((OR 8.880 (1.214–218.8)) while a history of antihistamine prescription (OR 0.07144 (0.003671–0.4236), non-white ethnicity ((OR 0.03401 (0.0007419 to 0.3972)) and male sex ((OR 0.2640 (0.08891–0.6915)) were protective.
Discussion: These data are the first to describe the incidence and prevalence of syncope in the UKAF. Orthostatic-mediated reflex syncope is the most common cause in soldiers further exacerbated by heat exposure. These data could be used to target interventions for SP who have previously fainted or to prevent fainting during SCPD.
Funding: This study was supported by the Ministry of Defence.

Poster #111

Vagal dominance in patients with cardioinhibitory reflex syncope revealed by heart rate variability assessment in ultra-short time segments during head-up tilt testing

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Background: Reflex syncope can sometimes occur so quickly that short-term (5 min) analysis of heart rate variability is not possible to use. Therefore we applied ultra-short analysis of heart rate variability for syncope evaluation.
Purpose: Heart rate variability analysis during head-up tilt testing in time period closely surrounding syncope or the end of testing for the purpose of autonomic control evaluation.
Methods: Head-up tilt testing (45 min protocol at 60 degree in standard conditions) in 48 patients with history of syncope divided in group A (CONTROL) without syncope during testing (24 patients, 14 men, average age 33.7 years, tilting duration 2700 s = 45 min) and group B (BRADYCARDIAC) with cardioinhibitory reactions during testing, defined according to ESC guidelines (24 patients, 13 men, average age 40.5 years, tilting duration from 66 to 1976s with average 988 s, average duration of asystolia 11 s). Heart rate variability parameters: LF (low frequency) in n.u., HF (high frequency) in n.u., LF/HF ratio were evaluated in the last 1 min time segment with sinus rhythm in tilting position before the end of tilting or syncope and in the first minute in recovery supine position. Mann–Whitney U test, Chi-square test p-value and Shapiro-Wilkov test were used for statistical data processing with p-value significance level 0.05.
Results: Both study groups were not significantly different neither in sex (p 0.771) nor in age (p 0.208). The last minute of tilting: Groups A:B median values: LF 84.7:74.9 (p 0.018), HF 15.3:25.2 (p 0.018), LF/HF 6.25:3.4 (p 0.025). The first minute of recovery in supine position: Groups A:B median values: LF 76.9:64.9 (p 0.001), HF 23.1:35.1 (p 0.001), LF/HF 4.4:1.85 (p 0.0002).
Conclusion: Heart rate variability analysis in ultra-short time segments closely surrounding cardioinhibitory syncope revealed significantly higher median values of high frequency component related to vagal activity and significantly lower median values of low frequency component as well as LF/HF ratio reflecting vagal predominance in autonomic balance in comparison to patients without syncope during head-up tilt testing.

Poster #112

Pain associated with intravascular instrumentation reduces orthostatic tolerance and predisposes to vasovagal reactions in healthy young adults

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Background: Vasovagal syncope (VVS) is frequently triggered by pain, fear, or emotional distress, especially with blood-injection-injury stimuli in medical settings. Previous literature has also suggested that intravascular instrumentation reduces orthostatic tolerance (OT; time to presyncope) in individuals without a fear of blood or needles, however, the mechanisms underlying this phenomenon remain poorly understood. We aimed to examine the impact of intravenous (IV) instrumentation on OT in healthy young adults, and evaluate the impact of associated pain, as well as the presence of the needle in the blood vessel, as possible factors that predispose to syncope. We hypothesized that pain associated with IV procedures would reduce OT.
Methods: In this randomized, double-blind, placebo-controlled crossover study, participants (N = 19; 12 females; age: 24.4 ± 4.8 years) underwent a 60° head-up-tilt (HUT) test to presyncope with combined lower body negative pressure on three separate days, during which they were randomized to three different exposures: (1) IV cannulation with local anesthetic cream (EMLA; IV + EMLA); (2) IV cannulation with placebo anesthetic cream (E45 moisturizing cream; IV + placebo); (3) sham IV cannulation with local anesthetic cream (Sham + EMLA). Participants rated pain associated with IV procedures on a 1–5 scale. Cardiovascular (finger plethysmography and electrocardiogram; Finometer Pro) and forearm vascular resistance (FVR; brachial Doppler) responses were recorded continuously and non-invasively.

Results: Compared to Sham + EMLA (26.5 ± 2.8 min), OT was significantly reduced in IV + placebo (20.9 ± 3.2 min; p = 0.031), but not in IV + EMLA (25.2 ± 2.6 min; p = 0.798). Pain ratings associated with IV procedures were significantly increased in IV + placebo (3.0 ± 0.2) compared to both IV + EMLA (2.2 ± 0.3; p = 0.007) and Sham + EMLA (1.1 ± 0.1; p = 0.002). Maximal FVR responses mounted during HUT were reduced in IV + placebo (+ 131.6 ± 18.2%) compared to both IV + EMLA (+ 206.0 ± 29.5%; p = 0.006) and Sham + EMLA (+ 174.5 ± 12.7%; p = 0.049). Smaller maximal HR responses in IV + placebo, relative to Sham + EMLA, were associated with greater reductions in OT (r = 0.770; p < 0.0001).
Conclusion: Pain plays a key role in predisposing to VVS following venipuncture, and our data suggest that this effect is mediated through a reduced capacity to achieve maximal sympathetic activation. Topical anesthetics, such as EMLA, may be useful for reducing the frequency and severity of pre-syncopal symptoms and VVS during procedures requiring needles and intravascular instrumentation, such as during vaccinations and blood draws.
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Poster #114

Effects of six hours daily lower body negative pressure on orthostatic tolerance and cardiac performance during 30 days strict head-down tilt bedrest

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Introduction: Orthostatic intolerance commonly occurs in astronauts returning to earth. Head-down tilt bedrest (HDTBR), which models cardiovascular adaptation to weightlessness, decreases orthostatic tolerance by 34–60% without any countermeasure. We hypothesized that daily six hours lower-body-negative-pressure (LBNP, − 25 mmHg) ameliorates orthostatic tolerance, plasma volume, and cardiovascular deconditioning during HDTBR.
Methods: We submitted 23 healthy persons (12 women, 34.5 ± 9 years, 23.9 ± 2.8 kg/m^2) to 30 days of strict HDTBR (SANS-CM study). Subjects were assigned to 6 h upright seating (positive control, n = 11) or − 25 mmHg LBNP (n = 12) per day. We measured left ventricular outflow tract diameter (LVOT) and LVOT-stroke volume by pulsed wave doppler echocardiography during 15 min of 80° head-up tilt testing (HUT) with incremental LBNP until presyncope before and after HDTBR. We determined plasma volume with CO-rebreathing two days before and at HDTBR day 27.
Results: With HDTBR, orthostatic tolerance decreased 289 ± 89 s (− 23%) in the seated and 284 ± 95 s (− 22%) in the LBNP group (p < 0.001 vs. baseline, p = 0.968 between groups). Plasma volume decreased 569 ± 114 ml in the seated and 604 ± 104 ml in the LBNP group (p < 0.001 vs. baseline, p = 0.813 between groups). While supine stroke volume decreased 8 ± 1 ml in the seated and 9 ± 4 ml in the LBNP group (p < 0.001 vs. baseline, p = 0.874 between groups), supine cardiac output did not change in either group. Both groups showed similar reductions in upright stroke volume following HDTBR, however, stroke volume at presyncope did not change with HDTBR.
Conclusions: Six hours daily moderate intensity LBNP or seating did not fully attenuate orthostatic intolerance, plasma volume loss, or cardiovascular deconditioning during 30 days HDTBR. However, both interventions better maintained orthostatic tolerance compared with previous 30–60 days HDTBR studies without countermeasures.
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Poster #115

Vasovagal syncope triggered by recent moderate weight loss?

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Aim: In adults the onset of vasovagal syncope is often unexplained. We wished to explore if moderate weight loss triggers the onset of vasovagal syncope (VVS).
Methods: A retrospective case–control study comparing demographic characteristic, syncope symptoms, and tilt-table results of patients who had recently lost weight (n = 57), with randomly selected weight-stable patients (n = 73), and controls, patients without syncope (n = 24).
Results: VVS was diagnosed in 480 out of 1209 clinic patients of whom 57 (11.9%) reported moderate weight loss. The mean (SD) reported weight loss was 11.5 (7) kg over 18.7 (13) months. Age and gender did not differ between groups: in the weight loss, weight stable, and control groups the mean age was 44.8, 45.2, and 44 years respectively; and proportion female 60%, 64%, and 54%. Body weight, mass index and calculated blood volume at presentation were also similar in the different groups. Weight loss preceded or coincided the onset of syncope in 80% of patients; the length of time over which weight loss occurred was associated with the length of time of syncope symptoms, product moment correlation coefficient 0.45, p = 0.001. Syncope in childhood and teenage years was less frequent in the weight loss group compared to the weight stable group: 37% versus 53%. After 10 min of head-up tilt, stroke volume was preserved in both syncope groups compared to controls; percentage of baseline mean (SD) in the weight loss, weight stable, and control groups: 71 (18), 69 (10), and 61 (11), respectively; despite lower blood pressure in the weight loss groups with mean (SD) 90 (14) mmHg, 93 (13) and 103 (14), respectively.
Conclusions: Some patients have onset of VVS within a few months of weight loss resulting in earlier presentation to clinic. The physiological mechanism for this is uncertain.

Poster #116

Sleep syncope: a prospective cohort study

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Purpose: Sleep syncope is a form of vasovagal syncope characterised by severe nocturnal episodes. Long term follow-up has not been reported.
Methods: Between 1999 and 2013 we diagnosed vasovagal syncope in 1105 patients of whom 69 also had sleep syncope. We compared the sleep group to 118 patients with classical vasovagal syncope consecutively investigated between 1999 and 2003. We compared baseline demography, syncope history, tilt test results and follow-up findings.
Results: At baseline, age and gender distribution for classical vasovagal versus sleep syncope were similar: 47 ± 15 versus 46 ± 21 yrs ($p = 0.53$), and 55 versus 66% female ($p = 0.28$). Abdominal discomfort and vagotonia (during syncope) were far more frequent in the sleep group: 8 versus 80% and 2 versus 33% [$p < 0.001$], as was a history of childhood syncope and blood needle phobia: 15 versus 58% and 19 versus 69% ($p < 0.001$). Tilt results were similar: 93 versus 91% positive ($p = 0.56$). Blood pressure, heart rate and stroke volume changed similarly from baseline to syncope ($p = 0.32$, 0.34 and 0.18). Median electronic record follow-up times for classical vasovagal syncope and sleep syncope were 17 (3–21) and 15 [7–27] years, respectively. Rates of mortality and permanent pacemaker insertion and were similar: 16.2 versus 7.6% ($p = 0.09$) and 3 versus 3% ($p = 0.9$). Incidence of sleep episodes decreased from 1.9 ± 3 to 0.1 ± 0.3 episodes per year ($p < 0.001$).
Conclusion: Sleep syncope is a sub-type of vasovagal syncope with characteristic symptoms. Despite the severity of the sleep episodes, the prognosis is very good. Very few patients require permanent pacing and nearly all respond to education and reassurance.

Poster #117

Blood pressure and pharmacodynamic response of ampreloxetine, a norepinephrine reuptake inhibitor, in patients with symptomatic neurogenic orthostatic hypotension

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Background: Ampreloxetine is a selective norepinephrine reuptake inhibitor recently investigated in a Phase 3 program for the treatment of symptomatic neurogenic orthostatic hypertension (nOH) in patients with pure autonomic failure (PAF), Parkinson's disease (PD) and multiple system atrophy (MSA). The purpose of this study was to evaluate the pharmacodynamic and blood pressure (BP) response to ampreloxetine.
Methods: Patients with nOH were enrolled in sequential Phase 3 trials. Patients received ampreloxetine (10 mg) or placebo once-daily for 4 weeks in a randomized double-blind placebo-controlled study [SEQUOIA] before rolling over into a randomized withdrawal study comprised of a 16-week open-label phase and a 6-week randomized withdrawal period where patients were randomized to placebo or ampreloxetine (10 mg) [REDWOOD]. Plasma concentrations of norepinephrine (NE) and its main neuronal metabolite 3,4-dihydroxyphenylglycol (DHPG) were measured at baseline and after ampreloxetine administration. Standing and supine BP were also assessed.
Results: Ampreloxetine administration was associated with a 48% increase ($p < 0.05$) in plasma NE levels and a concomitant 22% decline ($p < 0.05$) in plasma DHPG during the initial 4-week study. No change in plasma NE or DHPG levels was observed after placebo administration. Continued administration of ampreloxetine for an additional 4 weeks was associated with a further 10% increase in NE plasma levels and 13% decline in DHPG. Similar changes in plasma NE and DHPG levels were observed in MSA, PD and PAF patients. Standing BP (3 min) was maintained in the ampreloxetine-treated patients at the conclusion of the 6-week randomized withdrawal treatment period; standing systolic BP was 8.6 mmHg [95% CI: 0.8, 16.3; $p < 0.05$] higher in the ampreloxetine-treated patients relative to placebo. The effect of ampreloxetine on standing systolic BP (3 min) was most pronounced in patients with MSA; standing systolic BP was 15.7 mmHg [95% CI: 3.2, 28.1; $p < 0.05$) higher in the ampreloxetine-treated patients with MSA relative to placebo. No clinically relevant changes were observed in supine BP between treatment groups.
Conclusions: Ampreloxetine induces persistent elevation of plasma NE and reductions in DHPG that are consistent with reduced neuronal reuptake and metabolism of NE. The resulting pressor effect of ampreloxetine is most pronounced in patients with MSA.

Poster #118

Faintly tired: a systematic review of fatigue in patients with orthostatic syncope

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Background: Orthostatic syncope (transient loss of conscious when standing—fainting) is common and negatively impacts quality of life. Many patients with syncope report experiencing fatigue, sometimes with "brain fog", which may further impact their quality of life, but the incidence and severity of fatigue in patients with syncope remains unclear. In this systematic review we report evidence on the association between fatigue and conditions of orthostatic syncope.
Methods: We performed a comprehensive literature search of four academic databases to identify articles that evaluated the association between orthostatic syncope (postural orthostatic tachycardia syndrome [POTS], vasovagal syncope [VVS], orthostatic hypotension [OH]) and fatigue. Studies were independently screened using a multi-stage approach by two researchers to maintain consistency and limit bias. A meta-analysis was then conducted to compare the data from the selected studies.
Results: Our initial search identified 2,797 articles, of which 13 articles met our inclusion criteria (POTS n = 10; VVS n = 1; OH n = 1; VVS and POTS n = 1). Fatigue scores were significantly higher in patients with orthostatic syncope than healthy controls, and were particularly severe in those with POTS. Fatigue associated with orthostatic syncope disorders spanned multiple domains, with each dimension contributing equally to increased fatigue. "Brain fog" was an important symptom of POTS, negatively affecting productivity and cognition. Finally, fatigue was negatively associated with mental health in patients with POTS.

Conclusion: In conditions of orthostatic syncope, fatigue is prevalent and debilitating, especially in patients with POTS. Consideration of fatigue in patients with orthostatic disorders is essential to improve diagnosis and management of symptoms, thus improving quality of life for affected individuals.

Poster #119

A retrospective analysis of young unexplained sudden cardiac arrest survivors

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In approximately 50% of cardiac arrests in the young, no etiology is identified despite a thorough investigation. During syncope, cardiovascular autonomic control switches from sympathetic to parasympathetic activity. This switch is not always seamless, and sometimes the body can utilize both pathways simultaneously (autonomic conflict). This phenomenon, which can potentially lead to cardiac arrest, has seldom been considered in the context of fainting. We aimed to investigate whether cardiac arrest survivors with known and unknown causes experienced syncope symptoms or known autonomic triggers prior to their event. We conducted a retrospective analysis of a national registry (CASPER) on cardiac arrest survivors < 25 years of age, who only had one cardiac arrest, who had no abnormality on testing, and who had no recurrent events. We compared the autonomic symptoms and situational triggers to those in young adults who had a known diagnosis for their cardiac arrest.
Our inclusion criteria yielded a sample size of 69 individuals, 22 (11 females) of whom had an explanation for their cardiac arrest (explained), and 47 (16 females) of whom did not (unexplained). The explained group was significantly more likely to report presyncope symptoms than the unexplained group ($p = 0.043$). Exercise was the most common circumstance leading up to the arrest in both groups. The unexplained group was more likely to be standing up during their arrest ($p = 0.0511$). Genetic test results show that the explained group had significantly more cardiac genetic mutations than the unexplained group ($p = 0.0405$). Of these mutations, there were significantly more pathogenic/likely pathogenic variants in the explained group ($p = 0.003$). There were no significant differences in responses to adrenaline challenge, stress test, ECG, or echocardiogram between groups.
These preliminary results can improve understanding of the mechanisms and physiologic triggers of cardiac arrest in young people. Evaluation of the relationships between syncope, autonomic conflict, the autonomic nervous system, and cardiac arrest have yet to be considered as contributors to the mechanisms of previously unexplained cardiac events in the young. Future investigations should consider the patient perspective on the causes and circumstances of their cardiac arrest.

Poster #120

Pupil size change reflects a change in cardiac sympathetic nervous activity in seated patients whose stellate ganglion is blocked by interscalene brachial plexus block

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Introduction: As a side effect of interscalene brachial plexus block (ISBPB), stellate ganglion block (SGB) causes reductions in pupil size (Horner's syndrome) and cardiac sympathetic nervous activity (CSNA). The reduced CSNA is associated with hemodynamic instability when patients are seated. Therefore, instantaneous measurements of CSNA are important in seated patients presenting with Horner's syndrome. However, there are no effective tools to measure CSNA intraoperatively. To evaluate the usefulness of pupillometry in measuring CSNA, we investigated the relationship between pupil size and CSNA.
Methods: In this prospective observational study, we enrolled 48 ASA physical status 1 patients undergoing right arthroscopic shoulder surgery under ultrasound-guided ISBPB. The C5-to-C7 nerve roots were blocked using 25 ml of 0.75% ropivacaine. Pupil diameters were measured at 30 Hz for 2 s using a portable pupillometer. To obtain CSNA, the linearly interpolated RR intervals from a 5-min-long electrocardiogram were resampled at 4 Hz. The resampled data were detrended and underwent fast Fourier transform. By integrating the area between 0.04 and 0.15 Hz, the low frequency power (LF) was calculated. The natural-log-transformed LF (lnLF) represented CSNA. The bilateral pupil diameters and CSNA were measured before ISBPB (pre-ISBPB) and 15 min after the sitting position following ISBPB (post-sitting). Changes in pupil diameter [(right pupil diameter for post-sitting—left pupil diameter for post-sitting)—(right pupil diameter for pre-ISBPB—left pupil diameter for pre-ISBPB)] and those in CSNA (lnLF for post-sitting—lnLF for pre-ISBPB) were calculated and the linear relationship between them was evaluated with a simple linear regression.
Results: Out of 48 patients, 6 patients were excluded due to arrhythmia, severe ptosis, intolerance to sitting position, no visualization of the C7 nerve root, protocol violation, and conversion to general anesthesia. Forty-one patients (97.6%) developed Horner's syndrome. Right pupil diameter and lnLF significantly decreased upon sitting after ISBPB. In the linear regression model ($R^2 = 0.242$, $P = 0.001$), one-unit-decrease (1 mm) in the extent of changes in pupil diameter reduced the extent of changes in lnLF by 0.659 ln (ms^2/Hz) [95% confidence interval (0.090, 1.228)].
Conclusions: Pupillometry is a useful tool to measure changes in CSNA after the transition to sitting following ISBPB.
Funding: This work was supported by the Research Institute of Medical Science, Daegu Catholic University (No. 201802).

Poster #121

Permanent cardiac pacing for treatment of vasovagal syncope: a systematic review and meta-analysis

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Introduction: Vasovagal syncope (VVS) is a common clinical condition with limited therapies despite its association with significant

morbidity. Clinical practice guidelines vary in their recommendations for cardiac pacing in recurrent VVS. The objective of the current study was to systematically review and synthesize the available literature that reported the efficacy of permanent pacemaker implantation as a treatment for VVS.
Methods: A systematic electronic search was performed in MEDLINE and Embase without language restriction from database inception through May 2022. The proportion of VVS patients experiencing syncope recurrence after pacemaker implantation was extracted from all studies. Additionally, the risk ratio (RR) of syncope was extracted from randomized controlled trials (RCTs). Weighted proportions and pooled RRs were estimated using random effects meta-analysis techniques. A continuity correction was applied to studies with either zero or all events.
Results: Thirteen single-arm observational studies (n = 628) and 13 clinical trials (n = 707) were included. Overall, cardiac pacing was found to reduce syncope recurrence, with only 11% (95% confidence interval [CI]: 7% to 18%) of patients experiencing events after device implant (I^2 = 75%). The DDD closed-loop stimulation (DDD-CLS) algorithm yielded the most significant and consistent reduction in syncope across nine studies (n = 371), with only 8% (5% to 14%; I^2 = 28%) of patients experiencing syncope on follow-up. However, the event rate with DDD-CLS was higher in double-blinded RCTs (13% [8% to 21%]; I^2 = 16%; n = 109). In studies utilizing a DDD rate-drop-response algorithm, there was only a 7% (2% to 27%; I^2 = 58%) recurrence of syncope in unblinded RCTs (n = 83), but 32% (22% to 43%; I^2 = 54%) in double-blinded RCTs (n = 102). Three studies directly comparing DDD-CLS to other dual-chamber pacing algorithms (n = 167) demonstrated that DDD-CLS was more effective in reducing the risk of syncope (RR = 0.09 [0.03 to 0.32], $p < 0.01$; I^2 = 0%), but none of these three studies were double-blinded.
Conclusions: There is substantial heterogeneity across studies assessing the use of cardiac pacing for prevention of VVS, owing to the heterogenous pacing modes and blinding methods across studies. The DDD-CLS algorithm is the most promising to prevent syncope recurrence, but additional studies are required to refine patient selection to determine who would benefit most from these therapies.

Poster #123

Hemodynamic effects of the osmopressor response: a systematic review and meta-analysis

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Aims: Autonomic disorders, including orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS), are commonly treated with various pharmacological and non-pharmacological approaches. Treatment by rapid consumption of 350–500 mL water has been proposed as a safe and practical therapy, but its efficacy has not been well established across disorders. This study aims to determine the effect of rapid 350–500 mL water consumption on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) by conducting a systematic review and meta-analysis of published studies.
Methods: Eligible randomized controlled trials (RCTs) and prospective cohort studies (PCTs) were identified in MEDLINE (1946-) and Embase (1974-) databases. Studies were appraised for risk of bias using the Cochrane Collaboration's risk of bias tool for RCTs or the Newcastle–Ottawa Scale for assessing the quality of non-randomized studies. Mean differences (MD) was used to quantify the maximal hemodynamic effects of rapid water consumption past 15 min with 95% CI calculated using random-effects models. Study heterogeneity was estimated using the I^2 statistic.
Results: A total of 11 PCTs and 5 RCTs with 232 participants met inclusion criteria. For OH patients, 8 studies reported blood pressure (BP) measures while 6 reported HR measures. In healthy participants, 5 papers reported BP while 4 reported HR. POTS patients were studied in 3 papers. In OH participants, the intervention was found to substantially increase both SBP [MD = 26.50 (19.51; 33.49)] and DBP [MD = 13.07 (8.31; 17.84)] and decrease HR [MD = − 3.43 (− 5.25; − 1.62)]. Findings were similar for patients with multiple system atrophy (2 studies) and pure autonomic failure (3 studies). In healthy participants, there were small increases seen in SBP [MD = 1.18 (0.46; 1.90)] and DBP [MD = 2.94 (2.26; 3.61)], but no significant findings for HR [MD = − 0.78 (− 4.38; 2.82)]. Bolus water ingestion had no significant hemodynamic effects on POTS patients.
Conclusions: Rapid 350–500 mL water-bolus consumption produces relatively quick, safe, and substantial increases in SBP and DBP, whilst also decreasing HR in OH patients. Similar, but blunted, changes were seen in healthy participants, but not in POTS patients.

Poster #124

The utility of the Valsalva maneuver for detecting candidates of prolonged head-up tilt table test (HUTT)

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Introduction and Methods: Delayed orthostatic hypotension (dOH) was originally defined as OH occurring after the first 3 min of standing, but routine testing now includes a 10 min upright tilt (HUTT). This study was designed to determine Valsalva maneuver (VM) parameters that can identify patients that require a more prolonged HUTT to diagnose dOH. A retrospective database from 2,498 patients who completed autonomic function tests (AFTs) in Korea University Annam Hospital between March 2016 to May 2022 was analyzed. Patients who were diagnosed with OH (n = 176), early dOH (n = 68, diagnosed between 3–10 min), or late dOH (n = 32, diagnosed after 10 min) were included in the analysis. A normal autonomic function test group (NAFT), defined by a composite autonomic scoring scale (CASS) of '0' and normal HUTT results, was used as a control group (n = 114). VM parameters included pressure recovery time (PRT), BP recovery (BP at phase 2 − BP at baseline), baroreflex sensitivity BRSa, BRSv, Valsalva ratio (VR), and heart rate difference between baseline and phase 3 (ΔHR phase 3).
Results: Thirty-two patients (24.6%) were diagnosed with late dOH. VM parameters were compared among edOH, ldOH, and NAFT groups. PRT was the highest in edOH and the lowest in NAFT, while systolic BP recovery, VR, and Δ HR phase 3 were the highest in NAFT and the lowest in edOH. When compared to age-gender matched NAFT subjects, the ldOH group had higher PRT and lower BRSa and ΔHR phase 3, while the other parameters were similar. A receiver operating characteristic (ROC) curve analysis revealed that PRT (cut-off: 2.38 s), SBP recovery (cut-off: − 10 mm Hg), BRSv (cut-off: 3.3 ms/mm Hg), Valsalva ratio, and Δ HR phase 3 (cut-off: 17 bpm) distinguished late dOH from NAFT group. However, only PRT (cut-off: 2.14 s) and Δ HR phase 3 (cut-off: 15 bpm) remained significant after age-gender matching with NAFT. The multivariable logistic regression revealed longer PRT and lower Δ HR phase 3 were

more likely to have late-onset dOH (PRT, RR = 2.189 [1.579–3.036], Δ HR phase 3, RR = 0.897 [0.847–0.951]).
Conclusion: These results show that the characteristic of late dOH differs from NAFT in terms of VM parameters. VM may be clinically helpful to screen the candidate patients who need prolonged HUTT for more than 10 min.

Poster #125

The effect of water temperature on orthostatic tolerance: a randomised crossover trial

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Purpose: Bolus water drinking, at room temperature, has been shown to improve orthostatic tolerance (OT), probably via sympathetic activation; however, it is not clear whether the temperature of the water bolus modifies the effect on orthostatic tolerance or cardiovascular responses to orthostatic stress. The aim of this study was to assess if differing water temperature would alter time to presyncope and/or cardiovascular parameters during incremental orthostatic stress.
Methods: Fourteen participants underwent 3 head up tilt tests (HUT) with graded lower body negative pressure (LBNP) continued until presyncope. Fifteen minutes prior to each tilt test participants drank a 500 ml bolus of water which was randomised, in single-blind cross-over fashion, to either room temperature water (20 °C) (ROOM), ice-cold water (0–3 °C) (COLD), or warm water (45 °C) (WARM). Cardiovascular parameters were monitored continuously. \
Results: There was no significant difference in orthostatic tolerance in the COLD (33 ± 3 min, p = 0.3321) and WARM (32 ± 3 min, p = 0.6764) conditions in comparison to ROOM (31 ± 3 min). During HUT the heart rate and cardiac output were significantly reduced ($p < 0.0073$) with significantly increased systolic blood pressure, stroke volume, cerebral blood flow velocity and total peripheral resistance ($p < 0.0054$) when comparing COLD to ROOM.
Conclusions: Bolus cold water drinking results in favourable orthostatic cardiovascular responses during HUT/LBNP without significantly altering OT. Using a cold water bolus may result in additional benefits in patients with orthostatic intolerance above that conferred by bolus water at room temperature (by ameliorating orthostatic tachycardia and enhancing vascular resistance responses). Further research in patients with orthostatic intolerance is warranted.
Funding: This study was supported by grants from the National Sciences and Engineering Research Council of Canada (NSERC) awarded to VEC (Discovery RGPIN/02982–2021 and Discovery Accelerator Supplement RGPAS/2021-00012-2021).

Poster #126

Rapid changes in vascular compliance contribute to cerebrovascular adjustments during vasovagal syncope (VVS)

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Background: The rapid reduction in arterial pressure (AP) during VVS is associated with a characteristic decline in diastolic cerebral blood velocity (CBV) and maintained systolic CBV as measured by transcranial Doppler. This increased CBV pulsatility was originally considered to be indicative of a "paradoxical" increase in cerebrovascular resistance (CVR). Conversely, it may represent a passive Windkessel mechanism (by virtue of increased cerebrovascular compliance; Ci) in the presence of rapid hypotension. We tested the hypothesis that Ci increases during pre-syncope in VVS patients.
Methods: Finger AP and right middle cerebral artery blood velocity were recorded from 14 otherwise healthy patients (n = 11 female, 34 ± 11 years, 25.4 ± 5.0 kg/m^2) at rest and during head-up tilt (HUT; 80°, 5 to 28 min). Three time-points were analyzed: (i) baseline (45 heartbeats), (ii) mid-tilt (25 heartbeats), and (iii) VVS (30 heartbeats). Individual AP and CBV waveforms of every fifth heartbeat were input into a modified Windkessel model to calculate Ci.
Results: Upright posture resulted in a decrease in CBV (− 9 ± 8 cm/s; one-way ANOVA: $P < 0.01$ vs. baseline), an increase in Ci (132 ± 72%; $P < 0.01$), but no change in AP ($P = 0.14$). Compared to mid-tilt, systolic (− 34 ± 13%) and diastolic (− 37 ± 10%) AP experienced similar reductions during VVS ($P = 0.23$ vs. systolic CBV). In contrast, there was a large reduction in diastolic CBV (− 18 ± 9 cm/s; $P < 0.01$) in the presence of sustained systolic CBV (0 ± 12 cm/s; $P > 0.99$). CVR decreased by 14 ± 20% during VVS ($P = 0.03$ vs mid-tilt). The increase in CBV pulsatility during VVS (81 ± 50%; $P < 0.01$) occurred simultaneous to an increase in Ci (657 ± 410%; all $P < 0.01$), with a peak response ranging from 192–1395%.
Conclusions: Our results suggest that an increase in CBV pulsatility is indicative of an increase in Ci, which may protect against reductions in cerebral perfusion during VVS. These results support the existence of a protective Windkessel mechanism that helps defend against rapid hypotension by preserving systolic CBV.
Funding: This work was supported by NSERC (Natural Sciences and Engineering Research Council of Canada) and Western University's Undergraduate Student Research Initiative.

Poster #128

Atomoxetine for suppression of vasovagal syncope

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Background: Vasovagal syncope (VVS) is a common clinical condition that lacks effective medical therapies despite being associated with significant morbidity. The norepinephrine transport inhibitors reboxetine, sibutramine, and atomoxetine (Strattera) all prevent the induction of vasovagal syncope on tilt table testing. We hypothesized that atomoxetine would be effective in suppressing syncope in patients with recurrent VVS.
Methods and Results: This was a retrospective, open-label, observational case series of 12 patients taking atomoxetine for compassionate-use suppression of recurrent VVS. We compared syncope frequency in the periods 1 year before atomoxetine and

while subjects were taking atomoxetine. We used novel applications of the Poisson distribution to describe the results as a collection of n = 1 studies. The Poisson distribution is ideal for assessing the significance of distributions with few events per subject. Calgary Conjoint Health Ethics Research Board REB20-1937. There were 12 subjects, 8 female, with age 47 years and a mean Calgary Syncope Score of 2. The atomoxetine dose was 66 ± 16 mg (1.06 ± 0.21 mg/kg). While taking atomoxetine all patients appeared to improve and 8/12 had no syncope in followup (p = 0.0013). The mean syncopes/year decreased from 9.5 ± 11.1 to 0.51 ± 0.92 (p = 0.019, T test). Syncope frequency decreased from a median 5.5 (IQR 4, 6.75) syncope per year to 0 (IQR 0, 0.88) syncope per year (p = 0.0015, Wilcoxon test). All 4 patients who fainted in follow-up improved from a previous year count of 5.75 ± 1.26 syncopes to 1.52 ± 1.03 syncopes per year on atomoxetine (p = 0.0006). According to the Poisson distribution 7/12 subjects were each significantly improved with p values of < 0.0001 to 0.023, and an eighth subject had borderline significant improvement (p = 0.082). Of the 5 subjects who did not improve significantly one fainted once and 4 did not faint but lacked a significantly long follow-up duration. In total 8/12 subjects were significantly or nearly significantly improved (p = 0.005, T test), and 4/12 subjects had insignificantly long follow-up times to test whether they responded significantly.
Conclusions: In this case series atomoxetine was effective in preventing vasovagal syncope. The novel use of the Poisson distribution permits per patient assessment of improvement and detects insufficient follow up despite apparent improvement.

Poster #129

Different responses of the cerebral macro- and microvasculature to transient hypotension

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Healthy responses to transient orthostatic stress are characterized by rapid and brief hypotension in the presence of sustained cerebral blood flow (as assessed by transcranial Doppler ultrasound; TCD). However, our knowledge of how the different cerebral vascular segments are coordinated, particularly during this rapid and transient hypotension, remains poorly understood. The aim of the current study was to establish the relation between hemodynamic characteristics in a large cerebral artery and a downstream microvascular segment under conditions of transiently reduced mean arterial pressure (MAP). We report data from nine young, healthy participants (n = 5 women; 26 ± 4 years) acquired continuously during a 15 s bout of lower body negative pressure (LBNP; − 80 mmHg). Simultaneous changes in cerebral blood flow were determined for microvascular flow (BFi) using diffuse correlation spectroscopy and for middle cerebral artery (MCA) blood velocity ($MCAv_{mean}$) using TCD. MAP (finger photoplethysmography) was used to calculate cerebrovascular conductance for each of the MCA (CVC_{MCA}) and BFi (CVC_{BFi}) blood flow metrics (Δflow/ΔMAP). Compared to baseline, rapid-onset LBNP decreased MAP by 22 ± 16% (P < 0.01) and BFi by 31 ± 16% (P < 0.01). However, $MCAv_{mean}$ was preserved (− 8 ± 16%; P = 0.09). Compared to baseline, MCA pulsatility (systolic–diastolic) and CVC_{MCA} increased during LBNP-induced hypotension (all P ≤ 0.03). In contrast, CVC_{BFi} remained stable throughout LBNP but increased during the BFi reactive hyperaemia upon cessation of LBNP (36 ± 26%, P = 0.0496). This study provides novel evidence that large cerebral arteries respond to transient hypotension with rapid increased compliance (indicated by pulsatility) and dilation (indicated by CVC_{MCA}) while the microcirculation exhibits minimal and slow changes in vascular contractile state.
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Poster #130

Long-term efficacy of atomoxetine for the treatment of symptomatic neurogenic orthostatic hypotension

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Introduction: Patients with neurogenic orthostatic hypotension (NOH) are at risk for syncope, falls and have poor quality of life. It is reported that atomoxetine acutely improved upright blood pressure and symptoms in NOH, mostly in multiple system atrophy (MSA) patients. However, the long-term efficacy of atomoxetine for the treatment of NOH is unknown.
Hypothesis: The aim of the study is to assess orthostatic intolerance symptoms in NOH during chronic treatment with atomoxetine.
Methods: This is a multicenter, double-blind, placebo-controlled, 2X2 crossover study (IRB160415). After initial atomoxetine dose-titration [10 or 18 mg TID], NOH patients were randomized into 1st arm (4-week treatment with atomoxetine followed by 4-week placebo), or 2nd arm (vice versa). The primary outcome was reduction of symptoms after 2 weeks of treatment using the orthostatic hypotension questionnaire (OHQ) composite score, calculated from the OH symptoms Assessment (OHSA) and the OH Daily Activity Scale (OHDAS). Secondary endpoints were orthostatic vital signs.
Results: 40 subjects (68 ± 8 yo, %60 males, BMI 26.2 ± 4.8 kg/m^2) were enrolled. We found no difference in OHQ scores between atomoxetine and placebo (4.8 ± 2.4 vs. 4.5 ± 2.1, P = 0.73). Subanalysis splitting MSA and non-MSA showed in the latter group significant reduction in OHSA (2.6 ± 1.8 vs. 3.6 ± 1.8, p = 0.03), specifically visual disturbances (1.9 ± 1.9 vs. 0.9 ± 1.7, p = 0.04) and weakness (4.6 ± 2.7 vs. 3.3 ± 2.6, p = 0.03). At 4-week, atomoxetine effect on upright SBP persisted (3.4 ± 20.61 vs. − 5.5 ± 14.82 mm Hg, p = 0.037).
Conclusions: There was no significant reduction in OHQ. Diagnosis based sub-analyses showed non-MSA had a significant improvement in OHSA. Upright SBP persisted after 4-week treatment suggesting no tachyphylaxis.
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Poster #131

Immediate effect of lumbosacral spinal cord epidural stimulation on cerebral hemodynamics during orthostatic stress in individuals with chronic spinal cord injury

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Introduction: Orthostatic hypotension (OH), defined as a substantial drop in arterial blood pressure (BP) when assuming an upright position, commonly occurs after spinal cord injury (SCI). OH can cause cerebral hypo-perfusion and is difficult to manage. Controlled tilt is able to provoke OH and is limited by clinical symptoms of reduced cerebral blood flow. We previously showed that lumbosacral spinal cord epidural stimulation (scES), optimized for cardiovascular function (CV-scES), specifically optimized to stablize BP, mitigates OH in individuals with chronic SCI. This study evaluated the immediate effects of CV-scES on cerebral blood flow velocity (CBFv).
Methods: Ten individuals with chronic cervical SCI and OH or chronic low BP had a 16-electrode array implanted over the lumbosacral spinal segments. Personalized stimulation parameters were identified to maintain systolic BP between 110–120 mmHg. Orthostatic tolerance was tested with a 70° head-up tilt maneuver lasting up to 30 min, with and without CV-scES. Beat-to-beat CBFv at the middle cerebral artery and BP at the finger were monitored simultaneously. Stability measure of BP and CBFv (magnitude and rate of deviation from normative systolic BP, or from supine systolic CBFv), and cerebrovascular pulsatility index [(systolic minus diastolic) devided by mean CBFv] were calculated. Dynamic buffering of BP oscillations by cerebro-autoregulation was evaluated by using phase synchronization index derived from wavelet decomposition analysis.
Results: Compared to tilt without stimulation, CV-scES increased tilt time (10 ± 3 vs. 30 ± 0 min), reduced the fall in systolic BP (-45 ± 9 vs. -4 ± 17 mmHg), mean BP (-28 ± 4 vs. -2 ± 4 mmHg) and mean CBFv (-16 ± 2 vs. -8 ± 1 cm/s) and improved autoregulation of CBFv across participants, manifesting in two distinct patterns: (Group 1) increased stability of systolic CBFv without change in pulsatility index, and (Group 2) reduced pulsatility index without change in systolic CBFv stability. Dynamic buffering of BP oscillations within the sympathetically mediated ultra-low-frequency range (0.025–0.03 Hz) during heat-up tilt was more impaired in Group 1 compared to Group 2, which was improved by acute CV-scES.
Conclusions: The maintenance of BP that rapidly follows CV-scES initiation during orthostatic stress is associated with improved cerebral hemodynamics and prolonged orthostatic tolerance in individuals with chronic cervical SCI.
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Poster #132

Anthropometric factors affecting cardiovascular responses to postural sway and other discrete counterpressure maneuvers

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Background: Counterpressure maneuvers (CPM) are movements used to delay or prevent syncope through exploiting the skeletal muscle pump. Although commonly prescribed, approximately one-third of patients have difficulties employing CPM due to practical barriers. We recently showed that exaggerated postural sway produces protective cardiovascular and cerebrovascular responses against syncope and may hold utility as an accessible CPM. Here, we evaluated responses to other discrete movements alongside exaggerated sway and assessed the role of anthropometry in movement efficacy.
Methods: We tested 26 healthy adults (12 female) aged 29 ± 1.4 years. Following supine rest, participants performed a baseline stand (BL) on a force platform, followed by three randomized trials of discrete movement (exaggerated anterior–posterior sway, AP; toe curling, TC; rhythmic gluteal clenching, GC). Non-invasive beat-to-beat blood pressure (Finometer Pro), heart rate (HR, electrocardiogram), and cerebral blood flow velocity (CBFv; transcranial Doppler) were measured continuously. Total peripheral resistance (TPR) was calculated as mean arterial pressure/cardiac output (CO) using Modelflow. Muscularity was assessed using bioelectrical impedance. Responses were expressed as changes from supine.
Results: Compared to BL, both AP sway and GC improved systolic arterial pressure (BL: $+1.8 \pm 2.1$ mmHg; AP: $+10.7 \pm 2.0$ mmHg, $p < 0.001$; GC: $+9.7 \pm 2.1$ mmHg, $p < 0.001$) and blunted orthostatic reductions in stroke volume (SV) (BL: $-25.0 \pm 1.8\%$; AP: $-15.4 \pm 2.3\%$, $p < 0.001$; GC: $-17.8 \pm 2.2\%$, $p < 0.001$), while TC had no effect. However, all three movements improved CO (BL: $-7.0 \pm 2.2\%$, AP: $+3.7 \pm 2.2\%$, GC: $+4.1 \pm 2.2\%$, TC: $+0.3 \pm 2.6\%$; $p < 0.001$) and lowered TPR (BL: $+16.3 \pm 4.1\%$, AP: $+8.8 \pm 2.7\%$, GC: $+7.5 \pm 3.0\%$, TC: $+9.9 \pm 3.6\%$; $p < 0.001$). Despite improved cardiovascular stability, orthostatic reductions in CBFv were only improved during AP (BL: $-29.4 \pm 2.7\%$, AP: $-22.7 \pm 3.0\%$; $p = 0.054$). Those with greater orthostatic deficits at BL experienced larger cardiovascular enhancements in SAP ($R = -0.311$, $p = 0.006$), HR ($R = -0.276$, $p = 0.016$), SV ($R = -0.417$, $p < 0.001$), CBFv ($R = -0.411$, $p < 0.001$), CO ($R = -0.704$, $p < 0.001$), and TPR ($R = -0.53$, $p < 0.001$) when using CPM. Physical parameters of BL sway (path length, height, total muscularity, and average leg muscularity) effectively predicted the extent of cardiovascular enhancements (SV:$\beta = -18.7$, $p < 0.001$; CO:$\beta = -32.2$, $p < 0.001$; TPR:$\beta = 8.1$, $p < 0.001$).
Conclusion: Discrete movements of AP sway and GC improved cardiovascular control compared to quiet standing, however, TC was not very effective as a CPM. Those with more severe orthostatic impairment experienced greater benefit from CPM. AP sway was the only movement to show cerebrovascular benefit, and may therefore be most optimal to bolster against syncope.
Funding: This work was supported in part by a grant-in-aid from the Heart and Stroke Foundation of Canada of British Columbia and Yukon awarded to V.E.C. (#G-18-0022174).

Poster #133

Counter pressure and other maneuvers for syncope prevention: a semi-systematic literature review and meta-analysis

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Background: Physical counter pressure maneuvers (CPM) are movements that are recommended to delay or prevent syncope (fainting) by recruiting the skeletal muscle pump to augment cardiovascular control. However, these recommendations are largely based on theoretical benefit, with limited data evaluating the efficacy of CPM to prevent syncope in the real-world setting.
Methods: We conducted a semi-systematic literature review and meta-analysis to assess CPM efficacy, identify literature gaps, and highlight future research needs. Articles were systematically identified through a literature search (PubMed, April 28, 2022) of peer-reviewed publications evaluating the use of counter pressure or other lower body maneuvers to prevent syncope. Two team members independently screened records for inclusion and extracted data. Articles with common themes (N = 34) were included in various meta-analyses, while the remaining articles were discussed as a narrative review.
Results: From 476 unique records identified by the search, 45 met inclusion criteria. Articles considered various syncopal conditions (vasovagal = 12, orthostatic hypotension = 8, postural orthostatic tachycardia syndrome = 1, familial dysautonomia = 2, spinal cord injury = 1, blood donation = 10, healthy controls = 11). Maneuvers assessed included hand gripping, leg fidgeting, stepping, tiptoeing, marching, calf raises, postural sway, tensing (upper, lower, whole body), leg crossing, squatting, "crash" position, and bending foreword. CPM were assessed in laboratory-based studies (N = 28), the community setting (N = 4), both laboratory and community settings (n = 3), and during blood donation (N = 10). CPM improved standing systolic arterial pressure ($+ 14.8 \pm 0.6$ mmHg, $p < 0.001$) and heart rate ($+ 1.4 \pm 0.5$ bpm, $p = 0.006$), however, responses of total peripheral resistance, stroke volume, or cerebral blood flow were not widely documented. Most patients experienced symptom improvement following CPM use (laboratory: $60 \pm 4\%$, community: $72 \pm 9\%$). The most prominent barrier to employing CPM in daily living was the inability to recognize an impending faint. Patterns of postural sway may also recruit the skeletal muscle pump to enhance cardiovascular control, and there is emerging evidence that postural movement may be linked to orthostatic cardiovascular and cerebrovascular control. The potential of postural sway as a discrete, proactive CPM requires further evaluation.
Conclusion: Physical CPM were successful in improving syncopal symptoms and producing cardiovascular responses and thus may bolster against syncope; however, practical limitations limit applicability for use in daily living.
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PEDIATRIC AUTONOMIC DISORDERS

Poster #134

Mast cell activation in children, adolescents, and young adults with dysautonomia and small fiber autonomic neuropathy

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Background: Small fiber autonomic neuropathy (SFAN) affects nociceptive nerve fibers, particularly minimally myelinated A Delta and unmyelinated C fibers. It is often associated with multiple symptoms that include neuropathic pain, paresthesia, fatigue, brain fog, tremors, headache, dizziness, syncope, gastrointestinal disorders, and significantly decreased quality of life. Many of these patients present with symptoms of mast cell disease activation (MCA) such as chronic urticaria, pruritis, transient non-specific rash, and flushing. The association between MCA and SFAN is poorly understood, particularly in children, adolescents and young adults (CAYA).
Objective: To determine the prevalence of MCA in CAYA with SFAN and dysautonomia.
Methods: CAYA patients previously diagnosed with dysautonomia who presented with neuropathic symptoms were identified for SFAN testing with epidermal skin biopsy (ESB) and/or quantitative sudomotor axon reflex testing (QSART). Electronic medical records of those tested in a pediatric autonomic clinic were reviewed from December 2020-April 2022. Data collected were blood laboratory results of small fiber and mast cell disease panels, ESB, and QSART findings, and clinical symptoms.
Results: Sixty-two records reviewed with 87% female (n = 54), mean age of 16 years (range 10–21), and 95% (n = 59) Caucasian race. 68% (n = 42) positive for SFAN by ESB. 59% (n = 23) of 39 patients that completed QSART were abnormal. ESB and QSART results correlated (r = 0.32, p = 0.02). 52% (n = 22) of those with SFAN on ESB and/or QSART had an antecedent inflammatory event such as infection, surgery, or head concussion. Symptoms reported by 100% of the sample were profound fatigue, brain fog, and numbness, tingling, or nerve pain. 63% (n = 39) reported MCA associated symptoms and had serum testing. 56% (n = 22) of those tested demonstrated elevated histamine (> 10 nmol/L), however, none in the sample were found to have raised tryptase or any other mast cell specific marker. Higher levels of histamine correlated with the presence of SFAN in those with ESB and/or QSART positive results (r = 0.26, P = 0.05).
Conclusions: Symptoms of MCA are common in CAYA with SFAN. Elevated levels of plasma histamine are common and correlate with SFAN. No other MCA serum markers were found. Our results may suggest a common mechanism for both SFAN and MCA.

Poster #135

BASCULE syndrome: the Mayo Clinic experience of a recently described clinical entity

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Background: Bier anemic spots, cyanosis with urticaria-like eruption (BASCULE) syndrome was only recently described among the pediatric patient population in 2016. This condition has been categorized as a benign and episodic vasomotor dermatosis resulting in urticarial lesions on a background of cyanosis, often affecting the lower extremities, and associated with variable degrees of pruritus or pain. It has been proposed that BASCULE syndrome is temporarily induced by venous stasis secondary to standing or mechanical compression and exhibits spontaneous resolution upon repositioning. A possible association with postural orthostatic tachycardia syndrome (POTS) or orthostatic intolerance remains controversial. Currently, there is a paucity of published information on the condition, limited to few case reports.

Methods: We performed an IRB-approved retrospective chart review on patients seen at Mayo Clinic Departments of Dermatology, Pediatric and Adolescent Medicine, and Cardiovascular Diseases from April 2021 to May 2022 with a clinical diagnosis of BASCULE syndrome.
Results: A total of 15 patients with BASCULE syndrome were identified (11 female, 4 male). Referral diagnoses included erythromelalgia, orthostatic acrocyanosis, livedo reticularis, and dysautonomia. Median age at diagnosis was 16 years (range 12–22) with reported symptom onset at 12 years (range 9–17). Lower extremities were involved in all 15 patients. Reported sensory symptoms were pruritus (8), and burning sensation or pain (6), with 3 patients denying sensory changes. Episode triggers were standing (9), showers or hot environments (5), and no clear trigger (4). Autonomic dysfunction (including orthostatic intolerance and POTS) was present in 11 patients (9 supported by autonomic reflex screen (ARS), and 2 meeting clinical criteria). Recommended treatments included beta-blockers (6), second-generation antihistamines (5) and conservative measures alone (5). Among those with available follow up data, 1 patient reported resolution with short acting propranolol 2–3 times daily, and 1 patient reported 50% improvement with high dose cetirizine.
Conclusion: We present epidemiologic data from 15 patients with BASCULE syndrome, expanding the limited existing knowledge on etiopathogenesis as well as treatment considerations. This data further supports the association with autonomic dysfunction and suggests a vasomotor etiology. Additional data will promote education of all clinicians and improve care of patients with BASCULE syndrome.

Poster #136

Ten-minute active standing test *vs.* head-up tilt test in children and young people: diagnostic yields for orthostatic hypotension and postural tachycardia

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Objective: The Head-Up Tilt Test (HUTT) takes more time and resource than the 10-min Active Standing Test (AST), and in our hands requires a separate hospital visit. The AST is quicker and easier to apply, e.g., in an out-patient clinic, and our preliminary data suggested it was more sensitive in demonstrating postural tachycardia (PT), but not orthostatic hypotension (OH) (AAS Virtual Meeting, 2020). We have now updated our review to include 100 children.
Hypothesis: The AST will detect more PT, but less OH than HUTT.
Methods: This was a retrospective clinical chart review, and registered clinical audit of unselected consecutive children and young people undergoing 45–50 min 60° HUTTs immediately preceded by 10-min ASTs. The first 10 min of HUTT were compared to the 10-min AST. Standard thresholds were used.
Results: Data on 100 children and young people, 66/100 female, aged 2–18 years (median 13) is presented. Of 100 with complete heart rate data, 13/100 had PT only on AST; 5/100 only on HUTT; 6/100 on both. So, AST picked up 19 cases of PT, while HUTT picked up only 11 cases. However, AST on its own missed 5/24 (21%) cases. Of 98 with complete blood pressure data, 5/98 had OH only on AST; 11/98 only on HUTT; 2/98 on both. So, HUTT picked up 13 cases of OH, while AST picked up only 7 cases. However, HUTT on its own missed 5/18 (28%) cases. While AST yielded more cases with significant rises in HR (by $\geq$ 40 bpm) than HUTT (19% *vs.* 11%), combining the tests gave the highest yield (24%). While HUTT yielded more cases with significant falls in BP (either BPS fell $\geq$ 20 mmHg and/or BPD $\geq$ 10 mmHg) than AST (13% *vs.* 7%), combining the tests gave the highest yield (18%).
Conclusions: The data supports our hypothesis: AST is better at eliciting PT than a 10-min HUTT, and even a short (10 min) HUTT is better at eliciting OH than an AST, although it missed a significant minority of cases. We recommend routinely undertaking a 10-min AST prior to all HUTTs in children and young people.

Poster #137

Disorders of the autonomic nervous system: experience of a paediatric neurology syncope clinic

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Objective: To review the referral pathway, case mix, and outcomes of children and young people referred to a paediatric neurology syncope clinic.
Hypotheses: Most referrals would come from our traditional catchment area; outcome data would be available at 1 year for most referrals; most cases would have improved at 1 year follow-up.
Methods: This was a retrospective, observational, clinical chart review of consecutive cases referred over 2 years. A Clinical Global Impression (CGI) outcome assessment was made by one author (GD) not directly involved in the clinic, from the clinical charts, where there was sufficient follow-up.
Results: 55/61 (90%) were referred for assessment of a possible disorder of the autonomic nervous system: 31/55 (56%) with transient loss of consciousness (TLOC) or syncope; 19/55 (34%) with symptoms or a diagnosis of postural tachycardia syndrome (POTS). Ages ranged from 2–17 years (median 13; IQR 8–15), and 34/55 (62%) were female. 37/55 (67%) were referred by hospital or community-based paediatricians; 27/55 (49%) came from outside the paediatric neurology catchment population. Final diagnoses included 10/55 (18%) with reflex asystolic syncope (RAS), 17/55 (31%) with vasovagal syncope (VVS), 9/55 (16%) with orthostatic intolerance (OI) not otherwise specified, and 13/55 (24%) with POTS. Treatments included slow sodium, slow sodium with fludrocortisone, e.g., for those with VVS and POTS, and glycopyrronium for some with RAS. Outcomes for the 20 with TLOC and follow-up demonstrated significant improvement in CGI in 13/20 (65%) by 1 year. Outcomes for the 15 with orthostatic intolerance, including POTS, and follow-up, demonstrated significant improvement in in CGI in 11/15 (73%) by 1 year.
Conclusions: The data support the three hypotheses, but almost half the patients were referred from outside our regional catchment area, suggesting a shortage of local expertise. Outcomes at one year were available in 65% and 79% of those referred with TLOC and OI, respectively, and were good in 2/3–3/4. We recommend routine telephone or MS Teams or similar follow-up at one year of all patients seen. That the patients had previously failed to improve with general paediatric and local services suggests that the paediatric neurology syncope clinic was effective.

POST-COVID AUTONOMIC DISORDERS

Poster #138

Minimal objective autonomic dysfunction in long-COVID

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Background: Many patients report persistent symptoms that continue beyond the acute phase of COVID-19 (SARS-CoV-2) infection, variably called "long-COVID", "post-COVID syndrome", or "long-haul COVID". Common symptoms include fatigue, orthostatic intolerance, palpitations, cognitive impairment, and syncope, similar to the symptom profile of postural tachycardia syndrome (POTS). Although highly prevalent (estimated to affect 33–87% of hospitalized and 37% of non-hospitalized COVID patients), the pathophysiology of long-COVID is still not well understood. It has been speculated that long-COVID patients have POTS or some other immune-mediated dysautonomia. UT Southwestern has a robust clinical program for long-COVID (COVID Recover clinic). Our aim was to characterize the autonomic symptoms, severity and objective measures of autonomic function in these patients.
Methods: Retrospective analysis approved by UT Southwestern IRB. We identified 50 patients from COVID Recover clinic who had been referred to the UT Southwestern autonomic laboratory for testing. Prior to testing, all patients were evaluated with supine and standing orthostatic vitals and completed symptom questionnaires.
Results: Of 50 long-COVID patients who underwent standard autonomic testing, 24 patients had normal autonomic function testing, 6 met heart rate criteria for POTS (by tilt table), 1 had severe diffuse autonomic failure with neurogenic orthostatic hypotension, 3 had mild length-dependent sudomotor impairment, 8 had mildly abnormal testing attributable to medication effects, 4 had mild non-specific cardiovagal impairment, 3 had mild non-specific cardiovagal and sympathetic vasomotor impairment, and 3 had mild non-specific post-ganglionic sudomotor impairment. The median CASS score was 0 (mean 1.0, range 0–8). The mean COMPASS-31 score was 43.4 (n = 43 patients), indicating severe symptoms. This score was similar in severity to our previously studied POTS cohort (COMPASS 31 46.01, n = 205).
Conclusion: Although these long-COVID patients had severe symptoms, the majority of patients had normal autonomic function tests or non-specific mild abnormalities (86%). Only 12% had testing consistent with POTS, 20% had mild non-specific autonomic dysfunction, and 2% had significant autonomic failure. This is the largest cohort to date of autonomic testing in patients with long-COVID. Long-COVID symptoms are usually not associated with POTS or other clear evidence of autonomic dysfunction. An updated larger cohort will be presented.

Poster #139

Autonomic dysfunction in COVID-19 long haulers

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Introduction: Patients with Coronavirus Disease 2019 [COVID-19], caused by the SARS-CoV-2 virus, have been associated with many neurological complications. Some may involve the peripheral nervous system, mainly the motor unit and large efferent fibers, neuromuscular junction, and striatal muscle. However, those affecting the autonomic nervous system are not well characterized.
Objective: To describe the demographics, clinical features, and autonomic nervous system study findings on patients with PCR-proved COVID-19 patients.
Methods: A retrospective chart review of all patients referred to the Cleveland Clinic Florida's autonomic nervous system laboratory with confirmed COVID-19 via PCR testing, subsequently developing autonomic symptoms between March 1, 2020 through December 31, 2021.
Results: 10 patients (80% women) were referred to the Autonomic Laboratory for dysautonomia assessment. Mean age 51.9 years [27–72 y]. The most common reason for testing (RFT) was postural tachycardia (POTS) in 5, lightheadedness in 4, dizziness in 2, presyncope, and syncope in 1, respectively. Some patients had more than one RFT. The neurological exam was normal in 6, decreased vibration in 2, 1 with asymmetric proximal leg weakness, and 1 with Parkinsonism. MRI of the brain and lumbosacral spine was abnormal in 1, respectively. Overall, 70% had a mild degree and 30% a moderate degree of autonomic failure based on the Composite Autonomic Scoring Scale (CASS). Of the total, 50% had cardiovagal [parasympathetic] failure, 20% had neurogenic orthostatic hypotension, and 20% had postural tachycardia (POTS) on tilt table testing. Cardiovascular heart rate index (a composite index assessing cardiac adrenergic and parasympathetic function and baroreflex function) was abnormal in 60% of patients. The sudomotor index (a surrogate marker for sympathetic cholinergic sudomotor function closely associated with small fiber nerve involvement) was abnormal in 80%. Some patients had more than one system involved.
Conclusions: Dysautonomia may follow after COVID-19 infection; cardiovascular adrenergic, cardiovagal, and POTS are the most common consequences of COVID-19. Syncope was uncommon. Testing for autonomic dysfunction is essential and must be considered in patients with autonomic failure symptoms.

Poster #140

Prevalence and patterns of symptoms of dysautonomia in patients with long-COVID syndrome: a cross-sectional study

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Background: The association between autonomic dysfunction and long-COVID syndrome is established. However, the prevalence and patterns of symptoms of dysautonomia in long-COVID syndrome in a large population are lacking.

Objective: To evaluate the prevalence and patterns of symptoms of dysautonomia in patients with long-COVID syndrome.
Methods: We administered the Composite Autonomic Symptom Score 31 (COMPASS-31) questionnaire to a sample of post-COVID-19 patients who were referred to post-COVID clinic in Assiut University Hospitals, Egypt for symptoms concerning long-COVID syndrome. Participants were asked to complete the COMPASS-31 questionnaire referring to the period of more than 4 weeks after acute COVID-19.
Results: We included 320 patients (35.92 ± 11.92 years, 73% females). The median COMPASS-31 score was 26.29 (0–76.73). The most affected domains of dysautonomia were gastrointestinal, secretomotor, and orthostatic intolerance with 91.6%, 76.4%, and 73.6%, respectively. There was a positive correlation between COMPASS-31 score and long-COVID duration ($p < 0.001$) and a positive correlation between orthostatic intolerance domain score and post-COVID duration ($p < 0.001$). There was a positive correlation between orthostatic intolerance domain score and age of participants ($p = 0.004$). Two hundred forty-seven patients (76.7%) had a high score of COMPASS-31 > 16.4. Patients with COMPASS-31 > 16.4 had a longer duration of long-COVID syndrome than those with score < 16.4 (46.2 vs. 26.8 weeks, $p < 0.001$).
Conclusions: Symptoms of dysautonomia are common in long-COVID syndrome. The most common COMPASS-31-affected domains of dysautonomia are gastrointestinal, secretomotor, and orthostatic intolerance. There is a positive correlation between orthostatic intolerance domain score and patients' age.

Poster #141

Autonomic function testing in long-COVID syndrome patients with orthostatic intolerance

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Background: The morbidity of COVID-19 extends behind the acute phase and causes long-term sequelae, described as long-COVID syndrome. The association between dysautonomia and long-COVID syndrome has gained considerable interest.
Objective: To characterize the findings of the autonomic reflex screen (ARS) in long-COVID patients presenting with orthostatic intolerance (OI).
Methods: A retrospective medical record review was conducted between March 2020 and March 2022. We identified all patients referred for the ARS or the head-up tilt table (HUTT) at SUNY Upstate Medical University for evaluating OI that emerged or significantly worsened after a laboratory-confirmed (polymerase chain reaction or antibody testing) SARS-CoV-2 infection.
Results: Fourteen patients were identified. Twelve patients (85.7%) were female and 2 male patients. Age ranged from 20 to 63, with a median of 34.5 years. Orthostatic symptoms included lightheadedness or dizziness was reported by 14/14 patients. Heart racing or palpitation was reported by 11/14, tiredness by 9/14, vertigo by 7/14, shakiness by 6/14, difficulty thinking by 4/14, clamminess by 3/14, blurry vision by 3/14, and syncope by 2/14. Nausea and vomiting were reported by 6/14 patients. All patients had normal cardiovagal function and 2 patients had abnormal sudomotor function. HUTT was significantly abnormal in 3 patients showing postural orthostatic tachycardia syndrome (POTS). Supine HR ranged from 52 to 91 beats per minute (bpm) with a median of 71.5. During HUTT, maximum HR ranged from 68 to 134 bpm with a median of 98, HR changes ranged from + 7 to + 61 bpm with a median of + 25.5, systolic BP changes ranged from − 16 to + 18 mmHg with a median of + 3, and diastolic BP changes ranged from − 9 to + 18 mmHg with a median of + 9. The composite autonomic severity score (CASS) ranged from 0 to 2. The most common clinical scenario was symptoms of orthostatic intolerance without demonstrable HUTT orthostatic tachycardia or orthostatic hypotension (OH) (n = 8, 57%).
Conclusions: In our case series, most long-COVID patients presenting to our laboratory with OI had no significant HUTT abnormalities; only 3 patients met the criteria for POTS.

Poster #142

Objective cardiovascular autonomic abnormalities in post-acute sequelae of COVID-19 (PASC): overall and sex-based prevalence

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Background: The novel coronavirus has negatively impacted the health and economy of the world. While most patients recover, many are left with symptoms several months after resolution of the acute illness ("Post-Acute Sequalae of COVID-19" [PASC]). Symptoms include fatigue, light-headedness, and tachycardia/palpitations, which are features of cardiovascular autonomic disorders such as postural orthostatic tachycardia syndrome (POTS), initial orthostatic hypotension (IOH), orthostatic hypotension (OH), and inappropriate sinus tachycardia (IST). Currently, we do not know the prevalence of objective autonomic abnormalities in PASC patients, nor if there are sex-differences.
Objective: We aimed to determine the prevalence of objective autonomic abnormalities, and whether there was a sex-difference among patients with PASC.
Methods: PASC patients (n = 65; F = 52; 46 ± 11y) underwent autonomic function testing with beat-to-beat hemodynamics supine for 10 min followed by a 10 min active stand 402 ± 129 days after their PCR-confirmed COVID-19 infection. Patients were evaluated for hemodynamic criterion for POTS (↑HR ≥ 30 bpm within 10 min), IOH (transient ↓SBP ≥ 40 mmHg within 15 s), OH (↓SBP ≥ 20 mmHg within 3 min), and IST (supine HR > 100 bpm). Categorical data were analyzed with a Fisher's Exact test.
Results: The POTS criterion was met in 19 (29%) PASC patients, while the IOH criterion was met in 42 (65%) patients. The OH criterion was seen in 2 patients and IST in 1 patient. Overall, 47 (72%) patients met the hemodynamic criterion for at least one autonomic disorder and 18 (28%) did not. The POTS criterion was met in 19 (37%) females, but no males ($p = 0.01$), whereas the IOH criterion was met in females and males at a similar frequency (67% vs. 54%; $p = 0.4$). The two OH patients and single IST patient were female. Overall, there was a trend for more females than males (77% vs. 54%; $p = 0.096$) meeting the criterion for at least one disorder.
Conclusion: Many patients with PASC have objective evidence of autonomic cardiovascular abnormalities, most commonly IOH, followed by POTS. IOH will be missed unless an active stand protocol is used. POTS was much more common in females than males, but IOH was equally evident between sexes. Overall, there is a trend toward increased frequency of autonomic cardiovascular abnormalities in females than males with PASC.
Funding: Canadian Institutes of Health Research.

Poster #143

Objective cardiovascular autonomic abnormalities in post-acute sequelae of COVID-19 (PASC): role of initial COVID illness severity and symptoms

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Background: Many COVID-19 patients are left with a constellation of symptoms several months after resolution of the acute illness, termed "Post-Acute Sequalae of COVID-19" (PASC). Symptoms include fatigue, dyspnea, tachycardia/palpitations, and light-headedness. Some PASC patients meet hemodynamic criteria for autonomic disorders. It is unknown if hospitalized COVID patients (SEVERE) have greater hemodynamic abnormalities or PASC symptoms than non-hospitalized patients (MILD).
Objective: We tested the hypothesis that hemodynamic abnormalities and symptoms would be more frequent in hospitalized (SEVERE) vs. non-hospitalized (MILD) PASC patients.
Methods: PASC patients (n = 65; F = 52; 46 ± 11 years) completed a standard active stand test with beat-to-beat hemodynamics (heart rate, blood pressure) recorded throughout. After a 10-min supine baseline, patients were instructed to stand within a few seconds and remain standing unaided for 10 min. PASC patients were clinically evaluated for initial orthostatic hypotension (IOH), orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS), and inappropriate sinus tachycardia (IST). PASC patients also completed a survey assessing symptoms including fatigue, dyspnea, palpitations, and light-headedness. Categorical data were analyzed with a Fischer's Exact test.
Results: More PASC patients were MILD (n = 56; 86%; 44 ± 11 years, F = 46) than SEVERE (n = 9; 14%; 44 ± 11 years, F = 6). Most PASC patients had at least 1 hemodynamic disorder (72%), but this was similar in MILD vs. SEVERE patients (73% vs. 67%; p = 0.6). IOH was similar between the groups (64% vs. 67%; P = 0.9). There was a non-significant trend towards a higher rate of POTS in the MILD vs. SEVERE patients (11% vs. 32%; p = 0.2). MILD and SEVERE patients experienced symptoms at similar frequencies, including fatigue (93% vs. 89%; p = 0.7), dyspnea (78% vs. 78%; p = 0.98), and light-headedness (79% vs. 67%; p = 0.3). There was a trend for more palpitation in MILD vs. SEVERE patients (73% vs. 44%; p = 0.08).
Conclusion: PASC patients hospitalized due to their COVID-19 infections did not have increased rates of cardiovascular hemodynamic abnormalities, or symptoms, compared to non-hospitalized patients. These findings suggest that even MILD COVID-19 infections may result in the development of long-term hemodynamic abnormalities and symptoms.
Funding: Canadian Institutes of Health Research.

Poster #144

Objective cardiovascular autonomic abnormalities in post-acute sequelae of COVID-19 (PASC): impaired sympathetic and parasympathetic modulation

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Background: Many COVID-19 patients are left with a constellation of symptoms several months after resolution of the acute illness, termed "Post-Acute Sequalae of COVID-19" (PASC). Some PASC patients meet hemodynamic criteria for clinical autonomic disorders. It is not known if sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) tone are different among PASC patients with (ObjCVAbn) or without (NoObjCVAbn) objective cardiovascular hemodynamic abnormalities.
Objective: We tested the hypothesis that PASC patients with ObjCVAbn will have increased SNS activity and reduced PNS activity.
Methods: PASC patients (n = 65; F = 52; 46 ± 11 y) completed an active stand test with beat-to-beat heart rate and blood pressure (Nexfin, BMEYE) data sampled digitally for off-line analyses. PASC patients were evaluated for hemodynamic criteria for initial orthostatic hypotension (IOH), orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS), and inappropriate sinus tachycardia (IST). 10-min supine data were used to calculate tonic PNS measures included percentage of consecutive beat intervals differing by > 50 ms (pNN50) and high frequency heart rate variability (HF-HRV). Tonic SNS was assessed using low frequency systolic blood pressure variability (LF-BPV), and reflexive baroreceptor sensitivity (BRS) was assessed using cross-spectral transfer function gain. Continuous data were analyzed using Student t-tests. Data are reported as mean ± SD.
Results: At least one hemodynamic criterion was evident (ObjCVAbn) in 47 patients (72%; 46 ± 11 y, F = 40), whereas no criterion was present (NoObjCVAbn) in 18 patients (28%, 43 ± 10 y, F = 12). ObjCVAbn patients had significantly lower pNN50 compared to NoObjCVAbn (6.16 ± 6.23% vs. 9.75 ± 8.65%; p = 0.047). HF-HRV was trending lower in ObjCVAbn vs. NoObjCVAbn (510 ± 452 ms^2 vs. 749 ± 656 ms^2; p = 0.1), indicating reduced PNS tone. In contrast, LF-BPV was trending higher in ObjCVAbn vs. NoObjCVAbn (6.57 ± 6.03 $mmHg^2$ vs 4.07 ± 4.18 $mmHg^2$; p = 0.2), indicating increased SNS tone. BRS was significantly lower in ObjCVAbn vs. NoObjCVAbn (9.4 ± 5.4 ms/mmHg vs. 14.4 ± 9.4 ms/mmHg; p = 0.02).
Conclusion: Compared to PASC patients not meeting criteria for clinical hemodynamic disorders, PASC patients with disorders have altered autonomic nervous system tone, with a shift toward increased SNS tone, reduced PNS tone, and lower baroreflex sensitivity.
Funding: Canadian Institutes of Health Research.

Poster #145

Sex-based differences in the PASC patient experience

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Background: Some patients who have had COVID-19 are experiencing prolonged symptoms, a phenomenon known as Post-Acute Sequelae of COVID-19 (PASC; or Long-COVID). PASC's effects on different populations have yet to be well characterized. The aim of the present study was to describe the PASC patient experience in males versus females.
Methods: Patients who had a PCR-confirmed COVID diagnosis and who had been experiencing residual symptoms for at least three months were recruited. Eligible participants completed a survey that

explored demographics, symptoms, medical history, and employment. Results are reported as percentages for categorical data and as median [interquartile range] for continuous data. Statistical analyses were done using Pearson chi-square and Mann–Whitney U tests.
Results: A total of 76 eligible participants (62F, 14 M) completed the survey. Mean age was not different between females and males (42.0 [36.0–51.0]y vs. 43.0 [32.0–59.0]y; p = 0.5). Females were more likely than males to have experienced headaches (70% vs. 29%; p = 0.004), fatigue (95% vs. 79%; p = 0.04), and loss or change in taste (37% vs. 7%; p = 0.03) since their COVID infection. Females also experienced palpitations (77% vs. 43%; p = 0.01) and constipation (37% vs. 7%; p = 0.03) more commonly than their male counterparts. Most females and males reported having consulted a general practitioner or nurse practitioner in the past 3 months (90% vs. 100%; p = 0.2). Females reported having had more appointments with a physiotherapist in the past three months (1.0 [0.0–6.0] vs. 0.0 [0.0–0.3]; p = 0.005). The same was true of appointments with a psychologist (1.0 [0.0–3.3] vs. 0.0 [0.0–0.0]; p = 0.002). Finally, of the participants whose occupation had changed since their COVID diagnosis (60% vs. 43%; p = 0.251), males and females were equally as likely to have had a decrease in earnings (100% vs. 80%; p = 0.485) and equally likely to report that their work status changed as a result of poor health or sick leave (M = 83% vs. F = 81%; p = 0.895).
Conclusion: Symptom profiles differ between female and male patients with PASC, and females receive a greater amount of specialized professional help. Females and males with PASC suffer similar adverse career impacts.
Funding: Canadian Institutes of Health Research (CIHR).

Poster #146

Palpitation and lightheadedness are associated with poorer health-related quality of life in post-acute sequelae of COVID-19 (PASC) patients

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Purpose: Many patients have ongoing symptoms lasting months to years after recovering from acute COVID-19, called Post-Acute Sequelae of COVID-19 (PASC; or Long-COVID). Many PASC patients appear to have features of chronic orthostatic intolerance (COI), including symptoms such as lightheadedness and palpitations. We hypothesized that patients with both self-reported palpitation and lightheadedness (BOTH) have reduced health-related quality of life (HRQoL) compared to patients without both symptoms.
Methods: PASC patients (n = 59, F = 47, 45 ± 2 years) completed the RAND-36 (HRQoL), NeuroQOL (anxiety and depression symptoms during illness), and the modified Malmo score (orthostatic symptoms). Data were analyzed using Student's t-tests and reported as mean ± SEM. More favourable health states were indicated by higher RAND-36, lower NeuroQOL, and lower Malmo scores.
Results: PASC patients with palpitations (n = 42, F = 37, 42 ± 2 y) reported greater Malmo than patients without palpitations (n = 17, F = 10, 52 ± 3 y) (60.7 ± 3.4 vs. 40.9 ± 4.9, p = 0.002). Patients with lightheadedness (n = 45, F = 36, 44 ± 2 y) reported greater Malmo than patients without lightheadedness (n = 13, F = 11, 48 ± 3 y) (58.5 ± 3.5 vs. 40.3 ± 4.8, p = 0.01). PASC patients with BOTH (n = 36, F = 31, 49 ± 2 y), compared to PASC patients with only one or no symptoms (n = 23, F = 16, 49 ± 2 y), reported reduced HRQoL in physical functioning (40.3 ± 3.7 vs. 61.3 ± 5.9, p = 0.002), role limitations due to physical health (0.7 ± 0.7 vs. 29.3 ± 8.6, p = 0.003), emotional well-being (50.8 ± 3.6 vs. 64.3 ± 4.0, p = 0.02), energy and fatigue (19.2 ± 2.5 vs. 33.0 ± 4.5, p = 0.005), social functioning (29.9 ± 3.5 vs. 54.9 ± 5.4, p < 0.001), pain (40.0 ± 3.0 vs. 70.4 ± 5.4, p < 0.001) and general health (32.4 ± 2.9 vs. 47.2 ± 4.2, p = 0.004), but not role limitations due to emotional problems (p = 0.6). Patients with BOTH had higher NeuroQOL anxiety (23.9 ± 1.1 vs. 18.4 ± 1.5, p = 0.004) and NeuroQOL depression scores (19.8 ± 1.2 vs. 13.8 ± 1.5, p = 0.001) compared to patients without BOTH.
Conclusion: PASC patients with combined palpitation and lightheadedness reported increased orthostatic symptoms, worse HRQoL, and increased anxiety and depression symptoms, compared to PASC patients without both symptoms.
Funding: Canadian Institutes of Health Research (CIHR).

Poster #147

Post-acute sequelae of COVID-19 (PASC) patients experience losses of work productivity

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Purpose: Many patients have ongoing orthostatic symptoms lasting months to years after recovering from acute COVID-19, called Post-Acute Sequelae of COVID-19 (PASC; or Long-COVID). Symptoms include light-headedness, fatigue, palpitations, orthostatic intolerance, mental clouding and cognitive dysfunction. The study objective was to characterize work productivity losses in PASC patients.
Methods: PASC participants were provided a modified version of the validated patient-reported outcome measure, the Productivity Costs Questionnaire (PCQ) from the Institute of Medical Technology Assessment. This PCQ measures and values absenteeism (i.e., missed work due to illness), presenteeism (i.e., able to work but with impaired function), and lost productivity from unpaid work (i.e., unable to perform usual unpaid labour, such as household work or volunteer work). The average hourly wage for Canadian full-time employees was used in the productivity loss calculations from the patient perspective. All scores are reported as mean ± SEM.
Results: Of 76 PASC participants, 62 (age = 45 ± 1 years, female = 89%) reported employment prior to COVID-19 infection. The majority of PASC patients with prior employment (n = 52, 84%) reported taking sick leave due to COVID-19 illness for an average of 238 ± 29 days. Of the 34 participants who reported returning to work post-COVID, there was a decrease in working hours of over 50% (8.4 h/day pre-COVID versus 3.6 h/day post-COVID). The average lost wages from being absent from work or reduced work hours due to illness in a four-week period was $7,919 ± 562. Assuming an ongoing reduction in work hours post-COVID, the estimated annual lost wages would be $27,120 compared to pre-COVID work hours. Among the patients who returned to work post-COVID, 25 PASC participants suffered from physical or psychological problems impairing their ability to function while at work. The average productivity loss from presenteeism was $689 ± $115 in a four-week period. The average lost productivity of unpaid work in a four-week period is $3,566 ± $587.

Conclusion: PASC patients experienced large productivity losses due to absenteeism, presenteeism and unpaid work. In the context of emerging data on the prevalence of PASC in the general population, these findings have substantial economic implications at the population level.
Funding: Canadian Institutes of Health Research (CIHR).

Poster #148

Characterization of autonomic symptom burden in long COVID: a global survey of 2,314 adults

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Purpose: Autonomic dysfunction is a common complication of post-acute sequalae of SARS-CoV-2 (PASC)/long COVID, however, prevalence and severity rates are unknown. The primary goal of this study was to assess the frequency and severity of autonomic symptoms in PASC. We also aimed to determine whether severity of acute SARS-CoV-2 infection is associated with severity of autonomic dysfunction and assess symptom burden in PASC through well-validated questionnaires.
Methods: We conducted a cross-sectional online survey of 2,314 adults with PASC that were recruited through long COVID support groups between October 2020 and August 2021. The survey consisted of several validated questionnaires including the Composite Autonomic Symptom Score 31 (COMPASS-31). We included participants who tested positive for COVID-19 (test-confirmed) and those with a diagnosis based on clinical symptoms alone (test-unconfirmed). Test-unconfirmed participants were included in order to access a larger global population of PASC patients, including those infected early in the pandemic without access to COVID testing. Correlation coefficients were calculated to assess strength and alignment of associations between COMPASS-31 scores and other survey measures.
Results: Sixty-seven percent of PASC patients had a COMPASS-31 score > 20, suggestive of moderate to severe autonomic dysfunction. COMPASS-31 scores did not differ between test-confirmed hospitalized and non-hospitalized participants (28.95 [15.62, 46.60] vs. 26.4 [13.75, 42.10]; $p = 0.06$). Test-unconfirmed participants had higher COMPASS-31 scores than test-confirmed participants (26.8 [13.9, 42.8] vs. 34.7 [19.2, 47.0]; $p < 0.0018$). The test-unconfirmed group had longer symptom duration, with 82.4% of participants noting symptom onset ≥ 6 months prior, compared to 37.2% percent in the test-confirmed group. Participants with a history of asthma, vitamin D deficiency, autoimmune disease, food/environmental allergies, anxiety, depression, smoking/vaping (test-confirmed only), and obesity (test-unconfirmed only) had significantly higher COMPASS-31 scores than those who did not report these conditions. A pre-existing diagnosis of autonomic dysfunction was reported by 5.1% of test-confirmed and 8.3% of test-unconfirmed participants, with POTS being the most reported autonomic disorder.
Conclusions: Moderate to severe autonomic dysfunction was seen in all PASC groups in our study, independent of hospitalization status, suggesting that autonomic dysfunction is highly prevalent in the PASC population and not necessarily dependent on the severity of acute COVID illness.

Poster #149

Central and peripheral hyperadrenergic symptoms significantly contribute to symptom burden in people with post-acute sequela of COVID-19

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Background: Even after recovery from acute COVID-19 infection (HxCOVID +), many individuals experience persistent symptoms and worsened physical and mental health. These post-acute sequelae of COVID-19 (PASC) include many symptoms that are also observed in postural orthostatic tachycardia syndrome (POTS), where they have been attributed to increased peripheral adrenergic signaling, such as postural and exertional intolerance, dyspnea, and palpitations. Centrally mediated symptoms of fatigue, cognitive dysfunction, insomnia, depression, and anxiety also occur in PASC and are common in posttraumatic stress disorder (PTSD) and following traumatic brain injury (TBI), where they have been attributed to excessive central adrenergic signaling, often treated with adrenergic antagonists.
Hypothesis: COVID-19 infection will be associated with increased rates of persistent hyperadrenergic symptoms attributable to concurrent peripheral and central dysregulation of adrenergic signaling, significantly mediating the burden of PASC.
Design: Longitudinal questionnaire- and online-cognitive testing based cohort study of participants age 21–65 who report a known history of COVID-19 infection (HxCOVID +, N = 52) or no known history of COVID-19 infection (HxCOVID-, N = 25). A 31-item internally developed Adrenergic Symptom Inventory (ASI) was used to quantify peripheral and central adrenergic symptoms (internal reliability is $\alpha = 0.94$ [95% CI 0.93–0.96]).
Findings: HxCOVID + participants report poorer physical (WHOQoL-D1) and mental health (WHOQoL-D2), and scored significantly higher on total ASI, peripheral ASI components, and a validated self-report instrument for autonomic symptoms (COMPASS-31) compared to HxCOVID-participants (all $p < 0.0001$). COMPASS-31 total score was strongly associated with both the ASI and ASI-peripheral total scores ($p < 0.00001$). On mediation analysis, COMPASS-31 total and the ASI-peripheral scores mediated 0.55 and 0.65, respectively, of the overall impact of COVID-19 on physical health (WHOQoL-D1, both $p < 0.0001$). HxCOVID + participants who underwent online neurocognitive testing (via testmybrain.org) performed worse on choice reaction time ($p = 0.01$), remembering words ($p = 0.03$), and matrix reasoning ($p = 0.01$).
Conclusions: Symptoms commonly associated with increased peripheral and central adrenergic signaling are prevalent, co-occurring, and significantly related to overall symptom burden in PASC. These findings suggest that co-occurring dysregulation of central and peripheral adrenergic signaling may be an important pathophysiologic mechanism underlying symptom expression in PASC, and a potential target for pharmacologic modulation.
Funding: Garvey Institute for Brain Health Solutions Innovation Grant Program (1 year) and VA Clinical Sciences Research and Development Service Career Development Award IK2CX001774.

Poster #150

Incidence of post-COVID19 autonomic syndrome in working-age patients within 6 months from hospital discharge

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Background: Symptoms attending the so called "Long-COVID" may involve autonomic dysfunction following SARS-CoV-2 infection (post-COVID19 autonomic syndrome, C19AS). The incidence of C19AS is still unknown, particularly in working age individuals.
Aim: To evaluate the C19AS incidence in working-age patients admitted to Hospital for COVID19 within 6 months after their hospital discharge.
Methods: This prospective study enrolled consecutively 45 patients (age 53.6 ± 8.4 y; BMI 28.3 ± 4.0 kg/m^2; M/F 32/13) admitted to Humanitas Research Hospital for COVID19 during the second pandemic wave in Italy (Dec 2020-Mar 2021). Autonomic dysfunction was quantified through a complete clinical investigation and COMPASS-31 questionnaire. COMPASS-31 total score (CTS, 0–100), and Orthostatic Intolerance domain (OI, 0–40) were evaluated at the time of enrollment (T0), at one month (T1) and 6 months (T6) after hospital discharge. The patients' condition before hospitalization (PRE) was explored retrospectively to identify those who developed new occurrences of C19AS, i.e., patients who scored less than 16.44 (Greco C et al., 2017) on CTS at PRE and more than 16.4 at T6. The remaining patients who did not develop C19AS represented our internal control group. The investigation was approved by the Internal Review Board (#2742/2020). A written consent was signed by all participants.
Results: Fifteen patients developed C19AS within the 6-month follow-up. At T1, CTS and OI were higher (22.62 ± 16.86 and 12.29 ± 12.30) than PRE (5.41 ± 3.56 and 1.07 ± 4.13T6, $p < 0.05$). At T6, CTS and OI were still higher (30.48 ± 14.95; 17.07 ± 9.3, $p < 001$) than PRE. In contrast, no changes on CTS and OI were observed within the 6-month follow-up in the remaining 30 working-age patients. Clinical features, demographics and disease severity were similar in the two groups.
Conclusion: The incidence of C19AS in our group of working-age patients was of 30% in the 6-month follow-up. The orthostatic intolerance was the most reported symptom. In this group of patients, the autonomic symptoms were still present long after the resolution of potential physical deconditioning characterizing the post-acute COVID19.
Funding: Partially funded by CardioCalm, Montichiari, Brescia, Italy.

Poster #151

Relationships between autonomic symptoms and work ability in post-COVID19 autonomic syndrome

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Background: "Long-COVID19" remains a poorly understood phenomenon which may include an autonomic dysfunction related symptoms (post-COVID19 autonomic syndrome, C19AS). Autonomic symptoms such as fatigue, orthostatic intolerance and "brain fog", may negatively impact work ability and make return to work difficult.
Aim: To evaluate the relationship between autonomic symptom intensity and work ability in patients who developed C19AS at 6 months after their hospital discharge.
Methods: Design: prospective observational study. Population: fifteen working-age patients (age 52.8 ± 9.4 y; M/F:10/5; BMI 28.3 ± 3.95 kg/m^2) admitted to Humanitas Research Hospital during the second wave of pandemic in Italy (Dec 2020-Mar 2021), who developed C19AS within 6-month follow-up. C19AS was defined the new occurrence of autonomic symptoms that were not present before Sars-Cov2 infection. The intensity of autonomic symptoms and work ability were assessed by COMPASS-31 total score (0–100, CTS) and Work Ability Index (7–49; WAI), and compared at one (T1) and 6 months (T6) after patients' hospital discharge. The same questionnaires were retrospectively fulfilled by the patients to assess their condition before Sars-Cov2 infection (PRE). Linear regression analysis was used to evaluate the relationship between CTS and WAI at T6. The investigation was approved by the Internal Review Board (#2742/2020). A written consent was signed by all participants.
Results: At T1, CTS was higher (22.62 ± 16.86) and WAI was lower (33.85 ± 6.48) compared to PRE (CTS 5.41 ± 3.56, $p = 0.02$; WAI 42.33 ± 6.30, $p = 0.006$). At T6, although the CTS was further increased (30.48 ± 14.95) compared to PRE ($p < 0.0001$) the WAI seemed to be partially restored (36.62 ± 7.62). An inverse relationship between CTS and WAI was observed at T6 ($r = -$ 0–86; $p < 0.0001$) thus indicating that the higher the autonomic symptom intensity the lower the work ability.
Conclusion: The autonomic dysfunction produced by SARS-CoV-2 infection in working age patients may play a role in the observed long-lasting work ability impairment. Quantifying post-COVID19 autonomic abnormalities may be helpful to guide occupational doctors' decision making in optimizing both the type of job and the timing of work return after COVID-19 infection.
Funding: Partially funded by CardioCalm, Montichiari, Brescia, Italy.

Poster #152

Autonomic nervous system abnormalities in patients with post-acute COVID syndrome (long-haul COVID)

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Objective: To evaluate autonomic nervous system (ANS) function in patients with post-acute COVID syndrome (PACS).
Background: Several core symptoms of post-acute COVID syndome (PACS, or "Long COVID") may result from ANS dysfunction, such as fatigue, excessive tachycardia, lightheadedness, orthostatic intolerance, and exercise intolerance. Prior studies have suggested that autonomic symptoms are common in these patients. However, it remains unknown whether patients with PACS have objective ANS dysfunction during autonomic reflex testing (ART).

Design/Methods: This retrospective study reviewed 650 patients (6/2021 to 3/2022) who were referred to the Dartmouth PACS clinic. 73/650 patients were referred to Neurology. We reviewed all neurology patients' charts for demographics, PACS symptoms, past medical history, and ART results. Patients were excluded if the referral was for a disorder established prior to COVID infection, if the referral was declined, or if the patient had not yet been evaluated by Neurology.
Results: 56 patients (82% female, mean 44.8 ± 12.3 years) were seen in PACS subspecialty Neurology clinic. 24/56 patients were referred for ART (91% female, 20 females, 2 males, median age 41.3, SD 11.1 years, compared with 32 other patients who were not (75% female, age 47.5 ± 12.5). 2 patients were still awaiting ART. Patients undergoing ART more frequently reported exercise tolerance, tachycardia, presyncope and fatigue ($p < 0.01$, Chi-square). 6 of 22 patients who had completed ART had sustained excessive orthostatic tachycardia with active standing (accompanying reported orthostatic intolerance), but otherwise normal (or borderline) ART, fulfilling consensus criteria for postural tachycardia syndrome (POTS). 1 patient had cardiovagal dysfunction, and 7 patients had mild or borderline abnormalities of uncertain significance (e.g., abnormalities attributable to medication use). 8 patients had completely normal ART. 20 patients had ≥ 1 follow-up encounter. All 6 patients with POTS improved with salt, fluids, physical therapy, and propranolol, compared with 3/5 patients without a POTS diagnosis receiving treatment. 9 patients were untreated.
Discussion: Autonomic symptoms are common in PACS. However, apart from excessive orthostatic tachycardia in patients with POTS, significant abnormalities on routine ART are rare. Patients with PACS and POTS seem to respond well to standard therapies, highlighting the importance of prompt diagnosis and treatment.

Poster #153

Postural orthostatic tachycardia syndrome is prevalent in post-acute sequela of Covid-19?

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Introduction: Several observational studies have reported autonomic dysfunction in those with post-acute sequalae of Covid-19 (PASC). However, the absence of control groups in such studies has made definitive conclusions elusive. Here, we compare the autonomic function of those with PASC compared to those with postural orthostatic tachycardia syndrome (POTS) and healthy adults.
Methods: Ethics approval was obtained from University of Adelaide. Consecutive POTS patients referred to a specialist treatment clinic in Australia were invited to register. Healthy adults and PASC participants were recruited via this clinic and social media. Diagnosis of POTS was established as per international criteria. Participants were accepted as having PASC if unexplained symptomology persisted for ≥ 3 months post Covid-19 infection. Haemodynamic testing was undertaken using Finapres® NOVA for beat-to-beat assessment. Autonomic assessment included Valsalva response, respiratory sinus arrhythmia (RSA) and 10-min standing test (ST). The Composite Autonomic Symptom Score (COMPASS-31) assessed autonomic symptomology. One way analysis of variance was used to compare differences between groups. Significance was set at p value of < 0.05.
Results: 36 participants were recruited (n = 12 POTS, n = 12 PASC and n = 12 healthy adults). Mean age in years was = 27.17, SD 9.92; 40.42, SD 14.63 and 29.92, SD 10.92 for POTS, PASC and healthy adult groups, respectively. Female gender was predominant amongst all cohorts (POTS 92%, PASC 83% and healthy adults 75%). There was no significant difference in body mass index between groups. Mean maximum standing heart rate was significantly higher in POTS (137.08 bpm, SD 11.50) and PASC (110.92 bpm, SD 13.26) compared to healthy adults (89.17 bpm, SD 11.77); $p \leq 0.001$. There was a significant difference in standing delta HR amongst POTS (55.25, SD 12.72), PASC (37.67, SD 9.20) and healthy adults (21.42, SD 7.06); $p \leq 0.001$. COMPASS-31 scores were significantly higher in POTS (51.17, SD 17.30) and PASC (40.90, SD12.85) compared to healthy adults (9.79, SD 10.39); $p \leq 0.001$. The majority of PASC participants (80%) met the criteria for POTS diagnosis compared to 8.3% of healthy adults and 100% of POTS cohort.
Conclusion: POTS is prevalent amongst those with PASC. Further studies are required to quantify the burden of POTS in PASC.
Funding: Standing Up To POTS—Research Grant 2021, Australian Government Research Training Program (RTP) Scholarships.

Poster #154

Hypermobility is associated with dysautonomia in post-acute sequelae of Covid-19

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Background: Generalised joint hypermobility (GJH) has previously been associated with autonomic dysfunction. This is the first study to characterise dysautonomia and GJH in post-acute sequelae of Covid-19 (PASC), postural orthostatic tachycardia syndrome (POTS) and healthy controls.
Objective: To explore associations of GJH with autonomic dysfunction in POTS and PASC populations compared to healthy controls.
Methods: Consecutive POTS and PASC patients referred to a specialist centre in Australia were invited to register. Healthy adults were recruited via social media and flyers. PASC was defined as persistent, unexplained symptomology for ≥ 3 months post diagnosis with SARS-CoV-2 infection. A diagnosis of POTS was established as per accepted international criteria. The 5-point hypermobility questionnaire (5-PHQ) was used to assess generalized joint hypermobility. Scores ≥ 2 were considered indicative of GJH as per previous tool validation. The Composite Autonomic Symptom Score (COMPASS-31) questionnaire was used to assess autonomic symptomology. One-way between-groups analysis of variance was used to explore differences between groups.
Results: A total of 36 participants were enrolled (POTS = 12, PASC = 12 and healthy adults = 12). Mean age in years was 27.17 ± 9.9 (POTS), 40.42 ± 14.6, (PASC) and 29.92 ± 10.9 (healthy adults) and majority were female (POTS 92%, PASC 83% and healthy adults 75%: $p = 0.549$). Hypermobility was significantly greater amongst those with POTS (75%) and PASC (42%) compared to healthy adults (17%); $p = 0.016$. Those with GJH had significantly worse autonomic function than non-hypermobile participants with COMPASS-31 sub scores demonstrating higher orthostatic intolerance (23.25 vs. 13.20; p = 0.008), vasomotor (2.55 vs. 1.17; $p = 0.014$), secretory motor (5.36 vs. 2.25; $p = 0.026$) and pupillary motor function (2.48 vs. 1.55; $p = 0.019$) scores than non-

hypermobile participants. GJH was also associated with significantly worse bladder (1.74 vs. 28; $p = 0.001$), gastrointestinal function (11.27 vs. 5.36; $p \leq 0.001$) and total autonomic function on COMPASS-31 (46.65 vs. 23.80; $p = 0.001$).
Conclusion: In this study, general joint hypermobility was statistically more prevalent amongst POTS and PASC populations than healthy controls and was associated with significantly worse autonomic dysfunction. There is an urgent need for strategies to improve treatments for these cohorts.
Funding: Standing Up To POTS—Research Grant 2021, Australian Government Research Training Program (RTP) Scholarships.

Poster #155

Cortical hypoxia, measured with near-infrared spectroscopy (NIRS), in post-acute sequelae of COVID-19 (PASC)

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Background: Many individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience persistent symptoms. This condition, also called post-acute sequelae of COVID-19 (PASC), includes symptoms such as orthostatic intolerance, which might result from brain hypoxia. Here, we hypothesize that cortical hypoxia exists in PASC and affects orthostatic changes in the brain oxygen.
Objectives: We aimed to use near-infrared spectroscopy (NIRS) to study cerebral microvasculature tissue oxygen saturation (S_tO_2 (%)), as a measure of hypoxia and orthostatic changes in brain oxygen, in PASC.
Methodology: Seventy patients with PASC (45 ± 11 years, F = 55) participated in this study. Among those patients, 28 have completed their 3-month follow-up appointments. Previously collected data from fifty-five healthy participants (48 ± 13 years, F = 38) during a seated resting-state were used for comparison. Frequency-domain NIRS (fdNIRS) was used to quantify the cortical microvasculature S_tO_2 during 10-min supine, 3-min unaided-standing, and 1-min seated resting-state. Hypoxia was defined as S_tO_2 values 2SD below the mean value of the healthy participants during the seated resting-state. Data are reported as mean ± SD. A paired-samples t-test was conducted for the patients who completed both baseline and follow-up appointments to compare the S_tO_2, during the whole protocol, between baseline and 3-month follow-up measures.
Results: Healthy participants had seated resting-state S_tO_2 values of 62.3 ± 3.6%, compared to 58.5 ± 5.9%, in PASC patients measured at baseline ($p < 0.001$). These data showed that 14 (20%) PASC patients were hypoxic (S_tO_2 = 49.2 ± 4.3%), defined as the seated resting-state S_tO_2 below 55.1%, and the rest were normoxic (S_tO_2 = 60.8 ± 3.5%). Data from the 3-month follow-up appointments show that 14 (50%) PASC patients were hypoxic. Among these, 12 patients who were normoxic became hypoxic, and hypoxic patients showed decreased oxygenation, becoming more hypoxic. A paired t-test shows a significant difference in continuous StO2 between baseline (S_tO_2 = 59.2 ± 5.2%) and 3-month follow-up (S_tO_2 = 53.1 ± 8.4%) appointments ($p < 0.001$).
Conclusion: Using NIRS, we show that cortical hypoxia exists in PASC patients. Moreover, over three months of follow-up, brain hypoxia seems to persist or get worse, and not improve. Further work is needed to understand the implications of brain hypoxia detected by NIRS.
Funding: Canadian Institutes of Health Research (CIHR).

Poster #157

Understanding cardiovascular symptoms during recovery from Covid-19

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Purpose: Post Covid-19 cardiovascular symptoms have been and continue to be a growing concern noted in as many as one-fourth of patients hospitalized with the virus accounting for up to as much as 40% of all Covid-19 deaths (Williamson L, 2020). Symptoms expressed include dizziness up to and including syncope, palpitations, irregular heart beat, shortness of breath and chest pain. Cause has been linked to post viral inflammation in as many as 60% of these patients (Williamson L, 2020). The goal of this paper is to provide autonomic measurements in patients who after surviving Covid-19 are presenting to Stern Cardiovascular Foundation for evaluation of symptoms mentioned above. Initial visit and second visit have previously been presented. The following will include data from additional third and fourth follow up visits.
Methods: Forty-seven patients presenting for cardiac and then autonomic evaluation due to persistent symptoms following recovery from Covid-19 are described. Average age was 40.96 years. Symptom inventories and orthostatic evaluations were performed at initial and second visit. Thirty-one were seen at visit three. Seventeen of these patients were seen for a fourth visit.
Results: Symptoms at initial visit in order of prevalence included fatigue (95.7%), dizziness (93.6%), gastric symptoms (91.5%), palpitations/tachycardia (63.8%), dry eyes/mouth (55.3%) and chest pain or discomfort (29.8%). At visit 3, fatigue was reported by 67.7%, dizziness (67.7%), gastric symptoms (64.5%), palpitations/tachycardia (36.4%), dry eyes/mouth (22.6%) and chest pain or discomfort (0%). Exam findings included orthostatic measurements of systolic and diastolic blood pressure as well as heart rate variability (HRV). Heart rate variability was the primary measurement of interest. HRV lying to standing increased by 14.03% from initial visit to visit 3 and showed further increase of 21.8% from initial visit to visit 4. SBP and DBP were initially elevated and showed persistent increase until visit 4 where all orthostatic BP measurements were lower SBP initial visit to visit 4 decreased by 4.3% and DBP initial visit to visit 4 decreased by 22.6%.
Conclusion: Initial autonomic evaluation post Covid-19 demonstrated decline in measures of parasympathetic activity with progressive improvement following cholinergic support ± antioxidant and H2 blockade. Improvements in autonomic tone are described in reduction of symptoms, improved heart rate variability and blood pressure.

Poster #158

Long-COVID postural tachycardia syndrome exhibits altered cardiac vagal modulation

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Background: About 10% of patients infected with Sars-CoV2 have persistent symptoms beyond 4 weeks and some of them meet diagnostic criteria for postural tachycardia syndrome (Long-COVID

POTS). The pathophysiology of Long-COVID POTS is unknown, but autonomic dysfunction may play a role.
Hypothesis: We hypothesize that Long-COVID POTS patients have impaired cardiovascular autonomic reflexes and altered cardiac sympathovagal balance.
Methods: We conducted a case–control study (IRB#220550) with patients recruited from the Vanderbilt Autonomic Dysfunction Center and an historical population of healthy controls (IRB#190703). Hemodynamic parameters were measured before and during 75° head up tilt. Supine ECG and finger blood pressure were continuously measured for spontaneous heart rate variability analysis. The Low Frequency (0.04–0.15 Hz, LF_{RR}) and High Frequency (0.15–0.4 Hz, HF_{RR}) oscillatory modulations of sino-atrial node discharge were computed in supine position.
Results: Data are mean ± SEM. We included 14 Long-COVID POTS patients and 15 controls matched by age (33 ± 2 vs. 28 ± 2 years; $p = 0.11$) and BMI (25.5 ± 1.0 vs. 23.0 ± 0.8; $p = 0.06$). As expected, the orthostatic HR increase was higher in Long-COVID POTS compared to controls (40 ± 6 vs. 21 ± 3 bpm, $p < 0.05$). Spectral analysis of heart rate variability in 9 patients and 15 controls showed that Long-COVID POTS had reduced HF_{RR} (363 ± 141 vs. 933 ± 259 ms^2; $p < 0.05$) and similar LF_{RR} (798 ± 199 vs. 962 ± 278 ms^2; $p = 0.68$), resulting in a greater LF/HF ratio (3.7 ± 1.0 vs. 1.4 ± 0.3; $p < 0.05$).
Conclusion: Patients with Long-COVID POTS have reduced markers of cardiovagal modulation, but normal cardiac sympathetic activation. Our results suggest that parasympathetic dysfunction contributes to the pathophysiology of Long-COVID POTS.
Funding: NIH: R01-HL142583.

Poster #159

Neuromuscular and autonomic features in Long Covid-19: a single-center retrospective review of clinical and objective findings

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Background: Symptoms associated with Long COVID-19 include pain, paresthesias, fatigue, and orthostatic intolerance. Involvement of large and small-nerve fibers with or without autonomic dysfunction has been implicated as a cause of these symptoms.
Objective: To characterize the clinical and objective findings in a sample of patients experiencing neuromuscular and autonomic symptoms with Long COVID-19.
Methods: We reviewed clinical presentation, medical records and test results of patients referred for suspected neuromuscular and autonomic dysfunction from Long COVID-19 Clinic, Beth Israel Deaconess Medical Center, Boston, Massachusetts, over a 16-month period.
Results: Six-hundred-and-fifty-five patients were seen in the Long COVID-19 clinic; 57 (9%) were referred to neuromuscular and autonomic clinics with symptoms suggestive of peripheral neuropathy (44/57) and/or autonomic dysfunction (39/57). Neuromuscular evaluation was completed in 51/57 patients. Abnormal sensory findings were present on examination in 20/51 (39%) patients. Based on clinical presentation, patients were referred for neurophysiological testing (11 patients completed testing), autonomic function testing (14 patients completed testing), and skin biopsies (16 patients completed testing). Axonal, demyelinating, or myopathic changes were not detected in any patients on neurophysiological testing. Six patients had abnormalities on autonomic testing that included postural tachycardia (4), transient-early-orthostatic hypotension (1), and parasympathetic abnormality/reduced heart-rate variability (1). Skin biopsies, completed in 16 symptomatic patients, were normal.
Conclusion: Symptoms suggestive of peripheral nerve and autonomic dysfunction associated with Long COVID-19 were reported in less than 10% of patients seen in a Long COVID-19 clinic. None of those patients referred for testing had objective findings of a peripheral neuropathy on nerve conduction studies or skin biopsy. Autonomic abnormalities were noted in a small subset of patients. Limitations include a single-tertiary referral center, with only symptomatic patients referred for evaluation, and only patients with salient symptoms receiving indicated tests. Despite these limitations, these findings do not support a high prevalence of autonomic dysfunction or peripheral neuropathy in Long COVID-19 patients.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

Poster #160

Pectus excavatum: a secondary cause of postural tachycardia or an associated condition?

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Objective: To characterize autonomic dysfunction and associated symptoms in patients with pectus excavatum planned to undergo Nuss procedure.
Background: Postural orthostatic tachycardia syndrome (POTS) is a common autonomic disorder that requires a thoughtful diagnostic evaluation to rule out secondary causes or mimics. Pectus excavatum (PE) is thought to be a sporadic disorder and is also associated with connective tissue disorders. Symptoms of PE including palpitations, exertional intolerance, syncope, and postural lightheadedness can mimic autonomic dysfunction. Characterization of autonomic signs and symptoms and results of autonomic testing in patients with PE have not been reported.
Methods: Patients diagnosed with PE at Mayo Clinic Arizona from 2019–2021 who described significant positional lightheadedness were evaluated with autonomic testing in addition to cardiac evaluations for pre-surgical planning. Those with abnormal autonomic testing were further evaluated in the autonomic neurology clinic.
Results: 36 patients with PE (12 male, 24 female) ages 15–55 (median age 24) were seen in the autonomic neurology clinic. 30/36 (85%) were diagnosed with excessive postural tachycardia, phenotypically resembling POTS based on autonomic testing and clinical symptoms, 8 with a neuropathic variant. 2/36 (6%) had findings of autonomic neuropathy with mild cardiac adrenergic impairment and 2/36 had findings of limited autonomic neuropathy with focal isolated impairment in sweat output. Composite Autonomic Scoring Scale (CASS) ranged 0–3 (median 1). 11 patients completed the COMPASS-31 questionnaire and total weighted scores ranged from 17.8–58.3 (average 42.7). Reduction in right ventricular outflow tract time velocity interval (RVOT TVI) from the supine to sitting/leaning forward position due to right ventricular compression ranged from 2.52–50.84%. Haller index ranged from 2.1–7.5 (median 3.61)

with ≥ 3.25 corresponding to severe PE. Of those with severe PE (n = 23), 18 (78%) had POTS.
Conclusion: Patients with PE have symptoms that may resemble autonomic impairment or may result from co-morbid autonomic dysfunction. Heterogeneous autonomic test findings were seen in PE patients. While the relationship between autonomic signs and symptoms and PE is at this point unclear, PE should be considered a possible POTS mimic. Further studies are necessary to establish whether potential autonomic signs and symptoms improve or resolve following definitive surgical correction.

Poster #161

Stroke volume and not blood pressure drives postural hyperventilation in disorders of orthostatic intolerance

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Background: While often considered in isolation, the chemoreflex and baroreflex are linked in control of blood pressure (BP), sympathetic nervous system activity and ventilation (V_E). For example, increasing BP decreases V_E, whereas decreasing BP increases V_E. However, postural hyperventilation with subsequent hypocapnia is evident in several disorders of orthostatic intolerance, including postural orthostatic tachycardia syndrome (POTS), in the absence of reduced BP, suggesting BP alone may not drive the ventilatory response.
Objective: We tested the hypothesis that reduced stroke volume (SV) contributes to postural hyperventilation in patients with POTS and orthostatic hypotension (OH).
Methods: To delineate the influence of SV vs. BP on postural hyperventilation, we performed an orthostatic challenge in 7 healthy volunteers (F = 7; 34 ± 7 years; normal SV&BP), 12 POTS patients (F = 12; 36 ± 6 years; drop in SV, normal BP), and 8 OH patients (F = 4; 62 ± 17 years; $p < 0.001$; drop in SV&BP). Breath-by-breath V_E and beat-to-beat hemodynamics (heart rate [HR], BP, SV, cardiac output [CO], and cerebral blood flow velocity [CBFv]) were measured throughout. Changes in V_E and hemodynamics between groups were compared using a one-way ANOVA with a Tukey's post-hoc comparison. Linear regressions were used to assess the relationship between V_E and hemodynamics.
Results: In response to an orthostatic challenge, POTS patients had a larger increase in ΔV_E compared to healthy volunteers (4.5 ± 2.6 vs. 1.9 ± 1.6 L/min; $p = 0.02$). ΔV_E in OH (3.1 ± 0.9 L/min) was not different from healthy ($p = 0.4$) or POTS ($p = 0.3$). OH patients had significantly larger drops in systolic BP (SBP) (− 26.2 ± 18.0 mmHg) compared to POTS (+ 8.6 ± 12.1 mmHg; $p < 0.001$) and Healthy (+ 13.2 ± 8.0 mmHg; $p < 0.001$). Regression analyses across groups showed that ΔV_E was inversely related to ΔSV ($r^2 = 0.33$; $p = 0.002$), whereas there was no relationship between ΔV_E and ΔSBP ($r^2 = 0.01$; $p = 0.12$). ΔV_E was also inversely related to ΔCBFv ($r^2 = 0.36$; $p = 0.002$), and directly related to ΔHR ($r^2 = 0.55$; $p < 0.001$).
Conclusion: These data suggest reduced SV and CBFv, and not SBP, may contribute to postural hyperventilation in patients with orthostatic intolerance. Reduced SV may predispose patients to reduced brain blood flow, stimulating a central ventilatory-baroreflex mechanism. More work is needed to better power the current study, and to explore central ventilatory-baroreflex mechanisms.
Funding: Canadian Institutes of Health Research (CIHR), Libin Cardiovascular Institute Post-Doctoral Fellowship in Women's Cardiovascular Health and the NSERC Brain CREATE Program (JB); CIHR Post-Doctoral Fellowship (AI); Alberta Support for People and Patient-Oriented Research Unit (SIR); Standing Up To POTS.

Poster #162

Hemodynamic consequences of hypocapnic hyperventilation in POTS

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Background: Postural orthostatic tachycardia syndrome (POTS) is a chronic form of orthostatic intolerance primarily affecting females of child-bearing age. Adults with POTS experience a heart rate (HR) increase of ≥ 30 bpm within 10 min of standing, in the absence of orthostatic hypotension (> 20/10 mmHg decrease in blood pressure [BP]) and is associated with chronic orthostatic symptoms. Patients also experience mild hyperventilation upon standing, which drives a small decrease in carbon dioxide (CO_2) in the blood (i.e., hypocapnia). In POTS, hypocapnia may exacerbate splanchnic hyperemia, and compromise venous return and stroke volume (SV).
Objective: We tested the hypothesis that hypocapnic hyperventilation reduces SV in POTS patients.
Methods: While supine, 10 POTS patients (36 ± 6 years) and 8 healthy controls (HC) (31 ± 9 years; $p = 0.1$) hyperventilated for 3-min to induce hypocapnia. Breath-by-breath respiratory (ventilation, ETO_2, $ETCO_2$) and beat-to-beat hemodynamics (HR, BP, SV, cardiac output [CO], and systemic vascular resistance [SVR]) were measured. Data are reported as mean ± SD. Continuous variables were compared using Student's t-tests. Linear regressions assessed the relationship between $ETCO_2$ and hemodynamics. An ANCOVA was used to test slope differences.
Results: Hypocapnia was similar in POTS and HC (− 13.2 ± 2.3 vs. − 14.8 ± 2.5 mmHg; $p = 0.2$). During hyperventilation, ΔHR was not different between groups (13.4 ± 6.5 vs. 12.7 ± 5.0 bpm; $p = 0.8$). However, ΔSV was significantly larger in POTS compared to HC (− 10.5 ± 7.6 vs. − 0.9 ± 3.3 mL; $p = 0.004$), ΔCO was lower (0.2 ± 0.6 vs. 0.9 ± 0.4 L/min; $p = 0.02$), and ΔSVR was lower (− 180.6 ± 192.7 vs. − 538.4 ± 207.0 dyne/s/cm^5; $p = 0.002$). In POTS and HC, regression analyses showed $\Delta ETCO_2$ was inversely related to ΔHR (POTS: $r^2 = 0.92$, $p < 0.001$; HC: $r^2 = 0.98$, $p < 0.001$) and ΔCO (POTS: $r^2 = 0.92$, $p < 0.001$; HC: $r^2 = 0.99$, $p < 0.001$), and $\Delta ETCO_2$ was directly related to ΔSVR (POTS: $r^2 = 0.72$, $p = 0.02$; HC: $r^2 = 0.96$, $p < 0.001$) and ΔSV in POTS only (POTS: $r^2 = 0.91$, $p < 0.001$; HC: $r^2 = 0.44$, $p = 0.1$). A slope comparison between groups showed ΔSV was significantly more sensitive to $\Delta ETCO_2$ ($p = 0.002$) in POTS, whereas the ΔCO was less sensitive to $\Delta ETCO_2$ ($p = 0.003$).
Conclusion: Hypocapnic hyperventilation may compromise venous return in POTS resulting in significantly reduced SV and lower CO, with comparable increases in HR. Future studies are needed to parse out the effects of ventilation vs. $ETCO_2$ on the observed changes.
Funding: Canadian Institutes of Health Research (CIHR), Libin Cardiovascular Institute Post-Doctoral Fellowship in Women's Cardiovascular Health and the NSERC Brain CREATE Program (JB); CIHR Post-Doctoral Fellowship (AI); Alberta Support for People and Patient-Oriented Research Unit (SIR); Standing Up To POTS.

Poster #164

Evaluation of waist-high compression garment use in patients with postural orthostatic tachycardia syndrome in a community setting

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Background: Postural orthostatic tachycardia syndrome (POTS) is a common form of orthostatic intolerance. POTS patients have excessive tachycardia, and debilitating symptoms, when upright. Compression garments are a non-pharmacological treatment. We have previously demonstrated a reduction in heart rate (HR) and symptoms with body compression in an acute laboratory setting, using a proof-of-principle waist-high compression garment (WHC). We sought to determine the effectiveness of commercially available WHC in a community setting (real-life environment). We evaluated acute response to compression, and response after several hours to determine if benefits are sustained over time.
Methods: POTS patients completed 4 × 10 min standing tests with WHC (ON) and without WHC (OFF), in the morning (AM; acute effects) and afternoon after several hours of use (PM; sustained effects) on one study day (Test 1: AM-OFF, Test 2: AM-ON, Test 3: PM-ON, Test 4: PM-OFF). Test 4 was included as a PM baseline due to diurnal HR variability. A Holter monitor was provided to record HR, and participants reported Vanderbilt Orthostatic Symptom Scores (VOSS). Data are presented as mean ± standard error and paired t-tests were used for comparisons.
Results: This study is ongoing, with 14 female participants enrolled thus far (mean age: 35 ± 2 years). Prescription WHC was used by 11 participants (10–40 mmHg) and 3 participants used athletic-style WHC. Delta HR (supine to standing) was significantly reduced after 30 min of WHC use, compared to baseline without WHC (AM-ON: 26 ± 3 bpm vs. AM-OFF: 39 ± 4 bpm, $p < 0.001$). After removing the WHC after 3 + hours of use (PM-OFF), HR significantly increased compared to while wearing the WHC (PM-ON; 31 ± 4 bpm vs. 22 ± 3 bpm, $p = 0.007$). VOSS symptoms were significantly reduced after 30 min of WHC use, compared to no WHC (AM-ON: 26 ± 3 vs. AM-OFF: 35 ± 6, $p = 0.007$). After removing the WHC (PM-OFF), there was a significant worsening in VOSS symptoms compared to PM-ON (30 ± 5 vs. 24 ± 3, $p = 0.04$).
Conclusions: This simple non-pharmacological treatment is effective in a community setting with commercially available waist-high compression garments. Orthostatic tachycardia and symptoms were reduced in patients with POTS both acutely and over several hours. This builds on the prior proof-of-principle data.

Poster #165

Patient-reported severity of disease in postural orthostatic tachycardia syndrome and neurogenic orthostatic hypotension

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Background: Patients with neurogenic orthostatic hypotension (nOH) are severely disabled due to their inability to maintain upright blood pressure. Patients with postural orthostatic tachycardia syndrome (POTS) present with similar chronic orthostatic intolerance symptoms despite normal autonomic reflex function. Considering that there is limited research directly comparing the level of disability between these disorders, we determined the differences in symptoms and activities of daily living (ADLs) between POTS and nOH patients evaluated in our center using a standardized survey.
Methods: Observational cross-sectional study, the cohort was comprised of 89 patients (50 POTS and 39 nOH) enrolled in the Vanderbilt Phenotyping Autonomic Study. Patients with Parkinson's disease, multiple system atrophy, or dementia with Lewy bodies were excluded. Demographics, autonomic function testing, symptom assessment, and ability to perform activities of daily living were collected in custom-designed case report forms using Research Electronic Data Capture (REDCap). Data was analyzed using system-based symptom approaches and group analyses were performed using Student's t-tests and chi-squared tests.
Results: As expected, POTS patients were younger than nOH patients (30 ± 8 vs. 59 ± 17 years, $p < 0.001$) and were predominantly women (98% female). Significantly, POTS patients do not suffer from orthostatic hypotension, whereas patients with nOH experience a systolic blood pressure decrease of more than 30 mmHg upon standing. Nonetheless, POTS patients experienced significantly more orthostatic intolerance symptoms (44% vs. 24%, $p = 0.01$) and had a similar amount of difficulty performing ADLs (36% vs. 22%, $p = 0.26$) when compared with nOH patients. With regards to system-based assessment, both groups had similar neurological motor symptoms (20% vs. 18%, $p = 0.42$). However, POTS patients had worse neurocognitive symptoms (33% vs. 24%, $p = 0.04$) and significantly more joint hypermobility (13% vs. 3.7%, $p = 0.04$) compared with nOH.
Conclusions: Despite nOH patients being much older and having a significant fall in blood pressure upon standing, POTS patients had significantly worse symptoms in all system-based assessments, including orthostatic intolerance, musculoskeletal, and neurocognitive symptoms. Due to these symptoms, the younger POTS patients and older nOH patients experience a similar amount of difficulty executing activities of daily living.

Poster #166

Autonomic symptoms and postural orthostatic tachycardia syndrome in patients with joint hypermobility disorders

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Introduction: Orthostatic intolerance syndromes are common in patients with joint hypermobility disorders. Previous studies were limited by assessment and case definition variability of joint hypermobility disorders, and the lack of appropriate controls. We aim to determine the association of autonomic symptoms (AS) and postural orthostatic tachycardia syndrome (POTS) with hypermobile Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorder (HSD).
Methods: A total of 793 patients were evaluated at a multidisciplinary EDS clinic, and a diagnosis of hEDS, HSD, or neither (control) was determined by the same physician. All patients completed a pre-evaluation self-reported questionnaire that included questions about AS and previous evaluation for POTS. Fischer's exact tests were used to evaluate differences between either hEDS and HSD versus controls in the prevalence of AS and POTS. More granular multivariate analyses will be conducted.

Results: Of 793 patients, 194 (24.5%) had hEDS, 459 (57.9%) had HSD, and 134 (16.9%) had neither (controls). In each group, patients were predominantly female (88.7%, 95.4% and 85.8%, respectively), white (95.4%, 96.5% and 92.5%, respectively), and young (mean ages 34.6, 34.6 and 39.1 years, respectively). Compared to controls, patients with hEDS had more AS: postural dizziness (89.7% vs. 78.4%, P = 0.004), palpitations (84.6% vs. 69.4%, P = 0.001), and syncope (45.6% vs. 30.6%, P = 0.004). Compared to controls, patients with HSD also had more AS: postural dizziness (86.7% vs. 78.4%, P = 0.03), palpitations (80.8% vs. 69.4%, P = 0.008), and syncope (39.2% vs. 30.6%, P = 0.04). The proportion of patients previously diagnosed with POTS were 23.2% in the control group, 26.9% in the hEDS group (P = 0.5 compared to controls), and 26.1% in the HSD group (P = 0.5 compared to controls).
Conclusion: At our comprehensive EDS clinic, AS were more prevalent in patients diagnosed with hEDS or HSD than in those who did not meet the criteria for a joint hypermobility disorder. These differences were statistically significant. However, there appears to be no difference in the prevalence of POTS between either hEDS or HSD cases and controls.
Research authorization: This study was approved by the Mayo Clinic Institutional Review Board (IRB # 19-011260).

Poster #167

Postural orthostatic tachycardia syndrome after mRNA COVID-19 vaccine

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Purpose: To report the clinical characteristics and autonomic testing results of a case series of patients who developed postural orthostatic tachycardia syndrome (POTS) after receiving the mRNA COVID-19 vaccine.
Methods: We conducted a retrospective review of all patients with confirmed POTS after receiving the mRNA COVID-19 vaccine.
Results: We identified 5 patients; age ranged from 17 to 47 years, time to develop symptoms after receiving the mRNA COVID-19 vaccine ranged from 7 to 21 days, with a median of 14 days. Head up tilt table (HUTT) test showed orthostatic tachycardia without OH, consistent with a diagnosis of POTS, heart rate changes ranged from + 38 to + 75 mmHg with a median of + 53, and systolic blood pressure changes ranged from + 13 to + 30 mmHg with a median of + 16. All patients had symptoms of orthostatic intolerance during HUTT.
Conclusion: Rare cases of POTS can occur after receiving the mRNA COVID-19 vaccine and should not discourage people from receiving the appropriate vaccination.

Poster #168

A novel real-time magnetic resonance imaging approach to study orthostatic intolerance mechanisms in patients with hypermobile Ehlers-Danlos syndrome

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Background: Patients diagnosed with the hypermobile Ehlers-Danlos syndrome often experience orthostatic intolerance, particularly the postural tachycardia syndrome (POTS). To discern hemodynamic mechanisms limiting orthostatic tolerance in these patients, we applied a novel approach combining real-time magnetic resonance imaging (MRI), physiological monitoring, and orthostatic testing through lower body negative pressure (LBNP).
Materials and Methods: We recruited 9 women with hypermobile Ehlers-Danlos syndrome and POTS (33 ± 7 years; 22.5 ± 4.8 kg/m^2) and 5 matched healthy controls (35 ± 10 years; 23.8 ± 3 kg/m^2). One patient with pure autonomic failure (PAF) served as positive control. We performed real-time cardiac MRI without and during − 30 mmHg LBNP with 33 ms temporal resolution to measure stroke volume in the ascending aorta and venous flow in the inferior vena cava. We recorded brachial blood pressure, beat-to-beat finger arterial blood pressure, ECG, and respiration.
Results: LBNP increased heart rate by 24.7 ± 10.9 bpm in patients and by 8.2 ± 6.7 bpm in control persons ($p < 0.01$). Blood pressure did not change significantly in either group. Cardiac stroke volume decreased 24.3 ± 6.6 ml in patients and 19.7 ± 7.2 ml in control persons (p = 0.079). However, cardiac output responded similarly in both groups. With LBNP, inferior vena cava flow decreased 688 ± 25 ml/min (n = 4) in patients and 510 ± 42 ml/min in control persons. Middle cerebral artery blood flow remained unchanged during LBNP, only the right side showed a reduced peak velocity (p = 0.027). In the patient with PAF, blood pressure decreased from 118/74 to 58/35 mmHg with LBNP, heart rate remained unchanged, stroke volume decreased 45%, and middle cerebral artery blood flow decreased 0.06 ± 0.01 l/min during LBNP.
Conclusion: Combination of cardiac real-time MRI and LBNP is a feasible approach to study hemodynamic mechanisms contributing to orthostatic intolerance in patients. The unobtrusive nature of the test, which does not require breath-holding or ECG triggering, and the ability to measure absolute vascular flow are distinct advantages.

Poster #169

Headache characteristics and subspecialty evaluation in pediatric patients with postural tachycardia syndrome

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Objective: To identify common headache characteristics in pediatric patients diagnosed with postural tachycardia syndrome (PoTS), and to identify opportunities for more precise documentation criteria to facilitate treatment and referral in both primary care and subspecialty settings.
Introduction: Headache is a common comorbidity in patients with PoTS and a common diagnosis in pediatric neurology. While prior authors have proposed a possible pathophysiologic overlap between the two clinical conditions, few reports have systematically evaluated features of headache in pediatric patients with PoTS, and the incidence of ICHD-3 based primary headache diagnoses has not been described.

Materials and Methods: In this retrospective study, we reviewed the medical charts of 42 patients aged 18 years and under who had been diagnosed with PoTS via tilt table testing. Patients with a documented history of headache, migraine, or positional headache at the time of testing were identified. Additional clinical notes were then reviewed to determine if patients met criteria for a primary headache disorder based on the International Classification of Headache Disorders 3rd Edition (ICHD-3).
Results: Forty-two patients between ages 9 and 18 were identified meeting diagnostic criteria for PoTS. Of these 42 patients, 78% (33) had a documented history of headache. Only 12 of these 33 had undergone a dedicated headache evaluation by a neurologist at the time of autonomic laboratory testing. An additional 6 patients had full or partial headache histories either as part of the clinical autonomic visit or at a later clinic visit. Of the 18 patients with documented headache histories, only 4 included sufficient information to determine whether the patient met ICHD-3 criteria for a primary headache disorder.
Discussion: Headaches are an extremely common finding in children and adolescents with PoTS. Despite the high prevalence, a majority of patients with headache and PoTS are not evaluated by a neurologist or headache specialist, and most do not have sufficient clinical information documented to meet criteria for a primary headache disorder. These data highlight the need for awareness of headache in this patient population, and indicate a potential role for dedicated headache evaluations in pediatric PoTS.

Poster #170

Asymptomatic postural orthostatic tachycardia syndrome incidentally detected in tilt table test

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Postural orthostatic tachycardia syndrome (POTS) is an autonomic disorder associated with orthostatic tachycardia and various systemic symptoms. Standardized continuous monitoring of blood pressure and pulse rate using a tilt table helps objective diagnosis of POTS, but often exhibits incidental postural tachycardia without apparent clinical symptoms of POTS. The purpose of this study is to identify the difference between clinical and incidental POTS and find out the clinical implications of incidental POTS. We retrospectively reviewed patients who underwent an autonomic function test (AFT) at Samsung Medical Center, from January 2016 to March 2022. AFT results were analyzed in patients with an increased heart rate over 30 on tilt. The composite autonomic symptom score 31 (COMPASS-31) questionnaire was used to collect symptoms of autonomic dysfunction. Patients with orthostatic intolerance were classified as "Clinical POTS" and as "incidental POTS" who were not. Among 126 patients who showed postural tachycardia, 65 (51.6%) patients were female and the mean age was 31.08 ± 12.5. One hundred and seven patients answered COMPASS-31 and 89 patients had orthostatic intolerance while 18 did not. Underlying or causative diseases such as Parkinson's disease, multiple systemic atrophy, or peripheral neuropathies were found in 26 (20.6%) patients. Incidental POTS patients showed male predominance (72.2% vs. 44.9%, p = 0.035). Maximal heart rate increment or composite autonomic scoring score (CASS) were not different between two groups. The decrement of pulse pressure during tilt was significantly lower in incidental POTS (11.19 ± 6.26 vs. 7.67 ± 7.81, p = 0.039). In incidental POTS, underlying diseases were more frequent (33.3% vs. 18.0%, p = 0.142) and the incidence of syncope events was lower (11.1% vs. 32.6%, p = 0.067) than those in clinical POTS. Though the female predominance is well known in POTS, AFT demonstrates incidental POTS more frequently in males. Incidentally detected POTS did not differ significantly in autonomic function test from clinical POTS even though they do not have any orthostatic symptom, suggesting that accurate diagnosis of POTS requires careful clinical evaluation and follow-up study.

Poster #172

Cutaneous phosphorylated alpha-synuclein deposition may predict prognosis in POTS patients

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Background: In 2020, we reported 22 patients with suspected neuropathic POTS who had skin biopsies to evaluate intra-epidermal nerve fiber density (IENFD) and detection of phosphorylated alpha-synuclein (P-SYN). Thirteen were normal, and 8/22 had either small fiber neuropathy 2/22, P-SYN detection (3/22) or both (4/22). The patients with P-SYN were more likely to be male, have symptoms suggestive of REM sleep behavioral disorder, and documented gastroparesis.
Objective: To follow up this cohort of patients to determine if decreased IENFD or p-syn deposition correlated with disease progression.
Methods: All patients were seen in the Honor Health Neurology department and enrolled in the multidisciplinary POTS clinic after the diagnosis of POTS was confirmed. We retrospectively reviewed the patient's charts an average of 22 months from the date of the skin biopsy (range 14–29 months). Patients were considered to have improved if there was a clear improvement in ADLs, work capacity, or reduction in pharmacologic treatments for POTS. Patients were considered to have worsened if they had documentation of new autonomic symptoms, or a requirement for increased medication for treatment of POTS, or decreased ADLs. Patients not falling into these groups were considered stable.
Results: Of the 13 patients with normal IENFD and no p-syn accumulation, 11 improved while 2 worsened. The two patients with reduced IENFD but no p-syn deposition also improved. Of the 4 patients with p-syn deposition and reduced IENFD, all worsened. Of the 3 patients with abnormal p-syn deposition but normal IENFD, 2 worsened during and one remained stable.
Conclusions: Evidence of cutaneous phosphorylated alpha-synuclein in people with POTS was associated with disease burden at follow up. Determination as to whether P-SYN deposition is indicative of a progressive autonomic disorder will require larger prospective studies with a longer duration of follow up.

Poster #173

Autonomic cardiovascular control following 30 days strict head down tilt bedrest with six hours of daily lower body negative pressure training

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Background: Autonomic cardiovascular regulation is impaired both after bedrest and after space flight. Impaired autonomic control likely limits cardiovascular adaptation to physiological stresses such as standing. We hypothesized that 6 h daily lower body negative pressure (LBNP) helps maintain heart rate (HR), heart rate variability (HRV) and baroreflex sensitivity (BRS) following strict head-down tilt bedrest, an established terrestrial space-analogue.
Methods: We included 23 healthy persons (12 women, 34.5 ± 9 years, 23.9 ± 2.8 kg/m^2) in the 30 days SANS_CM strict head down tilt bedrest study. Subjects were randomly assigned to 6 h daily LBNP training with moderate intensity (LBNP, − 25 mmHg) or 6 h daily sitting (seated, positive control). We measured HR and finger blood pressure before bedrest and at the end of bedrest during head-up tilt testing. We assessed HRV in the time and frequency domains, systolic blood pressure variability in the low frequency range (LF-SBP), and baroreflex sensitivity using cross spectral analysis (BRS-LF). We analyzed stationary time series during the last 5 min supine and during minutes 2–6 at 80 degrees head-up tilt.
Results: Supine HR increased during bedrest (LBNP group: 67 ± 9 vs. 74 ± 11; seated: 66 ± 10 vs. 71 ± 12 bpm; $p < 0.001$) and the orthostatic HR response was enhanced (HR upright: 90 ± 10 vs. 112 ± 13 bpm; 86 ± 12 vs. 109 ± 13 bpm; $p < 0.0001$). HRV in the time domain was reduced after bedrest while supine (rmssd: 37 ± 24 vs. 27 ± 14 ms; 50 ± 44 vs. 30 ± 20 ms; $p < 0.017$) and upright (15 ± 5 vs. 8 ± 4 ms and 28 ± 21 vs. 14 ± 10 ms; $p < 0.001$). HRV in the frequency domain (total power, LF- and HF power) tended to decrease while supine and standing but the bedrest effect did not reach significance. Supine and upright LF/HF ratios did not differ after bedrest. The tilt induced increase of LF-SBP tended to be enhanced after bedrest ($p = 0.0547$). Baroreflex mediated vagal HR control was reduced after bedrest at rest ($p = 0.011$) and during tilt ($p < 0.0001$). No interactions between groups and conditions were detected.
Conclusions: Six hours of daily moderate intensity LBNP training or seating do not completely preserve autonomic cardiovascular autonomic control during 30 days strict head-down tilt bedrest. Additional countermeasures, such as physical exercise, may be required.

Poster #174

Effects of Q-Collar on hypoxic cerebral blood flow velocity in postural orthostatic tachycardia syndrome (POTS)

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Background: Postural orthostatic tachycardia syndrome (POTS) is associated with orthostatic symptoms including increased ventilation. Nardone et al. found that POTS patients wearing a Q-Collar (Q30 Innovations) exhibited reduced respiratory rate and orthostatic symptoms. This may be due to the compression of the jugular veins or the carotid chemoreceptors (or both) in the neck which may influence cerebral blood flow (CBF) and ventilation.
Objective: We aimed to 1) evaluate the effects of a Q-Collar on CBF velocity (CBF_V) during hypoxia in POTS patients, and 2) determine whether previously observed reductions in respiratory rate while wearing a Q-Collar were due to changes in carotid chemoreflex sensitivity. We hypothesized that wearing a Q-Collar would increase CBF_V in POTS and reduce ventilation in response to hypoxia.
Methods: Preliminary data are presented from 6 out of a target 15 POTS patients. Six female patients (36 ± 9 years) inspired air with end-tidal O_2 (ETO_2) ramping down to 50 mmHg with constant end-tidal CO_2 ($ETCO_2$). The test was repeated with the Q-Collar (QC) and without the Q-Collar (noQC). Ventilatory parameters (ventilation, ETO_2 and $ETCO_2$) and middle cerebral artery CBF_V were assessed throughout. Data are reported as mean ± SD. Paired t-tests were used to assess the influence of the Q-Collar on the CBF_V and ventilatory responses to hypoxia.
Results: The CBF_V response to hypoxia was greater with Q-Collar compared to no Q-Collar (+ 3.1 ± 3.0 cm/s vs. − 2.6 ± 3.2 cm/s; $p = 0.003$). The ventilatory response to hypoxia was not different between patients with the Q-Collar and patients without the Q-Collar (− 0.06 ± 0.10 L/min/mmHg vs. − 0.10 ± 0.06 L/min/mmHg; $p = 0.4$).
Conclusion: The compound effect of breathing hypoxic gas and wearing the Q-Collar increases CBF_V. The hypoxic gas intervention alone may not be sufficient to illicit an increase in CBF_V. However, Q-Collar compression of the neck may result in additional hypoxic blood in the brain. The cumulated hypoxia may be enough to initiate a compensatory increase in CBF. Our preliminary data show no significant influence of the Q-Collar on the ventilatory responses, suggesting that it does not alter chemoreflex sensitivity. Additional participants are required to increase statistical power.
Funding: Stand Up to POTS Libin BRAIN CREATE Studentship (NSERC)—graduate studentship; AbSPORU Patient-oriented Research Studentship (Alberta Innovates)—graduate studentship.

Poster #175

Effects of hypocarbia on heart rate in patients with postural orthostatic tachycardia syndrome (POTS): a systematic review

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Background: Postural orthostatic tachycardia syndrome (POTS) is a chronic form of orthostatic intolerance defined by an excessive upright increase in heart rate (HR) of ≥ 30 bpm, in the absence of orthostatic hypotension. POTS is associated with orthostatic symptoms including hyperventilation in the form of hyperpnea. Hyperventilation reduces arterial carbon dioxide (CO_2; hypocarbia). Currently, available studies in POTS only report changes in end-tidal (ET) CO_2 concurrent with changes in HR upon assumption of an upright posture via head-up tilt tests (HUT). These studies have not investigated how $ETCO_2$ and HR relate to each other. The concept of CO_2 impacting cardiovascular hemodynamics has not been systematically reviewed.

Objective: We conducted a systematic review of the effect of hypocarbia on HR in patients with POTS.
Methods: Studies were identified from databases (MEDLINE and EMBASE) without language restriction from inception to June 1, 2022. All studies reporting HR outcomes associated with acute hypocarbia (≥ -5 mmHg $ETCO_2$) in POTS patients were selected for review. A Mann–Whitney U test (two-tailed) was used to compare the mean reduction in $ETCO_2$ during HUT between the POTS and healthy control (HC) groups. Data are reported as mean ± SD. A Spearman's correlation test was performed to assess the relationship between $ETCO_2$ and HR overall and within the individual groups.
Results: Nine studies met inclusion criteria (n = 340, 54% POTS). Mean reduction in $ETCO_2$ during HUT was significantly greater in POTS compared to HC (-9.2 ± 3.4 mmHg vs. -2.4 ± 0.8 mmHg; $p < 0.0001$). Overall, there was an inverse relationship between $ETCO_2$ and HR (slope = -2.7 bpm/mmHg, $r_S = -0.8$, $p < 0.0001$), but not within the individual groups.
Conclusion: Our results suggest a strong negative correlation between $ETCO_2$ and HR overall, but not in specific groups. HR response to hypocarbia may be confounded by the HR increase associated with HUT. Mechanistic investigations of hypocarbia interventions are necessary to isolate and clearly identify the effects of hypocarbia on HR in patients with POTS.
Funding: Standing Up to POTS, Libin BRAIN CREATE Studentship (NSERC)—Graduate Studentship AbSPORU POR Studentship (Alberta Innovates)—Graduate Studentship.

Poster #176

POTS & PANTS: improving cerebral perfusion using lower body compression in patients with postural tachycardia syndrome (POTS) is independent of heart rate

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Background: Many symptoms of orthostatic intolerance (such as brain fog and light-headedness) are thought to be related to cerebral hypoperfusion. Evidence for this is limited and often inferred only from abnormal systemic hemodynamic responses to orthostatic stress. Lower body compression significantly reduces postural tachycardia and improves stroke volume (SV), but its impact on cerebral blood flow in POTS is unclear. We therefore assessed the impact of inflating military anti-shock trousers (MAST) during 80° head-up tilt (HUT) to determine which hemodynamic parameters, if any, correlate with changes in cerebral perfusion.
Methods: Data from 30 POTS patients (28 women; mean age 25.5) evaluated between 2008 and 2020 were reviewed. EKG, finger BP and right middle cerebral artery (MCA) cerebral blood velocity (CBV) were continuously recorded. Beat-to-beat measurements of SV and cardiac output (CO) were derived using Modelflo. Cerebrovascular resistance (CVR) was calculated after correcting for hydrostatic pressure. Two-minute averages of all parameters were made before and during HUT (minute 1–3; before MAST inflation to 40–50 mmHg; final 2 min of MAST inflation). Main effects were evaluated with repeated measures ANOVA, correlations with Spearman tests and interactions modeled using stepwise linear regression.
Results: During HUT, heart rate (HR) increased by a mean of 53.3 bpm (95%CI 47.8–58.2 bpm), mean CBV decreased to 81.1% (95%CI 76.1–86.1%) of baseline. MAST inflation halved HR and increased mean CBV to 89.1% (95%CI 85.1–93.1%) of baseline. CVR did not change from baseline values either during HUT or MAST inflation. Changes in mean CBV during HUT or MAST inflation were not predicted by changes in HR, SV, or CO using stepwise linear regression. Spearman's test revealed a weak correlation only between changes in mean CBV and CO during HUT before (rho = 0.46, 95%CI 0.1–0.71) and during MAST inflation (rho = 0.55, 95%CI 0.23–0.77).
Conclusion: Lower body compression substantially reduced postural tachycardia but only caused a small improvement in CBV and had no effect on CVR. The effect on CBV could not be reliably predicted by changes in any hemodynamic parameter measured. Our findings suggest that therapeutic strategies aimed directly at reducing the heart rate may not impact cerebral perfusion in POTS.

Poster #177

POTS & PANTS: cardiac output during orthostatic stress in individuals with postural tachycardia syndrome (POTS)—moving away from the focus on heart rate

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Background: Although exaggerated heart rate (HR) without blood pressure (BP) decline is the cardinal feature of POTS, the role of HR in maintaining cardiac output (CO) during orthostatic stress is questionable. Consequently, pharmacologic strategies aimed at reducing the HR of POTS patients to "normal" values are often of limited efficacy. We therefore studied the hemodynamic responses of patients with POTS during 80° head-up tilt (HUT) before and during partial restoration of central volume by leg compression with military anti-shock trousers (MAST).
Methods: Data from 30 POTS patients (28 women; mean age 25.5) evaluated between 2008 and 2020 were reviewed. EKG and finger BP were continuously recorded. Beat-to-beat measurements of stroke volume (SV) and CO were derived using Modelflo. Two-minute averages of hemodynamic parameters were made before and during HUT (minute 1–3; before MAST inflation to 40–50 mmHg; final 2 min of MAST inflation). Main effects were evaluated with repeated measures ANOVA, correlations with Pearson and Spearman tests and interactions modeled using stepwise linear regression.
Results: During HUT, baseline HR (77.7 bpm) increased by 53.0 bpm (95%CI 47.8–58.2 bpm), while SV decreased to 50.3% (95%CI 46.8–53.8%) of baseline. CO decreased to 84.9% (95%CI 78.9–90.9%) of baseline. During MAST inflation, HR partially recovered to 26.6 bpm (95%CI 21.5–31.8 bpm) above baseline while SV returned to 70.5% (95%CI 66.1–75.0%) and CO nearly normalized to 94.5% (95%CI 88.5–100.4%). SV and HR both contributed similarly to CO while supine (SV $R^2 = 0.480$; HR improved the model to $R^2 = 0.988$). During HUT, the decline in CO was primarily due to a decline in SV ($R^2 = 0.811$), the model only slightly improved with the addition of HR ($R^2 = 0.988$). Only when central volume was partially restored by MAST inflation was the HR contribution to CO again apparent (SV $R^2 = 0.672$; combined SV and HR $R^2 = 0.982$).
Conclusion: As expected, while supine, SV and HR contribute nearly equally to CO. During orthostatic stress, however, large HR increases contribute little to maintaining CO. Only when central volume was partially restored did slower HR play a small role in maintaining CO. "The heart cannot pump blood that it does not receive" (Wieling et al. 2014).

Poster #178

Baroreflex sensitivity and sympatho-vagal function in postural orthostatic tachycardia syndrome

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Background: Postural orthostatic tachycardia syndrome (POTS) is characterized by an exaggerated increase in heart rate while standing and is associated with symptoms of lightheadedness and fatigue. However, its pathophysiology has not yet been fully elucidated. Also, there are few clinical indicators of severity and prognosis in patients with POTS. A recent study suggested that the phase 2 pressor response of the Valsalva maneuver is blunted in neuropathic POTS.
Aim: We evaluated the association between indices of baroreceptor reflex, blood pressure variability, heart rate variability, and symptoms during orthostatic testing in patients with POTS.
Subjects and Methods: Nine POTS patients (23 ± 10 years old, eight females) were evaluated for baseline cardiovascular autonomic functions, orthostatic hemodynamics, and plasma catecholamines during 60 degrees of head-up tilt test (HUT). Baroreceptor sensitivity (BRS) was measured by sequential method (Tonam2C ver. 1.044, Suwa Trust Ltd) in a quiet supine position.
Results: We found baseline plasma epinephrine and Valsalva ratio correlated well ($R^2 = 0.68$, $p = 0.01$). Valsalva ratio and heart rate increases during the HUT were positively correlated ($R^2 = 0.63$, $p = 0.01$). The BRS and Valsalva ratios of symptomatic patients during the HUT tend to be higher than those of asymptomatic patients (9.4 ± 0.2 ms/mmHg vs. 8.8 ± 13.6 ms/mmHg, n.s. 1.61 vs. 1.51, n.s.). Indices of heart rate variability, blood pressure variability, and plasma catecholamine levels were not correlated to BRS.
Conclusion: In this study, POTS patients with more significant heart rate increases during HUT also showed a more elevated Valsalva ratio. It might suggest that patients with higher orthostatic tachycardia could have higher sympathetic and parasympathetic nervous activity. Future studies are planned to evaluate hemodynamics and symptoms by clinical subtype of POTS.

Poster #179

Long lasting changes in symptoms and autonomic profile after 14-day tVNS in hyperadrenergic postural orthostatic tachycardia syndrome (POTS)

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Background: Sympathetic over-activity and reduced cardiac vagal modulation underlie most of the symptoms in postural orthostatic tachycardia syndrome (POTS) with hyperadrenergic phenotypes. We previously showed that 14-day transcutaneous vagus nerve stimulation (tVNS) enhanced cardiac vagal modulation and improved dysautonomia symptoms. However, it is unknown whether tVNS effects persist after stopping treatment.
Aim: To evaluate the changes in dysautonomia symptoms, cardiac autonomic profile and post-ganglionic sympathetic nerve activity from baseline, after chronic tVNS, and after 1-month of tVNS cessation (Washout), in hyperadrenergic POTS.
Methods: Sixteen hyperadrenergic (upright plasma norepinephrine > 600 pg/ml; supine $HF_{RR} < 200\ ms^2$) POTS patients (15 F, age 43.1 ± 3 yrs) were evaluated before intervention (Pre-tVNS), after chronic tVNS applied to right ear for 4 h/day for 14 days (Post-tVNS), and after Washout. COMPASS31 questionnaire (range 0–100) assessed autonomic symptoms. ECG, blood pressure, respiratory activity, and muscle sympathetic nerve activity (MSNA) were continuously recorded while supine and during a stepwise increased head-up tilt (HUT), till 75°. Autoregressive spectral analysis of heart period variability provided the cardiac vagal modulation index (high frequency power, HF).
Results: Significant changes ($P < 0.05$) were seen from Pre-tVNS to Post-tVNS, and from Post-tVNS to Washout in COMPASS31 total symptom score (52.9 ± 3.8 vs. 30.3 ± 3.3 vs. 48.6 ± 4.0), orthostatic intolerance (28.8 ± 2.4 vs. 14.8 ± 2.5 vs. 25.0 ± 2.9), and gastrointestinal domains (9.5 ± 0.8 vs. 5.0 ± 0.9 vs. 9.8 ± 1.1). Significant ($P < 0.05$) MSNA burst rate decrease was seen from Pre-tVNS to Post-tVNS both in supine and during HUT (30.4 ± 3.7 vs 18.6 ± 1.4; 38.4 ± 4.4 vs 24.4 ± 2.2 bursts/min, respectively). Washout MSNA was reduced compared to pre-tVNS only during HUT (38.4 ± 0.4.4 vs 20.6 ± 2.9 burst/min, $P < 0.05$). HF_{RR} increased significantly ($P < 0.05$) from Pre-tVNS to Post-tVNS while supine and during HUT (127.6 ± 13.9 vs 183.6 ± 28.3; 18.6 ± 5.7 vs 26.5 ± 9.2 $msec^2$, respectively). There was a significant ($P < 0.05$) further increase in HF_{RR} during Washout (supine 211.3 ± 29.5, HUT 41.0 ± 8.3 $msec^2$) compared to pre-tVNS.
Conclusion: Results suggested an enhanced cardiac vagal modulation and reduced sympathetic neural discharge to vessels, which persisted over 4 weeks after tVNS cessation. However, symptoms intensity returned to those seen Pre-tVNS. The latter possibly indicate the persistence of central sensitization and associated distorted symptoms sensation, which are likely to be overcome only by a longer-lasting and periodical tVNS.
Funding: Funded by Dysautonomia International Grant (IRB-ID 986).

Poster #180

Autonomic profiles and symptoms of hyperadrenergic versus non-hyperadrenergic POTS patients and their response to chronic tVNS

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Background: Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous disorder with several underlying etiologies not fully understood at present. In hyperadrenergic POTS, transcutaneous vagus nerve stimulation (tVNS) rebalanced the autonomic profile and improved symptoms. Differences in tVNS response between POTS subtypes have not yet been investigated.
Aim: To compare the autonomic profile and symptoms severity of hyperadrenergic and non-hyperadrenergic POTS patients and assess their responses to tVNS.
Methods: Fifty-eight POTS patients underwent chronic tVNS (4 h/day for 14 days). ECG, beat-to-beat blood pressure, respiratory activity, and muscle sympathetic nerve activity (MSNA) were continuously recorded while supine and during a stepwise 75° head-up tilt (HUT), before and after tVNS. Spectrum analysis of RR variability provided the index HF_{RR} evaluating cardiovagal modulation. COMPASS-31 questionnaire (range 0–100) assessed autonomic symptoms. The criteria of $HF_{RR} < 200mec^2$ was used to separate 25 hyperadrenergic (age 40 ± 12 years, F = 23) from 33 non-hyperadrenergic patients ($HF_{RR} > 200ms^2$; age 32 ± 11 years, F = 27).
Results: At baseline, hyperadrenergic patients had higher ($P < 0.05$) heart rate (81.8 ± 3 vs. 69.8 ± 1.5 b/min in supine; 122.9 ± 3.9 vs. 110.3 ± 3 b/min in HUT) and MSNA (31.5 ± 2.8 vs. 24.2 ± 2.2 bursts/min in supine; 41.1 ± 3.5 vs. 32.0 ± 2.1 bursts/min in HUT) than non-hyperadrenergic patients. While supine, tVNS reduced ($P < 0.05$) MSNA from 31 ± 2.8 to 20 ± 1.7 bursts/min and increased HF_{RR} from 109.7 ± 12.6 to 168.1 ± 22.2 $msec^2$ in hyperadrenergics. Non-hyperadrenergics showed a similar trend in MSNA and HF_{RR}. tVNS reduced upright MSNA in both groups ($p < 0.05$) but the reduction was greater in hyperadrenergics (Δ− 16 ± 4.3 vs. Δ− 7 ± 3.5 bursts/min; $P < 0.05$). tVNS improved ($p < 0.05$) the total score of the COMPASS-31 questionnaire in both hyperadrenergic (Δ− 18 ± 3.3 from 53 ± 3.8) and non-hyperadrenergic (Δ− 17 ± 2.7 from 51 ± 2.3) groups.
Conclusions: Before tVNS, the hyperadrenergic group had lower cardiovagal and greater cardiovascular sympathetic modulation. Symptom severity was similar in the two groups. In the hyperadrenergics, tVNS significantly enhanced cardiac vagal modulation and reduced overall cardiovascular sympathetic activity. There was a similar but not significant trend in the non-hyperadrenergics. Both groups improved symptoms. This suggests that tVNS may influence cortical perception of symptoms, irrespective of the underlying hyperadrenergic state.
Funding: Funded by Dysautonomia International Grant (IRB-ID 986).

Poster #181

Abnormal blood pressure fall during hyperventilation maneuver in postural tachycardia syndrome

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Introduction: Postural orthostatic tachycardia syndrome (POTS) might have altered endothelial function, causing abnormal vasomotion in the body and in cerebral vessels. Non-cardiac symptoms experienced by these patients suggest that they may be especially sensitive to acute reduction of arterial CO_2 concentration during hyperventilation (HV).
Hypothesis: We hypothesized that HV induces more significant blood pressure (BP) fall with compensatory higher HR increase in POTS.
Methods: Subjects previously diagnosed with POTS and gender-matched controls were enrolled (IRB190703). ECG, finger BP, and $EtCO_2$ were continuously recorded during hyperventilation (1 breaths/sec) over 30 s. Hemodynamic parameters were computed in absolute and change.
Results: We studied 14 POTS and 15 controls matched for age (29 ± 2 vs. 30 ± 3; p = 0.63) and BMI (24.1 ± 0.8 vs. 23.0 ± 0.7; p = 0.34). At baseline mean HR (79 ± 4 vs. 70 ± 3 bpm, p = 0.12) was comparable and SBP was higher (113 ± 3 vs. 105 ± 2 mmHg, $p < 0.05$) compared to controls. $EtCO_2$ values were comparable at baseline (35 ± 1 vs. 38 ± 1 mmHg, p = 0.14) and at the end of the maneuver (20 ± 1 vs. 21 ± 1 mmHg, p = 0.58). POTS had greater SBP drop (− 27 ± 2 vs. − 19 ± 2 mmHg, $p < 0.05$) and a comparable HR increase (34 ± 3 vs. 29 ± 2 bpm, p = 0.11), despite POTS reached a higher absolute maximal HR (113 ± 4 vs. 99 ± 2 bpm, $p < 0.05$). Recovery time for HR (31 ± 4 vs. 34 ± 4 s, p = 0.68) and SBP (27 ± 7 vs. 18 ± 4 s, p = 0.42) were similar.
Conclusions: POTS have greater SBP drop with less adequate compensatory HR increase during HV. These results suggest that vascular responsiveness to hypocapnia is especially strong in POTS and it can contribute to orthostatic stress and symptoms.
Funding: National Institutes of Health (NIH [1R56HL142583-01]).

Poster #182

Randomized neck suction reveals elevated sympathetic central gain in postural tachycardia syndrome

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Introduction: White noise perturbations using neck suction (NS) can be applied to identify open loop transfer function in a closed loop baroreflex system. It allows an estimation of central arc transfer function (H1) which represents how afferent baroreceptor information is translated into sympathetic outflow and peripheral arc transfer function (H2) which describes how muscle sympathetic nerve activity (MSNA) affects blood pressure (BP).
Hypothesis: We hypothesize that patients with postural tachycardia syndrome (POTS) have elevated central gain compared to healthy controls (CONT).
Methods: We recorded raw MSNA (NeuroAmp, ADInstruments) and continuous finger BP (NOVA, Finapres) during randomized NS (0 to − 50 mmHg, 0.03–0.3 Hz) and controlled breathing at 0.25 Hz for 6 min in 10 female POTS and 9 female CONT (IRB#190703). Both groups were matched for age (28.4 ± 2.1 vs. 31.9 ± 3.0 p = 0.80) and BMI (23.0 ± 0.7 vs 24.5 ± 1.0, p = 0.25). Using a customized software (Physiowave, A.D.) in Matlab (Mathworks) we derived the continuous spike rate using wavelet-based denoising. Through closed loop identification we estimated low (LF: 0.04–0.15 Hz) and high (HF: 0.15–0.4 Hz) frequency ranges for the median central gain in H1 and the peripheral gain in H2.
Results: We found that POTS have significantly higher central gain in LF range (2.44 ± 0.38 vs. 1.56 ± 0.23 spikes/s/mmHg, p = 0.035, mean ± SE) but not in HF range (9.02 ± 3.02 vs. 5.48 ± 0.68 spikes/s/mmHg, p = 0.661). Peripheral gains were comparable in LF

(0.68 ± 0.15 vs. 0.57 ± 0.09 mmHg/spikes/s, $p > 0.99$) and HF ranges (0.18 ± 0.02 vs. 0.20 ± 0.03 mmHg/spikes/s, $p = 0.604$).
Conclusions: Our results indicate that POTS has higher recruitment of neural sympathetic spike activity during BP oscillations in the LF range, while peripheral gain was similar between the two groups. This finding could explain why higher sympathetic activation/modulation and greater BP fluctuations in the LF range are found in POTS.
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Poster #183

Report on the progress of iSTAND study, a randomized controlled trial of intravenous immunoglobulin for autoimmune neuropathic postural orthostatic tachycardia syndrome

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Background: POTS is heterogeneous; a subset may have autoimmunity contributing to dysautonomia or small fiber neuropathy. Retrospective case series suggest benefit of treatment with intravenous immunoglobulin (IVIG); however, controlled trials are lacking.
Methods: iSTAND is a double-blind, controlled trial to evaluate safety and efficacy of IVIG compared to intravenous albumin in a two-phase cross-over design. Each study phase consists of four weekly infusions followed by four alternate week infusions with six-week washout between treatment phases. Primary outcome is autonomic symptom severity evaluated by COMPASS-31. Secondary outcomes are also assessed. Recruitment goal is 30 participants completing the first phase of randomized treatment. Data from all participants who begin treatment will be analyzed in an intention-to-treat analysis. Eligible participants are adults who have POTS by heart rate criteria with moderate to severe symptom burden who also have evidence suggesting an autoimmune neuropathic etiology. The latter requires 3 of the following 5 criteria: (1) clear history of subacute onset, (2) confirmed personal or family history of defined autoimmune disorder, (3) severe gastrointestinal dysmotility, (4) one of more serum autoantibody or immune markers, (5) evidence of small fiber neuropathy by skin biopsy or QSART.
Results: As of June 2022, over 200 patients have been considered for the study. 24 participants (23 women) have been enrolled and started treatment. Two with confirmed Sjogren disease, one each with celiac disease, MCTD and psoriatic arthritis. Mean age 33 (18–55); initial COMPASS-31 score 57 (34–91). 18 have completed the initial 12 week randomized treatment phase and 12 completed both phases of the randomized cross-over trial. Three discontinued during first treatment phase (two due to medical events and one who started IVIG elsewhere); one discontinued during second treatment phase with infusion-related headache. Although blinded, there are measurable improvements in autonomic symptoms (predominantly in the orthostatic symptom domain) and tolerability of treatment has been good. 7 (of 18 completing phase 1) had improvement in autonomic symptoms, 10 had no change and one worsened.
Conclusions: Recruitment is nearing completion. Longer term controlled randomized immunotherapy trials in POTS are challenging but very important to provide high quality evidence for therapeutics.
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Poster #184

Semi-supervised exercise training program more efficacious for individuals with postural orthostatic tachycardia syndrome

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Introduction: To be effective, exercise like any medication not only needs to be taken, the correct dose (frequency, duration, and intensity) is necessary. Physical therapy, exercise consultations or recommendations from a primary provider to exercise for 150 min/week is the standard of care (SOC) for providing exercise guidance to patients who do not qualify for cardiac or pulmonary rehabilitation. The aim of this study was to assess if a semi-supervised exercise training (ET) program would be more efficacious at improving aerobic fitness (VO_{2PEAK}), exercise tolerance and symptoms in individuals with postural orthostatic tachycardia syndrome (POTS) compared to SOC.
Methods: Subjects were randomized to either the ET or SOC groups (n: 26 vs. 24; age: 33 ± 11 vs. 37 ± 10 yrs; VO_{2PEAK}: 18.8 ± 5.0 vs. 19.2 ± 6.0 mL/min/kg or 66 ± 15 vs $62 \pm 15\%$ predicted, ET vs. SOC respectively, $p > 0.05$). Composite Autonomic Symptom Score (COMPASS 31), 10-min stand test and cardiopulmonary exercise test were performed at baseline and following 12-weeks. The study was approved by the Mayo Clinic Institutional Review Board and all participants provided written informed consent. The ET group received an exercise consultation where intensity for the interval training was personalized based on the exercise test. Training was semi-supervised with 8 in-person or virtual exercise sessions over 12-weeks and progression individualized.
Results: The ET group demonstrated a greater improvement in VO_{2PEAK} than the SOC group (3.4 vs. − 0.2 mL/min/kg, $p < 0.0001$). Individuals in the ET group reported a significant improvement in orthostatic intolerance domain score ($p = 0.02$) and though not statistically significant demonstrated less orthostatic tachycardia (ΔHR with standing: − 6.2 vs. − 1.7 bpm, $p = 0.09$) and a greater improvement in total COMPASS score (− 11.38 vs. − 6.49, $p = 0.09$). ET group demonstrated a greater reduction in heart rate (− 9 vs. 2 bpm, $p = 0.014$), dyspnea rating (− 1 vs. − 0 points, $p = 0.023$), perceived exertion (− 2 vs. − 0.5 points, $p = 0.029$) and increased frequency of reduced symptom severity ($p = 0.01$) at their anaerobic threshold compared to the SOC group.
Conclusion: Exercise training was more efficacious for individuals with POTS leading to greater improvements in aerobic fitness, symptoms, and exercise tolerance when intensity and progression was personalized and delivered with minimal supervision compared to the standard of care.
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