Wednesday, October 29, 2008
Oral Presentations

Hypotension and cognitive impairment in the elderly

Does chronic hypotension cause cognitive impairment (CI)? This hypothesis has received considerable recent attention, but the data are unclear. Accordingly, we administered the Cognitive Abilities Screening Instrument (a validated test for global cognitive function) to 3,734 Japanese–American men ages 71–93 years from the Honolulu Heart Program and the Honolulu-Asia Aging Study serially over a 6 years period. BP was measured by standard manometer at baseline. Subjects were divided into four groups for systolic BP (SBP): <120, 120–139, 140–159, and ≥160 mmHg. Chi Square Tests, general linear regression and logistic regression models were used for analyses. Six percent had prevalent dementia and 10% had prevalent CI. Prevalent dementia and CI were significantly more common (P < 0.0001) in the low SBP group than in those with normal or high BP. Multiple logistic regression analyses adjusting for age, education, apoE4, stroke, diabetes and smoking found that low SBP was significantly associated with prevalent dementia (OR = 2.70, 95% CI = 1.68–4.35, P < 0.0001), with normal SBP (120–139) as reference. Those with low SBP were more likely to have prevalent Alzheimer’s Disease (OR = 2.20, 95% CI = 1.04–4.66, P = 0.04), but not vascular or mixed/other dementias. Multivariate models found no association between low SBP and cognitive decline or incident dementia over 6 years. Those with low SBP had significantly higher rates of prevalent CHD, stroke and functional impairment, suggesting that the association with prevalent dementia may be due to chronic disease rather than causal. In conclusion, low SBP in late life had a significant association with prevalent dementia and Alzheimer’s Disease, but not with 6-year cognitive decline or incident dementia. Those with low BP were significantly sicker and no longer reflected a healthy group of elderly subjects.

Prospective differentiation of multiple system atrophy from Parkinson’s disease
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Objective: The severity and distribution of autonomic failure appears to be different in multiple system atrophy (MSA) compared with Parkinson’s disease (PD), but reports have been retrospective reviews. We report preliminary results of a prospective ongoing study of MSA and PD to evaluate autonomic indices that distinguish MSA from PD.

Methods: We used Consensus criteria, detailed autonomic studies (composite autonomic symptom score (COMPASS), composite autonomic severity score (CASS), thermoregulatory sweat test percent anhidrosis (TST%), plasma catecholamines, and functional scales (United MSA rating scale (UMSARS) I–IV, Hoehn-Yahr grading) on a prospective, repeated and ongoing basis.

Results: We report the results of a study based on 52 patients with MSA (61.1 ± 7.8 years; BMI 27.2 ± 4.6; Hoehn-Yahr grade, 3.2 ± 0.9; UMSARS_1 21.5 ± 7.4; UMSARS_2, 22.7 ± 9.0) and 29 patients with PD, including PD with autonomic failure (66.0 ± 8.1 years; BMI 26.6 ± 5.5; Hoehn-Yahr grade, 2.2 ± 0.8; UMSARS_1 10.4 ± 6.1; UMSARS_2, 13.0 ± 5.9). Autonomic indices were highly significantly more abnormal in MSA than PD (P < 0.001) for each of: CASS (5.9 ± 1.9 vs. 3.3 ± 2.3), COMPASS (54.4 ± 21.8 vs. 24.7 ± 20.5), TST% (57.4 ± 35.2 vs. 9.9 ± 17.7). These differences were sustained and greater at 1 year follow-up indicating a greater rate of progression of dysautonomia in MSA than PD.

Interpretation: The severity and distribution of autonomic and functional deficits at entry will distinguish MSA from PD when quantitative validated instruments are used. These differences continue and increase with follow-up. Our ongoing conclusion is that severity, distribution, and progression of autonomic failure separates MSA from PD and that it should be possible to eventually generate an algorithmic MSA probability score.

CCHS: Distribution of PHOX2B mutations in a large cohort
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The paired-like Homeobox 2B (PHOX2B) gene acts as a transcriptional activator in promotion of pan-neuronal differentiation in the autonomic nervous system (ANS) in early embryologic development, with a primary role in the sympathetic noradrenergic phenotype in vertebrates. PHOX2B is the disease-defining gene for Congenital Central Hypoventilation Syndrome (CCHS). The vast majority of subjects with CCHS will be heterozygous for a polyalanine repeat expansion mutation (PARM), with a range of 24–13 alamines on the affected allele (the normal allele has 20 alamines). The genotype range for the PARMs is 20/24–20/33. The remaining subjects with CCHS will be heterozygous for a non-polyalanine repeat mutation (NPARM) including missense, nonsense, or frameshift mutations in PHOX2B. It has become apparent that the PHOX2B mutation will determine the severity of the CCHS phenotype in terms of ventilatory requirements, symptoms of ANS dysregulation (ANSD), and risk for cardiac asystoles, Hirschsprung disease, and tumors of neural crest origin: the greater number of repeats in a PARM and/or the presence of an NPARM, the more severe the phenotype (albeit determined in small cohorts). To better understand the distribution of the PHOX2B mutations, and to anticipate the spectrum of phenotype severity, we have studied more than 350 subjects with the CCHS phenotype. PHOX2B testing was performed by patented assay methodology (Am J Med Genet 123A:267–278, 2003), with follow-up sequencing as indicated. The distribution by PHOX2B genotype is as follows: 20/24: 0.6%; 20/25: 29%; 20/26: 23%; 20/27: 29%; 20/28: 0.9%; 20/29: 0.3%; 20/30: 1.7%; 20/31: 0.9%; 20/32: 0%; 20/33: 2.9%; and NPARMs: 11.7%. Among the NPARMS, distribution among the NPARMS is as follows: frameshift: 77.5%; missense: 17.5%; and nonsense: 5%. 15% of the remaining subjects with CCHS will be heterozygous for a non-polyalanine repeat mutation including missense, nonsense, or frameshift mutations in PHOX2B. It has become apparent that the PHOX2B mutation will determine the severity of the CCHS phenotype in terms of ventilatory requirements, symptoms of ANS dysregulation (ANSD), and risk for cardiac asystoles, Hirschsprung disease, and tumors of neural crest origin: the greater number of repeats in a PARM and/or the presence of an NPARM, the more severe the phenotype (albeit determined in small cohorts). To better understand the distribution of the PHOX2B mutations, and to anticipate the spectrum of phenotype severity, we have studied more than 350 subjects with the CCHS phenotype. PHOX2B testing was performed by patented assay methodology (Am J Med Genet 123A:267–278, 2003), with follow-up sequencing as indicated. The distribution by PHOX2B genotype is as follows: 20/24: 0.6%; 20/25: 29%; 20/26: 23%; 20/27: 29%; 20/28: 0.9%; 20/29: 0.3%; 20/30: 1.7%; 20/31: 0.9%; 20/32: 0%; 20/33: 2.9%; and NPARMs: 11.7%. Among the NPARMS, distribution among the NPARMS is as follows: frameshift: 77.5%; missense: 17.5%; and nonsense: 5%. 15% of the individuals with the 20/25 genotype presented in later infancy, childhood or adulthood—in contrast to all remaining subjects who presented in the neonatal period. 10% of parents studied are mosaic for the PHOX2B PARM with genotypes 20/26 and 20/27. Taken together, with the introduction of PHOX2B testing and the definitive diagnosis of CCHS it is apparent that CCHS is no longer as rare as once anticipated nor is it a disorder exclusively of childhood. Introduction of sophisticated autonomic testing among large cohorts of CCHS subjects will more clearly delineate the effect of PHOX2B on the maturing ANS from infancy through adulthood.
Neuronal source of plasma dopamine

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Background: Determinants of plasma norepinephrine (NE) and epinephrine levels are well known; those of the third endogenous catecholamine, dopamine (DA), remain poorly understood. We tested the hypothesis that DA enters the plasma after co-release with NE during exocytosis from sympathetic noradrenergic nerves.

Methods: Plasma catecholamine data were reviewed from patients referred for autonomic testing and control subjects, during supine rest and in response to orthostasis; i.v. yohimbine (YOH), isoproterenol (ISO), or glucagon (GLU), which augment exocytotic release of NE from sympathetic nerves; i.v. trimethaphan (TRI) or pentolinium (PEN), which decrease exocytotic NE release; or i.v. tyramine (TYR), which releases NE by non-exocytotic means. Groups of patients with pure autonomic failure (PAF), bilateral thoracic sympathectomies (SNS-x), or multiple system atrophy (MSA) were included, since PAF and SNS-x are associated with noradrenergic denervation, and MSA is not.

Results: Orthostasis, YOH, ISO, and TYR increased and TRI/PEN decreased plasma DA levels. Individual values for changes in plasma DA concentrations were correlated positively with those for changes in NE in response to orthostasis (r = 0.72, P < 0.0001), YOH (r = 0.75, P < 0.0001), ISO (r = 0.71, P < 0.0001), GLU (r = 0.47, P = 0.01), and TYR (r = 0.67, P < 0.0001). PAF and SNS-x patients had low plasma DA levels. It was estimated that DA constitutes 2—4% of the catecholamine released by exocytosis from sympathetic nerves and that 50—90% of plasma DA has a sympathetic neural source.

Conclusions: Plasma DA is derived substantially from sympathetic noradrenergic nerves.

Time course of changes in vasomotor sympathetic activity during normal human pregnancy

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Previous work has shown that sympathetic activity increases in women during normal pregnancy, and to be even greater in hypertensive pregnant women and those with preeclampsia during the late stage of pregnancy. However, it is completely unknown whether sympathetic hyperactivity develops early during pregnancy, remaining high throughout the entire gestation, or whether this sympathetic activation only occurs at term in humans, providing the substrate for preeclampsia and other pregnancy associated cardiovascular complications. We found in six healthy Caucasian women (age range 24—35) that during early pregnancy (less than 8 weeks of gestation), supine muscle sympathetic nerve activity (MSNA) was very high [33 ± 7 (SD) bursts/minutes, similar to those of congestive heart failure patients], while paradoxically their blood pressure and peripheral vascular resistance were normal. This finding is counter to the prevailing wisdom regarding the neurohormonal adaptation to normal pregnancy, which suggests that sympathetic activation occurs only in late pregnancy, and to our knowledge, there are no published nerve recordings in early human pregnancy. Surprisingly, one Asian woman in early pregnancy had a much less prominent increase in vasomotor sympathetic activity, raising the possibility that marked sympathetic activation may be race-dependent. Supine MSNA decreased by approximately 15% (28 ± 9 bursts/minutes), while blood/plasma volume expansion and increased cardiac output. Within 10 weeks after delivery, supine MSNA decreased dramatically (8 ± 6 bursts/minutes). These observations need to be verified in more pregnant women of different races. If the results obtained in other pregnant women are the same as in our pilot data, it would radically alter the understanding of how blood pressure is regulated in pregnancy as well as provide insights into the development of gestational hypertension and its most feared outcome, preeclampsia.

Genetic markers for autonomic dysfunction in healthy children of Andean Highlanders

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Chronic mountain sickness (CMS), a maladaptation syndrome found in the Andes, is a disease of adults characterized by vasomotor abnormalities, mild peripheral neuropathy and enhanced orthostatic tolerance. Autonomic dysfunctions in CMS occur in association with severe hypoxia, decreasing hypoxic ventilatory drive, increasing red cell mass and finally, right-sided heart failure. CMS has important social implications for highlanders. We recently identified the molecular signature (distinct patterns of gene expression) of CMS. Here we report on the molecular signature of highland children. We find biomarkers that distinguish clinically healthy children, fathered by CMS patients, from those fathered by normal highlanders. We compared molecular signatures in children of men with CMS (n = 10), men without CMS (n = 10) and in sea level children (n = 20). CMS-scores were determined for the fathers. Gene expression in white blood cells was assessed at native altitude (4,338 m.) and then, in the same subjects, at sea level. Highland children had higher expression levels of hypoxia related genes regulated by HIF (hypoxia inducible factor) and lower levels of genes involved in glycolysis and in the tricarboxilic acid (TCA) cycle. Pyruvate dehydrogenase kinase 1 (PDK1) and HIF prolyl hydroxylase 3 (HPH3) mRNA expressions were lowest in children of CMS men, at altitude. At sea level, the molecular signatures in the three groups were indistinguishable. Deficient PDK1 and HPH3 mRNA expression at altitude in children of CMS men predisposes them to hypoxia-induced Reactive Oxygen Species (ROS) accumulation while still young. We propose that the persistent increased ROS levels are likely to lead to CMS later in life. The identification of genetic biomarkers years before CMS makes its clinical appearance provides an opportunity for preventive measures that can impact public health and social well being in the Andes and Altiplano. Funded by NMHEMC Research Foundation, Albuquerque, NM, and NIH grant: RO1 NS37814 to A.V.

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See p. 44 for Kalsbeek abstract
pH sensitive ion channels contribute to carotid body hypersensitivity in spontaneously hypertensive rats (SHR)

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Increased chemoreceptor sensitivity of the carotid body has been recognized in hypertension and heart failure. We have recently reported that Acid-Sensing Ion Channels (ASICs) and Tandem pore-domain Acid Sensing K+ channels (TASK) function as low pH sensors in rat glomus cells (Circ Res 2007;101:1009-1019.). We tested the hypothesis that glomus cells from SHR have exaggerated pH sensitivity of ASICs and TASKs channels that may explain the enhanced chemoreceptor activity of carotid body seen in the SHR. Low pH evoked rapidly inactivating inward currents (perforated whole-cell patch clamp) in glomus cells isolated from carotid bodies of young (4-6 weeks) SHR and WKY rats. The threshold of current activation was at pH 7.0 or higher and the half-maximal activation (pH 50) was at 6.5 in both WKY (n = 6) and SHR (n = 5). However, the amplitude and density of these currents were significantly higher in SHR than WKY (P < 0.05). Values at pH 6.0 were 16.5 ± 6.0 pA, 3.5 ± 0.8 pA/pF (n = 28) and 6.9 ± 1.8 pA, 1.5 ± 0.4 pA/pF (n = 36) in SHR and WKY, respectively. Under current-clamp conditions, low pH (6.0) triggered greater (P < 0.01) transient and sustained depolarizations in SHR (24.4 ± 3.7 and 39.2 ± 2.3 mV; n = 16) than in WKY (12.7 ± 2.3 and 29.5 ± 2.6 mV; n = 26). In addition low pH caused more action potentials during depolarizations in SHR. Amiloride (200 μm), a selective blocker of ASIC, blocked, in both SHR and WKY, the pH-induced inward currents (23.1 ± 1.7 vs. 1.7 ± 0.5 pA; n = 7) and the transient depolarizations (24.4 ± 6.2 vs. 2.0 ± 1.2 mV) but not the sustained depolarization (33.4 ± 1.6 vs. 33.6 ± 3.6 mV). Using real-time PCR technique, we found that mRNAs encoding the most acid-sensing subtypes ASIC1b, ASIC3, TASK1 and TASK3 were significantly increased by 150, 75, 100 and 20%, respectively in carotid bodies of SHR compared with WKY rats (n = 5). We conclude that overexpression of pH sensitive ASIC and TASK channels in glomus cells of SHR explains the exaggerated chemoreceptor activity of carotid bodies and may contribute to excessive sympathetic nerve activity and development of hypertension.

Spinophilin and blood pressure regulation

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Spinophilin (SPL) controls intensity/duration of G protein-coupled receptor (GPCR) signaling and is involved in the regulation of synaptic activity. We hypothesize that SPL affects blood pressure (BP) via central mechanisms. We measured BP and heart rate (HR) in homozygous SPL-deficient (SPL−/−), heterozygous SPL-deficient (SPL+/−) and wild-type (SPL+/+) mice by telemetry combined with fast Fourier transform (FFT) analysis of BP and HR and pharmacological autonomic testing. Furthermore, we assessed peripheral vascular reactivity. SPL−/− had higher mean arterial pressure (MAP) than SPL+/− and SPL+/+ (121 ± 2, 112 ± 1 and 111 ± 1 mmHg). HR was inversely related to SPL expression (SPL−/−: 565.4 ± 0.4, SPL+/−: 540.8 ± 4.7, SPL+/+: 524.7 ± 7.7 beats/minutes). The response to prazosin, to ganglionic blockade with trimetaphane and the HR response to metoprolol were stronger in SPL−/− than SPL+/+ mice, while HR response to atropine was attenuated in SPL−/−. Vasoactivity in response to Ang II, phenylephrine, and the thromboxane mimetic (U46619) which reflect parasympathetic tone, were attenuated in SPL−/− mice. We suggest that an increase in the central sympathetic out-flow plays a role for increases in BP and HR in SPL−/− mice. The elevated BP in SPL−/− mice is associated with an attenuated BRS and a decreased parasympathetic activity. Our study is the first to show a role for the SPL gene in BP regulation.

Muscle sympathetic nerve activity during mental stress: responders vs. nonresponders

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Mental stress has been reported to increase, decrease, and not change muscle sympathetic nerve activity (MSNA) in humans. In contrast, mental stress consistently increases heart rate (HR) and arterial blood pressure (BP). The purpose of the present study was to re-examine neural and cardiovascular responses to mental stress by probing for differences between responders (≥3Δ bursts/minutes) and nonresponders (<3Δ bursts/minutes). Leg MSNA, BP, HR, and perceived stress levels were recorded during 5 minutes (n = 22) or 5 minutes (n = 50) of mental arithmetic. The length of the mental stress trial (3 minutes vs. 5 minutes) did not elicit different responses, thus data were pooled to provide a total of 33 responders (20 men, 13 women) and 39 nonresponders (27 men, 12 women). Mental stress increased MSNA in responders (Δ ± 1 bursts/minutes; P < 0.001), but did not change MSNA in nonresponders (Δ ± 1 ± 1 bursts/minutes). Mental stress increased mean BP and HR similarly in responders (Δ15 ± 1 mmHg and Δ17 ± 1 beats/minutes; P < 0.001) and nonresponders (Δ15 ± 1 mmHg and Δ19 ± 2 beats/minutes; P < 0.001). Perceived stress levels were similar in responders (2.7 ± 0.1 units) and nonresponders (2.7 ± 0.1 units), and no sex differences were detected, thus perceived stress and sex do not appear to influence MSNA during mental stress. MSNA responses to mental stress were not correlated to changes in HR, systolic, diastolic, or mean BP in either responders or nonresponders. In conclusion, cardiovascular responses to mental stress are similar in responders and nonresponders, despite significantly different sympathetic neural outflow. The apparent disassociation of MSNA and BP responses to mental stress between groups suggests greater vasodilation in responders or greater vasoconstriction in nonresponders.

Enhancement of vestibular ocular counter-roll with subthreshold stochastic resonance galvanic stimulation

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The vestibular system, specifically the otoliths, assists in the autonomic response to the upright posture. Loss of otolith function occurs with both disease and aging, however treatment options remain limited. The goal of this work was to determine if subsensory stochastic resonance noise stimulation improves otolith function as measured by ocular counter-roll. Ocular torsion was assessed during sinusoidal roll tilt of ±25 degrees at 0.03125 Hz (32 seconds per cycle), 0.125 Hz (8 seconds per cycle), 0.25 Hz (4 seconds per cycle) for control trials and subsensory stochastic noise galvanic stimulation trials. Stimulation was applied through electrodes over the mastoid process and levels were set as 90% of sensory threshold or level in which nystagmus first developed. Ocular torsion was assessed using polar cross-correlation of iris landmarks from infrared images of the eyes in the dark with subjects fixed on an LED at center of rotation. Application of galvanic stimulation increased ocular torsion in 8 of 17 subjects 24 ± 13% during 0.03215 Hz rotation, 31 ± 11% during 0.125 Hz, and 17 ± 5% during 0.25 Hz. Torsion was not significantly different in the nine subjects who did not respond (~1 ± 3%, 0.03125 Hz; ~4 ± 3%, 0.125 Hz; ~1 ± 5%, 0.25 Hz). Responders had lower baseline ocular torsion (0.09 ± 0.02 vs. 0.15 ± 0.03 deg torsion/deg tilt at 0.03125 Hz, P = 0.13). These results are the first to demonstrate that otolith sensitivity to tilt stimuli can be increased by galvanic stimulation applied below perceptual threshold. One limitation is that ~50% of subjects did not show an increase in torsion. However, this may have been due to an inappropriate level of stimulation. Further work is necessary to determine stimulation levels that will produce the greatest increase in otolith function. The finding that subjects with lower torsion demonstrated the greatest improvement suggests this method may be useful to treat vestibular loss. Supported by NASA.

Respiratory modulation and baroreflex control of heart rate after eight days in space

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During everyday life, baroreflex-mediated cardiovascular adjustments are essential in maintaining blood pressure control on a beat-to-beat basis. In astronauts in space, gravitational pressure gradients do not arise in the circulation so that baroreflex function remains chronically unchallenged. The way in which this may affect neural control of heart rate and blood pressure is incompletely understood. We studied nine male cosmonauts who each took part in seven different space missions aboard the ISS (age 40–52 years, height 1.69–1.85 m, weight 67–90 kg). Data collection was performed between 30 and 45 days before launch in the standing and supine positions, and after 8 days into spaceflight. Cosmonauts were carefully trained to perform in-flight data collection by themselves. They were instructed to pace their breathing to a fixed rate of 12 breaths per minute (0.2 Hz) for a total duration of 3 minutes. The electrocardiogram and beat-by-beat finger arterial blood pressure were recorded at 1-kHz sample rate. Respiratory rate was evaluated using an abdominal pressure sensor. We used power spectral analysis to calculate respiratory sinus arrhythmia (RSA) as well as the low-frequency (0.04–0.15 Hz) powers of spontaneous oscillations in heart rate and systolic blood pressure. Baroreflex sensitivity (BRS) was estimated in the time domain using cross-correlation analysis. As expected, there was a rise in heart rate upon assuming the standing position before spaceflight (59 ± 6 to 79 ± 11 beats per minute; P < 0.001). This was accompanied by an increase in mean arterial blood pressure (84 ± 6 to 93 ± 6 mmHg; P < 0.001). Standing up further induced a marked increase in the low-frequency powers of systolic blood pressure oscillations (8 ± 7–17 ± 11 mmHg²; P = 0.018), whereas those in heart rate remained unchanged (445 ± 512 to 621 ± 799 mmHg²; P = 0.315). Alternatively, there was a reduction in RSA from 346 ± 167 to 158 ± 298 ms² and in spontaneous BRS from 14 ± 5 to 6 ± 2 ms/mmHg upon changing from supine to standing (both P < 0.001). After a week of weightlessness in space, heart rate (61 ± 8 beats per minute) and mean blood pressure (83 ± 6 mmHg) did not differ from the pre-flight supine values. This was also true for the low-frequency powers of systolic blood pressure (7 ± 4 mmHg²) and of heart rate (741 ± 716 ms²), as well as for RSA (465 ± 269 ms²) and spontaneous BRS (14 ± 4 ms/mmHg). Our data show that both heart rate and blood pressure in space correspond to pre-flight supine values. In-flight cardiovascular control is further characterized by chronically increased vagal-cardiac modulation and suppressed sympathetic vasomotor activity, compared with the upright posture on Earth.

Lack of evidence for nitric oxide deficiency contributing to hypertension in humans

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Nitric oxide (NO) deficiency is thought to contribute to hypertension (HT). If true, then the pressor response to inhibition of NO synthesis with L-NMMA should be reduced in HT. We combined this approach with autonomic blockade with trimethaphan (TriMT) to eliminate baroreflex buffering and autonomic/NO interactions. We studied a total of 57 subjects: 17 lean normotensives (LNT), 7 lean HT (LHT), 7 obese HT (OHT), and nine heavy smokers (Smk) with BMI of 23 ± 0.6, 23 ± 0.7, 32 ± 0.9, 28 ± 0.6 and 26 ± 1.2, and seated SBP of 111 ± 3, 137 ± 4, 140 ± 2, 119 ± 2 and 113 ± 5 mmHg, respectively. Smk were included as “positive” controls because of their documented NO deficiency. After autonomic blockade with TriMT, phenylephrine was titrated to achieve similar SBP in all groups (103 ± 1, 107 ± 1, 108 ± 2, 106 ± 4 and 105 ± 4 mmHg, respectively). NO synthase inhibition with L-NMMA produced similar increase in SBP except among smokers, who show the smaller increase. Our results suggest that NO is one of the most potent metabolic determinants of BP in humans, tonically restraining it by ~30 mmHg, but we found no evidence of NO deficiency contributing to hypertension. However, we cannot exclude that NO contributes to hypertension through interactions with the autonomic nervous system, which were excluded in this study.

Autonomic regulation of circulation profile in patients with severe left ventricle of heart myocardial hypertrophy depending on the blood pressure level

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Hypertrophic cardiomyopathy and essential hypertension combination possibility is disputable if a single patient located. Aim: to assess autonomic nervous system of circulation profile in patients with severe hypertrophy (SH) of interventricular septum (IVS) depending on arterial hypertension availability.

Patients and methods: 32 patients with SH of IVS (215 mm), mean age 55, 2 ± 10, were divided into two groups: patients without concomitant arterial hypertension (SH+AH−), n = 16; and with arterial hypertension (SH+AH+), n = 16. Both groups had similar intracardiac haemodynamics and subaortic stenosis severity. 20
patients with essential hypertension and without SH (SH–AH+),
n = 20, and 20 healthy volunteers serve as control groups. All
patients were comparable in age and sex composition. In all patients
were examined vasomotor component of cardiopulmonary reflex
(VCCPBR), spontaneous arterial reflex sensitivity (ABR), Valsalva’s
ratio (VR), heart rate variability analysis (HRV) both in rest and
orthostasis. Haemodynamics parameters were registered by beat-to-
beat method with the help of Finometer FMS machine (Amster-
dam).

Results: significant VCCPBR reduction (0.02 ± 0.20) was de-
tected in the group SH+AH+ in comparison with the other patients
groups: the patients SH+AH+ group −0.21 ± 0.19, P < 0.05; the
patients SH–AH+ group −0.22 ± 0.12, P < 0.05 and healthy sub-
jects −0.29 ± 0.07, P < 0.001. However VR (1.43 ± 0.25), ABR
(9.77 ± 4.29 ms/mmHg) and sympathovagal index of HRV
(2.1 ± 1.7) did not differ from the healthy people group results
(1.47 ± 0.22; 11.1 ± 4.5 ms/mmHg and 1.75 ± 1.21), P > 0.05, while,
these parameters were different in patients with AH (with
and without SH) compare to healthy subject. There was sympatho-
vagal index increase (3.1 ± 1.7 and 3.0 ± 1.5 in contrast to
1.75 ± 1.21, P > 0.05), VR level decrease (1.33 ± 0.12 and 1.35 ± 11
in contrast to 1.47 ± 0.22, P > 0.05, P = 0.51), ABR decrease
(6.3 ± 3.9 and 7.2 ± 3.5 in contrast to 11.1 ± 4.5 ms/mm Hg,
P < 0.005, P < 0.01).

Conclusion: autonomic nervous system of circulation profile in
patients with severe myocardial hypertrophy and arterial hyper-
tension has significant distinctions in contrast to the patients
with hypertrophy cardiomyopathy and has a certain similarity to
parameters of patients with essential hypertension.

Tonic inhibitory influence of cerebellar cortex on the 10-Hz
rhythm in sympathetic nerve discharge

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It is well established that electrical or chemical activation of the
posterior cerebellar cortex (lobeul IX of vermis; uvula) elicits
decreases in mean arterial pressure (MAP) and sympathetic nerve
discharge (SND) in anesthetized cats and rabbits. The current study
was designed to determine whether this region of the cerebellum
exerts a tonic influence on MAP and SND. For this purpose, we
studied the changes in MAP and postganglionic inferior cardiac
SND produced by gentle aspiration of lobules X (nodulus) and IX
(uvula) of the posterior vermis in baroreceptor-denervated and
vagotomized cats anesthetized with urethane. Autospectral analysis
was used to determine whether the rhythmic (10-Hz) and wide-
band, low frequency components (≤6 Hz) of SND were differentially
affected by removal of lobules X and IX. Ablation induced statis-
tically significant increases in MAP and 10-Hz power in SND. In
contrast, low frequency power in SND was not significantly affected.
As expected, electrical stimulation of sites in lobule IX abruptly
reduced MAP and SND before ablation of this region was per-
formed. These results demonstrate for the first time, a tonic and
selective inhibitory influence of cerebellar cortex on the 10-Hz
rhythmic component of SND.

Spectral analyses of cardiovascular control in spinal cord
injured rats and humans

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Spectral analyses of cardiovascular signals are routinely used in
the clinic to evaluate autonomic cardiovascular control. We aimed to
evaluate whether this technique could provide a translatable
assessment of cardiovascular autonomic function in rodent models
of spinal cord injury (SCI). We determined heart rate and blood
pressure variability from beat-to-beat data obtained via a left car-
otid artery cannula in nine male rats 1 month after T3-4 SCI (complete
section) or sham injury (control, n = 8). Recordings were per-
fomed for 10 minutes in conscious free-moving rats in
home cages. Univariate autoregressive spectral analyses were per-
formed on the time series extracted from the beat-to-beat systolic
arterial pressure (SAP), and RR interval (RRI) data. Low frequency
(LF), high frequency (HF) and very low frequency (VLF) peaks
were identified for each spectrum and the power and central frequency
of each peak calculated by computation of the residuals. Data in ro-
dents were qualitatively compared to those from healthy humans
and individuals with SCI (1). SCI rats had faster heart rates
(P < 0.01), and markedly reduced VLF (control 36.0 ± 14.0 ms2;
SCI 2.9 ± 1.4 ms2; P < 0.05), LF (control 14.8 ± 7.2 ms2; SCI
0.7 ± 0.2 ms2; P < 0.05) and total variability of RRI. HF oscillations
in RRI and SAP occurred with higher central frequencies in SCI
rats, reflecting faster respiratory rates. VLF (control 24.6 ± 11.4 mmHg2;
SCI 3.9 ± 1.5 mmHg2; P = 0.07) and LF (control 55.1 ± 11.8 mmHg2;
SCI 26.5 ± 5.6 mmHg2; P < 0.05) power in SAP were reduced in SCI rats. The reduced LF
varia-
ibility of blood pressure and heart rate in SCI rats is compatible
with the destruction of descending sympathetic pathways. The re-
duced VLF oscillations in BP suggest a reduction in myogenic vascular
regulation. Reduced VLF RRI is a marker of cardiovascular disease
risk. These findings are similar to those in humans with high level
autonomically complete SCI (1). Spectral analyses of cardiovascular
variability can document the cardiovascular autonomic deficit fol-
lowing complete thoracic SCI in rodent models of SCI and may
facilitate the translation of SCI research from the bench to the bedside,
and vice versa. Support: Rick Hansen Man In Motion Research
Foundation; Heart & Stroke Foundation of Canada.

(1) V.E. Claydon and A.V. Krassioukov (2007) Clinical corre-
lates of frequency analyses of cardiovascular control after spinal

Evaluation of a novel non model driven assessment of
cardiac autonomic activity: response to combined graded
orthostatic and heat stress

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We have previously reported results using a novel time domain
method that decomposes beat to beat changes in R–R intervals
(RRI) into two continuous sets of causal activities that reflect the
parasympathetic and sympathetic components of cardiac auto-
nomic activity. We have found that our measure of cardiac vagal
activity is robust. However our measure of sympathetic activity is
critically dependent on the presence of cardiovagal activity and if
this activity is eliminated, baseline sympathetic velocity shifts up-
ward and fluctuations in sympathetic velocity are attenuated. To
determine whether this measurement limitation pertains to more
physiologically relevant conditions, we reanalyzed data from 15
normal subjects during 5 minutes of head-up tilt (HUT) alone or in
combination with heat stress achieved by perfusing a tube-lined suit
with warm water. HUT alone increased heart rate (HR) from a
baseline of 84.2 ± 2.5–123.8 ± 2.8 bpm. Baseline sympathetic
velocity increased to levels approximately equivalent to that ob-
tained during HUT without heat stress again without substantial
change in parasympathetic velocity. During combined HUT and
heat stress sympathetic velocity substantially increased to a level approximately threefold that obtained during HUT alone. Parasympathetic velocity was reduced in approximately half of the subjects tested but overall the averaged parasympathetic activity was unchanged from baseline. These observations provide confirmation of the method’s ability to rapidly detect changes in spontaneous cardiac sympathetic activity although our measure of this activity is limited when cardiovagal activity is absent.

**CO2-NO axis: a novel pathway in mediating cerebrovascular vasodilatation**

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Hypercapnia and hypocapnia affect peripheral and cerebral hemodynamics through unknown mechanisms. Our previously-published findings in humans suggested that a carbon dioxide-nitric oxide axis (CO2–NO axis) could be a key mechanism in cerebral blood flow (CBF) regulation. Therefore, we postulated that nitric oxide synthase (NOS) in the endothelium could be a delicate sensor to changes in cerebral blood pCO2. In order to test this hypothesis, we studied the influence of high CO2 levels on NO release in human brain microvascular endothelial cells (HBMECs). These cells were transiently exposed either to high CO2 levels (~20%) or to normal CO2 conditions (~5%) for 30 minutes and NO release was measured. The cells were also treated with acetazolamide, a carbonic anhydrase (CA) inhibitor, L-NAME, a NOS inhibitor, and changes in the pH of the culture medium were performed. High CO2 levels induced a 73.5 ± 27.5% significant increase in NO release. The high CO2-induced increase in NO release was blocked by treating the HBMECs with L-NAME. CA inhibitor normalized the NO release effect induced by high CO2. Lower pH levels in the culture medium caused reduction in NO release. Endothelial and neuronal mRNA expressions of HBMECs were found down-regulated in high CO2 conditions. This study confirms directly the existence of CO2–NO axis in humans. Indeed, high CO2 concentrations enhance NOS activity independently of mRNA transcription. This CO2-induced NO release requires the mediation of CA, suggesting that changes in intracellular pH is necessary. Yet, this newly described molecular mechanism needs further exploration.

**The use of real-time ultrasonography in microneurography**

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Traditionally, the success rate of peroneal microneurography by experienced researchers has been quoted to be between 70 and 80%, but in certain subject populations (e.g. subjects with lower body obesity) our success rate is lower. In our ongoing study of obesity measuring muscle sympathetic nerve activity (MSNA), one of the investigators who is experienced in performing ultrasound-guided regional anesthesia nerve blocks (TBC) has started placing microelectrodes with two-dimensional, real-time ultrasound guidance using a high-frequency probe (3–13 MHz). Using an “in-plane” approach, the microelectrode can be visualized advancing into the cross-sectional image of the peroneal nerve and only fine adjustments are needed to obtain satisfactory muscle sympathetic nerve signals. In recent studies (n = 5), our success rate in subjects who are obese has increased since we started use of ultrasound. Such preliminary data suggest that success rates will at least equal the historic rates in our laboratory in non-obese populations by experienced microneurographers. We believe that ultrasound can be a useful tool for peroneal microneurography. However, it is essential the person placing the microelectrode be familiar with all aspects of microneurography for subject safety and data quality. Potential advantages of this technique include increased success rates, decreased time to successful placement, no requirement for transcutaneous localization (i.e. “external stimulation”), and the ability to manipulate the microelectrode in the nerve under direct visualization. Whether this technique can be used with other nerves or is useful in all subject populations is not known.

**Quantifying sweat gland innervation — a comparison of two novel unbiased methods**

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**Objective:** To evaluate two novel methods to quantify the density of nerve fibers surrounding sweat glands in healthy control and diabetic subjects.

**Method:** Thirty diabetic and 64 healthy control subjects were examined and had punch skin biopsies at the distal leg, distal thigh, and proximal thigh. Nerve fibers surrounding sweat glands, stained with PGP 9.5, were digitally imaged by light microscopy. Nerve fiber density within the sweat gland was quantified by computer automated surface area analysis, and by manual morphometry. Three subjects had punch biopsies analyzed by confocal microscopy with complete Z-stack images combined with an unbiased stereologic quantification scheme as a gold standard.

**Results:** Diabetic subjects had reduced sweat gland nerve fiber density (SGNFD) compared to controls at the distal leg (P < 0.01) and distal thigh (P < 0.05) using both techniques. The reduction in SGNFD measured with the automated and manual techniques correlated with the neuropathy impairment score in the lower limb (NIS-LL) (r = 0.81, P < 0.01 automated; r = 0.89, P < 0.001 man-
The automated and manual methods correlated with an unbiased stereologic confocal quantification ($r = 0.76, P < 0.05$ automated; $r = 0.93, P < 0.01$ manual). There was a positive correlation between the intra-epidermal nerve fiber density and the SGNFD, using the automated ($r = 0.62, P < 0.01$) and manual ($r = 0.66, P < 0.01$) quantification schemes. Although differences were seen between patients and controls using both methods, the manual approach was more sensitive to abnormalities at the proximal leg ($P < 0.01$) and proximal thigh ($P < 0.05$).

Interpretation: We describe two methods to quantify the density of nerve fibers surrounding sweat glands. Both methods differentiate groups of patients with mild diabetic neuropathy from healthy control subjects, but the manual morphometric technique has greater diagnostic discrimination and correlates with an unbiased control subjects, but the manual morphometric technique has a reliable structural measure of sweat gland innervation that complements the investigation of small fiber neuropathies.

STREETEN LECTURE

Catecholamines 101

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For more than a century, from the discovery of adrenaline as the active principle of the adrenal gland, to the identification of norepinephrine, adrenaline’s chemical father, as a key neurotransmitter of the sympathetic nervous system, to the elucidation of the role of dopamine, adrenaline’s chemical grandfather, as a neurotransmitter in the brain, research based on the adrenaline family—the catecholamines—has proven remarkably consistently fruitful and led to many Nobel Prizes. Catecholamines constitute the only neurochemical messengers where virtually all steps in an entire functional cycle are amenable to scientific study—from central neural changes to nerve impulses to transmitter release to transmitter deactivation to receptor function to cellular activation to afferent information back to the central nervous system. Norepinephrine and adrenaline are major effector chemicals of the autonomic nervous system, and norepinephrine and dopamine are classical central neurotransmitters, thought to participate importantly in movement, vigilance, memory, pain, and neuroendocrine manifestations of distress. Catecholaminergic systems also provide models for the three main mechanisms of regulation of the internal environment—via neurotransmitters, hormones, and autocrine/paracrine factors. Finally, measurements of levels of endogenous catecholamines and their metabolites can yield important information related to the diagnosis, assessment of treatment, and mechanisms of drug action in a variety of both common and rare disorders of the autonomic nervous system.

The balancing act between sympathetic nerve activity and cardiac output: differences between young men and women

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Among young normotensive men a reciprocal balance between cardiac output (CO) and muscle sympathetic nerve activity (MSNA) is important in the regulation of arterial pressure. In young women, the balance between CO, total peripheral resistance (TPR) and sympathetic nerve activity is unknown. There is some evidence, however, that the mechanisms of arterial pressure regulation differ between the sexes. Consequently, the aim of this study was to examine the relationship of CO and TPR to muscle sympathetic nerve activity (MSNA) in young women. Multi unit recordings of MSNA at the peroneal nerve were obtained in 15 women (Mean ± SD; age, 24 ± 3 years; body mass, 64 ± 9 kg; height, 167 ± 5 cm) and 21 men (age, 25 ± 5 years; body mass, 80 ± 11 kg; height, 180 ± 6 cm). CO was measured via acetylene rebreathing and arterial pressure was recorded via a brachial catheter. Mean resting MSNA was lower in the women compared to men when expressed as bursts incidence (34 ± 5 bursts/100 bs vs. 43 ± 2, $P < 0.05$), as was mean arterial pressure (MAP; 88 ± 1 mmHg vs. 94 ± 2, $P < 0.05$). Total peripheral resistance (TPR), however, was not different between sexes (women, 17.9 ± 0.7 mmHg/l/minute vs. men, 15.8 ± 0.8). MAP was not related to MSNA (bursts/minutes) in men ($r = -0.05$) or women ($r = -0.05$). There was a positive relationship between TPR and MSNA (bursts/minutes) in men ($r = 0.63, P < 0.05$). Unexpectedly, in women, there was an inverse relationship between TPR and MSNA (bursts/minutes; $r = -0.59, P < 0.05$). Moreover, the correlation between CO and MSNA (bursts/minutes) was negative in men ($r = -0.69, P < 0.05$) whereas in women CO was positively related to MSNA ($r = 0.56, P < 0.05$).

Therefore, the sympathetic regulation of blood pressure in women appears to be different to that observed in men. The underlying mechanism(s) remain unclear but future studies may provide evidence which explains the reason for differences in the prevalence of hypertension and orthostatic intolerance between men and women.

Friday, October 31, 2008

Oral Presentations

Pathogenesis and treatment development in transgenic mouse models of multiple system atrophy and α-synuclein accumulation

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Multiple system atrophy (MSA) is a progressive, neurodegenerative disease manifested by parkinsonism, ataxia and autonomic dysfunction. This condition is characterized neuropathologically by the presence of α-synuclein immunoreactive glial cytoplasmic inclusions in oligodendrocytes. Several transgenic mouse lines expressing α-synuclein from neuronal (PDGFβ) and oligodendroglial (MBP, CBP) promoters that mimics aspects of Parkinson’s disease and MSA respectively have now been generated. These models display extensive accumulation of α-synuclein in glial and neuronal cell groups, accompanied by motor deficits, autonomic dysfunction, demyelination and neuronal degeneration. Alterations in the production of glial derived trophic factors and oxidized proteins appears to play an important role. Both neurons and glial cells display mitochondrial anomalies and accumulation of α-synuclein electron dense deposits. Moreover, accumulation of α-synuclein in glial cells reduce their ability to produce laminin and fibronectin and disrupts the mechanisms of oligodendrocyte-neuronal communication. Therefore, strategies directed at reducing α-synuclein accumulation, either by increasing trophic factor expression, reducing oxidative stress, blocking aggregation or increasing clearance via lysosomal pathways might represent useful experimental strategies for the treatment of these disorders. Among the anti-aggregation compounds we have tested the effects of rifampicin, an antibiotic with a naphthohydroquinone and anti-oxidants. Our initial studies indicate that long term treatment with rifampicin reduces the motor deficits and accumulation of α-synuclein in glial in the mice. Additional studies are underway to confirm these findings. In conclusion, the MBP-synuclein model represents a useful paradigm to understand the mechanisms of degeneration in MSA and develop new treatments. Supported by grants from NIA and NINCDS.
Sympathetic and parasympathetic outflow imbalance is involved in blood pressure increase in db/db mice

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Leptin, a hormone that affects energy balance, is thought to influence sympathetic outflow with elevations in blood pressure (BP). We evaluate the yet unclear BP regulation in the hyperleptinemic db/db mice using telemetry. Autonomic nervous system activity was assessed by challenging db/m and db/db mice with metoprolol (β-adrenergic receptor blocker, 8 mg/kg), trimetaphan (ganglion blocking, 120 mg/kg) and atropine (muscarinic receptor antagonist, 4 mg/kg). The baroreceptor heart rate reflex (BRS) was investigated using spontaneous changes in systolic BP (SBP) and heart rate (HR). Clear-cut day/night BP and HR rhythm was observed in both strains, even though MAP and HR amplitude tended to be attenuated in db/db mice (MAP amplitude: 6.3 ± 0.7 vs. 3.7 ± 0.8; HR amplitude: 45.1 ± 3.3 vs. 32.8 ± 4.8). Both, BP and HR were found higher during the resting period in db/m compared to db/db mice (MAP: 117 ± 3 vs. 108 ± 10 ± 1.0 mmHg; HR: 488 ± 12 vs. 436 ± 8 beats/minutes; P < 0.05, n = 10). Captopril had stronger effect in BP of db/m than in db/db mice, while enalapril effect was similar in both strains. HR response to metoprolol (−59 ± 12 vs. −5 ± 4 beats/minutes), and BP and HR response to trimetaphan (MAP: −43 ± 5 vs. −27 ± 3; HR: −106 ± 7 vs. −62 ± 4) were greater in db/db mice than in db/m. Moreover, HR increase after atropine was attenuated in db/m mice (59 ± 17 vs. 144 ± 24 beats/minutes). BRS was significantly attenuated in db/m compared to db/m mice (BRS-up: 1.1 ± 0.1 vs. 2.0 ± 0.2; BRS-LF: 1.7 ± 0.3 vs. 3.3 ± 0.5). Low frequency of heart rate spectra (LF-HRV) thought to describe parasympathetic tone was also found strongly attenuated in db/db mice (4.0 ± 1.0 vs. 16.3 ± 2.3). In summary, simultaneous increase of MAP and HR observed in db/db is at least in part due to increased sympathetic outflow accompanied by attenuated baroreceptor reflex sensitivity and vagal tone.

Insulin neuritis: can excessive glucose control impair autonomic function?

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Background: Insulin neuritis is a disorder characterized by the sudden onset of acute pain in patients with rapid improvements in glucose control, often due to insulin administration. We report the simultaneous onset of acute pain in patients with rapid improvements in glucose control, followed by testing the simultaneous onset of insulin neuritis.

Methods: We report 13 patients (7 with type 1 diabetes (T1DM); 6 female, 1 male; 6 with type 2 diabetes (T2DM), all male) who developed the sudden onset of severe pain after rapidly improving glucose control. Within 3 months of treatment, 13 patients reported the sudden onset of severe pain after rapidly improving glucose control. Within 3 months of treatment, 13 patients reported the symptoms and signs of autonomic dysfunction and were referred for autonomic testing.

Results: The mean decrease in HgA1c over a 3 months period was 8.4 ± 2.4 (T1DM) and 6.3 ± 2.8 (T2DM). The mean ages were 27 ± 6.3 (T1DM) and 43.8 ± 7.5 (T2DM). The mean duration of diabetes was 13 ± 4.2 (T1DM) and 8 ± 3.8 (T2DM). Reported symptoms of autonomic dysfunction included: orthostatic intolerance (90%), gatroesophageal reflux (70%), sweating abnormalities (50%). Patients with T1DM had greater autonomic dysfunction than those with T2DM on direct testing: Valsalva ratio 1.29 ± 0.11 vs. 1.53 ± 0.72 (P < 0.01), resting heart rate 88 ± 7.4 vs. 70 ± 3.1 beats/minute (P < 0.001). Subjects with T1DM had lower resting BP and larger drops in BP during tilt and stand (P < 0.05). Drops in blood pressure on tilt were 22/12 mmHg (T1DM) and 11/7 mmHg (T2DM) P < 0.05. One year later, 92% of patients reported improvement in symptoms of autonomic dysfunction.

Interpretation: Insulin neuritis is a disease characterized by the severe onset of pain as a consequence of rapid improvement in glucose control. We report the development of autonomic dysfunction coincident with the onset of pain. The patients reported no symptoms of autonomic dysfunction prior to the improvement in glycemic control, suggesting that rapid changes in glucose control adversely affected autonomic function. These data suggest that insulin neuritis is an important cause of acute and reversible autonomic dysfunction in patients with diabetes.

Anatomical and functional changes in baroreceptor afferent, central and efferent components of the baroreflex circuitry in type 1 diabetic mice (OVE26)

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OVE26 diabetic and FVB control mice (6–9 months; n = 6–9 experimental group) were used to examine effects of diabetes on baroreflex control of HR and identify the location of changes in baroreflex circuitry. First, HR responses to phenylephrine (PE)- and sodium nitroprusside (SNP)-induced mean arterial pressure changes (ΔMAP) were measured in conscious mice. Second, TMR-D was injected into the nodose ganglion to label aortic depressor nerve (ADN). Third, Dil was injected into the nucleus ambiguus (NA) to label parasympathetic cardiac afferents in Fluoro-Gold-labeled cardiac ganglia. Fourth, baroreceptor function was characterized by measuring ADN activity (ADNA) in response to SNP- and PE-induced ΔMAP. Fifth, HR responses to electrical stimulation of left ADN and right vagus nerve were assessed. Sixth, HR responses to L-glutamate (0.2 mMol/L, 20 nl) microinjection into the NA were measured. The number of NA motoneurons was examined using Nissl staining. Compared to FVB control, our data demonstrated that in OVE26 mice (P < 0.05): 1) baroreflex-mediated bradycardia and tachycardia were decreased. 2) Baroreceptor afferents innervate the aortic arch with “flower-sprays” and “end-nets”-like terminals. The size of these terminals was reduced. However, ADNA in response to MAP increase did not differ (P > 0.01). 3) Vagal efferents innervated cardiac ganglionic principal neurons (PNs) with basket endings. The percent of vagal-innervated PNs and the number of Dil-labeled synaptic-like varicosities around PNs were decreased. However, bradycardic responses to vagal efferent stimulation were increased. 4) Bradycardic responses to ADN stimulation and L-glutamate injection into NA were decreased. The number of NA motoneurons was reduced. We conclude that diabetes impairs baroreflex sensitivity, remodels baroreceptor afferent and vagal efferent terminal structures, and reduces the central mediation of baroreflex. Since ADNA was preserved in response to MAP increase and HR responses to vagus stimulation were augmented, we conclude that the central deficit contributes to the decreased baroreflex sensitivity in OVE26 diabetic mice.

Attenuated baroreflex function in response to antecedent hypoglycemia — does this play a role in the mortality associated with rigorous control of diabetes?

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Objective: To investigate the autonomic cardiovascular response during transient, short-term hemodynamic fluctuations induced by sequential boluses of nitroprusside and phenylephrine (modified Oxford technique) after an exposure to hypoglycemia.
**Background:** Recent evidence suggests that while intensive control of hypoglycemia improves the outcome of individuals with diabetes and critically ill patients, hypoglycemia may be associated with a high mortality risk. This mortality is not directly related to hypoglycemia. We hypothesized that prior exposure to hypoglycemia would impair the autonomic responses to cardiovascular stress and that this impairment may contribute to the increased mortality observed with rigorous glycemic control.

**Methods:** Healthy subjects participated in two 3-day admissions, separated by 1–3 months. During each admission, modified Oxford test was performed on Days 1 and 3 with a 2 hours hyperinsulineemic [hyperglycemic (50 mg/dl) or euglycemic (90 mg/dl)] clamp performed in the morning and repeated in the afternoon of Day 2. Cardiac vagal baroreflex function was characterized by sigmoid function curve. Threshold, mid and saturation values of blood pressure and RR interval were mathematically identified, arterial baroreflex sensitivity was calculated as the slope of the quasi-linear part of the sigmoid baroreflex curve.

**Results:** Blood pressure and heart rate measured at baseline were similar on both Day 3 sessions (mean arterial pressure: 82 ± 5 vs. 83 ± 7 mmHg; heart rate: 64 ± 9 vs. 65 ± 9 bpm). The baroreflex sensitivity was significantly reduced on the post-hypoglycemia compared to the post-euglycemia Day 3 (11.9 ± 4.5 vs. 15.6 ± 7.5 mmHg/mmHg, P < 0.05) while the baroreflex sigmoid function curve shifted towards higher blood pressure (systolic blood pressure midpoint of the sigmoid curve: 132 ± 10 vs. 127 ± 12 mmHg, P < 0.05; RR interval midpoint of the sigmoid curve: 977 ± 138 vs. 913 ± 267 ms, P = NS).

**Conclusion:** The present data suggest that cardiac baroreflex response is attenuated following antecedent hypoglycemia and the baroreflex function curve resets to a higher blood pressure. Attenuation of baroreflex sensitivity is an independent predictor of mortality in post-myocardial infarction patients and thus may contribute to the increased mortality observed in some studies of rigorous glycemic control.

### Loss of coupling between cerebral blood flow and blood pressure in diabetic autonomic neuropathy

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**Background and purpose:** Previous researches utilized cross-correlation function (CCF) to assess the dynamics of cerebral autoregulation (CA) by investigating the phase-shift relationship between mean arterial blood pressure (MABP) and mean cerebral blood flow velocity (MCBF) in normal subjects and diabetics. In this study, we adopted modified CCF to assess the coupling between MABP and MCBF and the effects of the severity of diabetic autonomic neuropathy (AN) on dynamic CA.

**Materials and methods:** Three groups of subjects were included in this study: group (1) 11 normal subjects (8 M/3 F; mean age = 56.5 ± 8.6 y/o); group (2) 15 diabetes without autonomic neuropathy (DM) (10 M/5 F; mean age = 56 ± 16.0 y/o); (3) 18 diabetes with severe AN (DAN) (12 M/6 F; mean age = 61.6 ± 10.9 y/o). MABP and MCBF signals were acquired respectively using Finapres and TCD, in severe AN (DAN) (12 M/6 F; mean age = 61.6 ± 10.9 y/o). MABP and MCBF were measured during supine position.

**Results:** The average delayed time in supine position was decreased significantly from normal subjects (1.65 seconds + 0.60) to DM group (1.42 seconds + 0.61) but increased in DAN group (4.85 seconds + 2.25). The percentage of coupling of MABP and MCBF curve significantly decreased from above 60% in normal subjects to below 20% in DAN. The tilting phase-shift relationship of MABP and MCBF was much more inconsistent in all groups.

**Conclusions:** Our study showed that there is close linear relationship between MABP and MCBF in normal subjects. Loss of coupling between MABP and MCBF occurs and is related to the severity of diabetic AN.

### Head-up tilt induced vasoconstriction is preserved in dopamine-β-hydroxylase deficiency

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**Background:** Dopamine-β-hydroxylase (DBH) deficiency is characterized by a complete lack of noradrenaline and profound orthostatic hypotension. Affected individuals are treated with L-threo-dihydroxyphenylserine (L-DOPS, droxidopa), which is converted directly into noradrenaline. During head-up tilt (HUT), the sympathetic nervous system, with noradrenaline as key neurotransmitter, maintains blood pressure by peripheral vasoconstriction. However, in spinal cord-injured individuals, who lack central sympathetic input, HUT induced vasoconstriction is preserved.

**Methods:** A 26-year-old female with DBH deficiency was studied twice: two weeks after stopping her daily L-DOPS medication (resulting in undetectable noradrenaline levels) and two months after resuming L-DOPS medication. Leg blood flow (LBF) (echo Doppler) of the superficial femoral artery and mean arterial blood pressure (MAP) (Portapres) were measured during supine and 30° HUT on both occasions. Leg vascular resistance (LVR) was calculated as MAP divided by LBF.

**Results:** Baseline LVR off medication (0.30 ± 0.02 AU) was significantly lower than baseline LVR on medication (0.69 ± 0.06 AU). On medication, LVR increased during 30°HUT to 3.27 ± 0.92 AU. Surprisingly, when off medication, LVR also increased during 30°HUT to 1.02 ± 0.10 AU, but this increase was significantly lower than on medication.

**Conclusions:** In DBH deficiency, HUT induced vasoconstriction is preserved when a patient is off L-DOPS medication for 2 weeks. Apparently, noradrenaline is not essential for HUT induced vasoconstriction. Since the increase in LVR off medication is lower than on medication, compensation for the absence of circulating noradrenaline is incomplete.

### A steep fell in cardiac output is the main determinant of hypotension during drug free and nitroglycerine induced orthostatic vasovagal syncope

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**Background:** It is unknown how much of the hypotension occurring during a tilt-induced vasovagal response is cardiac output-mediated and how much can be ascribed to a fall in systemic vascular resistance. The contribution of both determinants may be affected by the use of vasoactive drugs.
Methods: A total of 56 patients with suspected vasovagal syncope and a positive response to tilt testing were included (age 36 ± 19 years, 37 females). During tilt testing, presyncope was provoked in 29 patients by 0.4 mg sublingual NTG, administered after 20 minutes in the passive head-up tilt position. In the other patients (n = 27), mean time from the beginning of tilt to drug-free presyncope was 20 ± 11 minutes. Finger arterial pressure was monitored continuously (Finometer). Left ventricular stroke volume was computed from the pressure pulsations (Modelflow).

Results: After NTG administration, there was a marked rise in heart rate, with peak heart rate similar to that in patients with a drug-free tilt-induced vasovagal response (106 ± 18 vs. 103 ± 18 bpm; P = 0.532). During the last 4 minutes prior to presyncope, none of the circulatory data differed significantly between groups. On average in all patients, hypotension was mediated by a fall in CO (P < 0.001), while SVR was well maintained until the onset of presyncope. Also in those patients who had a reduction in SVR at presyncope (22 out of 56), the main determinant of hypotension was a fall in CO.

Conclusions: Hypotension in routine tilt testing is cardiac output-mediated, the mechanism of which is not dependent on the administration of 0.4 mg sublingual NTG. In some patients, there is an accompanying fall in systemic vascular resistance; however, our data challenge the conventional idea that systemic vasodilatation is the overriding cause of hypotension during a tilt-induced vasovagal response.

Inadequate cutaneous vasoconstriction in the heat stressed human at the onset of syncopal symptoms during an orthostatic challenge

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Background: As much as 50% of cardiac output is distributed to the skin in the heat stressed human. Therefore, in this thermal condition neural control of cutaneous vascular conductance (CVC) becomes critical for the maintenance of blood pressure during an orthostatic challenge. This project tested the hypothesis that under such conditions inadequate cutaneous vasoconstriction may contribute to heat stress-induced orthostatic intolerance.

Methods: Data were analyzed from 36 heat stress orthostatic challenges, in which each subject experienced syncopal symptoms resulting in termination of the orthostatic challenge. Subjects were instrumented for the measurement of internal temperature (telemetry pill), forearm skin blood flow (laser-Doppler flowmetry), arterial blood pressure (Finometer or brachial artery catheterization), and heart rate (ECG). CVC was calculated as skin blood flow/mean arterial blood pressure × 100. While heat stressed (increase internal temperature (~1°C)), subjects were exposed to LBNP (n = 31) or 70° upright tilt (n = 5). Data were averaged from the period while subjects were normothermic, while heat stressed immediately prior to the orthostatic challenge, and at 5 seconds increments for the 2 minutes period preceding syncopal symptoms and subsequent cessation of the orthostatic challenge.

Results: Whole-body heat stress significantly increased heart rate (57 ± 9 to 87 ± 15 bpm; mean ± SD) and CVC (30 ± 19 to 156 ± 54 CVC units), without altering mean arterial blood pressure (83 ± 7 to 81 ± 6 mmHg). Immediately prior to termination of the orthostatic challenge due to syncopal symptoms, mean arterial blood pressure was reduced to 55 ± 8 mmHg (P < 0.001). At test termination CVC was significantly decreased to 131 ± 55 units, relative to before the orthostatic challenge; however at this time CVC was ~4 fold greater when compared to normothermic CVC.

Conclusion: A relatively trivial reduction in CVC during the orthostatic challenge, at a time of pronounced baroreceptor unloading, suggests that an inadequate cutaneous vasoconstrictor response may contribute to reduced orthostatic tolerance in heat stressed humans.

Diminished diurnal variations of blood pressure in postural tachycardia syndrome

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Background: Circadian profile of blood pressure (BP) particularly with lack or attenuation of night time BP lowering (dipping) has been reported associated with abnormal sympathetic nervous activities and autonomic dysfunction. Many patients with postural tachycardia syndrome (POTS) have excessive sympathetic activity during daytime. However, little is known about the diurnal blood pressure variations in POTS. We hypothesize that POTS patients have excessive sympathetic nerve activity during night which prevents blood pressure dipping.

Methods: We recorded ambulant 24-hours BP and heart rate (card(X)Trace, Meditech Ltd, Hungary) every 30 minutes in patients with POTS (n = 15, 14 female, age = 34 ± 10) and control subjects (n = 8, seven female, age = 30 ± 5). We collected 24-hours urine to measure urine catecholamines. Blood draw to measure plasma catecholamines were performed after at least 30 minutes supine and 15 minutes upright position. Autonomic function tests were also performed. The dipper subjects were defined as those whose nocturnal decrease of systolic BP was >10% of daytime BP.

Results: POTS had a significant lower number of dippers with 33% as compared to healthy control with 88% (Chi-Square P = 0.013). Mean supine and upright plasma catecholamines were significant higher in POTS patients. Urine volume and catecholamines level had no differences between POTS patients and control subjects. Patients with POTS who have non-dipper pattern showed extremely exaggerated Valsalva ratio compared to dipper pattern POTS patients (2.02 ± 0.50 and 1.59 ± 0.26 respectively, P < 0.05).

Conclusions: This study suggests that most POTS patients have diminished diurnal variation of BP. It possibly relates to altered sympathetic autonomic outflow and could be used for pathophysiological differentiation.

Low dose propranolol is effective at decreasing orthostatic tachycardia and improves symptoms in postural tachycardia syndrome (POTS)

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Background: While counter-intuitive, many patients with POTS (HR increase >30 bpm on standing) report symptomatic deterioration when treated with beta-blockers. Stewart found that a beta-1 antagonist did not improve orthostatic intolerance or hemodynamics. Our anecdotal experience has been that patients with POTS respond quite well to low dose beta-blockade. We prospectively tested the hypothesis that low dose propranolol would decrease orthostatic tachycardia and improve symptoms in POTS.

Methods: Patients with POTS (n = 38; 34 female, 33 ± 2 years) underwent a randomized single-blind crossover trial with oral propranolol 20 mg and placebo on separate mornings. Patients were studied 2 hours after breakfast in a drug-free state. Non-invasive heart rate (HR) and blood pressure (BP) were measured with the patient seated comfortably. At baseline, and hourly for 4 hours post-medication, the patients stood for up to 10 minutes, and their standing HR and BP recorded. Symptoms were self-recorded q2 hourly. Only complete datasets for each parameter were
One month of non-selective beta-adrenergic blockade treatment normalizes vasomotor sympathetic activity without improving symptoms during upright tilt in the postural orthostatic tachycardia syndrome

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Background: Recent studies have shown that patients with the POTS have enhanced vasomotor sympathetic activity during orthostasis. We tested the hypothesis that one month of non-selective beta-adrenergic blockade normalizes upright sympathetic activity in these patients.

Methods: Seventeen POTS patients (16 females and 1 male, aged 29 ± 9 (SD) year) were treated with either placebo (n = 10) or propranolol (n = 7, oral 80 mg qd) for one month. A tilt-table test (60° for 45 minutes or till presyncope) was performed pre- and post-treatment. Female patients were studied during the luteal phases of their menstrual cycles. Muscle sympathetic nerve activity (MSNA), blood pressure (BP), and heart rate (HR) were recorded continuously, while blood samples for catecholamines were taken intermittently in the supine position and during upright tilt. Patients’ quality of life was assessed using a SF-36 form pre- and post-treatment.

Results: Propranolol did not alter orthostatic tolerance in POTS patients (tilt time, 34 ± 15 pre- vs. 36 ± 16 minutes post-treatment; P = 0.469). MSNA was lowered modestly but significantly by propranolol in both supine and upright positions (from 18 ± 9 supine to 50 ± 12 bursts/minutes after 5 minutes of tilt pre- vs from 11 ± 7 to 40 ± 14 bursts/minutes post-treatment; P = 0.030 for treatment, 0.001 for protocol, and 0.452 for treatment x protocol); after treatment, MSNA was not different between patients and healthy controls (from 14 ± 8 supine to 35 ± 10 bursts/minutes upright; P = 0.920 for groups, <0.001 for protocol, and 0.082 for group x protocol).

Propranolol tended to decrease plasma norepinephrine concentration in both supine and upright positions (P = 0.063 for treatment, 0.003 for protocol, and 0.245 for treatment x protocol). As expected, HR was markedly lowered by propranolol in POTS patients (from 89 ± 14 supine to 117 ± 14 beats/minutes upright pre- vs. from 72 ± 16 to 93 ± 17 beats/minutes post-treatment; P = 0.002 for treatment, <0.001 for protocol, and 0.209 for treatment x protocol). BP did not change significantly after one month of propranolol treatment. Despite these changes, patients’ quality of life remained unchanged after treatment [for physical health P = 0.861 for groups (placebo or propranolol)], 0.145 for treatment, and 0.511 for group x treatment; for mental health P = 0.785 for groups, 0.557 for treatment, and 0.576 for group x treatment].

Conclusions: These results suggest that although non-selective beta-adrenergic blockade normalizes vasomotor sympathetic activity and heart rate during orthostasis in patients with POTS, it does not improve the quality of life in these patients. More effective therapies to improve not only the POTS symptoms but also patients’ overall well-being are needed.

Saturday, November 1, 2008
Oral Presentations

The cutaneous architecture of autonomic nerve fiber innervation

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Objective: To identify the sympathetic adrenergic and sympathetic cholinergic innervation of cutaneous dermal structures.

Background: Pathologic evaluation of the autonomic nervous system is traditionally relegated to post-mortem study. However, the skin is abundantly innervated by autonomic nerve fibers that are easily accessible by punch biopsy. To date, there are no systematic studies of cutaneous autonomic innervation. Cutaneous nerve fibers have noradrenergic origins and differentiate into both noradrenergic and cholinergic neurons in early life; these make up a substantial proportion of all nerve fibers in the skin.

Design/methods: Punch skin biopsies were obtained from healthy control subjects at the leg, thigh, and forearm. Tissues were double or triple stained by immunofluorescence using combinations of protein gene product (PGP) 9.5, tyrosine hydroxylase (TH), vasoactive intestinal peptide (VIP), substance P (SP), calcitonin gene related peptide (CGRP), platelet endothelial adhesion molecule (CD31) and collagen IV. Confocal digital images were obtained and nerve fiber location and density was analyzed.

Results: Arrector pili muscles are primarily innervated by sympathetic adrenergic fibers (TH). Most of the nerve fibers surrounding sweat glands are sympathetic cholinergic (VIP), but there is some colocalization with sympathetic adrenergic fibers (TH). Sweat glands are highly vascular structures, with dense networks of capillaries weaving through the glands. The cutaneous vascular network has complex innervation that includes sympathetic cholinergic (VIP), sympathetic adrenergic (TH) and sensory fibers (SP). Hair follicles are predominantly innervated by sensory fibers, with few sympathetic cholinergic but no sympathetic adrenergic innervation.

Conclusions: Evaluation of the skin by 3 mm punch biopsy provides a unique window of access to the autonomic nervous system through a minimally invasive, repeatable procedure. Abundant autonomic innervation can be readily identified around a variety of dermal structures and may present a novel approach to the diagnosis and treatment of disorders of the autonomic nervous system.

Intradermal angiotensin-II administration attenuates the local cutaneous vasodilator heating response

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The vasodilation response to local cutaneous heating is nitric oxide (NO) dependent, blunted in postural tachycardia (POTS) but reversed by angiotensin-II type-1 receptor (AT1R) blockade. We tested the hypothesis that localized infusion of angiotensin-II attenuates vasodilatation to local heating in healthy volunteers. We heated skin of the calf at 42°C and measured local blood flow to assess conductance (%CV)max in eight healthy volunteers aged 19.5–25.5 years. Initially, two experiments were performed: in one, Ringer solution was perfused in three catheters, the response to
heating measured, 2 μg/l losartan, 10 mM NLA, or NLA + losartan were added to perfusate, and the heat response was remeasured; in another 10 μM Ang-II was given, the heat response measured, losartan, NLA, or NLA + losartan were added to Ang-II, and the heat response reassessed. The heat response decreased with angiotensin-II, particularly the plateau phase (47 ± 5 vs. 84 ± 3 %CV/max). Losartan increased baseline conductance in both experiments (from 8 ± 1 to 20 ± 2 and 12 ± 1 to 24 ± 3). Losartan increased Ang-II response (83 ± 4 vs. 91 ± 6 in Ringer). NLA decreased both angiotensin and Ringer responses (31 ± 4 vs 43 ± 3). NLA+ losartan to confirm graded responses. Sodium ascorbate (10 mM) restored the Ang-II blunted heating plateau. NOS and AT1R inhibition cause an NO-independent angiotensin-mediated vasodilation with local heating. Angiotensin-II mediates AT1R blunting of local cutaneous vasodilator heating response.

Intradermal norepinephrine administration attenuates the local cutaneous vasodilator heating response

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The vasodilation response of non-glabrous skin to local heating is characterized by a plateau phase that is nitric oxide (NO) dependent. Implicit is its independence from adrenergic vasoconstriction. To investigate this assumption we tested the effect of norepinephrine and phenolamine administered by intradermal microdialysis on the local heating response measured by laser Doppler Flowmetry (LDF) in 5 healthy volunteers. α-adrenergic blockade with 100 μM phenolamine and presynaptic depletion of endogenous NE with 10 mM bretylium tosylate caused a significant increase in basal cutaneous blood flow (220%, P < 0.004, and 170%, P < 0.004, respectively compared to control). NE (0.01–1,000 μM) was infused through catheters previously containing bretylium and had no effect on basal cutaneous blood flow. Local heating of phenolamine and norepinephrine containing catheters was performed at 41°C for at least 30 minutes until a plateau was reached. All concentrations of NE tested caused a dose dependent decrease in amplitude of the “first” heat peak, a diminished “nadir” amplitude and a lowered “plateau” amplitude (P < 0.05) while phenolamine caused an increase. NE also shortened the time to achieve these values. We performed additional experiments using the nonspecific NOS inhibitor nitro-L-arginine (NLA 10 mM). This reduced all phases of the heat response which was further attenuated by 1 μM NE resulting in further reduction in the first peak amplitude (41%, P < 0.03), nadir amplitude (37%, P < 0.02), and plateau amplitude (35%, P < 0.005) when compared to NLA alone plus heat. The response of local skin blood flow to α-adrenergic blockade, depletion of NE stores and alteration of the heat response by NE, with and without NO inhibition indicate that regulation of local blood flow is accomplished by the interactions of receptor mediated, α-adrenergic mechanisms as well as the local productions of NO.

A dynamic analysis of sudomotor function in a human model of small fiber neuropathy

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Objective: To characterize the changes in sudomotor response over time in a human model of neuropathy.

Background: Quantitative direct and indirect reflex testing (QDIRT) is a novel method to assess sudomotor function. We have previously shown that capsaicin, applied in an occlusive dressing, creates a reliable model of autonomic nerve fiber degeneration and regeneration and leads to functional changes in sudomotor testing. We utilize the capsaicin model of neuropathy to study the changes in sudomotor function over time with QDIRT.

Methods: Ten healthy subjects had 0.1% capsaicin applied in a 48-hour occlusive dressing to one thigh with placebo applied to the opposite thigh. QDIRT testing involved iontophoresis of 10% ace- tycholine (2 mA for 5 minutes) followed by application of Alizarin red to identify sweat droplets. High-resolution photographs of both sites were taken every 15 seconds for 7 minutes. The sweat droplets were quantified by size, distribution and percent surface area in a 3 cm² region. QDIRT testing was done prior to and for 6 weeks following capsaicin/placebo treatment.

Results: The total sweat response and sweat droplet number did not change significantly in the placebo area during the study. Capsaicin caused a 36 ± 8% decline in direct sweat production (P < 0.05 vs. baseline) by day 7 mediated by a reduction in sweat droplet size (P < 0.05 vs. baseline) but not droplet number. Indirect sweat production decreased by 24 ± 6% (P < 0.05 vs. baseline) as a consequence of a decline in both sweat droplet number and size (P < 0.05 vs. baseline for number and size).

Conclusion: QDIRT allows for detailed quantification of the distribution and chronology of sweat droplet production in an autonomic model of neuropathy. The dynamic changes evident in total sweat area and droplet number suggest QDIRT may play a valuable role in studies of small fiber neuropathy.

Quantitative sudomotor axon reflex test (QSART) in HIV-infected patients with anti-retroviral therapy (ART)-associated neuropathy

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HIV-infection is well known to cause autonomic neuropathy and small-fiber predominant polyneuropathy. Cardiac autonomic reflex abnormalities have previously been described in HIV-positive patients, but sudomotor evaluation using QSART has not been studied in this population. Thirteen HIV-positive patients with symptoms and signs of neuropathy and seven without either, all of whom on ART were evaluated with QSART, a brief neurological survey, and the Utah early neuropathy score (UENS). Six were female and ten were of non-white race, with median age 47.5 years, CD4 390 cells/mm³, and viral load 50 copies/mL. Median sweat volume (μl) was lower in cases vs. controls at all testing sites except the forearm (P = 0.01). The total UENS score and pin sensation subscore were higher in cases than controls (P = 0.015 and 0.016 respectively). Sweat volume at the foot correlated with pin sensation subscore of UENS (r = -0.564, P = 0.045) and deep tendon reflexes at the ankle (r = -0.675, P = 0.01). QSART is abnormal in HIV-positive patients with peripheral neuropathy. QSART was highly correlated with neuropathy specific scores. Further testing is needed to determine if sudomotor abnormalities correlate with other measures of autonomic function in HIV-positive patients.

Enhancement of CGRP receptor signaling: a novel approach to improving autonomic regulation in normal and hypertensive states

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Calcitonin gene-related peptide (CGRP) is a powerful vasodilator. In addition, CGRP and its receptor are expressed in sensory nerves and brain regions that regulate autonomic function. We hypothesized that
enhancement of CGRP receptor signaling would improve autonomic regulation. We tested this hypothesis by measuring blood pressure (BP), heart rate (HR), and autonomic indices in conscious hRAMP1 transgenic (n = 5) and littermate control mice (n = 5). hRAMP1 mice express human Receptor Activity-Modifying Protein-1, a component of the CGRP receptor known to enhance responses to CGRP. Telemetric recordings of BP and HR were obtained at baseline and during angiotensin-II (Ang-II)-induced hypertension (1,000 ng/kg/minute for 2 weeks). Compared with control mice under baseline conditions, hRAMP1 mice were normotensive (113 ± 3 vs. 120 ± 3 mmHg, NS); possessed much higher baroreflex sensitivity (BRS, sequence technique) (2.83 ± 0.31 vs. 1.59 ± 0.10 ms/mmHg), HR variability (SD of pulse intervals, 5.9 ± 0.9 vs. 2.2 ± 0.8 ms), and beat-to-beat parasympathetic modulation of pulse interval (RMSSD, 4.1 ± 0.3 vs. 1.4 ± 0.3 ms); and lower BP variability (SD of systolic BP, 5 ± 1 vs. 25 ± 2 mmHg) (P < 0.05 for all comparisons). Ang-II induced hypertension was accompanied by decreases in BRS and HR variability, and increased BP variability. During Ang-II infusion, hRAMP1 mice exhibited less hypertension (129 ± 3 vs. 170 ± 4 mmHg), less BP variability (6 ± 1 vs. 39 ± 5 mmHg), higher BRS (1.88 ± 0.12 vs. 0.73 ± 0.03 ms/mmHg), and higher HR variability (11.2 ± 1.5 vs. 1.4 ± 0.3 ms) (P < 0.05 for all comparisons).

Conclusions: Transgenic expression of hRAMP1 improves autonomic regulation and attenuates Ang-II-induced hypertension. The results suggest a novel role for CGRP in mediating cardiovascular protection via favorable effects on autonomic balance and identify RAMP1 as a therapeutic target in hypertension.

Tilt training increases the vasoconstrictor reserve in patients with neurally mediated syncope evoked by head-up tilt testing

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Tilt training is a useful therapeutic option in neurally mediated syncope. We tested the hypothesis that tilt training will restore orthostatic tolerance by increasing the degree of vasmotor reserve during sustained orthostatic stress. In this follow-up study, 17 patients (age 31 ± 22 years, 11 females) with a clinical diagnosis of neurally mediated syncope and two consecutive positive tilt tests were enrolled. The head-up tilt test was repeated day after day: one session per day. ECG and finger arterial blood pressure (Portapres) were recorded during subsequent tilt testing. Left ventricular stroke volume, cardiac output and systemic vascular resistance were computed from the pressure pulsations (Modelflow). Spontaneous cardiac baroreflex sensitivity was estimated by cross-spectral analysis of heart rate and systemic blood pressure. In all patients, orthostatic tolerance was restored after 4.1 ± 0.9 tilt sessions, median 4. This was accompanied by a significant rise in systemic vascular resistance to compensate for a postural reduction in stroke volume in the sustained head-up tilt position. No evidence could be provided of altered baroreflex control of heart rate after tilt training. Tilt training restores orthostatic tolerance at least in part by increasing the amount of sympathetic vasoconstriction that can ultimately be made available during sustained orthostatic stress.

The effect of nitroglycerine and desmopressin on blood pressure, nocturnal polyuria and morning orthostatic tolerance in the hypertension of autonomic failure

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Supine hypertension affects about half of patients with primary autonomic failure (AF), complicates the treatment of orthostatic hypotension (OH) and induces nocturnal polyuria, resulting in worsening of morning OH symptoms. We hypothesized that the combination of a vasodilator (nitroglycerine patch [NTG] 0.1 mg/hour) and an antidiuretic (desmopressin [DDAVP] 0.2 mg po) would decrease both nighttime blood pressure (BP) and nocturnal polyuria with improvement of orthostatic tolerance in the morning. Seven patients with severe AF and supine hypertension (5 men, 66 ± 2.7 year) received placebo, NTG and the combination NTG and DDAVP at 8 pm on separate nights in a single blind, crossover study. NTG was removed at 6 am. BP was monitored every 2 hours for 12 hours and orthostatic BP was measured at 8 am. Compared with placebo, NTG and the combination decreased systolic BP during the night by a maximum of −40 ± 11 and −35 ± 8 mmHg, respectively (P < 0.05). Nighttime diuresis (8 pm to 8 am) was significantly reduced with the combination (561 ± 48.5 ml vs. 1229.5 ± 179.5 ml with placebo, P < 0.01), whereas the decrease with NTG was not significant (711.5 ± 72.3 ml). At 8 am, supine SBP was similar between groups (173 ± 5 mm Hg with placebo vs. 172 ± 6 and 176 ± 6 mm Hg with NTG and the combination, respectively). Upright SBP at 1 minute. was not different between groups, but orthostatic tolerance (standing time) improved with the combination compared to placebo (P < 0.05). In conclusion, NTG is effective in controlling supine hypertension in AF. The addition of DDAVP decreases nighttime diuresis and improves orthostatic tolerance in this morning. This might be a useful alternative to treat patients with this condition.

Acute sympathetic vasoconstrictor tone reduction with electrical carotid sinus stimulation in patients with refractory hypertension

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Background: In animals, electrical field stimulation of baroreceptor afferents elicits a depressor response through sympathetic inhibition. Whether or not a similar response occurs in human subjects is unknown.

Methods: We studied twelve patients with treatment resistant arterial hypertension (seven men and five women, 43–70 years, arterial pressure 193 ± 9/94 ± 5 mmHg on medications). In all patients, a bilateral electrical baroreflex stimulator at the level of the carotid sinus (RHEOS, CVRx) had been implanted at least one month before the study. We measured intra-arterial blood pressure, heart rate, muscle sympathetic nerve activity (MSNA), and plasma renin concentration. Measurements were performed under resting conditions with and without electrical baroreflex stimulation for at least six minutes during the same experiment.

Results: Acute electrical baroreflex stimulation decreased systolic blood pressure by 32 ± 10 mmHg (range +7 to −108 mmHg, P = 0.01). The depressor response was correlated with reduction in MSNA (r = 0.42, P < 0.05). In responders, MSNA decreased sharply when electrical stimulation was begun. Then, MSNA increased but remained below the baseline level throughout the stimulation period. Heart rate decreased 4.5 ± 1.5 bpm with stimulation (P < 0.05). Plasma renin concentration was lowered by 27% (P < 0.05).
Conclusion: Electrical field stimulation of carotid sinus baroreflex afferents acutely decreases arterial blood pressure in a sub-group of patients with treatment resistant arterial hypertension. The depressor response is mediated through sympathetic inhibition.

Ongoing clinical trials of droxidopa. An interim update

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Currently, there are two pivotal, proof-of-efficacy, global, Phase III studies of droxidopa, a synthetic precursor of norepinephrine, being conducted in patients with neurogenic orthostatic hypotension (NOH). Droxidopa 301 is a randomized induction design study; Droxidopa 302 is a randomized withdrawal design study. Both studies employ a unique titration-to-effect, enrichment phase in the treatment protocol. We will provide an overview of the status of these clinical trials as of the time of the meeting. Specifically, preliminary data on open-label, titration-to-effect phase in both studies will be presented. We will also present data on the utility of the enrichment design approach, as well as an estimate of the optimal dose and magnitude of benefit.

POSTER SESSION I

Poster #1
Alpha adrenergic contribution to the resting autonomic support of arterial blood pressure in healthy men versus women

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The autonomic nervous system (ANS) plays a critical role in the regulation of resting arterial blood pressure (BP). Tonic support of BP by the ANS has been shown to differ with aging as well as between premenopausal women and men of similar age. The purpose of this study was to evaluate the contribution of the alpha adrenergic receptors to resting blood pressure level in young men and women. The maximal decrease in BP after alpha adrenergic blockade by phentolamine was compared between 17 normotensive young men (age, 26 ± 1 years; body mass index 25 ± 1 cm/kg², mean ± SEM) and 17 women (age, 24 ± 1 years; body mass index 22 ± 1 cm/kg²). As a further measure of the alpha adrenergic contribution to BP regulation, the change in BP after phentolamine was correlated to resting multi unit muscle sympathetic nerve activity (MSNA). Men had significantly lower baseline BP (brachial artery catheter) compared to men (SBP 126 ± 1 mmHg vs. 139 ± 3, P < 0.001; DBP 70 ± 1 vs. 75 ± 1, P = 0.003; MAP 90 ± 1 vs. 96 ± 2, P = 0.008). There was a significantly smaller decrease in SBP and MAP in the women during phentolamine infusions compared to men (ASBP −6.4 ± 1.9 mmHg vs. −12.7 ± 2.2, P = 0.028; ΔMAP −10.0 ± 1.2 vs. −13.3 ± 1.1, P = 0.048), however, DBP only trended toward a difference (ΔDBP −9.7 ± 0.9 mmHg vs. −11.9 ± 0.9, P = 0.067). There was also a trend towards a lower baseline MSNA in the women (BF 20 ± 3 vs. 24 bursts/minutes ± 1, P = 0.091; B1 33 ± 5 bursts/100 hb vs. 42 ± 3, P = 0.055). In addition, baseline MSNA (BF) showed a modest negative correlation to changes in BP in women (r = −0.46, P = 0.061) but not in men (r = −0.16, P = 0.554). These data suggest there is a smaller role for the alpha adrenergic system in the tonic autonomic support of BP in women versus men.

Poster #2
Influences of gender on the interaction between sympathetic nerve traffic and central adiroposity

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Aim. Sympathetic activation promotes insulin resistance and arterial hypertension with increasing adiroposity. A difference in the relationship between adiposity and sympathetic activity between women and men could contribute to the known gender difference in cardiovascular disease risk. Objective. We tested whether or not muscle sympathetic nerve activity (MSNA) is correlated differently with waist circumference in women and in men.

Materials and methods: We pooled data from two microneurography centers (Berlin, Germany; Gdansk, Poland) for a cross-sectional study. We studied 111 normotensive, healthy Caucasian subjects (70 males and 41 females). Age ranged between 19 and 62 years and body mass index ranged between 18 and 40 kg/m². Supine heart rate, blood pressure, and MSNA were recorded after at least 30 minutes rest.

Results: MSNA in bursts/minutes was age-dependent in both sexes (r male = 0.56, r female = 0.34, P < 0.01). Controlling for waist and hip circumferences, age-dependence remained highly significant in men (r = 0.43) and women (r = 0.43). Controlling for age, in men, waist circumference (r = 0.25) and waist-hip ratio (WHR; r = 0.34) were predictive for MSNA and directly correlated (P < 0.01) but not in women.

Conclusion: Abdominal fat is an important adipose tissue depot linking obesity with MSNA in men but not in women. The phenomenon may contribute to the sexual dimorphism in cardiovascular disease risk.

Poster #3
Nitric oxide tonically modulates heart rate in humans

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We have previously reported that nitric oxide (NO) synthase inhibition with L-NMMA induces a potent pressor effect in humans (increase of ~30 mmHg in systolic blood pressure, SBP) if baroreflex buffering is eliminated with ganglionic blockade. We also observed a modest but consistent decrease in heart rate (HR), even in autonomically blocked subjects, suggesting a positive tonic modulation of NO on HR. Here we tested this hypothesis by comparing the heart rate effects of L-NMMA to equipressor doses of phenylephrine. In 12 normotensive subjects, L-NMMA (250 mcg/kg/minutes for 15 minutes) increased SBP by 28 ± 2 mmHg during autonomic blockade with trimethaphan (4 mg/minutes, to eliminate the baroreflex and autonomic/NO interactions). Phenylephrine boluses were titrated (100-300 mcg) to obtain similar increases in SBP (26 ± 3 mmHg). Autonomic blockade was documented by virtual abolition of HR and SBP variability (LFRRI decreased from 1545 ± 418 to 5 ± 2 ms, HFRRI from 1305 ± 505 to 4 ± 1 ms. LFSBP from 13.1 ± 2.6 to 2.4 ± 0.7 mmHg²). HR decreased signif-
Effects of atrial natriuretic factor on renal sympathetic nerve activity in anaesthetized rats

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Atrial Natriuretic Factor (ANF), a 28 amino acid peptide, is a circulating hormone that is synthesized, stored and released by atrial myocytes in response to increases in blood volume. A number of studies have shown that ANF play a pivotal role in the regulation of cardiovascular activity as well as renal homeostasis. It has potent biological activities, including vasodilation, natriuresis, diuresis, and inhibition of the secretion and actions of renin, angiotensin II, aldosterone, arginine vasopressin, ACTH and endothelin. However, little is known about the central action of circulating ANF on sympathetic outflow. Thus, in these experiments we investigate the effects of ANF, administered intravenously, on renal sympathetic nerve activity (RSNA). Experiments were carried out on male Sprague-Dawley rats anaesthetized with 1.3 g/kg urethane. After tracheotomy to facilitate breathing, and cannulation of both femoral artery and vein for direct blood pressure recording and administration of drugs, respectively, a branch of the renal nerve was dissected free from the surrounding connective tissues and placed on a bipolar electrode for RSNA recording. The neural signals were amplified and filtered (Neurolog) and displayed and analyised using a PowerLab data acquisition system (AD Instruments). Changes in blood pressure, heart rate and RSNA were measured following i.v. bolus infusions of ANF (250 ng, 500 ng and 5 ug). RSNA values were expressed as percentage changes from the baseline. The results showed that ANF exert dual actions. A low dose (250 ng) caused increases in RSNA (18 ± 4%) while higher doses (500 ng and 5 ug) caused no change or slight reductions in nerve activity (2 ± 6% and 0 ± 2% respectively). The increase in RSNA was attenuated by prior intrathecal infusions of a V1a antagonist. Acknowledgments: This work was supported by a grant from the Ministry of Higher Education, Malaysia. FRGS 203/PFARMASI/671153.

Cardiovascular and cardiac sympathetic contributions to respiratory sinus arrhythmia

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Objective: To evaluate the selective contributions of cardiac sympathetic and vagal activity to the respiratory sinus arrhythmia (RSA) generated by rhythmic deep breathing. Background: RSA is widely used clinically as a pure and independent estimate of cardiovascularg outflow. However cardiac sympathetic activity also exhibits strong respiratory modulation that should be reflected in the RSA. RSA is strongly dependent on the level of cardiac sympathetic activity and is enhanced by beta adrenergic blockade. RSA may also be generated by mechanical stretch of the atria induced by large fluctuations in tidal volume.

Design/methods: In order to obtain further insight into the simultaneous changes in cardiovascularg and cardiac sympathetic activity during RSA, we recorded beat to beat changes in RR intervals (RRI), and finger arterial pressure in 15 subjects breathing at 6 breaths/minute. We applied a novel time domain method which exploits the inherent property of scale covariance of signals to analyze RRI in the time domain. This non model driven methodology appears to decompose the beat to beat changes in RRI into velocities that reflect the parasympathetic and sympathetic components of cardiac autonomic activity.

Results: RSA typically consisted of a gradual decrease in RRI followed by a plateau phase and then a rapid increase in RRI. A clear pattern was observed in 9/15 subjects. In these subjects the initial tachycardia was due to decrease in vagal velocity while the plateau phase was associated with an increase in both vagal and sympathetic velocity. Abrupt bradycardia occurred as vagal velocity continued to increase while sympathetic velocity diminished.

Conclusions/relevance: Generation of RSA often reflects the complex interplay of changes in cardiovascularg and cardiac sympathetic activity. In some cases RSA appears to be generated by rhythmic deep breathing in the absence of obvious fluctuations in autonomic activity.

Progesterone alters Schwann cell growth in culture

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Background: It is not clear why dysautonomias predominantly affect women. We have observed autonomic dysfunction in a subset of peri- and post-menopausal patients that is relieved by hormone replacement therapy. We hypothesize that fluctuating levels of progesterone and estrogen in these patients may result in autonomic dysfunction, as these neuroactive steroids may exert neuroprotective actions. Changes in autonomic function may reflect abnormal responses of different cell types within the PNS, such as Schwann cells, to many different factors, including neuroactive steroids. Therefore, we investigated the action of progesterone on Schwann cells.

Materials and Methods: We examined whether a 10 minute incubation with 10 and 100 nM progesterone induces a selective change in the cellular responses of Schwann cells. We compared the action of progesterone with that of estrogen, and observed that progesterone and estrogen in these patients may result in autonomic dysfunction, as these neuroactive steroids may exert neuroprotective actions. Changes in autonomic function may reflect abnormal responses of different cell types within the PNS, such as Schwann cells, to many different factors, including neuroactive steroids. Therefore, we investigated the action of progesterone on Schwann cells.

Discussion: Inhibition of ERK (p42/44 MAPK), p38 MAPK, and JNK has been reported to alleviate neuropathic pain. Progesterone and estrogen in these patients may result in autonomic dysfunction, as these neuroactive steroids may exert neuroprotective actions. Changes in autonomic function may reflect abnormal responses of different cell types within the PNS, such as Schwann cells, to many different factors, including neuroactive steroids. Therefore, we investigated the action of progesterone on Schwann cells.

The pressor effect of water: mechanism and location of action

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Water ingestion induces a robust pressor response in patients with autonomic dysfunction and in mice post sinoaortic deafferentation.
Heart rate variability during the Valsalva maneuver partially explains ethnic differences in blood pressure in a rural population in Hawaii

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Background: Large ethnic disparities in the incidence of hypertension have been observed in many clinical and epidemiological studies. Clinical studies examining heart rate variability in relation to blood pressure have suggested autonomic dysfunction plays a significant role in determining blood pressure regulation. We examined the relationship of ethnicity and heart-rate variability during the Valsalva maneuver in relation to systolic and diastolic blood pressure in a multiethnic population in Hawaii in a preliminary study of the first 115 participants of this multiethnic study.

Methods: All participants were free of diabetes, and refrained from use of medications or drugs known to alter HRV, nor used over-the-counter medications for 24 hours prior to testing. The major ethnic groups represented in the study population were Asian, Caucasian, and Hawaiian/Part-Hawaiian. Heart rate was recorded during a Valsalva maneuver. The Valsalva ratio (VR) was calculated as the ratio between the longest R–R interval shortly after the maneuver and the shortest R–R interval during the maneuver. General linear models were used to compare ethnic differences in mean SBP and DBP while adjusting for VR.

Results: Caucasian participants had significantly lower SBP (P < 0.01) and DBP (P < 0.05) compared to either Asians or Hawaiians, and these differences were not explained by ethnic differences in age, gender or body weight distributions. The association between VR and both SBP (r = 0.32, P < 0.0) and DBP (r = 0.27) were statistically significant (P < 0.05), and were independent of ethnicity. The associations between ethnicity and either SBP or DBP were only slightly attenuated after adjustment for VR.

Conclusions: The VR is driven largely by the parasympathetic system, suggesting decreased parasympathetic tone partially explains ethnic variation in SBP and DBP. The persistent ethnic variation in both blood pressure parameters suggest other mechanisms also play an important role in explaining the observed ethnic disparity. Future analyses will assess the possible independent effects of sympathetic tone, diet, and physical activity.
Methods: We tested 77 participants in four communities on the Island of Hawaii. None had diabetes, were current smokers, used medications or drugs known to alter HRV, nor used over-the-counter medications for 24 hours prior to testing. Heart rate was recorded during a Valsalva maneuver, and during spontaneous and paced deep breathing at 6 breaths per minute. The Valsalva ratio was calculated as the ratio between the longest R–R interval shortly after the maneuver and the shortest R–R interval during the maneuver. Multiple linear regression was used to estimate the association between VR and each pulmonary parameter with adjustments for age and height. Forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were selected by American Thoracic Society criteria from 6–8 maneuvers per subject.

Results: Neither VR nor any of the spirometry measurements differed significantly by community, so all analyses were pooled. Decreased VR was associated with decreasing FEV1 (P = 0.008) and FVC (P = 0.01). This association persisted after adjusting for height 2.

Conclusion: The relationship between pulmonary function and HRV in this normal population was similar to earlier reports among patients with COPD. While the premise that chronic hypoxia may be associated with autonomic dysfunction cannot be dismissed, the absence of severe pulmonary pathology in this population suggests other mechanisms are also important in explaining this association.

Poster #11
Heart rate variability during autonomic blockade
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Introduction: The study aimed at analysing the effects of beta-adrenoeceptor and muscarinic receptor blockade on heart rate variability in young healthy men.

Patients and Methods: 12 men aged 26 ± 2.4 years were included. They were studied on two occasions receiving constant infusion of saline or metoprolol in random order. A priming dose of 5 mg metoprolol was followed by infusion of 0.025 mg minutes kg−1 four times with an interval of 20 minutes. Before and following each atropine dose, subjects were submitted to 10 minutes of head-up tilt to 60 degrees. Heart rate variability was quantified by mean and standard deviations of normal R–R interval length (meanNN and SDNN, respectively), root mean successive squared difference (RMSSD) and through frequency analysis by low and high frequency components (LF and HF).

Results: Beta-blockade had no effect on heart rate variability in the supine or in the tilted position. In the supine position, the first dose of atropine induced an increase in meanNN and in RMSSD on both occasions, whereas HF only increased during beta-blockade. Following this, atropine caused a dose dependent decrease in meanNN, SDNN, and RMSSD on both occasions in the supine position, whereas LF increased and HF decreased in this position only after beta-blockade. In the tilted position, the first dose of atropine caused an increase in SDNN without beta-blockade and in meanNN during beta-blockade. Following this, atropine caused a dose dependent decrease in mean NN, SDNN, and RMSSD on both occasions during tilt, whereas LF increased and HF decreased only without concomitant beta-blockade.

Conclusion: Heart rate variability was unaffected by beta-blockade. Muscarinic blockade showed agonism at low and antagonism at higher doses. The responses were unaffected by body position and were less consistent using frequency analysis.

Poster #12
Use of wavelet analysis of heart rate variability in the differentiation of normal and emphysema subjects while at rest and during exercise
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Significant respiratory effects limit evaluation of autonomic modulation by standard frequency analysis of heart rate variability (HRV) in exercise and other dynamic states. We developed a method using wavelet statistical analyses combined with cluster analysis to evaluate HRV in the face of such respiratory effects.

Method: Ten emphysema subjects (ES) and five matched controls (CS) were evaluated using wavelet entropy (WE) of heart rate data during rest and exercise. The model included wavelet source separation via a discrete wavelet decomposition of heart rate and respiration signals. Data were analyzed blinded, and prediction of group assignment (ES vs. CS) was performed using cluster analysis.

Results: Using WE, the source separation model was able to predict actual classification of individuals with 93% accuracy at rest (4/5 CS, 10/10 ES) and 100% accuracy at exercise. The most significant factors for principal component analysis were identified for resting and exercise states. The factors for rest were entropy in the high and low frequency ranges (SwtHF and SwtLF); and for exercise, the percentages of entropy contained in the high and low frequency ranges (PHF and PLF).

Conclusion: Novel utilization of wavelet analysis in combination with principal component analysis allows for differentiation between normal and diseased respiratory states at rest and in dynamic states. VIDDA Foundation

Poster #13
Analysis of cardiopulmonary dynamics using wavelet analysis methods
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Interpretation of frequency analysis of heart rate variability (HRV) is often severely affected by respiratory entrainment. Therefore, our aim was to determine to what extent the respiratory component of the cardiac autonomic activity could be removed through use of a statistical implementation of the wavelet analysis technique.

Methods: Five minute resting ECG and respiration waveforms were recorded at 200 Hz (N = 5). Subjects breathed at their natural, un-paced rate. The inter-beat interval (IBI) signal was derived from the ECG and reverse interpolated to 200 Hz. Respiration and HRV signals were decomposed into a set of time signals at various frequencies. The correlation between signals at specific frequencies was used to separate respiratory influence from HRV signal. A threshold of correlation (r = 0.75) was used to decide which frequency content would be removed from the signal via deconvolution. The remaining time-frequency signals were then reconstructed via inverse wavelet transform into a time series for further analysis.

Results: Content remained in both the high (HF) and low (LF) frequency ranges after removal of the respiration signal. The LF values overall changed from a mean of 194.20 to 67.20 ms2; variance changed from 31403.60 to 4702.33 ms4, (P < 0.05). HF values
overall changed from a mean of 123.57 to 58.21 m², variance from 13063.33 to 4723.96 m² (P < 0.05). Retention of the information from the original waveform was verified through reconstruction of the frequency waveform via inverse wavelet analysis.

**Conclusions:** This technique was able to remove the effect of respiration from both LF and HF bands while maintaining the nonrespiratory content. After removal of the respiratory content from the HRV signal, parasympathetic activity was still present, suggesting that vagal modulation is not purely driven by respiration. Additional studies are required to determine the influence of respiration during dynamic states. VIDDFA Foundation.

**Poster #14**

**Oral leak size influences hemodynamic responses to the Valsalva maneuver**

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**Introduction:** Analysis of the Valsalva maneuver (VM) involves traditional (Valsalva ratio [VR]) and newer parameters. An oral leak in the closed tubing apparatus for this test ensures that the expiratory pressure equals the subject's intrathoracic pressure.

**Hypothesis:** Oral leak size would significantly influence newer hemodynamic parameters.

**Methods:** Heart rate, blood pressure (Ohmeda 2300 Finapres), and intraoral pressure were recorded before, during, and after the VM in 38 healthy volunteers. Data were computerized via Biopac systems. Oral leak size was controlled by interchangeable inserts in random order: 0.35, 0.71, 1.01, and 1.40 mm. VM was performed at 40 mmHg for 15 seconds. Three trials were averaged for each oral leak size. VR and newer parameters, tachycardia latency (TL), bradycardia latency (BL), overshoot latency (OVL), late phase II amplitude (IILA), and pressure recovery time (PRT), were measured. Analysis of variance was used to compare results.

**Results:** The following values (mean ± SEM) were recorded with increasing leak size. VR, 1.93 ± 0.08, 2.00 ± 0.08, 2.00 ± 0.09, 1.97 ± 0.07 seconds; P = 0.48. TL, 2.4 ± 0.2, 2.1 ± 0.1, 2.0 ± 0.01, 1.6 ± 0.1 seconds; P < 0.001). BL, 6.8 ± 0.7, 5.4 ± 0.06, 6.6 ± 0.8, 7.7 ± 0.7 seconds; P < 0.02. IILA, 11.6 ± 1.2, 12.4 ± 1.3, 14.2 ± 1.1, 22.0 ± 1.5 mmHg; P < 0.001). PRT, 3.3 ± 0.6, 3.6 ± 0.6, 4.0 ± 0.8, 4.8 ± 0.9 seconds; P = 0.49. VR was essentially unaffected by oral leak size. Significant differences (P < 0.05) were found in TL, BL, and IILA. The largest leak size resulted in the lowest TL and the highest BL and IILA.

**Conclusion:** Newer hemodynamic parameters of VM are significantly affected by oral leak size, indicating a need for standardization.

**Poster #16**

**Up-regulation of hemeoxygenase 1 in an animal model of takotsubo cardiomyopathy**

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Catecholamine intoxication and disturbance of coronary microcirculation, both of which may be responsible for pathogenesis of takotsubo cardiomyopathy, could trigger the oxidative stress response in the heart. We investigated expression and localization of inducible hemeoxygenase 1 (HO-1), one of the oxidative stress-related factors in the heart of immobilization stressed (IMO) rats, an animal model of takotsubo cardiomyopathy. In response to IMO, the levels of HO-1 mRNA were slightly increased at 90 minutes, and increased 3 times at 3 hours compared with control levels in the heart and in the aorta. The signals for HO-1 mRNA were expressed in the scattered cells in the myocardium. Double fluorescence immunohistochemistry showed that HO-1 immunoreactive cells were also ED-1 and ED-2 positive, indicating that these cells were the macrophages. The number of ED-1 and ED-2 positive cells was constant, while the number of HO-1 positive cells was increased 5 times at 6 hours compared with control levels. Blocking of both alpha and beta-adrenoceptors attenuated up-regulation of HO-1 mRNA levels in the heart. Thus, emotional stress and surge of catecholamine up-regulate HO-1 in the cardiac macrophages.

**Poster #17**

**Markers of disease in familial dysautonomia; is there a phenotype in carriers?**

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**Background:** Familial dysautonomia (FD) is an autosomal recessive disease with complete penetrance and variable expressivity caused by tissue-specific exon skipping of the IKBKAP gene resulting in reduced levels of IKAP/EFLP-1 protein and functional Elongator. Aberrant splicing is most profound in neuronal tissue.
Objective: To determine if FD subjects and carriers have characteristic IKBKAP mRNA levels in peripheral blood leukocytes. We believe that manipulation of IKBKAP expression is a novel, potential therapeutic modality in FD. As we prepare for trials in FD patients, it is necessary to identify markers of disease expression.

Methods: We recruited 95 subjects (45 FD, 26 carriers, and 24 noncarriers) for participation. Each participant had a single sample of blood taken for IKBKAP RNA extraction. We used the average ΔCt of the noncarriers as the calibrator. Mixed model analyses of covariance and variance were used to compare IKBKAP levels among the FD subjects and carriers with and without adjustment for age/sex. Linear regression was used to assess effect of age and sex on the association between carrier and FD subject IKBKAP mRNA levels within families.

Results: Estimated mean IKBKAP mRNA levels, were significantly different for the two groups when they were and were not adjusted for age and sex (P < 0.001). Comparison of IKBKAP mRNA levels of 22 FD subjects and their related carriers showed a strong correlation, providing evidence for genetic control of splicing fidelity.

Conclusions: We have identified one marker of genetic expression in FD, IKBKAP mRNA in peripheral blood leukocytes. It has previously been reported that carriers have no phenotype, however we have now demonstrated that carriers have decreased IKBKAP splicing efficiency, thus suggesting the possibility of a subclinical phenotype. We now seek to identify other biomarkers in FD patients and in carriers as we conduct neurophysiologic studies as well as translational research with agents that affect splicing, such as kinetin.

Poster #18
Glucose homeostasis in younger patients with neurogenic orthostatic hypotension
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Background: Insulin has both metabolic effects on glucose metabolism, as well as, sympato-excitatory and vasodilatory effects on blood vessels. Neurogenic orthostatic hypotension (NOH) results from dysregulation of the autonomic nervous system with inadequate vasoconstriction in response to upright posture, and symptoms of cerebral hypoperfusion, which are similar to hypoglycemia. Reactive Hypoglycemia results from excess insulin release with hypoglycemia upon return to normal postprandial blood glucose levels. The goal of this study was to evaluate insulin secretion and sensitivity, as well as the frequency of reactive hypoglycemia in patients with NOH.

Methods: Standard measures of insulin secretion [blood glucose (mmol/L), C-peptide (ng/ml), Insulin levels (μU/ml), Insulinogenic Index], as well as, insulin sensitivity parameters [Glucose/Insulin Ratio, HOMA, RHOMA, QUICKI] were evaluated in response to a carbohydrate challenge, using a standardized 5 hours-75 gram Oral Glucose Tolerance test, in 45 patients with NOH (mean age = 42 ± 1.9 years) (11 males: 34 females) (Diagnoses = PAF/OI, autoimmune, Mitral Valve Prolapse)(BMI 26.9 ± 6.44); 64% of NOH also complained of GI symptoms (bloating, IBS, etc). Autonomic Neuropathy was documented by abnormal bedside tilt table test, RR Expiratory/Inspiratory ratios, and QTC intervals.

Results: 87% NOH had reactive hypoglycemia with Fasting blood glucose = 4.94 ± 0.01, decreasing to 3.72 ± 0.09 (Δ = 1.21 ± 0.09; maximal decrease of −2.66 mmol/dl), which occurred at 3.17 ± 1.25 hours with maximal Insulin levels of (81.37 ± 8.00) by 1.2 ± 0.2 hours, and C-peptide (fasting = 2.95 ± 0.3 to maximal = 11.21 ± 0.5). Patients with reactive hypoglycemia had lower fasting Insulin levels (3.17 vs. 4.80 ± 0.77), with a higher Insulinogenic Index (0.381 ± 0.053 vs. 0.243 ± 0.057), but lower Glucose/Insulin Ratios (18.07 ± 2.39 vs. 27.98 ± 5.92), HOMA (2.626 ± 0.555 vs. 3.101 ± 1.909), lower RHOMA (1.002 ± 0.127 vs. 1.27 ± 0.404), but no difference in QUICKI. Males had a higher Insulinogenic Index and lower HOMA than females. In response to the glucose challenge, the lowest standing SBP was observed by 2.7 ± 1.7 hours. Symptoms of orthostatic hypotension were also exacerbated in the postprandial state.

Conclusion: Symptoms of NOH due to cerebral hypoperfusion (such as dizziness, lightheadedness, etc) are similar to those of hypoglycemia. Since NOH commonly have both postprandial exacerbation of OH and reactive hypoglycemia, with lower insulin secretion and higher insulin sensitivity, it is important to clarify their symptoms, and thus recommend appropriate management for these patients. This study also suggests that the autonomic nervous system may play a role in regulating glucose homeostasis. Supported in part by the Veterans Affairs

Poster #19
Autonomic testing in patients with interstitial cystitis
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Background: Autonomic abnormalities are present in patients with many painful disorders such as fibromyalgia (FM) or complex regional pain syndrome. The aim of this investigation was to determine whether generalized abnormalities on autonomic testing occur in patients with interstitial cystitis (IC), an idiopathic visceral pain syndrome.

Methods: We compared results of autonomic testing of 24 patients who met NIDDK criteria for IC based on questionnaire answers with 24 age and gender matched patients who met criteria for FM. Testing included assessment of parasympathetic cardiac function using cardiac responses to deep breathing, sympathetic cardiac and vasomotor functions using cardiovascular responses to the Valsalva maneuver and to an upright tilt table test, and post-ganglionic sudomotor sympathetic function using quantitative sudomotor axon reflex test (QSART).

Results: The average age of the 24 (20 female) IC patients was 36 ± 15. For FM (21 females), the average age was 38 ± 16. Autonomic testing identified 11 IC patients with an autonomic neuropathy or borderline sudomotor responses, nine with postural tachycardia syndrome (POTS), six with orthostatic intolerance, 1 with syncope, 1 with orthostatic hypotension; all tests were normal in one patient. Autonomic testing diagnoses were nearly identical for patients with FM. Conclusion: To our knowledge, this is the first report of autonomic testing in patients with IC. In this population (skewed by referral to an autonomic laboratory), an autonomic abnormality occurred in 23 of the 24 patients. More than half of the patients (14/24) were found to have POTS or orthostatic intolerance, a common comorbidity for other autonomic disorders such as migraine headaches, irritable bowel syndrome and FM. Results were not significantly different from findings in an age-matched group of patients with FM. This investigation would be strengthened by evaluation of autonomic testing in IC patients who do not present with other autonomic symptoms.

Poster #20
Co-morbid autonomic disorders in interstitial cystitis
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Background: Patients with interstitial cystitis (IC) frequently harbor other autonomic disorders, such as postural tachycardia syndrome
(POTS), fibromyalgia, and migraine headaches. The purpose of this investigation is to determine the prevalence of co-morbid autonomic disorders associated with IC.

Methods: Data were collected using the previously reported ODYSA questionnaire. The questionnaire includes a question set for each of 12 disorders using established inclusion criteria where available. The frequency of each disorder was analyzed in a group of 30 subjects who fulfilled questionnaire-based NIDDK criteria. The 30 subjects presented with IC (7), POTS (7), neuropathy (5), migraine headaches (2), irritable bowel syndrome (IBS) (2), fibromyalgia (2), syncope (2), complex regional pain syndrome (CRPS) (1) and 2 family members of probands with IC and POTS.

Results: The average age of the subjects was 40 ± 17 with 24 females and 6 males. Compared to subjects with other autonomic diagnoses, patients with IC carried a higher frequency of POTS (80% vs. 60%), syncope (20% vs. 12%), irritable bowel syndrome (53% vs. 30%), migraine headaches (63% vs. 42%), and complex regional pain syndrome (47% vs. 16%). In addition, only complex regional pain syndrome carried a higher rate of fibromyalgia (58% vs. 50% vs. 25%).

Discussion: Based on the ODYSA questionnaire, patients with IC have a high probability of having a co-morbid autonomic disorder, especially POTS, migraine headaches, IBS, fibromyalgia and CRPS. We were surprised to find that IC had the greatest number of associated disorders, as we expected a more generalized syndrome, such as fibromyalgia, to have a greater number of associations. If IC occurs later in the progression of autonomic disorders, with patients first presenting with a more common disorder, such as POTS or migraine headaches, this would account for the large number of co-morbidities for this disorder.

Poster #21
Validation of a survey of self-reported symptoms for the screening and diagnosis of complex regional pain syndrome

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Objective: To assess the validity of using a subset of the Ohio Dysautonomia Survey (ODYSA) questionnaire in screening for and diagnosis of complex regional pain syndrome (CRPS).

Methods: The ODYSA survey contains several sets of questions; each set is intended to determine the probability that a specific autonomic disorder is present. One set probes for the presence of the symptoms specified in the diagnostic criteria for CRPS, as proposed by Harden and Bruhl in 2004. These symptoms divide into four categories: Sensory (hyperesthesia or allodynia), Vasomotor (temperature asymmetry, skin color changes), Sudomotor/Edema (edema and/or sweating changes), and Motor/Trophic (decreased range of motion, tremor, weakness, dystonia, and/or trophic changes of the hair, nails, or skin). Respondents in the ODYSA survey are requested to report whether symptoms were mild, moderate, or severe. If at least 1 moderate or severe symptom or at least 2 mild symptoms were reported within a category, the category was scored as positive; otherwise, the category was scored as negative. If and only if at least three categories were scored as positive, the respondent was considered to have a probable diagnosis of CRPS. A chart review was performed on each patient whose ODYSA questionnaire suggested a diagnosis of CRPS. Using the physician’s diagnostic impression from the chart as the standard, we calculated the sensitivity and specificity of the ODYSA CRPS question set.

Results: 46 patients meeting criteria for CRPS and 61 controls were identified. Patients with CRPS were less likely to have functional dyspepsia than controls (7% vs. 39%, P < 0.0002). CRPS patients were more likely to have fibromyalgia (67% vs. 36%, P = 0.0026), chronic fatigue syndrome (16% vs. 0%, P = 0.0019), and interstitial cystitis (32% vs. 9%, P = 0.0129) compared to controls. Differences in age and gender between the two cohorts were not significant.

Conclusions: Chronic fatigue syndrome, fibromyalgia, and interstitial cystitis often occur as comorbid conditions in patients with CRPS. In our population, which consisted of patients referred to an autonomic clinic, functional dyspepsia occurs less frequently among patients with CRPS than controls.

Poster #22
Demographics and comorbidities of patients with complex regional pain syndrome

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Objective: To determine the demographics and comorbidities of patients with complex regional pain syndrome (CRPS).

Background: The simultaneous incidence of CRPS and other autonomic disorders has been observed, but to our knowledge there has been no formal exploration of the incidence of comorbid disorders in CRPS.

Methods: Cohorts were identified from the Ohio Dysautonomia Survey (ODYSA) database, a record of survey results from over 800 respondents who were patients or family members of patients seen at three metropolitan autonomic clinics. The survey is designed to indicate the presence of specific autonomic disorders, including CRPS. Inclusion criteria for our CRPS cohort required questionnaire responses endorsing the presence of symptoms from at least 3 of 4 categories: Sensory, Vasomotor, Sudomotor/Edema, and Motor/Trophic. Our control cohort consisted of all respondents who completed the CRPS survey and did not meet inclusion criteria for the CRPS cohort. Respondents who were not seen by a physician in one of the clinics were excluded from both cohorts. Demographic data and coexisting medical conditions were compared.

Results: 46 patients meeting criteria for CRPS and 61 controls were identified. Patients with CRPS were less likely to have functional dyspepsia than controls (7% vs. 39%, P < 0.0002). CRPS patients were more likely to have fibromyalgia (67% vs. 36%, P = 0.0026), chronic fatigue syndrome (16% vs. 0%, P = 0.0019), and interstitial cystitis (32% vs. 9%, P = 0.0129) compared to controls. Differences in age and gender between the two cohorts were not significant.

Conclusions: Chronic fatigue syndrome, fibromyalgia, and interstitial cystitis often occur as comorbid conditions in patients with CRPS. In our population, which consisted of patients referred to an autonomic clinic, functional dyspepsia occurs less frequently among patients with CRPS than controls.

Poster #23
Autonomic dysfunction in Allgrove syndrome

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Allgrove syndrome is a rare autosomal recessive multisystem disorder characterized by alacrima, achalasia, adrenal insufficiency and a variety of dermatological and neurological features. Involvement of the autonomic nervous system is common and has been variably attributed to a preganglionic or a postganglionic disorder. A patient with Allgrove syndrome is presented with delayed onset of adrenal insufficiency and neurological features whose autonomic testing disclosed evidence of a preganglionic dysautonomia. The patient is a 54-year-old African American man who presented with a 14 years history of adrenal insufficiency and a 9 years history of a spastic gait disorder. During early childhood he had problems with regurgitation and underwent esophageal dilation at age 8 years for achalasia. He was never able to develop tears. At age 40 he was diagnosed with adrenal insufficiency and at age 45 he developed a spastic gait. MRI imaging of the brain and cervical spine were normal. Since age 48 he has noted erectile dysfunction, excessive sweating, and occasional orthostatic lightheadedness. He has four siblings all of whom are well. BP 120/80, P 88 supine and 98/60, P 84 after standing. He is of short stature, 158 cm, and has

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patchy hyperpigmentation, and hyperkeratosis of his palms and soles. Neurological exam was notable for spastic quadriparesis, with hyper-reflexia and clonus at the ankles. Plantar signs were flexors. Autonomic testing revealed reduced heart rate response to deep breathing, a reduced Valsalva ratio and a reduced BP response to phase IV of the Valsalva maneuver. Tilt test was normal and QSART was normal at all sites. The autonomic testing is consistent with a preganglionic autonomic disorder. This patient illustrates the remarkable heterogeneity of this syndrome with unusually late onset of the neurological and autonomic features as well as the adrenal insufficiency.

Poster #24
On-admission autonomic nervous cardiac tone predicts the success of myocardial reperfusion in acute ST elevation myocardial infarction
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Background: We tested the hypothesis whether on-admission autonomic cardiac tone evaluation can predict the success of myocardial reperfusion therapy in subjects with ST elevation acute myocardial infarction (STEAMI).

Methods: Twenty subjects with STEAMI were selected from consecutive 600 patients admitted to the intensive cardiac care unit. Patients were excluded if they have previously diagnosed ischemic heart disease, or they have any pathology or drug affecting the autonomic nervous system. ECG and hemodynamic monitoring were started immediately on admission and continued for 3 hours. Cardiac autonomic nervous system tone was evaluated by heart rate variability (HRV) analysis. Plasma levels of catecholamines were measured on admission and hourly during monitoring.

Results: Successful reperfusion was observed in 65% of the cases. The on-admission, both time and frequency domain, vagal indices disclosed higher activity in the successful reperfusion group, as opposed to the failed one. Root mean square of successive NN interval differences (rMSSD = 49.7 ± 6.8) and percent of successive NN interval differences >50 ms (pNN50 = 9.7 ± 3.6) were significantly increased in the successful reperfusion group as compared to failed group (P = 0.0003 and P = 0.03 respectively). High frequency (HF) domain power was 791 ± 203 and 128 ± 31 ms in the successful and failed reperfusion groups respectively (P = 0.01). Low frequency (LF) domain power, was 88.8 ± 7.1 n.u. in the failed reperfusion group and 47.6 ± 4.5 n.u. in the successful reperfusion group (P = 0.0004). Plasma norepinephrine levels were higher in the failed reperfusion group.

Conclusion: Patients with STEAMI and successful reperfusion have on-admission lower sympathetic tone and higher vagal cardiac tone as compared to patients with failed reperfusion. This data may justify pharmacological interventions, such as beta blockade, with the aim of modulating the cardiac sympatho-vagal tone prior to the reperfusion therapy.

Poster #25
Microinjection of NMDA in the RVLM produces an enhanced increase in RSNA in rats with heart failure (HF)
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Chronic heart failure (HF) condition is well characterized by increased sympathetic drive that aggravates the disorder. The goal of the present study was to examine if NMDA mediated changes in RSNA are altered in rats with HF. Left coronary artery ligation was used to induce HF. The rats in the HF group displayed infarcts greater than 30% of the left ventricular wall and LVEDP of >15 mmHg. Sham operated control rats (no ligation) had no observable damage to the myocardium and LVEDP of <2 mmHg. In alpha-chloralose and urethane anesthetized rats, microinjection of NMDA into the RVLM (50, 100 and 200 pmol in 25–100 nl) produced dose-dependent increases in RSNA, BP and HR in sham operated control rats and HF rats. There was a potentiation (twofold higher response at the highest dose) of the increase in RSNA due to NMDA receptor activation in HF rats compared to sham operated control rats. In contrast, blockade of NMDA receptors in the RVLM with AP-5 induced (16 nmol) significantly greater decreases in RSNA, BP and HR in HF rats compared to sham rats. These data support the conclusion that an enhanced endogenous glutamatergic mechanism within the RVLM may contribute to the exaggerated sympatho-excitation during HF.

Poster #26
Prevalence of OH in a nursing home and rehabilitation population before and after initiation of a standardized treatment protocol
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OH is a common finding in patients admitted to nursing home and rehabilitation units. We performed OH BP assessments at the time of admission and at the time of discharge for one year to determine the admission and discharge prevalence of OH in our population. In the second year, we initiated a standardized treatment protocol for all subjects who were admitted with OH or developed OH during their stay. The initial protocol included med review, bed wedge, increased dietary salt and fluid, education, standing exercise program. If they remained orthostatic then fluidrocortisone, salt tablets, midodrine, or other treatments were added. In the observation year 168 eligible subjects had at least three admission and two discharge orthostatic BP assessments. The Autonomic Society definition of OH was used. The admission prevalence of at least one OH reading was 33.4% and the discharge prevalence of at least one OH reading was 35.1% (n = 168). 67% of subjects who had OH on admission, still had it at discharge. In the treatment phase, subjects were treated for OH if they had it on admission, or developed it during their stay. The admission prevalence of OH (n = 93 subjects) was 34.4% and the discharge prevalence of OH was 20.1% (P = 0.02). Of the 66% of subjects with OH on admission, 41.2% still had it at discharge (P = 0.043). These data suggest that OH can be successfully treated using a standardized treatment protocol, but that a significant percentage of subjects still have OH at the time of discharge. Further work is needed to strengthen the intervention, and to determine whether treatment improved functional outcomes.

Poster Session II
Poster #27
Role of head-up tilt and carotid massage in patients with unexplained syncope referred to an autonomic unit
J. Freitas1,2,3, E. Azevedo3, R. Santos1, C. Abreu-Lima3, M.J. Maciel2
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Neuro-mediated syncope (NMS) is the most frequent cause of loss of conscience. The diagnosis is only possible when tilt table test (TTT) reproduces symptoms. Many of these patients frequently are misdiagnosed. The aim of this study was to characterize laboratory
Diagnostic value of co-morbid conditions in neurally mediated syncope (NMS)

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Objective: NMS is diagnosed based on loss of consciousness at rest, while sitting or standing, usually leading to falling, with warning symptoms, and spontaneous recovery in ≤2 minutes, as a result of global cerebral hypoperfusion. We evaluated whether a history of co-morbid conditions helps identify NMS from other types of syncope.

Methods: The records of 111 children, aged <19 years, who were evaluated by the primary investigator for syncope from 2000 to 2004 in an outpatient clinic were reviewed. Patients were classified into two groups: NMS or Other Syncope, based on NMS's clinical characteristics, as listed above, and results of diagnostic work up.

Results: Seventy-three children had NMS, ages 1–18 years (mean 12.8), while 38 had Other Syncope, ages 5–17 years (mean 12.2) (P = NS). 48 of NMS patients were females vs.19 in Other Syncope group (P = 0.08). While the difference in prevalence (NMS vs. Other Syncope) of migraine (64% vs. 50%), tension-type headache (23% vs. 18%), and dizziness (30% vs. 24%) was not significant (P = NS), both orthostatic, transient, binocular, visual loss (TVL) (16% vs. 3%) and heavy menses (70% vs. 2%, menstruating females: n = 37 NMS, n = 11 Other Syncope) were significantly more prevalent in NMS (P = 0.032 and P = 0.002, respectively). The prevalence of unexplained chronic fatigue of ≥3 mo (UCF) approached significance (29% vs. 13%, P = 0.054). The sensitivity, specificity, and positive predictive values (%) were 16, 97, and 91 for TVL; and 70, 82, and 93 for heavy menses; and 30, 86, and 80 for UCF, respectively.

Conclusions: a history of TVL, heavy menses, or UCF helps identify NMS from other causes of syncope in a large percentage of patients.

The hemodynamic pattern of the progressive orthostatic hypotension syndrome

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1 Department of Cardiology, 4th Medical Clinic, University of Medicine and Pharmacy, Targu Mures, Romania; 2 Department of Cardiology and Arrhythmologic Centre, Ospedali del Tigliuolo, Lavagna, Italy; 3 “CC Iliescu” Heart Institute, University of Medicine and Pharmacy, Bucharest, Romania

Progressive orthostatic hypotension (POH) is characterized by a slow progressive decrease of systolic blood pressure on the assumption of a standing position. Typically these patients remain asymptomatic initially after standing and develop hypotensive symptoms that cause orthostatic intolerance after a few minutes of standing. Thus, their hemodynamic profile on standing differs from that of immediate hypotension. Aim of the study was to investigate the hemodynamic mechanisms underlying the syndrome of POH.

Methods: Non invasive beat to beat hemodynamic monitoring was performed by means of a Task Force Monitor in 13 patients (seven women, mean age 68 ± 14 years) affected by POH and in nine control subjects (four women, mean age 68 ± 8 years) during 20 minutes tilt testing.

Results: The systolic blood pressure progressively decreased in patients from 125 ± 15 at baseline to 75 ± 15 (P < 0.001) mmHg at the end of test while in controls it decreased from 132 ± 17 to 121 ± 20 mmHg (P = 0.3). Total peripheral resistance (dyn · seconds · m²/cm5) progressively decreased in patients from 1,800 ± 335 to 943 ± 286 while in controls the corresponding values were from 1,779 ± 890 to 1,645 ± 625. In patients, the heart rate (bpm) progressively increased from 78 ± 10 to 91 ± 14 bpm and in control it decreased from 73 ± 13 to 71 ± 14. Stroke volume and cardiac output did not change significantly neither in patients nor in controls.

Conclusion: the POH syndrome is characterised by a concomitant decrease of systolic blood pressure and total peripheral resistance and a compensatory increase in heart rate; stroke volume and cardiac output remain unchanged.

The validity of “empty heart syndrome” in the pathogenesis of neurocardiogenic syncope

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The Cleveland Clinic, Cleveland, OH, USA

One of the most important mechanisms proposed in the pathogenesis of neurocardiogenic (vasovagal) syncope considers a dramatic decrease in ventricular filling during diastole with consequent neuro-autonomic imbalance, so-called “empty heart syndrome”. The aim of our study was to examine the atrio-ventricular coupling by analyzing the PR dynamic change, an important surrogate of ventricular diastolic filling, during the head-up tilt (HUT) test, to assess the validity of the above hypothesis. In a pilot study of 121 patients with unexplained syncope, we evaluated retrospectively the PR dynamic change during HUT. The hemodynamic responses to HUT were divided into four groups: Vasovagal response (VVR), postural tachycardia syndrome (POTS), postural orthostatic hypotension (POH), and normal response (NR). Multiple electrocardiographic recordings were collected at baseline and different
phases of HUT. To address our hypothesis, we analyzed data in VVR versus NR only. We calculated the PR dynamic change during HUT as the percentage of shortening of PR from baseline to minimum PR in the late phase of HUT. There were 21 VVR patients and 24 NR patients. There was no significant difference of PR dynamic change between VVR group (mean change of -12%) and NR (mean change of -10%). In conclusion, the lack of a significant PR dynamic change during HUT between VVR and NR suggests possible role of other neuro-mechanical pathways in addition to "empty heart syndrome" in the development of VVR. A larger study is currently underway to confirm the above preliminary findings.

Poster #31
Orthostatic syndromes are associated by sympathetic withdrawal as demonstrated by non-invasive autonomic monitoring

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1 Division of Cardiovascular Medicine, Department of Medicine, The Chicago School of Medicine, Chicago, IL, USA; 2 ANSAR Medical Technologies, Inc.

Background: Sympathetic withdrawal (SW) defines the continuum of orthostasis, and blood pressure (BP) and heart rate (HR) changes differentiate its forms: orthostatic hypotension (OH−), orthostatic intolerance (OI), orthostatic hypertension (OH+), and postural orthostatic tachycardia syndrome (POTS). Our objective was to determine if non-invasive autonomic monitoring can reliably detect clinical and pre-clinical Orthostasis.

Methods: Autonomic profiling of 210 consecutive Orthostatic patients recruited from ambulatory clinics was performed using the ANX-3.0 (Ansar, Inc., Philadelphia, 11.6; 30 Diabetics; 132 Females) included 28 controls ± PA). The cohort (age = 58.9 with known associated physiologic syndromes. Pearson Correlation was performed using the supine position, patients underwent head-up tilt testing (Leeds protocol: 60° head-up tilt for 20 minutes, followed by 10 minutes each at lower body negative pressure of -20 and -40 mmHg) until (pre)syncope occurred. We measured heart rate, brachial blood pressure, and cardiac stroke volume before and at 2 minutes of head-up tilt. Heart rate and blood pressure variability, as well as spontaneous baroreflex sensitivity, were assessed in the supine position and during the first 5 minutes of head up tilt. Correlation and multivariate linear regression analysis were performed after correction for age and gender.

Results: Time to (pre)syncope was 1,674 ± 49 seconds (range 141–2,603). The Table shows parameters that were significantly correlated with the time to (pre)syncope. The best single correlation was seen for the increase in heart rate with head-up tilt. In the multivariate model age, supine diastolic blood pressure, supine LF/HF_sbp, tilt-induced changes in diastolic blood pressure, and tilt-induced heart rate changes predicted about 40% of time to (pre)syncope variability (r2 = 0.41, P < 0.001).

Table 1
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<th>Parameter Correlation</th>
<th>P</th>
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<td>Age</td>
<td>0.036</td>
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<tr>
<td>Height</td>
<td>-0.194</td>
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<tr>
<td>Supine</td>
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<td>Heart rate</td>
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<td>ΔLF/HF_rri</td>
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<td>ΔBRS</td>
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BP blood pressure, HF spectral power of high frequency oscillations, LF/HF ratio of spectral power of low frequency oscillations (LF) to HF, rri RR interval, BRS baroreflex sensitivity.

Conclusions: In patients with recurrent syncope, hemodynamics, heart rate variability, blood pressure variability, and baroreflex sensitivity in the supine and in the upright position contribute weakly to the variability in orthostatic tolerance. The major part of the variability in orthostatic tolerance remains unexplained.

Poster #32
Orthostatic tolerance predictors in patients with recurrent syncope

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Background: The mechanisms predisposing to neurally-mediated syncope are not fully understood. Therefore, we determined whether or not early hemodynamic and autonomic responses during head-up tilt would predict orthostatic tolerance upon head-up tilt testing in patients with recurrent syncope.

Methods: We retrospectively analyzed data (mean ± SEM) from 100 consecutive patients with recurrent syncope (68 women, age 44 ± 2 years, 22 ± 3 syncopal events in the last 10 ± 1 years). After baseline recordings in the supine position, patients underwent head-up tilt testing (Leeds protocol: 60° head-up tilt for 20 minutes, followed by 10 minutes each at lower body negative pressure of -20 and -40 mmHg) until (pre)syncope occurred. We measured heart rate, brachial blood pressure, and cardiac stroke volume before and at 2 minutes of head-up tilt. Heart rate and blood pressure variability, as well as spontaneous baroreflex sensitivity, were assessed in the supine position and during the first 5 minutes of head up tilt. Correlation and multivariate linear regression analysis were performed after correction for age and gender.

Results: Time to (pre)syncope was 1,674 ± 49 seconds (range 141–2,603). The Table shows parameters that were significantly correlated with the time to (pre)syncope. The best single correlation was seen for the increase in heart rate with head-up tilt. In the multivariate model age, supine diastolic blood pressure, supine LF/HF_sbp, tilt-induced changes in diastolic blood pressure, and tilt-induced heart rate changes predicted about 40% of time to (pre)syncope variability (r2 = 0.41, P < 0.001).

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BP blood pressure, HF spectral power of high frequency oscillations, LF/HF ratio of spectral power of low frequency oscillations (LF) to HF, rri RR interval, BRS baroreflex sensitivity.

Conclusions: In patients with recurrent syncope, hemodynamics, heart rate variability, blood pressure variability, and baroreflex sensitivity in the supine and in the upright position contribute weakly to the variability in orthostatic tolerance. The major part of the variability in orthostatic tolerance remains unexplained.

Poster #33
Beta2-adrenoeceptor mediated syncope during upright tilt in humans

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Vasovagal syncope is a common type of syncope in humans, and sympathetic withdrawal contributes to a final abrupt drop in arterial pressure. We studied retrospectively 26 young individuals (four men and 22 women, age range 16–50) who had no previous history of syncope but had presyncopal episodes during 45-minutes of 60° upright tilt in our laboratory in the past 4 years. Muscle sympathetic nerve activity (MSNA), heart rate, blood pressure (BP), and respiratory waveforms were recorded continuously, while blood samples were taken in the supine position, 5 and 20 minutes after tilting, and immediately after returning to supine due to presyncope. We found that BP decreased progressively and then further decreased rapidly 100 and
20 seconds prior to presyncope in all subjects. Twenty-three of them (about 88%, Group A) had a clear sympathetic withdrawal 20 seconds before the onset of presyncope, while three subjects (about 12%, Group B) had no significant changes in sympathetic activity levels. MSNA was markedly greater in Group B than in Group A 20 seconds prior to presyncope (60 ± 23 SD) vs. 25 ± 18 burst/min; P = 0.005). Plasma norepinephrine concentration was not different between the groups at any time point. However, plasma concentration of epinephrine was threefold greater in Group B than in Group A immediately after returning to supine due to presyncope (195 ± 140 vs. 60 ± 43 pg/ml; P = 0.031), while minimal mean BP was not different between the two groups (59 ± 13 vs. 47 ± 14 mmHg; P = 0.154). The time to presyncope during tilting did not differ between the groups. These results suggest that stimulation of beta2-adrenergic receptors without any changes in vasomotor sympathetic activity may also elicit syncope in humans, though this must be tested in a prospective design.

Poster #34
Neuroendocrine changes during head-up tilt and syncope
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Introduction: We studied neuroendocrine changes induced by head-up tilting and compared these changes between subject with a normal tilt test and subjects who experienced a reflex syncope.

Patients and Methods: A total of 77 patients (51 women) aged 51 ± 20 years referred for suspected syncope were included. They were submitted to 20 minutes of head-up tilt to 60 degrees followed by sublingual nitroglycerin (0.4 mg) with continued tilting for 15 minutes or till the occurrence of syncope. Blood pressure and heart rate were monitored continuously. Blood samples were collected after 20 minutes of supine rest, after 10 and 20 minutes of head-up tilt and in the supine position 1 minutes after termination of the tilt test. Blood samples were analyzed for norepinephrine (NE), pancreatic polypeptide (PP), and aldosterone (Aldo).

Results: Forty-six subjects experienced a reflex syncope leading to premature termination of the tilt test (Sync). The groups did not differ with respect to age and sex. Systolic blood pressure and heart rate did not differ between groups in the supine position but heart rate increased more in the Sync group (4.9 ± 1.3 vs. 8.6 ± 1.9 minutes1, P = 0.007) in response to tilt. NE increased from supine to tilt in both groups (P = 0.001). PP decreased upon tilting only in the Sync-group (P = 0.008). Aldo increased progressively in both groups during tilt reaching the highest value upon termination of the test (P < 0.0001). NE decreased upon termination of the tilt only in the group with a normal tilt test (P = 0.011). PP increased in the Sync group following syncope (P < 0.0001). Inter-group comparisons were only significant with respect to PP, changing in opposite directions.

Conclusion: Tilt testing showed the expected changes in sympathetic activity and in the renin-angiotensin-aldosterone system. Syncope patients differed only by more pronounced vagal withdrawal during tilt and by higher vagal activity following syncope.

Poster #35
Was Sir Thomas Lewis right?
L.J. Norcliffe-Kaufmann, M.J. Tellez, A. Voustianiouk, S. Lenina, H. Kaufmann
Dysautonomia Research Laboratory, NYU School of Medicine, New York, NY, USA

Blood pressure falls similarly during vasovagal syncope and syncope due to autonomic failure, but the heart rate changes are different. Whether the heart rate changes are useful in the differential diagnosis has been disputed. With this in mind, we analyzed the relationship between electrocardiographic R–R intervals and beat-to-beat blood pressure (finger plethysmography) during the acute fall in blood pressure in thirty-three patients with a typical history and tilt-induced vasovagal syncope (age, 40 ± 10 years; 22 men and eight women; 21 multiple system atrophy, nine pure autonomic failure). In patients with autonomic failure, during the fall in blood pressure, heart rate always increased so that there was an inverse relationship between blood pressure and R-R intervals (y = 2.882x2 + 459.51, R2 = 0.9828, P < 0.001). The slope of this relationship was, as expected, much less steep than in normal subjects with similar (pharmacologically induced) hypotension. During vasovagal syncope, a series of at least 7 heart beats (average, 33 ± 2; range, 7–57 beats) in which there was a significant positive relationship between blood pressure and R-R intervals (y = 0.9797x2 – 136.25x + 5,531, R2 = 0.9622, P < 0.001) was always identified. The heart rate changes that accompany the fall in blood pressure clearly distinguish between vasovagal syncope and syncope due to autonomic failure. The positive relationship between blood pressure and R-R intervals during vasovagal syncope is best explained by vagal activation, something that never occurs in patients with autonomic failure. This feature has clear diagnostic value. Our results are in full agreement with Sir Thomas Lewis, who in 1932 emphasized the role of the vagus nerve and named this hemodynamic phenomenon vasovagal syncope.

Poster #36
Initial orthostatic hypotension of the young is attenuated by static handgrip
D.A. Clarke, I. Tanega, M.S. Medow, J.M. Stewart
Department of Pediatrics, New York Medical College, Valhalla, NY, USA

Initial orthostatic hypotension in the young is common and is associated with transiently reduced cardiac output. It is related to the rapid movement of blood from the thorax to dependent parts of the body during orthostasis that occurs before neurovascular compensation. Our prior research illustrates that the static handgrip increases blood pressure and heart rate, due to the increase in central blood volume (cardiac preload), contractility and total peripheral resistance (TPR). We hypothesized that if standing is preceded by handgrip and accompanied by static handgrip, then the effects (changes in BP, HR, CO and TPR) caused by active standing will be attenuated. To test this hypothesis, subjects were asked to perform a handgrip exercise while supine. Approximately forty seconds after initiating a static handgrip maneuver (80% of maximal); subjects were instructed to stand while they continued this isometric exercise. Subjects were dizzy with reduced postural tone during standing alone, when standing was coupled with handgrip, presyncopal symptoms upon standing were abolished. Handgrip induced an increase in MAP preceding and continuing throughout the stand and blunted the fall in BP while HR showed a similar increase. Upon standing, MAP dropped by 84%, while the heart rate increased by 64%, CO fell by 14%, and TPR increased 21%. However, standing following handgrip caused a MAP decrease of 12%, HR increase of 68%, CO increase of 80%, and a 60% decline in TPR. Cardiac output was enhanced during the period of Stand + Handgrip compared to handgrip alone. As a consequence, there was a decrease in TPR throughout the maneuver. The present study indicates that decreases in blood pressure and increases in heart rate at the onset of active standing can be attenuated by using static handgrip. Hence, the initial orthostatic hypotension of the young is attenuated by static handgrip.
Effect of posture on the autonomic responses to an inspiratory apnea

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Previous studies indicate pulmonary stretch reflex produces bradycardia and hypotension. We used deep inspiratory apnea (IA) as a model to study pulmonary stretch reflex. Twelve healthy subjects (nine females, three males; 19–27 years) performed a maximal inspiratory apnea by holding their breath with an open glottis at maximal inspiration both supine and after 10 minutes of head up tilt to 70 degrees (HUT). Heart rate (HR) by EKG, blood pressure, (BP) (Finpresp), respiration (Respirtrace) and MSNA (microneurography) were measured, while cardiac output (CO) and total peripheral resistance (TPR) were calculated. Beat to beat oxygen saturation (PaO2) was estimated by capnography. HUT increased inspiratory apnea time by 19% (29.6 ± 3 seconds supine vs. 35.1 ± 3.5 seconds HUT), resting MAP from 75 ± 5 to 3.6 to 93 ± 5.8 mmHg; HR from 66 ± 2.5 to 72 ± 3 bpm; TPR from 20.2 ± 5.3 to 30 ± 4.6 mmHg/l/minutes; MSNA from 18.8 ± 2.6 to 34.1 ± 2.5 (bursts/minutes) and decreased CO from 4.9 ± 0.5 to 3.2 ± 0.4 l/minutes (P < 0.05). In contrast, non significant changes in ETCO2 from 40 ± 2 to 37 ± 2.4 and PaO2 from 98 ± 2 to 97 ± 1.5 mmHg were observed with HUT. Following inspiratory apnea, MSNA showed three predominant phases—an initial quiescent phase due to pulmonary stretch, a second phase of elevated MSNA and a separate third phase of further increased MSNA activity. The first phase of quiescent MSNA was associated with a fall in MAP (12.5% supine vs. 17% HUT), HR (23% supine vs. 18% HUT), CO (31% supine vs. 6.5% HUT) and TPR (20% supine vs. 43% HUT). The second phase of increased MSNA (100% supine vs. 26% HUT, P < 0.05) was associated with baroreflex mediated recovery of MAP (12% supine and 17% HUT), HR no recovery (supine vs. 17% HUT), CO (10% supine and 46% HUT) and peripheral resistance (46% supine and 15% HUT). During the third and final phase of increased MSNA activity, the MAP, HR, CO and TPR were maintained and the increased MSNA was likely to be due to chemoreceptor mediated stimulation of increased ETCO2 (50% supine and 48% HUT, P < 0.05). Maximal inspiratory apnea therefore results in a pulmonary stretch induced initial suppression of MSNA followed by an increased arterial baroreflex mediated increased sympathetic response which is more pronounced during HUT.

Is postural tachycardia syndrome (POTS) associated with syncope?

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Background: There are conflicting opinions on whether POTS predisposes to syncope. We investigated this relationship.

Materials and methods: We queried our autonomic laboratory database of over 4,500 patients. “Research POTS” was defined as >30 bpm rise in heart rate within 10 minutes of upright tilt accompanied by orthostatic symptoms and further rise in heart rate during the remainder of the tilt study. “Research Syncope” was defined as an abrupt decrease in heart rate and blood pressure (less than 3 minutes in duration) requiring termination of the tilt table study. Statistical analysis utilized Fisher’s exact test.

Results: Of 810 patients referred for POTS, 189 (23%) met research criteria, and 661 did not while of 1,153 patients referred for syncope, 195 (17%) met research criteria and 1,018 did not. 37% of research POTS patients had research syncope while 36% of the research syncope patients had research POTS. In comparison, for all other diagnoses referred to our lab (3602 patients), 125 qualified for research syncope (3.5%) (P < 0.0001). The range of tilt table duration prior to syncope (1–44 minutes) was not different between the POTS and non-POTS groups. Additionally in 581 records with conventionally defined orthostatic hypotension, 45 demonstrated research syncope (7.7%; P < 0.0001 compared to research POTS).

Discussion: Our results demonstrate that even in a large population referred for autonomic dysfunction, syncope occurs far more commonly in patients who have POTS than in patients with other dysautonomias, including orthostatic hypotension. This last finding might in part reflect a tendency to tilt study termination after establishing a diagnosis of orthostatic hypotension. The high rate of association between POTS and syncope is striking, and suggests that these two disorders may actually share a common etiology, or may each constitute a strong predisposing factor for the occurrence of the other.

Cardiac vagal control in POTS

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Objective: To investigate the role of cardiac vagal control in patients with postural tachycardia syndrome (POTS).

Background: Cardiac vagal outflow is the primary effector of beat-to-beat heart rate control. Several lines of evidence suggest that the exaggerated heart rate in POTS patients may be related to altered cardiac vagal outflow. In the current study, we assessed cardiac vagal tone in healthy controls and POTS patients using atropine titration.

Methods: The atropine titration was performed in the supine position. Atropine sulfate was administered by consecutive intravenous bolus doses at 10 minutes intervals until two consecutive doses of atropine produced no further increase in heart rate or until the maximum dose of 40 mcg/kg was reached. Heart rate and blood pressure were continuously monitored throughout the protocol.

Results: Baseline RR interval was significantly lower in POTS patients compared to controls (779 ± 48 vs. 923 ± 140 ms; P < 0.05). Both POTS patients and controls showed an increase in RR interval in response to low dose atropine. The maximum increase in RR interval to low dose atropine was not different between patients and controls (128 ± 48 vs. 132 ± 55 ms; P = 0.9). Both POTS patients and controls showed a significant decrease in R–R interval in response to maximum dose of atropine. The R–R interval at the maximum dose of atropine was not different between patients and controls (545 ± 86 vs. 606 ± 106 ms; P = 0.3) while the difference between the baseline R–R interval and the R–R interval at the maximum dose of atropine, i.e., cardiac vagal tone was smaller in POTS patients compared to controls (235 ± 58 vs. 316 ± 79 ms; P = 0.09). Neither the peak vagomimetic dose (1.9 ± 0.5 vs. 2.1 ± 0.3 mcg/kg) nor the maximum dose of atropine (18.3 ± 6.0 vs. 19.8 ± 3.2 mcg/kg) was different between patients and controls. The most common side effect of atropine was dry mouth in both groups.

Conclusion: The present data suggest that the cardiac vagal tone in supine POTS patients is less than in supine healthy controls.
Neurohormonal and autonomic responses to acute orthostatic stress are not clear in patients with postural tachycardia syndrome. The goal of this study was the assessment of neurohormonal and autonomic changes to passive tilting that could characterize patients with postural tachycardia syndrome. We studied 12 normo-volunteer control subjects (C) and eight patients with postural tachycardia syndrome (POTS), aged-matched. Blood was sampled at supine rest (S) and passive orthostatic stress (T). We measured atrial and brain natriuretic peptides (ANP and BNP) and catecholamines (NOR, EPI and DOP). We also calculated the Heart Rate Variability, Systolic Blood Pressure Variability and Baroreceptor Gain with FFT spectral analysis. Main results:

- For ANP (pmol/l)-C(S): 7 ± 4; C(T): 7 ± 5; POTS(S): 3 ± 1; POTS(T): 3 ± 2
- For BNP (pmol/l)-C(S): 2 ± 2; C(T): 2 ± 1; POTS(S): 1 ± 1; POTS(T): 1 ± 1
- For NOR (pg/ml)-C(S): 166 ± 083; C(T): 363 ± 201; POTS(S): 135 ± 037; POTS(T): 475 ± 129
- For EPI (pg/ml)-C(S): 14 ± 11; C(T): 32 ± 24; POTS(S): 22 ± 17; POTS(T): 49 ± 30
- For DOP (pg/ml)-C(S): 7 ± 4; C(T): 8 ± 2; POTS(S): 6 ± 2; POTS(T): 10 ± 7
- For BRG (mmHg/ms)-C(S): 15 ± 7; C(T): 8 ± 3; POTS(S): 16 ± 7; POTS(T): 3 ± 2
- For HP RR (ms²)-C(S): 550 ± 376; C(T): 657 ± 539; POTS(S): 30 ± 21
- For LF HR-C(S): 1.2 ± 0.8; C(T): 3.5 ± 2.8; POTS(S): 1.6 ± 1.4; POTS(T): 5.3 ± 2.2
- For LF SBP(mmHg²)-C(S): 3.4 ± 1.9; C(T): 9.1 ± 7.3; POTS(S): 3.3 ± 2.5; POTS(T): 15.0 ± 3.5 and
- For HR (bpm).C(S): 75 ± 8; C(T): 88 ± 7; POTS(S): 80 ± 11; POTS(T):122 ± 8.

Natriuretic peptides do not change after orthostatic stress in any group but are lower in POTS, probably due to the significant hypovolemia observed in these patients. Norepinephrine showed a huge rise in POTS. Vagal responses are marked reduced to orthostatism and summarized.

Inflammatory cytokines are increased in postural tachycardia syndrome

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Sympathetic activity is proposed to play a role in inflammatory responses. Accordingly, we tested the hypothesis that inflammatory cytokines are elevated in patients with postural tachycardia syndrome (POTS) who have increased sympathetic activity. We studied 18 POTS patients (30 ± 2 years old, BMI 21.9 ± 0.8, 17 females), and compared them to 13 normal controls (30 ± 3 years old, BMI 22.8 ± 0.4, 8 females). Patients with known inflammatory conditions, tobacco use or obesity were excluded. POTS patients had the expected increase in heart rate on standing (from 73 ± 2 to 127 ± 5 bpm) without orthostatic hypotension (107/67 ± 2/2 to 110/73 ± 3/3 mmHg). Plasma norepinephrine increased from 320 ± 58 supine to 900 ± 209 pg/ml standing. Increased sympathetic activation was also evidenced by an increase in low frequency variability of systolic blood pressure even at rest (8.2 ± 1.7 mmHg² in POTS vs. 4 ± 0.9 mmHg² in normal controls, P < 0.05). The following plasma cytokines were found to be increased in POTS compared to normal controls: IL-8 (7.14 ± 0.9 pg/ml in POTS vs. 1.95 ± 0.2 pg/ml in controls, P < 0.0001), TNF-alpha (7.8 ± 4.3 pg/ml in POTS vs. 0.58 ± 0.33 pg/ml in controls, P = 0.0028) and IL-10 (6.9 ± 1.9 pg/ml in POTS vs. 0.69 ± 0.26 pg/ml in controls, P < 0.0001). IL-6 tended to be higher in POTS, but not significantly (6.1 ± 2.7 pg/ml in POTS vs. 0.79 ± 0.25 pg/ml in controls). We conclude that patients with postural tachycardia syndrome have increased circulating inflammatory cytokines, which may contribute to their pathophysiology.

Conclusion: Despite the autonomic dysfunction associated with POTS, no unexpected hemodynamic instability was observed in these cases.

References
Background: Patients with the postural orthostatic tachycardia syndrome (POTS) have high renin but low aldosterone during prolonged orthostasis. Whether this blunted adrenal response contributes to the occurrence of POTS, or whether it is simply a consequence of deconditioning remains unknown. We tested the hypothesis that increases in physical fitness levels with short-term exercise training normalize the renin-aldosterone response, while lowering heart rate by standard pharmacologic therapies, such as beta-adrenergic blockade cannot improve the adrenal function in patients with POTS.

Methods: Thirteen female POTS patients aged 26 ± 9 years (SD) completed 3 months of an “optimized” exercise training program, while 9 patients aged 27 ± 9 years were treated with a non-selective beta-adrenergic blockade, propranolol (oral 80 mg qd) for one month. A 2-hours active standing test was performed before and after either exercise training or medication treatment. All patients completed a constant diet containing 200 mEq sodium, 100 mEq potassium, and 1,000 mg calcium 3 days prior to study. Female patients were tested during the luteal phases of their menstrual cycles. Blood pressure (BP), heart rate (HR), and respiratory waveforms were recorded continuously during prolonged orthostasis. Blood samples for catecholamines, plasma renin activity (PRA), and aldosterone (ALDO) were taken intermittently in the supine position, and after 30, 60, and 120 minutes of standing. Patients’ quality of life was also assessed before and after either training or treatment.

Results: BP was not affected significantly by exercise training or propranolol treatment. Upright HR was lowered more dramatically by propranolol (~28 beats) than by training (~15 beats). PRA decreased while ALDO remained unchanged, and therefore, the ALDO-to-PRA ratio increased by 120 minutes stand after exercise training (4.7 ± 2.5 pre- vs. 6.1 ± 2.9 post-training; P = 0.089). Conversely, both PRA and ALDO decreased, so that the ALDO-to-PRA ratio remained unchanged after propranolol treatment (3.7 ± 1.8 pre- vs. 3.4 ± 1.8 post-treatment; P = 0.322). Plasma catecholamine responses during 2-hour standing were not affected by either training or propranolol treatment in these patients. Patients’ quality of life was improved significantly with exercise training, but not with propranolol treatment (P = 0.004 for pre- and post-training, 0.216 for pre- and post-propranolol treatment, 0.103 for interaction).

Conclusions: These results suggest that the blunted adrenal function in POTS patients appears to be a consequence of deconditioning. Increases in physical fitness levels with exercise training can increase the renin-aldosterone response and improve patients’ quality of life, while lowering heart rate by standard pharmacologic therapies, such as beta-adrenergic blockade, does not improve the adrenal function and symptoms in patients with POTS.

Poster #45
The role of autonomic testing in elucidating symptom mechanism and guiding etiologic determination in a pediatric population

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Background: No reports evaluate the clinical utility of autonomic testing in the pediatric population. We evaluated its contributions toward the elucidation of symptom mechanism and directing etiologic determination.

Methods: We reviewed the testing data, clinical interpretation, and all clinician and hospital records that were available for patients under age 18, who underwent autonomic testing at this facility between 1993 and 2007. We ranked the utility of the autonomic test with respect to elucidating symptom mechanism and guiding etiologic search on a 3-point scale: unhelpful, somewhat helpful, and very helpful.

Results: Of 150 autonomic tests (tilt table test, Valsalva response, cardiac deep breathing response, and quantitative sudomotor axon reflex testing) and 14 thermoregulatory sweat tests performed on 142 patients, 130 tests had adequate data for evaluation of utility. The mean age of this population was 13.2 ± 3.6 (range 0.6–17) and 63% were female. The reason for referral was gastrointestinal in 54%, orthostatic symptoms in 26%, neurological in 11%, and thermoregulatory or for the assessment of a known disease in 5% each. Autonomic testing revealed a postural tachycardia syndrome in 65%, an autonomic neuropathy in 29%, reflex syncope in 17%, non-specific autonomic dysfunction in 12%, normal in 6%, and orthostatic hypotension in 4%. In elucidating symptom mechanism 12% were unhelpful, 36% were somewhat helpful, and 52% were very helpful. Regarding search of disease etiology 65% were unhelpful, 22% were somewhat helpful, and 13% were very helpful.

Conclusion: Autonomic testing is more useful in determining possible mechanisms, such as orthostasis, by which the symptoms
are generated (88% of patients) than in providing evidence toward a pathologic diagnosis (only 35%), such as an autonomic neuropathy. This may result in part from the dearth of known common pathologic autonomic diagnoses at this juncture. (Data presented in part in 2005 AAS meeting).

**Poster #46**

**Analysis of treatment outcomes in relation to autonomic testing results in a pediatric population**

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**Background:** The therapy of pediatric autonomic disorders has not been studied.

**Methods:** We reviewed testing data, clinical interpretation, and available clinician and hospital records for patients under 18 years of age, who underwent autonomic testing between 1994 and 2006. Treatment benefit was ranked, blinded to autonomic test results, on a 5-point scale with worsening of symptoms, 1 severe and 2 mild, no change in symptoms 3, symptom relief, 4 mild and 5 excellent. The utility of the autonomic test results in elucidating symptom mechanism was ranked on a 3-point scale. Statistical analysis utilized \( \chi^2 \) test.

**Results:** Adequate information was available in 64 patients who underwent 63 autonomic tests (tilt, Valsalva, deep breathing response, and QSART) and 6 thermoregulatory sweat tests. Mean age was 13.9 ± 2.9 (range 4 – 17); 61% were female. The autonomic tests revealed these diagnoses: postural tachycardia syndrome (66%), reflex syncope (27%), and migraine (9%). Of these diagnoses, 35% had migraine, 28% had postural tachycardia syndrome, and 27% had reflex syncope. Treatments revealed these diagnoses: postural tachycardia syndrome (66%), reflex syncope (27%), and migraine (9%). Of these diagnoses, 35% had migraine, 28% had postural tachycardia syndrome, and 27% had reflex syncope. The proportions of these diagnoses were similar to those in the migraine group (\( P > 0.05 \)). Compared to healthy controls, patients with CVS had more orthostatic intolerance (47% vs. 5.6%, \( P = 0.0002 \)) and fibromyalgia (40% vs. 5%, \( P = 0.001 \)). Interestingly, CVS and control patients had the same frequency of migraine syndrome, functional dyspepsia, syncope and interstitial cystitis.

**Conclusion:** Patients with CVS demonstrated a wide range of autonomic diagnoses. They were not significantly different than the migraine group in support of the presumed common pathophysiology. Orthostatic intolerance and fibromyalgia occurred far less frequently in the normal control group.

**Poster #48**

**Sleep apnea induces deoxygenation in familial dysautonomia patients**

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**Introduction:** Familial dysautonomia (FD) patients are at risk of sudden unexplained death during sleep. Fatalities may be associated with compromised respiration.

**Objective:** To evaluate respiratory changes during sleep in FD.

**Methods:** 11 FD patients (5 females, 28 ± 11 years) and 11 age- and sex-matched controls (6 females, 28 ± 11 years) underwent one night polysomnography. We determined the number of sleep apneas (>90% airflow decrease for at least 10 seconds). Responses to apneas were classified as oxygen desaturation (≥4% SaO2 decrease within 30 seconds after apnea) and arousals (≥2 seconds abrupt shift in electroencephalographic frequencies to alpha- or theta-activity or frequencies >16 Hz). Numbers of patients and controls with apnea, desaturation or arousal were compared by \( \chi^2 \) test. Numbers of individual apneas, desaturations or arousals per night were compared between patients and controls by U test. Significance was assumed for \( P < 0.05 \).

**Results:** 9 patients and 4 controls had apneas (\( P < 0.05 \)). Subsequent oxygen desaturation occurred in 9 patients and 1 control (\( P < 0.05 \)), subsequent arousals occurred in 3 patients and one control. In individual patients, numbers (median, 25th percentile; 75th percentile, range) of apneas (8, 5; 18, 0 – 28) were higher in than controls (0; 0; 1; 0 – 2; \( P < 0.05 \)). Individual numbers of subsequent desaturations also was higher in patients (6; 2; 10; 0 – 26) than controls (0; 0; 0; 0 – 1; \( P < 0.05 \)) while numbers of arousals were similar between patients (0; 0; 1; 0 – 2) and controls (0, 0, 0, 0 – 1).

**Conclusion:** Sleep apneas were very frequent in FD patients and mostly induced oxygen desaturation instead of arousal, the physiologic response (Hlavac et al. Sleep. 2006;29:624 – 631). In FD patients, oxygen desaturation may induce additional hypoventilation, arterial hypotension, bradycardia, and asystole (Bernardi et al. Am J Respir Crit Care Med. 2003;167:141 – 149). Therefore, the results necessitate a detailed analysis of cardiovascular responses to the nocturnal apneas and subsequent desaturations.
Poster #49
Non-psychiatric co-morbidities in pediatric functional gastrointestinal disorder (FGID): an area in need of exploration
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Background: Though adults with IBS have many co-morbidities including fibromyalgia, interstitial cystitis and orthostatic intolerance, the known pediatric associations are primarily psychiatric.

Aim: The aim of this investigation was to identify non-psychiatric co-morbidities of FGID.

Methods: We solicited enrollment in this IRB approved study from the family of every child tested in the autonomic laboratory who met the ROME II criteria for FGID. All had autonomic testing and completed the ODYSQA questionnaire, a tool that evaluates the presence of 12 different autonomic diagnoses: IBS, functional dyspepsia (FD), functional abdominal pain, syncope, fibromyalgia, postural tachycardia syndrome (POTS), complex regional pain, chronic fatigue syndrome, Raynaud’s syndrome, cyclic vomiting syndrome (CVS), interstitial cystitis and migraine headache.

Results: Of 40 children with FGID, 19 had IBS, 13 functional dyspepsia, 4 CVS and 4 abdominal migraine. Subjects with FGID had an average of 1.3 co-morbid diagnoses identified by ODYSQA, 32 had orthostatic intolerance, 8 had migraine and 6 had fibromyalgia. In addition, autonomic testing identified an autonomic neuropathy (AN) in 22, POTS in 26, orthostatic hypotension in 5 and syncope in 11. Taking the results of the ODYSQA questionnaire and the autonomic testing, the subjects had an average of 2 non psychiatric co-morbidities per subject.

Conclusions: Co-morbid autonomic diagnoses occur commonly in children with FGID, with orthostatic disorders predominating in 80%, followed by an autonomic neuropathy, and migraine headaches. The complexities of the associated diagnoses contribute to the difficulties in treating these patients and the need for multidisciplinary approach. Limitation of this study is the skewed population investigated, since they were enrolled from the autonomic lab. Further studies need to investigate all children with FGID, comparing them to control subjects without FGID.

Poster #50
Pain can obscure autonomic dysfunction in acute, acquired small fiber neuropathy in children
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Two children (7 y.o. boy and 11 y.o. girl) presented with acute onset of excruciating, debilitating limb pain. Sensory examinations were limited by marked hyperalgesia and allodynia but both children had normal muscle power and muscle stretch reflexes. Normal MRI head scan, motor and sensory nerve conduction studies and CSF findings led to preliminary diagnosis of psychosomatic disease during initial clinical evaluation. Careful history revealed evidence of other autonomic dysfunction (labile hypertension, postprandial vomiting, sweating irregularity in the boy and vomiting with orthostatic dizziness in the girl). Both children had experienced mild antecedent viral upper respiratory infections. Thermoregulatory sweat tests demonstrated widespread anhidrosis: 63 and 86%, respectively. QSART responses were absent in the boy and unable to be evaluated due to hyperthermia in the girl. Heart rate response to deep breathing and Valsalva ratios were normal. Tilt testing demonstrated blood pressure fluctuations but was otherwise normal. Testing revealed no underlying cause of small fiber dysfunction with normal values for: blood and urine porphyrin metabolites, alpha-3 ganglionic acetylcholine receptor antibody titers, alpha-galactosidase and extensive vasculitis screens. Treatment included medications directed toward management of neuropathic pain (combinations of clonidine, amitriptyline, gabapentin and pregabalin) and beta-blockade for tachycardia and labile hypertension. Over weeks, spontaneous pain and hyperalgesia improved in both children. Clinical followup over 9 years in one patient demonstrated sustained pain relief with minimal improvement in the pattern of sweating.

Conclusion: Autonomic dysfunction can be masked by severe pain in a form of acute, acquired small fiber neuropathy in children. Pathophysiology is presumed to be inflammatory; however, confirmation by nerve biopsy was not obtained. Thermoregulatory Sweat Testing is an invaluable tool to evaluate small nerve fiber function in children with unexplained pain syndromes.

Poster #51
Loss of dopaminergic neurons in the ventral periaqueductal gray in autonomic synucleinopathies
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Studies in rats led to the identification of a group of dopaminergic neurons in the ventral portion of the periaqueductal gray matter (pVAG) that may have a critical role in maintenance of the wake state. Disorders of wakefulness, including excessive diurnal somnolence (EDS), are common manifestations of multiple system atrophy (MSA) and Lewy body disorders (LBD). Although EDS in MSA and LBD is multifactorial, we sought to determine whether loss of dopaminergic neurons in the pVAG could have a contributory role. We studied the midbrain obtained at autopsy from 12 patients (8 M, 3 F, age 68 ± 5) with neuropathologically proven MSA, 12 patients (11 M, 1 F, age 80 ± 1) with limbic or neocortical stage LBD, and 12 age-matched controls. Six of the MSA and six of the DLB cases had history of EDS. Fifteen micron sections obtained throughout the midbrain immunostained for tyrosine hydroxylase (TH) or a-synuclein and co-stained with thionin, and cell counts were performed every 400 μ in the PAG. Compared to controls, there was marked loss of TH (presumably dopaminergic neurons) in the pVAG in all MSA (23 ± 3 vs. 40 ± 5; P < 0.01) and in DLB (16 ± 2 vs. 40 ± 5; P < 0.001) cases. There were no clear differences in the degree of neuronal loss between MSA or DLB cases with and those without history of EDS. In the pVAG, there were abundant a-synuclein-immunostained gial cytoplasmic inclusions (GCIs) in the MSA and Lewy bodies and neurites in the DLB cases. These findings suggest that loss of dopaminergic neurons in the pVAG may contribute to EDS in MSA and LBD. However, loss of other brainstem monoaminergic and cholinergic groups are also likely to have an important role.

Poster #52
Pupil reaction to olfactory stimuli in Parkinson’s patients and healthy controls
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Studies in rats led to the identification of a group of dopaminergic neurons in the ventral portion of the periaqueductal gray matter (pVAG) that may have a critical role in maintenance of the wake state. Disorders of wakefulness, including excessive diurnal somnolence (EDS), are common manifestations of multiple system atrophy (MSA) and Lewy body disorders (LBD). Although EDS in MSA and LBD is multifactorial, we sought to determine whether loss of dopaminergic neurons in the pVAG could have a contributory role. We studied the midbrain obtained at autopsy from 12 patients (8 M, 3 F, age 68 ± 5) with neuropathologically proven MSA, 12 patients (11 M, 1 F, age 80 ± 1) with limbic or neocortical stage LBD, and 12 age-matched controls. Six of the MSA and six of the DLB cases had history of EDS. Fifteen micron sections obtained throughout the midbrain immunostained for tyrosine hydroxylase (TH) or a-synuclein and co-stained with thionin, and cell counts were performed every 400 μ in the PAG. Compared to controls, there was marked loss of TH (presumably dopaminergic neurons) in the pVAG in all MSA (23 ± 3 vs. 40 ± 5; P < 0.01) and in DLB (16 ± 2 vs. 40 ± 5; P < 0.001) cases. There were no clear differences in the degree of neuronal loss between MSA or DLB cases with and those without history of EDS. In the pVAG, there were abundant a-synuclein-immunostained gial cytoplasmic inclusions (GCIs) in the MSA and Lewy bodies and neurites in the DLB cases. These findings suggest that loss of dopaminergic neurons in the pVAG may contribute to EDS in MSA and LBD. However, loss of other brainstem monoaminergic and cholinergic groups are also likely to have an important role.
Objective: To evaluate pupil reaction to different olfactory and trigeminal stimuli in patients with idiopathic Parkinson's syndrome and compare them to our group of healthy control subjects.

Methods: We analyzed the patients with Parkinson's disease Hoehn & Yahr stages II and III, aged 55–72 years (3 male, 1 female). All four patients had marked hyposmia when olfactory function was tested using sniffin' sticks. In a randomized order two trigeminal (CO₂ 20% and CO₂ 40%) and four olfactory stimuli (thiol and rose, both in high and low concentration) were applied intranasally for two seconds through an olfactometer. Pupil responses were simultaneously recorded for eight minutes with a standard pupillograph. Each application was repeated three times consecutively. The data was then compared to 22 healthy subjects aged 18–35 years, who were previously analyzed in an identical matter.

Results: Lower concentrations of thiol or CO₂ evoked responses with smaller amplitudes and longer latencies than higher concentrations. When repeated consecutively for three times, the amplitude of the pupil reaction to both concentrations of thiol scent decreased significantly. Compared to healthy controls, pupil reactions evoked by CO₂ did not significantly differ regarding latencies of the reaction and amplitudes. In none of the Parkinson’s patients could a pupil response be evoked by rose scent, whereas a pupil dilatation could be obtained in healthy controls. Pupil responses to thiol showed lower amplitudes in Parkinson’s patients than in healthy controls. However, this was not significant.

Poster #53
Image analysis based detection of sweat in the thermoregulatory sweat test

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The thermoregulatory sweat test (TST) is clinically used to evaluate disorders that affect central and peripheral sympathetic sudomotor pathways. Typically, the patient is placed in a temperature (45–50°C) and humidity (35–40%RH) controlled room or chamber, and a powder mixture (alginin red, corn starch, sodium carbonate) is applied to the exposed skin surface. The powder changes color from pale orange when dry to dark purple when wet. Exposure to the powder, both direct and airborne, should be limited because it can irritate skin and mucous membranes. This is a safety concern not only for the patient, but also for the technician because of repetitive powder exposures. Additionally, patients often report that the purpl coloration of the skin requires several washings to remove. The objective of this ongoing project is to eliminate the use of powder in the TST, and instead detect sweat with image analysis techniques that exploit the difference in reflection at specific light wavelengths between wet and dry skin. This will make the TST more convenient and safe for both the patient and technician, and may provide information about the temporal development of sweat distribution patterns. Using a fixture constructed to provide uniform lighting with variable intensity, digital photographs of the hand (dry and with drops of artificial sweat) were taken under a variety of lighting conditions. To date, optimal results have been obtained using illumination with blue light, and processing by convolving the grayscale image of the green component, Gaussian kernel smoothing, Canny edge detection, and then Gaussian kernel smoothing again to identify the outline of the hand and drops of sweat. Sweat drops not readily visible under white light illumination are well delineated by this processing method. Current efforts are focused on optimizing the illumination wavelength and intensity, and the parameters in the image processing algorithms. Subsequently, the sensitivity and specificity of image analysis based detection will be compared to powder based detection, including the detection threshold, and effects of skin color, blemishes, and disorders.

Poster #54
Questionnaire based assessment of pelvic organ dysfunction in multiple system atrophy

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Aims: Multiple system atrophy (MSA) is a neurodegenerative disease characterized clinically by any combination of autonomic, cerebellar, and extrapyramidal symptoms. Autonomic symptoms are usually severe, and urinary symptoms are one of the cardinal features of MSA. Bowel dysfunction and sexual dysfunction are also common in MSA. Quality of life (QOL) in patients with MSA is severely impaired by the presence of pelvic organ dysfunction. Therefore, we aimed to examine the prevalence of pelvic organ dysfunction in patients with MSA.

Materials and methods: We recruited 256 patients with MSA seen at our neurology clinic. The mean age was 62 years old. The control group comprised 158 individuals and the mean age 52 years old. We administered a questionnaire on pelvic organ dysfunction to the MSA and control groups. The questionnaire had sections focusing on the bladder, bowel, and sexual function. Dysfunction, as described in the responses, was evaluated as normal, mild (> once a month), moderate (> once a week), or severe (> once a day). The Mann–Whitney U test was used for statistical analysis.

Results: As compared with the control group, in the MSA group, the prevalence of pelvic organ dysfunctions were significantly higher for urinary urgency (75% of the women, 64% of the men), daytime frequency (45%, 43%), nighttime frequency (65%, 69%), urgency incontinence (75%, 66%), retardation in initiating urination (62%, 73%), prolongation poor stream (71%, 81%), difficulty in expulsion (66%, 59%), fecal incontinence (14%, 18%) decrease in libido (92%, 84%), decrease in sexual intercourse (95%, 92%). QOL in MSA group was therefore significantly impaired in urinary dysfunction (70%, 76%), bowel dysfunction (52%, 40%), sexual dysfunction (26%, 45%), respectively.

Conclusion: Pelvic organ dysfunction is common in MSA, and severely impaired QOL in patients with MSA. Amelioration of pelvic organ dysfunction, particularly urinary and bowel dysfunction, is important in patients with MSA.

Poster #55
The diagnostic and therapeutic implication of cardiac MIBG scans in cases of clinically uncertain parkinsonian patients

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Background: Imaging with Cardiac MIBG has been described as a useful measure of early sympathetic dysfunction in Parkinson disease (PD) and may be used to differentiate Parkinson disease (PD) from multiple system atrophy (MSA).

Methods: We describe 17 cases of clinically uncertain akinetic rigid dominant parkinsonian cases, labeled as MSA. In 8, abnormalities/low uptake on cardiac MIBG suggested an alternative diagnosis of Parkinson’s disease with autonomic failure allowing subsequent alteration in therapeutic interventions. Parkinsonian patients (mean age mean 66.3 ± 8.5, mean duration of disease 4.5 ± 4.1, mean HY score 2.6 ± 0.5) with akinesia dominant syndrome and
thought to have MSA on the basis of poor response to levodopa/ dopamine agonists and postural hypotension, underwent cardiac MIBG and MIBI scans.

Results: MIBG uptake values at 15 minutes and 3 hours (R1 and R2) were calculated and R2 values were low (mean R2: 1.46 ± 0.36 normal local cutoff level is 1.5) in 8 cases. DaTscan showed reduced putamen DaT binding and clinically all responded to high dose levodopa treatment at 6 months follow up.

Conclusions: In selected cases of clinically uncertain akinetic rigid dominant parkinsonian cases, cardiac MIBG scans showing low R2 values may help revise a diagnosis of MSA and enable the clinician to use high dose levodopa treatment assuming the diagnosis to be PD with autonomic failure.

Poster #56

Time-frequency analysis of resting pupillary oscillations in small fiber neuropathy

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Objectives: 1. To evaluate the effectiveness of time-frequency analysis as a method of assessing reactivity of the pupil in patients with small fiber neuropathy (SFN). 2. To assess differences in pupillary reactivity at rest between patients with SFN and healthy controls.

Background: SFN is a disease of the somatic and/or autonomic C-fibers. This condition frequently involves the autonomic nervous system. The pupil has been shown previously to be affected by SFN in its response to light.

Methods: We tested 30 patients (60 eyes) with SFN using Infrared Dynamic Pupillometry (FIT 2000, PMI Inc., Maryland, USA, Cleveland Clinic Regular Software). Patients were asked to fixate a dim light during 20 seconds while their pupil diameter was recorded at a sampling rate of 60 Hz. The same method was used on 7 healthy age-matched controls (14 eyes). We compared the pupil diameter variability between the 2 groups.

Results: We performed time-frequency analysis of the signal variability, using the short-time Fourier transform (STFT). The following parameters were evaluated: the power spectral instability factor, the frequency instability factor and 4 parameters describing changes in total PSD in four frequency ranges. Statistical analysis included normality analysis using the Shapiro–Wilk test and significance analysis using t test and U Mann–Whitney test, for both normal and non-normal distributions. The results showed significant differences in the power spectral instability factor and in each of the 4 PSD parameters, between healthy subjects and patients (P < 0.05).

Conclusions: Our results confirm that the proposed method and parameters enable the detection of differences in pupillary diameter variability between patients and healthy subjects and enable the assessment of these differences. Further studies are needed to correlate these changes with the severity of the disease and the degree of autonomic dysfunction.

Poster #57

Proximal leg fatigue as a manifestation of a neurogenic process with small fiber polyneuropathy predominance. Clinical, electrophysiological, autonomic testing and pathological data

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Objective: To characterize a cohort of patients presenting with proximal leg fatigue symptoms, as part of their small fiber predominant polyneuropathy.

Methods: A retrospective chart review of 150 consecutive patients seen in a tertiary care autonomic disorder clinic was performed. The entry criteria were: subjective complaints of proximal leg muscle fatigue, weakness, stiffness and myalgias. Patients with large fiber polyneuropathies, radiculopathies or for whom a definite etiology for the leg complaints was known, were excluded. Patients underwent clinical evaluations, standard electromyographic studies, laboratory testing for muscle enzymes and also underwent autonomic testing (4 site QSART’s, TST, heart rate to deep breathing and tilt table testing). Patients also had muscle and skin biopsies (4 sites, immunofluorescence method with confocal microscopy) performed.

Results: Out of 150 patients, 30 had proximal leg muscle fatigue as one of their main complaints. Out of these, 17 patients had muscle biopsies. All 17 patients had a clinical diagnosis of autonomic dysfunction and had abnormal autonomic testing: 17 sudomotor, 3 vasomotor, 4 cardiovagal. Skin biopsies were performed in 8 patients and were abnormal in all cases. Muscle biopsies had neurogenic changes in 14 patients. One biopsy was normal. Other abnormalities were: type II fiber atrophy (4), mild non-specific inflammation (2), mitochondrial proliferation (4), complex III deficiency (2). All patients had normal strength and reflexes. CPK elevation <3 times normal was noted in 4 patients. Electromyography showed normal nerve conduction studies in all but one patient in which borderline low sural response was recorded. Needle examination was normal except for proximal myopathic potentials with normal insertional activity in 4 patients. One patient also had a sural nerve biopsy which showed mild diffuse myelinated fiber loss.

Conclusions: When rigorously evaluated, patients presenting with proximal lower limb fatigue, subjective weakness, and myalgias in the absence of objective weakness are more likely to have mild neurogenic than myopathic findings. The clinical manifestations of a small fiber-predominant neuropathy may be more varied than previously thought.

Poster #58

Coexistent autoimmune autonomic ganglionopathy and myasthenia gravis as a paraneoplastic syndrome in non-small cell lung cancer

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We report a case of coexistent autoimmune autonomic ganglionopathy (AAG) and myasthenia gravis (MG) in a man with both muscle and ganglionic acetylcholine receptor (AChR) antibodies and non-small cell lung cancer. The ganglionic and muscle AChR antibodies are immunologically distinct, and produce different disease states: AAG is associated with sympathetic and parasympathetic failure, and MG results in bulbar and limb weakness. To our knowledge there are no reports of patients with both antibodies presenting with both disorders. We report a 55-year-old man with non-small cell lung cancer who underwent radiation, chemotherapy with carboplatin and paclitaxel, and left upper lobe removal in 2006. He was evaluated for symptoms of orthostatic hypotension, fatigue which responded to upright rest, and constipation with episodes of ileus, and was treated with five plasma exchanges (PE). Paraneoplastic antibody panel revealed 0.66 nmol/l titer of muscle AChR binding antibody (0.70 nmol/l) and ganglionic AChR antibody (0.34 nmol/l). Clinical examination revealed mild ptosis bilaterally, fatiguable neck flexor weakness and hip flexor weakness. Single
fiber EMG (SFEMG) of the right extensor digitorum communis revealed normal mean MCD (jitter) but had several pairs with jitter greater than 100 μs which improved after PE. PE also normalized responses to posture and Valsalva. Pre-exchange BP fell from 113/69 supine to 66/47 mmHg 5 minutes standing without a compensatory increase in heart rate (57 to 59 bpm); post-exchange: 105/68 supine to 118/82 mmHg standing, 66 to 79 bpm. Plasma norepinephrine pre-exchange: 79 pg/ml supine to 330 standing; post-exchange: 194 supine, 763 standing. Response to Valsalva pre-exchange: 97/62 baseline to 68/25 phase 4, HR ratio 1.0; post-exchange: 96/50 baseline to 146/70 phase 4, HR ratio 1.47. We conclude that AAG and MG can coexist, and suggest that patients with AAG complaining of fatigue improved with non-supine rest should be evaluated for possible coexistent MG.

Poster #59
Parasympathetic heart rate reserve in autonomic failure patients
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Baroreflex loading during alpha-2 adrenoreceptor stimulation provides a graded increase in parasympathetic activity. The approach may distinguish functional from structural changes in cardiac parasympathetic control. We tested the methodology in 5 patients with autonomic failure (PAF). Patients were given incremental intravenous phenylephrine infusions with and without clonidine (1 μg/kg). BP was foundly increased during clonidine plus phenylephrine in one PAF patient and in one MSA patient. Our results suggest that baroreceptor sensitivity identifies autonomic failure patients with relatively preserved cardiac parasympathetic regulation. The observation further supports the idea that renal function can be compromised by excessive supine blood pressure and heart rate before and during 60° passive head-up tilt in 151 patients (PAF, n = 19; 13 males and 6 females; age, 65 ± 2 years; disease duration, 6 ± 1 years. MSA, n = 56; 38 males and 18 females; age, 59 ± 0.8 years; disease duration, 5 ± 0.2 years. PD, n = 76; 51 males and 25 females; age, 74 ± 0.8 years; disease duration, 9 ± 0.9 years, mean ± SD).

Results: Supine blood pressure was 156 ± 8/90 ± 5 mmHg in patients with PAF, 157 ± 2/92 ± 1 mmHg in patients with MSA and 155 ± 3/83 ± 2 mmHg in patients with PD. During 60° passive head-up tilt all patients had OH (fall of at least 20 mmHg systolic or 10 mmHg diastolic blood pressure). In all three autonomic synucleinopathies there was a linear relationship between the fall in blood pressure during head-up tilt and blood pressure when supine (P < 0.0001). All patients with PAF were taking fludrocortisone, 27% of the patients with MSA were tested before and after taking fludrocortisone, and 13 (17%) of the 76 patients with PD were taking fludrocortisone. Supine blood pressure was higher and the orthostatic fall in blood pressure was greater in patients with MSA and PD who were taking fludrocortisone (P < 0.0001). However, the relationship between orthostatic hypotension and supine hypertension was significant regardless of fludrocortisone treatment.

Conclusion: Supine hypertension is a frequent feature of the autonomic synucleinopathies. It is exacerbated by, but does not depend on fludrocortisone treatment. Supine hypertension is likely related to the magnitude of OH suggesting a shared mechanism for both abnormalities. Part of this study was presented at the American Academy of Neurology Meeting, Chicago, 2008.

Poster #60
Association between orthostatic hypotension and supine hypertension in autonomic synucleinopathies
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Objective: To determine the relationship between orthostatic hypotension (OH) and supine hypertension in patients with autonomic synucleinopathies including Parkinson’s disease (PF), pure autonomic failure (PAF) and multiple system atrophy (MSA).

Background: OH is a well-known feature of patients with autonomic synucleinopathies. Many of these patients, however, also have hypertension when supine.

Materials and methods: We analyzed the clinical characteristics, blood pressure and heart rate before and during 60° passive head-up tilt in 151 patients (PAF, n = 19; 13 males and 6 females; age, 65 ± 2 years; disease duration, 6 ± 1 years. MSA, n = 56; 38 males and 18 females; age, 59 ± 0.8 years; disease duration, 5 ± 0.2 years. PD, n = 76; 51 males and 25 females; age, 74 ± 0.8 years; disease duration, 9 ± 0.9 years, mean ± SD).

Results: Supine blood pressure was 156 ± 8/90 ± 5 mmHg in patients with PAF, 157 ± 2/92 ± 1 mmHg in patients with MSA and 155 ± 3/83 ± 2 mmHg in patients with PD. During 60° passive head-up tilt all patients had OH (fall of at least 20 mmHg systolic or 10 mmHg diastolic blood pressure). In all three autonomic synucleinopathies there was a linear relationship between the fall in blood pressure during head-up tilt and blood pressure when supine (P < 0.0001). All patients with PAF were taking fludrocortisone, 27% of the patients with MSA were tested before and after taking fludrocortisone, and 13 (17%) of the 76 patients with PD were taking fludrocortisone. Supine blood pressure was higher and the orthostatic fall in blood pressure was greater in patients with MSA and PD who were taking fludrocortisone (P < 0.0001). However, the relationship between orthostatic hypotension and supine hypertension was significant regardless of fludrocortisone treatment.

Conclusion: Supine hypertension is a frequent feature of the autonomic synucleinopathies. It is exacerbated by, but does not depend on fludrocortisone treatment. Supine hypertension is likely related to the magnitude of OH suggesting a shared mechanism for both abnormalities. Part of this study was presented at the American Academy of Neurology Meeting, Chicago, 2008.
Spectral analysis of heart rate and blood pressure variability discriminates autonomic dysfunction associated with Parkinson’s disease and MSA-P

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Autonomic dysfunction frequently appears in multiple system atrophy (MSA) and idiopathic Parkinson’s disease (IPD). Degeneration of the autonomic nervous system is predominantly peripheral in IPD and predominantly central in MSA [1]. The aim of our study was to determine whether spectral analysis of heart rate (HR) and blood pressure (BP) variability during tilt discriminates IPD and MSA-P in patients with symptoms of autonomic dysfunction. We enrolled each 10 patients with IPD and MSA-P with features of autonomic dysfunction matched for age, gender, and Hoehn & Yahr; none had heart disease or diabetes. Changes of HR and BP variability in reaction to tilt was assessed by spectral analysis: Low frequency variability of BP (LF_BPV), a marker for sympathetic activity [2], and the ratio of low to high frequency HR variability (LF/HF_HRV), reflecting the sympatho-vagal balance [3]. Compared to rest, LF_BPV response to tilt showed a higher increase in IPD than in MSA-P (n.s.). The response of LF/HF_HRV ratio to orthostatic stress was significantly blunted in MSA-P compared to IPD (p < 0.05). Our results may reflect the difference in lesion distribution between IPD and MSA. However, side effects of levodopa may also have modified the sympatho-vagal balance. Our data suggest that spectral analysis of HR and BP variability may represent a useful tool for the differentiation of autonomic dysfunction associated with parkinsonian disorders. Future studies should include larger numbers of patients and healthy controls to corroborate the blunted tilt-induced increase of sympatho-vagal balance in MSA-P compared to IPD.

References

Treatment of multiple system atrophy using intravenous immunoglobulins: preliminary report

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Background: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder leading to widespread loss of various brain cells that results in parkinsonian, cerebellar and autonomic dysfunction. Available treatment is symptomatic only and does not alter the course of disease. Although the cause of MSA remains unclear, there is evidence of presence of common neuroinflammatory mechanisms in the MSA brains including activation of microglia and production of toxic cytokines. This clinical trial protocol is based on hypothesis that the MSA progression can be altered by blocking the neuroinflammatory activity using intravenous immunoglobulins (IVIg).

Study design: This is a single interventional arm, single center, open-label, phase II study assessing effects of IVIg in MSA. Primary outcome measure is to evaluate safety of the IVIg infusions for treatment of MSA. Secondary outcome measure is to evaluate preliminary efficacy of IVIg for treatment of MSA. Interventions include monthly infusions of IVIg, dose 0.4 g/kg, for 6 months. We plan to enroll 10 subjects with diagnosis of probable MSA and each subject will be enrolled for 1 year. We expect to start the study in June 2008 and to complete the study within 2 years. The unified MSA rating scale (MSARS), quantitative imaging of white matter using 3T MRI and number of inflammatory markers will be obtained before and after the treatment. In addition the MSARS will be obtained during each treatment visit.

Expected results: We expect to obtain sufficient evidence of efficacy of IVIg in treatment of MSA that will lay a foundation for larger scale multi center trials. The preliminary results will be discussed.

Dysautonomia has been called the “invisible disease” often going unrecognized by all levels of health care providers in spite of its prevalence affecting a population of at least one million Americans. Autonomic dysfunction results from several primary and numerous secondary causes. Known causes grow in number each year with recent cases being linked to viral or biochemical origins. Prevalence of this condition continues to rise while recognition of organ and system compromise related to autonomic dysfunction remains low. This is due in part to the omission of information related to this condition from most medical and nursing curricula. This research utilization project is designed to equip providers to recognize this condition and provide effective care for those suffering from autonomic dysfunction. This multimedia presentation is prepared as an educational offering for providers interested in common presentations, currents diagnostics, and basic treatment modalities utilized in caring for those with various autonomic syndromes. The basic educational content of this presentation is supplemented with movie scenes which are representative of the impact of living with autonomic dysfunction. This formatting was developed to help the provider understand not only what we are trying to accomplish but also gain insight into the difficulties of those we serve.

Role of the nucleus tractus solitarius in mediating cardiovascular and gastric responses evoked by auricular and body acupuncture stimulation

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Background and objective: The nucleus tractus solitarius (NTS) is an important neural substrate in regulation of autonomic changes. The aim of this study is to examine the role of NTS neurons in modulation of cardiovascular and gastric changes using auricular and body acupuncture.

Methods: In anesthetized SD rats, acupuncture was applied to auricular point Heart and body acupuncture points PC6, ST36 and ST25, and NTS neuronal activity as well as arterial blood pressure, heart rate and intragastric pressure were monitored.

Results: Auricular acupuncture was more powerful in evoking depressor and bradycardiac responses than body acupuncture. While NTS neurons responded to both body and auricular acu-
puncture, those neurons that displayed cardiac rhythms were more responsive to stimulation of the auricular point than to the body acupuncture. Blockade of central and peripheral muscarnic receptors with atropine sulfate (2 mg/kg, i.v.) abolished the depressor and bradycardiac responses evoked by auricular acupuncture, but did not abolish those evoked by body acupuncture, and at the same time, attenuated the responsiveness of neurons that displayed cardiac rhythms to stimulation of the auricular point. Blockade of peripheral muscarinic receptors only by atropine methyl nitrate (2 mg/kg, i.v.) attenuated the depressor and bradycardiac responses evoked by auricular acupuncture, leaving those evoked by body acupuncture unaffected. Ipsilateral ligaturetine microinjection into the caudal NTS blocked the depressor and bradycardiac responses evoked by auricular acupuncture, with little effect on those evoked by body acupuncture. Taken together, our findings suggest that auricular and body acupuncture have different characteristics in cardiovascular inhibition, due to distinct mechanisms of action. The NTS play a pivotal role in mediating autonomic changes evoked by auricular acupuncture.

Poster #66
Serotonin innervation of the nucleus tractus solitarius (NTS) augments sympathetic and ventilatory responses to hypoxia

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Previously, we found that hindbrain serotonin nuclei positively modulate sympathetic responses to central chemoreflex stimulation. Here, we tested whether serotonin projections to the NTS positively modulate sympathetic responses to peripheral chemoreflex activation. Blood pressure (BP), heart rate (HR), sympathetic and ventilatory responses to increasing doses of KCN (3, 10, 30, 100 μg/kg, i.v.) were measured in conscious male Sprague Dawley rats subjected to selective (n = 9–6) or sham (n = 6–5) destruction of serotonin nerve terminals in the NTS. Selective and sham lesions were made under sodium pentobarbital anesthesia (65 mg/kg, i.p.) using bilateral injections of the serotonin neurotoxin, 5,7-di-hydroxytryptamine or ascorbic acid vehicle (0.01%) respectively within regions of the NTS that receive cardiovascular afferents. Six days later, rats were implanted with vascular catheters and recording electrodes for measurement of renal sympathetic- and diaphragmatic EMG activity. The next day, BP, HR, renal sympathetic nerve activity (RSNA) and diaphragmatic EMG were recorded during peripheral chemoreflex activation with KCN. Lesioned rats showed an attenuated pressor response (6.4 ± 4.9 vs. 29.0 ± 5.3 ΔmmHg, P < 0.01) at the 100 μg/kg KCN dose. RSNA responses to 10 (135.4 ± 38.6 vs. 336.4 ± 60.8 Δ% baseline, P < 0.05), 30 (187.3 ± 48.3 vs. 389.6 ± 61.4 Δ% baseline, P < 0.05), and 100 (259.8 ± 29.4 vs. 588.9 ± 93.18 Δ% baseline, P < 0.01) μg/kg KCN were reduced in lesioned rats. Tidal volume (499.2 ± 134.2 vs. 2095.4 ± 680.5 Δ% baseline, P < 0.05) and minute ventilation (364.4 ± 105.5 vs. 1994.0 ± 869.6 Δ% baseline, P < 0.05) were also reduced at the highest dose in lesioned rats. Neither the bradycardia or tachypnic responses to KCN differed between groups. In conclusion, serotonin projections to the NTS were found to augment the sympathetic and ventilatory components of the peripheral chemoreflex in conscious rats.

Poster #67
Cardiopulmonary reflexes influence on the circulation rapid regulation

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The rise of blood pressure variability that in normal conditions is smoothed by fluctuations of heart rate (HR) and vascular tone within the Mayer range (near 0.1 Hz) can be associated with the increase of cardiovascular events risk. While the importance of arterial baroreflexes is not doubted, the influence of cardiopulmonary baroreflex (CPBR) on the hemodynamics rapid regulation processes is insufficiently studied. The aim of this study was to assess of CPBR contribution to the maintenance of arterial pressure stability. Twelve healthy subjects were examined. Mean age was 25.7 ± 4.9 years. Cardiac rhythm and arterial pressure were recorded with the use of finapress technique (Finometer FMS-Amsterdam) at rest and in the course of lower body negative pressure application (~10 mmHg). Using the modelflow method and special software the additional parameters of system hemodynamics, HR, blood pressure (BP) and its cross-spectral power density were calculated. Arterial baroreflex sensitivity (ABR) was estimated by sequential techniques.

Results: Both BP and HR levels did not change significantly as a result of CPBR deactivation. But in the course of the test stroke volume and cardiac output was decreased. That associated with the rise of total peripheral resistance. At the same time the increase of BP variability in all spectral ranges was noted: VLF (4.6 ± 2.5 and 15.4 ± 7.3 mmHg², P < 0.01), LF (3.4 ± 1.8 and 6.0 ± 4.0 mmHg², P < 0.05) and HF (2.8 ± 0.6 and 4.8 ± 1.8 mmHg², P < 0.01). Besides the redistribution of spectral power towards VLF spectral component was noted (41.2 ± 10.1 and 56.1 ± 13.0%, P < 0.01) together with distinct tendency to the decrease of LF component (31.0 ± 13.1 and 22.2 ± 6.0, P = 0.051). In spite of the cross-spectral power significant increase (0.00184 ± 0.00081 and 0.00264 ± 0.0009 mmHg / s, P < 0.05), arterial baroreflex wasn't change during of CPBR deactivation: 15.5 ± 2.2 and 14.9 ± 4.1, P > 0.05.

Conclusion: CPBR deactivation is accompanied by the increase of BP variability in all spectral ranges, and especially in VLF range. It takes place in spite of the arterial baroreflex stability that indirectly shows the increasing role of the slow regulating mechanisms. Thus CPBR is involved in the process of vessel tone fine regulation by means of both slow and rapid regulating mechanisms.

Poster #68
A new noninvasive method to assess adrenergic baroreflex sensitivity

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Background/objectives: Microneurography of muscle sympathetic nerve activity (MSNA) or changes in mean arterial blood pressure (BP) is the gold standard in assessing the adrenergic limb of the baroreceptor reflex. However, the technique is time-consuming, invasive, and not feasible as routine tool in the clinical autonomic laboratory. There has been much recent interest in noninvasive means to assess adrenergic baroreflex sensitivity (BRS), and we proposed and validated a method relating the BP recovery time following the Valsalva maneuver (VM) to the preceding BP drop during earlier phases of the maneuver. We now propose a new, more intuitive, and physiologically appealing technique to noninvasively assess adrenergic BRS.

Methods: The new index relates beat-to-beat changes of BP during early phase II of the VM to the 4–8 beat delayed BP response to these changes. The latter is quantified as function of the slope of the BP curve during phase II. There is a negative linear relationship between the BP drop and resulting changes of the BP curve which can be expressed as adrenergic baroreflex gain (BRG_a). Following validation of this new index using microneurographic recordings, we verified it against age- and sex-matched groups of patients with graded severity of adrenergic failure (orthostatic hypotension, n = 15; borderline orthostatic hypotension, n = 15; impaired reflex vasconstriction without orthostatic BP change, n = 15) and normal controls (n = 15).

Results: BRG_a provided a better separation of groups than previously reported indices of adrenergic BRS. The index was
Paradoxical heart rate and muscle sympathetic activity modulation in a patient with isolated carotid baroreflex failure

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We report a patient with afferent baroreflex failure. He is a 39-year-old caucasian male with paragangliomas who underwent bilateral surgical resection and radiotherapy of the carotid body at age 19 years. He presented with labile hypertensive episodes (160/100 mmHg), alternating with episodes of lightheadedness with upright posture. We performed autonomic function tests, pharmacological baroreflex estimation, and neck suction while recording ECG for heart rate (HR), blood pressure (BP), respiration, and peroneal muscle sympathetic nerve activity (MSNA). Baroreflex impairment was confirmed by reduced baroreflex sensitivity (BRS) estimated by bolus injections of phenylephrine (3.07 μg/ml/MmHg) and nitroprusside (2.64 μg/ml/MmHg) and absent modulation of heart rate and muscle sympathetic activity during bilateral neck suction. Supine BP and HR were normal (113/67 mmHg, 67 bpm), while upright BP was low (85/53 mmHg, 82 bpm). Supine BP variability was not decreased (LFnen = 8.9 mmHg2, LFin = 6.2 mmHg2). Supine MSNA was elevated at rest (39 bursts/minutes, 54 bursts/100 beats) and most bursts were pulse synchronous. Heart rate variability (SD = 41.3 ms, RMSSD = 17.8 ms) was reduced mostly in the high frequency (HF) spectral component (HFren = 59.7 ms2). While the respiratory sinus arrhythmia was quantitatively normal (1.40), we found a paradoxical inverse respiratory sinus arrhythmia response characterized by heart rate acceleration and maximal MSNA activity during expiration. In response to Valsalva, there was an exaggerated fall in systolic BP (~70 mmHg) during phase 2. There was a pronounced initial heart rate fall (~22.8 bpm) and total absence of MSNA throughout the entire straining period. MSNA activity recovered during phase IV, even though there was no BP overshoot. In summary, this patient with isolated afferent carotid baroreflex failure but apparently preserved cardiopulmonary reflex had elevated basal sympathetic activity. His heart rate and MSNA patterns were paradoxical, and could reflect by primary modulation by cardiopulmonary reflexes.

Neuroendocrinologic change in Creutzfeldt-Jakob disease

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Creutzfeldt-Jakob disease (CJD) is a fatal progressive neurodegenerative disease by the accumulation of pathogenic prion protein in the brain. From the onset in several months, the patients become bedridden akinetic mutism and are usually fed via nasal tubes. These patients often sweat well without bacterial infections. We examined the hormonal function of CJD patients. Six patients (5 sporadic CJD and familial CJD), diagnosed probable CJD according to the WHO criteria, were examined pituitary hormones and other hormones at rest. All patients had myoclonus, periodic synchronous discharge in electroencephalogram and abnormal signals in MRI diffusion weighted images. Serum norepinephrine levels were high in five patients and the other serum hormone levels were within normal range. These findings suggest that pituitary grand and sympathetic nerves were hard to be denatured until the terminal stage of CJD.

Dysfunction of autonomic nervous system activity in schizophrenia

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Schizophrenic patients have been reported to experience cardiovascular disease more likely than general population. Although variability of heart rate and blood pressure were supposed to be risk factors for these diseases, detailed autonomic nervous system (ANS) activity in schizophrenia was unclear. We investigated the ANS activity in schizophrenic patients and examined the influence of neuroleptics on the ANS activity. Subjects were 127 Japanese patients with schizophrenia and 32 healthy controls. All subjects received an explanation of our study and written informed consent was obtained. ANS was assessed by means of heart-rate variability (HRV) power spectral analysis, which enables us to identify separate frequency components, i.e., total power (TP: overall ANS), low-frequency (LF: sympatho-vagal) power, and high-frequency (HF: vagal) power, during a resting condition. Statistical analyses were performed using t tests to determine the presence of differences in ANS activity. We found significantly higher mean heart rate (HR, P < 0.001) and lower TP (P = 0.017) in schizophrenic patients than controls. There were no significant differences in LF and HF between two groups. When only considering subjects who were under 64 years old to exclude an influence of age gap, we found an even more significant differences in HR (P < 0.001), TP (P = 0.011), LF (P = 0.001), and HF (P = 0.042) between two groups. On the other hand, there was no association between ANS activity and neuroleptics dose. Our findings suggest that schizophrenic patients possess reduced ANS activity, which might be associated with increased cardiovascular mortality. On the other hand, there was no association between ANS activity and neuroleptics dose. However our sample power still may not allow a solid conclusion. Additional clinical data with larger number of subjects including psychiatric severity and physical activity are needed to assess ANS activity in schizophrenic patients.

Diurnal variation of orthostatic blood pressure control after ischemic stroke

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Objectives: Ischemic stroke affects acutely diurnal blood pressure (BP) control. We investigated whether autonomic BP responses to orthostatic stress remain impaired in patients with chronic ischemic infarctions.

Methods: We studied 43 subjects with large middle cerebral artery (MCA) territory infarctions (15 normotensive and 28 hypertensive) and 45 age- and gender-matched controls (30 normotensive and 15 hypertensive). A sit-to-stand test was administered to measure diurnal responses in orthostatic BP (AM1, noon, PM, and also in cerebral blood flow velocity (BFV)(AM2). BP was measured intermittently during 5 minutes of sitting with legs elevated 90° and after 1, 3, and 5 minutes of standing. Beat-to-beat BP and BFV using transcranial Doppler ultrasound were recorded during AM2 sit-to-stand test.

Results: In hypertensive and normotensive controls, systolic and diastolic BP declined after minute 1 of standing in the morning and recovered during minutes 3 and 5 (P = 0.0001), while BP remained stable during orthostatic stress at noon and in the evening. This diurnal pattern was not observed in stroke subjects, who maintained stable orthostatic BP (P = 0.27). The percent BP decline in the morning was higher in control subjects (P = 0.013) compared to stroke subjects. Average sitting and standing systolic BP (stroke = 131.7 ± 15.6; control = 129.99 ± 20.2; 130.63 ± 22.9 mmHg), and diastolic BP (stroke = 67.36 ± 8.3; 69.47 ± 10.1, control = 69.27 ± 10.7; 70.54 ± 10.7 mmHg) values were not different between the groups. In the hypertensive and normotensive stroke groups, the average mean BFV was lower on the stroke side and on the non-stroke side during sitting (P = 0.026 and P = 0.027) and standing (P = 0.029 and P = 0.027) when compared to hypertensive and normotensive control subjects. Average BFV did not decrease in stroke subjects during standing.

Conclusion: Stroke has long term effects on blood pressure control and diurnal blood pressure variation is reduced after stroke. Average cerebral blood flow velocity is reduced after stroke but is maintained during orthostatic stress. The impact of these findings on stroke recovery and risk for recurrent stroke requires further investigations.

Poster #73
Hypertensive patients demonstrate low resting autonomic activity

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Background: The Holter literature indicates that higher parasympathetic (P) activity (low sympathovagal balance, SB) is associated with longevity, especially in females, and perhaps is associated with fewer co-morbidities. The normal range for SB is 0.4–3.0.

Hypothesis: SB is correlated with co-morbidities.

Design: Autonomic profiling of 125 consecutive hypertensive, male patients in the age range of 70 ± 11.4, was performed using the ANX-3.0 Autonomic Monitor (Ansar, Inc, Philadelphia, PA). The cohort included 61 Diabetics and 65 with CAD.

Methods: ANS profiling was based on patient responses to a standard clinical study that includes a 5-minutes resting baseline. Patients with arrhythmia were excluded. SB is the ratio of sympathetic activity over P activity. Data were analyzed with SPSS 14.0.

Results: The average number of cardiovascular co-morbidities over the entire cohort was 2.05. All SB states, but low-normal, were higher than the cohort average. Low-normal SB resulted in an average of 1.39 co-morbidities. Overall, SB was significantly correlated with the number of co-morbidities (P = 0.047, 2-tailed). Age was also significantly correlated with co-morbidities (P = 0.001, 2-tailed).

Conclusion: Older patients generally presented with a greater number of co-morbidities on average. Irrespective of age, patients with low-normal SB had significantly fewer co-morbidities. The cause or effect of low-normal SB in the geriatric patients needs to be further established.

Poster #74
Age matched attenuation of autonomic activity in both branches in chronic hypertension

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Background: Autonomic dysfunction as evidenced by reduced low frequency (LF) and high frequency (HF) power of baseline heart rate variability (HRV) has been implicated in chronic hypertension. However, thus far there is very little consensus on the validity of the correlation between LF power and hypertension. Moreover, LF power from traditional HRV analysis has been shown to be an inaccurate indicator of sympathetic activity. Autonomic nervous system (ANS) profiling using HRV and respiratory activity (RA) simultaneously yields accurate measures of sympathetic (SNS) activity (LF Area or LFa), parasympathetic (PSNS) activity (Respiratory Frequency Area or RFa), and sympathovagal balance (LFa/RFa ratio).

Methods: Serial ANS testing was performed on 74 hypertensive patients (Females = 2; Age = 66.6 ± 12.2) with and without co-morbidities (Diabetes = 43; Coronary Artery Disease = 43) using the ANX-3.0 Autonomic Monitor (ANSAR, Inc., Philadelphia, PA). The data were compared with preexisting data for normal controls (Ages 40–90) with no history of diabetes, or cardiovascular and autonomic disorders.

Results: Baseline SNS and PSNS levels were found to be significantly reduced in chronic hypertension patients compared to normal controls. An age-distributed investigation revealed that the SNS and PSNS activity decrease with age, a trend similar to that of normal controls. However, these differences between normal controls and hypertensives are much more marked in the younger population and gradually decrease with age. These trends were observed regardless of any co-morbidities or medications. The SNS and PSNS values for 45 year-old hypertension patients were similar in magnitude (or lower) than those of 85 years old normal controls.

Conclusion: Both parasympathetic and sympathetic activity appear to be significantly decreased in chronic hypertensives compared with age-matched normal controls. Whether these observations suggest autonomic decline as the effect of hypertension, or as the cause of hypertension, remains to be established.

Poster #75
Altered sympathetic and parasympathetic activity is associated in patients with chronic coronary artery disease

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Background: Chronic coronary artery disease (CAD) may lead to a reduction in the low and high frequency power (LF and HF, respectively) of baseline heart rate variability (HRV). Respiratory analysis (RA) has been shown to be a necessary addition to tradi-
tional HRV in order for properly and non-invasively quantify sympathetic (SNS) and parasympathetic (PSNS) activity; independently and simultaneously.

Methods: Serial ANS testing was performed on 52 CAD patients (Females = 1; Age = 65.5 ± 13.3) with and without co-morbidities (Hypertension = 42; Diabetes = 25) using the ANX-3.0 Autonomic Monitoring System (Ansar, Inc., Philadelphia, PA). The data was compared with preexisting data for normal controls (Age Range = 40–90) with no history of diabetes, or cardiovascular and autonomic disorders.

Results: Baseline SNS as well as PSNS levels were found to be significantly reduced in chronic CAD patients compared to normal controls. An age-distributed investigation revealed that the SNS and PSNS activity decrease with age, a trend similar to that of normal controls. However, these differences between normal controls and CAD patients are much more marked in the younger population and gradually decrease with age. These trends were observed regardless of any co-morbidities or medications. The SNS and PSNS values for 45 year-old CAD patients were similar in magnitude (or lower) than those of 85 years old normal controls.

Conclusion: Overall autonomic activity appears to be significantly decreased in CAD patients compared with age-matched normal controls, suggesting that CAD may affect an acceleration in the (physiological) aging process of patients as compared to age-matched controls. Whether decreased autonomic activity in CAD patients is cause or effect needs to be established in future studies.

Poster #76
Altered autonomic activity with atrial fibrillation as demonstrated by non-invasive autonomic monitoring

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Introduction: Sympathovagal Balance (SB) may provide insight into autonomic involvement in arrhythmia.

Methods: Serial ANS assessment (ANX 3.0, ANSAR, Philadelphia, PA) was performed on 270 patients diagnosed with AFib without CAD from 4 ambulatory cardiology clinics (191 Females, 56.2 ± 15.7). Assessments averaged 6.23 ± 0.57 months apart and the average patient had 3.1 ± 0.22 tests over the 3 years period of this study. SB is computed as the ratio of the average sympathetic to parasympathetic activity (normal: 0.4 < SB < 3.0) over a 5 minutes rest period. All patients were treated for AFib at the time of the assessment. If SB was abnormally low, then the patient had a normal autonomic involvement in arrhythmia.

Results: Of the patients included in this cohort, 22 (8.15%) were in AFib for each assessment, 87 (32.22%) patients were never in AFib during an assessment, 161 were in and out of AFib. Of the 161, 131 (81.3%) reported fewer episodes and symptoms subsequent to ANS therapy, 43 (15.9%) reported a total absence of episodes and symptoms subsequent to ANS therapy; 39 (90.7%). The average SB for the group who were in AFib is 0.76 ± 0.13, indicating a mild (yet normal) parasympathetic tendency. The average SB for the group who were not in AFib is 1.39 ± 1.21, indicating a mild (yet normal) sympathetic tendency. The average SB for the group who reported fewer symptoms, the SB changed from 3.15 ± 2.98 before the change in therapy to 1.78 ± 1.91 after the therapy change. This change suggests a normalization of the autonomic balance.

Conclusion: SB may determine autonomic components of AFib. It seems as if these autonomic components can be treated.
medications. According to BP four groups were identified: 1) HT was defined as S BP > 140 and/or D > 90, and those with previous history of HT; 2) HO: include: (a) SBP < 90 and/or (b) DBP < 60 and/or (c) drop between supine SBP and immediate standing BP of 20 and/or 10 mmHg en SBP or DBP; (3) HT-HO those with both characteristics and (4) Normal BP (N) those without previous conditions.

Results: (1) HT: 301 (previously diagnosed 109), 54.8% f, age 57.3 (12.1; 30–87), SBP 150.4 (19.2; 121–229.5), DBP 91.43 (10.2; 68–128); 2) N: 377, age 44.7 (9.5; 27–81), 55.2% f; SBP 116.6 (10; 93–139); DBP 76.6 (6.67; 61–89); 3) HO: 116; age 47.96 (9.9; 30–75); 56.3% f; SBP 114.9 (15.5; 86–166), DBP 73.1 (8.9; 55–89); 4) HT-HO: 57, age 55.41 (9.07; 40–74), 55.9%f, SBP 153.8 (18.34; 128–210); DBP 88.37 (9.98, 64–106). After adjustment for age and gender in 691 individuals without treatment shown no significant differences in SBP between HO and N and HT-HO.

Conclusion: Four BP groups were identified. We’d like to see how HO (14.5%) modified risk factors and other variables.

Poster #79
Blood pressure characterization of essential hypotension and/or orthostatic hypotension
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Objective: Hypotension is not always easy to diagnose. Blood pressure (BP) in supine (S), immediate (1) and 1 minute (1 m) standing in patients with hypotension an/or orthostatic hypotension (Hypo) is described.

Methods: Hypo was defined as a drop of 20 or 10 mmHg, in systolic (S) and diastolic (D) BP respectively, with or without symptoms, or as SBP < 90 and diastolic BP < 60 mmHg. Measurements of ambulatory BP monitoring (ABPM) were significant different from normo (N) or hypertension (HT). Several patients’ blood pressure measurements were search and the highest drops (supine – immediate) and lower BP levels were taken. Lower BP in supine, immediate and 1 minute standing position were recorded. Patients were without medication. Patients with both, HT and Hypo were excluded.

Results: 1100 patients, 716 females (f), age 50.4 (18.4) years old. N 190 (53.7%), 405 HT (52.8%) and 505 (79.2%) HO with 39.6 (16.6). S SBP 107.2 (13.2; 70–180), S DBP 65.8 (8.6; 90–40), S heart rate (HR) 70.1 (11; 108–40), I SBP standing 89.9 (16; 154–88), DBP I 61.6 (10.6; 100–38), 1 HR 155.7 (15.3; 100–189), 1 m SBP 103 (14; 180– 53), 1 m HR 109.1 (15.6; 144–44); maximum (max) dropping in SBP 27.5 (12.3; 108–1), minimum (min) SBP 78.4 (12.7; 140–48), max DBP dropping 12.3 (11.3; 98–0), minutes DBP 52.8 (8.14; 70–33), minutes supine SBP 94.3 (11.1; 130–60), minutes supine DBP 57.7 (6.64; 76–40). In 24 hours. ABPM, SBP 113.6 (10.6; 151–91), DBP 69.8 (7.5; 97–49), SBP day 115.9 (13.6; 151–11), PAD day 71.9 (8.3; 116–49), SBP night 103.8 (11.5; 145–80), DBP night 62.7 (8.5; 94–44). 118 patients had orthostatic symptoms.

Conclusions: This data are statistically different from those with N or HT. Is easy to obviate the diagnosis, so do not ruled out it before several BP taken in the adequate way.

Poster #80
Hemodynamics of fibromyalgia syndrome
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Purpose: Fibromyalgia syndrome (FMS) is a chronic pain disease that takes a complex condition. A peculiar mind-body correlation to the patient is potential in the pain appearance of disease. Delius L pointed out that the changes appeared in the hemodynamics, and advocated dysdynamic syndrome in such a case. The hemodynamics of FMS were evaluated based on this concept.

Objectives and methods: The hemodynamic reactions according to the tilting examination of Schellong’s tests were examined for 50 FMS patients. During at rest with supine position for more than 6 minutes then positive standing position for 10 minutes, hemodynamics were examined every 2 minutes non-invasively (by ParamTech GP303s). The examination classified into high reactive type (hyperkinetic type) of 3 Uminutes/m2 or more and the following low reactive types (hypokinetic type) according to cardiac index (CI), and examined differences in the hemodynamic study of both.

Results: There were no significant differences in the age, sex, the number of pressure pain points, and the oxidative stress defense system. In hyperkinetic type, systolic blood pressure (SBP), heart rate (HR), stroke volume (SV) were significantly higher in supine position, nut in hypokinetic type SBP, HR, SV showed adverse reaction. This reaction became remarkable for the time of the standing positioning of pass.

Consideration: The hemodynamics of FMS showed a quite different reaction in hyper kinetic type and hypokinetic type. The hemodynamics strongly receives the influences from the central nervous system. It was thought that it was necessary to take the situation of the circulation of the blood movement into consideration, and to treat according to a reactive type when FMS was treated.

SATELLITE SYMPOSIUM
The First International Symposium on Cardiac Sympathetic Neuroimaging

Oral Presentations
Cardiac and extra-cardiac noradrenergic denervation in Parkinson disease
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Objective: This presentation provides an update about the status of cardiac and extra-cardiac noradrenergic innervation in Parkinson disease (PD) and related disorders, based on sympathetic neuroimaging using 6-[18F]fluorodopa positron emission tomographic (PET) scanning. Methods: Neuroimaging results were analyzed from patients with PD and neurogenic orthostatic hypotension (PD + NOH), PD without NOH, multiple system atrophy (MSA), and pure autonomic failure (PAF). Brain 6-[18F]fluorodopa PET scanning was also done. Skeletal muscle microdialysate levels of dihydroxyphenylglycol (DHPG) provided a neurochemical index of extra-cardiac noradrenergic innervation in patients off levodopa. Results: Virtually all patients with PD + NOH had intraventricular septal myocardial 6-[18F]fluorodopa-derived more than 2 standard deviations below the normal mean. PD + NOH was also characterized by decreased radioactivity in the renal cortex, whereas PD without NOH was not. PD + NOH patients had lower microdialysate DHPG levels than did PD patients without NOH (P < 0.001). Among PD patients without NOH, a substantial minority had decreased radioactivity confined to the apex or free wall. The putamencocciplatal cortex (PUT-Occ) ratio of 6-[18F]fluorodopa-derived was unrelated to septal 6-[18F]fluorodopa-derived radioactivity. PAF patients had normal PUT-Occ ratios but decreased substantia nigra (SN):Occ ratios that resembled those in PD. Post-mortem analyses of tissues from a PAF patient and a PD patient showed similarly low SN tissue concentrations of dopamine and tyrosine hydroxylase activity, but the PD patient had 10-fold
lower PUT dopamine and the PAF patient 15-fold lower myocardial norepinephrine concentrations.

Conclusions: In PD, NOH is associated with generalized noradrenergic denervation, whereas PD without NOH is not. The extent of cardiac sympathetic denervation in PD is unrelated to that of striatal dopaminergic terminals. This is more severe loss of striatal dopaminergic terminals in PD than in PAF and more severe loss of sympathetic noradrenergic terminals in PAF than in PD. These differences explain the distinctive clinical manifestations of the two Lewy body diseases.

Correlation between cardiac 123I-MIBG and odor identification in patients with Parkinson’s disease

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Objective: It is well known that patients with Parkinson’s disease (PD) have markedly impaired olfactory function and an impairment in olfactory function is an early manifestation of the neuropathological process in PD. We directly compared the diagnostic value of diffusion tensor imaging (DTI) and cardiac MIBG scintigraphy of the heart in patients with PD and AD. The severity of olfactory impairment was assessed according to the classification in Hoehn and Yahr (H and Y).

Methods: We prospectively enrolled 26 patients with PD, and 15 healthy controls. PD was diagnosed according to the United Kingdom Society Brain Bank Clinical Diagnosis Criteria. For assessing olfactory function and the cardiac uptake experiments, the Cross-Cultural Smell Identification (CCSI) test and the ratio of 123I-MIBG uptake in the heart to that in the mediastinum were used. The severity of parkinsonism was assessed according to the classification of Hoehn and Yahr (H and Y).

Results: The mean CCSI score in patients with PD was 4.4 ± 2.2, which was significantly lower than that in controls (7.3 ± 2.6). The CCSI score and cardiac 123I-MIBG showed a significant inverse correlation with age (r = 0.39, P = 0.048 and r = 0.62, P = 0.001, respectively); however, neither the CCSI score nor cardiac 123I-MIBG uptake were significantly correlated with the disease duration or the H&Y stage. There was a significant positive correlation between cardiac 123I-MIBG uptake and the CCSI score in patients with PD (r = 0.56, P = 0.003), and the correlation remained significant after adjusting for age (r = 0.47, P = 0.014).

Conclusions: Our data suggest that in PD patients, the functional losses of the olfactory and cardiac sympathetic systems are closely coupled and are independent of the clinical rating of motor status.

Brain and cardiac neuroimaging to distinguish Parkinson’s disease from multiple system atrophy

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Objective: To directly compare the diagnostic value of diffusion weighted magnetic resonance imaging (DWI) of the basal ganglia and meta-iodobenzylguanidin (MIBG) scintigraphy of the heart in patients with Parkinson’s disease (PD) versus the parkinson variant of multiple system atrophy (MSA-P).

Methods: PD and MSA-P were diagnosed according to standard clinical criteria. Patient groups were matched for age and disease severity. Regional trace of diffusion tensor values were determined in the putamina. Cardiac MIBG uptake was quantified by the Heart/Mediastinum (H/M) ratio.

Results: Sensitivity of MIBG scintigraphy versus putaminal trace of diffusion tensor for the differentiation of MSA-P from PD was 55.6% vs. 100%, specificity 88.8% vs. 100%.

Conclusions: Our data suggest that DWI is superior to MIBG scintigraphy in the differential diagnosis of PD versus MSA-P.

Cardiac noradrenergic denervation in Lewy body disease: clinical-pathologic correlations

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Objective: Reduced cardiac uptake of meta-iodobenzylguanidine (MIBG) on [123I]-MIBG myocardial scintigraphy or fluorodopamine on 6-[18F] fluorodopamine positron emission tomography has been reported in patients with Lewy body disease such as Parkinson’s disease (PD) and dementia with Lewy bodies (DLB), even in the early disease stages. These imaging approaches are sensitive diagnostic tools that potentially differentiate PD and DLB from other related movement disorders including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) as well as Alzheimer’s disease (AD). The objective of this study is to see clinical-pathologic correlations of cardiac noradrenergic denervation in Lewy body disease.

Methods: We immunohistochemically examined cardiac tissues obtained at autopsy from patients with PD, DLB, other related movement disorders, AD and ILBD (incidental Lewy body disease), which represents presymptomatic stage of PD, using antibodies against tyrosine hydroxylase (TH) as a marker for sympathetic nerves, phosphorylated neurofilament (NF) as a marker for all axons and phosphorylated a-synuclein as a marker for abnormal aggregates.

Results: Not only TH- but also NF-immunoreactive (ir) axons in the epicardial nerve fascicles were markedly decreased in Lewy body disease, but not in MSA, PSP, CBD and AD. Various degrees of involvement were observed in half of the patients with ILBD. a-Synuclein aggregates were observed in the epicardial nerve fascicles abundantly in ILBD and less abundantly in PD.

Conclusions: These findings indicate that cardiac noradrenergic denervation specifically occurs in Lewy body disease even in the early disease stages, which accounts for the reduced cardiac uptake of MIBG and fluorodopamine in Lewy body disease. Moreover, a-synuclein aggregates are strongly involved in cardiac noradrenergic denervation in Lewy body disease.

Effects of candesartan on cardiac sympathetic nerve activity in patients with chronic heart failure and preserved left ventricular ejection fraction

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Objective: Approximately 50% of patients with chronic heart failure (CHF) show preservation of the left ventricular ejection fraction (LVEF). It has been reported that angiotensin receptor blocker
(ARB) therapy improves cardiac sympathetic nerve activity in CHF patients and a reduced LVEF. However, the effect of ARB therapy on cardiac sympathetic nerve activity evaluated by $^{123}$I-meta-iodobenzylguanidine (MIBG) scintigraphy has not been determined in CHF patients with preserved LVEF. Accordingly, this study was performed to determine whether candesartan could improve cardiac sympathetic nerve activity in patients with CHF and an LVEF of above 40%.

**Methods:** We selected 50 patients with nonischemic CHF and an LVEF greater than 40% who were treated with standard therapy. Twenty-five patients were randomized to additionally receive candesartan, while the remaining 25 patients received a placebo. The delayed heart/mediastinum count (H/M) ratio, delayed total defect score (TDS), and washout rate (WR) were determined by $^{123}$I-MIBG scintigraphy before and after 6 months of therapy. The left ventricular end-diastolic volume (LVEDV) and LVEF were determined by echocardiography, and the plasma brain natriuretic peptide (BNP) concentration was also measured.

**Results:** In patients receiving candesartan, TDS decreased from $28 \pm 8$ to $23 \pm 8$ ($P < 0.0005$), the H/M ratio increased from $1.87 \pm 0.24$ to $2.00 \pm 0.22$ ($P < 0.005$), and WR decreased from $37 \pm 11\%$ to $32 \pm 8\%$ ($P < 0.005$). In addition, LVEDV decreased from $114 \pm 38$ to $90 \pm 27$ ml ($P < 0.05$), and LVEF increased from $37 \pm 11\%$ to $32 \pm 8\%$ ($P < 0.05$). In contrast, there were no significant changes in these parameters in the patients receiving the placebo. There was a significant correlation between the changes in TDS, H/M, and WR determined by $^{123}$I-MIBG scintigraphic findings and the percent change in BNP from baseline to 6 months in patients receiving candesartan. The left ventricular volume and cardiac function were also improved due to candesartan therapy. Furthermore, the plasma BNP concentration was decreased significantly. These findings suggest that adding candesartan to standard therapy can improve cardiac sympathetic nerve activity and left ventricular performance in CHF patients with preserved LVEF.

**SPECIAL POSTER SESSION**

**Poster #51**

**Differential diagnostic value of normal uptake but increased $^{123}$I-MIBG washout in Parkinsonism**

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**Background:** $^{123}$I-metaiodobenzylguanidine (MIBG) imaging has recently been reported to be useful to differentiate Parkinson’s disease (PD) from other conditions involving parkinsonism. Decreased cardiac MIBG uptake—especially decreased initial uptake—is characteristic of PD; however, some PD patients may have normal initial uptake and increased MIBG washout. The purpose of the present study was to assess whether increased MIBG washout has an independent diagnostic value in patients with PD and to clarify the clinical significance of the washout rate (WR).

**Methods:** One hundred three patients (67 ± 11 y.o, 57 female) with parkinsonism (excluding patients with diabetes mellitus and obvious cardiac disease) were enrolled in the study. All patients underwent MIBG scintigraphy, and the heart to mediastinum ratio (H/M) of MIBG cardiac uptake was calculated both for the initial (15 minutes) and delayed (4 hours after injection) images. The WR from initial to delayed images was also calculated. Decreased initial H/M was defined as ≤1.6 based on our institutional control studies. Final diagnosis was confirmed based on clinical findings during more than 6 months of follow-up. Clinical diagnosis and findings such as age, tremor, rigidity, bradykinesia, and orthostatic hypotension (OH) were compared to MIBG WR.

**Results:** In 103 patients, neurologists diagnosed 62 with PD (66 ± 11 y.o), 6 with DLB (77 ± 8 y.o), and 35 with Parkinson syndrome (PS) (68 ± 12 y.o). PD and DLB were classified into one group as Lewy body disease (LBD: 71 patients). Initial H/M, delayed H/M, and WR in LBD vs. PS were $1.79 \pm 0.44$ vs. $2.32 \pm 0.53$ ($P < 0.0001$), $1.65 \pm 0.58$ vs. $2.34 \pm 0.70$ ($P < 0.0001$), $50.1 \pm 24.2$ vs. $28.5 \pm 23.1\%$ ($P < 0.0001$). When initial H/M ≤ 1.6 was assumed to indicate LBD, the positive predictive value (PPV) was 91% (29/32) and negative predictive value (NPV) 45% (32/71). Among 71 patients with H/M > 1.6 (high H/M group), a WR > 30% had 72% sensitivity, 66% specificity, 72% PPV and 66% NPV for the diagnosis of LBD. Multivariate analysis showed that WR was independently correlated with diagnosis of LBD ($r = 0.26$), age ($F = 10$), and OH ($F = 9$) ($r = 0.55$, $P < 0.0001$) among the clinical parameters.

**Conclusions:** MIBG washout has an incremental diagnostic value to differentiate PD/DLB from PS among patients with normal or borderline values for initial H/M; however, WR is also increased in

**Takotsubo cardiomyopathy: a form of severe, reversible heart failure evoked by emotional distress in post-menopausal women**

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The term, *takotsubo* cardiomyopathy, refers to a relatively recently described form of acute, reversible cardiomyopathy, in which apical akinesia gives the heart the shape of a *takotsubo*, a Japanese fishing pot for trapping octopus. *Takotsubo* cardiomyopathy seems to occur mainly in elderly women soon after exposure to severe emotional distress. Symptoms mimic acute myocardial infarction; however, coronary angiography fails to demonstrate coronary occlusion. The condition can trigger sudden cardiac failure or death, yet in survivors cardiac function typically normalizes within a few weeks. *Takotsubo* cardiomyopathy features remarkably elevated plasma catecholamine levels and depressed cardiac contractile function. Clinical analysis of autonomic nervous function has revealed a transient increase of sympathetic nervous activity and decrease of vagal nervous activity. Immobilization stress (IMO) of rats can reproduce the electrocardiographic and left ventricular changes that occur in takotsubo cardiomyopathy, both of which are prevented by combined blockade of α- and β-adrenergic receptors. Estrogen supplementation partially attenuated these cardiac changes. It also attenuated the IMO-induced increase of c-Fos immunoreactivity, or c-fos mRNA expression in the lateral septum, medial amygdaloid nucleus, paraventricular hypothalamic nucleus, dorsomedial hypothalamic nucleus, laterodorsal tegmental nucleus and locus coeruleus; these regions contain central sympathetic neurons and neurons with immunoreactive estrogen receptors. It also down-regulated c-fos mRNA expression in the adrenal gland and the heart, suggesting an increase of estrogen attenuated the stress-induced hypothalamo-sympathoadrenal outflow from the central nervous system to the target organs. Estrogen treatment also up-regulated the levels of cardio-protective substances such as ANP and βSP70 in the heart. These data suggest that reduction of estrogen levels following menopause might be involved in the primary cause of takotsubo cardiomyopathy both by indirect action on the nervous system and by direct action on the heart.
elderly subjects and OH patients without PD/DLB, which should be considered when this parameter is used.

**Poster #52**

123I-meta-iodobenzylguanidine scintigraphy is a useful diagnostic tool to differentiate early phase of Lewy body disease from other movement disorders

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**Background:** Decreased cardiac uptake of 123I-meta-iodobenzylguanidine (MIBG) on single photon emission computed tomography may indicate cardiac sympathetic nervous degeneration in Lewy body diseases including Parkinson disease (PD) and dementia with Lewy bodies (DLB). In this study, we examined MIBG scintigraphy in patients with early parkinsonism and assessed its usefulness for differential diagnosis.

**Methods:** Seventeen patients with more than one parkinsonian symptom (resting tremor, akinesia, rigidity, retropulsion, masked face, or parkinsonian gait) within two years from their onset were enrolled in this study. Eight men and 9 women (average age 67.2 ± 7.9 years) were examined by MIBG scintigraphy. The uptake ratio of heart to mediastinum (H/M) and washout ratio (WR) were calculated. All 17 patients were reassessed after more than a year, when a final clinical diagnosis was made. The diagnoses were as follows: PD, 10 cases; DLB, 1 case; essential tremor (ET), 3 cases; multiple system atrophy (MSA), 1 case; multiple cerebral infarctions (MCI), 1 case; and idiopathic normal pressure hydrocephalus (iNPH), 1 case.

**Results:** In the group with PD or DLB, mean H/M was 1.55 ± 0.24 and WR 35.2 ± 5.3%. In the group without PD or DLB, mean H/M was 2.05 ± 0.29 and WR 24.5 ± 5.9%. There were statistically significant differences in both H/M (P = 0.002) and WR (P < 0.001) between the PD/DLB group and the non-PD/DLB group.

**Conclusions:** Evaluation of both H/M and WR is useful to differentiate PD and DLB from other related disorders. Recent pathological studies have suggested that cardiac sympathetic denervation occurs in early PD and DLB. Therefore, MIBG scintigraphy may be useful for differential diagnosis in the early phase of neurodegenerative disorders.

**Poster #53**

123I-MIBG scintigraphy in PSP, CBD and IPD

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**Background:** Scintigraphic imaging with 123I-metaiodobenzylguanidine (123I-MIBG) has demonstrated extensive loss of cardiac sympathetic neurons in idiopathic Parkinson's disease (IPD). In contrast, normal cardiac innervation has been observed in 123I-MIBG studies of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP).

**Object:** The purpose of this study was to investigate myocardial uptake of 123I-metaiodobenzylguanidine (MIBG) in patients with IPD, PSP, CBD, and idiopathic Parkinson’s disease (IPD).

**Methods:** 16 patients with PSP, 8 with CBD, and 10 with IPD underwent myocardial 123I-MIBG scintigraphy, as did 10 control patients.

**RESULTS:** Heart-to-mediastinum (H/M) ratios of 123I-MIBG-derived radioactivity were significantly lower in patients with IPD than in patients with CBD or PSP and in the controls. Six patients with PSP had low H/M ratios, whereas the ratios were not significantly different between patients with CBD and controls.

**Conclusion:** Cardiac sympathetic denervation is found in some patients with PSP but not in CBD.

**Poster #54**

Myocardial sympathetic degeneration correlates with olfactory function in Parkinson’s disease

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**Objective:** Autonomic dysfunctions and olfactory dysfunction are recognized as non-motor abnormalities in Parkinson’s disease (PD). These may be markers for preclinical diagnosis of PD, because pathological changes in the olfactory and autonomic systems can start before motor symptoms develop. In this study, we investigated whether there is an association between cardiac autonomic function and olfactory function in PD.

**Methods:** Subjects were thirty-seven non-demented patients with idiopathic PD (23 men and 14 women, mean age 65.5 ± 11.9 years) with a disease duration of 6–168 months (53.1 ± 39.8 months). Motor performance was assessed using the Hoehn and Yahr Staging scale (H&Y), and the motor section (part III) of the unified Parkinson’s disease rating scale (UPDRS). Eight patients were in H&Y stage I, 18 in stage II, 10 in stage III, and 1 in stage IV. For 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, planar scintigraphic imaging in the anterior view was obtained using a single head gamma camera 15 minutes (early) and 4 hours (delayed) after intravenous injection of MIBG (111 MBq). To measure MIBG uptake, heart (left ventricle) and mediastinal regions of interest were drawn manually. The heart to mediastinum ratio (H/M) for both early and delayed images and the myocardial washout rate (WR) for 4 hours were calculated. The smell identification test included 12 odors. The subject sniffed odor and then chose 1 of 6 possible answers: 4 pictures of entities associated with the odors labeled with their names, 1 of which was correct, and 2 other ones (“unknown” and not detected”).

**Results:** The number of correct answers in the smell identification test correlated significantly with the H/M ratio, in both the early and delayed phases, and with the WR (P < 0.001). There was no correlation between UPDRS scores and the number of correct answers, H/M ratios, or WR. Disease duration correlated with the H/M ratio in the early phase (P < 0.005) and the delayed phase (P < 0.05).

**Conclusion:** The results suggest that the cardiac sympathetic nervous system degenerates in parallel with the olfactory system in patients with idiopathic PD.

**Poster #55**

MIBG myocardial scintigraphy in the diagnosis of dementia

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**Background:** 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy is considered to be useful in diagnosing dementia with Lewy bodies (DLB). In this study we performed MIBG scintigraphy in cases with progressive dementia, to assess the frequency with which decreases in cardiac uptake of MIBG are observed among dementia patients. In addition, clinical symptoms over time were examined, for the purpose of assessing the significance of MIBG scintigraphy in the differential diagnosis of dementia.

**Methods:** MIBG scintigraphy was performed in a series of 105 outpatients with symptoms and signs of progressive dementia. The
cases were examined at the time of initial examination for the presence of important symptoms for diagnosing DBL, such as hallucination, fainting or orthostatic hypotension, parkinsonism, and fluctuations in cognitive function during the follow-up observation period (1–3 years).

Results: There were 23 cases demonstrating decreased cardiac uptake of MIBG—more than 20% of the patients. Over half of the 23 cases were suspected of having DLB using diagnostic criteria at the initial examination. In addition, the majority of these 23 cases had findings characteristic of DBL during the follow-up observation period and were diagnosed as having probable or possible DBL. Several cases, however, did not satisfy clinical diagnostic criteria for DBL initially or during follow-up.

Conclusions: MIBG scintigraphy seems to be useful in diagnosing cases of dementia differentially; however, there are some cases for which it is difficult to diagnose DBL clinically. It will therefore be necessary to conduct a more detailed study incorporating a longer observation period and adding post-mortem pathological studies.

Poster #56
123I-metaiodobenzylguanidine myocardial scintigraphy and susceptibility-weighted imaging of the substantia nigra in patients with Parkinson’s disease

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Background: Susceptibility-weighted imaging (SWI) is a new method of magnetic resonance imaging (MRI). We have shown that SWI is useful in identifying the substantia nigra (SN) of Parkinson’s disease patients (PD) and in evaluating the SN signal intensity. An increase of the SN signal correlates with clinical severity of parkinsonism. 123I-metaiodobenzylguanidine (MIBG) uptake in the heart can evaluate the function of autonomic noradrenergic terminals, which may be a supportive diagnostic tool because of a decrease even in mild PD.

Objective: We investigated the myocardial MIBG uptake ratio to the mediastinum as a function of the SN signal intensity measured by SWI in PD.

Methods: We recruited PD patients and obtained axial SW images of the midbrain and the SN signal intensity. We divided patients into subgroups based on the SN signal intensity. We also performed MIBG myocardial scintigraphy and obtained an uptake ratio of the heart to the mediastinum (HMR), which was statistically compared in the subgroups of SN signal intensity.

Results: We registered 10 PD patients, divided into 2 groups. The SN signal intensity and HMR were decreased in all patients. HMR was lower in the group with higher signal intensity than in the group with lower signal intensity.

Discussion: The two neuroimaging methods yielded similar results. SWI may be as clinically useful in PD diagnosis as is MIBG myocardial scintigraphy. Recently, Orimo et al. reported that Lewy body disease is seen first in cardiac noradrenergic terminals and only later in the ganglionic cell bodies. We propose that a combination of MIBG myocardial scintigraphy and SWI of the SN might supply valuable information to track the pathological progression of PD in vivo.

Poster #57
Longitudinal observation of MIBG myocardial scintigraphy in patients with multiple system atrophy

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Objective: MIBG myocardial scintigraphy is useful for distinguishing multiple system atrophy (MSA) from Parkinson’s disease (PD). The correlation of myocardial MIBG uptake with clinical features in PD patients has been mentioned in many studies; however that in MSA patients has been less commonly reported. In the present study, longitudinal observation using MIBG myocardial scintigraphy was carried out in a relatively large MSA population, to evaluate whether there is an association of myocardial MIBG uptake with clinical features of the disorder.

Methods: MIBG myocardial scintigraphy was performed in 52 MSA patients. The heart/mediastinum (H/M) ratio of MIBG uptake at 240 minutes after injection of the tracer was calculated. The H/M ratio was analyzed in relation to disease duration and severity. Temporal changes in H/M ratios were evaluated in several patients who underwent the examinations more than twice.

Results: A total of 96 MIBG examinations were performed in 52 MSA patients. The H/M ratio was below the lower limits in 16 MSA patients (31.3%). Overall, the H/M ratio correlated with neither disease duration nor severity. In the follow-up observations, the H/M ratio did not show any certain trends, in contrast with the continuous decrease observed in PD.

Conclusions: The present data demonstrate that myocardial MIBG uptake is decreased in approximately 30% of MSA patients, without any correlation with clinical features, and that MIBG uptake remains unchanged over time in MSA.

Poster #58
Preclinical investigation of 11C-phenethylguanidines as radiotracers for quantifying cardiac sympathetic nerve density with PET

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Objectives: We hypothesize that a radiolabeled norepinephrine transporter (NET) substrate must possess two kinetic properties to be optimal for quantitative kinetic analyses: a slow NET transport rate and a long neuronal retention time. The goal of this work was to characterize several 11C-phenethylguanidines (11C-PGs) as prospective PET radiotracers capable of quantifying regional cardiac sympathetic nerve density using compartmental modeling methods.

Methods: Neuronal uptake rates (Kuv, ml/minutes/g wet) and neuronal retention times (T1/2, minutes) of fifteen 11C-PGs were measured in an isolated rat heart system. Biodistribution studies in rats were performed for six 11C-PGs. MicroPET imaging studies in rhesus macaque monkeys were performed with five 11C-PGs to assess in vivo myocardial kinetics and imaging properties. For the most promising agent, N-[11C]guanyl-meta- octopamine (GMO), radiometabolite formation in monkey plasma was determined.

Results: Several 11C-PGs were found to possess slow neuronal uptake rates and extremely long retention times in the sympathetic neurons of isolated rat hearts. In microPET studies, GMO exhibited the most favorable kinetics and provided high quality heart images. Applying GMO metabolism data to image-derived input functions from microPET studies in monkeys yielded stable compartmental model fits of GMO myocardial kinetics, with a neuronal uptake rate constant k2 = 0.102 ± 0.024 minutes⁻¹. Also, Patlak graphical analysis of GMO kinetics yielded highly linear Patlak slopes (Kg = 0.103 ± 0.021 ml/minutes/g).

Conclusion: 11C-PGs are a promising new class of cardiac sympathetic nerve imaging agents. Successful pilot studies of GMO kinetics in monkeys suggest this tracer could be used to quantitate regional cardiac sympathetic nerve density in humans. Supported by NIH R01-HL079540.
Poster #59

PET measurement of cardiac and nigrostriatal denervation in parkinsonian syndromes

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Objectives: 123I-Metaiodobenzylguanidine (MIBG) studies have demonstrated extensive losses of cardiac sympathetic neurons in idiopathic Parkinson’s disease (IPD) patients, but normal innervation in multiple-system atrophy (MSA) and progressive supranuclear palsy (PSP) patients. This study tested the hypothesis that cardiac denervation can be used to differentiate IPD from MSA and PSP by using the sympathetic nerve imaging agent 123I-meta-iodobenzylguanidine (HED) and PET. Also, striatal presynaptic monoaminergic nerve density was measured with 18F-dihydroxy-tetrahydroxyphenidine (DTBZ) to assess if nigrostriatal denervation correlated with cardiac denervation.

Methods: HED and DTBZ scans were obtained for patients with IPD (n = 9), MSA (n = 10), and PSP (n = 8) and age-matched controls (n = 10). Global and regional measurements of HED retention were made to assess the extent of cardiac denervation. DTBZ binding was measured in caudate nucleus, anterior putamen and posterior putamen.

Results: Cardiac HED scans demonstrated extensive cardiac denervation in 4 of the 9 IPD patients. However, global cardiac denervation was also seen in 2 of the 10 MSA patients. Substantial regional denervation was also seen in 2 additional MSA patients and 2 of the 8 PSP patients. DTBZ studies demonstrated striatal denervation in all IPD patients and in most MSA and PSP patients. No correlation was found between cardiac HED retention and striatal DTBZ binding.

Conclusion: Cardiac denervation was observed not only in IPD patients but also in MSA and PSP patients, suggesting that this clinical finding cannot be used independently to discriminate IPD from other movement disorders. Supported by NIH grants P01-NS15655, P50-AG08671 and R01-HL079540.

Poster #510

Importance of renal function in cardiac iodine-123 metaiodobenzylguanidine scintigraphy for predicting prognosis of heart disease patients

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Objective: Cardiac iodine-123-metaiodobenzylguanidine (MIBG) can be used to evaluate cardiac sympathetic nerve function and is useful for assessing the prognosis of patients with heart disease. Renal impairment in heart failure patients has been recognized as an independent risk factor for morbidity and mortality and has been associated with abnormal cardiac uptake and washout of MIBG. In patients with renal failure, MIBG disappearance from blood is decreased. The purpose of this study was to evaluate the prognostic value of cardiac MIBG imaging in heart disease patients with chronic kidney disease (CKD), who either had a glomerular filtration rate (GFR) < 60 ml/minute/1.73 m² or did not.

Methods: Heart disease patients (n = 167, male/female: 111/56, mean age: 63 years, coronary artery disease/dilated cardiomyopathy/myocarditis: 54/78/35, mean left ventricular ejection fraction: 49%, non-CKD/CKD: 107/60, hemodialysis: 21) underwent cardiac MIBG imaging and were followed for a mean of 2.7 years. GFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation. Cardiac MIBG imaging was done 15 minutes and 4 hours after isotope injection. The parameters analyzed for cardiac MIBG imaging were the heart-to mediastinum ratio (H/M) on the delayed planar image and the cardiac washout rate. The disappearance rate of MIBG from blood was also calculated.

Results: Cardiac events (hospitalization due to congestive heart failure and cardiac death) were observed in 22 of 107 patients (21%) without CKD and in 25 of 60 patients (42%) with CKD. The event ratio was significantly higher in patients with CKD than in patients without CKD (P < 0.001 by Kaplan–Meier survival curves). In patients without CKD, Cox regression analysis showed that cardiac MIBG imaging was the most powerful predictor of cardiac events (delayed H/M, hazard ratio: 0.98, P = 0.021); however, in patients with CKD, the utility of cardiac MIBG imaging could not be demonstrated. The disappearance rate of MIBG from blood was significantly slower in patients with CKD than in patients without CKD (29% vs. 35%, P < 0.001), and a weak but significant correlation was observed between GFR and the disappearance rate of MIBG from blood (r = 0.29, P = 0.001).

Conclusions: A delayed H/M is a powerful predictor of cardiac events in heart disease patients who do not have CKD.

Poster #511

Marked reduction of cardiac 123I-MIBG uptake in REM sleep behavior disorder compared with Parkinson’s disease

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REM sleep behavior disorder (RBD) reportedly is an indicator of presymptomatic Parkinson’s disease (PD), RBD and PD are known to share Lewy body pathology. Diseases with Lewy body pathology may be associated with reduced cardiac 123I-MIBG uptake. If RBD is an early sign of PD, the characteristic cardiac 123I-MIBG uptake reduction might coincide with early PD. In the present study, we compared the mean heart/mediastinum (H/M) ratio of cardiac 123I-MIBG uptake reduction might coincide with early PD. In the present study, we compared the mean heart/mediastinum (H/M) ratio of cardiac 123I-MIBG uptake in patients with RBD, PD, and controls. H/M ratios at early and delayed images were reduced in both RBD and PD when compared with controls. The variance of H/M ratios in RBD was significantly smaller than in PD. In patients with PD, the variance was reduced to the same extent when disease severity was Hoehn and Yahr stage 3 or more. The results suggest that the lesion responsible for RBD is at least as closely associated with reduced cardiac uptake of 123I-MIBG as is the lesion responsible for motor symptoms of PD. It is also suggested that RBD is not necessarily a presymptomatic manifestation of PD.

Poster #512

Evaluation of Parkinson’s disease and related disorders using cardiac MIBG scintigraphy

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Objectives: The objectives of this study were to clarify the characteristics of cardiac 123I-metaiodobenzylguanidine (MIBG) uptake in Parkinson’s disease (PD) and related disorders and the relationship between uptake and disease progression in PD. We examined the clinical usefulness for differential diagnosis of parkinsonism and for detection of sub-clinical PD in drug-induced parkinsonism (DIP).

Methods: We performed MIBG myocardial scintigraphy in 183 patients, including 71 with PD, 29 with dementia with Lewy bodies (DLB), 12 with progressive supranuclear palsy (PSP), 5 with the parkinsonian form of multiple system atrophy (MSA-P), 10 with the cerebellar form of MSA (MSA-C), 10 with vascular parkinsonism (VP), 7 with drug-induced parkinsonism (DIP), 4 with juvenile parkinsonism (JP), 13 with parkinsonism of undetermined etiology, other movement disorders. Supported by NIH grants P01-NS15655, P50-AG08671 and R01-HL079540.

Conclusion: Cardiac denervation was observed not only in IPD patients but also in MSA and PSP patients, suggesting that this clinical finding cannot be used independently to discriminate IPD from other movement disorders. Supported by NIH grants P01-NS15655, P50-AG08671 and R01-HL079540.
2 other patients, and 20 controls. We used the late phase of the heart-to-mediastinum (H/M) ratio and excluded patients with cardiac disease or diabetes mellitus or taking the drugs interfering with MIBG uptake.

**Results:** The mean H/M ratios in PD (1.47) and DLB (1.24) were significantly low compared to those in controls (2.15), whereas the mean ratios in PSP (1.95), MSA-P (1.75), MSA-C (2.10), VP (1.89), DIP (1.95), and JP (1.97) did not differ from those in controls By Hoehn-Yahr (H-Y) stages in PD, H/M ratios averaged 1.91 (I), 1.50 (II), 1.48 (III), 1.29 (IV), and 1.19 (V). The H/M ratios correlated negatively with disease progression. In DIP, 4 of 7 patients had low H/M ratios. All the JP patients and 3 patients with PD in H-Y III had normal H/M ratios.

**Conclusions:** MIBG scintigraphy is useful for differential diagnosis of parkinsonism; however, the H/M ratio in some patients with MSA-P is low. The finding of normal H/M ratios in some PD patients suggests either there is a PD group showing delayed cardiac sympathetic involvement or that PD is heterogeneous, especially in diseases such as JP. DIP patients with low H/M ratio may have subclinical PD, and MIBG myocardial scintigraphy in DIP might be useful for early detection of PD in such patients.

**Poster #513**

**Translating cardiac neuroimaging to clinical practice: a novel approach to neurogenic orthostatic hypotension**

D.S. Goldstein, Y. Sharabi

(See oral presentations on Thursday, October 30, 2008, p. 6)

**Daily rhythms in the autonomic nervous system: clock genes or the hypothalamus?**

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The mammalian biological clock is harbored in a brain area called the hypothalamus and imposes its temporal structure on the organism via its influence on the neural and endocrine outputs of the hypothalamus. In the past decade, we investigated how the biological clock is able to modulate the hypothalamic output to the neuroendocrine and autonomic nervous system by studying the genesis of different hormone rhythms. Amongst others, we were able to show that the biological clock, located in the suprachiasmatic nuclei (SCN) in the anterior hypothalamus, uses its projections to neuroendocrine and pre-autonomic hypothalamic neurons to control the daily rhythms in plasma corticosterone, melatonin and luteinizing hormone. Recently, we demonstrated that the biological clock uses its GABAergic projection to the orexin neurons in the perifornical hypothalamus to control the daily rhythm in endogenous glucose production. More specifically, our results indicate that pre-autonomic hypothalamic neurons are controlled by an interplay of inhibitory and excitatory inputs. Both sympathetic and parasympathetic pre-autonomic neurons receive glutamatergic inputs either from the biological clock (sympathetic pre-autonomic neurons) or from non-clock areas (para-sympathetic pre-autonomic neurons). The timing information is mainly provided by the inhibitory (GABAergic) outputs of the biological clock. Pineal- and liver-dedicated sympathetic pre-autonomic neurons (responsible for melatonin synthesis and hepatic glucose production, respectively) and pancreas-dedicated parasympathetic neurons (responsible for insulin release) are controlled by inhibitory GABAergic contacts that are mainly active during the light period. More recently, we were able to show how light may “use” the autonomic nervous system to reach clock genes and glucoregulatory enzymes in internal organs such as the liver. Moreover, via their feedback action on the brain also peripheral hormones such as insulin and thyroid hormone are able to "use" the pre-autonomic neurons in the hypothalamus to convey their message to the rest of the organism.
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