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ABSTRACTS

27TH INTERNATIONAL SYMPOSIUM ON THE AUTONOMIC NERVOUS SYSTEM

Manchester Grand Hyatt
San Diego, California
November 2–5, 2016

Preliminary Program

WEDNESDAY, NOVEMBER 2, 2016

7:30 AM–5:30 PM	**Autonomic Disorders Workshop for Generalists** Coronado AB (separate registration required)
1:00–5:00 PM	**UCNS Autonomic Disorders Certifying Examination Review Course** Marina Room (separate registration required)
6:30–7:30 PM	**Registration** Coronado Foyer
7:30–9:00 PM	**Poster Session I** Coronado CDE

THURSDAY, NOVEMBER 3, 2016

8:00–8:30 AM	**Continental Breakfast** Coronado CDE
8:30–9:30 AM	**Plenary Lecture** Influences of female reproductive hormones on regulation of body temperature and blood pressure in humans Nisha Charkoudian, Ph.D. Natick, MA, USA **Chair: Qi Fu** Coronado AB

Session 1: Autoimmune Autonomic Neuropathy Symposium Sponsored By NuFACTOR
Chairs: Chris Gibbons & Wolfgang Singer
Coronado AB

9:30–10:00 AM	**Invited Expert Speaker** Autoimmune autonomic disorders Steve Vernino, M.D., Ph.D. Dallas, TX, USA
10:00–10:15 AM	**AAS-Lundbeck Travel Fellowship Award** Dysautonomia due to ganglionic nicotinic acetylcholine receptor autoimmunity J.K. Cutsforth-Gregory, E.A. Coon, D.M. Sletten, A. McKeon, M. Suarez, P. Sandroni, W. Singer, E.E. Benarroch, R.D. Fealey, P.A. Low Rochester, MN, USA
10:15–10:30 AM	Seronegative autoimmune autonomic neuropathy is clinically distinct from autoimmune autonomic ganglionopathy E. Golden, S. Vernino Dallas, TX, USA
10:30–10:45 AM	**AAS-Lundbeck Travel Fellowship Award** The prevalence of ganglionic AChR antibodies in postural tachycardia syndrome (POTS) S. Vernino, M. Bryarly, S. Hopkins, L.E. Okamoto, B.K. Black, S.Y. Paranjape, S.R. Raj Dallas, TX, USA

10:45–11:00 AM Autonomic function in Sjogren's patients with and without positive serologies
P.K. Jones, I. Bonyhay, R. Romero, R. Bhavaraju-Sanka
San Antonio, TX, USA

11:00–11:30 AM **Coffee Break**
Coronado CDE

Session 2: Autonomic Failure
Chairs: David Goldstein & David Robertson
Coronado AB

11:30–11:45 AM Phosphorylated and total alpha-synuclein in Parkinson disease
C. Gibbons, N. Wang, J. Garcia, L. Shih, R. Freeman
Boston, MA, USA

11:45–12:00 PM Blood pressure-lowering effect of local passive heat in autonomic failure patients with supine hypertension
L.E. Okamoto, J.E. Celedonio, A. Gamboa, C.A. Shibao, S.R. Raj, A. Diedrich, S. Paranjape, B.K. Black, D. Robertson, C.G. Crandall, I. Biaggioni
Nashville, TN, USA

12:00–12:15 PM Clinical characteristics of African American patients with autonomic failure
A.C. Arnold, L.E. Okamoto, B.K. Black, S.R. Raj, D. Robertson, I. Biaggioni, C.A. Shibao
Nashville, TN, USA

12:15–12:30 PM Dysautonomic syndrome and heart rate variability in patients of spinocerebellar ataxia type 2 with different clinical stages
G. Sánchez-Cruz, L. Velázquez-Pérez, J.M. Iglesias, L.E. Almaguer-Mederos Holguin, Cuba

12:30–12:45 PM **AAS-Lundbeck Travel Fellowship Award**
Complexity analysis of cardiovascular oscillations in amyotrophic lateral sclerosis
B. De Maria, G. Mora, K. Marinou, R. Sideri, A. Porta, R. Furlan, L. Dalla Vecchia
Milan, Italy

12:45–1:00 PM The natural history of pure autonomic failure: a US prospective cohort
H. Kaufmann, L. Norcliffe-Kaufmann, J.A. Palma, I. Biaggioni, P. Low, W. Singer, D. Goldstein, A. Peltier, C. Shibao, C. Gibbons, R. Freeman, D. Robertson, on behalf of the Autonomic Disorders Consortium
New York, NY, USA

1:00–4:00 PM **Free Time**

4:00–5:00 PM **Clinical Autonomic Research Editorial Board Meeting**
Nautical

5:00–6:00 PM **Trainee Social**
Coronado Terrace

6:00–7:00 PM **Streeten Lecture**
Recruitment strategies in efferent sympathetic nerve activity: old hypotheses gain momentum in human multi-unit recordings
J. Kevin Shoemaker, Ph.D.
London, ON, Canada
Chair: David Jardine
Coronado AB

Awards Session
Chairs: Victoria Claydon, Chris Gibbons & Lucy Norcliffe-Kaufmann
Coronado AB

7:00–7:15 PM **Streeten Travel Fellowship Award**
Carotid body denervation prevents the worsening of cardiac function and heart failure in rat models of myocardial infarction and hypertension
K. Fujii, Y. Oga, A. Nishizaki, T. Takehara, T. Akashi. K. Saku, K. Sunagawa. T. Kishi
Fukuoka, Japan

7:15–7:30 PM **FMS/Peňáz Wesseling Travel Fellowship Award**
The optimal intermittent calf compression paradigm to improve orthostatic fluid shifts and cardiovascular control
B.C.D. Hockin, G.K. Brar, I.A. Ruiz-Romero, V.E. Claydon
Burnaby, BC, Canada

7:30–7:45 PM **FMS/Peňáz Wesseling Travel Fellowship Award**
Baroreflex sensitivity impairment during hypoglycemia is associated with an increase in interleukin-6
B.M.W. Illigens, A.D. Rao, I. Bonyhay, S. Ballatori, M. Casasola, C.H. Gibbons, G. K. Adler, R. Freeman
Boston, MA, USA

7:45–8:00 PM **AAS-Lundbeck Travel Fellowship Prize Presentation**

8:00–9:30 PM **Poster Session II**
Coronado CDE

FRIDAY, NOVEMBER 4, 2016

8:00–8:30 AM **Continental Breakfast**
Coronado CDE

8:30–9:30 AM **Plenary Lecture**
Reflex circuits in immunity
Kevin J. Tracey, M.D.
Manhasset, NY, USA
Chair: Thomas Chelimsky
Coronado AB

Session 3: Multiple System Atrophy Symposium Sponsored By The MSA Coalition
Chairs: Eduardo Benarroch & Horacio Kaufmann
Coronado AB

9:30–10:00 AM **Invited Expert Speaker**
Update on recognition and course-modifying treatment of multiple system atrophy
Phillip A. Low, M.D.
Rochester, MN, USA

10:00–10:15 AM **Don Summers Memorial Multiple System Atrophy Travel Award**
Cardiovascular autonomic dysfunction in autopsy-confirmed multiple system atrophy: predictors of bad and good outcome
E. Vichayanrat, E. De Plabo-Fernandez, F. Valerio-Silva, L. Watson, J. Navarro-Otano, J.L. Holton, N.P. Quinn, C.J. Mathias, V. Iodice
London, UK

10:15–10:30 AM **Don Summers Memorial Multiple System Atrophy Travel Award**
Circadian blood pressure control in afferent versus efferent lesions in the arterial baroreflex
J. de Jong, L. Norcliffe-Kaufmann, J.-A. Palma, W. Wieling, H. Kaufmann
Amsterdam, The Netherlands

10:30–10:45 AM Decreased L-aromatic-amino-acid decarboxylase activity and vesicular storage contribute to putamen dopamine depletion in Parkinson's disease and multiple system atrophy
D.S. Goldstein, P. Sullivan, Y. Jinsmaa, C. Holmes, D.C. Mash, I.J. Kopin, Y. Sharabi
Bethesda, MD, USA

10:45–11:00 AM Spinal fluid biomarkers for multiple system atrophy—a pilot study
W. Singer, A. Schmeichel, D.M. Goldstein, J.D. Schmelzer, A.D. Zeller, T.L. Gehrking, P.A. Low
Rochester, MN, USA

11:00–11:30 AM **Coffee Break**
Coronado CDE

11:30–12:00 PM **Presentations From Top 4 Posters**
Chairs: Qi Fu & Satish Raj
Coronado AB

Session 4: Postural Orthostatic Tachycardia Syndrome (POTS)
Chairs: Qi Fu & Satish Raj
Coronado AB

12:00–12:15 PM Can we predict the course of postural orthostatic tachycardia syndrome in children?
B. Kakavand, E. Nunlist
Orlando, FL, USA

12:15–12:30 PM The face of postural tachycardia syndrome: a cross-sectional community-based survey
S.R. Raj, L. Stiles, B. Shaw, E.A. Green, C.A. Dorminy, C.A. Shibao, L.E. Okamoto, E.M. Garland, A. Gamboa, A. Diedrich, I. Biaggioni, D. Robertson
Calgary, AB, Canada

12:30–12:45 PM Cerebral regional oxygen saturation during head-up tilt testing (HUT) in children and adolescents with postural orthostatic tachycardia syndrome (POTS) and matched controls
C. Panicker, A. Sadowski, S. Rizvydeen, C.M. Rand, M.S. Carroll, N.L. Kuntz, D.E. Weese-Mayer
Chicago, IL, USA

12:45–1:00 PM **AAS-Lundbeck Travel Fellowship Award**
Assessment of vascular endothelial function in postural tachycardia syndrome and healthy controls
J.E. Celedonio, V. Nwazue, R. Figueroa, S.Y. Paranjape, B.K. Black, E.M. Garland, L.E. Okamoto, C.A. Shibao, D. Robertson, A. Diedrich, S.R. Raj, I. Biaggioni, A. Gamboa
Nashville, TN, USA

1:00–1:15 PM Role of sleep disturbances in children with autonomic complaints
K. Gundrum, T.C. Chelimsky, N.A. Norins, P. Simpson, M. Nugent, G. Chelimsky
Milwaukee, WI, USA

1:15–1:30 PM Characteristics of POTS patients in a large pediatric program
J.R. Boris, T. Bernadzikowski
Philadelphia, PA, USA

1:30–7:00 PM **Free Time**

1:30–3:30 PM **AAS Board Meeting**
Nautical

5:30–6:30 PM **AAS Committee Meetings**
Coronado Terrace

7:00–10:00 PM **Presidential Dinner**
Roy's San Diego Waterfront (333 W Harbor Drive, San Diego, CA 92101)

SATURDAY, NOVEMBER 5, 2016

8:00–8:30 AM **Continental Breakfast**
Coronado CDE

8:30–9:00 AM **AAS Business Meeting**
Coronado AB

Session 5: Orthostatic Hypotension & Syncope
Chairs: Max Hilz & Jens Tank
Coronado AB

9:00–9:15 AM Cardiovascular regulatory profile in subjects with constitutional hypotension
G. Jacob, F. Barbic, F. Dipaola, M. Glago, A. Porta, R. Furlan
Tel Aviv, Israel

9:15–9:30 AM Post-synaptic α1-adrenergic vasoconstriction is impaired in young patients with vasovagal syncope and is corrected by nitric oxide synthase inhibition
J.M. Stewart, R. Sutton, M. Suggs, S. Merchant, C. Terilli, P. Visintainer, M.S. Medow
Hawthorne, NY, USA

9:30–9:45 AM Durability of effect with long-term droxidopa treatment in patients with symptomatic neurogenic orthostatic hypotension
L.A. Hewitt, S. Isaacson, J. Lisk, G. Liang, G.J. Rowse
Deerfield, IL, USA

9:45–10:00 AM Can blood pressure responses to the Valsalva maneuver predict orthostatic hypotension?
W. Singer, T.L. Gehrking, D.M. Sletten, J.A. Gehrking, P.A. Low
Rochester, MN, USA

10:00–10:15 AM Sit-to-stand testing can effectively measure orthostatic vitals and diagnose orthostatic hypotension when lower diagnostic cut-offs are used
B.H. Shaw, E.M. Garland, B.K. Black, S.Y. Paranjape, C.A. Shibao, L.E. Okamoto, A. Gamboa, A. Diedrich, I. Biaggioni, D. Robertson, S.R. Raj
Calgary, AB, Canada

10:15–10:45 AM **Coffee Break**
Coronado CDE

Session 6: Diabetic & Autonomic Neuropathy
Chairs: Roy Freeman & Janice Gilden
Coronado AB

10:45–11:00 AM Treatment induced neuropathy of diabetes: an autonomic dysrecognition syndrome
C.H. Gibbons
Boston, MA, USA

11:00–11:15 AM Prevalence of autonomic neuropathy in the metabolic syndrome compared to impaired glucose tolerance
L. Zilliox, D.M.P. Morado, S. Dunlap, J.W. Russell
Baltimore, MD, USA

11:15–11:30 AM Interaction between circadian blood pressure rhythm and autonomic nervous function in diabetic patients with chronic kidney disease
G. Yasuda, S. Komiya, T. Hase, A. Fujiwara, N. Hirawa
Yokohama, Japan

11:30–11:45 AM Epidermal and dermal neurovascular quantification in patients with type 2 diabetes
B.C. Suh, E. Sohn, M. McCormick, N. Wang, C. Gibbons, R. Freeman
Seoul, Korea

11:45–12:00 PM Statins exert an antiarrhythmic effect in an animal model of ventricular arrhythmia after myocardial infarction in Type I diabetes: reversal of autonomic imbalance and calcium alternans
C.M. Welzig, H. Jin, M. Rajab, A. Albano, B. Wang, M. Aronovitz, R. Blanton, M. Link, H. Park, S.F. Neujaim, J.B. Galper
Milwaukee, WI, USA

12:00–12:15 PM **Closing Remarks**
Dr. Chris Gibbons
President, American Autonomic Society

POSTER SESSION I
WEDNESDAY, NOVEMBER 2, 2016
7:30–9:00 PM
Coronado CDE
Trainee Poster Competition Judges: Mark Chapleau, Victoria Claydon, Roy Freeman, Qi Fu, David Jardine, Horacio Kaufmann, Lucy Norcliffe-Kaufmann, Vera Novak, Satish Raj, David Robertson, Wolfgang Singer, Jens Tank

Orthostatic Hypotension & Syncope

Poster #1 Effect of droxidopa on fear of falling
L.A. Hewitt, S. Isaacson, C. François, G. Peng, G.J. Rowse
Deerfield, IL, USA

Poster #2 The new face of baroreflex failure in 2016
K. Carter, B.D. Levine
Dallas, TX, USA

Poster #3 Utility of electroencephalography (EEG) during tilt table evaluation for syncope
S. Muppidi, M. Miglis, B. Razavi, S. Jaradeh
Palo Alto, CA, USA

Poster #4 Dissociation between peripheral hemodynamic responses and central regulatory autonomic feedback mechanisms in treated hypertensive patients during orthostasis in comparison to healthy control subjects
S.F.S. Al-Rawas, H.N. Al-Mahrouqi
Muscat, Oman

Poster #5 Orthostatic heart rate changes in young patients with vasovagal syncope
M.S. Medow, S. Merchant, M. Suggs, C. Terilli, J.M. Stewart
Valhalla, NY, USA

Poster #6 Cardiovascular components of pressor response to isometric handgrip exercise in vasovagal syncope
J. Idiaquez, J.F. Idiaquez, R. Iturriaga
Vina del Mar, Chile

Poster #7 The relationship between symptoms and blood pressure in individuals with orthostatic hypotension
C. Gibbons, R. Freeman
Boston, MA, USA

Poster #8 Progressive orthostatic hypotension and reduced vasomotor reactivity in patients with vasovagal syncope
O. Mamontov, A.V. Kozlenok, M.I. Bogachev, E. Shlyakhto
St. Petersburg, Russia

Poster #9 Implementing a program to reduce the burden of orthostatic hypotension in patients of a neurology clinic
M.K. Jeroudi, M. Chang, S. Philip, P. O'Suilleabhain
Dallas, TX, USA

Poster #10 Cerebrovascular responses to the Valsalva maneuver in pediatric patients with vasovagal syncope
B.C.D. Hockin, M.G. Lloyd, C.L. Protheroe, K. Armstrong, S. Sanatani, V.E. Claydon
Burnaby, BC, Canada

Poster #11 Usefulness of lower body negative pressure in the clinical autonomic laboratory
J.A. Palma, L. Norcliffe-Kaufmann, C. Fuente Mora, J. Martinez, H. Kaufmann
New York, NY, USA

Genetic Autonomic Disorders

Poster #12 Familial dysautonomia: a disease with hidden tears
C. Mendoza-Santiesteban, L. Norcliffe-Kaufmann, J.A. Palma, H. Kaufmann
New York, NY, USA

Poster #13 Afferent baroreflex failure and lack of nocturnal blood pressure dipping: a mystery solved?
J. de Jong, L. Norcliffe-Kaufmann, B. Tijero, J.-A. Palma, H. Kaufmann
Amsterdam, The Netherlands

Poster #14 Serum chloride levels and electrodermal activity in hereditary sensory and autonomic neuropathy type III
J. Martinez, J.A. Palma, L. Norcliffe-Kaufmann, H. Kaufmann
New York, NY, USA

Poster #15 Beta-adrenergic agonists vs. anti-cholinergics in obstructive lung disease in familial dysautonomia: A controlled clinical trial
L. Norcliffe-Kaufmann, B. Bar-Aluma, C. Fuente Mora, J. Martinez, O. Efrati, H. Kaufmann
New York, NY, USA

Autonomic Failure

Poster #16 Predictors of response to droxidopa in patients with neurogenic orthostatic hypotension
J.A. Palma, J. Martinez, M. Perez, L. Norcliffe-Kaufmann, H. Kaufmann
New York, NY, USA

Poster #17 Vagal and adrenergic baroreflex sensitivity induced by Valsalva Maneuver in patients of SCA1, SCA2 and SCA3
D. Tamuli, A.K. Jaryal, A.K. Srivastava, K.K. Deepak
New Delhi, India

Poster #18 The influence of subthalamic nucleus deep brain stimulation and levodopa on cardiovascular autonomic function in patients with Parkinson's disease
K. Li, R. Haase, H. Rüdiger, M. Reimann, H. Reichmann, M. Wolz, T. Ziemssen
Dresden, Germany

Poster #19 Impedance plethysmography testing reveals different vascular responses during orthostatis in Parkinson's disease and multiple system atrophy with parkinsonism
S. Roy, A.K. Jaryal, A.K. Srivastava, K.K. Deepak
Erlangen, Germany

Poster #20 Long-term effects of deep brain stimulation on autonomic function in patients with Parkinson's disease
C.-C. Huang, Y.-F. Chen, W.-F. Chen, F.-Y. Shih, Y.-Y. Chang
Kaohsiung, Taiwan

Poster #21 Repetitive somato-sensory mechanical stimulation decreases cardiovascular sympathetic activity and blood pressure in Parkinson's disease
F. Barbic, M. Bulgheroni, M. Minonzio, R. Zamuner, C.P. Andrade, M. Corato, S. Lalli, F. Dipaola, R. Furlan
Rozzano, Italy

Poster #22 Electrodermal activity in synucleinopathies
J. Martinez, J.A. Palma, J.C. Gomez-Esteban, L. Norcliffe-Kaufmann, A. González, M.A. Acera, B. Tijero, I. Gabilondo, H. Kaufmann
New York, NY, USA

Poster #23 REM behavior disorder in pure autonomic failure
M.G. Miglis, S. Muppidi
Palo Alto, CA, USA

Poster #24 Growth hormone responses to clonidine stimulation differentiates between multiple system atrophy and pure autonomic failure
V. Iodice, F. Valerio-Silva, L. Watson, A. Owens, C.J. Mathias, E. Vichayanrat
London, UK

Poster #25 Haemodynamic responses to the somatostatin analogue, octreotide, in patients with pre and post ganglionic lesions of the autonomic nervous system
F. Valerio-Silva, E. Vichayanrat, G.T. Ingle, E.M. Hagen, C.J. Mathias, V. Iodice
London, UK

Poster #26 **AAS-Lundbeck Travel Fellowship Award**
Pure autonomic failure and Lewy body dementia: red flags of evolution to a widespread alpha synucleinopathy
F. Valerio-Silva, E. Vichayanrat, A. Owens, L. Watson, C.J. Mathias, V. Iodice
London, UK

Poster #27 The natural history study of synucleinopathies
H. Kaufmann, L. Norcliffe-Kaufmann, G. Wenning, J.A. Palma, F. Krismer, W. Singer, V. Iodice, A. Albanese, A. Antonini, K. Bhatia, P. Cortelli, R. Freeman, R. Furlan, C. Gibbons, D.S. Goldstein, J.C. Gomez-Esteban, A. Iranzo, S. Jaradeh, U.J. Kang, H.J. Kim, M.R. Luquin, M. Merello, M. Miglis, P. Pastor, M.T. Pellecchia, A.C. Peltier, J. Schmahmann, C.A. Shibao, S. Vernino, R. Walsh, D. Robertson, I. Biaggioni, P.A. Low
New York, NY, USA

Poster #28 Baseline supine norepinephrine levels predict the improvement in orthostatic symptoms after atomoxetine in patients with neurogenic orthostatic hypotension
C.A. Shibao, L. Norcliffe-Kaufmann, H. Kaufmann, I. Biaggioni
Nashville, TN, USA

Poster #29 Elevated cerebrospinal fluid ratios of cysteinyl-dopamine/3,4-dihydroxyphenylacetic acid in parkinsonian synucleinopathies
D.S. Goldstein, C. Holmes, P. Sullivan, Y. Jinsmaa, I.J. Kopin, Y. Sharabi
Bethesda, MD, USA

Poster #30 Biomarkers of catecholaminergic neurodegeneration predict Parkinson's disease. Results at 3 years of follow-up in the NINDS PDRisk study
D.S. Goldstein, C. Holmes, G.J. Lopez, T. Wu, Y. Sharabi
Bethesda, MD, USA

Autonomic Regulation: Basic Science & Animal Studies

Poster #31 Homeostasis, biocybernetics, and autonomic neuroscience
D.S. Goldstein, I.J. Kopin
Bethesda, MD, USA

Poster #32 Cytokine abnormalities in young patients with autonomic dysfunction
R. Martinez, J. Lankford, M.T. Numan, I.J. Butler
Houston, TX, USA

Poster #33 The impact of baroreflex on the dynamic renal vascular mechanical properties and renal circulatory regulation
T. Nishikawa, T. Arimura, K. Fujii, M. Shinoda, T. Tohyama, K. Yoshida, H. Tsutsui, K. Saku, T. Kishi, K. Sunagawa
Fukuoka, Japan

Poster #34 Identification of open loop transfer function of baroreflex using the power spectral analysis of arterial pressure
H. Mannoji, K. Saku, T. Nishikawa, T. Tohyama, Y. Oga, K. Abe, K. Kamada, T. Kishi, H. Tsutsui, K. Sunagawa
Fukuoka, Japan

Poster #35 Left ventricular hypertrophy induced heart failure inhibits the hypothalamic paraventricular nucleus neurotransmission to parasympathetic cardiac vagal neurons of the brainstem
J. Dyavanapalli, D. Mendelowitz
Washington, DC, USA

Poster #36 **AAS-Lundbeck Travel Fellowship Award**
Cardiac autonomic function impairment in concussed adolescents during a sit-to-stand protocol
M.E. Moir, K.C. Abbott, S.A. Fischer, J. Elfassy, L.K. Fischer, D.D. Fraser, J.K. Shoemaker
London, ON, Canada

Poster #37 Programming of neurogenic hypertension in offspring from obese mothers
K. Lim, S.L. Burke, G.A. Head
Melbourne Australia

Poster #38 Imidazoline receptor agonist rilmenidine reverses synergistic pro-oxidant actions of angiotensin II and MsrA deficiency: implications in dysautonomia and hypertension
R. Sabharwal, R.N. El Accaoui, R.M. Weiss, M.K. Davis, F.M. Abboud, M.W. Chapleau
Iowa City, IA, USA

Poster #39 Ang-(1-7) improves autonomic function, delays disease progression, and increases lifespan in superoxide dismutase 1 (SOD1) mice with amyotrophic lateral sclerosis
L. Yang, L. Gutmann, R. Sabharwal
Iowa City, IA, USA

Poster #40 Autonomic influence on myocardial repolarisation analysed from T-waves in the ECG
A.-B. Mehlsen, M. Cesario, H.B.D. Soerensen, J. Mehlsen
Copenhagen, Denmark

Postural Orthostatic Tachycardia Syndrome (POTS)

Poster #41 Is autonomic dysfunction a possible side effect to vaccination against human papilloma virus?
J. Mehlsen, K. Pors, L.S. Brinth
Frederiksberg, Denmark.

Poster #42 Electrodermal activity during head-up tilt in patients with POTS
S. Balegh, M. Robin, J. Benoit, B. Ditto, R. Schondorf
Montrea, QC, Canada

Poster #43 Ivabradine: a potential treatment in postural orthostatic tachycardia syndrome (POTS)
H. Mistry, S. Eziukwu, M.M. Ahsan, A. Butt, S. Hamid, A. Suleman
McKinney, TX, USA

Poster #44 Nutcracker syndrome of left renal vein in postural orthostatic tachycardia syndrome (POTS)
H. Mistry, S. Lingampally, A. Butt, S. Hamid, S. Eziukwu, A. Suleman, J. Bard
McKinney, TX, USA

Poster #45 A case report on a novel mutation in Ehlers-Danlos syndrome (EDS) and postural orthostatic tachycardia syndrome (POTS)
H. Mistry, S. Eziukwu, A. Butt, A. Suleman
McKinney, TX, USA

Poster #46 A case study on the usefulness of autonomic test screening in Lyme disease
H. Mistry, M.M. Ahsan, A. Butt, S. Eziukwu, A. Suleman, R. Wilson
McKinney, TX, USA

Poster #47 Therapeutic trial of Midodrine in non-postural orthostatic tachycardia syndrome (POTS) patients with orthostatic intolerance
S. Eziukwu, H. Mistry, M.M. Ahsan, A. Butt, A. Suleman
McKinney, TX, USA

Poster #48 Heart rate dynamics in postural orthostatic tachycardia syndrome
P. Kumar, S. Gupta, B. Kaul, S. Raghavan
New Delhi, India

Poster #49 Quantitative assessment of autonomic symptom burden in postural tachycardia syndrome
M. Friesz, N. Rea, C.L. Campbell, E.Palmer, M.M. Cortez
Salt Lake City, UT, USA

Poster #50 Biofeedback intervention in pediatric patients with postural orthostatic tachycardia syndrome (POTS)
K.J. Homan, C. Harbeck-Weber, M. Hord, J. O'Connor
Rochester, MN, USA

Poster #51 Vagal dysfunction in patients with neuropathic POTS
G. Jacob, L. Diedrich, K. Sato, S.R. Raj, D. Robertson, I. Biaggioni, A. Diedrich
Tel Aviv, Israel

Poster #52 Chronic intravenous hydration as a treatment for adults with refractory postural orthostatic tachycardia syndrome
D.S. Saperstein
Phoenix, AZ, USA

Poster #53 "Which came first - the chicken or the egg?" Vitamin D deficiency in POTS patients
A. Luehrs, C.-A. Haensch
Moenchengladbach, Germany

Poster #54 The diagnostic experience in postural tachycardia syndrome: insights from a cross-sectional community-based survey
S.R. Raj, L. Stiles, B. Shaw, E.A. Green, C.A. Dorminy, C.A. Shibao, L.E. Okamoto, E.M. Garland, A. Gamboa, A. Diedrich, I. Biaggioni, D. Robertson
Calgary, AB, Canada

Poster #55 Carbidopa fails to decrease urinary sodium excretion or improve orthostatic tachycardia in postural tachycardia syndrome
E.M. Garland, J.E. Celedonio, V. Nwazue, S.Y. Paranjape, B.K. Black, A. Diedrich, D. Robertson, S.R. Raj
Nashville, TN USA

POSTER SESSION II
THURSDAY, NOVEMBER 3, 2016
8:00–9:30 PM
Coronado CDE
Trainee Poster Competition Judges: Eduardo Benarroch, Italo Biaggioni, Thomas Chelimsky, William Cheshire, Christopher Gibbons, David Goldstein, Max Hilz, Yrsa Sverrisdotter

Cardiovascular Disease, Obesity & Aging: Human Studies

Poster #56 Exaggerated pressor and sympathetic responses to short-duration static handgrip in coronary artery disease patients: effect of six-months of cardiac rehabilitation
M.B. Badrov, K.N. Wood, S. Lalande, N. Suskin, J.K. Shoemaker
London, ON, Canada

Poster #57 Features of the autonomic circulatory control in patients with arterial hypertension depending on concomitant migraine
O.V. Mamontov, L. Babayan, A.V. Amelin, M. Bogachev, A.A. Kamshilin
St. Petersburg, Russia

Poster #58 Relationship between cardiovagal control and diastolic blood pressure in adult Native and Mexican Americans with a history of alcohol use disorders
J.R. Criado, D.A. Gilder, M.A. Kalafut, C.L. Ehlers
La Jolla, CA, USA

Poster #59 **AAS-Lundbeck Travel Fellowship Award**
The pathophysiology of carotid sinus hypersensitivity: sensory block of the sternocleidomastoid muscles does not increase responses to carotid sinus massage
M.G. Lloyd, T. van Leeuwen, J. Wakeling, M. Koehle, R.J. Drapala, V.E. Claydon
Burnaby, BC, Canada

Poster #60 Sympathetic activity does not contribute to hypertension in obese African American women
C.A. Shibao, A. Marinos, J.E. Celedonio, L.E. Okamoto, C.A. Arnold, A. Diedrich, A. Gamboa, I. Biaggioni
Nashville, TN, USA

Poster #61 Cardiac-vascular properties in older women with controlled hypertension
Q. Fu, Y. Okada, S.A. Best, S.S. Jarvis, M.M. Galbreath, B.D. Levine
Dallas, TX, USA

Poster #62 Higher within-person blood pressure associated with shorter sleep duration
P.M. Macey, L. Samy, M.-L. Brecht, K.E. Macey, S. Shaboyan, M. Sarrafzadeh
Los Angeles, CA, USA

Neuroimaging In Brain & Heart

Poster #63 Sex differences in insular cortex gyri responses to a hand grip challenge
P.M. Macey, N.S. Rieken, R. Kumar, J.A. Ogren, R.M. Harper
Los Angeles, CA, USA

Poster #64 Inter-individual sympathetic responses to experimental muscle pain: the central circuitry responsible for the increases or decreases in MSNA
S. Kobuch, A. Fazalbhoy, R. Brown, L.A. Henderson, V.G. Macefield
Penrith, Australia

Diabetic, Autoimmune & Other Autonomic Neuropathies

Poster #65 Autonomic dysfunction in Charcot Marie Tooth disease IA
R. Bhavaraju-Sanka, P. Jones
San Antonio, TX, USA

Poster #66 Symptomatic autonomic impairment in autism spectrum disorders
B.P. Goodman, J.A. Khoury, C. Hoffman-Snyder, B.K. Woodruff
Scottsdale, AZ, USA

Poster #67 Intraepidermal nerve fiber density quantification is more sensitive method than sudomotor test for detecting early neuropathy in type 2 diabetes
E.H. Sohn, K.S. Song, A.Y. Lee
Daejeon, South Korea

Poster #68 Association of hyperglycemia with autonomic dysfunction during sleep in patients with obstructive sleep apnea (OSA) and mild hyperglycemia
A. Peltier, K. Bagai, R. Harder, F. Iqbal, E.M. Garland, B.A. Malow, D. Robertson, A. Diedrich
Nashville, TN, USA

Poster #69 Effect of gastroparesis on glycemic variability in insulin-treated patients with diabetes mellitus
B. White, B.G. Theckedath, V. Nellaiappan, A. Gupta, R. Bhattaram, J.L. Gilden
North Chicago, IL, USA

Poster #70 Parasympathetic pupillary response is reduced in patients with ANCA-associated vasculitis and does not correlate with cardiovagal function
P. Moog, O. Eren, M. Witt, S. Kossegg, K. Valda, A. Straube, M. Gruenke, H. Schulze-Koops,
Munich, Germany

Healthcare Systems & Delivery In Autonomic Disorders

Poster #71 Autonomic neuropathy in adult Still's disease
G.A. Cook
Portsmouth, VA, USA

Gastrointestinal & Urogenital Systems, IBS, Cystitis

Poster #72 Autonomic disorders in a tertiary military referral clinic
G.A. Cook
Portsmouth, VA, USA

Poster #73 Psychophysiologic responses to a laboratory stressor in chronic pelvic pain conditions vs. healthy controls
D. Williams, J. Janata, G. Chelimsky, K. Pajer, J. Thayer, T. Chelimsky
Columbus, OH, USA

Poster #74 Chronic stress induced autonomic and mitochondria dysfunction in neuronal and non-neuronal cells: role in IC/BPS
F.A. Kullmann, A. Wolf-Johnston, B. McDonnell, A.J. Kanai, C. Corey, S. Shiva, T. Chelimsky, L. Rodriguez, L.A. Birder
Pittsburgh, PA, USA

Microneurography & Cardiovascular Reflexes In Humans

Poster #75 Head-down tilt bed rest increases sympathetic burst latency
S.A Klassen, S. De Abreu, P. Denise, J.K. Shoemaker, H. Normand
London, ON, Canada

Poster #76 Vascular sympathetic control in Sjögren syndrome
E. Brunetta, P. Mandelli, M.I.S. Achenza, E. Scannella, L. Boccassini, A. Marchi, F. Barbic, I. Bianchi, P.S. Puttini, A. Porta, R. Furlan
Rozzano, Italy

Poster #77 Can distraction play a role in sympathetic output and pain perception during experimental muscle pain?
R. Brown, S. Kobuch, V. Macefield
Campbelltown, Australia

Poster #78 Stimulation of the dorsal root ganglion (DRG) for medicine refractory chronic neuropathic pain: is there sympathetic involvement?
Y.B. Sverrisdóttir, J. Fitzgerald, A. Kent, J. Kramer, A.L. Green
Oxford, UK

Poster #79 Influences of experimental air pollution on human sympathetic nerve traffic: a double blind, randomized, twofold crossover study
K. Heusser, J. Tank, O. Holz, M. May, J. Brinkmann, A. Diedrich, T. Framke, A. Koch, A. Grosshennig, F.C.G.J. Sweep, W. Koch, N. Krug, J. Jordan, J.M. Hohlfeld
Hannover, Germany

Cerebral Blood Flow Regulation

Poster #80 Oscillatory lower body negative pressure impairs task related functional hyperemia in healthy volunteers
J.M. Stewart, K. Balakrishnan, P. Visintainer, Z.R. Messer, C. Terilli, M.S. Medow
Hawthorne, NY, USA

Poster #81 Influence of sex, menstrual cycle and oral contraceptives on autonomic function and cerebrovascular resistance
S. Abidi, M. Nili, S. Serna, S. Kim, H. Edgell
Toronto, ON, Canada

Poster #82 Cerebrovascular function and persistent headache after sports-related concussion: preliminary results
T. Albalawi, J.W. Hamner, W.P. Meehan III, C.O. Tan
Boston, MA, USA

Poster #83 Orthostatic cerebral hypoperfusion syndrome (OCHOs)
P. Novak
Boston, MA, USA

Novel Therapies & Clinical Trials

Poster #84 Safety and preliminary efficacy of intranasal insulin in Parkinson disease: a pilot study
P. Novak, D. Pimentel, V. Novak
Boston, MA, USA

Poster #85 Clinical observations regarding the use of ivabradine in autonomic dysfunction
A. Barboi, S. Moffat, V. Cadell, I. Furman
Glenview, IL, USA

Poster #86 Droxidopa for neurogenic orthostatic hypotension in autoimmune autonomic ganglionopathy
J.A. Palma, J. Martinez, L. Norcliffe-Kaufmann, H. Kaufmann
New York, NY, USA

Poster #87 Blood pressure normalization with cranial nerve modulation in migraine subjects
R.M. Harper, D. Snodgrass, F. Yan-Go, J. Jen, C.R. White, R.K. Harper, M. Yazdizadeh, E.K. Sauerland
Los Angeles, CA, USA

Poster #88 Droxidopa improved attention and hyperactivity in a patient with congenital insensitivity to pain with anhidrosis (HSAN IV)
C. Fuente Mora, C. Spalink, J.A. Palma, L. Norcliffe-Kaufmann, H. Kaufmann
New York, NY, USA

Poster #89 Dexmedetomidine: a novel approach to treating refractory adrenergic crisis in familial dysautonomia
R.C. Dillon, C. Spalink, L. Norcliffe-Kaufmann, J.A. Palma, D. Altshuler,
J. Papadopoulos, H. Kaufmann
New York, NY, USA

Poster #90 Hemodynamics and muscle sympathetic nerve activity in patients with end stage heart failure before and after left ventricular assist device implantation
K. Heusser, J. Boehm, J. Brinkmann, C. Bara, A. Haverich, A. Diedrich, J. Jordan, J. Schmitto, J. Tank
Hannover, Germany

Poster #91 **AAS-Lundbeck Travel Fellowship Award**
Cardiac pacemaker channel (HCN4) inhibition and atrial arrhythmogenesis following acute relief of cardiac sympathetic activation
K. Chobanyan-Jürgens, K. Heusser, D. Duncker, C. Veltmann, M. May, H. Mehling, F.C. Luft, C. Schröder, J. Jordan, J. Tank
Hannover, Germany

Patient Education & Social Media

Poster #92 How to leverage social media to advance the field of autonomic disorders
W.P. Cheshire Jr., L. Norcliffe-Kaufmann
Jacksonville, FL, USA

Pediatric Autonomic Disorders

Poster #93 Reduced vagal modulation of heart rate in pediatric functional gastrointestinal disorders (FGID)
L. Zhong, T. Chelimsky, C. Welzig, A. Silverman. G. Chelimsky
Milwaukee, WI, USA

Poster #94 Characterization of endocannabinoid (EC) changes with diffuse noxious inhibitory control (DNIC) in subjects with pediatric functional gastrointestinal disorders (FGID)
D. Wayer, T. Chelimsky, C. Hillard, A. Silverman, L. Conant, P. Simpson, C. Welzig, K. Hainsworth, G. Chelimsky
Milwaukee, WI, USA

Poster #95 **AAS-Lundbeck Travel Fellowship Award**
Low bioenergetics in functional disorders parallel disability score
T. Chelimsky, P. Simpson, L. Zhang, J. Banda, D. Dimock, S. Komas, E. Awe, G. Chelimsky
Milwaukee, WI, USA

Poster #96 Identification and evaluation of rare, congenital central hypoventilation syndrome (CCHS)-causing PHOX2B non-polyalanine repeat expansion mutations (NPARMs) and associated phenotypes
A. Zhou, P. Reineke, C. Moore, C.M. Rand, V. Speare, E.M. Berry-Kravis, L. Zhou, M. Yu, L.J. Jennings, D.E. Weese-Mayer
Chicago, IL, USA

Spinal Cord Injury & Autonomic Dysfunction

Poster #97 **AAS-Lundbeck Travel Fellowship Award**
Bowel management and quality of life following spinal cord injury: the influence of autonomic dysreflexia
V.E. Lucci, J.A. Inskip, M.S. McGrath, R. Willms, V.E. Claydon
Vancouver, BC, Canada

Exercise, Temperature Regulation & Hypoxia

Poster #98 Correlation between heart rate at rest and vagal reactivation after submaximal exercise test
G.L. Garcia, K.E. Fontana, C.J. Gomes, E.M.K.V.K. Soares, W.R. Alves, L.G.G. Porto, L.F. Junqueira Jr, G.E. Molina
Brasilia, Brazil

Sympathovagal Balance & Spectral Analysis

Poster #99 Vestibular dysfunction in the autonomic laboratory
S. Jaradeh, S. Muppidi, M. Miglis, L. Fong, F. Luc, T. Prieto
Stanford, CA, USA

Poster #100 The relationship between parasympathetic activity and aortic blood pressures in young healthy individuals
P.L. Latchman, G.J. Gates, W. Zhu, R.S. Axtell, R. Thiel, N.S. Stachenfeld, R.E. De Meersman
New Haven, CT, USA

Poster #101 State anxiety and nonlinear heart rate variability during examination stress
E.V. Saperova, D.A. Dimitriev
Cheboksary, Russia

Poster #102 **AAS-Lundbeck Travel Fellowship Award**
Short- and long-term effects of Fingolimod on cardiovagal gain in patients with relapsing-remitting multiple sclerosis
S. Roy, C. de Rojas Leal, R. Wang, M. Liu, D.-H. Lee, R.A. Linker, M.J. Hilz
Erlangen, Germany

Poster #103 Central autonomic dysregulation may cause inadequate cardiovagal modulation in multiple sclerosis patients after six months of Fingolimod-treatment
M.J. Hilz, R. Wang, F. Canavese, M. Liu, C. de Rojas Leal, S. Roy, D.-H. Lee, R.A. Linker
Erlangen, Germany

Poster #104 Heart rate variability in women working in hospital: a comparison between women with and without preschool children
L. Dalla Vecchia, B. De Maria, C. Andreotti, V. Mansi, A. Porta
Milan, Italy

Poster #105 Investigating the relationship between cardiac interoception and heart rate variability via interoceptive (active) inference
A.P. Owens, K.J. Friston, D.A. Low, C.J. Mathias, H.D. Critchley
London, UK

Autism Spectrum Diorders

Poster #106 Clinical autonomic testing in autism spectrum disorder
A.P. Owens, V. Iodice
London, UK

Poster #107 Autonomic symptoms endorsed by adults with autism spectrum disorders
B.K. Woodruff, J.B. Adams, M. Temkit, B.P. Goodman.
Scottsdale, AZ, USA

Autonomic Function Testing

Poster #108 Validity of bedside tests for evaluating sweating in normal and anhidrotic patients
R.K. Khurana, C. Russell
Baltimore, MD, USA

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THURSDAY, NOVEMBER 3, 2016

ORAL PRESENTATIONS

Plenary Lecture

Influences of female reproductive hormones on regulation of body temperature and blood pressure in humans

N. Charkoudian
US Army Research Institute of Environmental Medicine, Natick, MA, USA

Reproductive hormones exert important non-reproductive influences on autonomic physiology. In women, these include changes in the regulation of body temperature over the course of the menstrual cycle and at menopause, as well as changes in the regulation of blood pressure and blood flow across the lifespan. Estrogens promote heat dissipation, resulting in decreases in body temperature, whereas progesterone (or combined progesterone + estrogen) promotes increases in body temperature. In young women, the vasodilator influences of estrogens tend to decrease total peripheral resistance and arterial pressure, resulting in a decreased risk of hypertension, and an accompanying increased prevalence of "hypotensive" disorders, relative to young men. Since both thermal and blood pressure regulation rely on sympathetic neural control, mechanisms governing these two efferent responses may overlap. The goal of this talk is to summarize our current understanding of mechanisms related to female reproductive hormones and their influences on thermal and blood pressure regulation, and to discuss areas in which further work is needed.

Invited Expert Speaker

Autoimmune autonomic disorders

S. Vernino
UT Southwestern Medical Center, Dallas, TX, USA

Abnormalities of autonomic function are characteristic features of several autoimmune neurological disorders. Patients with autoimmune encephalitis related to NMDA receptor antibodies or voltage-gated potassium channel complex antibodies often have autonomic instability characterized by tachycardia, hyperhidrosis and BP instability. Similar autonomic instability as well as gastrointestinal hypomotility is commonly encountered with Guillain–Barre syndrome. Constipation, sexual dysfunction and sicca are characteristic features of Lambert-Eaton syndrome. The autoimmune autonomic neuropathies and ganglionopathies are particularly interesting since the peripheral autonomic nerves are direct targets of autoimmunity. Autoimmune autonomic ganglionopathy is a rare disorder where autoantibodies against the ganglionic acetylcholine receptor interrupt synaptic transmission leading to diffuse and severe autonomic failure with characteristic pupillary abnormalities. A similar clinical syndrome may occur as a paraneoplastic disorder, typically in the context of small cell cancer and with prominent gastroparesis. Autoimmune peripheral autonomic neuropathies (usually associated with peripheral sensory neuropathy) may occur in isolation of in the context of Sjogren syndrome. While these autoimmune autonomic disorders are uncommon, clinical recognition is important because these are potentially treatable conditions.

Dysautonomia due to ganglionic nicotinic acetylcholine receptor autoimmunity

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Objective: To describe the degree of autonomic failure (AF) associated with autoimmunity to the ganglionic nicotinic acetylcholine receptor (α3-AChR).
Background: The α3-AChR is present in sympathetic, parasympathetic, and enteric autonomic ganglia, consistent with clinical observations of widespread AF in patients with elevated titers of autoantibodies against α3-AChR. In small series, higher titers have correlated with severe generalized AF with orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, bladder dysfunction, sicca symptoms, and impaired pupillary light reflex. Limited phenotypes with milder dysautonomia have also been described, generally with lower antibody titers. The Composite Autonomic Scoring Scale (CASS), a validated measure of three indices (adrenergic, cardiovagal, sudomotor) derived from the autonomic reflex screen (ARS), quantifies severity and distribution of AF.
Methods: We searched our laboratory database of 926 α3-AChR-antibody-seropositive patients for initial titer ≥0.05 nmol/L and contemporaneous ARS from which CASS scores could be calculated.
Results: Of 289 patients who met inclusion criteria, 163 (56 %) were women, median age was 54 years (range 10–87), median antibody titer was 0.11 nmol/L (range 0.05–22.1), and median total CASS was 2.0 (range 0–10). Using ROC analysis, a titer above 0.40 nmol/L predicted severe AF (CASS ≥7) with 92 % specificity and 56 % sensitivity. For at least moderate AF (CASS ≥4), a titer above 0.20 nmol/L had 81 % specificity but only 36 % sensitivity. Titers below 0.20 nmol/L were not predictive of the presence or absence of AF.
Conclusions: Antibody titer above 0.40 nmol/L is a moderately sensitive and highly specific test for severe AF among patients with α3-AChR autoimmunity. Despite the association between high titer and severe AF, titer alone is insufficient to predict mild or moderate degrees of AF associated with α3-AChR antibody positivity. Future research should correlate α3-AChR antibody titer with autonomic symptoms and other clinical features not captured by CASS.

Seronegative autoimmune autonomic neuropathy is clinically distinct from autoimmune autonomic ganglionopathy

E. Golden, S. Vernino
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Objective: Describe and characterize a series of patients with rapid onset autonomic failure who are seronegative for ganglionic acetylcholine receptor (gAChR) antibody.
Background: Autonomic failure can be the result of immune-mediated processes. The classic example, autoimmune autonomic ganglionopathy (AAG), is associated with gAChR antibody in about 50 %.
Case Series: Six patients (ages 25–73, four male) presented with acute to subacute onset of autonomic failure. One patient had a history of prostate cancer. Orthostatic hypotension was a presenting complaint in all patients, and gastrointestinal complaints were also common. Autonomic testing revealed predominant sympathetic

failure in five and diffuse autonomic failure in one. Pupillometry was normal in three; the others had mildly slowed constriction velocities but none showed premature redilation. Three patients had evidence of significant sensory nerve involvement and pain. All were negative for gAChR antibodies. Patients received immunotherapy, often multiple courses: five plasma exchange (PE), four IVIG, two rituximab, three high-dose IV steroids, and five with oral immunosuppression. PE, IVIG, and rituximab yielded little benefit. Three patients achieved remarkable effect with IV steroids, and two stabilized and improved on oral immunosuppression.
Discussion: In these cases of acute to subacute autonomic failure, key differences from seropositive AAG emerge. AAG affects sympathetic and parasympathetic function equally, while these cases showed a predominance of sympathetic failure. AAG also has specific pupillary findings which were not seen in these patients. Prominent sensory symptoms are unusual in AAG but common in this series. Furthermore, AAG tends to respond to antibody-targeted immunotherapy such as PE and IVIG, while these patients responded best to high-dose steroids. Thus, seronegative autoimmune autonomic (and sensory) neuropathy seems to be a distinct clinical entity that may require a treatment approach that is different from AAG.

The prevalence of ganglionic AChR antibodies in postural tachycardia syndrome (POTS)

S. Vernino, *M. Bryarly*, S. Hopkins, L.E Okamoto, B.K. Black, S.Y. Paranjape, S.R. Raj
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Objective: To determine a better estimate of the prevalence and relevance of ganglionic AChR antibody in patients with POTS.
Background: POTS is a common form of autonomic dysfunction characterized by inappropriately excessive increase in heart rate when standing. The precise pathophysiology of POTS remains unclear, and several different etiologies may produce the same clinical syndrome. Association with various autoimmune disorders has been reported. Ganglionic acetylcholine receptors (gAChR) are responsible for synaptic transmission in autonomic ganglia, and high levels ($\geq$0.5 nmol/L) are frequently associated with autoimmune autonomic failure. In retrospective studies from the Mayo Clinic, low levels of gAChR antibodies were found in 7–14 % of POTS patients.
Design/Method: Through a patient support and advocacy group (Dysautonomia International), patients with dysautonomia volunteered to participate in a study of serological markers for POTS. Patients (and healthy family members) provided clinical information, blood samples, and orthostatic vital signs (supine/standing). Recruitment is still underway. So far, blinded blood samples from over 100 POTS patients and matched healthy controls were tested for gAChR antibodies using validated radioimmunoprecipitation assay.
Results: Eleven POTS patients (10.8 %) had gAChR antibodies (>0.02 nmol/L), but only five (5 %) of these had levels >0.05 nmol/L (normal <0.05). Five healthy controls (7.8 %) were positive for gAChR antibodies. Antibody levels (<0.13 nmol/L) in these patients were lower than those typically seen in autoimmune autonomic ganglionopathy.
Conclusions: In this prospective study of unselected subjects, prevalence of gAChR antibody in POTS patients (5 %; using a cutoff of 0.05 nmol/L) was lower than previous reports. All had low antibody levels ($\leq$0.13 nmol/L). Neither the seropositive rate nor antibody level was significantly different from the healthy control group. Low level of gAChR antibody appears to have little clinical significance in otherwise typical POTS.

Autonomic function in Sjogren's patients with and without positive serologies

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Objective: Characterize the autonomic dysfunction in patients with primary Sjogren's syndrome, with and without positive serologies (SSA/SSB).
Background: Sjogren's syndrome is an autoimmune disorder with diffuse systemic manifestations. We have observed clinical symptoms which correlated to autonomic dysfunction in Sjogren's patients. However, the clinical phenotype and autonomic function abnormalities in patients with and without positive serologies have not been evaluated. We report the demographics and autonomic function testing characteristics of Sjogren's patients with and without positive blood markers.
Design/Methods: We performed a retrospective analysis of 25 patients referred to the UT Neurology Autonomic lab with sicca complex and clinical diagnosis of Sjogren's syndrome. Autonomic testing with quantitative sudomotor axon reflex test (QSART), heart rate variability, Valsalva and tilt table test was performed using standard techniques. Autonomic function parameters were evaluated in relation to positive or negative blood serologies.
Results: Twenty-five patients (age 50 ± 15 years, 80 % female) were included in the analysis. Forty-four percent of patients had positive blood marker (SSA/SSB), and 12 % of patients had positive early marker (SP1 IgG). In the positive serology group, significantly more patients had abnormal sudomotor function compared to the negative serology group (92 vs. 54 %, $P < 0.05$). Also, significantly more patients had abnormal sympathetic adrenergic function in the positive group than in the negative group (69 vs. 20 %, $P < 0.05$). Although blood pressure tended to be lower in the positive group, measures of parasympathetic function and hemodynamic response to tilt test were not different between the groups.
Conclusions: Sjogren's syndrome is a chronic inflammatory disorder with widespread neurologic effects. Our results indicate a higher prevalence of sudomotor and sympathetic adrenergic abnormalities in patients with positive serologies compared to patients with negative serologies. The underlying mechanism behind the abnormal sudomotor and sympathetic adrenergic function in relation with positive blood markers in Sjogren's syndrome needs further investigation.

Phosphorylated and total alpha-synuclein in Parkinson disease

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Objective: To determine the relationship between total and phosphorylated alpha-synuclein in cutaneous skin biopsies of individuals with Parkinson's disease (PD).
Background: We have previously reported that total alpha-synuclein is detected in pilomotor and sudomotor nerve fibers of individuals with PD, and correlates with disease severity and autonomic dysfunction. However, the phosphorylated form of alpha-synuclein is the pathologic form and is pathognomonic for central nervous system involvement.
Methods: Thirty subjects with PD and 10 controls were recruited and had punch skin biopsies stained for total and phosphorylated alpha-

synuclein. Subjects also had detailed autonomic testing, symptom assessment and standardized examinations.
Results: Phosphorylated alpha-synuclein was detected in all skin biopsy samples of all participants with PD, and not in any control subjects. There was no correlation between phosphorylated alpha-synuclein and disease duration, exam severity or autonomic function. The total alpha-synuclein ratio was seen in all controls and subjects with PD. There was a relationship between total alpha-synuclein and the Hoehn and Yahr score ($r = 0.35$, $P < 0.05$), the UPDRS motor score ($r = 0.58$, $P < 0.01$) and UPDRS total score ($r = 0.47$, $P < 0.01$). There were correlations between total alpha-synuclein and orthostatic blood pressure ($r = 0.47$, $P < 0.01$), Valsalva phase 2 blood pressure ($r = 0.40$, $P < 0.01$) and phase 4 overshoot ($r = -0.34$, $P < 0.05$).
Conclusions: All individuals with Parkinson disease have phosphorylated alpha-synuclein within cutaneous autonomic nerve fibers, while control subjects do not. Individuals with Parkinson disease also have significantly greater total alpha-synuclein deposition than control subjects. Phosphorylated alpha-synuclein appears to provide a sensitive and specific diagnostic biomarker of disease, while the total alpha-synuclein ratio provides a sensitive and specific diagnostic biomarker of Parkinson disease severity.

Blood pressure-lowering effect of local passive heat in autonomic failure patients with supine hypertension

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Primary autonomic failure (AF) is characterized by disabling orthostatic hypotension that is acutely worsened by environmental heat. Given that about half of these patients have paradoxical supine hypertension, we hypothesized that controlled local passive heat would lower blood pressure (BP) in AF with supine hypertension. Fourteen AF patients with supine hypertension (age 71 ± 2 years, 9 men, systolic BP 172 ± 6 mmHg) were randomized to receive passive heat (40–42 °C, commercial heating pad over abdomen and pelvis), and sham control for up to 2 h in a 2-day crossover study. Hemodynamic parameters and core body and skin temperatures were measured in the supine position before and during the intervention. The heating pad increased abdominal skin temperature to 40.8 ± 0.4 °C and 40.1 ± 0.3 °C after 1 and 2 h of passive heat, respectively (vs. 35.2 ± 0.2 °C and 35.1 ± 0.4 °C in sham controls). Core body temperature significantly increased after 1 h (by 0.2 ± 0.1 °C [to 36.9 ± 0.8 °C] vs. 0.0 °C [to 36.7 ± 0.1 °C] in sham controls; $P = 0.04$) and 2 h (by 0.4 ± 0.1 °C [to 37.2 ± 0.1 °C] vs. 0.1 ± 0.03 °C [to 36.8 ± 0.1 °C] in sham controls; $P = 0.04$). Systolic BP significantly decreased during heat stress compared to sham control ($P < 0.01$ by mixed-effects model) with a maximal reduction at 1 h of -20 ± 4 mmHg (vs. -0.4 ± 4 in sham controls; $P < 0.01$). This BP drop was due to a decrease in cardiac output (-30 ± 5 % vs. sham -5 ± 3 %; $P = 0.02$) and stroke volume (-29 ± 5 % vs. sham -6 ± 3 %; $P < 0.01$). Systemic vascular resistance and heart rate were similar in both groups. In conclusion, low levels of local passive heat stress had a BP-lowering effect in AF patients with supine hypertension presumably due to an uncompensated decrease in central blood volume. The therapeutic application of this approach needs to be addressed in future studies.

Clinical characteristics of African American patients with autonomic failure

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Primary autonomic failure is a neurodegenerative disorder characterized by disabling orthostatic hypotension, which appears to predominately affect Caucasians. Racial differences in cardiovascular autonomic regulation are well established, with autonomic nervous system dysfunction commonly observed in African Americans (AA). There are no reports, however, on the presence of autonomic failure in this population. We describe the clinical presentation of 8 AA patients referred to our center for evaluation of primary autonomic failure (68 ± 2 years of age, 63 % male, 26 ± 1 kg/m^2 body mass index). For comparison, we examined data from 56 Caucasian primary autonomic failure patients (66 ± 2 years of age, 63 % male, 27 ± 2 kg/m^2 body mass index). Disease duration was similar between groups (6 ± 2 AA vs. 5 ± 1 years Caucasian, $p = 0.958$). The diagnosis of pure autonomic failure was higher in AA compared with Caucasian patients (75 vs. 54 %, $p = 0.020$). There was similar impairment in parasympathetic and sympathetic noradrenergic function during standardized autonomic function testing between groups. During orthostatic stress testing, both AA and Caucasian autonomic failure patients exhibited a substantial decrease in systolic blood pressure upon standing (-64 ± 11 and -67 ± 4 mmHg, $p = 0.952$), without an adequate compensatory increase in heart rate (15 ± 4 and 11 ± 1, $p = 0.368$). There were no significant differences in supine or standing plasma norepinephrine, renin activity or aldosterone levels between groups. The presence of comorbid supine hypertension was detected in 75 % of AA and in 68 % of Caucasian patients ($p = 0.683$). Of the patients with supine hypertension, all of the AA patients were non-dippers compared with 84 % of Caucasian patients. These findings illustrate the presence and similar clinical presentation of autonomic failure in the AA population.

Dysautonomic syndrome and heart rate variability in patients of spinocerebellar ataxia type 2 with different clinical stages

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Introduction: In advanced evolutionary stage of spinocerebellar ataxia type 2 (SCA2) are described generalized dysfunction of sympathetic and parasympathetic autonomic nervous system (ANS); however, in the other stages it is not known behavior.
Objectives: To describe the dysautonomic clinical picture at different evolutives stages of SCA2, and to relate their intensity with others clinical, molecular and heart rate variability (HRV) variables.
Subjects and Methods: The dysautonomic clinical picture, HRV, somatic (ICARS) and autonomic (SCOPA) clinical severity were evaluated in 250 patients with different evolutive stages of SCA2 and respective healthy controls.
Results: The 77.68 % of patients had dysautonomia. The visceral dysfunction (59.50 %) predominated among peripheral disorders, and sleep disorders (40.49 %) among the central alterations. SCOPA correlated significantly with the expanded CAG ($r = 0.5188$, $p = 0.0000$) and age at onset ($r = -0.4403$; $p = 0.0000$). The 79.33 % of patients presented impaired vagal tone. Analysis of variance showed significant differences ($p < 0.05$) of all HRV

variables between controls and patients; these correlated significantly ($p < 0.05$) with the time of evolution and the ICARS.
Conclusions: In all clinical stages of SCA2 were diagnosed clinical and electrophysiological alterations of the ANS that were related to the neurodegenerative process at different levels of the ANS. The size of the mutation, the age of onset and evolution time are related to the clinical and electrophysiological ANS damage.

Complexity analysis of cardiovascular oscillations in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that involves upper and lower motor neurons. Although the clinical hallmark is a progressive motor weakness, ALS is considered a multisystem disease, also impairing the cardiovascular neural modulation. The altered cardiovascular response to orthostasis and the presence of patients' clusters with different autonomic profiles have been described. The association between indices describing the cardiovascular control complexity and ALS clinical parameters has not been yet investigated. The aim of this study was to correlate the results of complexity analysis of RR interval (RR) and systolic arterial pressure (SAP) variability with patients' clinical markers. ECG and non-invasive arterial blood pressure were continuously recorded in 51 ALS patients while supine for 10 min. We considered the following clinical markers: (i) disease duration (DD), i.e. the number of months from onset to clinical evaluation; (ii) functional status, evaluated by Revised ALS Functional Rating Scale (ALSFRS-R) score and its bulbar subscore; (iii) rate of disease progression, calculated as the difference between two ALSFRS-R scores at two different evaluation times divided by the months between them. Complexity Index (CI) and Normalized CI (NCI), estimated by corrected conditional entropy, were calculated from RR and SAP series. Pearson correlation coefficient, *r*, between clinical markers and complexity indices was calculated. A statistically significant correlation between NCI of SAP series and DD ($r = -0.291$; $p = 0.0383$) was present. This finding suggests that in ALS patients the neural control of the cardiovascular system is affected. The progressive reduction of SAP complexity along with disease duration could be due to a progressive increase of the sympathetic modulation directed to the vessels. In conclusion, the use of complexity indices of SAP variability could be useful to better understand the pathophysiology of ALS, and it might also represent a prognostic marker. The study was partially supported by AriSLA, Fondazione Italiana di Ricerca per la Sclerosi Laterale Amiotrofica.

The natural history of pure autonomic failure: a US prospective cohort

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Background: Pure autonomic failure is a neurodegenerative synucleinopathy largely restricted to the peripheral nervous system. Later in the clinical course of the disease some patients may develop parkinsonism, cerebellar ataxia or cognitive impairment. The purpose of this study is to define the clinical features and biomarkers that predict which patients will retain a pure autonomic failure phenotype, and which will develop clinical deficits indicating spread of the synucleinopathy to the central nervous system.
Methods: One hundred patients with pure autonomic failure were recruited at 5 medical centers in the US. Participants were followed at 12-months intervals, for 4 years to determine whether they had developed motor/cognitive abnormalities and met the diagnostic criteria of Parkinson disease (PD)/dementia with Lewy bodies (DLB) or multiple system atrophy (MSA). Smell discrimination, occurrence of REM sleep behavior disorder (RBD) and sympathetic and parasympathetic cardiovascular autonomic functions were assessed.
Findings: Mean age of onset of autonomic failure was 61 ($\pm$12) years. Patients had a 10 % per year cumulative risk for developing a CNS synucleinopathy with locomotor dysfunction or dementia. All patients who developed a CNS synucleinopathy had subtle motor impairment and RBD at the time of enrolment. Factors that predicted a future diagnosis of MSA included younger age at onset of autonomic failure, severe bladder/bowel abnormalities, normal olfaction and a >10 bpm cardiac chronotrophic response to tilt. Factors that predicted future diagnosis of PD/DLB were abnormal olfaction, a lesser chronotrophic response to tilt and longer disease duration. Patients that retained a PAF phenotype had very low circulating norepinephrine levels, slow resting heart rate, no RBD or subtle motor deficits and preserved smell discrimination.
Interpretation: Pure autonomic failure can be a premotor stage of a central nervous system synucleinopathy or may remain as a restricted peripheral disorder. Patients who developed PD/DLB or MSA have distinct premotor features. Patients who retain a pure autonomic failure phenotype had more severe peripheral sympathetic involvement.
Funding: Rare Disease Clinical Research Network (RDCRN).

Streeten Lecture

Recruitment strategies in efferent sympathetic nerve activity: old hypotheses gain momentum in human multi-unit recordings

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In 1968, the first reported microneurographic recordings of muscle sympathetic nerve activity (MSNA) in humans revealed the bursty behaviour of efferent sympathetic nerve activity. Understanding the determinants of the efferent nerve activity should give insight into central mechanisms affecting sympathetic neuronal recruitment patterns and strategies and how these are affected by, or perhaps contribute to, disease processes. However, whereas the timing of bursts can be explained by baroreflex physiology, the variability in burst size has been more difficult to understand. In 1994, one the basis of the observation that larger integrated bursts expressed faster conduction velocities, Dr. Gunnar Wallin's group proposed three neurophysiologic possibilities of postganglionic sympathetic recruitment: (1) rate-coding variations of active fibres, (2) recruitment of a latent neuronal population comprised of larger, faster conducting axons, and/or (3) synaptic delay modulations within the central nervous system. However, based on the highly variable latencies of single axons that appeared to entrain to the onset of the burst, this

group also hypothesized that a set order of recruitment must be in place. Using evidence from experimental preparations in anesthetized smaller animals, to recent signal processing approaches with multi-fibre recordings in humans, this lecture will discuss the attempts to address these hypotheses. New information supports a variety of recruitment options available within the peripheral sympathetic nervous system that affect MSNA burst size and timing. Possible clinical applications of these concepts will also be approached.

Carotid body denervation prevents the worsening of cardiac function and heart failure in rat models of myocardial infarction and hypertension

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Background: Excessive sympatho-excitation in patients with heart failure (HF) is one of the fundamental mechanisms leading to poor prognosis. Carotid body denervation (CBD) has shown to reduce sympathetic nerve activity (SNA). We examined if CBD induced sympatho-inhibition prevents worsening of cardiac function thereby heart failure in rat models of myocardial infarction (MI) and hypertension (HTN).
Methods and Results: We removed tissues around the bilateral carotid bifurcation to establish CBD. We telemetrically recorded heart rate (HR) and blood pressure (BP). In MI groups, we used Sprague–Dawley rats and induced MI at 8 weeks. At 10 weeks, we randomly allocated them to CBD or Sham, and compared cardiac function and heart failure parameters at 4 weeks after CBD. In HTN groups, we used Dahl salt-sensitive rats with high salt diet and randomly allocated them to CBD or Sham at 7 weeks. We compared them at 9 weeks after CBD. In both MI and HTN, CBD significantly reduced HR and plasma norepinephrine (NE) (MI-CBD: 266 ± 55 vs. MI-Sham: 569 ± 91 pg/ml, $p < 0.05$ and HTN-CBD: 329 ± 27 vs. HTN-Sham: 423 ± 61 pg/ml, $p = 0.077$), an index of sympathetic drive. CBD significantly decreased left ventricular (LV) end-diastolic pressure (MI-CBD: 22 ± 6 vs. MI-Sham: 33 ± 6 mmHg, $p < 0.01$ and HTN-CBD: 5 ± 1 vs. HTN-Sham: 9 ± 1 mmHg, $p < 0.05$) and improved cardiac function (Ejection fraction; HTN-CBD: 71 ± 2 vs. HTN-Sham: 64 ± 2 %, $p < 0.01$). In MI, CBD reduced the number of inflammatory macrophages (345 ± 17 vs. 474 ± 28 counts/mm^2, $p < 0.05$) in the LV and plasma interleukin-1β ($p < 0.05$), indicating the CBD induced anti-inflammatory response. In HTN, CBD significantly reduced blood pressure (199 ± 5 vs. 220 ± 6 mmHg, $p < 0.05$) and markedly improved the survival rate with relative risk reduction of 64.8 % ($p < 0.01$).
Conclusion: CBD prevents the worsening of cardiac function and heart failure in rat models of MI and HTN. CBD can be one of neuromodulatory treatments for heart failure.

The optimal intermittent calf compression paradigm to improve orthostatic fluid shifts and cardiovascular control

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Orthostatic hypotension (OH) is characterized by a significant reduction in blood pressure when upright, exacerbated by increases in venous pooling and capillary filtration that reduce the effective circulating volume. OH is prevalent in the elderly and associated with increased morbidity and mortality. Static calf compression garments are frequently prescribed for the management of OH, but are largely ineffective. We showed previously that low frequency (LF) intermittent calf compression (0–100 mmHg; 4 s on and 11 s off) is effective at reducing orthostatic fluid shifts, while simultaneously increasing stroke volume (SV), allowing cardiac output to be maintained at a reduced heart rate (HR). We aimed to determine the optimal calf intermittent compression paradigm to improve orthostatic fluid shifts and hemodynamic control. LF calf compression was applied in random order at inflation pressures from 0–40, 0–60, 0–80 and 0–100 mmHg, with a placebo condition, in fifteen healthy controls during a series of five, ten-minute 60° head-up tilts. Strain gauge plethysmography was used to measure leg circumference changes. Cardiovascular responses were determined using finger plethysmography (Finometer). All compression paradigms significantly reduced leg circumference compared to placebo; after 10 min, inflation to 60 mmHg abolished the increase in leg circumference during orthostasis (−0.135 ± 0.030 %; $p < 0.05$). Compared to the placebo (SV: 64.4 ± 1.0 mL; HR: 82.4 ± 0.621 bpm) and 0–40 mmHg (SV: 65.0 ± 1.1 mL; HR: 81.0 ± 0.67 bpm) conditions, inflation of 0–60 mmHg (SV: 69.5 ± 1.0 mL; HR: 77.4 ± 0.62 bpm) increased SV and reduced HR (all $p < 0.01$) throughout tilt. Intermittent calf compression from 0–60 mmHg is the optimal LF intermittent compression paradigm to ameliorate orthostatic fluid shifts and improve hemodynamic control.
Funding: Collaborative Health Research Project Grant.

Baroreflex sensitivity impairment during hypoglycemia is associated with an increase in interleukin-6

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Background: Hypoglycemia is associated with increased morbidity and mortality and adverse effects of hypoglycemia on the cardiovascular system have been implicated. We have demonstrated that during and up to 16 h after hypoglycemia, cardiovagal baroreflex function is impaired but the pathophysiological mechanism is unknown. During hypoglycemia interleukin-6 (IL-6) is increased and may attenuate the cardiovagal baroreflex; IL-6 elevation has been implicated in cardiovascular disease and microinjection of IL-6 in the nucleus tractus solitarii attenuates baroreflex function. We therefore measured IL-6 concentrations and determined its relationship with baroreflex function during hypoglycemia.
Methods: 19 healthy subjects, aged 18–40 years, underwent a 2-h hyperinsulinemic-hypoglycemic clamp (target glucose 2.8 mmol/l). IL-6 levels and baroreflex sensitivity (BRS) were measured before and during the clamp.
Results: Hypoglycemia elicited a statistically significant increase in mean IL-6 levels from 3.38 ± 6.33 pg/mL over time to 41.04 ± 37.64 pg/mL ($F(3, 18) = 12.83$, $p < 0.0001$). Mean BRS was lower during hypoglycemia (7.93 ± 2.5 ms/mmHg) compared to euglycemia (19 ± 7.92 ms/mmHg, $p < 0.0001$). A linear regression model demonstrated an association between IL-6 concentration and BRS ($r = -0.3$, $p = 0.02$).
Conclusions: Our study shows that in hypoglycemia with an increase in interleukin-6 there is an associated impairment of BRS. This

suggests that interleukin-6 and possibly other proinflammatory cytokines, may negatively affect BRS and cardiovascular control. This has important implications for individuals with diabetes, especially those who undergo rigorous glycemic control.

FRIDAY, NOVEMBER 4, 2016

ORAL PRESENTATIONS

Cardiovascular autonomic dysfunction in autopsy-confirmed multiple system atrophy: predictors of bad and good outcome

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Background: Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic dysfunction, parkinsonian, cerebellar and pyramidal signs. Autonomic dysfunction is a cardinal feature in MSA and identifying autonomic markers of rapid progression is still an unmet need.
Aim: To undertake a retrospective study of autopsy-confirmed MSA and to evaluate cardiovascular autonomic markers of more rapid progression.
Methods: We reviewed the medical records of autopsy-confirmed MSA at the Queen Square Brain Bank who underwent autonomic function test. Clinical features including age, gender, age at onset, time from onset to testing, disease duration (from onset to death), cardiovascular autonomic function tests and plasma noradrenaline levels were evaluated. All patients underwent autonomic cardiovascular testing including head up tilt (HUT), deep breathing, Valsalva maneuver (VM), standing test and supine and tilted catecholamine levels.
Results: 47 MSA patients (60 ± 8 years; 28 Male) were identified. Time from onset to first autonomic evaluation was 4 ± 2 years and disease duration was 7.7 ± 2.2 years. Orthostatic hypotension (OH) was present in 44(94 %) patients. Mean supine plasma noradrenaline was 345.0 ± 145.6 pg/ml with a minimal rise on HUT (increase of 34.7 ± 51.0 pg/ml). Twenty (43 %) patients presented with widespread cardiovascular autonomic failure and 19 (40 %) patients with adrenergic dysfunction (OH and abnormal VM). Three (6.4 %) patients had normal cardiovascular testing and only 5 (11 %) patients had an isolated parasympathetic dysfunction. MSA patients with only adrenergic impairment (40 %) were significantly younger than those with widespread autonomic dysfunction (52 ± 7 vs 59 ± 7 years; $p < 0.05$). However, there was no difference in time from onset to autonomic evaluation between the two groups. Disease duration was significantly shorter in MSA patients with widespread autonomic failure compared with patients with less severe cardiovascular autonomic dysfunction.
Conclusion: MSA patients with widespread autonomic impairment progress more rapidly and autonomic cardiovascular failure represents a predictor of bad outcome in these patients.

Circadian blood pressure control in afferent versus efferent lesions in the arterial baroreflex

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Introduction: Patients with afferent or efferent lesions in the arterial baroreflex pathways can have orthostatic hypotension, but only those with afferent lesions have stress-induced paroxysmal hypertension. The effect of these different abnormalities on circadian blood pressure (BP) and heart rate (HR) profiles has not been systematically compared.
Methods: We prospectively collected 24-h ambulatory BP and HR recordings in 50 patients with *afferent* lesions (6 acquired and 44 developmental due to familial dysautonomia). We compared this with recordings obtained in 51 patients with *efferent* lesions (40 with Lewy body disorders and 11 with multiple system atrophy). A similar number of patients in both groups were taking fludrocortisone (25 %) and midodrine (37 %). Thirty-six percent of patients with *afferent* lesions were taking clonidine. Differences in age, medications, and diagnosis were used as co-variants.
Results: Patients with *afferent* lesions were younger, had lower average 24-h, daytime, and nighttime systolic ($p < 0.0001$, $p = 0.0002$, $p < 0.0001$) and diastolic blood pressures ($p = 0.006$, $p = 0.085$, $p = 0.0001$). However, with age as a covariant, these differences were not significant. HR was consistently higher in patients with *afferent* lesions ($p < 0.0001$). Variability of both diastolic BP (STD 19.35.9 vs. 12.63.9 mmHg, $p < 0.0001$) and HR (STD 11.53.5 vs. 8.54.2 bpm, $p = 0.0003$) were higher in patients with *afferent* lesions, and this was still significant with age and clonidine use as co-variants. Patients with *afferent* lesions had at least one diastolic hypertensive surge that was higher than those captured in patients with *efferent* lesions (11625 vs. 10516 mmHg, $p = 0.009$). Nighttime BP dipping (i.e., a fall >10 %) was present in 46 % patients with *afferent* lesions and only in 19 % of those with *efferent* lesions. Excluding patients taking clonidine did not change the significance of the results.
Conclusion: Patients with *afferent* lesions of the baroreflex have higher variability in BP and HR over a 24-h period than those with *efferent* lesions. Unstable blood pressure is a known risk factor for target organ damage. As these patients frequently have early onset renal disease, prospective trials to reduce blood pressure variability are warranted.

Decreased L-aromatic-amino-acid decarboxylase activity and vesicular storage contribute to putamen dopamine depletion in Parkinson's disease and multiple system atrophy

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Background: Drastic loss of dopamine in the striatum causes the parkinsonism found in Parkinson's disease (PD) and multiple system atrophy (MSA). The severity of putamen dopamine depletion in these parkinsonian synucleinopathies exceeds that explained by denervation alone. Decreased activities of tyrosine hydroxylase (TH) or L-aromatic-amino-acid decarboxylase (LAAAD) or decreased vesicular storage in residual terminals could make up the difference. Cysteinyl-DOPA (Cys-DOPA) and cysteinyl-dopamine (Cys-DA) are formed from spontaneous oxidation of the parent compounds in the neuronal

cytoplasm. Attenuation of TH activity would be expected to decrease DOPA, of LAAAD activity to decrease Cys-DA/Cys-DOPA, and a vesicular storage defect to increase Cys-DA/DA and decrease the ratio of DA to the sum of its deaminated metabolites. Decreased LAAAD activity and vesicular storage in series would increase Cys-DOPA substantially with respect to DA. We used post-mortem measurements of cysteinyl and parent catechols in putamen tissue to evaluate these possibilities.
Design/Methods: Putamen tissue samples from 17 PD and 25 MSA patients and from 30 controls were assayed for cysteinyl and parent catechols simultaneously.
Results: In PD and MSA, DA was 11 % of control ($p < 0.0001$), DOPA 61 % of control ($p = 0.009$), Cys-DA/Cys-DOPA 17 % of control ($p < 0.0001$), Cys-DA/DA 3.5 times control ($p < 0.0001$), the ratio of DA to the sum of its deaminated metabolites 56 % of control ($p = 0.002$), and Cys-DOPA/DA 84 times control ($p < 0.0001$).
Conclusions: Parkinsonian synucleinopathies entail neurochemical evidence for decreased TH and LAAAD activity and decreased vesicular storage. Putamen DA depletion in these diseases reflects not only nigrostriatal denervation but also functional abnormalities in residual terminals.

Spinal fluid biomarkers for multiple system atrophy—a pilot study

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Objective: To evaluate a comprehensive panel of cerebral spinal fluid (CSF) markers in multiple system atrophy (MSA) to define those with potential as future disease biomarkers.
Background: The diagnosis of MSA is currently mainly based on clinical consensus criteria which capture the disease at a late stage as indicated by the short median survival from diagnosis of only 1.8 years. The utilization of autonomic biomarkers allows for diagnosis at an earlier but still relatively advanced stage. Diagnosis at a yet earlier clinical, or even preclinical stage would have significant implications, not only in light of emerging potential disease-modifying therapies. Several novel CSF biomarkers for MSA have recently surfaced in the literature.
Design/Methods: CSF was collected in 24 well-characterized patients with early MSA (UMSARS I score $\leq$18) and 14 age-matched healthy controls. A panel of potential MSA biomarkers was analyzed using dedicated ELISA and HPLC assays to include markers of central axonal degeneration (neurofilament light chain, NFL), central dopaminergic and noradrenergic neuronal function (DOPA, 3,4-dihydroxyphenylacetic acid [DOPAC], norepinephrine [NE], dihydroxyphenylglycol [DHPG], and other catechols), α-synuclein (Asyn, as total, phosphorylated, and oligomeric form), as well as various cytokines including IL-6 and Flt-3 ligand.
Results: NFL was markedly increased in MSA providing perfect separation from controls (4880 ± 1711 vs 900 ± 262 ng/ml, $p < 0.0001$). Other markers with significant group differences between patients and controls included DOPAC (157 ± 70 vs 283 ± 103 pg/ml, $p = 0.0007$), NE (82 ± 37 vs 152 ± 75 pg/ml, $p = 0.005$), DHPG, DOPA, and total Asyn. Other markers tested were not significantly different between groups, but a subset of patients with elevated levels of both IL-6 and TNF-α was identified.
Conclusions: A comprehensive panel of CSF markers found several (NFL, catechols, total Asyn) to have biomarker potential for MSA. Studies are now ongoing to expand these pilot data, contrast the findings to other synucleinopathies, and explore the value of a combination of these markers as MSA CSF panel. The high IL-6 and TNF-α levels in a subset of patients may lend additional pathophysiologic insights. Supported by NIH (P01NS92624, K23NS075141, U54NS065736), Mayo CTSA (UL1TR000135), and Cure MSA Foundation.

Can we predict the course of postural orthostatic tachycardia syndrome in children?

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Introduction: Postural orthostatic tachycardia syndrome (POTS) in children is a chronic condition defined as a heart rate increase of at least 40 BPM within 10 min in upright tilt without hypotension and associated with symptoms. The course of the condition is variable and has been unpredictable. The aim of the study was to find a parameter to help predict the course.
Methods: Children until the age of 19 years diagnosed newly with POTS based on the above definition and age-matched control subjects were enrolled for this retrospective study. Institutional Review Board approval was obtained. All enrollees had undergone autonomic testing. A mild course of POTS was defined as symptom control within 2 visits from establishing the diagnosis and no further dose escalation or addition of new medications. Patients were enrolled in a home-based exercise program.
Results: Fifty eight patients (46 female; age 15.4 ± 1.7 years) and 18 control subjects (13 female; age 14.3 ± 2.5 years; $P = 0.5$) from Nemours Children's Hospital were enrolled. The heart rate increase on the tilt table among POTS patients was 44.6 ± 10 and 23.1 ± 10.8 BPM in control subjects ($p = 0.0001$). The blood pressure normalization (BPN), defined as time required for mean arterial pressure to recover from its peak in Phase IV of Valsalva to baseline levels, in all POTS patients and control subjects were 18 ± 14.1 and 9.6 ± 6.2 s, respectively ($p = 0.016$). Among all POTS patients, the group defined as mild course had a BPN of 13.5 ± 11.3 vs 25.7 ± 13.1 s in complicated patients ($p = 0.003$).
Conclusions: Our study was able to demonstrate that BPN may be able to predict the disease course in children with POTS. A shorter BPN was associated with a milder form of POTS.

The face of postural tachycardia syndrome: a cross-sectional community-based survey

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Introduction: Postural tachycardia syndrome (POTS) is characterized by an excessive heart rate increase $\geq$30 bpm, without significant changes in blood pressure upon standing and significant functional disability. Cardiologists and cardiac electrophysiologists often see POTS patients due to their marked heart rate abnormalities. Most studies of POTS have been single tertiary care center studies that are confounded by potential referral bias. Results might not be representative of POTS patients in the community. To address this issue, we conducted a large community-based cross-sectional survey of POTS in conjunction with Dysautonomia International, a patient-advocacy group.
Methods: The Vanderbilt University IRB approved the "Diagnosis and Impact of POTS" study. Links to the structured, web-based

survey were posted to patient websites and social media. Between July–October 2015, 3030 patients with a physician diagnosis of POTS completed the survey.
Results: POTS patients were overwhelmingly female (94 %) and Caucasian (93 %), with few African-Americans (0.6 %), Asians (0.4 %), and Hispanics (4 %). Most respondents were from the US (11 % non-US), and ≥18 years of age (88 %). The respondents had a mean 14.7 years of formal education. Symptom onset was at a median of 16 years (mean 20 years). Reported co-morbidities included migraines (41 %), irritable bowel syndrome (31 %), chronic fatigue syndrome (22 %), fibromyalgia (21 %), gastroparesis (16 %), neurocardiogenic syncope (13 %) and inappropriate sinus tachycardia (11 %). Patients reporting Ehlers-Danlos syndrome (28 %) were somewhat more likely to report comorbid autoimmune disease (18 %) than POTS patients not reporting EDS (16 %). The most commonly reported autoimmune diseases were Hashimoto's, Celiac, and Sjogren's.
Conclusions: In this large cross-sectional study of POTS, we find that POTS is a disorder seen primarily in Caucasian females, highly associated with migraines, bowel dysfunction and EDS, but only a small minority of POTS patients have neurocardiogenic syncope. These data arguably begin to offer a more accurate picture of POTS in the community.

Cerebral regional oxygen saturation during head-up tilt testing (HUT) in children and adolescents with postural orthostatic tachycardia syndrome (POTS) and matched controls

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Background: HUT is an effective tool for analyzing autonomic response to orthostatic stress. Prior reports in POTS patients indicate decreased cerebral blood flow velocity, altered cardiovascular responses, and symptoms of orthostatic intolerance (lightheadedness, fatigue, blurred vision) during HUT, suggesting altered cerebral regional oxygenation/blood flow (rSO_2) responses during orthostatic stress. Consequently, we hypothesized reduced cerebral rSO_2 in POTS cases during HUT compared to matched pediatric controls.
Methods: 17 POTS patients (mean ± standard deviation: 15.3 ± 2.1 years; 71 % female) and 34 age- and gender-matched healthy controls (14.7 ± 2.2 years) underwent HUT testing (baseline: 5-minute supine, HUT: 10-minute 70° incline, recovery: 2-minute supine) while rSO_2 (forehead), digit (finger) systolic and diastolic blood pressure and heart rate were continuously recorded. Beat-to-beat measures were analyzed in 60-second bins by repeated measures ANOVA.
Results: Measures of rSO_2 immediately declined on HUT in both POTS and controls. However, on average, POTS patients demonstrated a continuous downward trend of rSO_2 from baseline throughout HUT (−1.85 ± 3.03 % at initiation, −3.40 ± 4.07 % at 2nd minute, −4.37 ± 2.49 % at 5th minute, and −5.40 ± 3.27 % during 10th minute). In controls, rSO_2 declined at HUT initiation (−2.41 ± 1.21 %), stabilized at 2nd minute of HUT (−3.50 ± 1.97 %) and remained essentially unchanged through the 10th minute (−3.33 ± 1.83 %). POTS patients had significantly lower rSO_2 values at the 10th minute of HUT (vs. controls) ($p < 0.05$).
Conclusion: During HUT, the continuous decline in cerebral oxygenation during orthostatic stress in POTS patients indicates altered cerebrovascular response, possibly accounting for their presyncopal symptoms with upright posture. This raises the possibility that the sustained orthostatic tachycardia seen in POTS may be related to sympathetic activation from declining cerebral oxygenation. Investigation of cerebrovascular/cardiovascular (un)coupling in POTS patients during activities of daily living may further clarify these observations.

Assessment of vascular endothelial function in postural tachycardia syndrome and healthy controls

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Background: Postural tachycardia syndrome (POTS) is a heterogeneous disorder characterized by an excessive rise in heart rate and symptoms consistent with cerebral hypoperfusion in the upright position. Sympathetic activity impairs nitric oxide (NO)-function has been proposed to contribute to this disorder. We evaluated NO function using flow-mediated dilation (FMD) and Peripheral Artery Tonometry (PAT) in POTS patients and age-matched controls.
Methods: We studied 16 POTS patients (mean ± SD; 30 ± 9 years, BMI 22.3 ± 4.1 kg/m^2) and 7 healthy control subjects (HC; 31 ± 5 years, BMI 22.1 ± 2.7 kg/m^2). Medications affecting BP, blood volume, the immune system, and autonomic function, including β-blockers, were withheld for ≥5 half-lives before admission. Fludrocortisone was discontinued for ≥5 days. Healthy subjects were studied as outpatients in 2 different occasions (screening and study day), and followed the same low-monoamine, caffeine-free diet for ≥3 days before testing. Endothelial function was measured as the percentage change in FMD (%FMD) and using the reactive hyperemic index (RHI) for PAT on the same study day. We also measured autonomic function, plasma levels of catecholamines, renin activity (PRA) and aldosterone.
Results: POTS patients have a significantly blunted FMD (mean ± SEM; 6.11 ± 0.8 vs. 9.67 ± 1.6 %, $P = 0.049$), comparable to obese hypertensive females ($N = 13$, 5.7 ± 0.9 %). There were no differences in PAT between POTS and HC (RH-PAT: 2.08 ± 0.12, vs. 1.8 ± 0.13 RH-score, $P = 0.168$). POTS patients have an increase in heart rate (HR) upon standing (121 ± 6 vs. 90 ± 6 bpm, $P = 0.020$). There were no differences between POTS and HC in standing norepinephrine (765 ± 150 vs. 545 ± 39 pg/mL, $P = 0.955$), renin activity (5.3 ± 1.3 vs. 5.2 ± 1.6 ng/mL/h, $P = 0.735$) or aldosterone (19.6 ± 3.8 vs. 15.9 ± 5.5 ng/dL, $P = 0.129$).
Conclusion: POTS have endothelial dysfunction compared to healthy controls, measured by FMD.

Role of sleep disturbances in children with autonomic complaints

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Purpose: Little is known about the relationship between autonomic dysfunction and sleep disturbances. Children presenting with autonomic complaints frequently have comorbid sleep issues. This study aimed to identify patterns of sleep disturbances and autonomic dysfunction in a pediatric population.

Methods: A retrospective chart review of 16 children who underwent sleep and autonomic testing was performed. Subjects were divided into 3 groups based on sudomotor CASS score and POTS criteria. Sleep quality, sleep architecture, and number of comorbidities were compared among groups.
Results: There were no significant differences between groups in measures of sleep quality, sleep architecture and number of comorbidities.
Conclusions: Patients with POTS and other forms of autonomic dysfunction experience multiple sleep disruptions, but there is no pattern to these abnormalities. An underlying diagnosis of POTS correlates with neither symptom burden nor severity.

Characteristics of POTS patients in a large pediatric program

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There are few programs in the United States managing purely pediatric patients (i.e. under age 18 years) with postural orthostatic tachycardia syndrome (POTS). We opened the Children's Hospital of Philadelphia in January 2014, although patients with POTS were managed by a single provider since 2007 prior to formalization of the program. We reviewed 413 patients in our administrative database from 2007 through November 2014 in order to better define specific findings associated with these patients. We found a female predominance, with a ratio of 3.1:1. The median age of presentation was 15.3 years, with a range of 6.2–17.5 years. As many as 21.9 % of the patients had a temporally related trigger for their POTS due to an infection. The three most common infections included a viral upper respiratory infection, viral gastroenteritis, and Epstein-Barr virus. Concussions were noted to be a temporally-related trigger for POTS in 11.3 % of the patients. A history of an associated inflammatory disorder was noted in 5.7 % of patients, the three most common being autoimmune thyroiditis, celiac disease, and diabetes mellitus. Joint hypermobility was noted in a large number of patients, with 21.7 % of patients being diagnosed with hypermobile Ehlers-Danlos syndrome (EDS), and an additional 34.2 % of patients had a finding of any joint hypermobility without meeting diagnostic criteria of EDS. By further exploring the characteristics of pediatric and adolescent specific to POTS patients, we can look toward trying to understand potential pathophysiologic mechanisms of POTS.

SATURDAY, NOVEMBER 5, 2016

ORAL PRESENTATIONS

Cardiovascular regulatory profile in subjects with constitutional hypotension

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Background: Constitutional hypotension (CHT) is defined as systolic blood pressure below 100 mm Hg. Hypotension related symptoms are frequently reported in CHT, suggesting a perturbation of the autonomic nervous system. We compared the cardiovascular and autonomic profiles of CHT with those of age matched normotensive controls (NBP).
Methods: Fourteen CHT females and twelve NBP (systolic pressure >110 mmHg) were studied for symptoms and quality of life (QoL). BP and ECG were continuously recorded at rest and during head-up tilt for autonomic tests, spectral analysis of RR interval and blood pressure variability and baroreflex sensitivity assessment. Plasma renin activity, aldosterone (RAAS) and echocardiogram left ventricle mass (LVM) were determined.
Results: Systolic and diastolic BP were lower in CHT (97 ± 1.5 and 54 ± 1.5 mmHg) than in NBP (126 ± 3 and 70 ± 4 mmHg), whereas HR was similar (65 ± 1.5 and 63 ± 3 bpm). CHT presented higher prevalence of hypotensive symptoms and compromised indices of QoL. CHT had lower Valsalva's ratio (1.7 ± 0.07) and BP phase IV overshooting (19 ± 2.4 mmHg) than NBP (2 ± 0.07 and 28 ± 3 mmHg). BRS_{seq}, $alpha_{LF}$ and LF/HF were greater in CHT (29.2 ± 0.7 and 39.1 ± 4.7 ms/mmHg and 1.4 ± 0.2) compared to NBP (25 ± 1.6 and 20.1 ± 2.5 ms/mmHg and 0.7 ± 01). LF_{SBP} was lower in CHT (0.8 ± 0.2) than in NBP (1.5 ± 0.3 $mmHg^2$). During tilt, data were similar. Supine and tilt aldosterone and PRA were higher in CHT. LVM was lower in CHT compared to NBP.
Conclusion: CHT showed greater cardiac and lower vascular sympathetic control with greater baroreflex sensitivity than NBP. CHT had greater RAAS activation with reduced left ventricle mass.

Post-synaptic α1-adrenergic vasoconstriction is impaired in young patients with vasovagal syncope and is corrected by nitric oxide synthase inhibition

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Syncope is a sudden transient loss of consciousness and postural tone with spontaneous recovery; the most common form is vasovagal syncope (VVS). During VVS gravitational pooling excessively reduces central blood volume and cardiac output. In VVS, as in hemorrhage, impaired adrenergic vasoconstriction and venoconstriction result in hypotension. We hypothesized that impaired adrenergic responsiveness due to excess nitric oxide (NO) can be reversed by reducing NO. We recorded cardio-pulmonary dynamics in supine syncope patients and healthy volunteers, (all 15–27 years old) challenged with a dose–response (DR) using the α_1- agonist phenylephrine (PE), with and without the NO synthase inhibitor L-NMMA. Systolic and diastolic blood pressures among control and VVS were the same, although increased after L-NMMA and Saline + PE (volume and pressor control for L-NMMA). HR was significantly reduced by L-NMMA ($P < 0.05$) for control and VVS compared to baseline but there was no significant difference in HR between L-NMMA and Saline + PE. Cardiac output and splanchnic blood flow were reduced by L-NMMA for control and VVS ($P < 0.05$) compared to baseline while total peripheral resistance (TPR) increased ($P < 0.05$). Phenylephrine DR for splanchnic flow and resistance were blunted for VVS compared to control after Saline + PE, but enhanced after L-NMMA ($P < 0.001$). Post-synaptic α1-adrenergic vasoconstrictive impairment was greatest in the splanchnic vasculature and splanchnic blood flow was unaffected by phenylephrine. Forearm and calf α_1-adrenergic vasoconstriction were unimpaired in VVS and unaffected by L-NMMA. This indicates impaired post-synaptic α_1-adrenergic vasoconstriction in young adults with VVS can be corrected by NO synthase inhibition, demonstrated with our use of L-NMMA.

Durability of effect with long-term droxidopa treatment in patients with symptomatic neurogenic orthostatic hypotension

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Objective: Evaluate the long-term efficacy and safety of droxidopa.
Background: Neurogenic orthostatic hypotension (nOH) results from insufficient noradrenergic response to orthostatic challenge. Droxidopa is a norepinephrine prodrug approved for treatment of symptomatic nOH caused by primary autonomic failure, dopamine β-hydroxylase deficiency, and nondiabetic autonomic neuropathy.
Methods: In Study NOH306, 225 Parkinson disease patients were randomized to 2-week double-blind placebo or droxidopa titration, then 8-week double-blind treatment (100–600 mg TID). In Study NOH303, following a short-term double-blind trial, 102 symptomatic nOH patients continued open-label droxidopa for ≤1 year. Efficacy measures included Orthostatic Hypotension Symptom Assessment Item 1 (OHSA-1) and standing systolic blood pressure (sSBP).
Results: In NOH306, OHSA-1 score improved with droxidopa treatment relative to baseline: −2.5, −2.2, and −2.3 units at weeks 1, 4, and 8, respectively. Mean change from baseline to week 1 was significantly greater with droxidopa than placebo (treatment difference: −1.2 units; $P = 0.008$), with a trend favoring droxidopa at week 8 (−0.8 units; $P = 0.077$). Significantly more patients had improvements ≥1 to ≥4 units at week 1; more had improvements ≥4 units at weeks 4 and 8. sSBP increases were significantly greater with droxidopa at week 1 (treatment difference: 6.8 mmHg; $P = 0.007$) but not week 8 (3.0 mmHg; $P = 0.276$). In NOH303, mean improvements from baseline in OHSA-1 were −4.0, −3.9, −3.7, and −3.9 units at 1, 3, 6, and 12 months, respectively. Increases in sSBP were sustained: 13.7, 14.0, 10.4, and 12.3 mmHg at 1, 3, 6, and 12 months. Most treatment-emergent adverse events were mild or moderate and considered unrelated to study drug; headache (NOH306: 13.2 %; NOH303: 13.7 %) and dizziness (NOH306: 9.6 %; NOH303: 7.8 %) were common.
Conclusions: Clinically relevant improvements in OHSA-1 and sSBP were consistent and durable with long-term droxidopa treatment. Droxidopa had a good safety profile and was well tolerated.
Support: Lundbeck.

Can blood pressure responses to the Valsalva maneuver predict orthostatic hypotension?

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Objective: To evaluate if indices of cardiovascular adrenergic function derived from the Valsalva maneuver (VM) can predict orthostatic hypotension (OH) during head-up tilt.
Background: Blood pressure (BP) responses to the VM are in conjunction with head-up tilt routinely used to assess cardiovascular adrenergic function in the clinical autonomic laboratory. We recently demonstrated that the magnitude of late phase II and BP recovery time (PRT) following the VM are not only highly reproducible, but provide strong separation between groups of patients with different degrees of adrenergic impairment. It is unknown if and how well adrenergic indices derived from the VM can predict OH.
Design/Methods: We randomly selected 29 subjects with normal cardiovascular adrenergic function, 28 with mild/moderate, and 29 with severe adrenergic failure based on routine laboratory testing. Indices were derived for each subject from two technically adequate VMs as follows: BP drop and pulse pressure compression during early phase II, BP recovery during late phase II, BP overshoot during phase IV, PRT, 50 % PRT, and baroreflex sensitivity index. These indices were then correlated with the magnitude of orthostatic BP changes during head-up tilt. ROC analysis was performed to define each parameter's value in detecting OH and to derive cut-off values.
Results: All adrenergic indices showed a significant correlation with the magnitude of orthostatic BP changes during tilt. The strongest correlation was found for PRT ($R^2 = 0.70$, $p < 0.0001$), which also predicted best the presence of OH (ROC area = 0.96, $p < 0.0001$). A PRT cut-off value of 7 s had a sensitivity of 87 % and specificity of 92 % to predict an orthostatic BP drop of at least 20 mmHg systolic and/or 10 mmHg diastolic. The same cut-off value predicted an orthostatic BP drop of at least 30 mmHg systolic and/or 15 mmHg diastolic with a sensitivity of 97 % and specificity of 87 %.
Conclusions: Parameters used to assess adrenergic function derived from the VM are associated with the magnitude of orthostatic BP change induced by head-up tilt. This association is strongest for PRT, which can be a useful indicator to predict the occurrence of OH during head-up tilt. Supported by NIH (K23NS075141, P01NS92624, U54NS065736, UL1TR000135) and Mayo Funds.

Sit-to-stand testing can effectively measure orthostatic vitals and diagnose orthostatic hypotension when lower diagnostic cut-offs are used

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Background: Orthostatic hypotension (OH) is an important clinical finding when evaluating syncope and falls, especially in patients with conditions associated with autonomic neuropathy such as Parkinson disease, diabetes mellitus or amyloidosis. OH is diagnosed based on supine-to-standing testing; however, these tests can be impractical in settings like the outpatient clinic where the time is limited. An alternative is a sit-to-stand procedure. This test induces a milder orthostatic stress making conventional diagnostic cut-offs for OH difficult to reach. This study aimed to identify optimal blood pressure (BP) cut-offs to diagnose OH during sit-to-stand.
Methods: This study was a cross-sectional design made up of patients and healthy subjects who presented to the Vanderbilt University Autonomic Dysfunction Center. BP was measured while supine, seated, and standing (for 5 min). BP change was calculated from (1) supine-to-standing and (2) seated-to-standing. OH was diagnosed by a supine-to-standing systolic BP drop ≥20 mmHg or a diastolic BP drop ≥10 mmHg. Receiver operator characteristic curves identified optimal sit-to-stand cut-offs and the area under the curve (AUC) was calculated.
Results: Amongst the 994 subjects, more had systolic OH (n = 404 [41 %]) than diastolic OH (n = 349 [35 %]) during lying-to-standing. Both systolic and diastolic BP ROC curves were strong predictors (systolic BP AUC = 0.910, $p < 0.001$; diastolic BP AUC = 0.924, $p < 0.001$). A sit-to stand systolic BP drop ≥ 15 mmHg had optimal test characteristics (sensitivity = 79 %; specificity = 89 %; positive predictive value = 83 %; negative predictive value = 86 %), as did a diastolic BP drop ≥ 7 mmHg (sensitivity = 85 %; specificity = 88 %; positive predictive value = 79 %; negative predictive value = 91 %).

Conclusions: A sit-to-stand maneuver with lower diagnostic cut-offs for OH provides a simple screening test for OH. This may be of utility in multiple clinical environments where testing could quickly be done upon patient arrival at triage or while in the waiting room of a clinic.

Treatment induced neuropathy of diabetes: an autonomic dysrecognition syndrome

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Background: Treatment induced neuropathy of diabetes (TIND) is an iatrogenic disorder characterized by the acute development of autonomic and small fiber neuropathy in the setting of rapid improvements in glycemic control in individuals with both type 1 and type 2 diabetes.
Methods: The referring diagnosis, the final diagnosis, examination findings, laboratory studies and autonomic symptoms and signs for all individuals were compared to determine the capacity of primary providers and endocrinologists to recognize this disorder.
Results: A total of 954 individuals were referred for evaluation of diabetic neuropathy, of which 104 had TIND. Only 27 % of cases of TIND were correctly diagnosed by the referring physician. Individuals correctly diagnosed with TIND had higher glycosylated hemoglobin A1C (A1C) ($P < 0.001$), greater change in A1C ($P < 0.001$), greater neuropathic pain ($P < 0.001$), larger distribution of pain ($P < 0.01$) and a longer duration of pain ($P < 0.001$). In contrast, individuals with sudomotor dysfunction, gastroparesis, syncope, orthostatic hypotension or orthostatic intolerance were less likely to be correctly diagnosed with TIND (all $P < 0.05$).
Conclusions: In general, only those cases that fit the classic historical description of painful 'insulin neuritis' were correctly diagnosed by the referring physicians. Despite extensive involvement of the autonomic nervous system in individuals with TIND, any overt clinical manifestation of autonomic dysfunction reduced the likelihood of the proper diagnosis. Additional education and research into this entity is required to properly diagnose and prevent development of TIND.

Prevalence of autonomic neuropathy in the metabolic syndrome compared to impaired glucose tolerance

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Aim: Autonomic neuropathy is a well recognized complication of type 2 diabetes that is associated with increased morbidity and mortality. However, the presence of autonomic dysfunction has not been well characterized in the metabolic syndrome, which is a combination of medical conditions that increase the risk of developing cardiovascular disease and diabetes. The current study compares the prevalence of autonomic neuropathy in a group of patients with the metabolic syndrome (MetS) compared to a group with impaired glucose tolerance (IGT).
Methods: Cross-sectional data was collected on subjects with the MetS ($n = 63$) and IGT ($n = 28$) who had undergone autonomic testing (the survey of autonomic symptoms [SAS], tilt table, heart rate response to deep breathing, Valsalva, and Q-sweat).
Results: Overall, the prevalence of autonomic neuropathy was 40.6 % in the two groups and 70.6 % of subjects had symptoms of autonomic neuropathy on the SAS. There was not a significant difference in the prevalence of autonomic neuropathy, performance on individual tests of autonomic function, or the proportion of subjects with an abnormal SAS between subjects with the MetS compared to those with IGT only.
Conclusions: There is an increased prevalence of autonomic neuropathy in both patients with IGT and the MetS. The prevalence of autonomic neuropathy was not statistically different between subjects with MetS compared to those with IGT.

Interaction between circadian blood pressure rhythm and autonomic nervous function in diabetic patients with chronic kidney disease

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Objectives: Diabetic patients with chronic kidney disease (CKD) often show loss of the nocturnal decline of blood pressure (BP) and imbalance in autonomic nervous function. However, the relation between autonomic nervous function and the circadian BP rhythm is not yet fully understood. We evaluated 24-h BP pattern in such patients using ambulatory BP monitoring (ABPM). We also analyzed the power spectrum of heart rate variability as an index of autonomic cardiovascular modulation.
Methods: One hundred and twenty-seven diabetic patients with CKD participated in the study. They were divided based on estimated glomerular filtration rates (eGFR) into the A group ($30 < eGFR < 60$ mL/min, 63 ± 10 years old, men/women, 31/29) and the B group ($eGFR < 30$ mL/min, 62 ± 9 years old, men/-women, 35/32). Each patient underwent ABPM and was assessed the heart rate variability. The ratio of lower frequency (LF) to higher frequency (HF) of heart rate rhythmic oscillations was determined as an index of sympathovagal balance. The same examinations were also performed in age- and sex-matched healthy subjects (eGFR >60 mL/min, 63 ± 10 years old, men/women, 34/33) as the Control (C) group.
Results: Mean waking and sleeping systolic BP were 131 ± 14 (SD) and 120 ± 14 mmHg in the A group, respectively, which were lower ($P < 0.05$) than 157 ± 12 and 144 ± 10 mmHg in the B group but were as high ($P > 0.05$) as 128 ± 13 and 116 ± 12 mmHg in the C group. Mean waking and sleeping diastolic BP were 86 ± 12 and 76 ± 9 mmHg in the A group, respectively, which were also lower ($P < 0.05$) than 92 ± 10 and 81 ± 9 mmHg in the B group but were as high ($P > 0.05$) as 84 ± 12 and 74 ± 8 mmHg in the C group. There were no differences ($P > 0.05$) in the waking and sleeping systolic/diastolic BP ratios between $1.24 \pm 0.10/1.19 \pm 0.11$ in the A group and $1.27 \pm 0.14/1.18 \pm 0.13$ in the C group. They were higher ($P < 0.05$) than $1.13 \pm 0.10/1.09 \pm 0.09$ in the B group. However, there were no significant differences ($P > 0.05$) in waking time LF/HF ratios between 1.9 ± 0.7 (A group) and 1.7 ± 0.6 (B group) and sleeping time LF/HF ratios between 1.4 ± 0.5 (A group) and 1.3 ± 0.6 (B group), although they were lower ($P < 0.01$) than 2.5 ± 0.9 and 2.3 ± 1.0 in the C group, respectively.
Conclusions: Our findings suggest that sympathovagal imbalance occurs in the early stages of diabetes with CKD but plays less important roles in the loss of the nocturnal decline of BP and elevated BP.

Epidermal and dermal neurovascular quantification in patients with type 2 diabetes

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Background: Complications of diabetes mellitus include both microcirculatory abnormalities and peripheral neuropathy. Although both neuropathy and microcirculatory function are considered complications of 'microvascular' disease, the relationship between these problems is not fully established and more sophisticated methods to study the microcirculation are needed.
Aim: To quantify the cutaneous neurovascular system in patients with diabetes using cutaneous punch biopsies and comparing the results to healthy control subjects.
Method: We recruited 12 healthy controls (mean age: 54.6 ± 16.6) and 20 diabetic patients (DM, mean age: 58.8 ± 12.8). Three mm skin biopsies were taken from the distal leg (dL), distal thigh (dT) and proximal thigh (pT). Immunohistochemical double staining of skin biopsies included neuronal marker anti-PGP9.5 antibody and endothelial marker anti-CD31 antibody. Quantifying the results to a depth of 500 μm from the epidermal surface we measured nerves (neural density), blood vessels (vascular density) and areas of nerve and blood vessel co-localization (neuro-vascular density). We also quantified the capillary density and diameter. All tissue sections were 50 μm with results expressed as the number per mm.
Results: Neural, dermal vascular and neuro-vascular density was reduced at all 3 biopsy sites in individuals with diabetes compared to control subjects ($P < 0.05$ for all tests at all sites). Epidermal capillary density was similar between diabetes (2.7 ± 0.9 capillaries/mm) and controls (3.4 ± 1.3 capillaries/mm) but capillary diameter was reduced in diabetes compared to controls (9.8 ± 1.2 vs. 11.0 ± 1.1 μm; $P < 0.05$).
Conclusion: In individuals with diabetes, there is reduced cutaneous neural density, dermal vascular density, and neurovascular density compared to control subjects. We believe our newly developed neurovascular quantification technique is an important step forward in understanding the microvascular complications associated with diabetes.

Statins exert an antiarrhythmic effect in an animal model of ventricular arrhythmia after myocardial infarction in Type I diabetes: reversal of autonomic imbalance and calcium alternans

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Background: Diabetics have been shown to be twice as likely to die suddenly from out of hospital myocardial infarcts (MI) compared to non-diabetic patients. The mechanism of sudden death in the diabetic population is unclear. In an Akita Type I diabetic mouse we studied the effect of pravastatin on post MI ventricular tachycardia (VT).
Methods: ECG telemetry devices were implanted in wild type (WT), placebo and pravastatin treated diabetic (Akita) mice. Heart rate variability (HRV) analysis was performed to estimate autonomic function. Ligation of the left coronary artery resulted in MI which were monitored by echocardiography and tetrazolium chloride staining. Dual Ca^{2+}-voltage optical mapping was carried out on the isolated Langendorff heart. Left ventricular myocytes were isolated for Ca^{2+} imaging. Sarcomere shortening and Ca^{2+} transients measured by the Ionoptix system and Ca^{2+} sparks by confocal microscopy. VT events were detected, classified and quantified using wavelet and machine learning based algorithms.
Results: Akita mice demonstrated decreased HRV and heart rate response to atropine which was reversed in pravastatin treated mice. In the first 24 h post MI, Akita diabetic mice developed a high incidence of VT compared to WT, which decreased from 2651 ± 893 ($n = 12$) events in placebo treated Akita mice to 343 ± 115 ($n = 13$) events ($p < 0.05$) in statin treated mice. Optical mapping demonstrated pacing induced VT originating in the peri-infarction zone and Ca^{2+} alternans, decreased in the hearts of statin treated mice. Akita myocytes displayed both contractile and Ca^{2+} alternans at pacing rates above 1 Hz, which were attenuated in cells from statin treated mice. Ca^{2+} transient decay time (Tau) was 25 % higher ($n = 20$, $P < 0.05$) in ventricular myocytes from Akita vs WT, and decreased in cells from statin treated Akita. Ca^{2+} sparks were 3 fold higher in cells from Akita vs WT and decreased by 50 % compared to placebo treated mice. Cells from placebo treated Akitas demonstrated increased cytosolic Ca^{2+} and decreased SR Ca^{2+} compared to WT. Both were partially reversed in cells from statin treated mice.
Conclusions: Type 1 diabetic Akita mice demonstrate a high incidence of spontaneous post MI VT associated with Ca^{2+} alternans and pronounced Ca^{2+} dyshomeostasis. Pravastatin decreased the incidence of post MI VT and Ca^{2+} alternans in part via the reversal of Ca^{2+} dysfunction. In this new animal model for the study of the pathogenesis of VT in type 1 diabetes, pravastatin may play a role in the prevention of VT by attenuating parasympathetic dysfunction.

POSTER SESSION I

Poster 1

Effect of droxidopa on fear of falling

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([†]Lundbeck employee at the time of the study)

Objective: Assess the impact of droxidopa on fear of falling in patients with Parkinson disease and symptomatic neurogenic orthostatic hypotension (nOH) through a post hoc analysis of falls diaries.
Background: Symptomatic nOH results from autonomic failure in which there is an inadequate noradrenergic response to postural change. nOH is associated with an increased incidence of falls, and some patients may severely limit their movement and activity because of high anxiety resulting from previous falls. Droxidopa is an FDA-approved norepinephrine prodrug for the treatment of symptomatic nOH caused by primary autonomic failure, dopamine β-hydroxylase deficiency, and nondiabetic autonomic neuropathy.
Methods: Patients underwent ≤2 weeks of double-blind titration of droxidopa or placebo, then 8 weeks of double-blind maintenance (100–600 mg TID). Falls were recorded daily in electronic diaries. Patients who reported falls were subsequently asked whether they had a fear of falling. To account for the intensity of the fear, the cumulative number of times patients had a fear of falling was calculated over the 8-week treatment period.
Results: 62 and 58 patients receiving placebo and droxidopa, respectively, reported a fall; of the patients who fell, 61 receiving placebo and 56 receiving droxidopa completed the fear of falling question. More patients receiving droxidopa reported no fear of falling (57 vs 43 %, droxidopa vs placebo; not statistically significant); the total number for the cumulative fear of falls was lower in patients receiving droxidopa (137) vs placebo (249). The correlation between the numbers of falls and fear of falling was 0.58 (Spearman correlation coefficient, $P < 0.001$), suggesting that factors in addition to falls affect the fear of falling.
Conclusions: These preliminary results suggest a potential effect of droxidopa in reducing the fear of falling. However, caution is

warranted because of the small sample size and the post hoc nature of the analysis.
Support: Lundbeck.

Poster 2

The new face of baroreflex failure in 2016

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Previous reports have suggested that baroreflex failure is a rare syndrome, generally due to extensive neck surgery or radiation of the head and neck. However carotid atherosclerosis may also induce a form of baroreflex failure. Best practices for management are ill-defined.
Case Presentation: 71 year male presented with hypertension and orthostatic hypotension. Past medical history included atrial fibrillation, dyslipidemia, psoriatic arthritis, rotator cuff surgeries, and recent carotid endarterectomy. The patient reported multiple episodes of severe orthostatic lightheadedness over the last 10 years with one episode of syncope; hypertension was poorly controlled. Prior work-up: echocardiogram normal; cardiac catheterization—no obstructive disease, although extensive aortic and vascular calcifications were present. Medications: fluoxetine, metoprolol, apixaban, gabapentin, olmesartan, rosuvastatin, fenofibrate, omega-3-acid ethyl esters, diclofenac, tramadol, infliximab. Plasma catecholamines: norepinephrine: supine 466 pg/nl; upright 1041 pg/nl; 24 h ambulatory BP: average daytime BP 138/73, HR 73/night time BP 142/77, HR 70. Autonomic testing: absent HR variability, no cardioacceleration or BP stabilization during the Valsalva maneuver, and a 50 mmHg rise in BP with cold pressor.
Diagnosis: Baroreflex failure. Since the patient had no history of head or neck radiation or surgery we hypothesized that his baroreflex failure was from extensive calcific atherosclerotic disease. Given adequate day-time BP control with medical therapy we initiated non-pharmacological behavioral modifications including: (1) elevating the head of his bed to lower night-time BP; (2) a strong cup of coffee 30 min prior to meals; (3) When hypertensive, eat a carbohydrate snack; (4) When hypotensive use the osmopressor reflex by drinking 12–16 oz of water quickly; (5) Use a squeeze ball prior to standing; (6) Begin rehabilitative exercise with a recumbent bike to improve baroreflex and endothelial function. Upon follow-up the patient reported improvement in symptoms with behavioral modifications.
Conclusions: Baroreflex failure should be considered in patients with calcific atherosclerotic disease even without neck surgery or radiation. Behavioral modification is an essential component in the management of baroreflex failure.

Poster 3

Utility of electroencephalography (EEG) during tilt table evaluation for syncope

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Introduction: Tilt table testing is routinely performed for evaluation of unexplained syncope. Occasionally convulsive syncope is misdiagnosed as an epileptic seizure, and EEG with video during tilt table can help differentiate between them. However, the diagnostic utility of simultaneous EEG during tilt table testing is unknown. Prior studies have described multiple patterns of EEG changes with syncope, but these findings have not been replicated specifically during tilt table testing.
Methods: We retrospectively reviewed all tilt table studies performed with simultaneous EEG recording from May 2015 to May 2016. All patients had video EEG before (baseline) and during the tilt table study. All patients had at least 10 min of head up tilt table study. In addition, all patients performed deep breathing and Valsalva. All studies were supervised by autonomic specialists, and EEG was visually interpreted by trained epileptologists.
Results: Fifty two patients were included in the study. Mean age was 49 years, and 33 were women. Only 1 patient ($\sim$2 %) had syncope during tilt table. Three ($\sim$6 %) had significant neurogenic orthostatic hypotension with systolic blood pressure drop of more than 50 mmHg. Five ($\sim$10 %) had significant orthostatic tachycardia. Eleven ($\sim$21 %) had abnormal baseline EEG. However, none of the patients had any visually discernable EEG changes during the head up phase of tilt table study, including patients with syncope and severe orthostatic hypotension.
Conclusions: In our cohort, qualitative EEG analysis based on visual inspection during tilt table study did not find any EEG signal changes associated with syncope or severe orthostatic hypotension. Quantitative or computerized EEG analysis might be more objective and suitable for detecting cerebral hypoperfusion during tilt table studies.

Poster 4

Dissociation between peripheral hemodynamic responses and central regulatory autonomic feedback mechanisms in treated hypertensive patients during orthostasis in comparison to healthy control subjects

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An integral relationship between peripheral homodynamic responses and efficient central autonomic regulatory mechanisms during daily bodily activity is vital for net blood pressure control in healthy human subjects. We investigated the integrity of central autonomic mechanisms to orthostasis in patients with hypertension and compared it with healthy control subjects.
Methods: Non-invasive autonomic monitoring was conducted on 23 age match subjects; 12 hypertensive males (mean $\pm$ SD; 45 $\pm$ 14.4 years) and 11 (3 females, 8 males) controls (35.6 $\pm$ 9.7 y). The study was ethically approved and informed consent was obtained. The Neuroscope system (Medifit instruments Ltd, UK) was used for beat-by-beat measurements of peripheral arterial blood pressures (systolic, diastolic and mean) and central autonomic indices; cardiac vagal tone (CVT) in units of a linear vagal scale (LVS) and cardiac sensitivity to baroreflex (CSB) ms mmHg^{1}. The responses to orthostasis were assessed during changing posture from recline to supine, sitting up from supine position and standing up from low position. Statistical analyses were performed using paired student's test.
Results: Baseline values in HTN patients were: (mean SD); BPs (mmHg): SBP 152.619.9, DBP 69.414.8, MAP 97.115.6, HR 74.3 beats min$^{-1,}$ CVT 4.63.6 in the linear vagal scale (LVS), CSB 4.043.1 ms mmHg^{1}. In control subjects: SBP 122.211.7, DBP 63.49.2, MAP 82.99.7, HR 75.87.7, CVT 5.84.6, CSB 6.54.6. Different from control subjects hypertensive patients showed mismatch central autonomic regulatory mechanisms in response to peripheral hemodynamic blood pressures during all orthostatic tests.

Conclusion: Impaired central-peripheral autonomic relationship in responses to orthostasis in treated hypertensive patients compared to healthy control subjects could provide explanation to orthostatic symptoms like syncope and dizziness in patients with hypertension.

Poster 5

Orthostatic heart rate changes in young patients with vasovagal syncope

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Recurrent postural vasovagal syncope (VVS) is caused by transient cerebral hypoperfusion due to episodic hypotension and bradycardia. Diagnosis must be made by obtaining a characteristic medical history compatible with VVS in the absence of cardiac disease. Between episodes VVS patients are generally well. The vasovagal reflex is a normal response to central hypovolemia. Thus, upright tilt testing can produce syncope in patients and healthy volunteers who fail to have real-world fainting episodes. VVS contrasts with POTS, defined by chronic day-to-day symptoms of orthostatic intolerance associated with excessive upright tachycardia in the absence of hypotension during tilt testing. The diagnosis of POTS has recently been conflated with VVS when excessive tachycardia is succeeded by hypotension during upright tilt testing. We hypothesized that excessive tachycardia preceding hypotension and bradycardia is often part of the vasovagal response, and is observed during tilt table testing of diagnosed VVS patients who are free of day to day symptoms and therefore do not have POTS. To test this hypothesis, we subjected clinically diagnosed recurrent VVS subjects ($n = 47$, 20.3 ± 0.5 yr), who had fainted at least 3 times within the last year, and control subjects ($n = 15$, 18.1 ± 0.6 yr), recruited from age and BMI matched volunteers, to a 70° head-up tilt (HUT). A comparison of heart rate (HR) (supine vs. 5 and 10 min HUT or before faint in VVS) showed a significant increase in both control (65.1 ± 2.6 vs. 83.4 ± 3.6 vs. 85.3 ± 3.8, $p < 0.001$) and VVS (69.3 ± 1.7 vs. 103.3 ± 2.4 vs.109.1 ± 2.4, $p < 0.001$). HUT in controls maximally increased HR by 20.3 ± 2.9 bpm; the increase in VVS of 39.8 ± 2.1 bpm was significantly greater than control ($p < 0.001$). Interestingly, an increase in HR of $\geq$40 bpm by 5 and 10 min or before faint with HUT, occurred in 26 % and 43 % of VVS patients respectively, but did not occur in controls. Therefore, orthostasis in VVS is accompanied by large increases in HR that should not be construed as POTS.

Poster 6

Cardiovascular components of pressor response to isometric handgrip exercise in vasovagal syncope

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Background/Aims: Neurally mediated vasovagal syncope (VVS) is characterized by a transient instability of neurocardiovascular reflexes. Changes in posture and physical exercise involve activation of these reflexes. Healthy subjects (HS) during sustained handgrip (SHG) show individual differences in the components of pressor responses. Thus, we explored the hypothesis that VVS patients had different pattern of CO and TPR responses to SHG.

Methods: 24 VVS patients (21 women, aged (27.5 ± 2.6 years), and 30 age-matched healthy subjects (HS, 20 women). Diagnosis of vasovagal syncope was based upon clinical criteria. All patients had normal physical examination and normal cardiac evaluation. Orthostatic stress testing was performed with active standing. Valsalva maneuver, baroreflex sensitivity (BRS) and BP, HR and CO changes during sub maximum force (SHG) for 3 min were monitored in supine position using FINAPRES.
Results: Valsalva maneuver was not different between both groups, while BRS was reduced in VVS related to HS (8.1 ± 0.8 vs 11.0 ± 0.5 ms/mm Hg, respectively. $p < 0.05$). During SHG, both healthy and syncope groups showed significantly BP increases, although individual CO and TPR responses were different. Indeed, CO increases without changes in TRP in 45.8 vs 53.6 % (VVS vs HS); TPR increased without changes in CO in 29.1 vs 23.3 % (VVS vs HS); both CO and TPR increased in 8.3 vs 23.3 % VVS vs HS); and no increase of CO and TPR was observed in 7.1 vs 0 % (VVS vs HS) $p < 0.05$ Chi square.
Conclusion: VVS patients, pressor responses to SHG were similar to the healthy subjects. However, in VVS patients the pattern of individual differences in the components (CO and TRP) of the pressor response was different as compared with healthy subjects.

Poster 7

The relationship between symptoms and blood pressure in individuals with orthostatic hypotension

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Objective: To determine the relationships between orthostatic symptoms and blood pressure parameters in individuals with orthostatic hypotension (OH).
Background: Orthostatic hypotension is a frequent cause of orthostatic intolerance. However, many individuals with OH are asymptomatic. The relationship between the magnitude of blood pressure fall, the nadir of the blood pressure drop and the underlying disease has not been fully elucidated.
Methods: We reviewed the development of orthostatic symptoms in well-worked up individuals with orthostatic hypotension. We investigated the magnitude of blood pressure change, and blood pressure nadir in all individuals with OH and the associated underlying disease(s).
Results: Of 108 individuals with OH, 62 were asymptomatic, while 46 were symptomatic. Those with symptomatic OH tended to have lower systolic blood pressure (SBP) (91 ± 20 vs. 103 ± 21 mmHg, $P < 0.005$), although significant overlap between groups was noted. The magnitude of blood pressure fall was similar between symptomatic and asymptomatic groups. Individuals with alpha-synucleinopathies that developed symptoms of orthostatic intolerance had greater supine SBP (161 ± 22 vs. 138 ± 21 mmHg, $P < 0.01$), greater magnitude of drop in SBP (73 ± 14 vs. 45 ± 13 mmHg, $P < 0.01$) and lower blood upright SBP (88 ± 15 vs. 97 ± 18 mmHg, $P < 0.05$) prior to development of symptoms than those individuals with symptomatic OH without synucleinopathies.
Conclusions: The relationship between orthostatic hypotension and orthostatic intolerance is complex. The fall in blood pressure, the lowest drop in blood pressure and the rate of blood pressure fall may all predispose to the development of orthostatic symptoms. Individuals with synucleinopathies require larger changes in blood pressure prior to development of symptoms.

Poster 8

Progressive orthostatic hypotension and reduced vasomotor reactivity in patients with vasovagal syncope

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In some cases vasovagal syncope development is preceded by progressive blood pressure (BP) reduction.
Aim: Assessment of blood circulation autonomic control in patients exhibiting vasovagal syncope with background progressive orthostatic hypotension.
Materials and Methods: The study included 102 patients aged 23 ± 9 y with vasovagal syncope without significant comorbidities confirmed by the tilt-test, the average length of which was 21 ± 7 min duration. Additionally were performed hand-grip (HG) and Valsalva maneuver to obtain the Valsalva index (VI) and the vasomotor response (VRVM) by the dynamics of the average blood pressure at the end of phase II. Was calculated spontaneous arterial baroreflex (BRS).
Results: Depending on their systolic BP dynamics during orthostasis, patients were divided into 2 groups: those exhibiting progressive BP reduction greater than 30 mmHg compared to the baseline before the development of vasovagal reaction (PBPR), $n = 54$, and without significant blood pressure reduction (WBPR), $n = 48$. PBPR group contained younger patients compared to the WBPR group: 21 ± 7 vs 26 ± 10 y, $p < 0.05$. PBPR group also contained patients with vasomotor dysfunction more frequently, according to VRVM: 38 (73 %) vs 14 (30 %), respectively, $\chi^2 = 17.3$, $p < 0.001$. At the same time, VRVM significantly correlated with the dynamics of systolic BP during tilt-test: $r = 0.29$, $p < 0.005$. However, reaction to the HG, VI and BRS, as well as the duration of the tilt-test did not differ significantly (for all indicators $p > 0.05$). No differences in the types of syncope between studied groups could be observed.
Conclusions: Progressive hypertension is a widespread phenomenon in young subjects with vasovagal syncope which is associated with a reduction of vasomotor reactivity in response to the Valsalva maneuver and thus, apparently, acts as a trigger to initiate a vasovagal reaction in these patients.

Poster 9

Implementing a program to reduce the burden of orthostatic hypotension in patients of a neurology clinic

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Introduction: Orthostatic hypotension (OH) is prevalent in certain neurological diseases and can be disabling and dangerous. Neurologists vary in practices for identifying and treating OH. We sought to standardize via the electronic medical record (EMR) the screening and management of patients with OH in an ambulatory neurology practice.
Methods: The diagnosis and problem lists were used to identify patients enriched for OH risk. A Best Practice Advisory (BPA) prompted nurses to screen these patients. Criteria for a positive screen had been revised to optimize performance. A positive screen was defined as the combination of standing systolic blood pressure (SBP) ≤100 mmHg, postural drop ≥10 mmHg, and positive response to the first question of the Orthostatic Hypotension Assessment (OHSA-1). This prompted the clinician to choose from a menu of suggested interventions. Subjective and objective outcomes were then compiled into a registry for data-driven quality improvement.
Results: In March and April 2016, 513 patients were eligible for screening in a neurology specialty clinic. The standing SBP was ≤100 mmHg in 59 patients, of whom 42 had postural drop ≥10 mmHg. OHSA-1 response was recorded in only 28 of these, of whom 15 responded positively. All patients with standing SBP ≤90 mmHg and drop ≥10 mmHg who answered OHSA-1 gave a positive response. In addition, 29 of 134 patients with standing SBP >100 mmHg and without 10 mmHg drop gave a positive response to OHSA-1. Interventions by clinicians included: diary of orthostatic BP (8), non-pharmacological counseling (8), pharmacotherapy (2), cessation of offending medication(s) (2), and referral to hypertension specialist (2).
Conclusions: The EMR can be used to standardize several steps within a program to reduce the burden of OH, including screening and identification of patients and tracking outcomes of interventions. This data will be used to drive a series of quality improvement cycles.

Poster 10

Cerebrovascular responses to the Valsalva maneuver in pediatric patients with vasovagal syncope

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Vasovagal syncope (VVS) is the leading cause of recurrent fainting in young adults. The vasovagal response is characterized by a sudden paradoxical reversal of autonomic reflexes, leading to widespread vasodilatation and bradycardia that result in cerebral hypoperfusion and syncope. Patients with unexplained syncope are often referred for extensive and costly clinical autonomic tests. The Valsalva maneuvre (VM) is a short, simple and inexpensive test that can be easily administered and provides a stimulus that challenges cerebral autoregulation. Patients with VVS demonstrate impaired cerebral autoregulation during orthostatic stress; therefore, we hypothesized that patients with VVS would demonstrate impaired cerebral autoregulation during the VM. Paediatric VVS patients ($n = 14$) and healthy young controls ($n = 13$) performed two supine 40 mmHg, 20 s VM, separated by 1 min rest. They then underwent a graded 60° head-up-tilt test with combined lower body negative pressure continued until pre-syncope, to determine orthostatic tolerance in minutes. Beat-to-beat cardiovascular responses (finger plethysmography), and systolic middle cerebral artery blood flow velocity (CBFv) (transcranial Doppler) were determined continuously. There were no significant differences in R–R interval and blood pressure responses to the VM between patient and control groups. However, there were subtle differences in cerebrovascular parameters during phase 4 of the VM; the CBFv overshoot time integral tended to be decreased in patients (38.0 ± 7.1 au; $p = 0.080$) compared to controls (68.6 ± 15.5 au). Moreover, both the magnitude of the phase 2A CBFv drop ($r = 0.400$; $p = 0.058$) and the phase 4 CBFv overshoot ($r = -0.447$; $p = 0.022$) were correlated with orthostatic tolerance. This study is the first to evaluate and detect cerebrovascular responses to the VM in a pediatric population with orthostatic VVS. Although these differential responses are likely not sufficient to support diagnostic utility of the VM in the assessment of VVS, these findings demonstrate that impaired cerebral autoregulation is observable in

young people with orthostatic syncope during supine rest, without the presence of an orthostatic stressor.

Poster 11

Usefulness of lower body negative pressure in the clinical autonomic laboratory

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Background: Infusion of vasoactive agents in the assessment of orthostatic intolerance in the autonomic laboratory is controversial. The technique of lower body negative pressure (LBNP) was described two decades ago. LBNP exaggerates orthostatic stress by closely mimicking a physiologic stimulus, and has the advantage of being quickly reversible. However, it is not routinely used in clinical practice.
Objective: To describe our experience using LBNP in the clinical autonomic laboratory in patients with orthostatic intolerance of unclear origin.
Methods: We used a customized airtight cover, sealed to a tilt-table and to the subject at the level of the iliac crest. After 30 min of asymptomatic passive head-up tilt, LBNP was applied while the patient was still upright. Suction was briefly initiated at –20 mmHg for 1-min and then increased to −40 mmHg for the following 10-min. Blood pressure, heart rate and plasma catecholamines when supine, after 10-min of head up tilt, and during syncope or other paroxysmal event, were measured. Time from LBNP onset to episode was recorded.
Results: Fifteen subjects (8 men; aged 40 ± 20 years, range: 12–75 years) were enrolled. During LBNP, 7 subjects developed typical vasovagal syncope (after 3.8 ± 1.3 min of LBNP) with hypotension and bradycardia and marked increases in plasma levels of epinephrine and vasopressin. Six tolerated the procedure uneventfully. One patient became unresponsive and his head stooped forward but BP and HR remained stable without changes in plasma catecholamines. The remaining patient had flailing bilateral movements with no changes in consciousness, BP or HR, but a significant increase in plasma epinephrine levels. All patients recovered without sequelae.
Conclusions: LBNP is a useful technique in the differential diagnosis of patients with orthostatic intolerance of unclear origin and can be easily implemented in the clinical setting. In addition to its well-known value to induce vasovagal syncope, this technique can also be useful to induce psychogenic episodes.

Poster 12

Familial dysautonomia: a disease with hidden tears

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Familial dysautonomia (FD) is frequently referred to as a disease with no tears, but the underlying reason for this alacrima is unknown. Normally, nerves in the cornea stimulate the production of tears from lacrimal glands in the eye. Whether the absent/reduced tears in FD is due to denervation or an abnormality in the lacrimal glands themselves is unclear. To clarify this, we used pilocarpine (4 %, a parasympathetic M3 receptor agonist), which can be applied topically to the eye to stimulate the tear secretion directly in the lacrimal glands, bypassing the nerve pathways. We assessed corneal sensitivity using a Cochet-Bonnet esthesiometer. Tear volume was estimated with the Schirmer's test (a scaled paper strip placed in the lower eyelid and the length of moisture measured after 5 min). Schirmer's test was performed four times: (*1*) at baseline, (*2*) 30-min after instillation of normal saline (placebo, 2 drops), (*3*) 30-min, and (*4*) 3-h after pilocarpine instillation (2 drops). Basal tear secretion was 6.3 mm (±2.6 SD), and 6.9 mm 30 min after placebo (±3.0 SD, $p < 0.395$). Thirty minutes after the instillation of piloparpine, tear volume more than doubled to 19.6 mm (±8.3 SD, $p < 0.001$); and the increased tear production persisted at 3 h (12.6 mm ± 5.1 SD, $p < 0.001$). There was a significant positive correlation between corneal sensitivity and tear secretion at baseline ($R^2 = 0.74$). Our results indicate that patients with FD have functional lacrimal glands, which can be stimulated with an M3 agonist to produce tears. Basal tear secretion was directly related to corneal sensitivity. The findings suggest for the first time that tear production in patients with FD can be restored pharmacologically.

Poster 13

Afferent baroreflex failure and lack of nocturnal blood pressure dipping: a mystery solved?

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Background: Normally, during sleep, when cortical influences are minimized, blood pressure (BP) and heart rate (HR) fall (i.e., nocturnal dipping). In patients with afferent baroreflex failure, in whom BP and HR are highly dependent on cortical influences, this nocturnal dipping is usually preserved. There are, however, a number of patients with afferent baroreflex failure in whom BP does not dip at night. The reasons for this are unknown.
Methods: We examined the 24-hour ambulatory BP profiles in 50 patients with afferent baroreflex failure of acquired ($n = 6$) or genetic origin (familial dysautonomia $n = 44$). BP and HR were captured at 30-minute intervals over a 24-h period. Nighttime sleep periods were identified from the patient's diary. Dipping was defined as a 10 % or greater fall in systolic and diastolic blood pressure at night.
Results: Normal BP nocturnal dipping was present in only 50 % of the patients; 33 % of patients had reversal of the circadian rhythm with higher blood pressures at night. In the remaining 17 %, nocturnal BP was similar to daytime BP. Patients with preserved nocturnal dipping had a significantly higher glomerular filtration rate (8430 mL/min) than those that did not dip at night (6130 mL/min, $p = 0.043$).
Conclusions: Lack of nocturnal BP dipping in patients with afferent baroreflex failure was associated with impaired renal function. These findings suggest that in patients with FD, a non-dipping profile may involve abnormalities in extracellular volume and/or impaired regulation of vascular resistance (i.e., abnormal endothelial function).

Poster 14

Serum chloride levels and electrodermal activity in hereditary sensory and autonomic neuropathy type III

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The ability of the skin to conduct electricity depends on sweat secretion. This is referred to as electrodermal or electrochemical skin conductance. Recently, a technique has been developed to assess electrodermal activity using reverse iontophoresis dependent on sweat chloride levels. This method can reliably identify patients with cystic fibrosis, a disease with well-described increases in chloride concentration in sweat. Our goal was to determine the relationship between electrodermal response and serum chloride levels in other patient groups. We conducted a cross-sectional study involving 38 subjects with HSAN-III (familial dysautonomia, FD) and 20 healthy controls. Electrodermal activity of the soles was assessed using stainless steel-based plate electrodes applied under the soles of the feet for 3 min (Sudoscan®). The influence of age, serum electrolyte levels, and medications were analyzed.
Results: Electrodermal activity was normal (>60 microS) in 24 patients (63 %) and reduced (<60 microS) in the remaining 14. There was a direct correlation between electrodermal activity and serum chloride levels ($p = 0.007$). Reduced electrodermal activity was explained by low serum chloride in 6 patients, and likely by medications in 8 (clonidine). All controls had normal electrodermal activity, but because their serum chloride levels were normal in every subject (>97 mEq/L), no correlation could be established.
Conclusions: Low serum chloride levels result in reduced electrodermal activity. In addition to medications, serum chloride levels should be checked to properly interpret electrodermal activity measurements.

Poster 15

Beta-adrenergic agonists vs. anti-cholinergics in obstructive lung disease in familial dysautonomia: A controlled clinical trial

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Background: Patients with familial dysautonomia (FD) have asthma-like exacerbations with coughing, wheezing, and hypoxia. While many are treated empirically with bronchodilators, it is still unknown whether airway obstruction in these patients is pharmacologically reversible by modifying autonomic tone.
Methods: We conducted a two-center, randomized, placebo-controlled, double blind, crossover study to assess the safety and efficacy of albuterol (a direct acting sympathomimetic) vs. ipratropium bromide (a parasympatholytic muscarinic blocker). Albuterol (0.083 %, 2.5 mg/3 ml), ipratroprium bromide (0.02 %, 500 mcg/2.5 ml) and placebo (0.9 % sodium chloride 3 ml) were administered by nebulization in random order over 15 min in the seated position. Airway responses were assessed with spirometry and impulse oscillometry pre- and 30 min post-dose. Continuous blood pressure, RR-intervals and cardiac impedance were measured non-invasively (TaskForce Monitor, CNSystems, Graz, Austria). Raw data tracings were analyzed blindly.
Results: Fifteen patients were enrolled. All had a documented history of aspiration into the airway and acute episodes of coughing and wheezing. Beta-adrenergic activation with albuterol significantly increased forced vital capacity ($p = 0.041$) and forced expiratory volume within 1 s ($p = 0.002$). In line with this, impulse oscillometry at 5 Hz was significantly lower post-albuterol ($p = 0.006$), suggesting a reduction in total airway resistance. Blockade of muscarinic acetylcholine receptors with ipratroprium had less bronchodilatory effects. Both treatments were well tolerated and had no effects on blood pressure, heart rate or derived cardiac output.
Conclusions: In patients with FD, beta-adrenergic stimulation more effectively reversed airway obstruction than muscarinic blockade. Both treatments were well tolerated and had no measureable systemic effects.

Poster 16

Predictors of response to droxidopa in patients with neurogenic orthostatic hypotension

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Droxidopa, a synthetic norepinephrine precursor, was recently approved to treat symptomatic neurogenic orthostatic hypotension (nOH). The pressor response is variable with some patients responding to doses of 100 mg while others requiring up to 600 mg three times/day. It is not known which factors predict the magnitude of the pressor response to droxidopa. We prospectively evaluated the BP response to increasing doses of droxidopa in patients with nOH in an outpatient setting. BP supine and after 3-min standing was measured before and 1-h after oral administration of 100 mg of droxidopa. Droxidopa was progressively increased until (i) complete relief of symptoms, (ii) supine systolic BP >180 mmHg, (iii) occurrence of side effects, or (iv) the maximum dose of 600 mg was reached. Sixteen subjects with nOH (6 with Parkinson disease, 5 with pure autonomic failure, 3 with autoimmune autonomic ganglionopathy, and 2 with multiple system atrophy) were evaluated. Mean BP was $126 \pm 28/72 \pm 11$ mmHg supine, and $89 \pm 19/53 \pm 15$ mmHg after 3-min standing (fall of 37/18 mmHg). Mean plasma norepinephrine while supine was 192 ± 216 pg/ml. Maximum droxidopa dose during the titration was 212 ± 102 mg (range 100–400 mg). Droxidopa increased BP to an average of $148 \pm 53/90 \pm 13$ mmHg supine and $135 \pm 38/66 \pm 16$ mmHg after 3-min standing ($p < 0.001$). Plasma norepinephrine levels were inversely correlated with higher systolic BP after 3-min standing following droxidopa treatment ($R^2 = 0.42$; $p = 0.023$). Four patients (3 with AAG and 1 with PAF) with very low plasma norepinephrine levels (<90 pg/ml) experienced transient nausea, vomiting, and abdominal pain during titration with dosages of 200 mg. In these patients, treatment with 100 mg/day was effective and well tolerated. Diagnostic categories did not predict response to droxidopa. In patients with nOH, lower plasma norepinephrine levels are associated with a greater pressor response to droxidopa. This response is probably related to the degree of denervation supersensitivity. Supine norepinephrine levels may be useful to predict appropriate dosing of droxidopa in a clinical setting.

Poster 17

Vagal and adrenergic baroreflex sensitivity induced by Valsalva maneuver in patients of SCA1, SCA2 and SCA3

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Introduction: Baroreflex has an important role in maintaining blood pressure (BP). Valsalva maneuver (VM) can be used to quantify baroreflex sensitivity (BRS) which is of majorly two components: vagal baroreflex sensitivity (BRS_vagal) and adrenergic baroreflex sensitivity (BRS_a). Again, BRS_vagal has 2 indices: BRS_vagal_{dec} (from early ph II) and BRS_vagal_{inc} (from ph III- IV). In patients of spinocerebellar ataxia (SCA), autonomic dysfunction occurs but components of BRS are very poorly reported. Therefore, we evaluated different indices of BRS in patients of SCA1, 2 and 3.
Methods: The recordings of continuous HR and BP during VM were analyzed to determine BRS in genetically proven SCA1 ($n = 11$, age $= 36.6 \pm 8.2$ yrs), SCA2 ($n = 11$, age $= 33 \pm 8$ yrs) and SCA3 ($n = 7$, age $= 38 \pm 9.8$ yrs) patients. BRS_vagal_{inc} and BRS_vagal_{dec} were calculated as the regression slope of R–R interval and systolic BP during phase III-IV and early phase II of the VM, respectively. BRS_a was defined as the systolic BP decrement associated with phase 3 divided by the PRT (BP recovery time). Also, ICARS score has been evaluated to know the clinical severity of the three groups of SCA.
Results: The BRS_vagal_{dec} was assessed as 2.23 ± 1.45 ms/mmHg in SCA1, 4.43 ± 2.9 ms/mmHg in SCA2 and 3.96 (1.25–15.4) ms/mmHg in SCA3. On the other hand, BRS_vagal_{inc} was 3.89 ± 2.33 ms/mmHg, 5.67 ± 3.36 ms/mmHg and 6.04 ± 4.8 ms/mmHg in SCA1, 2 and 3, respectively. Again, BRS_a has been calculated as 21.33 (8.33–23) ms/mmHg, 21.12 ± 11.2 ms/mmHg in SCA2 and 16.19 ± 13.4 ms/mmHg in SCA1. For clinical severity, ICARS score was determined in SCA1 (32 ± 13), SCA2 (26 ± 13) and SCA3 (20 ± 9) patients.
Conclusions: The result indicates the trend of different components of BRS in the three patients groups. In case of BRS_vagal, SCA1 is lower following SCA2 than SCA3 (pattern is SCA1 > SCA2 > SCA3) whereas BRS_a is lower in SCA3 than SCA1 and 2 (pattern is SCA3 > SCA2 > SCA1). It may very informative for the two efferent limbs of BRS namely vagal and adrenergic component which is helpful for neurologist to manage these ataxias.

Poster 18

The influence of subthalamic nucleus deep brain stimulation and levodopa on cardiovascular autonomic function in patients with Parkinson's disease

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Objectives: Deep brain stimulation of subthalamic nucleus (STN-DBS) and levodopa are widely used in Parkinson's disease (PD), but their influence on cardiovascular autonomic function remains to be elucidated. The aim of the present study was to explore the effects of STN-DBS and levodopa on cardiovascular autonomic function in PD.
Methods: Twenty-six PD patients with bilateral STN-DBS in a stable state were tested under DBS off and dopaminergic medication off (OFF–OFF), DBS on and dopaminergic medication off (ON–OFF), and DBS on and medication (levodopa) on (ON–ON) statuses by recording continuously blood pressure, ECG and respiration at rest, during deep metronomic breathing, and head-up tilt test. Thirteen patients suffered of orthostatic hypotension. Baroreflex sensitivity (BRS) and spectral analyses were performed by trigonometric regressive spectral analysis.
Results: 1. STN-DBS and levodopa had multiple influences. (1) Systolic blood pressure (SBP) during tilt-up was reduced by STN-DBS, and then further by levodopa. (2) High frequency power of RR interval (RR-HF) during tilt-up was increased, while RR-LF (low frequency)/HF ratio and low frequency power of systolic blood pressure (SBP-LF) during tilt-up were decreased by levodopa. (3) RR-LF/HF ratio at rest was decreased by STN-DBS. 2. Levodopa decreased BRS and RRI only in the OH group, and had opposite effects on the non-OH group.
Conclusions: These findings indicate that STN-DBS and levodopa have different effects on cardiovascular autonomic function in PD, which are modulated by the presence of orthostatic hypotension as well.

Poster 19

Impedance plethysmography testing reveals different vascular responses during orthostatis in Parkonson's disease and multiple system atrophy with parkinsonism

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Background: Orthostatic hypotension (OH) is a prevalent sign of dysautonomia in Parkinson's disease (PD) and multiple system atrophy with parkinsonism (MSA-P). Yet, the pathophysiology remains unclear. Previous studies indicate cardiac compromise in PD and vascular incompetence in MSA-P but the cardiovascular autonomic response during orthostasis is rarely studied.
Objective: To evaluate the contribution of the end organ failure to OH in PD and MSA-P by assessing the cardiac, arterial and venous functions during orthostasis.
Methods: In 10 PD_{OH} patients and 14 $MSA\text{-}P_{OH}$ patients, we recorded continuous electrocardiogram and beat-to-beat systolic blood pressure (BPsys) for 2 min prior to, 5 min during and 2 min after the head-up-tilt test (HUTT) and calculated the changes in BPsys and heart rate (HR). We performed simultaneous impedance plethysmography (IPG) in a tetrapolar configuration and acquired data from the right lower limb to assess venous pooling.
Results: During HUTT, the BPsys reduction was similar in patients with PD_{OH} and $MSA\text{-}P_{OH}$ (36.50 ± 4.83 vs. 34.36 ± 4.85 mmHg, $p = 0.76$), the increase was significantly lower in patients with PD_{OH} than $MSA\text{-}P_{OH}$ (7.78 ± 5.47 vs. 14.09 ± 5.25 bpm, $p = 0.03$), therefore the HR increase per mmHg of BPsys fall was also significantly lower in the PD patients (0.23 ± 0.12 vs. 0.65 ± 0.66 bpm/mmHg, $p = 0.01$). The impedance change during HUTT was similar in both groups. Maximum change in impedance occurred in the first minute of HUTT in both groups due to venous pooling. However, the latency of recovery was different between the two. Recovery started occurring in the latter half of HUTT in PD_{OH} but was absent in $MSA\text{-}P_{OH}$. The HR increase in the last one minute of HUTT than baseline was significantly lesser in PD_{OH} than $MSA\text{-}P_{OH}$ (1.94 ± 1.85 vs. 8.88 ± 1.68 bpm, $p = 0.013$).

Conclusion: In PD_{OH}, compromised cardiac response could contribute to OH whereas in MSA-P_{OH} compromised vascular response might play a more important role.

Poster 20

Long-term effects of deep brain stimulation on autonomic function in patients with Parkinson's disease

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Background: Deep brain stimulation (DBS) has been used in treating Parkinson's disease (PD) for decades. Although several reports show improvement of autonomic function in patients undergoing DBS, autonomic side effects or even devastating outcome after DBS have also been reported. The aim of this study is to evaluate the long-term effects of DBS on autonomic function in patients with PD.
Patients and Methods: This is a retrospective study. The PD patients receiving DBS in Kaohsiung Chang-Gung Memorial Hospital were reviewed. Twenty-four patients (age 59.2 ± 10.9 years, male/female: 16/8) have done complete autonomic function testing, including quantitative sudomotor autonomic reflex test, heart rate response to deep breathing, Valsalva maneuver, and head-up tilt, before and after DBS. The testing in patients with DBS was performed during the off phase. In addition to each original autonomic parameter, Composite autonomic scoring scale (CASS) was also coded.
Results: The median interval between two times of autonomic function test was 1.5 [1.35, 1.7] years. CASS and sympathetic sudomotor subscore showed significant increment after DBS, whereas cardiovagal and adrenergic subscores revealed no significant change between the two exams.
Conclusion: The increment in sympathetic sudomotor subscore could be due to disease progression. The long-term effects of DBS on cardiovascular autonomic function in PD patients are not significant.

Poster 21

Repetitive somato-sensory mechanical stimulation decreases cardiovascular sympathetic activity and blood pressure in Parkinson's disease

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Background: In patients with Parkinson's disease (PD), single manual mechanical somato-sensory stimulation of specific sites of the forefoot (tip of the big toe and plantar surface of 1st metatarsal junction), improved gait, increased cardiac vagal modulation and decreased vascular sympathetic activity, 24 h after stimulation. A decrease in arterial blood pressure was also observed.
Aim: to evaluate the effects on blood pressure and cardiovascular autonomic profile of repetitive mechanical somato-sensory stimulations applied on the same feet sites previously found to be effective.
Methods: Sixteen patients (3F, 68.4 ± 2.0 yrs) with idiopathic PD (HY 2–3) were studied while supine, before (Baseline) and 72 h after (Post) five standardized stimulation procedures (6 s duration for each site, repeated 4 times) obtained by a pressure-controlled mechanical stimulator (Gondola®), each performed every 72 h. Blood pressure (BP) was assessed every 3 min for 15 min by a conventional non-invasive blood pressure monitor (Philips M3046A). ECG, beat by beat blood pressure and respiratory activity were continuously recorded for 15 min. Spectral analysis of RR and SAP variability furnished the indexes of cardiac (LF/HF) and vascular (LF_{SAP}) sympathetic modulation.
Results: In 11 out of 16 patients, spectral indices of cardiac and vascular sympathetic modulation were significantly lower in post (LF_{RR}/HF_{RR} 0.49 ± 0.32; LF_{SAP} 1.08 ± 1.33 $mmHg^2$) compared to baseline (LF_{RR}/HF_{RR} 1.41 ± 1.09; LF_{SAP} 3.71 ± 3.35 $mmHg^2$, $p < 0.005$). Blood pressure was also lower in post (Systolic Arterial Pressure, SAP 117 ± 19 mmHg, Diastolic Arterial Pressure, DAP 70 ± 4 mmHg) compared to baseline (SAP 135 ± 19 mmHg, DAP 74 ± 4 mmHg). RR interval was unmodified.
Conclusions: Somato-sensory stimulation was effective in reducing arterial pressure and cardiovascular sympathetic activity in this subset of patients and might be used as an additional tool for controlling recumbent hypertension in PD. Its hypotensive effect raises the possibility to employ that methodology in different disorders including essential hypertension.

Poster 22

Electrodermal activity in synucleinopathies

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Background: In synucleinopathies, deposits of α-synuclein occur in sympathetic neurons innervating sweat glands, leading to impaired sudomotor function. Hence, measurement of sweat production may be relevant as a diagnostic biomarker. We hypothesized that patients with synucleinopathies have decreased electrodermal activity, and that this is associated with sympathetic adrenergic impairment.
Objective: To evaluate electrodermal activity in subjects with synucleinopathies.
Methods: Cross-sectional study including 106 patients with synucleinopathies (55 with idiopathic Parkinson disease–PD-, 18 with probable multiple system atrophy–MSA-, 25 with pure autonomic failure–PAF-, and 8 with idiopathic REM behavior disorder–RBD-) and 57 healthy controls enrolled in New York University (New York, NY) and Hospital de Cruces (Bilbao, Spain). Electrodermal activity was assessed with a device (Sudoscan®). Standard cardiovascular autonomic testing (in all subjects) and I^{123}metaiodobenzylguanidine myocardial scintigraphy (in 30 patients with PD) were performed to quantify sympathetic adrenergic dysfunction.
Results: Electrodermal activity both in the palms and in the soles was lower in patients than in controls ($p < 0.01$). When considered

separately, MSA, PAF and RBD had lower electrodermal activity in the palms than in controls ($p < 0.001$), whereas electrodermal activity in the soles was lower in MSA, PAF and PD ($p < 0.05$). Linear regressions showed that reduced electrodermal activity was associated with markers of sympathetic adrenergic impairment ($p < 0.05$), but not with disease duration.
Conclusions: Decreased electrodermal activity in palms and soles is a frequent finding in synucleinopathies. Decreased electrodermal activity was associated with decreased sympathetic adrenergic function, suggesting a parallel degeneration of both adrenergic and cholinergic sympathetic fibers.

Poster 23

REM behavior disorder in pure autonomic failure

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Introduction: Pure autonomic failure (PAF) is a neurodegenerative disorder characterized by the deposition of α-synuclein in the peripheral autonomic nerves.[1] Rapid eye movement behavior disorder (RBD) correlates with the development of central nervous system (CNS) α-synucleinopathies,[1] however there is limited data on the prevalence of RBD in patients with PAF.
Methods: Patients ($n = 7$) were diagnosed with PAF based on clinical evaluation and autonomic testing. Symptom duration was ≥5 years, and no patient exhibited Parkinsonian or cerebellar signs. Autonomic testing included measurements of heart rate variability (HRV) with deep breathing, Valsalva maneuver, and head up tilt table testing at 70 degrees for a minimum of 10 min. Most patients also underwent quantitative sensory axon reflex (QSART) testing. All patients underwent in-lab polysomnography (PSG) with chin and extremity leads to evaluate for REM-without atonia (RWA). RWA was identified by augmentation of electromyogram tone during REM sleep according to current AASM criteria.[2]
Results: Mean age of patients was 68 years (75 % women), and mean duration of symptoms was 10.7 years. All patients exhibited evidence of sympathetic adrenergic impairment on tilt testing, with a mean SBP drop of 96 mmHg within the first 3 min. RWA was seen in 71 % of patients. All of these patients endorsed dream enactment behavior, meeting criteria for RBD.
Conclusions: Our results indicate that RBD may be more common than previously reported in PAF. The extent of CNS involvement in PAF warrants further investigation, and large natural history studies will be important to better understand the pathophysiology and prognosis of this rare condition.
References: 1. Iranzo A et al. Lancet Neurol 2013; 12:443–453. 2. The AASM Manual for the Scoring of Sleep and Associated Events, v. 2.1 (2015).

Poster 24

Growth hormone responses to clonidine stimulation differentiates between multiple system atrophy and pure autonomic failure

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Background: Multiple system atrophy (MSA) and pure autonomic failure (PAF) are characterized by chronic autonomic failure. The clinical diagnosis of PAF may be made in a patient who is in the earliest stage of developing MSA. Identifying markers of early diagnosis in these disorders might help recognizing very early MSA. Impaired growth hormone (GH) response to clonidine stimulation may be early manifestations of MSA and help differentiating MSA from PAF.
Aim: To evaluate GH response to clonidine stimulation in patients with MSA and PAF.
Methods: We retrospectively reviewed our cohort of MSA and PAF patients, who underwent clonidine stimulation test. Clinical features and cardiovascular autonomic tests including head-up tilting (HUT) and plasma growth hormone responses at 15, 30, 45 and 60 min after clonidine stimulation were evaluated.
Results: 42 MSA (61 ± 10 years, M/F: 27/15) and 18 PAF patients (62 ± 11 years, M/F: 7/11) were identified. There was no significant difference between time from onset to testing (OTT) between two groups ($p = 0.13$). There was no difference in baseline GH between MSA and PAF ($p = 0.59$). The GH response to clonidine was significantly lower in MSA than PAF at any time point after clonidine administration ($p < 0.01$). Plasma GH levels were not affected by OTT, presenting features, BP and HR responses to HUT. Among 42 patients with MSA, 5 had initial diagnosis of PAF and GH responses to clonidine were significantly lower compared to those in typical PAF, at the first evaluation.
Conclusions: GH response to clonidine stimulation is helpful in differentiating MSA from PAF patients. GH responses are impaired early in the disease course of MSA as confirmed by abnormal results in the pre motor phase (PAF presentation prior to evolving in MSA). Abnormal GH responses to clonidine stimulation test could represent a risk factor and indicate a high likelihood to progress to MSA.

Poster 25

Haemodynamic responses to the somatostatin analogue, octreotide, in patients with pre and post ganglionic lesions of the autonomic nervous system

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Background: The somatostatin analogue, octreotide, reduces postural hypotension and orthostatic intolerance in autonomic disorders. However, whether the haemodynamic responses to octreotide are different in patients with pre and post ganglionic lesions of the autonomic nervous system, has not been investigated in large cohort of patients.

Aim: To evaluate the haemodynamic responses to liquid meal ingestion, before and after the administration of octreotide, in patients with pre and post ganglionic lesions.
Methods: patients with chronic autonomic failure underwent a standard liquid meal test with and without a sub-cutaneous injection of octreotide (50mcg). Head-up tilt (HUT) was performed pre- and post-meal. BP and HR were measured using upper arm auto-sphygmomanometry. Patients with established diagnosis of MSA were classified as disorder with pre ganglionic lesion and patients with longstanding pure autonomic failure (PAF) as disorder with post ganglionic lesion.
Results: 32 patients were included, (16 females, 60.4 ± 9.6 years), 22 patients with longstanding diagnosis of PAF (post ganglionic lesion), and 10 patients with MSA (preganglionic lesion). After liquid meal ingestion, mean supine BP fell in both groups, but it was significantly lower in PAF (86 ± 17.8) compared to MSA patients (101 ± 11.8), ($p < 0.05$). The administration of octreotide produced a significantly greater increase in mean BP in PAF group (121 ± 15) compared to MSA (117.1 ± 10.9), ($p < 0.01$).
Conclusion: patients with postganglionic lesion have greater BP responses to octreotide consistent with supersensitivity to vasopressor agent. Octreotide may reduce post prandial hypotension by enhancing the release of local vasoconstrictor mediators such as Endothelin 1, and patients with postganglionic lesion might have greater sensitivity to vasoactive agents. Haemodynamic responses to octreotide are different in patients with pre and postganglionic lesions and using this pharmacological stimulation might help differentiate between not only in the treatment of post prandial hypotension, but also differentiate between those with pre from a post ganglionic lesion.

Poster 26

Pure autonomic failure and Lewy body dementia: red flags of evolution to a widespread alpha synucleinopathy

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Aim: Lewy body dementia (LBD) comprises clinically diagnosed dementia with Lewy bodies and Parkinson's disease dementia. Case reports of patients with a primary diagnosis of primary autonomic failure (PAF) evolving to LBD have been described. We aim to retrospectively evaluate our cohort of patients with longstanding diagnosis of PAF and describe those evolving to LBD.
Methods: Ninety seven patients with PAF underwent full clinical and autonomic assessments.
Results: Ten (10.3 %, all men) patients with longstanding PAF developed a combination of parkinsonism and cognitive impairment meeting the criteria for LBD at follow up. Mean age at onset was 58 ± 9.7 ys and 56 ± 11.7 ys in patients who evolved to LBD, and in those who remained PAF respectively. Mean disease duration prior to developing cognitive impairment and parkinsonism was 15 ± 7.7 ys in LBD group. REM behavior disorder (RBD) was present in 7 (70 %) patients and visual hallucinations were reported in 6 (60 %) patients with LBD. Median supine plasma noradrenaline (NA) was significantly higher in LBD group, when compared to PAF (204.5 pg/ml in patients with LBD and 141 pg/ml in those with PAF; $p = 0.019$), as was median tilted NA (236 pg/ml and 149 pg/ml in LBD and PAF respectively; $p = 0.05$).
Conclusions: A subgroup of patients with longstanding PAF might evolve in more diffuse alpha synucleinopathy. RBD and hallucination are potential red flags for PAF patients who will later evolve to LBD. Our preliminary data also suggests that lower supine and tilted NA are seen in patients with typical PAF indicating a prominent postganglionic involvement, comparing to those who develop LBD.

Poster 27

The natural history study of synucleinopathies

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Introduction: The Natural History Study of Synucleinopathies (NHSS) is a prospective, observational, international, multi-center study with particular emphasis on multiple system atrophy (MSA) and pure autonomic failure (PAF), two orphan diseases.
Objectives: The goals of the NHSS are: (I) to define the natural history of PAF by identifying biomarkers that predict progression to MSA or a Lewy body disorder and (II) to define the natural history of MSA, identify factors that predict the rate of progression, and other markers useful in the differential diagnosis.
Methods: The study is currently active. Patients with PAF and MSA are being enrolled and followed with standardized neurological, autonomic, and biomarker assessment at international clinical sites across 4 continents. Patients with rapid eye movement sleep behavior disorder (RBD), currently also considered a pre-motor synucleinopathy, are also being enrolled. Patients with Parkinson disease with and without orthostatic hypotension are included as well as a comparison group. Electronic case report forms are available and data capture occurs via an internet-based platform (RedCap). The NHSS relies on the partnership between federal agencies (National Institutes of Health), patients advocacy groups (MSA Coalition), industry, and academic institutions.
Conclusions: This multi-center approach will assemble a large international cohort. The project serves as the backbone for clinical data collection and as a platform for additional biomarker and epidemiological sub-studies. This ambitious strategy is intended to facilitate further funding and unite the field by bringing together expert clinical researchers focused on synucleinopathies at different sites. Our ultimate goal is to accelerate the path towards finding disease-modifying therapeutics.

Poster 28

Baseline supine norepinephrine levels predict the improvement in orthostatic symptoms after atomoxetine in patients with neurogenic orthostatic hypotension

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We previously reported that the norepinephrine transporter inhibitor, atomoxetine, improves upright blood pressure and pre-syncopal

symptoms as measured by the orthostatic hypotension symptom assessment (OHSA) in patients with neurogenic orthostatic hypotension (nOH). The purpose of this study was to determine the predictors of the improvement in orthostatic symptoms with atomoxetine. Our sample size consisted of 101 autonomic failure patients with nOH who participated in clinical trials (NCT00223691, NCT1316666) conducted in two national referral centers for autonomic disorders (Vanderbilt Autonomic Dysfunction Center and NYU Langone Medical Center Dysautonomia Center). The analysis was performed in patients with symptomatic nOH defined as item-1 OHSA (lightheadedness) equal or more than four points. Seated blood pressure was measured in three occasions before and 60 min after receiving 18 mg of atomoxetine. Standing blood pressure at 1, 3, 5 and 10 min and OHSA questionnaire was collected before and after the atomoxetine dose. Multiple linear regression was used to test for overall linear relations between the dependent variable (OHSA score after atomoxetine) and independent variables (baseline OHSA score, age, diagnosis, baseline supine norepinephrine levels) and to assess the significance of these relations after adjustments for each covariate.
Results: 47 patients (47 %) met criteria for symptomatic nOH. The average age at the time of evaluation was 67 ± 9 years, 47 % were males. 55 % were diagnosed as pure autonomic failure, 30 % as multiple system atrophy, 11 % as Parkinson disease and 4 % were patients with nOH of unknown etiology. Adjusted R^2 for this model was 0.3, only supine norepinephrine levels ($P = 0.047$) accurately predicted orthostatic symptoms following atomoxetine after adjusting for baseline OHSA, age and specific diagnosis.
Conclusions: Supine baseline norepinephrine levels predict the improvement in symptoms produced by atomoxetine in patients with symptomatic nOH.

Poster 29

Elevated cerebrospinal fluid ratios of cysteinyl-dopamine/3,4-dihydroxyphenylacetic acid in parkinsonian synucleinopathies

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Objectives: There is intense interest in identifying cerebrospinal fluid (CSF) biomarkers of Parkinson's disease (PD), for early diagnosis and to track effects of putative treatments. Nigrostriatal dopamine depletion characterizes PD. Predictably, CSF levels of 3,4-dihydroxyphenylacetic acid (DOPAC), the main neuronal metabolite of dopamine, are decreased in PD, even in patients with recent onset of the movement disorder. Whether low CSF DOPAC is associated specifically with parkinsonism has been unclear. In the neuronal cytoplasm dopamine undergoes not only enzymatic oxidation to form DOPAC but also spontaneous oxidation to form 5-*S*-cysteinyl-dopamine (Cys-DA). Theoretically, oxidative stress or decreased activity of aldehyde dehydrogenase in the residual nigrostriatal dopaminergic neurons would increase CSF Cys-DA levels with respect to DOPAC levels. PD, parkinsonian multiple system atrophy (MSA-P), and pure autonomic failure (PAF) are synucleinopathies; however, PAF does not entail parkinsonism. We examined whether an elevated Cys-DA/DOPAC ratio provides a specific biomarker of parkinsonism in synucleinopathy patients.
Methods: CSF catechols were assayed in PD ($n = 24$), MSA-P ($n = 32$), PAF ($n = 18$), and control subjects ($n = 32$).
Results: Compared to controls, CSF DOPAC was decreased in PD and MSA-P ($p < 0.0001$ each). In both diseases Cys-DA/DOPAC ratios averaged more than twice control (0.14 ± 0.02 and 0.13 ± 0.02 vs. 0.05 ± 0.01, $p < 0.0001$ each), whereas in PAF the mean Cys-DA/DOPAC ratio was normal (0.05 ± 0.01).
Conclusions: CSF Cys-DA/DOPAC ratios are substantially increased in PD and MSA-P and are normal in PAF. In synucleinopathies an elevated CSF Cys-DA/DOPAC ratio seems to provide a specific biomarker of parkinsonism.

Poster 30

Biomarkers of catecholaminergic neurodegeneration predict Parkinson's disease. Results at 3 years of follow-up in the NINDS PDRisk study

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Objectives: The intramural NINDS PDRisk study is testing whether in individuals with multiple risk factors for Parkinson's disease (PD), neuroimaging or neurochemical biomarkers of catecholamine deficiency predict outcome after 7.5 years of follow-up (5 1.5-year intervals). We report the results of data analysis after the first phase (3 follow-up years).
Methods: In this prospective cohort study, participants entered information about family history of PD, olfactory dysfunction, dream enactment behavior, and orthostatic hypotension at a protocol-specific website. After confirmation of at least 3 risk factors at the NIH Clinical Center, subjects underwent inpatient testing of central and cardiac catecholaminergic innervation, by putamen ^{18}F-DOPA and myocardial ^{18}F-dopamine positron emission tomographic scanning and by cerebrospinal fluid (CSF) DOPA and 3,4-dihydroxyphenylacetic acid (DOPAC) levels. Subjects were then followed at about 18-month intervals. The primary endpoint was a diagnosis of PD.
Results: Of 3176 individuals providing risk factor data, 388 had at least 3 risk factors, 31 underwent inpatient biomarkers testing, and 22 were followed for at least 3 years. Of the 22, 4 developed PD. Low values for septal myocardial ^{18}F-dopamine-derived radioactivity, the posterior/anterior ratio of putamen ^{18}F-DOPA-derived radioactivity, CSF DOPA, and CSF DOPAC each predicted outcome ($p = 0.0097, 0.0005, 0.0028, 0.0309$ by Chi-squared). The positive predictive value of having 3 or more positive biomarkers was 100 %, and the negative predictive value of having 2 or fewer positive biomarkers was also 100 %.
Conclusions: In people at risk for PD, biomarkers of central or cardiac catecholamine deficiency predict PD at 3 years of follow-up.

Poster 31

Homeostasis, biocybernetics, and autonomic neuroscience

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We describe here concepts presented during the last 150 years that have contributed to our current understanding of the mechanisms of feedback-regulated control—i.e., the biocybernetics—of the autonomic nervous system. Homeostasis and negative feedback are fundamental in autonomic neuroscience. The notion of comparator "homeostats" enables definitions of stress, allostasis, and allostatic load; is useful for predicting effects of manipulations of monitored variables in the setting of multiple effectors and effector sharing; and can help understand the progression of catecholaminergic neurodegeneration in autonomic synucleinopathies. There is no evidence, however, for the existence of physiological homeostats. Ashby's Good Regulator theorem and law of requisite variety give meaning to the homeostat in biocybernetic terms as an emergent property of complex physiological systems. One can conceptualize that hierarchies of input–output relationships function as good regulators determining levels of internal variables and act as if there were homeostatic comparators. The brain's good regulators develop in line with Nikolic's "practopoiesis," based on plasticity mechanisms at a lower level creating by their operations a neural network anatomy at a higher level. The consequences of models with vs. without homeostats remain the same in terms of allostatic load and the eventual switch from homeostatic negative feedback loops to destabilizing, pathogenic positive feedback loops. With further technological advances for assessing nodes and relationships in the central autonomic network and more powerful and sophisticated computer methods to model and predict regulation of multiple monitored variables simultaneously by autonomic effectors, homeostats will become unnecessary as theoretical constructs in autonomic neuroscience.

Poster 32

Cytokine abnormalities in young patients with autonomic dysfunction

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The autonomic nervous system regulates several bodily functions such as blood pressure, heart rate, gastrointestinal motility and respiration. Recently there has been increased awareness of the association between the autonomic nervous system and neuroinflammatory pathways. The vagus nerve appears a key component in this pathway controlling the release of splenic cytokines thus dampening serologic evidence and clinical manifestations of inflammation. Conversely, increased cytokine release may indicate the presence of dysfunction of the autonomic nervous system. At our center of dysautonomia, we have performed a retrospective evaluation of cytokine abnormalities in 81 patients (62 female), aged nine to 29 with symptoms of dysautonomia confirmed by head-up tilt test (HUTT). Subsequently, each patient had blood samples sent to an independent laboratory for evaluation of levels of TNF-α, Interleukin 1β, 2, 4, 5, 4, 6, 8, 10, 12, and 13, and Interferon-γ. Cytokine elevations were found in 60 of the 81 patients tested (74 %). There was no consistent pattern that correlated with clinical manifestations or severity of abnormalities on HUTT. To this point, the clinical relevance of such immune abnormalities is unclear but may be an indicator or trigger of autonomic system dysfunction. Moreover, the downstream effect of such elevations may further disrupt normal organ system functions and contribute to patient symptoms. Both the presence and the effect of increased cytokines in patients with autonomic dysfunction are deserving areas of future investigations.

Poster 33

The impact of baroreflex on the dynamic renal vascular mechanical properties and renal circulatory regulation

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Background: Baroreflex and kidney play major roles in regulating arterial pressure. We previously reported that baroreflex activation suppresses sympathetic nerve activity (SNA) and induces diuresis by steepening and shifting the pressure-diuresis curve to the left. We hypothesized that the baroreflex modulates the renal vascular properties which in turn changes the pressure-diuresis curve. Thus we examined the impacts of baroreflex on the renal vascular properties using renal arterial impedance (Z_R).
Method: In 4 anesthetized Sprague–Dawley rats (urethane and α-chloralose), we vascularly isolated bilateral carotid sinuses and controlled carotid sinus pressure (CSP). We measured abdominal aortic pressure near the renal artery (P_A) and flow in the left renal arterial (F_R). We irregularly paced the heart to estimate high precision Z_R while activating the baroreflex at various levels by changing CSP stepwise. We estimated Z_R in the frequency range of 0.12 and 100 Hz by applying Fourier transform.
Result: Baroreflex activation significantly decreased P_A (CSP 60: 102.8 ± 15.5 vs. CSP 160: 70.0 ± 13.7 mmHg, $p < 0.05$), while F_R remained unaltered (4.9 ± 1.0 vs. 4.5 ± 0.9 ml/min, N.S.). Z_R at CSP = 60 was relatively constant below 0.5 Hz and decreased above that frequency. Baroreflex activation (CSP = 160) parallelly shifted Z_R downward (0.1 Hz: 904 ± 290 vs. 664 ± 237 mmHg/ml/sec, $p < 0.05$, and 70 Hz: 165 ± 31 vs. 119 ± 8 mmHg/ml/sec, $p = 0.07$). These results indicated that baroreflex activation decreases renal resistance and increased compliance while its impact on characteristic impedance was unclear.
Conclusion: Baroreflex activation decreased Z_R over the wide frequency range and regulates renal flow. Although this mechanism may greatly contribute to the blood pressure regulation, how those changes in vascular mechanics are translated into the changes in the pressure-diuresis curve remains to be seen.

Poster 34

Identification of open loop transfer function of baroreflex using the power spectral analysis of arterial pressure

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Background: Although the open loop baroreflex transfer function (G) is the gold standard of baroreflex function, the lack of practical methods to identify G makes it difficult to serve as a clinical tool. Control theory indicates that the variability (P_D) added to a feedback system such as the baroreflex system is attenuated to $P_D/(1 + G)$. We repeatedly demonstrated that G of baroreflex approximates a first-order low pass filter with the fixed corner frequency of 0.05 Hz in rat. Thus, we hypothesized that power spectrum density (PSD) of arterial pressure (AP) time series below this frequency is attenuated by baroreflex, thereby the attenuation predicts G.

Methods: We used Wister-Kyoto rats (WKY, n = 9). For the stratification of baroreflex function, we conducted complete sinoaortic denervation (SAD) in three rats and partial SAD (denervation only in right side) in three rats. One week after SAD, we derived PSD from 12-h AP time series (telemetry) over the frequency range of 0.01–0.05 Hz (Baro frequency). At the end experiment, we surgically isolated baroreceptors and measured the G in each rat.
Results: Mean AP did not change, while the lability (standard deviation of AP) increased in partial SAD and SAD groups (sham: 6.8 ± 0.36, partial SAD: 8.74 ± 0.56, SAD: 16.37 ± 0.94 mmHg), suggesting the successful stratification of baroreflex function. The inverse of square root of integrated power spectrum of Baro frequency significantly reduced in partial SAD and SAD groups (sham: 0.29 ± 0.026, partial SAD: 0.22 ± 0.018 SAD: 0.11 ± 0.016 mmHg) and linearly correlated with the reference low frequency gain of G.
Conclusion: Since the corner frequency of G is the fixed value, we can identify the G of baroreflex. PSD of AP time series, considering its unique characteristics of G, allows us to estimate baroreflex function. The proposed framework may facilitate the noninvasive estimation method for baroreflex function.

Poster 35

Left ventricular hypertrophy induced heart failure inhibits the hypothalamic paraventricular nucleus neurotransmission to parasympathetic cardiac vagal neurons of the brainstem

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Heart failure (HF), a leading cause of morbidity and mortality, is associated with autonomic imbalance i.e., high sympathetic and depressed parasympathetic activities to the heart. This study seeks to identify mechanisms responsible for the diminished vagal activity to the heart in HF, and if this provides new targets for intervention. Parasympathetic activity to the heart originates from cardiac vagal neurons (CVNs) in the brainstem, whose activity is dictated by the synaptic activity arising from other regions of the brain, including paraventricular nucleus of the hypothalamus (PVN). Recent work has shown there is a powerful excitatory synaptic pathway to CVNs arising from PVN oxytocin (OXT) neurons. To identify the changes that occur within the brainstem to diminish the CVN activity, left ventricular hypertrophy was elicited in rats by aortic pressure overload using a transaortic constriction (TAC) approach. Selective activation of PVN OXT fibers projecting to CVNs was achieved by co-injecting viral vector expressing cre under OXT promoter (AAV1-OXT-Cre) with floxed ChR2 (AAV1-EF1a-DIO-hChR2). CVNs in the brainstem were identified with a retrograde tracer and studied 4–6 weeks post TAC using patch-clamp electrophysiological recordings in vitro. Cultured Chinese hamster ovary cells co-expressing OXT receptors and Ca^{2+} indicator, R-GECO were used to assess OXT release upon photoactivation of PVN fibers surrounding CVNs. In HF animals the excitatory neurotransmission from PVN OXT neurons to CVNs is diminished, with reduced amplitudes of evoked EPSCs and an absence of paired pulse facilitation. Further, there is also a blunted activation of CHO cells that serve as sniffer cells for the release of oxytocin upon photoactivation of ChR2 expressing PVN OXT fibers. These results indicate reduced PVN release of oxytocin onto CVNs likely contributes to depressed parasympathetic cardiac activity in HF. Future work will test if oxytocin neuron activation can restore CVN activity and blunt cardiovascular dysfunction in HF.

Poster 36

Cardiac autonomic function impairment in concussed adolescents during a sit-to-stand protocol

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Concussive injuries sustained during maturation place adolescent populations at increased risk for prolonged recovery, persistent symptoms, and long-term difficulties in cognitive functioning. A strong need exists to understand underlying neurological processes affected by concussion. Little data exist on neurocardiovascular outcomes in concussed adolescents despite the objectiveness and feasibility of such measures. We tested the hypothesis that cardiac autonomic adjustments to postural stress are impaired in concussed adolescents. Twenty-two adolescents diagnosed with a concussion (CONC; 14 females; 15 ± 2 years; 171 ± 6 cm; 68 ± 15 kg; 18 ± 17 days post-injury) and twenty-two healthy controls (CTRL; 11 females; 14 ± 2 years; 170 ± 9 cm; 67 ± 17 kg) completed a sit-to-stand task. Heart rate (HR), root mean square of successive differences in R–R intervals (RMSSD), mean arterial blood pressure (MABP), and cardiac output (CO) were evaluated during 2 min of sitting and 2 min of standing. Seated HR was higher in CONC versus CTRL (76 ± 8 vs. 71 ± 7 bpm; $p = 0.041$) whereas standing HR was similar between CONC and CTRL (90 ± 12 vs. 86 ± 14 bpm; $p = 0.256$). The standing-induced increase in HR was similar between CONC and CTRL (14 ± 6 vs. 15 ± 2 bpm; $p = 0.426$). Seated RMSSD was lower in CONC compared to CTRL (40 ± 9 vs. 66 ± 19 ms; $p = 0.006$) but was similar between groups in the standing posture (24 ± 13 vs. 32 ± 9 ms; $p = 0.149$). The change in RMSSD between sitting and standing was greater in CTRL compared to CONC (−34 ± 14 vs. −16 ± 10 ms; $p = 0.040$). Similar measures of MABP and CO were measured between CONC and CTRL in the seated and standing postures. Concussed adolescents appear to express impaired cardiac autonomic function at seated rest which limits adjustments to postural stress. Supported by the Children's Health Research Institute (London, Canada).

Poster 37

Programming of neurogenic hypertension in offspring from obese mothers

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We determined the changes in blood pressure, heart rate (HR) and sympathetic nerve activity (SNA) in response to maternal obesity in the offspring and assessed the contribution of leptin and melanocortin signalling in the hypothalamus. Female New Zealand White rabbits were fed a high fat diet (13 %; mHFD) or a control diet (4 %; mCD) during pregnancy and lactation. Offspring received normal diet after weaning. All offspring received a combined cannula (targeting the lateral ventricle; intracerebroventricular (ICV) and ventromedial hypothalamus; VMH) and a renal nerve recording electrode. Experiments were conducted in conscious rabbits and mean arterial pressure (MAP), HR and renal SNA were measured. Rabbits received

increasing doses of αMSH (α-Melanocortin stimulating hormone 1, 3, 10 nmol ICV or 0.3, 1 nmol VMH), SHU9119 (melanocortin receptor antagonist 0.19, 0.38 nmol ICV or 0.02, 0.04 nmol VMH), leptin receptor antagonist (100 μg ICV or 5, 10 μg VMH). Offspring from mHFD fed rabbits exhibited higher MAP (75.4 ± 1.9 mmHg) and Renal SNA (10.1 ± 1.3 nu) than mCD rabbits (70.2 ± 1 mmHg and 6.4 ± 0.6 nu $P < 0.01$, respectively). αMSH injection into the VMH increased MAP (+2.3 ± 1.4 mmHg), HR (+23 ± 6b/min) and RSNA(+6.8 ± 1.5 nu) and injection via ICV also increased MAP (+4.7 ± 1.5 mmHg), HR (+22 ± 6b/min) and RSNA(+5.2 ± 1.4 nu) in mHFD offspring. SHU9119 reduced MAP (−5.4 ± 1.3 mmHg) and RSNA (−0.2 ± 0.2 nu) when given into the VMH and injection via ICV also decreased MAP (−6.2 ± 0.6 mmHg), HR (−10.7 ± 2b/min) and RSNA(-1.6 ± 0.2 nu) in mHFD offspring ($P < 0.05$). Leptin receptor antagonist normalised hypertension in mHFD rabbits when injected into the VMH MAP (−4.8 ± 1.4 mmHg) and injection via ICV also decreased MAP (−2.9 ± 0.4 mmHg), HR (−5.9 ± 2b/min) and RSNA (−2.5 ± 0.2 nu) in mHFD offspring ($P < 0.05$).
Conclusion: Both leptin and α-MSH likely engage the same pressor and sympathoexcitatory pathways in the hypothalamus resulting in obesity-related hypertension. Maternal obesity leads to the programming of leptin and melanocortin receptor sensitivity. These changes appear to be associated with pathways mediating neuronal plasticity.

Poster 38

Imidazoline receptor agonist rilmenidine reverses synergistic pro-oxidant actions of angiotensin II and MsrA deficiency: implications in dysautonomia and hypertension

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We recently reported that mice deficient in the antioxidant enzyme methionine sulfoxide reductase A (MsrA), infused with angiotensin II (Ang II) exhibit exaggerated hypertension, dysautonomia, left ventricular (LV) dysfunction and aortic aneurysms. The aims of this study were to determine if Ang II-induced oxidative stress is enhanced in MsrA−/− mice, and if central administration of the sympathoinhibitory drug rilmenidine (RIL, an imidazoline and alpha-2 receptor agonist) reduces peripheral oxidative stress and its deleterious consequences. Mice were studied at a young age (12–16 wks, n = 3–8/group). Blood pressure (BP), LV function and ascending aorta diameter were measured by telemetry and echocardiography. Superoxide ($O_2^{\cdot}-$) (oxidative stress) was measured in tissue sections (DHE fluorescence) of LV and aorta from C57BL/6 and MsrA−/− mice, either untreated or infused with Ang II (1000 ng/kg/min) for 4 weeks. $O_2^{\cdot}-$ levels in LV and aorta were ~2-fold higher in untreated MsrA−/− vs. C57BL/6 mice ($P < 0.05$). Ang II-induced increases in $O_2^{\cdot}-$ were markedly enhanced in MsrA−/− (>300 %) vs. C57BL/6 (50–70 %) mice ($P < 0.05$). Furthermore, $O_2^{\cdot}-$ levels were positively correlated with sympathetic tone (HR response to receptor blocker propranolol) ($r^2 = 0.76$ for LV, $P < 0.05$). Remarkably, RIL infusion (2.5 mg/kg/day, ICV) during the last two weeks of Ang II infusion normalized tissue $O_2^{\cdot-}$ levels. RIL also markedly decreased BP and BP variability in both genotypes, and reversed LV dysfunction and aorta dilatation in Ang II-infused MsrA−/− mice ($P < 0.05$). We conclude: (1) MsrA−/− mice exhibit basal oxidative stress; (2) Ang II and MsrA deficiency synergistically increase oxidative stress; and (3) Central administration of RIL abolishes LV and vascular oxidative stress and its deleterious consequences in Ang II-infused mice, presumably by inhibiting sympathetic activity. The results identify MsrA and imidazoline receptors as therapeutic targets in dysautonomia and hypertension, and encourage testing of RIL in clinical trials. (HL14388, VA).

Poster 39

Ang-(1-7) improves autonomic function, delays disease progression, and increases lifespan in superoxide dismutase 1 (SOD1) mice with amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive loss of motor neurons leading to paralysis and premature death. Previously, we reported that SOD1 mice exhibit increased sympathetic tone, reduced vagal tone and baroreflex sensitivity, motor dysfunction, and die prematurely at 205 weeks of age *[Auton Neurosci Basic and Clinical 2015, 192:132]*. Angiotensin-(1-7) or Ang-(1-7), a newly identified peptide of the renin-angiotensin system, is known to exert sympathoinhibitory, antioxidant and vasodilatory actions. Therefore, we hypothesize that chronic Ang-(1-7) will improve autonomic function and lifespan in SOD1 mice. Control C57BL6 and SOD1 pups, at 3 weeks of age, were randomly assigned to one of the two subgroups—(i) vehicle (saline)-treated, and (ii) Ang-(1-7)-treated (osmotic minipump, 500 g/kg/day) until death. Blood pressure (BP), heart rate (HR) and locomotor activity were measured by telemetry in separate groups of vehicle and Ang-(1-7)-treated C57BL/6 (n = 4–6) and SOD1 mice (n = 4–7) at 9–10 weeks of age. Compared to vehicle-treated C57BL/6 mice, vehicle-treated SOD1 mice exhibit increased mean BP (104 ± 2 vs. 133 ± 2 mmHg) and HR (560 ± 14 vs. 643 ± 16 bpm) and autonomic dysfunction. Ang-(1-7) markedly reduced sympathetic tone (HR response to propranolol), increased vagal tone (HR response to methylatropine) and baroreflex sensitivity (sequence technique), and normalized BP and HR in SOD1 mice ($P < 0.05$). Notably, Ang-(1-7) increases median survival from 1347 days to 1645 days ($P < 0.0001$) and delays time to paralysis ($P < 0.001$) in SOD1 mice. In summary, our results indicate that (1) autonomic dysfunction at an early age exacerbates disease progression in ALS, and (2) Ang-(1-7) is a potential therapeutic target that restores autonomic function, delays disease progression, and increases lifespan in ALS. (Tarix Phamaceuticals)

Poster 40

Autonomic influence on myocardial repolarisation analysed from T-waves in the ECG

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Introduction: T-wave amplitude (TWA) may be used as an index of the autonomic innervation of the myocardium. We have developed a new robust T-wave delineation algorithm using a wavelet-based method. Using the QT database, we achieved a sensitivity of 99.9 % for the T wave peak and 99.4 % for the T wave end. The present study aimed at analysing the effects of the autonomic nervous system on TWA.

Patients and Methods: Eight healthy men aged 25.3 ± 2.7 years were randomly allocated to one session with infusion of saline and one with infusion of a beta-1-blocker. Metoprolol was given as a priming dose of 5 mg followed by an infusion of 0.025 mg min^{-1} kg^{-1}. Four bolus doses of 0.0025 mg kg^{-1} of atropine were given at 20 min intervals. At baseline and after each atropine bolus, the subjects underwent a 10-min head up tilt to 60°. The ECG was continuously recorded from one precordial lead with a sampling frequency of 1 kHz. Statistical analysis used mixed line-effect linear model and multiple comparisons with the Turkey test.
Results: Setting the baseline value to 1.0, TWA fell to 0.72 during saline infusion after full dose of atropine ($p < 0.005$). During beta-blockade there was an initial, nonsignificant increase in TWA to 1.24 returning to baseline at full atropine dose. TWA after full atropine dose was significantly smaller during saline compared to beta-blockade ($p = 0.035$). In response to tilt, TWA was reduced to 0.71 by full atropine dose during saline ($p = 0.025$) and unchanged during beta-blockade.
Conclusions: The present study shows that blockade of the autonomic activity in the heart has a profound influence on myocardial repolarisation as expressed by T-wave amplitude in the ECG. It is suggested that variations in TWA may be used as a supplement to heart rate variability measures in analysing autonomic innervation of the heart.

Poster 41

Is autonomic dysfunction a possible side effect to vaccination against human papilloma virus?

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Introduction: Vaccination against human papilloma virus (HPV) has a wide-spread use in the long-term prevention of cervical cancer. The vaccinations have been associated with possible, rare side effects involving the autonomic nervous system. We have studied signs and symptoms of autonomic dysfunction as well as measures of autonomic cardiovascular control in a group of patients referred for suspected side effects.
Patients and Methods: Fifty-two consecutively referred patients aged 12– 49 years (median: 24 years) filled out the COMPASS-31 questionnaire reflecting symptoms of autonomic dysfunction. They underwent analysis of heart rate and blood pressure response to active stand, head-up tilt test to 60 degrees (HUT), deep breathing at 0.1 Hz, and the Valsalva maneuver using an expiratory pressure of 40 mmHg. The ECG was sampled continuously from a single precordial lead as was blood pressure by finger photoplethysmography at a rate of 1 kHz.
Results: The COMPASS-score was 28.9–83.3 (mean: 53.9 ± 11.5). 30 % fulfilled the heart rate criteria for postural orthostatic tachycardia syndrome (POTS) during active stand and 40 % during HUT. 5.7 % had inappropriate sinus tachycardia, 18.9 % had reduced heart rate response to deep breathing, and 18.9 % had abnormal Valsalva response as judged by the ratio for heart rate in phase-IV. The patients with postural tachycardia had symptoms compatible with POTS. Patients with POTS differed from those without only with respect to body height and heart rate in the upright position.
Conclusion: Girls and young women referred for possible side effects to HPV-vaccination showed a high frequency of symptoms related to the autonomic dysfunction. We also found a high occurrence of abnormal outcomes in the standard methods used to testing the autonomic control of cardiovascular function. Presently, we do not know how these changes relate to HPV-vaccination, but we are considering a possible autoimmune reaction.

Poster 42

Electrodermal activity during head-up tilt in patients with POTS

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Individuals with POTS represent a complex patient population whose symptoms are often exacerbated by orthostatic stress. At present, heart rate (HR) elevation represents an imperfect biomarker of POTS symptomatology in that pharmacological normalization of HR does little to improve symptoms of POTS. In a previous study of patients with vasovagal syncope (VVS), we demonstrated that electrodermal activity (EDA) increased substantially prior to presyncope and persisted even after BP had normalized. Given this, we tested whether EDA might serve as an alternative biomarker that more readily captures the complex symptomatology of POTS. 44 POTS patients (40 women) aged 13–47 (mean = 27.3, SD = 9.7 years) were evaluated at rest, during HUT before, during and after inflation of MAST pants. An additional 9 patients were tested with HUT alone. EDA was inferred from the low-pass filtered EKG. HR (bpm Mean ± SD) was 83 ± 13 at baseline, 135 ± 13 during HUT, 107 ± 14 during MAST pants inflation and 132 ± 11 during MAST pants deflation. EDA almost never occurred while supine (48/53). Compared to the large EDA surge of syncope, the magnitude of any EDA increase during HUT in POTS was modest and less frequent (80 % VVS vs. 53 % POTS). The likelihood of EDA occurrence was independent of the magnitude of HUT induced tachycardia. In 38/44 patients, MAST pants inflation improved symptoms of lightheadedness, leg weakness and air hunger reported during HUT. In those with EDA during HUT (26/44), MAST pants inflation reduced or eliminated EDA in 18, increased EDA in 3 and had no discernable effect on EDA in 5. Contrary to our original hypothesis, we conclude that EDA is an imperfect biomarker of the severity of the autonomic arousal or of the symptoms experienced by POTS patients either at rest or during orthostatic stress.

Poster 43

Ivabradine: a potential treatment in postural orthostatic tachycardia syndrome (POTS)

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Background: POTS is a form of dysautonomia accompanied by symptoms including excessive tachycardia, syncope, dizziness, fatigue and exercise intolerance. Ivabradine (Corlanor) is a funny channel blocker expressed in the sino-atrial (SA) node, which slows down heart rate (HR). The SHIFT trial, April, 2015 showed the benefit of Ivabradine in reducing HR in chronic heart failure; starting dose 5 mg orally twice daily.
Objective: We will study the role, maximum tolerated dose, and adverse events of Ivabradine in POTS patients with prominent sinus tachycardia.

Methods: We performed a retrospective study of 374 POTS patients referred to our clinic from August 2015 to April 2016. Inclusion criteria included patients with sinus tachycardia, intolerant and/or contraindications to beta-blockers & failed treatment with Clonidine. Holter monitoring was performed in all the patients to record HR. Weekly follow up was advised to monitor the effects of medication and corresponding up-titration.
Results: Out of 374 patients, 325 were female (age = 32.88 ± 11.31), 46 patients were male (age = 30.26 ± 12.50). Total of 30 patients were provided Ivabradine treatment based on the inclusion criteria and Holter monitor with average minimum HR 53.60 ± 8.1 and maximum HR 134.46 ± 23.92, 26 were prescribed 2.5 mg once daily (QD) as starting dose (83.33 %), 4 patients with 5 mg OD (13.33 %) and 2 out of 4 had worsening tachycardia and headache; 1 patient with 7.5 mg QD (3.33 %) had worsening vision changes. 10 patients tolerated maximum dose of 2.5 mg QD (33.33 %), 9 patients with 5 mg QD (30 %), 5 patients with 10 mg QD (16.66 %), 2 patients with 7.5 mg OD (6.66 %) and 2 patients with 15 mg OD (6.66 %). All reported significant improvement in sinus tachycardia with median 2.5 mg QD starting dose and corresponding tolerated dose (100 %). Adverse reactions reported—scalding tongue (1 %), itching and burning (1 %), bradycardia (1 %), fuzzy vision and increased sensitivity to bright light (2 %).
Conclusions: First time, we studied the use of Ivabradine in POTS patients and concluded that it is safe to use with median starting dose of 2.5 mg QD with gradual up-titration, depending on the clinical course.

Poster 44

Nutcracker syndrome of left renal vein in postural orthostatic tachycardia syndrome (POTS)

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Background: POTS is a form of dysautonomia characterized by dizziness, syncope, palpitation, abdominal pain, nausea/vomiting, and chest pain. Nutcracker syndrome of the renal vein is the compression of left renal vein between aorta and superior mesenteric artery (SMA) causing symptoms including minimal hematuria, pelvic congestion, varicocele and varicose veins due to the disturbance of blood inflow from the inferior vena cava to the left renal vein.
Objective: We aim to study Nutcracker syndrome of the renal vein as a possible cause of pelvic congestion and leg pains in POTS patients.
Method: We did a retrospective study of 374 POTS patients referred to our clinic from June 2014 to April 2016. A celiac artery doppler, lower extremity venous doppler, CT angiogram of abdomen with and without contrast was done on the patients suffering from chronic lower abdominal pain, nausea, vomiting, bloating and leg pain & cramps.
Results: Out of 374 patients, 325 patients are female (age = 32.88 ± 11.31) and 46 patients are males (age = 30.26 ± 12.50). Our findings showed that 72 patients out of 374 patients are suffering from lower abdominal pain and leg pain & cramps (19.25 %) and audible celiac artery bruit in 7 patients. Celiac artery Doppler was done to check flow velocities of celiac artery, SMA, hepatic and splenic artery which showed 55 out of 374 had increased celiac artery velocity (14.7 %, Velocity = 327 ± 12.11). CT angiogram abdomen showed average 50 ± 13.56 % stenosis of celiac axis in 33 patients along with compression and narrowing of left renal vein by aorta and SMA diagnosed with nutcracker syndrome of renal vein. (8.82 %). 11 patients out of 33 patients showed gonadal venous congestion (33.33 %).
Conclusion: Our study is the first to show that Nutcracker syndrome of left renal vein can be a possible pathology associated with POTS and needs to be studied further.

Poster 45

A case report on a novel mutation in Ehlers-Danlos Syndrome (EDS) and postural orthostatic tachycardia syndrome (POTS)

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Background: POTS is a condition caused by a heterogeneous group of disorders. EDS is a group of inherited abnormalities of connective tissue characterized by skin hyperextensibility, joint hypermobility and evidence of pelvic pooling leading to dysautonomia in POTS. One study showed 18 % prevalence of EDS in POTS. In 90 % patients diagnosed with classical EDS clinically, there is mutation in collagen gene COL5A1 and COL5A2 which is inherited autosomal dominantly and is confirmed with whole exome sequencing. Previous studies showed that mutations in five CLC genes underlie human inherited disease, with symptoms of myotonia, renal salt loss, deafness, urinary protein loss, kidney stones, osteopetrosis, blindness, and lysosomal storage disease.
Objective: We present a case report on a patient with a unique mutation with possible role in EDS and POTS pathogenesis.
Methods and Results: A 26-year-old female pre-diagnosed clinically with EDS (Beighton score-7) presented to our cardiology clinic with dizziness, syncope, tachycardia, palpitations, shortness of breath and chest pain. Tilt table test showed rise of 43 beats per minute in heart rate within 10 min of tilt confirmed POTS. Whole Exome sequencing study was done which showed novel mutation in one copy of voltage gated chloride channel gene, CLCN 4 on chromosome X (heterogeneous, De novo inherited form) with variant p.q489K.
Conclusion: For the first time we report a case of novel mutation in CLCN 4 gene as a possible disease causing variant due to its role in epilepsy, dysautonomia and joint laxity. It correlates with previous studies which showed abundant presence of CLCN 4 channels in endothelial cells and its role in membrane depolarization and activation of chloride current after perturbation of cell volume in heart, brain and skeletal muscle by means of Cl−/H + anti porter activity.

Poster 46

A case study on the usefulness of autonomic test screening in Lyme disease

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Background: Postural Orthostatic Tachycardia Syndrome (POTS) is an autonomic dysfunction, known to be associated with other comorbidities and is estimated to impact between 1,000,000 to 3,000,000 American and millions more worldwide. Each year approximately 30,000 Lyme disease cases are reported in the U.S.A. Previous studies showed POTS is a component of "Post Lyme Disease Syndrome" which is characterized by fatigue, joint pain, muscle ache, brain fog, orthostatic palpitations, near-syncope and could lead to complications like heart block if left undiagnosed and untreated.

Objective: We present a case study on the usefulness of Autonomic Nervous System test (WRMed) & Tilt table test as a screening test in patients with Lyme disease.
Methods: We performed a retrospective study of 400 patients referred to our clinic from June 2014 to April 2016. Out of 400, 58 cases were pre-diagnosed with Lyme disease. Tilt table test and ANSAR was performed in all 58 cases.
Results: Out of 58 patients, 42 were females (age = 30.22 ± 12.02) and 16 were males (age = 28 ± 14.0). Clinical results showed patients suffering from orthostatic palpitations (46 %), fatigue (40 %), brain fog (20 %), near-syncope (8 %). Tilt table test result showed 26 cases out of those 58 patients had increase in 30 beats per minute (bpm) within 10 min of tilt (44.82 %), 24 patients showed 15-30 bpm rise within 10 min of tilt (41.37 %) and 8 patients showed rise of <15 bpm within 10 min of tilt (13.79 %). Autonomic Nervous System Testing showed abnormal results of autonomic control of heart in 20 cases (34.48 %). All patients showed improvement with employed treatment.
Conclusion: Tilt table test and Autonomic Nervous System testing is definitely useful for early screening in patients suffering from Lyme disease and may help to avoid Post Lyme disease syndrome & later complications like heart block.

Poster 47

Therapeutic trial of Midodrine in non-postural orthostatic tachycardia syndrome (POTS) patients with orthostatic intolerance

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Background: POTS is a form of orthostatic intolerance characterized by symptoms of palpitations, dizziness, chest pain, dyspnea, and syncope. Midodrine (also known as ProAmatine) is an antihypotensive medication. Its mechanism of action involves acting as an alpha-1 receptor agonist producing an increase in vascular tone and elevation of blood pressure. Midodrine has a fair response rate in POTS.
Objective: We aim to study the potential role of Midodrine in non-POTS patients and also its tolerated maximum dose and adverse effects.
Methods: We performed a retrospective study of 220 patients referred to our clinic from June 2014 to April 2016. Inclusion criteria included patients with orthostatic intolerance symptoms and intermediate tilt table test results (15–30 beats per minute within 10 min of tilt). Weekly follow up was advised to monitor the effects of medication and respective up titration.
Results: Out of 220 patients, 198 were females (age = 32 + 12.01) and 22 males (age = 29 + 13.45). Total of 43 patients were given Midodrine based on the inclusion criteria and average tilt table test result between 15–30 beats per minute at 10 min of tilt. 7 were prescribed 1.25 mg once daily (QD) as starting dose (16.27 %), 10 patients with 2.5 mg QD (10 %) and 7 patients with 2.5 mg twice daily (16.27 %) had improvement of their symptoms. 9 patients with 2.5 mg QD (20.93 %) did not respond to treatment initially but when titrated up to 5 mg QD, improved significantly. 40 patients had significant improvement of dizziness and palpitation with median starting dose of 2.5 mg QD and corresponding tolerated dose (93.02 %). Reported adverse effects like bradycardia (1 %), nausea and fatigue (1 %), tingling sensation (1 %).
Conclusions: We showed that therapeutic trial of Midodrine given in patients with intermediate tilt table results showed significant improvement in dizziness and palpitation and tolerated gradual uptitration.

Poster 48

Heart rate dynamics in postural orthostatic tachycardia syndrome

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Introduction: Heart rate variability (HRV) parameters, especially the newer non linear ones are not studied thoroughly in POTS. We report the heart rate dynamics in cases of postural orthostatic tachycardia syndrome (POTS).
Materials and methods: 3 cases of syncope were evaluated and diagnosed as POTS on tilt table testing. They met the criteria i.e. increase in heart rate of 30 beats per minute and/or more than 120 beats on tilt table testing within 10 min of tilt without a fall in blood pressure. ECG was taken at rest and during tilt. The change in HRV parameters i.e. both linear and non linear exactly at the time of tachycardia onset was noted.
Results: Among linear frequency domain measures LF, total power, LF/HF ratio was increased during tachycardia onset. Among time domain measures SDNN showed significant increase as did PNN50. Non linear measures were also higher during the tachycardia phase.
Conclusion: There is a sympathetic predominance in cardiac control during tilt especially during the tachycardia phase in POTS. We need to conduct detailed analysis of HRV with more POTS patients and with different types of POTS patients in future.

Poster 49

Quantitative assessment of autonomic symptom burden in postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) commonly presents with a wide array of symptoms referable to autonomic dysregulation, including, but not limited to those associated with postural change. Given that laboratory measures often do not correlate with the degree of clinical impairment, additional standardized assessments are needed to fully ascertain disease burden. We utilized a battery of questionnaire-based tools and standardized physiology assessment to evaluate the severity of autonomic dysfunction among clinically defined POTS patients and healthy controls. POTS diagnosis was based on clinical criteria, mimics were excluded; heart rate increment (HRI) with 10-min head-up tilt served as diagnostic criterion and a measure of amplitude of orthostatic tachycardia. Autonomic symptoms were assessed using the 31-item Composite Autonomic Symptom Scale (COMPASS-31); fatigue (FSS) and mood (GAD and PHQ) were also assessed. Differences in symptom burden and clinical features were compared between groups. We studied 32 POTS patients and 35 age/sex-matched controls. Among POTS patients, HRI was higher than controls ($p < 0.0001$; mean 42 bpm, range 30-63 vs 21, range 3-35). Total COMPASS-31 scores were significantly higher in POTS than controls ($p < 0.0001$; mean, SD: 48.7, 16.8 vs 9.3, 7.4), as were all domain scores (orthostatic, secretomotor, gastrointestinal, bladder, pupillomotor). Fatigue and mood scores were higher in POTS vs NH ($p > 0.001$); fatigue severity >4 in 94 vs 6 %, GAD-7 >9 in 28 vs 0 %, and PHQ-9 >9 in 53 vs 0 %. Autonomic symptoms in POTS patients were greater than controls as was

expected; importantly, the spectrum of symptoms was not limited to those referable to orthostatic challenge. While the symptoms assessed by these questionnaires are not specific to POTS, their severity and distribution comprise a major contribution to symptom burden, and additional validation of quantitative assessment tools is needed to best understand disease burden and follow treatment response.

Poster 50

Biofeedback intervention in pediatric patients with postural orthostatic tachycardia syndrome (POTS)

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While many studies have evaluated the impact of biofeedback on patients with chronic pain, no studies have been identified specifically evaluating the impact of biofeedback on adolescent patients with postural orthostatic tachycardia syndrome (POTS). Many patients with POTS report significant chronic pain and treatment strategies developed for chronic pain may be helpful in this population. Therefore, the objective of this two-part study was to determine whether biofeedback would be an effective treatment component for adolescent patients with POTS. For the first study, 38 adolescents (ages 12–21) diagnosed with POTS participated in biofeedback as part of the three week interdisciplinary Mayo Clinic Pediatric Pain Rehabilitation Program. In the second study, 164 adolescent patients diagnosed with POTS and 227 adolescent patients with a chronic pain diagnosis without POTS participated in the biofeedback intervention. The biofeedback intervention included three individual sessions measuring surface electromyography (sEMG) and respiratory rate and three group sessions measuring heart rate variability (HRV) and skin conductance. Shoulder tension and respiratory data was collected during the initial and final individual sessions. To measure impact of relaxation skills on function, patients were asked to rate their "ability to use breathing/relaxation skills to improve daily functioning." Patients in the first study showed a significant reduction in respiratory rates ($p < 0.0001$) and EMG surface readings ($p < 0.001$) following biofeedback treatment. Patients also rated their ability to incorporate relaxation principles into activities of daily living significantly higher ($p < 0.0001$) at discharge than admission. In the second study, both POTS and chronic pain patients demonstrated rapid initial breathing, but patients in the POTS group showed significant improvements in their breathing rates ($p < 0.001$) following biofeedback treatment. Results indicate that adolescent patients with POTS may benefit from traditional biofeedback sessions to learn improved physiological control while increasing confidence in their ability to use these strategies while engaging in functional activities.

Poster 51

Vagal dysfunction in patients with neuropathic POTS

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Introduction: Clinical and neurophysiological differences between neuropathic and non-neuropathic postural tachycardia syndrome (POTS) are not fully elucidated. Neuropathic POTS (~30 %) may respond differently to drug therapy. Therefore, it is important to characterize vagal and sympathetic control to optimize treatment in these patients.
Methods: We studied ten healthy controls and twelve POTS patients. Patients fulfill the classical criteria of POTS, but had normal plasma catecholamine levels during orthostatic challenge. We assessed hemodynamics and raw (rMSNA) and integrated neural activity (iMSNA) during autonomic function tests, heart rate and blood pressure variability, baroreflex sensitivity (BRS), and blood volume. In order to understand the vagal/sympathetic control we dissect the response of Valsalva maneuver (VM) in early phase (VM2e) and late phase (VM2 l).
Results: During standing, POTS increased HR 43 ± 3 bpm. Patients had normal plasma volume but reduced red blood cell volume (1.29 L vs. predicted 1.58 L, $p = 0.02$). During VM2e, systolic blood pressure (BP) dropped −31 ± 5 in POTS and −14 ± 4 mmHg in controls ($p = 0.01$), and overshoot of BP in VM4 was comparable. Vagal indices of HR variability, HF_{RRI} (430 ± 130 vs.1680 ± 900, $p = 0.04$), PN50 % and RMSSD were lower in POTS. LF_{RRI} to HF_{RRI} ratio tended to be higher in POTS. BRSseq_up was lower in patients compared to controls (14.5 ± 2 vs. 26.4 ± 6, $p = 0.057$), but the BRSseq_down was comparable. Patients showed a significant decrease in their vagal BRS as extrapolated from VM2e ($p = 0.04$), but not from the VM3-4 ($p = 0.35$). iMSNA was lower at rest in patients: 12 ± 1.5 vs. 20 ± 2 burst/min, $p = 0.004$, but response to tilt was comparable. rMSNA spike analysis showed compromised responses in POTS during VM2e, but not during VM2 l as compared to controls.
Conclusion: Patients with neuropathic POTS showed low resting sympathetic activity and compromised cardio-vagal control expressed with exaggerated hypotensive response during VM2e.

Poster 52

Chronic intravenous hydration as a treatment for adults with refractory postural orthostatic tachycardia syndrome

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Background: It remains controversial whether chronic use of intravenous fluid (IVF) hydration should have a role in the management of patients with orthostatic intolerance (OI). Although there is not a clear mechanism to explain why occasional IV hydration should produce lasting effects in such patients there are anecdotal reports of benefit and a recent series of 39 adolescents and young adults reported benefit in 79 %.
Methods: A retrospective review of patients with POTS treated with chronic IV hydration at single center identified 12 patients.
Results: All patients were female. The mean age was 34.8 years (range 15–49). Despite treatment with oral hydration, salt and several medications each remained symptomatic with limited quality of life (QOL) and interruptions of daily activities such as work or school. IVF was provided as 1 L of normal saline given 1–3 days per week. All patients had a port and received treatments through home health. 83 % (10/12) improved with IVF. Improvement consisted of increased ability to perform daily activities and self-reported QOL. 3 patients had substantial improvements consisting of return to work or school. In addition to symptoms of OI, most patients also noted improvements in GI symptoms and pain. There was one complication, consisting of a port infection in 1 patient.

Conclusions: In this retrospective assessment of chronic IVF therapy for POTS, 83 % experienced benefit. This was marked in 3 patients, leading to significant improvements in daily functioning such as return to work or school. Certainly the response to IVF could represent a placebo response, but these patients had all been treated with numerous other therapies without similar degrees of improvement. Chronic IVF appears to be well-tolerated, but not without risk as a port infection occurred in 8 % of patients. IVF warrants further study, ideally in a prospective, blinded fashion.

Poster 53

"Which came first–the chicken or the egg?" Vitamin D deficiency in POTS patients

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Following a large cohort of patients with postural orthostatic tachycardia syndrome, we measured vitamin D levels (25-OH-Vitamine-D) in the northern winter month. Measurement of vitamin D in winter month is the suggested time of collecting samples for valid results and not being disturbed by longer sun periods such as summer holidays. Further rat studies could show that a vitamin D deficit can lead to significantly higher norepinephrine levels in the body of the rat (Baski et al. 1986). Other studies (Antiel RM et al. 2011) showed that low iron levels and hypovitaminosis D is significantly higher in adolescents suffering from chronic fatigue or orthostatic intolerance. One single case of a POTS patient is reported where symptoms are milder when lifting up the vitamin D level (Chaudhari SA et al. 2012). We started measuring vitamin D levels in newly diagnosed POTS patients. All patients (total of 16, 10 women, 6 men, average age of 28 years) had vitamin D levels under the reference range (lower than 30 ng/ml), half of patients had extremely low levels in vitamin D (lower than 10 ng/ml). None of our patients had a relevant sun exposure in advance such as a sunny holiday or regularly visiting solariums. The aim which has to be followed in further investigations and greater studies is in which way the low vitamin D levels are a result of having a POTS and therefore not get sun-exposured as healthy persons do—or is the low level of vitamin D altering the noradrenergic responsiveness in humans such as in vitro studies suggest.

Poster 54

The diagnostic experience in postural tachycardia syndrome: insights from a cross-sectional community-based survey

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Introduction: Postural tachycardia syndrome (POTS) can be a disabling syndrome characterized by an excessive heart rate increase $\geq$30 bpm upon standing without a decrease in blood pressure. While cardiologists and cardiac electrophysiologists often see POTS patients due to their marked heart rate abnormalities, there are not good data on which specialties most commonly make the diagnosis of POTS. Further, many patients report frustration about a lack of physician-awareness about POTS, and resultant delays in diagnosis and treatment. We report on a large community-based cross-sectional study of POTS patients that addresses their diagnostic journey.
Methods: The "Diagnosis and Impact of POTS" is a structured, self-administered, web-based survey approved by the Vanderbilt University IRB. Between July–October 2015, 3030 patients with a physician diagnosis of POTS completed the survey.
Results: A cardiologist or a cardiac electrophysiologist diagnosed most POTS patients (65 %). POTS patients saw on average 7 physicians (median = 5) for POTS-related symptoms prior to diagnosis, with 23 % reporting that they saw $\geq$10 physicians before diagnosis, and 76 % reporting initial misdiagnosis. A psychiatric diagnosis was given to 77 % of POTS patients pre-POTS diagnosis, versus 39 % post-POTS diagnosis. 30 % of patients report currently receiving care for a psychological condition. Patients report a mean diagnostic delay of 1602 days, but this has decreased over time (1995–99, 4149 days; 2000–04, 2819 days; 2005–2009, 1406 days; 2010–2015, 403 days).
Conclusions: POTS patients often experience long diagnostic delays, lack of physician awareness of POTS, and over-diagnosis with psychiatric illness, before ultimately being diagnosed by a cardiologist or electrophysiologist. Medical awareness of POTS seems to be increasing over time, with a marked decreased in diagnostic delays over the last 20 years. Increased physician education efforts are needed to further reduce diagnostic delays and improve diagnostic accuracy.

Poster 55

Carbidopa fails to decrease urinary sodium excretion or improve orthostatic tachycardia in postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) is characterized by an excessive increase in heart rate (HR) when standing (>30 beats/min), chronic orthostatic symptoms, and no orthostatic hypotension. Patients frequently have low blood volume. Based on multiple reports of renal dopamine's (DA) natriuretic effect, we conducted a randomized, placebo-controlled crossover study with carbidopa. We proposed that inhibition of renal DA synthesis by carbidopa would decrease urinary Na^+ and improve orthostatic tachycardia and symptoms in POTS. Subjects included 8 patients with POTS (mean $\pm$ SD age 33 $\pm$ 10 years, BMI 23.1 $\pm$ 3.2 kg/m^2) and 15 healthy controls (HC; 33 $\pm$ 11 years, BMI 24.0 $\pm$ 2.4 kg/m^2, 1 male and 1 African-American). Carbidopa 200 mg or placebo was administered every 6 h for 5 doses. Urine was collected over 24 h before (BSL), during and after dosing. Supine and upright blood pressure, HR and symptoms were measured 2 h after the final dose. Carbidopa significantly increased 24 h excretion of L-3,4-dihydroxyphenylalanine (DOPA) in HC (19 $\pm$ 8 at BSL vs. 353 $\pm$ 244 μg, P = 0.001) and POTS (23 $\pm$ 15 vs. 442 $\pm$ 207 μg, P = 0.012) and significantly decreased 24 h excretion of DA in HC (185 $\pm$ 45 vs. 43 $\pm$ 20 μg, P = 0.001) and POTS (222 $\pm$ 51 vs. 47 $\pm$ 19 μg, P = 0.012). Despite these changes, carbidopa did not modify urinary Na^+ excretion in HC (184 $\pm$ 48 at BSL vs. 163 $\pm$ 46 mEq, P = 0.331) or POTS (173 $\pm$ 29 vs. 179 $\pm$ 34 mEq, P = 0.575). The supinestanding HR increase was 44 $\pm$ 3 beats/min after placebo and 44 $\pm$ 5 beats/min after carbidopa (P = 0.880) in patients with POTS. Upright symptom score was not improved by carbidopa (P = 0.913).

In another study, we monitored urinary DA in 14 patients with POTS and 13 HC, with similar demographics, as they consumed a low salt (10 mEq Na^+/day) or high salt diet (300 mEq Na^+/day) for 6 days, at least 1 month apart. Neither increases nor decreases in urinary Na^+ were accompanied by changes in urinary DA in patients or HC. Our findings question the physiological relevance of renal DA in natriuresis. Contrary to our hypothesis, carbidopa did not decrease Na^+ excretion and did not provide any improvement in patients with POTS.

POSTER SESSION II

Poster 56

Exaggerated pressor and sympathetic responses to short-duration static handgrip in coronary artery disease patients: effect of six-months of cardiac rehabilitation

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This study tested the hypotheses that: (1) Coronary artery disease (CAD) patients exhibit exaggerated pressor and sympathetic responses to short-duration static handgrip (SHG) exercise compared to older, healthy individuals; and (2) Six-months of exercise-based cardiac rehabilitation (CR) would normalize responses to levels observed in older, healthy individuals. Twenty CAD patients with preserved left ventricular function (4 women; 61 ± 8 yrs, 172 ± 9 cm, 86 ± 12 kg) were studied prior-to and following six-months of exercise-based CR. Twenty-two healthy, similarly-aged controls were also studied (CTRL: 7 women; 62 ± 10 yrs, 170 ± 8 cm, 75 ± 14 kg). Heart rate (HR; Electrocardiogram), mean arterial pressure (MAP; Finometer), and muscle sympathetic nerve activity (MSNA; Microneurography) were measured at baseline (30 s) and during the last half of a 20 s SHG contraction at 40 % maximal voluntary contraction. SHG was repeated four times, and an average of the four responses was calculated. Cardiac output (CO) was determined using the Finometer Modelflow algorithm and total peripheral resistance (TPR) was calculated. Prior-to CR, MAP increased in response to SHG in CAD (Δ7 ± 4 mmHg; $P < 0.001$) and CTRL (Δ5 ± 3 mmHg; $P < 0.001$), but increases were greater in CAD ($P = 0.02$). HR increased similarly in both groups (both $P < 0.001$), whereas CO increased in CTRL ($P < 0.001$), but not in CAD ($P = 0.11$). TPR increased in CAD ($P < 0.01$), but not in CTRL ($P = 0.93$). Finally, MSNA burst frequency increased in response to SHG in CAD (Δ12 ± 7 bursts/min; $P < 0.001$), but not in CTRL (Δ2 ± 7 bursts/min; $P = 0.27$), such that the response was greater in CAD ($P < 0.001$). Following CR, MAP (Δ7 ± 4 to Δ5 ± 3 mmHg; $P = 0.02$) and MSNA burst frequency (Δ12 ± 7 to Δ3 ± 5 bursts/min; $P < 0.001$) responses were reduced in CAD patients, such that no differences were observed between CAD and CTRL (both $P > 0.05$) following CR. In conclusion, six-months of exercise-based CR normalizes the exaggerated pressor and sympathetic responses to short-duration SHG exercise observed in CAD patients. Funded by CIHR.

Poster 57

Features of the autonomic circulatory control in patients with arterial hypertension depending on concomitant migraine

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Migraine (MG) in patients with arterial hypertension (AH) increases the risk cardiovascular complications that may be associated with circulatory regulation peculiar properties.
Aim: We studied the autonomic regulation features in patients with arterial hypertension depending on the presence of migraine.
Patients and Method: The study included patients with hypertension without target organ damage, aged 35 ± 10y: AH without MG (AH-MG), n = 38 and AH with MG (MG + AH), n = 27. Control groups: healthy volunteers (AH-MG), n = 78 and MG patients without AH (MG-AH), n = 76. All groups were matched for age and sex. All patients underwent Valsalva maneuver (VM) with assessment of Valsalva index (VI) and the dynamics of mean blood pressure (BP) at the end second phase, deep breathing (DB), handgrip (HG) and tilt-test, forearm vessels cold vasoconstriction (CV) and arterial baroreflex (BRS). Apparatus: Monitor Finometer-pro and occlusion plethysmograph.
Results: We found that the diastolic BP increased more pronouncedly in AH-MG (8.1 ± 4.7 mmHg) and AH + MG (8.3 ± 6.4 mmHg) patients compared to the AH-MG group (4.2 ± 6.4 mmHg), $p < 0.005$. BRS tended to decrease in AH-MG (10.2 ± 5.7, $p = 0.059$) and was lower in AH + MG (9.9 ± 5.6 ms/mmHg, $p < 0.05$) compared to the -AH-MG group (13.1 ± 8.2 ms/mmHg). AH-MG patients compared to AH + MG group had lower CV (32.7 ± 17.1 vs. 50.4 ± 17.3 %, $p < 0.001$), HG (15.8 ± 5.1 vs. 20.9 ± 6.8 mmHg, $p < 0.005$) and mean BP dynamics during MV (3.2 ± 7.4 vs. 8.1 ± 11.3 mmHg, $p < 0.005$). Three latter indicators did not differ significantly between MG-AH and AH + MG groups, with 49.7 ± 14.7 %, 20.8 ± 6.4 mmHg and 13.4 ± 14.7 mmHg, respectively. No differences of IV and DB between groups were identified.
Conclusion: Autonomic regulation in patients with hypertension is characterized by the BRS reduction and significant orthostatic diastolic hypertension. Concomitant migraine leads to an additional increase of vasomotor reactivity, which seems to be a general consequence of migraine regardless of hypertension.
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Poster 58

Relationship between cardiovagal control and diastolic blood pressure in adult Native and Mexican Americans with a history of alcohol use disorders

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Epidemiological studies and results of several meta-analyses have shown that heavy alcohol consumption is associated with an increased

risk of cardiovascular disease (CVD). We recently reported the presence of several CVD risk factors in Native and Mexican Americans at a high risk of developing an alcohol use disorder (AUD). Subsequent analyses in this sample suggested that the lower heart rate (HR) response to deep breathing (HR_{DB}) measure of cardiovagal control, resting HR (HR_{rest}) and lifetime history of AUD were significantly associated with higher mean diastolic blood pressure (DBP). However, whether reduced cardiovagal control increases the risk of alcohol relapse in participants with lifetime history of AUD at high risk of CVD is not well understood. This study investigated whether an association could be demonstrated between cardiovagal control, self-reported current drinking quantity (number of alcohol drinks during the past week) and the prevalence of diastolic pre-/hypertension in a community sample of Native and Mexican Americans with a history of alcohol and substance use disorders ($n = 258$; 18–40 years of age). Results from this study suggest that diastolic pre-/hypertension was associated with higher current drinking quantity and decreases in HR_{DB} and time- and frequency-domain metrics of cardiovagal control. Subsequent analyses showed that diastolic pre-/hypertension significantly increased current drinking quantity and reduced cardiovagal control in participants with lifetime history of AUD, but not in participants with no lifetime AUD. These results indicate that reduced cardiovagal control may be associated to an increase in drinking quantity in this sample of Native and Mexican Americans young adults with a history of AUD and at a higher risk for CVD.

Poster 59

The pathophysiology of carotid sinus hypersensitivity: sensory block of the sternocleidomastoid muscles does not increase responses to carotid sinus massage

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The arterial baroreflex is crucial for short-term blood pressure control—abnormal baroreflex function predisposes patients to syncope and falling. Hypersensitive responses to stimulation of the carotid baroreceptors using carotid sinus massage (CSM) are common in older adults and may be associated with syncope[1]. While the pathophysiology of this hypersensitivity is unknown, chronic denervation of the sternocleidomastoid muscles (ScM) is common in elderly patients with carotid sinus hypersensitivity (CSH)[2]. This phenomenon is proposed to interfere with normal integration of neural information from the carotid baroreceptors with proprioceptive feedback from the ScM, producing large responses to CSM. We hypothesized that simulation of ScM "denervation" using pharmacological blockade would increase cardiovascular responses to CSM. In six participants (aged 29 ± 2 years), tilted CSM was performed while cardiac (RRI; electrocardiography), systolic arterial pressure (SAP; Finometer), and forearm vascular resistance (FVR; mean arterial pressure [Finometer]/brachial blood flow velocity [Doppler ultrasound]) responses were recorded. Participants then received intramuscular injections (6–8 ml distributed over 4 sites) of 2 % lidocaine hydrochloride, and 0.9 % saline (placebo) in contralateral ScM. EMG was recorded during maximal unilateral ScM contraction both pre- and post-injection to confirm neural block with lidocaine. CSM was repeated following injections and responses compared to pre-injection. Data are presented as mean ± standard error. Following lidocaine injection, the EMG mean root mean square fell to 21 ± 0.05 % of the pre-injection value ($p < 0.001$), confirming neural block of the ScM. Pre-injection responses of RRI, SAP and FVR were small and not different between sides. Compared to pre-injection, responses were unchanged following lidocaine (RRI: +2 ± 20 ms, $p = 0.99$; SAP: −2 ± 2 mmHg, $p = 0.69$; FVR +4 ± 5 %, $p = 0.82$) and saline injection (RRI: +20 ± 20 ms, $p = 0.75$; SAP: −0.6 ± 2 mmHg, $p = 0.98$; FVR: +1 ± 5 %, $p = 0.99$). Post-injection comparisons between lidocaine and placebo were not different for RRI, SAP, or FVR responses. Neural block of the ScM does not increase cardiovascular responses to CSM. The pathophysiology of CSH remains unknown. 1. Moya, A. et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur. Heart J.* 30, 2631–71 (2009). 2. Blanc, J. J. et al. Assessment of a newly recognized association. Carotid sinus hypersensitivity and denervation of sternocleidomastoid muscles. *Circulation* 95, 2548–51 (1997).

Poster 60

Sympathetic activity does not contribute to hypertension in obese African American women

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African American (AA) women have an increased prevalence of hypertension (HTN) and obesity. We previously reported that sympathetic activation underlies obesity-HTN in Caucasians. In this study, we tested the hypothesis that sympathetic activity also contributes to HTN in obese AA women. We studied 42 obese women (16 Caucasian, 44 % with HTN and 26 AA, 46 % with HTN). Antihypertensive medications were discontinued for 2 weeks prior to the study day. All subjects underwent acute autonomic blockade by intravenous infusion of the ganglionic blocker trimethaphan (4 mg/min). Complete autonomic blockade was confirmed by lack of heart rate changes in response to ∼ 25 mm Hg increase in blood pressure produced by bolus infusion of the alpha 1 adrenergic agonist phenylephrine. Trimethaphan significantly decreased mean arterial blood pressure in obese HTN Caucasians compared with normotensives (NTN) (−27 ± 10 vs. −15 ± 8 mm Hg, $P = 0.016$). Trimethaphan produced a similar small decrease in mean arterial blood pressure between HTN and NTN obese AA women (−16 ± 11 vs. −12 ± 10, $P = 0.451$). Heart rate increased similarly with trimethaphan between HTN and NTN Caucasian (+9.1 ± 6 vs. 16 ± 9, $P = 0.109$) and AA women (+22 ± 7 vs. 21 ± 12 bpm, $P = 0.760$). These findings suggest that sympathetic activity does not contribute to hypertension in AA women.

Poster 61

Cardiac-vascular properties in older women with controlled hypertension

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Background: The prevalence of hypertension is high among older adults, especially women. Lowering blood pressure (BP) by antihypertensive agents decreases morbidity and mortality in patients with

hypertension. However, the risk of stroke, myocardial infarction, or congestive heart failure remains high in such patients even with adequate BP control. We tested the hypothesis that drug treatment lowers BP but does not normalize cardiac-vascular properties in older hypertensive women.
Methods: Twenty women with controlled hypertension on drug treatment (68 ± 6 [SD] yrs, ambulatory awake BP 128 ± 8/71 ± 9 mmHg), 20 with uncontrolled hypertension (70 ± 7 yrs, 152 ± 8/84 ± 10 mmHg), and 30 healthy normotensive women (69 ± 7 yrs, 127 ± 7/73 ± 7 mmHg) were recruited. Patients were weaned from antihypertensive drugs prior to cardiac-vascular assessments. Carotid-to-femoral pulse wave velocity (PWV), BP (SunTech), heart rate (ECG), cardiac output (Qc, acetylene rebreathing), stroke volume (SV = Qc/heart rate), total peripheral resistance (TPR = mean BP/Qc) and effective arterial elastance (Ea = 0.9 × systolic BP/SV) were measured during supine rest. Left ventricular (LV) mass and wall thickness were assessed with cardiac MRI.
Results: Carotid-to-femoral PWV was not different between women with controlled and uncontrolled hypertension (10.9 ± 2.1 vs 11.7 ± 2.7 m/s, $P = 0.26$), but it was greater compared to normotensive women (9.1 ± 1.9 m/s, $P < 0.01$). TPR remained elevated in controlled hypertensives (1925 ± 527 vs 2051 ± 323 dyn s cm^{-5} in uncontrolled hypertensives, $P = 0.43$) and it was higher than normotensives (1719 ± 308 dyn s cm^{-5}, $P < 0.01$). Ea was similar between controlled and uncontrolled hypertensives (2.1 ± 0.6 vs 2.3 ± 0.4 mmHg/ml, $P = 0.24$), and was greater compared with normotensives (1.9 ± 0.4 mmHg/ml; $P = 0.02$). LV mass (90 ± 23 in controlled and 90 ± 12 g in uncontrolled hypertensives vs 74 ± 10 g in normotensives, $P < 0.01$) or wall thickness (6.4 ± 0.8 and 6.7 ± 0.7 vs 5.7 ± 0.5 mm, $P < 0.01$) was not normalized in women with controlled hypertension.
Conclusions: Lowering blood pressure by antihypertensive agents does not normalize cardiac-vascular properties in older women, which may contribute importantly to the high risk for cardiovascular events in this patient population. Supported by NIH R01 HL091078 grant.

Poster 62

Higher within-person blood pressure associated with shorter sleep duration

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Introduction: Short sleep is associated with detrimental health effects, including higher blood pressure. However, the mechanisms and timing of how short sleep duration impacts blood pressure are unclear, including whether blood pressure variations occur within-person in response to changing sleep durations. The objective was to identify daily impact of short sleep duration on blood pressure within individuals.
Methods: Using a home wireless mobile system, we studied 11 healthy control participants for up to 42 days each over 6–12 weeks. Participants received a blood pressure monitor and phone with an app to record blood pressure data via Bluetooth, and guide them through the following ~15 min testing protocol: after setup, participants were asked about estimated sleep duration. Blood pressure and heart rate readings were obtained following 5 min' rest. Data were uploaded to UCLA Wireless Health Institute servers. Sleep duration was classified as short (≤5 h; SSD) or normal (<10 and >5 h; NSD), with long (≥10 h) excluded. Mean arterial pressure (MAP) was calculated from monitor readings. Using subjects with some SSD, we estimated the relationship between sleep duration and MAP or heart rate with generalized estimating equations (GEE), indicating repeated measures within subjects.
Results: After 582 tests, seven participants reported a mix of SSD (N = 87) and NSD (N = 224); the remaining four reported NSD only. In the seven participants with mixed sleep duration, GEE showed greater sleep duration predicting lower MAP (−2.06 mmHg/hour; p = 0.04). Heart rate showed only a trend towards increasing with sleep duration (1.86 bpm/hour; p = 0.07).
Conclusion: In this pilot study, within-subject short sleep duration was associated with a 2 mmHg/hour-of-sleep decrease in blood pressure over normal sleep duration. This finding suggests the impact of a short night's sleep is immediate, and may reflect elevated sympathetic nervous system activity due to the physiologic and psychological stress of inadequate sleep.
Funding: This work was supported by the NIH National Institute of Nursing Research NR013693 and the UCLA School of Nursing.

Poster 63

Sex differences in insular cortex gyri responses to a hand grip challenge

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Introduction: Sex-specific patterns of autonomic regulation may contribute to gender-based differences in cardiovascular illness. The insula, a key autonomic regulatory area, shows subregional sex differences in functional organization in the autonomic responses elicited by intrathoracic pressure changes in the Valsalva maneuver. Whether the sex variation in insular function differs by sensory-specific input from different challenge types is unclear; thus we examined insular functional organization in healthy female and male participants with a peripheral hand grip challenge.
Methods: We studied brain functional magnetic resonance imaging (fMRI) responses to four 16-s hand grip tasks in 22 healthy females (age ± std: 50.0 ± 7.9 yrs), and 36 healthy males (45.3 ± 9.2yrs). All subjects squeezed a bulb with their right hand to a subjective 80 % of maximum grip strength. We assessed fMRI signal responses with repeated measures ANOVA ($P < 0.05$).
Results: Heart rate increased throughout the strain period, and declined to baseline upon release. Females showed lower heart rate increases than males, and had lower oxygen saturation. The insular cortices showed similar patterns in all gyri, but with greater signal decreases in males than females (maximal differences all >1 %, sustained >0.5 %). Males showed higher (>0.2 %) left-sided (contralateral to grip) responses in all gyri, but females showed higher right-sided responses in the most anterior gyrus (anterior short gyrus), no lateralization in next two short gyri (mid and posterior short gyri), and very slight left-sided dominance (<0.1 %) in the posterior long gyri. Both sexes exhibited an anterior-posterior topographical organization of insular responses, with anterior short gyri showing higher responses than more-posterior long gyri.
Conclusions: The right-hand grip elicited left-dominant insular signal responses in males, but not females. Unlike the Valsalva, both sexes

showed similar anterior-posterior organization of responses. These findings demonstrate sex-based organization in insular function, likely resulting from different sensory input.
Funding: This work was supported by the NIH National Institute of Nursing Research NR013693.

Poster 64

Inter-individual sympathetic responses to experimental muscle pain: the central circuitry responsible for the increases or decreases in MSNA

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Background: Long-lasting muscle pain has been shown to bring about consistent inter-individual differences in cardiovascular responses (Fazalbhoy et al. 2012, 2014), which are not determined by baseline physiological or psychological parameters (Kobuch et al. 2015, 2016). Intramuscular infusion of hypertonic saline, causing pain lasting $\sim$60 min results in a sustained increase in muscle sympathetic nerve activity (MSNA), blood pressure, and heart rate in certain people, while evoking a decrease in others (Fazalbhoy et al. 2012, 2014; Kobuch et al. 2015, 2016).
Methods: By recording MSNA and performing functional magnetic resonance (fMRI) concurrently, we aimed to identify the central circuitry responsible for these divergent sympathetic responses. Spontaneous bursts of MSNA were recorded via a tungsten microelectrode inserted percutaneously into the right common peroneal nerve of 37 healthy subjects, whilst lying in a 3 T MRI scanner.
Results: Twenty-six subjects showed an increase in MSNA and 11 displayed a decrease. Significantly greater increases in Blood Oxygen Level Dependent (BOLD) signal intensity were apparent in the increasing MSNA group compared to the decreasing group in the hypothalamus and the orbitofrontal, dorsolateral prefrontal, and anterior cingulate cortices. Brainstem-specific analysis revealed increases in the rostroventrolateral medulla (RVLM) and dorsolateral pons in the increasing group, while signal intensity increased in the lateral periaqueductal grey (PAG) in the decreasing group.
Conclusions: These results suggest that differential activation of cortical and subcortical areas during long-lasting muscle pain determines whether a subject shows an increase or a decrease in MSNA.
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Poster 65

Autonomic dysfunction in Charcot Marie Tooth disease IA

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48-year-old female presented to clinic for evaluation of chronic pain and multiple falls. She also reported alternating constipation with diarrhea, dry eyes and dry mouth. She reported that she was clumsy as a child and pain started in her teens. Prior evaluation at Mayo Clinic with nerve conduction studies showed significantly slowed conduction velocities. A nerve biopsy showed hypertrophic neuropathy suggestive of hereditary motor and sensory neuropathy type 1. Her main symptoms had been chronic pain including abdominal and pelvic pain with severe abdominal cramps. She also needed nerve stimulator placement for urinary urgency, frequency and incontinence. Her exam showed mild distal leg atrophy with distal hand and foot weakness. She had length dependent loss of pinprick and vibration with absent reflexes at all sites except 1+ at the knee. Her bedside orthostatic testing showed 20 beat drop in systolic blood pressure with an 8 beat increase in heart rate. Her autonomic testing showed absent sweat response at all sites. Cardiovagal testing showed normal RR variability and Valsalva ratio. She had a 70 beat fall in BP in early phase II with absent late phase II and phase IV. Her tilt table testing showed a drop in BP from 120 to 80 mm hg with a 20 beat increase in HR. She was tilted back at 3 min due to pre-syncopal feeling. Her genetic testing revealed a heterozygous duplication of exons 1–5 on PMP 22 gene. This was thought to be autosomal dominant and predicted pathogenic. Genetic testing for TTR amyloidosis was negative. Autonomic neuropathy has been reported in some families with CMT 2B (RAB 7 mutations) and CMT IB (myelin protein zero mutations) but no reported case exists in CMTIA (PMP 22 mutation). We describe a novel phenotype of CMT1A presenting with chronic pain and autonomic neuropathy.

Poster 66

Symptomatic autonomic impairment in autism spectrum disorders (ASD)

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Objective: To report a case series of clinically significant autonomic dysfunction in ASD.
Background: Autonomic nervous system (ANS) impairment has been increasingly recognized in autism spectrum disorders (ASD). Abnormalities in pupillary light reflex, resting heart rate, heart rate response to social cognitive tasks, respiratory rhythm, and skin conductance suggest that autonomic dysfunction is common in ASD and may play a role in the social, behavioral, and communication problems that are the hallmark of this neurodevelopmental disorder. This case series confirms the presence of clinically significant multisystem ANS dysfunction in ASD.
Methods: Patients with a history of ASD who underwent an evaluation for suspected ANS dysfunction at our institution were identified. Clinical features, findings on autonomic testing, and laboratory results were reviewed.
Results: Seven patients with ASD underwent clinical and autonomic evaluation, ranging in age from 12 to 28, and autonomic symptom duration ranging from 10 months to 6 years. All reported postural lightheadedness, near-syncope, and rapid heart rate. Significant gastrointestinal (GI) symptoms were reported in all patients, including constipation, diarrhea, and early satiety. Autonomic testing revealed an excessive postural tachycardia with head-up tilt (HUT) in all patients, with a mean heart rate (HR) increment of 50 bpm, mean maximum HR on HUT of 119 bpm, absence of orthostatic hypotension on HUT. Abnormal blood pressure profile with the Valsalva maneuver was identified in three patients. All five patients were diagnosed with orthostatic intolerance. Supine norepinephrine (NE)

was low in three of the four patients tested and an inadequate rise in standing NE was noted in two of these patients. GI motility testing was performed in three patients, and suggested gastroparesis in one patient.
Conclusions: Clinically significant ANS dysfunction may occur in ASD, with symptoms suggestive of orthostatic intolerance and gastrointestinal dysmotility, and findings on autonomic testing demonstrating an excessive postural tachycardia.

Poster 67

Intraepidermal nerve fiber density quantification is more sensitive method than sudomotor test for detecting early neuropathy in type 2 diabetes

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Objectives: The aim of this study is to find the sensitive way for detecting early diabetic neuropathy and to evaluate relationship between the somatic and autonomic small nerve fiber function in diabetic neuropathy.
Materials and Methods: Type 2 diabetic patients with putative neuropathy based on clinical symptoms or signs were included prospectively. All patients were given clinical neurological examinations and had nerve conduction studies (NCS). Quantification of intraepidermal nerve fiber density (IENFD) and quantitative sudomotor axon reflex test (QSART) were done on the same site, distal leg. Heart rate variability tests during deep breathing (DB ratio) and Valsalva maneuver (Valsalva ratio) were done to quantify the cardiovagal function. The patients were divided into 2 groups; normal nerve conduction group named small fiber neuropathy group (SFN) and abnormal nerve conduction group defined as mixed fiber neuropathy group (MFN). The results of the tests were compared between SFN and MFN.
Results: Reduced IENFD was the most frequent abnormality, and abnormalities of QSART, NCS, and cardiovagal function were followed in total patients. Reduced IENFD was found more frequently than abnormalities of QSART and cardiovagal function in both SFN and MFN. Cardiovagal dysfunction, especially DB ratio, and NCS abnormality were significantly correlated with duration of the diabetes mellitus. There was no correlation between IENFD and QSART performed on the same site.
Conclusions: Quantitation of IENFD is more sensitive method than QSART to detect early diabetic neuropathy. The involvement degree of somatic small nerve fiber and sudomotor nerve fiber could be different in diabetic neuropathy, so analyses of IENFD and QSART might be complementary to each other in type 2 diabetes.

Poster 68

Association of hyperglycemia with autonomic dysfunction during sleep in patients with obstructive sleep apnea (OSA) and mild hyperglycemia

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Obstructive sleep apnea (OSA) has been hypothesized to cause a hypersympathetic state, which may be the mechanism for the increased incidence of cardiovascular disease in OSA. There is a high prevalence of hyperglycemia in OSA patients which may also contribute to autonomic dysfunction. We have shown previously that heart rate variability as measured during wakefulness demonstrated greater association with hyperglycemia than with measures of OSA. We hypothesized that there may be a difference between daytime resting heart rate variability and heart rate variability during sleep in patients with obstructive sleep apnea. Thirty-five patients with OSA and eleven controls with average body-mass index (BMI) of 32.0 ± 4.6 underwent polysomnography, glucose tolerance testing, autonomic function tests, lying and standing catecholamines, and baseline ECG and continuous blood pressure measurements for spectral analysis. Twenty-three OSA patients and two controls had hyperglycemia (increased fasting or two hour glucose using the ADA definition). Of these, 28 OSA patients and eight controls had adequate ECG tracings without artifact for heart rate variability for each sleep stage. We evaluated heart rate variability during polysomnography and compared heart rate during different sleep stages throughout the night in addition to daytime ECG samples collected during autonomic function testing. Linear regression models were used to study the effect of age, diagnosis, and hyperglycemia on each sleep stage. OSA patients had higher resting heart rates overnight, and higher ratio of low frequency power to high frequency (LF2HF), index of sympathetic activity) during NREM sleep. This is in contrast to daytime heart rate variability where AHI had no significant effect on LF2HF ratio and hyperglycemia was correlated with a decrease in LF2HF ratio ($p = 0.07$). These results suggest discordant results between daytime and sleeping heart rate variability and suggest the effects of OSA do not affect sympathetic tone during the daytime.

Poster 69

Effect of gastroparesis on glycemic variability in insulin-treated patients with diabetes mellitus

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Background: Glycemic variability has been implicated as a possible risk factor for the development of complications in diabetes mellitus (DM), independent of overall glycemic control. A delay in gastric emptying (gastroparesis) is a common complication due to autonomic dysfunction in long standing DM. The relationship between glycemia and gastric emptying is complex, with pre-prandial blood sugar affecting gastric emptying, while gastric emptying time contributes substantially to post-prandial glucose. The aim of this study was to investigate the impact of gastroparesis on glycemic variability, as measured by the 72 h. Medtronic iPro® Continuous Glucose Monitoring System (CGMS).
Methods: A retrospective chart review of male patients with insulin-treated DM, identified 23 who completed both outpatient CGMS and a gastric emptying study by scintigraphy [(14 with gastroparesis and 9 without) (6 Type 1: 17 Type 2) (age = 66. ± 10 yrs) (HbA1c = 7.9 ± 1.3 %) (duration DM = 21 ± 14 yrs) (BMI = 31.3 ± 6.3 kg/

m^2) (QTc = 387–476 ms)]. CGMS data were used to compare glycemic variability as measured by the standard deviation within days (SDw) and standard deviation of the daily means (SDdm). The number of hypoglycemic (<70 mg/dl; 3.9 mmol/L) and hyperglycemic (<180 mg/dl; 10.0 mmol/L) readings between the two groups were also compared.
Results: SDw for the gastroparesis group was 45.6 ± 15.6 mg/dl (2.5 ± 0.9 mmol/L), significantly lower than the control group 66.2 ± 18.3 mg/dl (3.7 ± 1.0 mmol/L) (p = 0.019). SDdm did not vary significantly between groups (p = 0.477). Additionally, there were no significant differences between the mean glucose, or in the number of hypoglycemic or hyperglycemic readings between the groups, as well as the patient characteristics.
Conclusion: The delay in gastric emptying present in gastroparesis due to autonomic neuropathy may serve to decrease glucose absorption in patients with diabetes mellitus, and with it, the rate at which the blood sugar changes after ingestion of food, thus accounting for the observed decrease in glycemic variability. This research is supported, in part, by the Captain James A. Lovell Federal Health Care Center

Poster 70

Parasympathetic pupillary response is reduced in patients with ANCA-associated vasculitis and does not correlate with cardiovagal function

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Objective: To assess parasympathetic and sympathetic responses of pupillary light reflex in patients with ANCA-vasculitis in correlation to autonomic symptoms and to heart rate variability.
Methods: Patients with ANCA-associated vasculitis and healthy controls underwent infrared dynamic pupillometry at rest and after sympathetic stimulation (cold pressor test). Three parasympathetic parameters (amplitude and relative amplitude of pupillary constriction, maximum constriction velocity) and one sympathetic parameter (late dilatation velocity) were assessed. Results were then correlated with clinical parameters (disease duration, number of affected organs), symptoms of autonomic dysfunction (COMPASS31 questionnaire) and heart rate variability during deep breathing test.
Results: 23 patients and 18 age-matched controls were enrolled. Patients had a smaller amplitude (1.44 vs. 1.70 mm; p = 0.009) and a slower constriction velocity (4.15 vs. 4.71 mm/s; p = 0.028) at baseline and after sympathetic stimulation (1.47 vs. 1.81 mm, p = 0.002; 4.38 vs. 5.19 mm/s, p = 0.007, respectively). Relative amplitude was not different between the groups at baseline but became significantly smaller in patients after 3 min of sympathetic stimulation (28.6 vs. 32.5 %; p = 0.043) and remained smaller throughout the rest of the testing. There was no difference in the sympathetically driven slow dilation velocity between the groups, neither at baseline nor after stimulation. No correlations were found between pupillometric parameters and autonomic symptoms, clinical parameters or parasympathetic control of heart rate variability.
Conclusion: Parasympathetic response of the pupillary light reflex is markedly reduced in patients with ANCA-associated vasculitis. The extent of parasympathetic pupillary dysfunction is independent of clinical parameters such as disease duration or disease severity and does not reflect the burden of autonomic symptoms assessed by COMPASS31 questionnaire. As there was no correlation between parasympathetic pupillary response and heart rate variability during deep breathing test, we conclude that dynamic pupillometry does not serve as a screening test for cardiovagal dysfunction.

Poster 71

Autonomic neuropathy in adult Still's disease

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Objective: Describe a case of small fiber autonomic and sensory neuropathy occurring with adult-onset Still's disease.
Background: Adult-onset Still's disease has very rarely been associated with large fiber polyneuropathies. Additionally, there is one reported case of neuropathic pain and one case of altered heart rate variability associated with adult Still's disease in the medical literature.
Methods: The clinical and diagnostic course of a patient with Still's disease-related small fiber autonomic and sensory neuropathy is discussed.
Results: A 40-year-old man presented with numbness, tingling, and burning pain in his bilateral feet. The symptoms began 17 months prior, initially involving only the right foot, but spread to involve the left foot, both legs, and left medial hand within a couple of months. The symptoms came on immediately after he was hospitalized for 2 weeks of fevers up to 40 °C (104 °F). He reported new-onset orthostatic lightheadedness, insomnia, increased stool frequency, and persistent arthralgias. He had a mildly elevated WBC count (10.1 k/mcL, 69 % neutrophils) and elevated CRP (3.1 mg/dL [<0.9]). AST and ALT were mildly elevated at 63 and 95 U/L, respectively [15–46, 21–72, respectively]. Laboratory testing for infectious and inflammatory processes, including blood cultures and chest radiographs, was otherwise normal. He had experienced two prior bouts of prolonged, unexplained fever 6 and 7 years prior. Laboratory testing during those periods, including CSF analysis, was normal. Serum ferritin was not checked during his fevers. His general physical examination was unremarkable. His neurologic exam revealed decreased temperature sensation in both feet, but was otherwise normal. Extensive laboratory evaluation for autoimmune and infectious processes, including CSF analysis, was normal. CT of the chest, abdomen, and pelvis was normal. Autonomic screening tests revealed length-dependent sudomotor deficit on QSART, mild orthostatic hypotension, with a normal heart rate response to deep breathing and normal blood pressure and heart rate responses to Valsalva maneuver. Nerve conduction studies of the lower extremities and right upper extremity were normal. Electromyography of selected muscles of the left lower extremity was unremarkable. Skin biopsy revealed normal epidermal nerve fiber (ENF) density in the calf while sweat gland nerve fiber (SGNF) density was abnormally low. ENF and SGNF densities were normal in the thigh. Sural nerve biopsy revealed perivascular inflammation. Because of the evidence of ongoing inflammation, he was treated with a short course of oral steroids (prednisone 60 mg daily) and started on oral methotrexate (15 mg weekly) with a planned treatment course of 1 year with continued monitoring.
Conclusions: Adult Still's disease may be accompanied by small fiber autonomic and sensory neuropathy. The views expressed are those of the author and do not necessarily reflect the policy or position of the Department of the Navy, Department of Defense, or the United States Government. Research data derived from an approved Naval Medical Center, Portsmouth, VA, IRB protocol.

Poster 72

Autonomic disorders in a tertiary military referral clinic

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Objective: Describe the patient population seen in a military autonomic disorders referral clinic.
Background: In January 2014, the first Autonomic Disorders referral clinic in the Department of Defense (DoD) was established at Walter Reed National Military Medical Center Bethesda (WRB). In July 2015, the Autonomic Disorders referral clinic transferred to Naval Medical Center Portsmouth (NMCP) and began taking regular referrals in September 2015. An autonomic testing laboratory remains active at WRB. The DoD's second autonomic testing laboratory was established at NMCP in June 2016. The Autonomic Disorders Clinic is open to military personnel; their spouses, children, and other dependents; and military retirees.
Methods: The clinical characteristics and diagnoses of patients seen in the DoD Autonomic Disorders Clinic between January 1, 2014 and February 29, 2016 were reviewed.
Results: A total of 103 individual patients were evaluated in 24 months. These clinical evaluations were separate from the referrals for laboratory testing. The mean age of patients was 39 years (range 12–85). Seven patients were under the age of 18. Forty-seven (45.6 %) were male. Forty-four (42.7 %) were in an active duty military status, 13 were retired military, and 46 were family members. Thirty-one (30 %) met diagnostic criteria for postural orthostatic tachycardia syndrome (POTS). Of those with POTS, 21 had evidence of autonomic neuropathy (either significantly low sudomotor response on QSART or abnormal skin nerve fiber density). In total, 47 patients evaluated (45.6 %) had evidence of autonomic neuropathy. Ten patients had confirmed autoimmune diseases (2 with SLE; 2 with Sjogren's; 1 each with Behcet's, neurosarcoidosis, and adult Still's disease; and 3 with undifferentiated connective tissue disease). Eight patients reported insomnia and 7 patients reported a history of traumatic brain injury. Neurally-mediated syncope was diagnosed in 11 patients and 31 patients had orthostatic hypotension. Six patients had Parkinson disease with orthostatic hypotension, 1 had multiple system atrophy, and 1 had pure autonomic failure.
Conclusions: Demand for specialized care for autonomic disorders in military healthcare is high and represents a varied population of patients and conditions. The views expressed are those of the author and do not necessarily reflect the policy or position of the Department of the Navy, Department of Defense, or the United States Government. Research data derived from an approved Naval Medical Center, Portsmouth, VA, IRB protocol.

Poster 73

Psychophysiologic responses to a laboratory stressor in chronic pelvic pain conditions vs. healthy controls

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Background and Methods: Some bladder conditions, such as Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS), demonstrate an aberrant stress response. Recently, our group showed that these conditions can impact high frequency heart rate variability (HF-HRV), a psychophysiological index of self-regulation, at rest and in response to a physiological stressor. The current investigation evaluates the psychological stress responses in IC/BPS, Myofascial Pelvic Pain or both, using the Trier Social Stress Test (TSST), a laboratory stressor. Anxiety was indexed using the Spielberger State Anxiety Inventory (STAI), and HF-HRV and cortisol were sampled. Subjects included healthy controls (HC, $n = 10$), and subjects with 1 or 2 chronic pelvic pain disorders (CPP1, $n = 5$, CPP2, $n = 5$).
Results: T-tests showed that STAI was elevated ($p < 0.016$ all points), peaking at $36 \pm 9/80$ in HC, 50 ± 10 in CPP1 and 55 ± 12 in CPP2. HCs demonstrated normal rise in cortisol, peaking at 20 min and slowly decaying. CPP1 peak was delayed, while CPP2's never peaked, demonstrating a continuous drop despite higher anxiety. Repeated measures analysis of variance (ANOVA) demonstrated that for the CPP2 group, HF-HRV remained relatively constant (no significant linear or quadratic trends). The CPP1 group showed a significant quadratic pattern, such that HF-HRV decreased then returned to baseline following the task ($F(1,11) = 5.16$, $p = .044$). HF-HRV for the HC group showed no significant linear or quadratic trends.
Discussion: Cortisol in HCs peaked at 20 min; however, HF-HRV remained stable, suggesting an initial stress response resulting in constant self-regulation. The CPP2 group did not show a peak in either cortisol or HF-HRV, suggesting underresponse to the TSST. In contrast, cortisol in the CPP1 group peaked after 30 min, accompanied by reductions in HF-HRV throughout the TSST. These data suggest differential physiological activity when psychological stress is induced in patients with one or two CPP disorders. Potential mechanisms underlying the current findings will be discussed.

Poster 74

Chronic stress induced autonomic and mitochondria dysfunction in neuronal and non-neuronal cells: role in IC/BPS

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Interstitial cystitis/Bladder pain syndrome (IC/BPS) is a debilitating chronic condition characterized by persistent pain related to bladder filling, urinary frequency and nocturia. In humans and animals with IC/BPS, psychological stress can exacerbate associated hyperalgesia and pain. Recently, mitochondria have been implicated in chronic pain conditions such as IC/BPS. We examined whether exposure to psychological stress (chronic water avoidance stress or WAS in Wistar Kyoto or WKY rats) alters mitochondrial function in urothelium and/or bladder primary sensory neurons, as a potential factor underlying structural or functional changes observed in IC/BPS. Cultured urothelial cells and dorsal root ganglion (DRG) neurons from control and WAS rats were loaded with various intracellular dyes to examine functional responses. These included: fura-2AM (to measure intracellular calcium concentration), DHR123 (to measure reactive oxygen species or ROS) and TMRM (to measure mitochondria membrane potential, Ψm). UT cells from WAS rat bladders exhibited more depolarized Ψm compared to control and smaller responses following FCCP stimulation (an uncoupler of mitochondria respiration from ATP production). WAS UT cells also showed both higher baseline and ROS production in response to H_2O_2 stimulation, as well as an increase in spare respiratory capacity and increased proton leak assessed using Seahorse methodology. Furthermore, WAS UT and DRG cells exhibited a number of intracellular Ca^{2+} changes (higher baseline, altered response to FCCP and impaired buffering ability). Some of these disturbances were reduced by pre-treatment of

rats with guanethidine (depletes norepinephrine from sympathetic nerve terminals). Taken together, these results suggest alterations in neuronal and non-neuronal cell homeostasis related to compromised mitochondria function and involving the autonomic nervous system. Our findings in an animal model of chronic stress induced IC/BPS, support the view that impaired mitochondria function may play a role in impaired voiding and pain sensations in IC/BPS.

Poster 75

Head-down tilt bed rest increases sympathetic burst latency

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Prolonged bed rest exerts inconsistent effects on efferent muscle sympathetic nerve activity (MSNA) in terms of the burst frequency metric. However, burst frequency alone does not provide information regarding the broader control of MSNA such as the central processes affecting burst latency and size. The current investigation examined the impact of 60 days head-down tilt (−6°) bed rest (HDBR) to augment sympathetic burst latency at baseline (BSL) as well as during a reflexive sympathoexcitatory manoeuvre that affects burst size. Heart rate (ECG), blood pressure (Finometer), and MSNA (microneurography) were measured pre and post-HDBR, during 10-min of supine BSL (n = 13, 30 ± 2 yr, 180.7 ± 1.5 cm, 77.7 ± 1.8 kg, 23.8 ± 0.4 kg/m^2), as well as during a maximal end-inspiratory apnea (APN, n = 8). Apnea duration was 74 ± 5 s in the pre, and 85 ± 7 s in the post-HDBR conditions ($P > 0.05$). MSNA burst latency was measured as the mean time interval (ms) from the ECG R-wave, to the peak of the corresponding MSNA burst in the integrated neurogram. BSL heart rate, mean arterial pressure, and MSNA burst frequency (pre-HDBR: 20.1 ± 1.8 vs. post-HDBR: 20.1 ± 1.5 bursts/min, $P > 0.05$) were unchanged with HDBR. Compared to pre-HDBR (1354 ± 24 ms), BSL burst latency was greater post-HDBR (1394 ± 22 ms, $P = 0.004$, r = 0.89, effect size = 0.99). Burst latency was reduced from BSL levels during the APN condition ($P = 0.005$). However, reductions in burst latency with APN were similar in pre (−23 ± 6 ms) and post (−23 ± 8 ms)-HDBR ($P > 0.05$), suggesting different mechanisms affect baseline versus reflexive changes in burst latency. Increases in burst latency may reflect changes in central synaptic delays and/or variations in recruitment of larger, faster conducting axons.

Poster 76

Vascular sympathetic control in Sjögren syndrome

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Sjögren Syndrome (SS) is a chronic autoimmune systemic disease mainly affecting salivary and lacrimal glands, but also vessels, heart, nerves and other organs. Severity of diseases is unrelated to the amount of organ inflammation. This raises the possibility that observed dysfunctions might be also related to an autonomic peripheral neuropathy, which in turn might be reflected in an altered systemic vasomotor neural control. The aim of the present study was to assess the sympathetic vasomotor control in a group of 7 patients with SS and controls, by using power spectrum analysis of blood pressure variability and the direct recording of the post-ganglionic sympathetic nerve activity (Muscle Sympathetic Nerve Activity, MSNA) using microneurography from the peroneal nerve. Every subject underwent ECG, beat by beat blood pressure, respiratory activity and MSNA at rest. Power spectrum analysis of systolic arterial pressure variability provided the spectral marker of sympathetic vasomotor control LF_{SAP} that is a comprehensive index that takes into account both the neural vasomotor control and the arterial smooth muscle responsiveness. Heart rate, systolic arterial pressure and respiratory activity were similar in patients and controls. The spectral index of sympathetic activity to the vessel (LF_{SAP}) was similar in the two groups (2.64 ± 0.94 vs 2.56 ± 1.69 mmHg^2/Hz), whereas the sympathetic neural firing (MSNA) was significantly greater in patients compared to controls (30.57 ± 2.75 vs 20.71 ± 3.29 burst/min). We hypothesize that, in SS patients, in a setting of potential arterial inflammation, there is the need of an enhanced neural sympathetic drive to the vessel to obtain a proper vasoconstriction and maintain adequate blood pressure values.

Poster 77

Can distraction play a role in sympathetic output and pain perception during experimental muscle pain?

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Background: Distraction is known to play a role in the perception of a person's pain level, where it can help dampen the effect and reduce anxiety. Less is known however, about the physiological parameters during distraction, specifically in muscle sympathetic nerve activity (MSNA). This study aims to address whether sympathetic output and perceived pain levels are altered due to audio-visual distraction during experimental muscle pain.
Methods: Pain was induced via hypertonic saline infusion into the tibialis anterior muscle. Subjects rated their pain level on a visual analogue scale (VAS) once a stable pain level of 5 out of 10 had been reached. Subjects rated their pain for 15 min prior to, and following, a 15-min audio-visual distraction. Continuous blood pressure, heart rate, and MSNA (via microneurography) were recorded throughout the procedure.
Results and Conclusion: Preliminary analysis in 7 subjects indicates that sympathetic output is not altered between the distraction and non-distraction components. Changes within subject VAS scores prior to and following the distraction were varied, ranging from 1 to 4. Additional subjects are required to determine whether distraction during experimental muscle pain can influence sympathetic output and perceived pain.

Poster 78

Stimulation of the dorsal root ganglion (DRG) for medicine refractory chronic neuropathic pain: is there sympathetic involvement?

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Lesion to a peripheral nerve may result in chronic pain syndromes only relieved by inhibiting the effect of efferent sympathetic impulses on primary afferent neurons. The dorsal root ganglion (DRG), which is a robust target for neuromodulation therapies, has been shown to be a site for such a coupling. Stimulation of the DRG may affect certain painful conditions by modulating sympathetic outflow, as well as being a useful target for other non-painful conditions that also involve the sympathetic nervous system. In order to elucidate whether stimulation of the DRG for pain relief alters sympathetic nerve traffic, this study evaluated sympathetic nerve activity in humans with DRG electrodes at spinal levels known to have sympathetic supply during periods of ON and OFF stimulation. Muscle sympathetic nerve activity (MSNA) was recorded during DRG stimulation ON and OFF in patients with chronic neuropathic pain due to peripheral nerve injury ($n = 15$). Arterial blood pressure (ABP), heart rate, respiration and pain perception (VAS) were monitored during the recording session. Stimulation of right sided L1–L5 and C6–C7 DRG electrodes, while giving adequate pain relief, showed no changes in MSNA burst frequency, heart rate and ABP, but resulted in a shift in burst amplitude distribution towards larger amplitudes which was related to pain perception (VAS). Stimulation of left sided L1–L3 DRG electrodes resulted in decreased MSNA burst frequency and ABP, which was related to pain perception and unchanged burst amplitude distribution. Stimulation of left sided L4–L5 DRG electrodes, resulted in an increase in heart rate and ABP, no changes in MSNA burst frequency, but a shift in burst amplitude distribution towards larger amplitudes. We have previously shown that electric deep brain stimulation (DBS) in midbrain nuclei in humans alters cardiovascular parameters by modulating baroreflex control of efferent sympathetic nerve traffic. Here we show that stimulation of the DRG for pain relief in humans can modulate sympathetic nerve traffic in a differential manner depending on electrode location. Our results may have implications in understanding abnormal sympathetic discharge in painful as well as non-painful conditions and provide an opportunity for therapeutic targeting.

Poster 79

Influences of experimental air pollution on human sympathetic nerve traffic: a double blind, randomized, twofold crossover study

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Background: Much of the evidence linking air pollutant exposure with changes in human cardiovascular autonomic regulation relied on epidemiological studies, exposure estimates, and indirect autonomic nervous system measurements. We tested the hypothesis that in healthy older individuals, experimental exposure to fine particles increases sympathetic nervous system activity and more so with addition of ozone.

Materials and methods: Eighteen healthy participants (age >50 - years) completed all study visits and were included in the final analysis. Participants were exposed to clean air ('placebo'), ultrafine particles (UFP, 50 $\mu g/m^3$), and combination of UFP + ozone (250 ppb) for 3 h combined with intermittent bicycle ergometer training in a randomized, three-period, cross-over, double-blind fashion. Three hours following exposure, respiration, ECG, blood pressure, and muscle sympathetic nerve activity (MSNA) were continuously recorded at supine rest, during deep breathing, and during a Valsalva maneuver. Venous blood samples for plasma catecholamine measurements were taken at baseline. Induced sputum was obtained at the end of each study day.

Results: Combined exposure to ozone and UFP but not UFP alone caused a significant increase in sputum neutrophils and circulating leucocytes. We did not detect significant effects on blood pressure or heart rate. Resting MSNA was 47 ± 12 with clean air, 47 ± 14 with UFP, and 45 ± 14 bursts/min with UFP + ozone. Maximum MSNA during Valsalva phase IIb was similar. Yet, plasma norepinephrine levels were significantly higher with UFP + ozone than with UFP. Respiratory sinus arrhythmia and Valsalva ratio as indices of parasympathetic heart rate control were unaffected by experimental air pollution.

Conclusion: Our study suggests that exposure to ultrafine particles with or without ozone does not elicit clinically relevant changes in central sympathetic or parasympathetic activity in healthy older subjects. The paradoxical norepinephrine increase with UFP + ozone may indicate a change in the coupling between electrical nerve activity and peripheral norepinephrine availability.

Poster 80

Oscillatory lower body negative pressure impairs task related functional hyperemia in healthy volunteers

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Neurovascular coupling refers to the link between an increase in neural activity in response to a task, and an increase in cerebral blood flow denoted "functional hyperemia". Recent work on postural tachycardia syndrome indicated that increased oscillatory cerebral blood flow velocity (CBFv) was associated with reduced functional hyperemia. We hypothesized that a reduction in functional hyperemia could be causally produced in healthy volunteers by using oscillations in lower body negative pressure (OLBNP) to force oscillations in CBFv. CBFv was measured by transcranial Doppler ultrasound (TCD) of the left middle cerebral artery (MCA). We used passive arm flexion applied during 8 periodic 60 s flexion–60 s relaxation epochs to produce 120 s periodic changes in functional hyperemia (at 0.0083 Hz). We used -30 mmHg of OLBNP at 0.03, 0.05, and 0.10 Hz, the range for cerebral autoregulation, and measured spectral power of CBF_v at all frequencies. Arm flexion power performed without OLBNP was compared with arm flexion power during OLBNP. OLBNP power performed in isolation was compared with power during OLBNP + arm flexion. Cerebral flow velocity oscillations at 0.05 Hz reduced and at 0.10 Hz eliminated functional hyperemia while 0.03 Hz did not reach significance. In contrast, arm flexion reduced OLBNP-induced oscillatory power at all frequencies. The interactions between OLBNP driven CBFv oscillations and arm flexion driven CBFv oscillations are reciprocal. Thus, induced cerebral blood flow oscillations suppress functional hyperemia and functional hyperemia suppresses cerebral blood flow oscillations. We

conclude that oscillatory cerebral blood flow produces a causal reduction of functional hyperemia.

Poster 81

Influence of sex, menstrual cycle and oral contraceptives on autonomic function and cerebrovascular resistance

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Women experience orthostatic intolerance more than men, and experience faintness more in the low hormone (LH) phase of the menstrual cycle. We investigated cardiovascular and cerebrovascular responses to autonomic testing in men and women in LH (day 2–5) and high hormone (HH; day 18–24) phases of the menstrual cycle with (OC) or without oral contraceptives (NOC). Men ($n = 13$, age: 25.8 ± 1.8), NOC ($n = 13$, age: 21.8 ± 0.5), and OC ($n = 14$, age: 22.0 ± 0.8) groups performed paced deep breathing (DB), Valsalva, and 10 min standing on a Wii balance board. Beat-to-beat blood pressure, normalized stroke volume (SVi), heart rate (HR), end-tidal carbon dioxide (ET_{CO2}), and middle cerebral artery blood velocity (MCA) were measured. *DB*: There were no differences between groups/phases for HR responses to DB. *Valsalva*: During late phase II of the Valsalva, there were no differences among groups in the increase of mean arterial pressure (MAP), yet women (all conditions) had a greater increase in diastolic MCA compared to men ($p < 0.05$). *Supine-to-sit-to-stand*: Standing reduced ET_{CO2} ($p < 0.001$), MCA ($p < 0.002$), and SVi ($p < 0.001$) while increasing HR ($p < 0.001$) and MAP ($p \leq 0.030$) in all groups. *Sex*: Men had lower MCA ($p < 0.036$) than women, and higher SVi than NOC at rest ($p < 0.030$) and OC-LH during stand ($p = 0.010$). Only men experienced higher resistance index (RI; $p < 0.001$) and pulsatility index (PI; $p < 0.001$) with standing. *OC:* OC had lower ET_{CO2} ($p = 0.002$) compared to NOC ($p = 0.030$) and men ($p \leq 0.067$). Compared to NOC, OC had higher SVi ($p = 0.029$) and more lateral ($p = 0.001$) and median ($p = 0.043$) movement of their centre of balance at the end of standing. *Phase:* HH tended to have lower MCA ($p = 0.054$) and higher SVi ($p = 0.054$) and PI ($p = 0.059$) than LH. *OC* × *Phase:* OC had higher MAP ($p = 0.014$) in LH compared to HH. Our results indicate that cycling estrogens/progestins can influence ventilatory, cardiovascular and/or cerebrovascular physiology at rest and during stress.

Poster 82

Cerebrovascular function and persistent headache after sports-related concussion: preliminary *Results*

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After a concussion, symptoms, including headache, may persist after the initial event, preventing return to daily activities. While the pathophysiology underlying persistent symptoms is multifactorial, one culprit may be a derangement in autonomic control of cerebral blood flow and consequent impediment of the metabolic needs of the brain. However, the role of cerebrovascular function in post-concussion symptoms is not well established. We explored cerebral vasoreactivity (the ability to buffer against changes in arterial gases) and autoregulation (the ability to buffer against pressure fluctuations), and their relation to chronic headaches in 14 concussion patients (26 ± 3 years; 4 asymptomatic) seen at an outpatients sports-concussion clinic within a period of 3 weeks to 1 year post-injury. Vasoreactivity and autoregulation were assessed from beat-by-beat relation of middle cerebral artery blood flow velocity (transcranial Doppler ultrasound) to, respectively, end-tidal CO_2 and arterial pressure (photoplethysmography). Headache severity was quantified using Walker headache density immediately before the study. Measures of vasoreactivity and autoregulation were compared to those obtained previously from 43 young healthy subjects. In patients who experienced a concussion, there was a significant reduction in vasoreactivity (0.020 ± 0.004 vs 0.058 ± 0.010 cm/s/mmHg per mmHg CO_2, $p < 0.05$). Moreover, autoregulation was impaired in a way that was proportional to their headache burden: with increasing headache severity, there was a reduction in the range of pressures within which autoregulation is effective (asymptomatic vs severe headaches: 6.5 ± 2.8 vs 2.7 ± 0.2 mmHg), as well as in the rate of flow changes in response to increases (0.59 ± 0.19 vs 0.21 ± 0.12 cm/s/mmHg) or decreases (0.59 ± 0.33 vs 0.18 ± 0.14 cm/s/mmHg) in pressure. Our data suggests that concussion impairs cerebrovascular function, and that the degree of this impairment may relate to chronic headache severity. A larger study with a more homogenous cohort is needed to confirm these preliminary findings.

Poster 83

Orthostatic cerebral hypoperfusion syndrome (OCHOs)

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Objective: Orthostatic dizziness without orthostatic hypotension (OH) is common but underlying pathophysiology is poorly understood. Orthostatic cerebral hypoperfusion syndrome (OCHOs) is a recently described syndrome associated with reduced orthostatic cerebral blood flow velocity (CBFv) without OH, bradycardia and excessive tachycardia. The clinical characteristics of OCHOs are largely unknown.
Methods: This retrospective study included patients referred for evaluation of unexplained orthostatic dizziness in which autonomic testing showed OCHOs. Standardized autonomic testing included 10 min or more of the tilt. The following signals were monitored: heart rate, end tidal CO_2, blood pressure and CBFv from the middle cerebral artery using transcranial Doppler.
Results: Ninety seven patients (59/38 women/men, age 48.1 ± 17.6) fulfilled criteria for OCHOS. Compared to normal controls, OCHOs patients had reduced orthostatic CBFv (age and gender adjusted CBFv score ($p < 0.005$) and elevated orthostatic cerebral vascular resistance (2.5 ± 1.0) compared to normal controls (1.6 ± 0.5, $p < 0.0005$). There was no difference in orthostatic heart rate, blood pressure and end tidal CO_2 compared OCHOs with controls. All OCHOs subjects had at least one orthostatic symptom during the tilt test including dizziness or lightheadedness ($n = 93$), palpitations (12), presyncope (44), sense of weakness (34), shortness of breath (6), chest pain (9), excessive sweating (22) and fatigue (67).

Conclusion: In addition to dizziness, OCHOS is frequently accompanied with other orthostatic symptoms. The symptoms are nonspecific and resemble symptoms associated with adrenergic sympathetic dysfunction.

Poster 84

Safety and preliminary efficacy of intranasal insulin in Parkinson disease: a pilot study

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Objective: To determine safety and preliminary efficacy of intranasal insulin on cognition in Parkinson disease (PD).
Research Design and Methods: This was a proof-of-concept, randomized, double-blind, placebo-controlled intervention study evaluating the effects of a 40-IU dose of intranasal insulin (INI) or saline for 4 weeks on safety and cognition in PD. Measurements included blood glucose, Unified Parkinson Disease Severity Scale, parts I-III, 7-meter walking test, Montreal Cognitive Assessment (MOCA), brief visuospatial memory test-revised (BVMT-R) and the verbal fluency test (FAS). The t test for repeated measures was used to evaluate the effect of insulin or placebo.
Results: Fourteen PD patients were enrolled in the study. Eight PD subjects were matched to INI and 6 PD subjects to placebo. No hypoglycemic episodes occurred. There was one serious adverse event (pneumonia) in a subject treated with INI not related to the study drug. The device for intranasal delivery malfunctioned in 2 subjects in the insulin arm. Five subjects treated with INI were included in the analysis. INI improved visuospatial memory using BVMT-R immediate recall ($p < 0.03$) and delayed recall ($p < 0.03$). The remaining outcomes were not different. Placebo had no significant effect on any variable.
Conclusions: Intranasal insulin administration appears safe, does not affect systemic glucose, and may provide improvements of cognitive functions in patients with PD. It is hypothesized that cognitive improvement may be related to vasodilatation in the anterior brain regions that regulates attention-related task performance. Larger studies are warranted to assess long-term effects of intranasal insulin therapy.
Trial Registration: ClinicalTrial: NCT02064166.

Poster 85

Clinical observations regarding the use of ivabradine in autonomic dysfunction

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Introduction: A significant number of patients with POTS are not helped or cannot tolerate exercise training, volume expansion (does not help all of their symptoms) and medications like beta blockers and calcium channel blockers. The aim of our study was to see if ivabradine is a useful and safe alternative for the symptomatic treatment of POTS patients.

Methods: This is a retrospective chart review study of adolescent and adult patients with a clinical and autonomic testing diagnosis of autonomic dysfunction who were intolerant to non-pharmacological measures, beta blockers and calcium channel blockers and who got converted to ivabradine. All patients were seen at one autonomic clinic since July, 2014. Pregnant patients were excluded. Baseline autonomic testing (QSWEAT 4 sites, heart rate range to deep breathing, heart rate and beat to beat blood pressure measurements to the Valsalva maneuver and head up tilt table testing) was obtained. Pretreatment and post treatment blood pressure (BP) and heart rate (HR) were documented. EKG was monitored for QTc (corrected QT interval) prolongation and qualitative measures of daily activities including exercise tolerance were followed.
Results: 24 patients, all women, average age 38.6 were identified. None of the patients had a history of cardiac ablation procedure and had normal baseline QTc measurements. Autonomic testing identified the following subcategories: routine POTS 6, inappropriate sinus tachycardia (IST)/POTS overlap 2, POTS with mild orthostatic hypotension 9, hyperadrenergic POTS 3, neuropathic POTS 1, post encephalitic autonomic dysfunction 2, post radiation therapy autonomic dysfunction 1 case. The main reason for conversion was uncontrolled tachycardia and intolerance to beta blockers due to orthostatic hypotension limiting the beta blocker dose and requiring the addition of another agent: midodrine or florinef. Other beta blocker side effects included excessive fatigue, chest pain, worsening depression, coexistence of mastocyte activation syndrome and moderate asthma. For calcium channel blockers the main limiting factor was worsening orthostatic hypotension. Lack of effect to flecainide and mestinon were also noted. 22 patients were dosed twice daily and 2 only once daily. Average ivabradine daily dose was 11.5 mg ranging from 5 to 20 mg daily. Benefits of the conversion were sustained and were noted in all patients: activities of daily living, exercise tolerance, less fatigue and allowed a decrease of the number of medications. Tolerance of ivabradine was very good (two patients reported rare phosphenes) including lack of abnormal QTc prolongation.
Discussion: The role of ivabradine in autonomic dysfunction needs to be further clarified. Preliminary data suggest good tolerance, lack of significant side effects, and allowance for limitation of the number and doses of medications taken on a daily basis.

Poster 86

Droxidopa for neurogenic orthostatic hypotension in autoimmune autonomic ganglionopathy

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Autoimmune autonomic ganglionopathy (AAG) is a rare condition characterized by acute-onset generalized autonomic failure. Some of these patients also develop severe sensory and motor deficits. Droxidopa, an oral norepinephrine precursor, has been previously reported as effective treatment of neurogenic orthostatic hypotension (nOH) in one patient with AAG. Here we report our experience using droxidopa to treat symptomatic nOH in 3 patients with suspected AAG. Patient #1 (35-year-old woman) presented with acute-onset recurrent syncope, urinary retention, constipation, dry mouth, and decreased sweating, but no motor or sensory deficits. Patient #2 (11 year-old boy) and patient #3 (43-year-old woman) presented with similar autonomic deficits as well as severe impairment in all sensory

modalities, but patient #3 also had severe generalized muscle weakness and had been initially diagnosed with Guillain–Barre syndrome. In all three patients, autonomic testing showed severe nOH confirmed by absent phase IV blood pressure overshoot after release of the Valsalva strain and very low or undetectable plasma norepinephrine levels. Ganglionic acetylcholine receptor antibodies were not detected in any patient. Droxidopa increased blood pressure and improved symptoms in all three patients. After 1 year, patient #1 is still receiving droxidopa 200 mg three times/day with normalization of standing BP, and continued symptomatic improvement. During the initial droxidopa titration, patients #2 and #3 experienced nausea, abdominal pain, and severe hypertension (>180 mmHg) with dosages >200 mg. Both have now been receiving 100 mg once/day for a year with improvement in orthostatic tolerance and BP, no side effects and no supine hypertension. In conclusion, droxidopa substantially increased blood pressure standing and reduced symptoms of orthostatic hypotension in adult and pediatric patients with suspected acute autonomic ganglionopathy.

Poster 87

Blood pressure normalization with cranial nerve modulation in migraine subjects

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Introduction: Migraine and trigeminal neuropathy pain are frequently accompanied by sometimes excessive hypertension or hypotension. During the course of documenting blood pressure (BP) changes following neuromodulation of cranial nerves V, VII, IX, X, and cervical nerves C2 and C3 for migraine or trigeminal pain, several subjects presented with exceptionally high or low baseline systolic values, the latter with orthostatic signs. The objective was to determine if cranial nerve modulation for pain dampened extreme BP values.
Methods: 26 moderate-to-severe migraine or trigeminal neuropathy subjects inadequately managed by pharmacologic agents or other intervention, underwent bilateral impressions of the auditory canal, with vibration devices later embedded within the impression. Conventional cuff BP measures were taken before and after intervention. ECG, breathing, and pulse oximetry sensors were placed, and inferred beat-by-beat BP values, together with cardiac waveform and thoracic movement values collected by a SomnoTouch recorder. A 10 min baseline rest period was obtained, followed by a 20 min stimulation period, and a 10 min post-stimulation baseline. Values between conditions were assessed with ANOVA.
Results: Overall trends for a smaller subset of these subjects were reported in abstract form earlier, and showed an overall decline in both systolic and diastolic pressure. This larger group also showed systolic and diastolic BP declines, from mean baseline values of 130 and 82 mmHg to 125 and 79 mmHg, followed by partial recovery. Five subjects showed excessive values, 4 with high systolic values (>150mgHg), and one with low values, showing orthostatic symptoms (94mgHg). Systolic values declined by 20–45 mm Hg in the high systolic group following intervention, while systolic values rose by 10 mmHg in the hypotensive subject.
Conclusions: Neuromodulation of peripheral cranial nerves may provide an immediate intervention for excessive hypertension or hypotension, and does so with minimal adverse effects.

Poster 88

Droxidopa improved attention and hyperactivity in a patient with congenital insensitivity to pain with anhidrosis (HSAN IV)

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Congenital insensitivity to pain with anhidrosis (CIPA, also known as hereditary sensory and autonomic neuropathy type IV) is a rare autosomal recessive disorder caused by mutations in the gene encoding for neurotrophic tyrosine kinase receptor type 1, a receptor for nerve growth factor (NTRK1-NGF). We recently described that patients with CIPA have very low or undetectable circulating norepinephrine levels. Since these mutations severely deplete the development of noradrenergic neurons in the periphery, they presumably also affect those in the central nervous system. Patients with CIPA have low IQ and behavioral problems including hyperactivity and reckless impulsivity, likely the result of a central deficiency in norepinephrine. We explored whether treatment with droxidopa, a synthetic norepinephrine precursor, which crosses the blood brain barrier, could improve behavioral features in a patient with CIPA. Our patient was a 29-year-old woman with a classic phenotype and molecular confirmation of a mutation in the *NTRK1* gene (c360-2A>C pathogenic variant). She had symptoms of attention deficit and hyperactivity and scored highly on the adult ADHD self-report scales (Scores Part A: 4/6 and Part B: 9/12). She had high scores in the attentional (17 and 4), motor (21 and 10), and planning (21 and 17) domains of Barratt impulsiveness scale. NICHQ Vanderbilt assessment scale also indicated attention deficits and hyperactivity. After two months treatment with droxidopa (at 400 mg/day), attention and hyperactivity scales scores decreased to the normal range (Scores Part A: 3/6 and Part B: 4/12). Impulsiveness scores assessed by Barratt impulsiveness scales also improved (attentional scores 15 and 11, motor scores 19 and 9 and planning scores 20 and 9). This case report suggests that behavioral deficits might be reversed in patients with CIPA by norepinephrine replenishment therapy. Clinical studies to evaluate the usefulness of droxidopa to treat behavioral problems in CIPA patients are warranted.

Poster 89

Dexmedetomidine: a novel approach to treating refractory adrenergic crisis in familial dysautonomia

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Background: Stress-induced adrenergic hypertensive crises are a cardinal feature of familial dysautonomia (FD). Classically, this is treated with clonidine and benzodiazepines, which cause excessive sedation and can lead to respiratory arrest. Dexmedetomidine is a recently introduced compound, 8 times more specific for central alpha-2 adrenergic receptors than clonidine, resulting in less sedation. Advantages over clonidine are also that dexmedetomidine can be administered intravenously (IV), and its half-life is shorter (12 vs. 2 h), which allows an easy titration.
Methods: Retrospective chart review of IV dexmedetomidine use to treat refractory hypertensive crisis in patients with FD.

Results: IV dexmedetomidine was used 15 times in 9 patients (mean age: 26 years; 44 % men) with acute adrenergic crisis. Crisis triggers included respiratory infection (n = 8), emotional stress (n = 3), surgery (n = 1), bacteremia (n = 1), gastroenteritis (n = 1) and bleeding gastric ulcer (n = 1). Before treatment, all patients had signs of adrenergic activation including skin flushing, nausea/retching, vomiting, diaphoresis, and agitation. Blood pressure (BP) was 1616/1026 mmHg and heart rate (HR) was 1134 bpm. IV dexmedetomidine was administered at an average rate of 0.510.13 mcg/kg/h. One hour post-infusion, BP decreased to 1165/586 mmHg ($p < 0.0001$) and HR to 975 bpm ($p = 0.002$). Drowsiness occurred in one patient, although he was easily arousable. There were no episodes of rebound hypertension or respiratory depression. In one case, rapid titration at a high dose resulted in paradoxical hypertension, which subsided immediately upon dexmedetomidine discontinuation.
Conclusions: IV dexmedetomidine is an effective, well-tolerated approach for managing adrenergic crises in patients with FD. In contrast to other commonly used medications, dexmedetomidine does not induce excessive sedation or respiratory depression. In a small percentage of patients, rapid IV dosing may result in paradoxical hypertension due to its direct action on peripheral postsynaptic alpha2-adrenergic receptors.

Poster 90

Hemodynamics and muscle sympathetic nerve activity in patients with end stage heart failure before and after left ventricular assist device implantation

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Background: Current left ventricular assist devices (LVAD) implanted in patients with end stage heart failure either produce continuous flow or pulsatile flow that is not coupled to native heart rate. While physiological blood pressure pulsatility is considered crucial for baroreflex regulation, hemodynamic control and muscle sympathetic nerve activity (MSNA) were paradoxically preserved in such patients. To confirm these observations, we assessed autonomic cardiovascular control before and after LVAD-implantation.
Materials and methods: Measurements before and after implantation were successful in eight heart failure patients (6 male, age 44–66 years). ECG, finger blood pressure, respiration, and MSNA were recorded continuously before LVAD-implantation, early after implantation (n = 5, 8–22 days), and late after implantation (n = 6, 185–725 days). Implanted LVAD-devices were HeartWare™ HVAD (n = 4), Thoratec HeartMate II™ (n = 2) and HeartMate III™ (n = 2).
Results: Heart rate (HR) increased early after implantation ($p = 0{,}012$) and returned to pre-implantation values later on (66 ± 10 bpm, 76 ± 9 bpm, and 63 ± 7 bpm, respectively). Pulse pressure was reduced profoundly following LVAD implantation (before: 35 ± 10 mmHg; early after implantation: 9 ± 3 mmHg, $p = 0.0005$; late after implantation: 11 ± 6 mmHg, $p = 0.017$). MSNA burst frequency was 56 ± 10 before, 61 ± 11 early after, and 46 ± 6 bursts/min late after implantation. Most patients showed severe ventricular and supraventricular arrhythmias following LVAD-implantation and altered breathing patterns making it difficult analyzing MSNA.
Conclusion: While profoundly attenuating blood pressure pulsatility, LVAD implantation is not associated with acute or chronic sympathetic excitation. Instead, sympathetic activity tends to decrease over time. We observed large inter individual variability in hemodynamic and sympathetic control in part secondary to cardiac arrhythmias and altered respiratory control.

Poster 91

Cardiac pacemaker channel (HCN4) inhibition and atrial arrhythmogenesis following acute relief of cardiac sympathetic activation

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Background: Cardiac pacemaker channels (HCN4) have been implicated in atrial arrhythmogenesis based on genetic investigations and clinical trials with ivabradine. Acute changes in cardiac autonomic tone predispose to atrial arrhythmias. Therefore, we applied a human model in which profound cardiac sympathetic activation was rapidly relieved to test influences of HCN4 inhibition with ivabradine on atrial arrhythmias.
Materials and Methods: We tested 19 healthy participants with ivabradine, metoprolol, or placebo in a double blind, randomized, cross-over fashion on top of selective norepinephrine reuptake inhibition with reboxetine. Subjects underwent combined head up tilt plus lower body negative pressure testing on all three study days followed by rapid return to the supine position. Continuous finger blood pressure and ECG recordings at baseline and following tilting back were analyzed by two experienced cardiac electrophysiologists, blinded for treatment assignment.
Results: Resting supine heart rate was 67 ± 1 bpm with placebo (mean ± SEM), 59 ± 1 with metoprolol, and 64 ± 1 with ivabradine. Heart rate during the last 10 s of HUT was 143 ± 6 bpm with placebo, 113 ± 5 bpm with metoprolol (<0.001 vs. placebo), and 128 ± 6 bpm with ivabradine ($p = 0.005$ vs. placebo). The numbers of atrial premature beats and atrial runs at baseline did not differ between treatments. The number of atrial premature beats after tilting back was 10 ± 3 with placebo, 7 ± 2 with metoprolol, and 16 ± 5 with ivabradine ($p = 0.061$, one way ANOVA for repeated measures). The number of atrial runs after tilting back was 2 ± 1 with placebo, 0 ± 0 with metoprolol, and 5 ± 1 with ivabradine ($p = 0.0009$). The numbers of ventricular arrhythmias and atrial pauses did not differ between treatments.
Conclusions: Unlike beta-adrenoreceptor blockade, HCN4 inhibition while lowering heart rate does not protect from atrial arrhythmias following experimental cardiac sympathetic activation.

Poster 92

How to leverage social media to advance the field of autonomic disorders

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Physicians who specialize in autonomic disorders think in terms of orthostasis, synapses, catecholamines, ganglionopathies, and baroreflexes. Patients, on the other hand, inhabit a world of streaming, downloads, hashtags, tweets, and blogs. In an increasingly digital era, if we are to communicate effectively with patients, we must understand their language, including that of social media. The cultural revolution of social media opens new opportunities for autonomic medicine. First, social media can direct patients to specialists who have the expertise to evaluate and treat their disorders when such expertise is not available locally. Listing contact information on reputable dysautonomia websites is an effective way to facilitate these connections, as is creating practice websites to showcase unique expertise and resources. Secondly, online platforms can empower the patient population through education. In clinical practice, we see how frequently patients turn to the Internet for medical information. However, search engines alone are inadequate because of the sheer volume of available information, much of which is unmonitored. Patients can quickly be led down a path of misinformation about their particular condition. Dr. Google is frequently wrong. Moreover, it takes on average 2.5 clicks to get from a headache to a brain tumor. As experts in the field, we have an obligation to participate online in the translation and dissemination of accurate medical information. It is important to consider the demographics of the target audience and how best to reach them, be it Facebook, Twitter, Instagram or Snap Chat. By doing this we can assist patients in understanding their autonomic disorders and managing their symptoms. Thirdly, social media can be an important tool for research. Social media platforms can be used to recruit research subjects with rare disorders and as a tool to promote the need for research funding from the public. Social media is undoubtedly an effective way to spread news and can be used to disseminate new knowledge arising from research, which allows patients to keep abreast of current breakthroughs. Lastly, social media can be leveraged to raise public awareness about autonomic disorders and their treatment, build community, share experiences, and engage patient groups in partnership.

Poster 93

Reduced vagal modulation of heart rate in pediatric functional gastrointestinal disorders (FGID)

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Background: Many chronic pain disorders such as fibromyalgia, back pain and pelvic pain are associated with reduced vagal function. The data in pediatric FGID is very limited.
Hypothesis: Cardiac vagal modulation is reduced in subjects with pediatric FGID.
Methods: This study included 37 subjects, including 5 female and 3 male healthy control (HC, range 10–16 years old), 25 female and 4 male FGID (range 11–21 years old). We analyzed heart rate variability (HRV) in: (1) lying and standing values in healthy subjects; (2) lying and standing values in patients with FGID (on active medications); and (3) supine values obtained from tilt table studies in subjects with FGID (autonomically active medications held). We performed time-domain and autoregressive analysis of HRV using Kubios v2.2 (University of Eastern Finland, Kuopio, Finland) on the penultimate 3 min prior to going upright, and the last 3 min of the upright period.
Results: As expected, the root mean square of the successive difference (RMSSD) and high frequency (HF) components of HRV significantly dropped from lying to standing in both HC and FGID groups. Lying (on exam table ± medications) and supine (on tilt table test off medications) did not differ significantly, though they showed a lower trend on the tilt table test. Importantly, RMSSD (HC supine 130.87 ± 18.37 ms, HC upright 45.11 ± 13.76 ms, $n = 8$; FGID supine 47.87 ± 7.45 ms, FGID upright 16.33 ± 2.73 ms, $n = 29$), HF (HC supine 8.43 ± 0.31, HC upright 6.04 ± 0.52, $n = 8$; FGID supine 6.33 ± 0.32, FGID upright 4.30 ± 0.30, $n = 29$), and LF (HC supine 8.00 ± 0.33, HC upright 7.01 ± 0.41, $n = 8$; FGID supine 6.14 ± 0.27, FGID upright 5.76 ± 0.25, $n = 29$) amplitudes of FGID subjects were 2 to 3-fold lower than HC. There is no difference in age between the HC and FGID subjects ($p = 0.37$).
Conclusion: As expected, HF and LF power decreases from lying to standing in all subjects. However, subjects with FGID have 2 to 3-fold lower values than HC in every position. This is in line with data found in other chronic pain disorders such as pelvic pain, fibromyalgia and lower back pain. These findings are not due to medications, since patients had higher values on medications than when off autonomically active medications. This study was supported by a Digestive Disease Center grant and Advancing Healthier Wisconsin Grant 5520298.

Poster 94

Characterization of endocannabinoid (EC) changes with diffuse noxious inhibitory control (DNIC) in subjects with pediatric functional gastrointestinal disorders (FGID)

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Background: FGID patients report pain outside the gastrointestinal tract, suggesting abnormal DNIC. ECs are reduced in psychiatric conditions. Their possible involvement in pain modulation led us to investigate EC changes with DNIC.
Hypothesis: Effective conditioned pain modulation corresponds with a rise in EC and higher baseline EC.
Methods: This exploratory study compared DNIC in ascending and descending immersion of the arm in 12 °C cold water, separated by 45 min rest. Fingers, wrist, forearm and shoulder were each immersed for 2 min with 5 min rest, and pain recorded every 15 s. DNIC = ascending (DNIC off)−descending (DNIC on) finger/wrist pain. Serum endocannabinoids (2-arachidonoylglycerol (2-AG) and *N*-arachidonylethanolamine (AEA)) were measured before and after each immersion session.
Results: Of 16 FGID subjects (1 male, range 13–17 years) and 5 controls (3 males, range 12-18 years), 7 FGID and 3 controls were excluded (NRS <2 or no EC values), leaving 9 FGID and 2 controls for analysis. Of those reporting pain, DNIC averaged 4.25 in FGID

and 5.70 in controls (NS). No EC baseline or change correlated with DNIC. In those with valid EC values (11 FGID, 4 controls), baseline 2-AG negatively correlated with general anxiety, obsessions/compulsions, depression (RCADS) and posttraumatic stress and dissociation (TSCC). Tree analysis showed Beighton score (hypermobility measure) >4.5/9 parsed baseline 2-AG into two significantly different groups with median values of 54.31 (19.56–70.07) vs 6.49 (1.34–38.23) pmol/ml when ≤4.5. Yet higher Beighton score (and total co-morbidities) correlated with worse functional status (FDI) ($r > 0.50$).
Conclusions: Although ECs do not predict DNIC in this small sample, baseline 2-AG concentrations inversely correlate with anxiety and several depression domains, mirroring adult findings. The surprising reverse relationship with Beighton score, despite the latter's association with poorer functional status, deserves deeper exploration. Supported by Advancing Healthier Wisconsin Grant #5520298.

Poster 95

Low bioenergetics in functional disorders parallel disability score

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Background: We hypothesized that patients with functional disorders (FD e.g. chronic migraine, functional gastrointestinal disorders, chronic fatigue syndrome, etc.,) show impaired mitochondrial bioenergetics.
Methods: We compared blood from youth with an FD with carefully screened healthy controls (HC). The Oxygen Consumption Rate and Extracellular Acidification Rate (ECAR) measurements utilized the Seahorse XF96 (North Billerica, MA), in unbuffered/serum free RPMI assay media supplemented with 1 mM pyruvate. Peripheral Blood Mononuclear Cells (PMBCs) seeded in a PS V7 cell culture plate at 325,000 cells/well were incubated 1 h without CO2. Oligomycin (1 μg/ml), Carbonyl cyanide-4-phenyl-hydrazone (FCCP) (1 μM) and Antimycin A (10 μM) determined the mitochondrial parameters. A Mann–Whitney test compared skewed variables, and Fisher's exact test dichotomous variables. Regression tree tested predictors (age, gender, basal, ECAR and SRC) of functional outcome (Functional Disability Inventory, FDI) optimized by least absolute deviation and 10 % leave out samples for cross validation.
Results: 45 subjects (36 female) with a median (range) age of 16 years (10, 20), did not differ by age or gender between 15 FD and 30 HC subjects. FD showed lower resting mitochondrial function (basal respiration BR: FD 33.7 [13.3, 96.8] pmol/min units for all values, HC 56.0 [27.1, 171.1] $p = 0.002$), and lower reserve energy (spare respiratory capacity–SRC: FD 68.4 [5.2, 264.7]; HC 118.0 [32.6, 377.3] $p = 0.016$). BR correlated with SRC ($p < 0.0001$). SRC best predicted clinical functional disability (SRC ≤80, median FDI of 30; SRC >80, median FDI of 14; $p = 0.06$) in the FD group. Non-mitochondrial energy generation did not differ (ECAR: FD 17.0 [5.6, 55.8]; HC 21.0 [12.0, 37.9] $p = 0.092$).
Conclusion: Both mitochondrial resting function and reserve energy are impaired in functional disorders, but not non-mitochondrial bioenergetics. Of great interest, the reserve energy (SRC) predicts clinical functional disability in FD, and could explain their profound fatigue. Supported by a Digestive Disease Center grant and Advancing Healthier Wisconsin 5520298.

Poster 96

Identification and evaluation of rare, congenital central hypoventilation syndrome (CCHS)-causing PHOX2B non-polyalanine repeat expansion mutations (NPARMs) and associated phenotypes

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Background: CCHS is a rare neurocristopathy caused by mutations in *PHOX2B*, a key gene in early embryologic development of the autonomic nervous system. While 90 % of CCHS-causing mutations are in-frame polyalanine repeat expansion mutations (PARMs), the remaining 10 % are non-PARMs (NPARMs). A clear genotype-phenotype relationship for PARMs has been established, allowing anticipatory management including artificial respiratory needs and risk assessment for Hirschsprung disease, cardiac sinus pauses, and neural crest tumors. However, the variability and rarity of NPARMs (<100 reported cases) have precluded such advances for these CCHS cases. This study represents a unique collaboration between commercial and academic laboratories to expand knowledge on NPARMs and associated phenotypes.
Methods: NPARM CCHS patients identified at Ambry Genetics, Rush University, and Ann & Robert H. Lurie Children's Hospital of Chicago (Northwestern University) were grouped by mutation type: missense, nonsense, frameshift, and stop codon. Available phenotypic information was included to evaluate relationship with NPARM type.
Results: 75 previously unreported NPARM cases were identified in this cohort. Combined with 91 published NPARM cases (166 total), mutation type/frequency included 27 % missense, 7 % nonsense, 61 % frameshift, and 4 % stop-codon mutations. Among those with available phenotypic information, we noted variable expression and incomplete penetrance in a subset of mutations, and a clear phenotype-mutation type relationship. Specifically, Hirschsprung disease and neural crest tumors (typically neuroblastoma) were more strongly associated with frameshift (49 and 21 %, respectively), missense (24 % for both), and stop codon (29 % for both) mutations than with nonsense mutations (9 % for both).
Discussion: By combining cohorts of *PHOX2B* mutations from academic and commercial laboratories, this study greatly expands awareness of these very rare NPARMs. This new knowledge allows delineation of phenotypic patterns associated with *PHOX2B* NPARM types, offering anticipatory management in these complex cases and clues to the pathogenic mechanisms involved with these mutation types.

Poster 97

Bowel management and quality of life following spinal cord injury: the influence of autonomic dysreflexia

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Autonomic dysfunction is common in individuals with spinal cord injury (SCI) and leads to cardiovascular and bowel abnormalities. In those with high level lesions, bowel care is a common trigger for autonomic dysreflexia (AD), paroxysmal hypertension provoked by sensory stimuli below the level of injury. Improving bowel care is integral for enhancing quality of life (QoL). We aimed to describe the relationship between bowel care, AD, and QoL in individuals with SCI. We gathered information from individuals living with SCI ($n = 287$) with a range of injury levels (C1-sacral) and severities (A-D) using an online survey. Questions were combined from the International Bowel Function Basic and Extended Data Sets and our Cardiovascular Symptoms Questionnaire. Individuals with a lesion level at T6 or higher were considered at risk for AD ($n = 158$). Survey completion rate was 74 % ($n = 211$). Responses are qualified as percent-response to each question. Average time since injury was 15.8 ± 13.5 years. Dissatisfaction with bowel care was reported by 58 %; it was reported to interfere with personal relationships (60 %), and prevent staying away from home (63 %), and working away from home (41 %). The typical bowel care duration was >60 min in 24 %; 32 % reported bowel incontinence at least once per month. The most common bowel management technique was digital rectal stimulation (59 %). Only 63 % of respondents used diet/lifestyle management to enhance their bowel care. Of those at risk for AD, 76 % reported at least one symptom of AD during bowel care, while 33 % described palpitations. AD was reported to interfere with activities of daily living in 35 %. Longer durations of bowel care ($p = 0.02$), increased frequency of incontinence ($p = 0.03$), and move severe symptoms of AD ($p = 0.04$) were associated with lower QoL. Bowel care is a key concern for individuals with SCI and is commonly associated with symptoms of AD. Further studies should explore ways to manage bowel dysfunction, increase self-efficacy and ameliorate the impact of AD to improve QoL.

Poster 98

Correlation between heart rate at rest and vagal reactivation after submaximal exercise test

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The heart rate (HR) in supine position and vagal reactivation (VR) after exercise testing has been shown to be a cardiovascular risk marker. The relationship between HR and VR is an incompletely explored issue after submaximal exercise testing (SET).
Purpose: To correlate the HR and VR by means of heart rate variability (HRV) after SET in physical active men.
Methods: VR assessed by rMSSD and SD1, both vagal indexes at the 1st to 5th min of passive recovery in orthostatic position following SET. VR was correlated with 5 min of HR at rest in supine position in 24 physical active men according to the IPAQ-questionnaire, aged 27 ± 4.4 yrs and BMI $= 24.8 \pm 1.8$ kg/m^2. The Polar RS800® was used to record HR at rest and R–R interval acquisition during recovery period. The HRV was analyzed by *Kubios* software. Due to non-normal distribution of variables (*Shapiro–Wilk test*) the *Spearman correlation test* was used at the 5 % level of significance.
Results: Negative correlation between HR with r-MSSD and SD1 after SET were observed, at the 2nd to 5th minute of recovery in both variables ($r_s = -0.46$; -0.62, $p = 0.01$–0.0006). No correlations were observed between resting HR and 1st min of recovery.
Conclusion: VR from the 2sd to 5th min of passive recovery in orthostatic position correlated to resting HR. Our *Results* reinforce the hypothesis that the capacity to re-establish vagal activity to the baseline levels after submaximal efforts, might be associated with HR at rest in supine position. In other words, the lower HR at rest the greater vagal reactivation after SET in younger physical activity men.

Poster 99

Vestibular dysfunction in the autonomic laboratory

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Objective: To evaluate and characterize the presence of vestibular signs in patients with chronic orthostatic intolerance.
Background: Orthostatic intolerance (OI) takes the form of orthostatic hypotension (OH) or postural orthostatic tachycardia (POTS). Clinically, patients often complain of orthostatic or positional dizziness in addition to lightheadedness and palpitations. We aimed to evaluate the presence of clinical vestibular symptoms and signs during the autonomic testing for OI.
Design/Methods: The study is a prospective analysis of 111 consecutive patients who had detailed autonomic cardiovascular testing, including tilt table testing in the past 6 months. We noted symptoms and signs of vestibular dysfunction (dizziness with or without vertigo, sustained nystagmus for more than 5 s) during tilt up and down in every patient.
Results: There were 35 men and 76 women, and the mean age was 42 years (range 16–92 years). In 15 patients, the hemodynamic tilt study was normal, but 4/15 showed vestibular signs during tilt up, tilt down or both. In the remaining 96 patients, the tilt study was abnormal (OH in 47; POTS in 43; syncope in 14). In this subgroup, 29/96 patients showed vestibular signs during tilt up, tilt down or both. The patients with vestibular signs reported significant dizziness and lightheadedness during tilt up, down or both, regardless of their tilt hemodynamic findings.
Conclusion: In patients with OI, concomitant vestibular abnormalities are present in a significant percentage of patients (33/111 in our series), even when tilt hemodynamic testing is negative. This factor should be taken into account while managing these patients.
Disclosures: None.
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Poster 100

The relationship between parasympathetic activity and aortic blood pressures in young healthy individuals

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Introduction: Blood pressure is not constant along the arterial tree. While elevated brachial blood pressure (BBP) is a risk factor for cardiovascular disease (CVD), aortic systolic blood pressure (ASBP) is considered to be a more robust indicator of CVD versus BBP. Sympathetic nervous activity is associated with increased BBP. Research has indicated a lack of relationship between sympathetic vasoconstrictor trafficking and resting arterial blood pressure, but a strong relationship with measures of aortic blood pressures (ABP). Parasympathetic nervous activity (PNA) is associated with a reduction in BBP but there is a paucity of research examining the relationship between PNA and measures of ABP.
Aim: To determine the relationship between PNA and measures of ABP and to examine potential gender differences in this relationship.
Materials and methods: We examined the relationship between PNA and ABP measures in 80 healthy participants and then divided this group by gender (men, 39; women, 41) and reexamined the relationship. PNA activity was assessed using spectral density analysis of R–R intervals (lnHF). ABP measures were assessed using applanation tonometry at the radial artery. Examined ABP measures were: ASBP, aortic diastolic blood pressure (ADBP), mean arterial pressure (MAP) and aortic pulse pressure (APP).
Results: When all participants were analyzed, lnHF did not correlate with ASBP, ADBP, MAP, or APP. When the group was divided by gender, lnHF in men did not correlate with ASBP, ADBP, and MAP but correlated with APP (r 46; $P < 0.01$). In women, lnHF was inversely correlated with ASBP (r-33; $P < 0.05$), ADBP(r-35; $P < 0.05$), and MAP (r-34; $P < 0.05$) but not APP.
Conclusions: When men and women were grouped together, no correlation was observed between lnHF and ABP. Grouped by gender, lnHF in men did not correlate with any measure of ABP except APP. In women, lnHF was inversely correlated with all measures of ABP except APP.
Discussion: Findings suggest that the relationship between PNA and ABP is gender specific. As PNA increased in women, there was a reduction in ASB, however not so in men, suggesting that PNA regulation of ASBP might be different between sexes. Since ASBP is a robust indicator of CVD, our findings also suggest that PNA in women might be a stronger predictor of CVD in women versus men.

Poster 101

State anxiety and nonlinear heart rate variability during examination stress

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Introduction: State anxiety (SA) is a state in which an individual is unable to instigate a clear pattern of behavior to remove or alter the event/object/interpretation that is threatening an existing goal. It is now generally accepted that nonlinear techniques are able to describe heart rate variability in a more effective manner. However, the ability of nonlinear measures of HRV to enhance our understanding of anxiety has only been partly explored. The current study sought to investigate the possible application of nonlinear analysis of heart rate variability to the study of state anxiety.
Methods: The study group consisted of 96 (15 men/81 women) healthy. ECG was recorded in the supine position for 5 min on two different days; the first recording was performed during the controlled resting condition (rest session), while the second one was conducted just before the university verbal examination (exam session). Nonlinear analysis of HRV was performed. The Spielberger's State-Trait Anxiety Inventory was used to assess the level of state anxiety.
Results: Before adjusting for heart rate, a Wilcoxon matched pairs test showed a significant decreasing of Poincaré plot measures (SD1, SD1/SD2, Complex Correlation measure (CCM)), sample entropy (SampEn), largest Lyapunov exponent (LLE), pointwise correlation dimension (PD2) and increasing of the short-term fractal-like scaling exponent of detrended fluctuation analysis during the exam session, compared to the rest period (Table 1).

Table 1 Comparison between the two conditions of the study for the HRV nonlinear analysis

HRV indexes	Rest	Exam
HR (bpm)	72.22 ± 0.93	83.39 ± 1.16#
SD1	35.84 ± 1.54	25.58 ± 1.39#
SD2	65.74 ± 2.12	59.18 ± 1.96#
SD1/SD2	0.55 ± 0.02	0.42 ± 0.01#
GI	0.51 ± 0.01	0.48 ± 0.01*
CCM	0.26 ± 0.01	0.19 ± 0.01#
TPVA	54.89 ± 1.7	56.44 ± 1.65
ApEn	1.21 ± 0.01	1.19 ± 0.01
SampEn	1.87 ± 0.02	1.68 ± 0.03#
α1	0.90 ± 0.02	1.10 ± 0.02#
α2	0.83 ± 0.02	0.88 ± 0.02*
LLE	0.30 ± 0.01	0.25 ± 0.01#
PD2	3.75 ± 0.09	3.57 ± 0.07#

Exam vs rest: * $p < 0.05$; # $p < 0.01$

These *Results* coincide with significant greater scores for SA during the exam session versus the rest period. Applying Pearson analysis indicated significant negative correlations between the dynamics of state anxiety and SD1/SD2, and between changes in state anxiety and changes of entropy measures. There was a strong negative correlation between the dynamics of SA and LLE ($r = -0.45$, $p < 0.05$). A significant positive correlation was found between the dynamics of SA and α1 ($r = 0.22$, $p < 0.05$). Declines of SD1, CCM, SampEn and LLE were still significant after adjusting for heart rate. Corrected α1 was also increased during the exam session. As before, dynamics of adjusted LLE were significantly correlated with the dynamics of SA.
Conclusions: This study shows that state anxiety is associated with alterations in the complexity of heart rate variability. Our results also suggest that the decrease in heart rate variability and the increase in the short-term fractal exponent are not uniform among all subjects, and that a prominent loss in the complexity of heart rate variability is associated with a qualitative change in state anxiety.

Poster 102

Short- and long-term effects of Fingolimod on cardiovagal gain in patients with relapsing-remitting multiple sclerosis

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Background: Fingolimod, an oral disease-modifying therapy for patients with relapsing-remitting multiple sclerosis (RRMS) has been shown to have a transient vagomimetic effect, causing reduction in heart rate that reaches a nadir after 4-5 h and recovers within 6 h after the first dose. The baroreflex mediated vagal modulation of the heart can be assessed by the cardiovagal gain (CVG). However, the transient and long-term effect of Fingolimod on the CVG in RRMS patients has not been studied yet.
Objective: To evaluate the chronologic changes of CVG with Fingolimod-initiation in patients with RRMS.
Methods: In 21 RRMS patients, we recorded RR-intervals (RRIs) and systolic blood pressure (BPsys) during Valsalva maneuver (VM) at 0.5, 1, 2, 3, 4, 5, 6 h and 6 months after Fingolimod initiation. We quantified CVG from the slope of the relationship between RRIs and BPsys during phase II of the Valsalva maneuver if the correlation coefficient (r) exceeded 0.80.
Results: There was a gradual increase in the CVG after Fingolimod initiation reaching its nadir at the 4th hour (3.92 ± 2.02 vs. 5.39 ± 3.48 ms/mmHg; $p = 0.027$) followed by a gradual decrease and reaching the pre-Fingolimod CVG state at the 6th hour (3.92 ± 2.02 vs. 3.90 ± 4.53 ms/mmHg; $p = 0.985$). However, after 6 months of the Fingolimod-therapy, the CVG was significantly lower than the pre-Fingolimod values (3.92 ± 2.02 vs. 1.84 ± 1.26 ms/mmHg; $p = 0.006$).
Conclusion: Fingolimod has a transient vagomimetic effect leading to an increase in the CVG. However, the long-term effect of Fingolimod is a significant decrease in CVG which could be attributed to the central autonomic network readjustment for counter-regulating the vagomimetic effects of Fingolimod in RRMS patients.
Disclosure: This study was financially supported by Novartis Pharma, Germany.

Poster 103

Central autonomic dysregulation may cause inadequate cardiovagal modulation in multiple sclerosis patients after six months of Fingolimod treatment

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Background: Central autonomic network (CAN) dysregulation may delay recovery of Fingolimod-induced heart rate (HR) slowing in some MS patients (Hilz et al. 2015). It is unclear whether Fingolimod-induced HR slowing is only evident upon Fingolimod initiation or persists even with long term Fingolimod treatment in MS patients.
Objective: To evaluate HR-responses to Fingolimod in MS patients with and without initially prolonged (>6 h) HR-slowing after 6 months of Fingolimod treatment.
Methods: Before and 6 months after Fingolimod treatment (0.5 mg/day), we monitored RR-intervals (RRI), systolic, diastolic blood pressures (BPsys and BPdia), and respiration at rest in 34 MS-patients (18 women, mean age 33.7 ± 10.2 years). We calculated parameters of total cardiac-autonomic modulatoin [RRI-standard-deviation (RRI-SD), RRI-coefficient-of-variation (RRI-CV), RRI-total-powers], sympathetic [RRI-low-frequency-powers (RRI-LF), BPsys-LF-powers] and parasympathetic modulation [Root-Mean-Square-of-Successive-RRI-Differences (RMSSD), RRI-high-frequency-powers (RRI-HF)], sympathetic-parasympathetic balance (RRI-LF/HF-ratio), and baroreflex sensitivity (BRS). Values were compared before and after 6 months of Fingolimod treatment in patients with and without initially prolonged HR-slowing (ANOVA with posthoc-testing; significance: $p < 0.05$).
Results: Upon Fingolimod initiation, 11 MS patients had prolonged HR-slowing. After 6 months, they had significantly higher RRI and lower RRI-SD, RRI-CV, RRI-LF-powers, RRI-total-powers than before Fingolimod treatment, while RMSSD, RRI-HF-powers, and BRS remained unchanged. In the other 23 MS-patients, parameters were significantly lower after 6 months than before Fingolimod initiation for RRI-SD, RRI-CV, RMSSD, RRI-LF-powers, RRI-HF-powers, RRI-total-powers, and BRS; all other parameters—including RRI—remained unchanged from pre-Fingolimod values.
Conclusions: After six months of Fingolimod treatment, all MS patients had reduced cardiac-autonomic modulation. However, only the 11 MS patients with initially prolonged HR slowing had unchanged parasympathetic modulation and lower HR than before Fingolimod, indicating an inability to withdraw cardiovagal modulation. While CAN adjustment seems to counterregulate Fingolimod-induced HR-slowing by lowering cardiovagal output in the 23 MS patients without initially prolonged HR-slowing, such CAN regulation seems to fail in the 11 MS patients with initially prolonged HR-slowing. MS lesion might interfere with the adequate CAN regulation in these 11 patients.
Disclosure: This study was financially supported by Novartis Pharma, Germany.

Poster 104

Heart rate variability in women working in hospital: a comparison between women with and without preschool children

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For women the conciliation between career and family is a relevant ongoing issue. Aim of this pilot study was to investigate the cardiac autonomic profile in working women with and without preschool children. We enrolled 34 women working in our hospital: 18 had preschool children (W-KIDS) and 16 did not (W-NOKIDS). Nurses, physicians, healthcare assistants, and physiotherapists were equally present in the two groups. A standard 5-lead 24-hour ECG recording was obtained during a regular working day. Long-term power spectral analysis was performed on the RR interval (RR) series during daytime (DAY) and nighttime (NIGHT). Mean RR (μ_{RR}), and RR series variance (σ^2_{RR}) were calculated. The absolute power in high frequency band (HF, 0.15–0.5 Hz) of the RR series, HF_{RR}, was considered as an index of the vagal modulation directed to the heart. During NIGHT, μ_{RR} was lower in W-KIDS than in W-NOKIDS (882 ± 133 vs 975 ± 139 ms); also, σ^2_{RR} and HF_{RR} were smaller in W-KIDS than in W-NOKIDS (1840 ± 1713 vs 5133 ± 4214 ms^2; 393 ± 355 vs 1845 ± 1979 ms^2). During DAY, these differences did not reach the statistical significance. Therefore, W-KIDS were characterized by a higher heart rate and a lower vagal activity directed to the heart compared to W-NOKIDS. These results suggest that the presence of preschool children influences the cardiac regulation of female workers. The higher sympathetic activation in resting condition, in particular during nighttime, could be the result of an increased level

of stress due to the combination of working condition and family management. Alternatively, it could represent a physiological adaptation favoring a prompt reaction of the mother in case of child's need.

Poster 105

Investigating the relationship between cardiac interoception and heart rate variability via interoceptive (active) inference

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Introduction: Predictive coding models, such as the 'free-energy principle', propose that the brain recognises the causes of sensory afferent input using probabilistic (Bayesian) inference. Recently, this has been discussed in terms of interoception (i.e., interoceptive inference) to understand how interoceptive predictions and prediction errors may inform autonomic mediation of homeostasis. We applied the theoretical principles of interoceptive inference to investigate the relationship between interoception and autonomic control in health and three disorders of aberrant sympathetic or parasympathetic over-excitation.
Methods: We studied 23 healthy controls, 21 postural tachycardia syndrome (PoTS), 20 vasovagal syncope (VVS) and 20 essential hyperhidrosis (EH) participants. Subjective (interoceptive sensibility), objective (interoceptive accuracy [IA]) and metacognitive (interoceptive awareness) measures of cardiac interoception were recorded with heart rate variability (HRV) during rest and autonomic arousal, which was induced actively (isometric exercise, cold pressor manoeuvres) and passively (head up tilt [HUT]).
Results: Compared to controls, IA—as measured by heartbeat tracking tasks—was diminished in PoTS, VVS and EH patients. In controls, IA positively significantly correlated with HRV at supine baseline and during pressor manoeuvres but not during HUT. Conversely, in patients with PoTS, VVS and EH, interoceptive measures were significantly negatively correlated with HRV during HUT.
Conclusions: Our data suggest PoTS, VVS and EH patients share a central pathophysiology underlying interoceptive deficits expressed across distinct cardiovascular (PoTS, VVS) and thermoregulatory (EH) peripheral pathophysiology. The reduced IA and negative correlations between interoceptive measures and HRV are consistent with a failure to modulate/contextualise ascending interoceptive prediction errors. In PoTS and VVS, this is reinforced by the concomitant failure to engage autonomic reflexes during HUT. Our study offers a new framework for conceptualizing how interoceptive afferent signals construct predictions about the homeostatic state of the body, and how the central and autonomic nervous systems synchronously respond to maintain homeostasis.

Poster 106

Clinical autonomic testing in autism spectrum disorder

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Introduction: Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterised by sensory and socio-emotional deficits. Previous studies report exaggerated sympathoexcitation in ASD but have predominantly focused on sudomotor, pupillary and oculomotor responses to sensory emotional stimuli in child cohorts. This study utilised clinical autonomic test protocols to examine sympathetic and parasympathetic cardiovascular function in 18 ASD subjects (12 male) in comparison to 19 age-matched (13 male) healthy control subjects.
Methods: Established and validated protocols assessed sympathetic vasoconstriction (mental arithmetic, isometric exercise, cutaneous cold pressor responses), vagal withdrawal (hyperventilation), cardiac vagal nerve function (respiratory sinus arrhythmia [RSA]), cardio-vagal and adrenergic function (Valsalva manoeuvre), orthostatic tolerance and adrenergic function during 10 min head-up tilt (HUT) and 45 min prolonged HUT (pHUT). During orthostatic challenges, patients' lower extremities were examined for signs (e.g., cyanotic discoloration) of pooling of blood, indicative of impaired venous return.
Results: 10 ASD subjects had a diagnosis of joint hypermobility syndrome (JHS)—a biomarker for impaired venous return and orthostatic intolerance (OI), 6 with postural tachycardia syndrome (PoTS), 5 with vasodepressor vasovagal syncope (VVS) and 2 with essential hyperhidrosis. In comparison to control data, ASD participants had increased baseline diastolic blood pressure (DBP) ($p = .003$) and heart rate (HR) ($p = .003$) throughout testing. During cold pressor ($p = .004$), mental arithmetic ($p = .002$) and HUT ($p = .002$), ASD subjects' HR was increased. Systolic blood pressure (SBP) ($p = .003$) and DBP ($p = .006$) responses were blunted in the ASD group during isometric exercise. ASD RSA indicated reduced vagally-mediated cardiac deceleration ($p = .001$).
Conclusions: The current findings implicate both the sympathetic and parasympathetic nervous systems in peripheral ASD pathophysiology. Our data suggests OI may be over-represented in ASD, potentially in association with JHS, which is common in ASD. The interaction of autonomic symptoms with cognitive-affective and socio-emotional symptomatology warrants further investigation in child and adult ASD patient groups.

Poster 107

Autonomic symptoms endorsed by adults with autism spectrum disorders

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Objective: To describe autonomic symptomatology endorsed by adults with autism spectrum disorders on the Compass 31, a survey instrument that captures multiple autonomic symptoms.
Background: Autonomic features such as abnormal skin conductance and pupillary responses have been reported in individuals with ASDs, but to our knowledge no systematic approach to identifying autonomic symptomatology has been conducted in adults with ASDs.
Design/Methods: The Compass 31, a quantitative measure of autonomic symptomatology was administered anonymously to 48 adults with ASDs. Subjects were recruited at local autism community meetings or were mailed the instrument after expressing interest in participation. The latter subjects were identified from a database maintained by the Arizona State University Autism/Asperger's Research Program.
Results: Weighted Compass 31 total and subscale scores [mean (SD), (range)] were as follows: Total score (Maximum = 100)–23.5 (16.1), (2.8–60.7); Orthostatic intolerance subscale (Maximum = 40)–9.5 (9.8), (0.0–28.0); Vasomotor subscale (Maximum = 5)–0.6 (1.2),

(0.0–4.2); Secretomotor subscale (Maximum = 15)–3.7 (3.2), (0.0–10.7); Gastrointestinal subscale (Maximum = 25)–6.2 (3.8), (0.0–18.7); Bladder subscale (Maximum = 10)–1.2 (1.5), (0.0–6.7); Pupillomotor subscale (Maximum = 5)–1.8 (1.3), (0.0–5.0). The most commonly endorsed subscales (weighted subscale score >0) in this sample were Gastrointestinal (97.9 %) and Pupillomotor (83.3 %).

Conclusions: Autonomic symptomatology was not uncommon in this sample of adults with ASDs, with gastrointestinal and pupillomotor symptoms commonly endorsed. Such symptomatology may represent autonomic dysfunction amenable to therapeutic intervention, which will need to be confirmed in future studies including clinical autonomic testing. Amelioration of such symptomatology may help to improve quality of life for a subset of individuals with ASDs. Supported by: Mayo Clinic Intramural Career Development Award.

Poster 108

Validity of bedside tests for evaluating sweating in normal and anhidrotic patients

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Background: Various bedside tests for determining the distribution of sweating are well known but of unproven validity.

Aim: To evaluate sensitivity and specificity of five bedside tests versus the thermoregulatory sweat test (TST) in a controlled prospective study.

Methods: A total of 146 patients were included (32 male, 114 female; mean age, 39.5 [range 16–83] years). Patients were off all medications for 5 days. Unclothed patients were acclimated at 80 °F and 35 % humidity for 10 min. Sweating was assessed with naked eye observation, light reflection, ophthalmoscopic magnification, skin palpation, and the spoon test. Seven representative bilateral symmetrical body sites were examined: lateral forehead, neck, upper chest, medial forearm, hand dorsum, proximal leg, and proximal foot. TST by starch-iodine method at 110–120 °F and 35–40 % humidity followed. The data were tabulated and each bedside test was compared to the results of TST, a gold standard, for evaluating sensitivity and specificity for detection of sweating.

Results: TST displayed generalized sweating (normal at all sites) in 130 patients and total anhidrosis in 16 patients. The spoon test had the highest sensitivity at all 14 sites, ranging from 4 % at the forearms and legs to 87 % at the neck. Sensitivity of naked eye examination was the lowest, ranging from 0 % at the leg to 5 % at the forehead. All bedside tests were more sensitive in detecting sweating at the forehead, neck, and upper chest. Every test except the spoon test exhibited 100 % specificity. The spoon test displayed specificity of 94 % at the forehead, 81 % at the chest, and 56 % at the neck.

Conclusions: (1) Although variable by methods and body site, sensitivity of bedside tests was low compared with TST for detecting sweating in the limbs. (2) The spoon test had higher sensitivity in detecting sweating at the forehead, neck, and chest but showed low specificity at the neck. (3) The spoon test is an inexpensive and convenient way of assessing sweating at the forehead and chest.