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ABSTRACTS

29TH INTERNATIONAL SYMPOSIUM ON THE AUTONOMIC NERVOUS SYSTEM

Newport Beach Marriott
Newport Beach, California
October 24–27, 2018

Preliminary Program

WEDNESDAY, OCTOBER 24, 2018

8:00 AM–5:00 PM	**Generalist Workshop and UCNS Review Course**
5:00–6:30 PM	**Registration**
6:30–9:00 PM	**Poster Session I and Trainee Poster Competition** (cheese and wine)

THURSDAY, OCTOBER 25, 2018

7:00–8:20 AM	**Continental Breakfast**
8:20–8:30 AM	**Welcome Remarks** William P. Cheshire, M.D President, American Autonomic Society
8:30–9:15 AM	**Robertson Plenary Lecture** The norepinephrine transporter and human cardiovascular disease Jens Jordan, M.D

Session 1: *Blood Pressure Regulation*
Chairs: André Diedrich and Rasna Sabharwal

9:15–9:30 AM	**FMS/Penaz Wesseling Travel Fellowship Award** Functional brainstem imaging reveals brainstem nuclei governing human baroreflex function D.A. Gerlach, J. Manuel, A. Hoff, H. Kronsbein, F. Hoffmann, K. Heusser, F. Beissner, J. Tank Cologne, Germany
9:30–9:45 AM	**FMS/Penaz Wesseling Travel Fellowship Award** Sex and age differences in sympathetic vascular baroreflex function: insights from neck collar stimulation and an orthostatic stress test M.G. Lloyd, V.E. Claydon Burnaby, BC, Canada
9:45–10:00 AM	Sex-differences in the sympathetic neural recruitment and hemodynamic response to head-up tilt in elderly hypertensives M.B. Badrov, Y. Okada, M.M. Galbreath, J.-K. Yoo, W. Vongpatanasin, J.K. Shoemaker, B.D. Levine, Q. Fu Dallas, Texas, USA
10:00–10:15 AM	Norepinephrine transporter dysfunction contributes to increased sympathetic tone in a mouse model of hypertrophic cardiomyopathy R.A. Larson, Y. Lu, L.K. Balcziak, M.W. Chapleau Iowa City, IA, USA
10:15–10:30 AM	Effects of 60-day head-down tilt bed rest on skeletal muscle-pump baroreflex M.F. Tremblay, D. Xu, R. Ruedl, N. Goswami, A.P. Blaber Burnaby, BC, Canada
10:30–11:00 AM	**Coffee Break**
11:00–11:45 AM	**Hot Topic Plenary Lecture** Neuromodulation focused therapeutics for cardiac disease: structure/function foundations Jeffrey Ardell, Ph.D Los Angeles, CA, USA
11:45–2:00 PM	**Poster Session II** (lunch)

2:00–4:00 PM **Free Time**
4:00–5:30 PM **Trainee Session**
(mentor–mentee round tables)
6:00–6:45 PM **Streeten Plenary Lecture**
Roy Freeman, M.D
Boston, MA, USA

Session 2: *Autonomic Neuropathy and POTS*
Chairs: Amanda Peltier and Steven Vernino

6:45–7:00 PM **Streeten Travel Fellowship Award**
Sweat gland nerve fiber density: development of a novel unbiased reconstruction methodology
K. Minota, A.M. Schmeichel, J.D. Schmelzer, J. Mandrekar, P.A. Low, W. Singer
Rochester, MN, USA
7:00–7:15 PM Familial amyloid polyneuropathy: impact of biopsies and mutations on diagnostic considerations
C.H. Gibbons, A. Gonzalez-Duarte, F. Barroso, M. Campagnalo, S. Rajan, J.Y. Kim, R. Freeman
Boston, MA, USA
7:15–7:30 PM Impact of patisiran on autonomic neuropathy in hereditary transthyretin-mediated (hATTR) amyloidosis patients
A. Gonzalez-Duarte, D. Adams, M. Mauermann, T. Coelho, C.C. Yang, M. Polydefkis, A. Kristen, I. Tournev, H. Schmidt, J.L. Berk, K.P. Lin, P.J. Gandhi, M. Sweetser, M. White, J. Gollob, O. Suhr
Mexico City, Mexico
7:30–7:45 PM Adrenal gland stimulation is intact in patients with postural tachycardia syndrome
S. Paranjape, E.M. Garland, V. Nwazue, B.K. Black, J. Celedonio, C.A. Shibao, L.E. Okamoto, A. Gamboa, A. Diedrich, I. Biaggioni, D. Robertson, S.R. Raj
Nashville, TN, USA
7:45–8:00 PM Epidemiology of postural tachycardia syndrome
M.A. AbdelRazek, P.A. Low, W. Rocca, A. Chamberlain, B. Abbott, W. Singer
Rochester, MN, USA
8:00–8:30 PM **The Felicia Axelrod Award**
Jose-Alberto Palma, M.D., Ph.D
New York, NY, USA
8:30–8:45 PM **Awards Presentations, FAAS**

FRIDAY, OCTOBER 26, 2018

7:00–8:30 AM **Continental Breakfast**
8:30–9:15 AM **Groundbreaking Research Plenary Lecture**
A novel autosomal recessive orthostatic hypotension syndrome: a new kid on the block
Ron A. Wevers
Nijmegen, The Netherlands

Session 3: *Orthostatic Hypotension, Supine Hypertension, and Syncope*
Chairs: Jens Jordan and Jose-Alberto Palma

9:15–9:30 AM Congenital CYB561 deficiency causing isolated noradrenergic failure
I. Biaggioni, E. Garland, B. Black, D. Robertson, C.A. Shibao
Nashville, TN, USA
9:30–9:45 AM Familial autonomic ganglionopathy caused by rare CHRNA3 genetic variants. Novel genetic cause of neurogenic orthostatic hypotension
C.A. Shibao, J.A. Phillips, J.D. Cogan, J.H. Newman, R. Hamid, J.H. Sheehan, B. Black, D. Robertson, I. Biaggioni; Collaborators of Undiagnosed Diseases Network (UDN)
Nashville, TN, USA
9:45–10:00 AM Acute, dose-dependent, blood pressure-lowering effect of continuous positive airway pressure in autonomic failure patients with supine hypertension
L.E. Okamoto, J.E. Celedonio, A. Diedrich, C.A. Shibao, A. Gamboa, B.K. Black, S. Paranjape, D. Robertson, I. Biaggioni
Nashville, TN, USA
10:00–10:15 AM Norepinephrine transporter inhibition with atomoxetine prevents tilt-induced vasovagal syncope: a randomized, placebo-controlled trial
L. Lei, J.C. Guzman, T. Kus, F. Araya-Paredes, J. Angihan, G. Bennett, C. Maxey, R.S. Sheldon, S.R. Raj
Calgary, AB, Canada
10:15–10:30 AM Is cerebrovascular autoregulation (CA) impaired during head-up tilt (HUT)-induced vasovagal syncope (VVS)? Inferences derived from selective falls in total peripheral resistance (TPR) or cardiac output (CO)
R. Schondorf, S. Balegh, J. Benoît, B. Ditto
Montreal, QC, Canada
10:30–11:00 AM **Coffee Break**

11:00–11:45 AM **MSA Plenary Lecture**
Multiple system atrophy: are we ready to tame the beast?
Gregor Wenning, M.D., Ph.D
Innsbruck, Austria

Session 4: *Multiple System Atrophy*
Chairs: William Cheshire and Wolfgang Singer

11:45–12:00 PM Discovery and validation of MRI morphometry features for early multiple system atrophy
P. Vemuri, Y. Varatharajah, A.M. Castillo, K.B. Thostenson, C. Ward, T.L. Gehrking, J.A. Gehrking, A.D. Zeller, C.R. Jack Jr, P.A. Low, W. Singer
Rochester, MN, USA

12:00–12:15 PM Cutaneous alpha-synuclein deposition in multiple system atrophy
C.H. Gibbons, N. Wang, S. Rajan, D. Kern, J.A. Palma, H. Kauffman, R. Freeman
Boston, MA, USA

12:15–12:30 PM Alpha-synuclein deposition in noradrenergically innervated pilomotor muscles distinguishes Lewy body forms of neurogenic orthostatic hypotension from multiple system atrophy
D.S. Goldstein, N. Wang, C.H. Gibbons, R. Freeman
Bethesda, MD, USA

12:30–1:00 PM **Presentations from Top 4 Posters**
(4 @ 5 min each)

1:00–7:00 PM **Free Time/Lunch on your own**

2:00–4:00 PM **AAS Board Meeting**

4:00–5:00 PM **CAR Editorial Board Meeting**

5:00–6:00 PM **AAS Committee Meetings**

7:00–10:00 PM **Presidential Dinner**

SATURDAY, OCTOBER 27, 2018

7:00–8:30 AM **Continental Breakfast**

8:30–9:15 AM **Cognitive Dysfunction in Autonomic Disorders Plenary Lecture**
Norepinephrine and cognition: revisiting an old friend
Daniel Claassen, M.D., M.S
Nashville, TN, USA

Session 5: *Autonomic Regulation of Heart and Vasculature*
Chairs: Saharnaz Balegh and Victoria Clayden

9:15–9:30 AM Cortical morphometric predictors of autonomic dysfunction in generalized anxiety disorder
L. Carneval, M. Mancini, J. Koenig, E. Makovac, D.R. Watson, F. Meeten, H.D. Critchley, C. Ottaviani
Rome, Italy

9:30–9:45 AM Active forelimb exercise mitigates susceptibility to cardiac arrhythmia compared to passive hindlimb cycling in rats with high-level spinal cord injury
V.E. Lucci, E.L. Harrison, K.M. DeVeau, K.A. Harmon, J. Liu, J. Squair, A. Krassioukov, D. Magnuson, C.R. West, V.E. Claydon
Burnaby, BC, Canada

9:45–10:00 AM Autonomic dysreflexia (AD) in individuals with SCI: the association between elevations in blood pressure and symptoms of AD over a 30 day observation period
C.G. Katzelnick, T.A. Dyson-Hudson, W.A. Bauman, S. Kirshblum, N.D. Chiaravalloti, J.M. Wecht
Bronx, NY, USA

10:00–10:15 AM Low frequency hemodynamic oscillations distinguish migraineurs from non-headache controls
M.M. Cortez, J.J. Theriot, N.A. Rea, D. Hunter, F.E. Gowen, K.C. Brennan
Salt Lake City, UT, USA

10:15–10:45 AM **Coffee Break**

10:45–12:00 PM **Case Presentations**
Introduction: Juan Guzman

12:00–12:30 PM **AAS Business Meeting**

12:30–12:45 PM **Closing Remarks**
William P. Cheshire, M.D.
President, American Autonomic Society

POSTER SESSION I
WEDNESDAY, OCTOBER 24, 2018
6:30–9:00 PM
Trainee *Poster Competition** Judges: AAS Board Members
Autonomic Failure

Poster #1* Non-motor symptoms and gender differences in multiple system atrophy
S. Eschlböck, T. Benke, S. Bösch, M. Delazer, A. Djamshidian-Tehrani, A. Fanciulli, R. Granata, B. Högl, C. Kaindlstorfer, G. Kiss, F. Krismer, K. Mair, M. Nocker, C. Raccagni, C. Scherfler, K. Seppi, A. Stefani, W. Poewe, G. Wenning
Innsbruck, Austria

Poster #2* Alpha-synuclein deposition in sympathetic noradrenergic nerves and cardiac noradrenergic deficiency distinguish Lewy body from non-Lewy body forms of neurogenic orthostatic hypotension
R. Isonaka, P. Sullivan, A. Corrales, A.Z. Rosenberg, C. Holmes, D.S. Goldstein
Bethesda, MD, USA

Poster #3 The impact of supine hypertension on target organ damage and mortality in patients with neurogenic orthostatic hypotension
J.A. Palma, G. Redel-Traub, A. Porciuncula, D. Samaniego-Toro, Y.W. Lui, L. Norcliffe-Kaufmann, H. Kaufmann
New York, NY, USA

Poster #4* Relationship between cardiac sympathetic modulation and inflammation after repetitive automatic mechanical somatosensory stimulation (AMSS) in Parkinson's disease
D. Shiffer, F. Barbic, M. Minonzio, A.R. Zamuner, C.P. Andrade, B. Bottazzi, C. Garlanda, R. Leone, B. Cairo, A. Porta, A. Mantovani, R. Furlan
Rozzano, Italy

Poster #5* Early onset of autonomic failure distinguishes the parkinsonian variant of multiple system atrophy from Parkinson's disease
A. Fanciulli, G. Goebel, G. Lazzeri, C. Scherfler, E.R. Gizewski, R. Granata, G. Kiss, S. Strano, C. Colosimo, F.E. Pontieri, H. Kaufmann, K. Seppi, W. Poewe, G.K. Wenning
Innsbruck, Austria

Supine Hypertension and Neurogenic Orthostatic Hypotension

Poster #6* Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS)
A. Fanciulli, J. Jordan, I. Biaggioni, G. Calandra-Buonaura, W.P. Cheshire, P. Cortelli, S. Eschlboeck, G. Grassi, M.J. Hilz, H. Kaufmann, H. Lahrmann, G. Mancia, G. Mayer, L. Norcliffe-Kaufmann, A. Pavy Le Traon, S.R. Raj, D. Robertson, I. Rocha, W. Struhal, R. Thijs, K.P. Tsioufis, J.G. Van Dijk, G.K. Wenning
Innsbruck, Austria

Autonomic Regulation: *Basic Science and Animal Studies*

Poster #7* Unresponsiveness of baroreflex sympathetic regulation leads to orthostatic intolerance in a rat model of type 2 diabetes mellitus
K. Kamada, K. Saku, H. Tsutsui, K. Sunagawa
Fukuoka, Japan

Poster #8 Human deep brain stimulation as a tool to study the neural control of blood pressure and heart rate
P. Kumar, J.A. Palma, A. Mogilner, H. Kaufmann, M. Pourfar
New York, NY, USA

Poster #9 Susceptibility to cardiac arrhythmia increases with sympathetic stimulation in rodents with high-thoracic spinal cord injury
V.E. Lucci, E.L. Harrison, K.M. DeVeau, K.A. Harmon, J. Liu, J. Squair, A. Krassioukov, D. Magnuson, C.R. West, V.E. Claydon
Burnaby, BC, Canada

Poster #10* Heart rate variability and gastric myoelectric activity in women with chronic pelvic pain: a pilot study
D.P. Williams, E.R. Muth, C. Ustine, P. Simpson, T. Chelimsky, J.F. Thayer, G.Chelimsky
Columbus, OH, USA

Cardiovascular Disease, Obesity and Aging: *Human Studies*

Poster #11* The association between cardiac parasympathetic activity and the lipid accumulation product
D.P. Williams, M.N. Jarczok, J.E. Fischer, J. Koenig, D. Boschiero, E. Poggiogalle, J.F. Thayer
Columbus, OH, USA

Poster #12* Determining sex-specific waist circumference cut-off values for cardiovascular disease risk in individuals with spinal cord injury
M.C. Dorton, S. de Groot, M. Post, V.E. Claydon
Burnaby, BC, Canada

Poster #13 Arterial stiffness and spontaneous baroreflex sensitivity in African American women
P. Latchman, G. Gates, R. Thiel, T. Yue, R. Axtell, Q. Yang, K, Gardner, R. De Meersman
New Haven, CT, USA

Poster #14 Significance of efferent autonomic innervation and reactivity of arterial pressure in prognosis of patients with arterial hypertension
O.V. Mamontov, A.V. Kozlenok, A.A. Kamshilin, I.S. Brodskaya, E.V. Shlyakhto
St. Petersburg, Russia

Cardiac Autonomic Innervation: Humans

Poster #15* Assessing individual human baroreflex-chemoreflex interactions using an n-of-1 trial design
H. Kronsbein, K. Heusser, D. Gerlach, A. Hoff, F. Hoffmann, H. Ehmke, J. Jordan, J. Tank
Cologne, Germany

Poster #16 Stress response and role of autonomic nervous system in Takotsubo cardiomyopathy
K. Sato, H. Akagawa, T. Nakaoka, Y. Kubo, T. Komiyama, H. Kobayashi, H. Sakura
Tokyo, Japan

Poster #17 Attention and information processing impairment in individuals with chronic SCI: role of autonomic dysfunction
J.M. Wecht, J.P. Weir, C.G. Katzelnick, G. Wylie, W.A. Bauman, N.D. Chiaravalloti
Bronx, NY, USA

Diabetic, Autoimmune and Other Autonomic Neuropathies

Poster #18 Sudomotor dysfunction in diabetic autonomic neuropathy is not a frequent finding
A. Barboi, S. Pocica, V. Patel
Evanston, IL, USA

Gastrointestinal and Urogenital Systems, IBS, Cystitis

Poster #19 Fingolimod does not seem to affect autonomic bladder function in patients with relapsing–remitting multiple sclerosis
M.J. Hilz, K.M. Hösl, M. Liu, S. Roy, K. Winder, R. Linker, D.-H. Lee, R. Wang
Nuremberg, Germany

Poster #20* Uroflowmetry and bladder ultrasonography non-invasively quantify slightly impaired autonomic bladder function in patients with relapsing–remitting multiple sclerosis
R. Wang, S. Roy, M. Liu, K.M. Hösl, K. Winder, R. Linker, D.-H. Lee, M.J. Hilz
Erlangen, Germany

Sympathovagal Balance and Spectral Analysis

Poster #21* Persistent baroreflex dysfunction in patients with a history of moderate or severe traumatic brain injury
S. Roy, M. Liu, R. Wang, F. Ammon, K.M. Hösl, J. Markus, D. Murasenu, M.J. Hilz
Erlangen, Germany

Poster #22 Psychological and physiological effects of 12 weeks of slow breathing exercise on healthy subjects
A. Gamboa, S. Paranjape, A. Diedrich, K. Nelson, A. Coppola, R. Abraham, H. Nian, K. Wallston, G. Birdee
Nashville, TN, USA

Poster #23 Prediction of systolic blood pressure responses to orthostasis in persons with spinal cord injury
M.F. La Fountaine, J.P. Weir, C.G. Katzelnick, A.T. Lombard, M.T. Maher, J.M. Levine, J.M. Wecht
Bronx, NY, USA

Poster #24* Optimization of heart rate variability testing
S. Rajan, M. Campagnalo, V. Galvis, C.H. Gibbons
Boston, MA, USA

Microneurography and Cardiovascular Reflexes in Humans

Poster #25 Reproducibility of Valsalva maneuver derived baroreflex parameters
C. Ustine, J. De Los Santos, P. Simpson, G. Chelimsky, T. Chelimsky
Milwaukee, WI, USA

Poster #26 Ventilatory and cerebrovascular response to metaboreflex activation while supine or upright in men and women
H. Joshi, H. Edgell
Toronto, ON, Canada

Poster #27* The effect of habitual physical activity on sympathetic vascular transduction
A.T. Robinson, M.C. Babcock, J.C. Watso, K.U. Migdal, W.B. Farquhar
Newark, DE, USA

Poster #28 Stimulation of the dorsal root ganglion (DRG) for medicine refractory chronic neuropathic pain: Is there sympathetic involvement?
Y.B. Sverrisdottir, J. Fitzgerald, A. Kent, J. Kramer, A.L. Green
Oxford, UK

Poster #29* Heightened sympathetic neural and blood pressure responses to cold pressor test in women with PTSD
J.-K. Yoo, M.B. Badrov, R.S. Parker, E.H. Anderson, A.M. Suris, Q. Fu
Dallas, TX, USA

Neuroimaging in Brain and Heart

Poster #30* Resting state fMRI functional connectivity of the PAG in healthy adolescents and adolescents with functional gastrointestinal disorder
C. Ustine, L. Conant, S. Rausch, D. Bierer, K. Yan, P. Simpson, T. Chelimsky, G. Chelimsky
Milwaukee, WI, USA

Poster #31 Distinguishing multiple system atrophy and Parkinson's disease using resting state functional MRI: a pilot study
M. Sklerov, N. Browner, E. Dayan
Chapel Hill, NC, USA

Poster #32* Evidence of cortical autonomic impairment in the pathophysiology of neurogenic orthostatic hypotension associated with peripheral autonomic dysfunction
J. Baker, J. Paturel, K. Kimpinski
London, ON, Canada

Orthostatic Hypotension and Syncope

Poster #33* The Orthostatic Discriminate and Severity Scale (ODSS): a tool to discriminate orthostatic from non-orthostatic symptomatology
J. Baker, J.R. Paturel, D.M. Sletten, P.A. Low, K. Kimpinski
London, ON, Canada

Poster #34* Can head-up tilt (HUT) be used to distinguish between clinical sub-groups of vasovagal syncope (VVS): the Heisenberg principle at play
S. Balegh, J. Benoit, B. Ditto, R. Schondorf
Montreal, QC, Canada

Poster #35 Effects of droxidopa treatment for neurogenic orthostatic hypotension in patients concomitantly on dopa decarboxylase inhibitors
S. Kymes, C. François, C. Sullivan, K. McLeod, A. Duhig, A. Ogbonnaya, A. Quillen, J. Cannon, I. Biaggioni, C.A. Shibao, B. Yue, R.A. Hauser
Palm Harbor, FL, USA

Poster #36* Diagnosis of orthostatic hypotension: contribution of diastolic blood pressure
S. Galvis, M. Campagnalo, S. Rajan, C.H. Gibbons
Boston, MA, USA

Poster #37 Can the Valsalva maneuver serve as a biomarker for syncope diagnoses?
B.C.D Hockin, C. Johnston, E. Williams, M.G. Lloyd, V.E. Claydon
Burnaby, BC, Canada

Poster #38 The relationship between changes in orthostatic blood pressure and symptoms in patients with orthostatic hypotension
B.M.W. Illigens, R. Lapusca, M. Campagnolo, A. Abuzinadah, D.I. Sinn, L. Walsh, J. White, C.H. Gibbons, R. Freeman
Boston, MA, USA

Pediatric Autonomic Disorders

Poster #39* Validation of finger blood pressure monitoring in children
N.D. Heeney, F. Habib, G. Brar, G. Krahn, D.A. Campbell, S. Sanatani, V.E. Claydon
Burnaby, BC, Canada

Poster #40* Menstrual irregularities in pediatric postural orthostatic tachycardia syndrome
K.N. Leopold, K.M. Klaas, A. Javed, E.E. Bolen, W.D. Bunn, S.H. Hasan
Rochester, MN, USA

Postural Orthostatic Tachycardia Syndrome (POTS)

Poster #41 Silicone breast implant rupture as a cause of postural orthostatic tachycardia syndrome (POTS)
W. Almardini, S.B. Alam, M.A. Nasri, H. Mistry, N. Noor, S. Alam, Z. Rehman, M. Rajumon, L.B. Gaied, B. Sheikh, A. Suleman
McKinney, TX, USA

Poster #42 Postural tachycardia syndrome and pregnancy: insights from a cross-sectional community based survey
K. Bourne, L. Stiles, B.H. Shaw, C.A. Shibao, L.E. Okamoto, E.M. Garland, A. Gamboa, A. Peltier, A. Diedrich, I. Biaggioni, D. Robertson, S.R. Raj
Calgary, AB, Canada

Poster #43 Small fiber neuropathies and related autoimmunity in postural orthostatic tachycardia syndrome
G.A. Cook
Bethesda, MD, USA

Poster #44* POTS patients vs. healthy controls: similar postural tachycardia, different symptom burden
E. Golden, M. Bryarly, L. Phillips, M. Vernino, S. Vernino
Dallas, TX, USA

Poster #45 Is pseudobulbar affect unique to PoTS? Emotional lability in orthostatic intolerance
R.K. Khurana
Baltimore, MD, USA

Poster #46 Antimuscarinic autoimmunity in postural tachycardia syndrome
H. Li, X. Yu, G. Zhang, D.C. Kem
Oklahoma City, OK, USA

Poster #47 Impaired glucose homeostasis in lean women with postural tachycardia syndrome
S.E. Mehr, S.Y. Paranjape, S. Scudder, S. Lonce, J. Celedonio, B. Preheim, B. Plunkett, C.A. Shibao
Nashville, TN, USA

Poster #48 Prevalence and treatment of small intestinal bacterial overgrowth (SIBO) in patients with postural orthostatic tachycardia syndrome (POTS)
Z. Rehman, M. Rajumon, S.B. Alam, W. Almardini, H. Mistry, A. Khan, N. Noor, L.B. Gaied, S. Alam, B. Sheikh, M.A. Nasri, A. Suleman
McKinney, TX, USA

Poster #49 Postural hyperventilation as a cause of POTS
J.M. Stewart, P. Pianosi, M.A. Shaban, C. Terilli, M. Svistunova, P. Visintainer, M.S. Medow
Valhalla, NY, USA

Poster #50 A rabbit model of autoimmune postural tachycardia syndrome
X. Yu, H. Li, G. Zhang, L. Zhou, D.C. Kem
Oklahoma City, OK, USA

POSTER SESSION II
THURSDAY, OCTOBER 25, 2018
11:45–2:00 PM
Autonomic Failure

Poster #51 Inter-rater agreement of thermoregulatory sweat testing (TST)
A. Arvantaj, J. Robinson, C. Geiger, B. Katirji
Cleveland, OH, USA

Poster #52 Quantification of thermoregulatory sweat testing (TST)
A. Arvantaj, J. Robinson, C. Geiger, B. Katirji
Cleveland, OH, USA

Poster #53 Neurogenic orthostatic hypotension unawareness in multiple system atrophy compared to peripheral autonomic neuropathy
W.P. Cheshire
Jacksonville, FL, USA

Poster #54 Symptom burden within one year differentiates rapidly progressive multiple system atrophy
E.A. Coon, D.M. Sletten, J.N. Mandrekar, M. Suarez, J.E. Ahlskog, J.H. Bower, P. Sandroni, E.E. Benarroch, P.A. Low, W. Singer
Rochester, MN, USA

Poster #55 Pure autonomic failure with sick sinus syndrome of reduced striatal DAT binding
M. Sugiura, K. Sato, Y. Nishimura, Y. Kubo, T. Nakaoka, K. Shibata, H. Sakura
Tokyo, Japan

Cardiac Autonomic Innervation: *Humans*

Poster #56 Neuroimaging evidence for decreased cardiac sympathetic innervation and a vesicular storage defect in residual nerves in Lewy body forms of neurogenic orthostatic hypotension
D.S. Goldstein, C. Holmes, Y.-S. Ding, Y. Sharabi
Bethesda, MD USA

Poster #57 Effects of different classroom temperatures on cardiac autonomic control and cognitive performance in students
M. Minonzio, F. Barbic, B. Cairo, D. Shiffer, A. Dipasquale, L. Cerina, A. Vatteroni, P. Verzeletti, F. Badilini, M. Vaglio, R. Iatrino, A. Porta, M. Santambrogio, R. Gatti, R. Furlan
Rozzano, Italy

Poster #58 Central acetylcholinesterase inhibitor, galantamine, prevents lipid-induced oxidative stress in African Americans
J.E. Celedonio, S.E. Mehr, S.Y. Paranjape, A. Diedrich, C.A. Shibao
Nashville, TN, USA

Cerebral Blood Flow Regulation

Poster #59 Comparison of cerebral oxygen saturation patterns in adolescents with autonomic dysfunction who experience syncope versus convulsive syncope during head up tilt testing
E.M. Smith, S.S. Hashmi, A. Gourishankar, M.T. Numan, I.J. Butler, J.E. Lankford
Houston, TX, USA

Poster #60 Hypocapnic cerebral hypoperfusion: a biomarker of orthostatic intolerance
P. Novak
Boston, MA, USA

Poster #61 Prevalence of convulsions in the pediatric population with orthostatic intolerance and neuro-cardiogenic syncope
M.T. Numan, H. Varner, J.E. Lankford, I.J. Butler
Houston, TX, USA

Comorbidities of Fibromyalgia, Migraine, Depression

Poster #62 What chronic disorders overlap with the migraine complex?
D. Bierer, E. Awe, A. Mueller, A. Husain, G. Chelimsky*, T. Chelimsky*
Milwaukee, WI, USA

Diabetic, Autoimmune and Other Autonomic Neuropathies

Poster #63 Quality improvement and practice-based research in autonomic neuropathy using the electronic medical record
A. Barboi, V. Patel, O. Kincaid, D. Randall, S. Pocica, L. Gardun, M. Szela, S
Evanston, IL, USA

Poster #64 Autoimmune component of diabetic autonomic gastroparesis
M.C. Yu, H. Li, S. Li, D.C. Kem
Oklahoma City, OK, USA

Exercise, Temperature Regulation and Hypoxia

Poster #65 A new approach in assessing vasomotor reactivity in response to cold stress using non-contact optical technology
O.V. Mamontov, V.V. Zaytsev, E.V. Shlyakhto, A.A. Kamshilin
St. Petersburg, Russia

Genetic Autonomic Disorders

Poster #66 Impaired sensorimotor control of the hand in congenital absence of functional muscle spindles
L.J. Smith, J.A. Palma, L. Norcliffe-Kaufmann, H. Kaufmann, V.G. Macefield
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ORAL PRESENTATIONS

Robertson Plenary Lecture

The norepinephrine transporter and human cardiovascular disease

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Much of the norepinephrine released from adrenergic neurons is reclaimed through the neuronal norepinephrine transporter and either repacked or enzymatically degraded. Yet, the norepinephrine transporter has been neglected in cardiovascular medicine. Observations in familial norepinephrine transporter dysfunction highlighted the importance of the mechanism in human norepinephrine homeostasis and in cardiovascular control. The dominant negative norepinephrine transporter mutation (A457P) segregated with increased upright heart rate and biochemical evidence for impaired norepinephrine uptake. Subsequent studies using selective pharmacological norepinephrine transporter inhibition reproduced the phenotype and provided insight in human cardiovascular physiology with implications for pharmacotherapy. Norepinephrine transporter inhibition attenuates sympathetic activity in the brain, tends to augment sympathetic activity in peripheral tissues, and redistributes sympathetic activity towards the heart. The clinical implication is that medications inhibiting norepinephrine transport increase cardiac sympathetic activity, which can be unmasked by measuring upright heart rate. Paradoxically, individuals with higher centrally generated sympathetic activity are less likely to exhibit a pressor response on such medications. Pharmacological norepinephrine transporter inhibition can serve as human model for increased cardiac sympathetic activity. Moreover, norepinephrine transporter inhibition influences on the sympathetic nervous system can be therapeutically exploited. For example, norepinephrine transporter inhibition prevented neutrally mediated presyncope and syncope during head-up tilt testing. Norepinephrine transporter inhibition also ameliorates orthostatic hypotension in autonomic failure patients with residual sympathetic function.

Functional brainstem imaging reveals brainstem nuclei governing human baroreflex function

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Introduction: Brainstem nuclei mediate baroreflex adjustments in efferent sympathetic and parasympathetic traffic. Yet, human brainstem physiology is poorly understood given the lack of suitable methodology. We developed a novel approach combining pharmacological testing, beat-by-beat cardiovascular monitoring, and high-resolution functional magnetic resonance imaging (fMRI) to assess human baroreflex regulation at the level of the brainstem.
Methods: In 10 healthy men (29.7 ± 6.9 years; 80.1 ± 9.9 kg), we monitored continuous finger arterial blood pressure and ECG using customized hardware during multiband fMRI brain acquisitions. We applied repeated intravenous phenylephrine (PHE, 25 and 75 µg, n = 8) and nitroprusside (NTP 25 and 75 µg, n = 8) boluses using a remote controlled injector. Brainstem and hypothalamus fMRI images were analyzed to identify brainstem nuclei involved in baroreflex-mediated blood pressure control using tensorial masked Independent Component Analysis (mICA). BP changes were correlated with the time-courses of blood-oxygen-level dependent (BOLD) signals by mixed-effects general linear model.
Results: Pharmacological testing yielded reliable baroreflex sensitivity measurements in the MRI scanner. fMRI combined with the measurement of baroreflex-mediated changes in heart rate and blood pressure revealed nuclei regulated through baroreflex input. The strongest correlations between BOLD time-course and BP was observed in the left solitary tract (NTP: deactivation $P < 0.001$; z-score: 6.9), the caudal ventrolateral medulla (NTP: activation, right side: $P = 0.0012$; z-score: 4.11, left side: $P < 0.001$; z-score: 5.05), the rostral ventrolateral medulla (NTP: activation, right side $P < 0.001$; z-score: 7.25) and in the left paraventricular nucleus (PHE: activation $P < 0.001$; z-score: 9.00; NTP: activation $P < 0.001$; z-score: 7.11). P-values were Bonferroni corrected for 60 independent components.
Conclusion: We developed novel approach testing baroreflex regulation at the level of the brainstem in humans. The methodology identified baroreflex-mediated activation and deactivation patterns consistent with previous investigations in animal models. The methodology can be applied to elucidate human physiology and mechanisms of autonomic cardiovascular disease.

Sex and age differences in sympathetic vascular baroreflex function: insights from neck collar stimulation and an orthostatic stress test

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The baroreflex buffers rapid changes in blood pressure by altering vascular resistance and heart rate (HR). Age-related changes in baroreflex function appear to be sex-dependent, but are incompletely understood. We investigated age- and sex-related changes in baroreflex function. We hypothesized that baroreflex responses would decrease with age, and cardiac baroreflex control would predominate in women. We measured forearm vascular resistance (FVR: mean arterial pressure [finger plethysmography]/brachial blood flow velocity [Doppler ultrasound]) and HR (electrocardiography) in 49 participants (26 females, aged 19–84 years) during carotid baroreflex stimulation (neck collar) and maximal orthostatic stress (head-up tilt with combined lower body negative pressure continued until presyncope). Neck suction/pressure was applied at − 60, − 40, − 20, 0, 20, 40, and 60 mmHg. Baroreflex sigmoid curves were fitted, and cardiac (cBRS) and vascular (vBRS) baroreflex sensitivities calculated from the first derivative. vBRS (younger $-2.2 \pm 0.2\%$ mmHg^{-1}, older $-1.5 \pm 0.2\%$ mmHg^{-1}, $p = 0.03$) and cBRS (younger $7.7 \pm 0.5\%$ mmHg^{-1}, older $5.3 \pm 0.6\%$ mmHg^{-1}, $p = 0.0009$) were larger in younger (19–45 years) than older

(45–84 years) participants. The vascular baroreflex centering point was left-shifted in younger compared to older participants (−14 ± 6 mmHg, p = 0.01), despite similar operating points (p = 0.08). cBRS was larger in women (7.5 ± 0.9 ms $mmHg^{-1}$) than men (5 ± 0.9 ms $mmHg^{-1}$, p = 0.065), but vBRS was not different between sexes. Vascular baroreflex centering points were left-shifted compared to cardiac baroreflex curves ($p < 0.0001$) independent of age and sex. Independent of age and sex, buffering of hypotensive stimuli was predominantly achieved by changes in vascular resistance, while buffering of hypertensive stimuli was predominantly achieved though changes in cardiac output ($p < 0.0001$). In older participants, the vascular predominance to simulated hypotension was exacerbated (+20 ± 6%, p = 0.01). The maximum FVR response during orthostasis was smallest in younger women (all $p < 0.03$). HR responses to orthostasis were smaller in older participants (younger ΔHR = 47 ± 3 bpm, older ΔHR = 35 ± 4 bpm, p = 0.0095). We describe age- and sex-related changes in baroreflex function and the relative importance of vascular and cardiac responses in the maintenance of blood pressure.

Sex-differences in the sympathetic neural recruitment and hemodynamic response to head-up tilt in elderly hypertensives

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The current study tested the hypothesis that elderly hypertensive (HT) women have exaggerated blood pressure (BP) and sympathetic neural responses to orthostasis compared to elderly HT men. We measured, in 12 HT men (71 ± 2 years; mean ± SE) and 12 HT women (67 ± 2 years), BP (SunTech), heart rate (HR; ECG), cardiac output (CO; acetylene rebreathing), and multi-unit muscle sympathetic nerve activity (MSNA; microneurography) at baseline (supine; 3-min) and during graded head-up tilt (HUT; 30° for 5-min and 60° for 20-min). Sympathetic action potential (AP) discharge patterns were studied using wavelet-based methodology. Mean arterial BP increased during HUT ($P < 0.001$); however, the increase was greater in HT women at 10-min (Δ13 ± 2 vs. 5 ± 3 mmHg) and 20-min (Δ14 ± 3 vs. 3 ± 4 mmHg; both P 0.05). COi (indexed to body surface area) decreased similarly in both sexes throughout HUT ($P > 0.05$); yet, values were lower in HT women ($P < 0.05$). TPRi increased during HUT ($P < 0.001$); however, the increase was greater in HT women at 10-min (Δ2435 ± 240 vs. 1094 ± 241 dyn·s/cm^5/m^2) and 20-min (Δ2759 ± 244 vs. 1501 ± 211 dyn·s/cm^5/m^2; both P 0.05). However, the number of sympathetic APs per integrated burst increased in HT women (all P 0.05), at 5-min (Δ6 ± 1 vs. 1 ± 1 spikes/burst), 10-min (Δ7 ± 1 vs. 1 ± 1 spikes/burst), and 20-min (Δ8 ± 2 vs. 2 ± 1 spikes/burst) of 60° HUT. As such, sympathetic AP firing frequency was greater in HT women during 60° HUT (all $P < 0.05$). Thus, elderly HT women display enhanced pressor and peripheral vasoconstrictor responses to orthostasis than elderly HT men, which is likely attributable to augmented sympathetic neural recruitment, rather than burst frequency, in the upright posture.
Funding: NIH R01 HL091078.

Norepinephrine transporter dysfunction contributes to increased sympathetic tone in a mouse model of hypertrophic cardiomyopathy

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Sarcomere gene mutations cause hypertrophic cardiomyopathy (HCM). Hallmark features include cardiac hypertrophy, fibrosis, excessive cardiac sympathetic tone, and increased risk of arrhythmias and sudden death. Our group has previously reported that cardiac sympathetic tone is increased in transgenic mice with cardiac-specific expression of mutated alpha-tropomyosin (Glu180Gly), a model of human HCM. Studies in patients suggest that decreased reuptake of norepinephrine into sympathetic nerve terminals contributes to increased cardiac sympathetic tone in HCM. In the present study, we tested the hypothesis that decreased neuronal norepinephrine transporter (NET) activity contributes to increased sympathetic tone in HCM mice. NET activity was assessed by measuring acute mean arterial pressure (MAP) and heart rate (HR) responses to intravenous injection of the selective NET inhibitor reboxetine (3.3 μg/g) in anesthetized, vagotomized mice; and the rate of uptake of a fluorescent NET substrate (Molecular Devices) into individual sympathetic neurons isolated from stellate ganglia. Baseline MAP and HR were not significantly different in anesthetized HCM and WT littermate control mice. As expected, reboxetine increased MAP and HR in both groups of mice. While reboxetine-induced increases in MAP were significantly less in HCM (+20.3 ± 4 mmHg, n = 5) vs. WT (+42.5 ± 5 mmHg, n = 5) mice ($P < 0.05$), increases in HR were not significantly different in the two groups (+104 ± 9 vs. +119 ± 15 bpm, respectively). NET activity measured in isolated sympathetic neurons was significantly less in HCM (4.5 ± 0.3 a.u. * min^{-1}, n = 115 neurons, from 4 mice) vs. WT (5.3 ± 0.4 a.u. * min^{-1}, n = 98 neurons, from 4 mice). mRNA expression of NET measured in stellate ganglia by qPCR was not different in HCM (n = 6) vs. WT (n = 6) mice. In conclusion, HCM mice exhibit decreased NET activity that contributes to increased sympathetic tone.
Funding: NIH HL14388, F32HL140880, T32HL007121, AAS-Lundbeck Fellowship.

Effects of 60-day head-down tilt bed rest on skeletal muscle-pump baroreflex

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Post-spaceflight orthostatic intolerance relates to compromised autonomic cardiovascular and deteriorating postural control. During quiet standing, the skeletal muscle-pump baroreflex (MPBR) works with the arterial baroreflex (A-BR) to regulate blood pressure. The effects of microgravity on muscle-specific MPBR is unknown. We assessed the effects of a 60-day 6° head-down tilt bed rest (HDBR) on MPBR. Previous data suggested that MPBR responses changed with A-BR. We hypothesized that MPBR activation would decrease post-HDBR. Nineteen physically-fit males completed a supine-to-stand test (STS) with 5-min supine and 6-min quiet stand 12 and 2 days before, and 90-min (R0) and 8 days (R8) after HDBR. Continuous beat-to-beat systolic arterial pressure (SAP), electrocardiography (ECG), and

electromyography (EMG) recordings of tibialis anterior (TA), medial and lateral gastrocnemius (MG, LG), and soleus (S) muscles were made. SAP and ECG were also recorded during HDBR. MPBR and A-BR activity was assessed using wavelet transform coherence analysis (response gain and percent-time-active) in (HF) and low (LF) frequency bands between SAP and EMG (MPBR) and SAP and ECG (A-BR). Mean heart rate increased over HDBR ($p < 0.0001$) showing cardiovascular deconditioning. A-BR gain was lower on R0 compared to pre-HDBR ($p < 0.001$; 1.8 ± 0.8 vs. 7.7 ± 0.8 ms $mmHg^{-1}$) with a corresponding reduction in percent-time-active ($p < 0.001$; 29 ± 3 vs. $45 \pm 3\%$). Across all muscles, MPBR response gain was unaffected by bedrest ($p = 0.260$); however, percent-time-active was reduced on R0 ($p < 0.001$; 29 ± 5 vs. $54 \pm 5\%$). Response gain was highest in MG and TA and lowest in LG and S at all timepoints ($p < 0.05$). HDBR has pronounced effects on cardiovascular responses to standing. Here we show a link between decreased activation rate of A-BR and MPBR along with decreased A-BR gain. Similar reductions in percent-time-active suggest blood pressure regulation changes, possibly at the level of cardio-postural integration within the brainstem.

Hot Topic Plenary Lecture

Neuromodulation focused therapeutics for cardiac disease: structure/function foundations

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Cardiac control is mediated via interdependent neural networks involving intra-thoracic intrinsic cardiac and extra-cardiac autonomic ganglia, spinal cord, brainstem and higher centers. Each of these processing centers contains afferent, efferent and local circuit neurons which interact locally and with the other levels to coordinate regional cardiac electrical and mechanical indices on a beat-to-beat basis. While these neural networks are optimized to respond to normal physiological stressors, they can be disrupted by cardiac pathology. Autonomic dysregulation, central to the evolution of both heart failure and arrhythmias, involves adverse remodeling in multiple levels of the hierarchy for cardiac control. Neuromodulation based approaches that target select nexus points within this hierarchy for cardiac control offer unique opportunities to positively impact therapeutic outcomes. Novel therapeutic interventions can target central and/or peripheral aspects of the cardiac neuroaxis to render cardiomyocytes stress resistant. For surgical and neural ablation interventions, it is the mitigation of destabilizing reflex processing within the cardiac nervous system that is central to cardioprotection. For bioelectronic interventions, the characteristics of the electrode-nerve interface, the stimulation protocol utilized, and the disease process itself are all relevant factors in determining the ultimate efficacy of neuromodulation. Taken together, it is the understanding the anatomical and physiological basis for such control in normal and pathological conditions that is necessary to implement effectively novel neuromodulation therapies.

Streeten Plenary Lecture

The art and science of clinical autonomic research

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Clinical research begins with the patient and the clinical method—the history, examination and testing that underlies the development of a differential diagnosis and a final diagnosis. The unanswered questions that emerge in that interaction—the mysterious symptom, the unexplained sign, the puzzling combination of symptoms and signs, the disease without pathophysiological explanation, and above all, the suffering patient—it is these that motivate the clinical researcher to develop and refine questions and seek answers.

Sweat gland nerve fiber density: development of a novel unbiased reconstruction methodology

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Background and Objective: Dermal structures are densely innervated by autonomic nerve fibers. Thus, it comes as no surprise that over the past decade, skin biopsies have sparked great interest in the evaluation of autonomic disorders. A number of groups have reported on sweat gland nerve fiber density (SGNFD) as a means to quantitate sudomotor innervation. However, methodologies vary significantly from imaging to analyzing techniques and although conventional stereology techniques are most commonly used, no standard technique has been established. In an attempt to bridge this gap, we sought to develop a reliable and reproducible technique to quantify SGNFD using 3D reconstruction of dermal nerve fibers.
Methods: Four-millimeter skin punch biopsies were collected from healthy individuals. Biopsies were cut by freezing microtome. Each section was stained with PGP 9.5 and Collagen IV antibodies to visualize nerve fibers and sweat gland (SG) basement membranes, respectively. SGs were imaged using confocal and wide-field microscopy. Image stacks were taken at 20× objective at 1-μm intervals. Volume was determined using a contouring function at the top and bottom of the Z-stacks. Images were optimized using deconvolution algorithms. Nerve fibers were reconstructed and nerve fiber length (NFL) was quantified using an automated 3D software platform (NL360). SGNFD was calculated by dividing NFL by volume. SGNFD was also assessed using grid-matrix stereology for comparison.
Results: Thus far, a total of 104 SGs derived from 5 subjects have been analyzed using both microscopy techniques. All images were analyzed by two independent observers to evaluate reproducibility. Using confocal microscopy, the software reliably traced nerve fibers surrounding sweat glands and required minimal operator adjustment. The rendering of nerve fibers was clearly inferior when using wide-field microscopy, often raising questions about true nerve signal versus artifact and requiring more operator input and adjustments to analysis settings. This is reflected in the intraclass correlation coefficient (ICC) for inter-reviewer reliability, which was ICC = 0.99 using confocal images versus ICC = 0.815 using wide-field images. Correlation between the optimized 3D-reconstructon and grid-matrix stereology was poor (ICC = 0.385).
Conclusions: The newly developed technique of SGNFD quantitation using deconvolution algorithms, 3D reconstruction of sweat gland nerve fibers and confocal microscopy, reliably traces sweat gland nerve fibers, shows outstanding reproducibility between observers, is

almost completely unbiased, and arguably superior to conventional stereology methods.
Funding: NIH (R01NS092625, U54NS065736, K23NS075141, UL1TR000135) and Mayo Funds.

Familial amyloid polyneuropathy: impact of biopsies and mutations on diagnostic considerations

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Introduction: Familial amyloid polyneuropathy is due to one of many mutations in the transthyretin (TTR) gene, resulting in a progressive fatal disease with sensory, motor and autonomic involvement.
Objective: To characterize the symptoms, signs and skin biopsy neuropathological findings in a cohort of individuals with TTR Mutations.
Methods: Individuals with a variety of TTR mutations underwent detailed neurological examinations including the Neuropathy Impairment Score in the Lower Limb (NIS-LL), the Utah Early Neuropathy Score (UENS), Coutinho staging, autonomic testing, symptom scores (using the EuroQol, Brief Pain Symptom Inventory, and the orthostatic hypotension Questionnaire). All subjects had 3 mm punch skin biopsies at the distal leg and distal thigh with analysis of amyloid burden by Congo Red, and neuropathy severity by staining with protein gene product 9.5.
Results: A total of 88 subjects participated with the following TTR mutations: 43- Val30Met, 30- Ser50Arg, 6- Gly47Ala, 5- Ser52Pro, 2- F64L, 1- I73 V and 1 with Y136H. Coutinho staging included 47 stage 0, 32 stage 1, 8 stage 2 and 1 stage 3. The diagnostic sensitivity for amyloid detection from a single skin biopsy was 72%, the diagnostic yield increased to 89% with 2 biopsies. Biopsies were positive for amyloid in 78% of individuals with no clinical evidence of neuropathy (NIS-LL scores of 0) and 94% for individuals with any evidence of neuropathy. Amyloid burden was inversely correlated with nerve density at the distal leg ($R = 0.59$, $P < 0.01$) and distal thigh ($R = -0.53$, $P < 0.01$), and correlated with the NIS-LL ($R = 0.48$, $P < 0.05$), and UENS ($R = 0.49$, $P < 0.05$).

Conclusion: Skin biopsy is a sensitive and specific pathological marker for tissue diagnosis of familial amyloid polyneuropathy across multiple mutations, even in individuals with no clinical evidence of disease. Amyloid burden correlates with neuropathy severity, both pathologically and by examination criteria; skin biopsies may prove informative for studies that seek to alter the natural history of the disease.
Funding: Pfizer (RF).

Impact of patisiran on autonomic neuropathy in hereditary transthyretin-mediated (hATTR) amyloidosis patients

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Introduction: hATTR amyloidosis is a rare, multi-systemic, life-threatening disease with heterogeneous clinical presentation including sensory, motor and autonomic neuropathy, and cardiac involvement. Clinical manifestations of autonomic dysfunction include chronic diarrhea and nausea/vomiting, orthostatic hypotension, and urinary tract infections. In the Phase 3 APOLLO study, patisiran, an investigational RNAi therapeutic, showed improvement in primary, secondary and exploratory endpoints compared to placebo; generally well-tolerated in hATTR amyloidosis patients. Here, data on measurements of autonomic symptoms from APOLLO are presented.
Methods: APOLLO was a multi-center, international, randomized (2:1), double-blind study of patisiran 0.3 mg/kg or placebo IV q3W in hATTR amyloidosis patients with polyneuropathy (NCT01960348). COMPASS-31, a 31-item questionnaire (range 0–100 points), was used to evaluate patient-reported autonomic neuropathy symptoms on six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor. Subjective perceptions of autonomic nerve function were captured within the Norfolk QOL-DN, a 35-item patient-reported scale. Postural blood pressure (PBP) was captured in the mNIS + 7 score. Among all 3 tools, higher scores are indicative of worsening autonomic symptoms.
Results: APOLLO enrolled 225 patients: mean age 61 (24–83), 74% males and 43% V30M. Overall, COMPASS-31 showed a least squares (LS) mean decrease (improvement) of − 5.29 points with patisiran compared to an LS mean increase (worsening) of 2.24 points with placebo, for an overall treatment difference of − 7.53 points at 18-months ($p = 0.0008$). Patisiran-treated patients experienced benefit compared to placebo across all COMPASS-31 domains, showing improvement relative to baseline in orthostatic intolerance and gastrointestinal domains. Similarly, autonomic improvement with patisiran and worsening with placebo was observed in autonomic domain of Norfolk QOL-DN and PBP component of mNIS + 7 with an LS mean change (SEM) compared to baseline for patisiran, placebo: [− 0.3 (0.19), 0.8 (0.39)] and [− 0.2 (0.06), 0.1 (0.11)], respectively. These findings were accompanied by a lower frequency of AEs of syncope, nausea, and urinary tract infection in the patisiran group compared to placebo group.
Conclusions: In APOLLO, multiple measures of autonomic symptoms and function showed a consistent benefit with patisiran versus placebo as well as an improvement compared to baseline resulting in lowering of GI symptoms (e.g., diarrhea and constipation) and orthostatic intolerance (e.g., inability to stand upright).
Funding: Study sponsored and funded by Alnylam Pharmaceuticals.

Adrenal gland stimulation is intact in patients with postural tachycardia syndrome

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Background: Many patients with postural tachycardia syndrome (POTS) have hypovolemia with a plasma volume deficit of 10–30%. Paradoxically, some patients with hypovolemia have low levels of aldosterone, and adrenal hormones, and consequently some POTS patients receive a diagnosis of "adrenal fatigue". The adrenal gland is stimulated by Angiotensin II to release aldosterone, and stimulated by adrenocorticotropin hormone (ACTH) to release aldosterone and cortisol. We sought to compare effects of IV ACTH stimulation on the adrenal release of aldosterone and cortisol in POTS patients and healthy volunteers.
Methods: While on a low Na^+ diet ($\sim$ 10 mEq/day), 8 female POTS patients and 5 female healthy subjects (HS) received low dose ACTH (1 μg) IV following a baseline blood sample. Venous aldosterone and cortisol levels were sampled every 30 min for 2 h. After 60 min, ACTH 249 μg IV was administered to ensure a maximal response. Aldosterone level at 60 min was the primary outcome, with a cortisol level at 60 min and maximal aldosterone and cortisol as secondary outcomes. Data are presented as mean ± SD.
Results: Baseline aldosterone was not different between POTS (33.7 ± 14.9 ng/dL) vs. HS (33.4 ± 18.6 ng/dL; P = 1.0). Aldosterone increased in both groups in response to ACTH, but was not different in POTS vs. HS at 60 min (52.5 ± 15.7 ng/dL vs. 57.9 ± 26.4 ng/dL; P = 0.7) or maximally (68.0 ± 21.6 ng/dL vs. 61.9 ± 24.3 ng/dL; P = 0.7). Baseline cortisol was not different between POTS (25.0 ± 7.5 μg/dL) vs. HS (22.3 ± 3.9 μg/dL; P = 0.5). Cortisol increased in both groups in response to ACTH, but was not different in POTS vs. HS at 60 min (41.5 ± 5.8 μg/dL vs. 40.7 ± 5.9 μg/dL; P = 0.8) or maximally (48.4 ± 10.4 μg/dL vs. 46.6 ± 6.8 μg/dL; P = 0.7).
Conclusions: ACTH injection appropriately increased the aldosterone and cortisol levels in POTS patients. These data suggest that stimulated adrenal function is normal in patients with POTS.
Funding: NIH Grant R01 HL102387.

Epidemiology of postural tachycardia syndrome

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Background and Objective: Although demographic and clinical characteristics of the postural tachycardia syndrome (POTS) have been well described, reliable epidemiological data are lacking. A perceived increase in incidence underlines the need for careful epidemiologic studies. We therefore sought to investigate the incidence of POTS in Olmsted County and its evolution over time.
Methods: We identified all patients in the clinical autonomic laboratory database of Mayo Clinic Rochester from January 1st 2000 through December 31st 2016, who fulfilled heart rate criteria for POTS during head-up tilt (increment $\geq$ 30 bpm if $\geq$ 20 years of age, $\geq$ 40 bpm if $\leq$ 19 years). Using the Rochester Epidemiology Project, we narrowed this search to those who fulfilled heart rate criteria while residents of Olmstead County. The identified records were carefully reviewed to confirm the laboratory and clinical diagnosis of POTS per 2011 consensus statement criteria. Census counts for the Olmstead County population from 2000 to 2016 were gathered from government records. Incidence was defined as the number of new cases per year among 100,000 residents.
Results: We identified 58 patients diagnosed with POTS while living in Olmsted County during the defined timeframe, 48 of which were female (86%). Mean age at diagnosis was 22.5 years, ranging from 11 to 50 years. The mean duration of documented orthostatic symptoms was 3 years. The most recent (2016) incidence rate was 6/100,000 person-year for the entire population (10.5/100,000 for women). The incidence rate among the population at risk (10–54 years of age) in 2016 was 10.1/100,000 person-year (17.6/100,000 for women). Both incidence rate for the total population and the population at risk showed a near fourfold increase from the year 2000, with the most dramatic increase noted between 2002 and 2005, and subsequently approaching a plateau.
Conclusion: Our epidemiologic data confirm as expected POTS as a disorder affecting predominantly young women. The rather abrupt rise of incidence based on laboratory diagnosis between 2002 and 2005 is intriguing, may reflect increased awareness of the syndrome among patients and physicians, but a true rise in incidence cannot be excluded.

FRIDAY, OCTOBER 26, 2018

ORAL PRESENTATIONS

Groundbreaking Research Plenary Lecture

A novel autosomal recessive orthostatic hypotension syndrome: a new kid on the block

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We describe two independent families, with four patients in total, experiencing severe life-threatening orthostatic hypotension because of a novel cause. As in dopamine β-hydroxylase deficiency, concentrations of norepinephrine and epinephrine in the patients were low. Plasma dopamine β-hydroxylase activity, however, was normal, and the *DBH* gene had no mutations. Molecular genetic analysis was performed to determine the underlying genetic cause. Homozygosity mapping and exome and Sanger sequencing revealed pathogenic homozygous mutations in the gene encoding cytochrome b561 (*CYB56)*. The *CYB561* gene was found to be expressed in many human tissues, in particular the brain. The CYB561 protein defect leads to a shortage of ascorbate inside the catecholamine secretory vesicles leading to a functional dopamine β-hydroxylase deficiency. The concentration of the catecholamines and downstream metabolites was measured in brain and adrenal tissue of *CYB561* knockout mice. The concentration of norepinephrine and normetanephrine was decreased in whole-brain homogenates of the *CYB561*(−/−) mice compared with wild-type mice ($P < 0.01$), and the concentration of normetanephrine and metanephrine was decreased in adrenal glands ($P < 0.01$), recapitulating the clinical phenotype. The patients responded favorably to treatment with L-dihydroxyphenylserine, which can be converted directly to norepinephrine. This study is the first to implicate cytochrome b561 in disease by showing that pathogenic mutations in *CYB561* cause an as yet unknown disease in neurotransmitter metabolism causing orthostatic hypotension.

Congenital CYB561 deficiency causing isolated noradrenergic failure

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We previously described patients with congenital deficiency of dopamine-beta-hydroxylase (DBH), the enzyme that converts dopamine (DA) into norepinephrine (NE). Biochemically, plasma NE is virtually absent and DA greatly increased. Clinically these patients

have isolated sympathetic failure and intact parasympathetic function. We recently reported patients who had mutations in the gene encoding cytochrome b561 (van der Berg et al., Circ Res 2018), the enzyme that ascorbate, a crucial cofactor for DBH, within the noradrenergic secretory vesicles. Here we report the clinical and biochemical characteristics of one of the families (2 sisters) previously reported, and an additional newly discovered male patient with a different mutation. All three patients had disabling orthostatic hypotension (OH) since infancy and episodes of hypoglycemia, but without ptosis (prominent in DBH deficiency). Valsalva maneuver (VM) was typical of sympathetic failure with exaggerated hypotension during phase 2 and absence of blood pressure overshoot during phase 4. Heart rate ratio to sinus arrhythmia and VM were normal. Cardiovagal response to neck suction and phenylephrine were intact. Plasma NE and its metabolite DHPG were undetectable but plasma DA was normal. Droxidopa restored NE and improved OH. Patients 1 and 2 (sisters) were homozygous for a nonsense mutation in Exon 2, c.131G > A, p.Trp44. Patient 3 was a compound heterozygous; one allele had a mutation in Exon 2, c157C > T, p.His.52Tyr, and the other had an Exon 2 deletion. Thus, we report patients with congenital CYB51 deficiency, the enzyme that generates ascorbate, which is critical for DBH activity. Therefore these patients have a clinical presentation similar to DBH deficiency with life-long OH (but without ptosis), virtual absence of plasma NE (but without increase in plasma DA), and who respond to droxidopa treatment.
Funding: NIH Autonomic Rare Diseases Clinical Research Consortium NS065736.

Familial autonomic ganglionopathy caused by rare CHRNA3 genetic variants. Novel genetic cause of neurogenic orthostatic hypotension

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Objective: To identify and determine the molecular basis of a new Mendelian cause of familiar case of neurogenic orthostatic hypotension (nOH).
Methods: The proband developed disabling nOH at 39 years of age. He was evaluated at the Vanderbilt Autonomic Dysfunction Center and was diagnosed with severe autonomic failure and small nonreactive pupil. Plasma norepinephrine were abnormally low while supine (34 pg/dl), and upon standing (156 pg/dl), dopamine levels were wnl. Of note, his sister had onset of nOH and miosis in her late teens. Their parents, brother and the proband's three children were healthy.
Results: Patient was referred to the UDN where whole exome sequencing of DNAs from the proband and his affected sister showed that both were compound heterozygotes for c.907_908delCT (p.L303Dfs*115)/c.688G > A (p.D230N) variants in the acetylcholine receptor, neuronal nicotinic, alpha 3 subunit (CHRNA3) gene. CHRNA3 is a subunit of nicotinic acetylcholine receptors (nAChRs) that regulates blood pressure through modulation of synaptic transmission in the autonomic ganglia. The fs and missense CHRNA3 variants were inherited from the sibs' mother and father, respectively, and their non-affected brother was a nl/p.D230N heterozygote. The fs variant is obviously pathogenic and the p.D230N variant is predicted to be damaging (SIFT)/probably damaging (PolyPhen2). Furthermore, we predict from structural modeling that the p.D230N variant lies on the interface between CHRNA3 and other nAChR subunits and that it would destabilize the nAChR pentameric complex. Interestingly, homozygous knock-out mice without detectable Chrna3 had autonomic failure and dilated pupils. In humans, the presence of nAChR autoantibodies against the alpha 3 subunit is associated with nOH and dilated pupils.
Conclusions: We report sibs affected with autonomic failure and miosis of unknown etiology who are compound heterozygotes for CHRNA3 variants that co-segregate with and have predicted effects on nAChR structure that suggest they likely cause this family's nOH.
Funding: Vanderbilt Autonomic Disorders Consortium, NIH, U54NS065736; Vanderbilt Undiagnosed Disease Network (Clinical Site), NIH, U01 HG007674.

Acute, dose-dependent, blood pressure-lowering effect of continuous positive airway pressure in autonomic failure patients with supine hypertension

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Primary autonomic failure (AF) is characterized by disabling orthostatic hypotension but half of these patients also have supine hypertension. We have previously shown that continuous positive airway pressure (CPAP 4, 8, 12 and 16 cm H_2O, each for 2 min) applied during autonomic blockade with trimethaphan acutely decreased systolic blood pressure (SBP) in hypertensive and normotensive subjects ($-$ 17 $\pm$ 2 and $-$ 8 $\pm$ 2 mmHg at 16 cm H_2O) due to decreases in cardiac output (CO) and stroke volume (SV). In this study, we hypothesized that CPAP would have an acute, dose-dependent, blood pressure-lowering effect in patients with autonomic failure with supine hypertension. Five CPAP levels (0, 4, 8, 12 and 16 cm H_2O, each for 2–3 min) were applied sequentially to 15 AF patients with supine hypertension (12 males, 70 $\pm$ 1 year). Hemodynamic parameters were measured at the end of each CPAP level. We found that CPAP levels of 4, 8, 12 and 16 cm H_2O significantly decreased SBP in a dose-dependent manner. The maximal SBP drop was $-$ 20 $\pm$ 3 mmHg with CPAP 16 (from 154 $\pm$ 4 to 134 $\pm$ 4 mmHg, $P < 0.01$), and was associated with a decrease in CO ($-$ 12 $\pm$ 4%) and SV ($-$ 13 + 4%). Neither systemic vascular resistance nor heart rate changed significantly with CPAP. SBP returned to baseline levels within 5 min after removal of the CPAP (REC). We conclude that, in AF patients with supine hypertension, CPAP acutely decreases SBP in a dose-dependent manner, due to decreases in CO and SV likely reflecting a decrease in venous return. These results suggest that CPAP could be used as a non-pharmacologic approach to treat the supine hypertension of AF. Future studies are needed to test the safety and efficacy of this approach.
Funding: NIH Grants U54 NS065736, RO1 HL122847 and UL1 TR002243 (CTSA award).

Norepinephrine transporter inhibition with atomoxetine prevents tilt-induced vasovagal syncope: a randomized, placebo-controlled trial

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Background: The norepinephrine transporter (NET) acts as a clearance mechanism in sympathetic neurons. Pharmacological NET inhibition increases sympathetic tone and has been shown to decrease tilt-induced syncope in healthy subjects. There is a paucity of effective therapies for vasovagal syncope (VVS). The aim of this study was to determine

whether treatment with atomoxetine (ATOX), a potent NET inhibitor, reduces the risk of syncope in patients with recurrent VVS.
Methods: The multicenter Prevention of Syncope Trial (POST6) study was a placebo-controlled, parallel-group, randomized trial of ATOX (40 mg PO BID; n = 27) vs. matched placebo (PLAC; n = 29). VVS patients were given two doses of study drug followed by a 60-min drug-free head-up tilt table test.
Results: VVS patients were 35 ± 14 years (73% female) with a median of 12 lifetime faints, and 3 faints in the last year. Patients fainted significantly less with ATOX than PLAC (24% vs. 63%; P = 0.003), but there was no difference in the rates of presyncope (76% vs. 78%; P = 0.87). The mean time-to-faint was longer with ATOX than PLAC (49.9 ± 18.8 min vs. 35.9 ± 21.1 min; P = 0.012). The logrank hazard ratio for fainting with ATOX:PLAC was 0.40 (95% CI 0.18–0.87).
Conclusion: NET inhibition with ATOX significantly decreased the risk of tilt-induced syncope in VVS patients. This is a promising novel pharmacological strategy for the treatment of VVS.
Funding: Cardiac Arrhythmia Network of Canada (CANet).

Is cerebrovascular autoregulation (CA) impaired during head-up tilt (HUT)-induced vasovagal syncope (VVS)? Inferences derived from selective falls in total peripheral resistance (TPR) or cardiac output (CO)

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During VVS, diastolic and hence mean cerebral blood flow velocity (CBFV) selectively declines while systolic CBFV remains stable. Some infer from the increased calculated CBFV pulsatility that cerebrovascular resistance (CVR) paradoxically increases at syncope because of impaired CA or increased sympathetic activity. However, CVR measured as [mean (BP/CBFV)], decreases at VVS indicating preserved CA that is ultimately overwhelmed by the blood pressure (BP) collapse at VVS. We and others have shown that as much as 75% of HUT-induced VVS is due to a selective reduction in CO whereas 25% results from a selective decrease in TPR. These 2 discrepant mechanisms could provide insight regarding CA at VVS. If CVR increases as a result of a primary decline in CO and decreases during a primary decline in TPR the profiles of diastolic CBFV would not superimpose and impaired CA would be inferred. Conversely, superimposed diastolic CBFV profiles, regardless of VVS mechanism indicate preserved CA. We studied 48 completely healthy medication-free VVS patients (age 33.8 + 12.1 years; 14 men) 12 of whom were TPR fainters and 36 CO fainters (27 primary decline in heart rate, 9 stroke volume). Finger BP and middle cerebral artery CBFV were continuously recorded. CO was derived from Modelflo. Averaged hemodynamic profiles (2.5 Hz resampling) were created from the last 4 min of HUT. We found that both mean BP and diastolic CBFV profiles were superimposable for CO and TPR fainters. Stepwise linear regression with partial least squares regression as a control for multicollinearity of CO, BP and TPR demonstrated that the decline in mean BP was virtually completely responsible for the decline in diastolic CBFV. These results indicate that the decline in BP at VVS is uniquely responsible for the simultaneous decrease in diastolic CBFV regardless of mechanism. This suggests that CA is preserved at syncope.

MSA Plenary Lecture

Multiple system atrophy: are we ready to tame the beast?

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MSA is increasingly recognized as a fatal neurodegenerative disorder associated with autonomic failure, ataxia and parkinsonism. In contrast to Parkinson's disease, MSA is characterized by oligodendroglial alpha synuclein aggregates that appear to be linked to selective neurodegeneration in the central autonomic network as well as striatonigral and olivopontocerebellar pathways. In the last decade there has been considerable progress in our understanding of the key pathogenic events leading to the discovery of candidate therapeutic agents primarily targeting alpha synuclein toxicity and its consequences. Although clinical trials have largely been negative so far, they have provided unique insights into trial methodology and they firmly established an international network that will facilitate future trial activities. 50 years after the introduction of the term MSA by Graham and Oppenheimer we are now ready to tame the beast.

Discovery and validation of MRI morphometry features for early multiple system atrophy

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Background and Objective: Although characteristic MRI findings are often seen in later disease stages of multiple system atrophy (MSA), there is currently a lack of validated imaging biomarkers for early MSA and imaging markers of disease progression. Our goal with this study was to identify key morphometric features for early MSA and examine the utility of these features for cross-sectional diagnosis and longitudinal tracking of disease progression.
Methods: We prospectively enrolled possible or probable MSA patients whose disease was still relatively early (UMSARS I: 5–16 and able to walk unaided) to undergo standardized T1 MPRAGE images on 3 T MRI scanners for morphometric MRI analysis. MRI morphometric features were computed using Freesurfer v5.3. In a discovery dataset of 24 MSA patients (19 MSA-C and 5 MSA-P), we performed unsupervised clustering of 109 MRI volumetric features that were scaled by the intracranial volume. We identified 'MSA regions' based on inter-cluster and intra-cluster similarity in those 24 patients. We then enrolled an independent validation data set which consisted of 16 early MSA (8 MSA-C and 8 MSA-P) and 13 normal subjects with MRI scans at baseline and follow-up scans at 12-months to examine the utility of 'MSA regions' for diagnosis and tracking of disease progression.
Results: The 'MSA regions' identified were brainstem, cerebellar white matter (WM), and total ventricular volume. In the independent validation sample, we found that both baseline brainstem and cerebellar WM volumes were significantly lower, while the 12 months decrease in volumes were significantly higher in MSA subjects when

compared to normal ($p < 0.001$). This difference was more pronounced for MSA-C than MSA-P in both regions.
Conclusions: We identified and validated regions of atrophy using MRI morphometry in early MSA using unbiased methodology. Morphometric analysis of cerebellar WM and brainstem allows for separating early MSA patients from control subjects, and detecting disease progression over 12 months. MRI morphometry of selected brain regions represents therefore a promising biomarker for the diagnosis of MSA and a potential surrogate marker of disease progression for future clinical trials in MSA.
Funding: NIH (P01NS44233, U54NS065736, K23NS075141, R01NS092625, UL1TR000135), FDA (R01FD004789), Cure MSA Foundation, and Mayo Clinic.

Cutaneous alpha-synuclein deposition in multiple system atrophy

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Background: We recently reported that α-synuclein can be detected within cutaneous autonomic nerve fibers of patients with Parkinson's disease (PD). We now report the deposition of phosphorylated and total alpha-synuclein in patients with MSA, and compare those findings to controls and individuals with PD.
Objective: To define the peripheral neural deposition of alpha-synuclein in MSA.
Methods: Twenty-nine individuals with MSA, 22 individuals with PD and 10 healthy control subjects had clinical examinations, autonomic function testing and skin biopsies taken from multiple proximal and distal sites. Skin biopsies were stained for PGP9.5, phosphorylated and total α-synuclein and results compared to autonomic function tests.
Results: Patients with MSA had evidence of peripheral phosphorylated α-synuclein deposits in all subjects ($P < 0.001$ vs. controls, where no α-synuclein was detected) at proximal and distal biopsy sites. Significant differences in synuclein deposition between MSA subjects and PD subjects ($P < 0.01$) was noted at all biopsy sites.
Discussion: We report the largest study of cutaneous alpha synuclein in individuals with multiple system atrophy. Contrary to expectations, peripheral deposition of phosphorylated α-synuclein was present in all subjects with MSA and PD. These findings may offer insights into the different patterns of synuclein deposition across a spectrum of neurodegenerative diseases. The results carry significant implications for disease diagnosis, prognosis and therapeutic interventions that alter the natural history of the disease.
Funding: Study supported by the MSA Foundation (RF) and NIH U54 NS065736.

Alpha-synuclein deposition in noradrenergically innervated pilomotor muscles distinguishes Lewy body forms of neurogenic orthostatic hypotension from multiple system atrophy

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Background: Biomarkers are needed that can distinguish among forms of neurogenic orthostatic hypotension (nOH)—especially Lewy body diseases vs. multiple system atrophy (MSA). Both disease types involve deposition of the protein alpha-synuclein (AS). Measurement of total alpha-synuclein (AS) alone does not take into account possible concurrent loss of AS-containing sympathetic noradrenergic fibers in Lewy body diseases.
Methods: Punch biopsies (3 mm, lateral leg) from 11 patients with Lewy body nOH and 8 with MSA were analyzed by immunofluorescence microscopy. AS was measured in pilomotor muscles, which receive pure noradrenergic innervation. AS content was adjusted for local sympathetic innervation by calculating the ratio of AS to PGP 9.5, a pan-axonal marker. All the subjects had Parkinson's disease with orthostatic hypotension, dementia with Lewy bodies, pure autonomic failure, or MSA based on clinical diagnosis and research laboratory tests including 18F-dopamine positron emission tomographic scanning. Three patients had autopsy-proven diagnoses by neuropathology and catecholamine neurochemistry.
Results: The Lewy body group had a higher mean (± SEM) AS/PGP 9.5 ratio than did the MSA group (0.90 ± 0.02 vs. 0.66 ± 0.04, $p = 0.0001$). A receiver operating characteristic curve for the AS/PGP 9.5 ratio showed 100% sensitivity at 86% specificity in separating the groups. 18F-Dopamine-derived radioactivity in the left ventricular free wall was lower in the Lewy body group (3247 ± 240 vs. 7924 ± 1095 nCi-kg/cc-mCi $p = 0.0002$).
Conclusions: Among patients with nOH, the AS/PGP9.5 ratio in pilomotor muscles in skin biopsies and cardiac sympathetic neuroimaging efficiently distinguish Lewy body diseases from MSA.
Funding: Division of Intramural Research, NINDS, NIH.

SATURDAY, OCTOBER 27, 2018

ORAL PRESENTATIONS

Cognitive Dysfunction in Autonomic Disorders Plenary Lecture

Norepinephrine and cognition: revisiting an old friend

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Loss of noradrenergic neurons and reductions in central norepinephrine levels are described in many neurodegenerative disorders, including Alzheimer's disease (Kelly et al., 2017), Parkinson's disease (Braak, 2003; Zarrow et al., 2003), dementia with Lewy bodies (Vermeiren et al., 2017; Dickson et al., 2008), and multiple system atrophy (Benarroch EE, 2012). In PD, α-synuclein accumulation and cell death in the locus coeruleus precedes that in the substantia nigra (Braak, 2003; Dickson, 2009), resulting in a measurable norepinephrine deficiency early in the disease (Goldstein, 2012; Hurst, 1985). Given the widespread projections from the locus coeruleus to areas such as the cortex, basal forebrain, limbic system, thalamus, and cerebellum, central norepinephrine deficiency may play a major role in many of the motor and non-motor symptoms in PD, particularly those that do not respond well to traditional dopaminergic interventions.

Norepinephrine repletion is a therapeutic target for a wide variety of PD symptoms including cognitive impairment, apathy, depression, freezing of gait, and autonomic dysfunction (Espay, 2014). Droxidopa, a norepinephrine precursor, was historically used to treat PD patients with freezing of gait (Narabayashi et al., 1987; Fukada et al., 2013). Atomoxetine, a selective norepinephrine reuptake inhibitor, may improve cognitive function and neuropsychiatric symptoms in

PD patients. Ultimately, enhanced central norepinephrine appears to influence fronto-striatal networks, which may be mediated through improvements in cerebral metabolism and blood flow.

My overarching aim is to review cognitive effects of norepinephrine, with a focus on cognitive neuroscience methods and assessments of motor control and reward-based learning. Preliminary work from our group will be presented, and this work emphasizes the role of norepinephrine therapies in mediating improvements to inhibitory action control, and reward-based learning. I will also describe novel non-invasive imaging investigations of cerebral norepinephrine integrity, and review imaging methods that assess cerebral blood flow, metabolism, and locus coeruleus integrity. This review will hopefully stimulate further investigations to the cognitive effects of noradrenergic modulation.

Cortical morphometric predictors of autonomic dysfunction in generalized anxiety disorder

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Generalized anxiety disorder (GAD) is associated with autonomic dysfunction, notably decreased vagally-mediated heart rate variability (vmHRV). Regional differences in brain morphometry correlate with psychopathology in GAD, and with vmHRV in healthy individuals. Here, we used both categorical and dimensional models of GAD pathology to test the hypothesis that specific focal abnormalities in cortical structure in GAD underpin decreased vmHRV. Adult female patients with GAD (n = 17) and matched controls (n = 18) underwent structural magnetic resonance imaging after characterization of symptoms and quantification of resting vmHRV derived from continuous pulse oximetry. Cortical reconstruction was performed using the FreeSurfer image analysis suite. Compared to controls, patients with GAD showed cortical thinning of the (i) left rostral anterior cingulate cortex (ii) left medial orbitofrontal cortex, and (iii) right isthmus cingulate gyrus. Significant negative relationships were identified between the severity of anxiety symptoms and cortical thickness of the left medial orbitofrontal cortex and right isthmus cingulate gyrus. These results extend evidence in GAD for structural abnormalities within cortical areas implicated in emotion regulation and cognition. Compared to controls, patients with GAD showed decreased vmHRV at rest. In controls only, cortical thickness of the left caudal anterior cingulate cortex correlated positively with resting vmHRV. Our findings implicate abnormal integrity of anterior cingulate cortex in the psychophysiological expression of GAD. These insights suggest that interventional targeting of this region to normalize autonomic activity may improve entrenched psychological and behavioural symptoms of GAD.

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Active forelimb exercise mitigates susceptibility to cardiac arrhythmia compared to passive hindlimb cycling in rats with high-level spinal cord injury

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Introduction: High-level spinal cord injury (SCI) is associated with injury to spinal autonomic (sympathetic) pathways, with abnormal control of heart rate (HR). Individuals with high-level SCI have increased susceptibility to cardiac arrhythmia. Active upper-limb and passive lower-limb exercise interventions are commonly used in SCI populations to enhance motor function and rehabilitation. It is unclear whether these exercise modalities influence susceptibility to cardiac arrhythmia. We aimed to evaluate whether: (i) susceptibility to arrhythmia is increased in a rodent-model of SCI; (ii) exercise ameliorates this arrhythmia risk.
Methods: Experiments were conducted in 29 Wistar rats: controls (SHAM, n = 7) and second thoracic level contusive SCI in 3 subgroups—non-exercisers (T2, n = 7), and exercisers (30 m/day 5 day/week) completing active forelimb swimming (SWIM, n = 6) or passive hindlimb cycling (PHLC, n = 7). Electrocardiogram (ECG) data were evaluated pre-, 1- and 5-weeks post-SCI. Indices of arrhythmia risk (P-wave duration [PWD] variability, marker of atrial arrhythmia risk; Tpeak-Tend variability, marker of transmural dispersion of repolarisation; QT interval corrected for HR (QTc) and the QT variability index (QTVI), markers of repolarisation) were determined from ECG. R-R interval (RRI) was determined.
Results: RRI increased over time in both PHLC ($p < 0.001$) and SWIM ($p = 0.013$), but not SHAM ($p = 0.8$) or T2 ($p = 0.8$), reflecting the effect of exercise training on HR. Tpeak-Tend and PWD variability increased over time in T2 ($p = 0.002$, $p = 0.009$) and PHLC ($p = 0.001$, $p = 0.002$), but not SHAM ($p = 0.594$, $p = 0.98$) and SWIM ($p = 0.628$, $p = 0.816$). QTVI tended to increase over time, in T2 only ($p = 0.06$). QTc variability increased over time in T2 ($p = 0.04$), and tended to increase in PHLC ($p = 0.08$), but not in SHAM ($p = 0.5$) or SWIM ($p = 0.75$).
Conclusion: SCI increases susceptibility to atrial and ventricular arrhythmia that can be ameliorated by exercise training. However, not all exercise modalities are equal in mitigating arrhythmia risk progression post-SCI; active upper-limb exercise was associated with better outcomes than passive hindlimb exercise.

Autonomic dysreflexia (AD) in individuals with SCI: the association between elevations in blood pressure and symptoms of AD over a 30 day observation period

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Objective: Although individuals with spinal cord injury (SCI) often have episodic increases in systolic blood pressure (SBP) that reflect AD, it has been assumed that many of these individuals remain asymptomatic (a condition termed, "silent AD"). The association between elevations in SBP that reflect AD and the awareness of symptoms that suggest AD over a 30-day observation period are reported.
Participants: Individuals with SCI (n = 69) were categorized as having AD, which was defined as having at least 1 SBP $\geq$ 20 mmHg their average 30-day SBP (AD: n = 58) and those who had no rise in SBP that met criteria (noAD: n = 11).
Methods: Participants with SCI recorded SBP values 3-times/day for 30 days and were asked to complete an AD symptoms survey at the end of each week (i.e., 4 surveys/subject).
Results: We observed a total of 6167 SBP recordings over the 30-day period; 533 (8.6%) reflected AD. Participants in the AD group were older (46 ± 13 years) and had a longer duration of injury (17 ± 13 years) than those in the noAD group (30 ± 5 and 4 ± 3 years, respectively; $p < 0.001$). Although the average 30-day SBP did not differ significantly between the groups, maximum 30-day SBP was increased in the AD group (156 ± 24) compared to the noAD group (122 ± 15 mmHg; $p < 0.001$); those in the AD group had an average of 9.2 episodes of

elevated SBP that were identified as being AD. However, there were no significant group differences in AD symptoms reported and 43% (n = 25) of participants in the AD group had an absence of symptoms reported over the 30-day period suggesting silent AD.
Funding: Craig H. Neilsen Foundation (#284196) and VA RR&D Service (#B2020-C).

Low frequency hemodynamic oscillations distinguish migraineurs from non-headache controls

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Background: Surface imaging is a promising, non-invasive approach to assess autonomically mediated regional perfusion in craniovascular disorders such as migraine.
Methods: We used optical imaging to examine differences in facial blood volume at baseline and in response to ammonia inhalation (a noxious stimulus), as well as standardized measures of cardiovascular autonomic function, in normal controls (n = 43) and in inter-ictal migraine subjects (n = 21).
Results: Resting facial cutaneous oscillation frequency was significantly different in migraine compared to healthy, non-headache controls. Following ammonia inhalation, controls showed a significant increase in resting facial cutaneous oscillation frequency, whereas this response was blunted in the migraine group. Head-up tilt table testing produced a significant decrease in facial hemodynamic oscillation frequency in both groups. Standardized autonomic reflex parameters did not differ significantly between study groups, and facial cutaneous activity did not correlate with standardized cardiovascular autonomic reflex parameters, suggesting a potentially differing generator for facial hemodynamic responses.
Conclusions: This approach to the assessment of craniofacial hemodynamic function appears to exhibit differing mechanisms from previously available techniques, and represents a promising new biomarker for the study of craniofacial vascular function in migraine and potentially other craniovascular disorders.
Funding: AAS-Lundbeck Research Fellowship (MMC).

WEDNESDAY, OCTOBER 24, 2018

POSTER SESSION I

Poster #1

Non-motor symptoms and gender differences in multiple system atrophy

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Objective: To determine the frequency and gender differences of non-motor symptoms (NMS) in patients with multiple system atrophy (MSA).
Background: NMS are a core feature in MSA and may precede onset of motor symptoms. Although NMS are gaining awareness as significant cause of morbidity, the frequency of symptoms among MSA subtypes and gender differences remain to be thoroughly characterized.
Methods: The clinical features of patients diagnosed clinically as probable or possible MSA who were treated at the movement disorder unit of Innsbruck, Austria between 2000 and 2017 were analysed. NMS were evaluated based on a review of medical records.
Results: Data from 175 MSA patients (51.4% men) were included in the analysis. Early autonomic dysfunction as defined by occurrence of at least one symptom within 1 year of motor onset was recorded in 49.1% of the patients. Overall the most frequent NMS reported by patients at any time throughout the disease course were bladder symptoms (94.8% of cases), depression (80.7%) and symptoms of REM sleep behavior disorder (78.8%) followed by postural dizziness/syncope (77.8%) and constipation (75.2%). Constipation and sudomotor symptoms were more prevalent in MSA-P (parkinsonian variant) patients compared to MSA-C (cerebellar variant) patients (p men) and early autonomic failure (men > women).

Poster #2

Alpha-synuclein deposition in sympathetic noradrenergic nerves and cardiac noradrenergic deficiency distinguish Lewy body from non-Lewy body forms of neurogenic orthostatic hypotension

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Background: Lewy body diseases are characterized by deposition of the protein alpha-synuclein (AS) in autonomic nerves and a high frequency of neurogenic orthostatic hypotension (nOH) due to sympathetic neurocirculatory failure. We examined whether measurement of AS in noradrenergically innervated skin constituents and cardiac sympathetic neuroimaging by 18F-dopamine positron emission tomographic scanning distinguish Lewy body from non-Lewy body forms of nOH.
Methods: Skin biopsies were analyzed from 12 patients with Lewy body nOH and 12 with non-Lewy body nOH (multiple system atrophy, autoimmune autonomic ganglionopathy, autoimmunity-associated autonomic failure with sympathetic denervation, nOH after cardiac transplantation, pure autonomic failure without Lewy bodies). AS was quantified by the AS signal in regions of interest (ROIs) delineated by smooth muscle actin and by a statistical index of co-localization of AS with tyrosine hydroxylase (TH), a marker of catecholaminergic neurons.
Results: In the patients with Lewy body forms of nOH the mean intensities of AS signal in arrector pili muscles, blood vessels, and sweat glands were 19, 6.5, and 15 times those in patients with non-Lewy body forms of nOH ($p < 0.0001$ each). The mean values for the AS/TH co-localization index in the Lewy body nOH group averaged 9 times that in the non-Lewy body nOH group ($p = 0.0001$). Combining myocardial 18F-dopamine-derived radioactivity with AS deposition by either the ROI or AS/TH co-localization method completely separated the Lewy body from the non-Lewy groups.
Conclusions: AS quantification in noradrenergically innervated skin constituents combined with cardiac sympathetic neuroimaging efficiently distinguishes Lewy body from non-Lewy body forms of nOH.
Funding: Division of Intramural Research, NINDS, NIH.

Poster #3

The impact of supine hypertension on target organ damage and mortality in patients with neurogenic orthostatic hypotension

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In addition to neurogenic orthostatic hypotension (nOH) patients with autonomic failure frequently have supine hypertension. The consequences of both problems are difficult to disentangle. We hypothesized that supine hypertension in patients with nOH increases the risk of end-target organ damage and negatively impacts survival. Patients with autonomic failure underwent standardized autonomic function tests, full neurological examination, and ambulatory 24-h blood pressure monitoring (ABPM). We assessed end-target organ damage by measuring cerebral white matter hyperintensities (WMH), left ventricular hypertrophy (LVH), and renal function. We prospectively followed these patients for 27 months (range: 12–56 months) and recorded incident cardiovascular events and all-cause mortality. Fifty-seven patients (35 with multiple system atrophy, 14 with Parkinson disease and 8 with pure autonomic failure) with nOH completed autonomic, cardiovascular, renal, and brain magnetic resonance imaging evaluations, and had ABPM. Thirty-eight patients (67%) had supine hypertension (systolic BP > 140 mmHg). These patients had higher blood urea nitrogen levels ($P = 0.005$), lower estimated glomerular filtration rate ($P = 0.008$), higher prevalence of LVH ($P = 0.040$), and higher WMH volume ($P = 0.019$) compared to those without hypertension. Within 27.1 ± 14.5 months of follow-up, 25 subjects (6 without, 19 with supine hypertension) had died (22 patients), had nonfatal myocardial infarction (1 patient), or had nonfatal stroke (2 patients). Time to cardiovascular event/death was shorter in patients with supine hypertension compared to patients without supine hypertension (36 vs. 50 months; $HR = 3.28$, $P = 0.010$). Supine hypertension in patients with autonomic failure is associated with an increased risk for end-target organ damage, cardiovascular adverse events, and premature death. Our findings have therapeutic implications.
Funding: NIH, Dysautonomia Foundation.

Poster #4

Relationship between cardiac sympathetic modulation and inflammation after repetitive automatic mechanical somatosensory stimulation (AMSS) in Parkinson's disease

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Introduction: Parasympathetic prevalence is associated with anti-inflammatory effects whereas sympathetic over-activity may contribute to local and systemic inflammation maintenance. Systemic inflammation might promote disease progression in Parkinson's disease (PD). We previously showed that single manual mechanical somatosensory stimulation of both forefeet resulted in a decrease of spectral indices of cardiac and vascular sympathetic modulation in PD.
Aim: To assess whether repeated automatic mechanical somatosensory stimulation (AMSS) could induce a reduction of sympathetic cardiac modulation in PD patients together with a decrease in their inflammatory profile.
Methods: Sixteen PD patients underwent baseline ECG recording while supine for 20 min. Blood samples were withdrawn for soluble interleukin-1 receptor II (sIL1-RII, pg/ml) assessment, a systemic inflammatory marker. Cardiac autonomic control was evaluated by RR variability analyses: a. power spectrum analysis provided the index of cardiac sympatho-vagal relationship (LF/HF). b. Symbolic analysis provided the percentage of sequences of three heart periods with no significant change in RR interval (0 V%) and that with two significant unlike variations (2 UV%), reflecting changes in cardiac sympathetic and vagal modulatory activity, respectively. AMSS was delivered to two specific points of both forefeet using the Gondola device (Ecker-Tech. Switzerland). After the first AMSS, additional AMSSs were repeated every 72 h. Sixteen days post first AMSS, cardiac autonomic function and sIL1-RII were re-evaluated.
Results: LF/HF ratio and 0 V% decreased (-0.95, $P = 0.0007$; -12.1, $P = 0.049$, respectively), 2 UV% slightly increased (n.s.) compared to pre-AMSS. In patients who reduced LF/HF ($N = 15$) and 0 V % ($N = 10$) a correlation was seen between LF/HF and 0 V% reduction and sIL1-RII decrease ($r = 0.495$, $P = 0.030$; $r = 0.600$, $P = 0.037$, respectively).
Conclusion: Repeated AMSS reduced resting cardiac sympathetic modulation in PD. After AMSS, the greater the reduction of sympathetic markers the lower were the systemic indices of inflammation. This finding might bear a potential favorable influence on the systemic inflammation observed in PD.

Poster #5

Early onset of autonomic failure distinguishes the parkinsonian variant of multiple system atrophy from Parkinson's disease

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Objective: To assess the diagnostic yield of early-onset autonomic failure in distinguishing the parkinsonian variant of multiple system atrophy from Parkinson's disease.

Methods: Three-hundred and three patients with an MRI-supported diagnosis of multiple system atrophy—Parkinsonian (n = 71) or Parkinson's disease (n = 232)—were retrospectively studied. According to their disease stage and duration at the time of cardiovascular autonomic function testing, patients were divided into early disease (Hoehn and Yahr stage < 3 AND/OR disease duration < 2 years) or advanced disease (Hoehn and Yahr stage ≥ 3 AND disease duration ≥ 2 years) and features predictive of multiple system atrophy at last-available visit were investigated. A diagnostic probability score was generated based on the discriminant variables in the early disease group.
Results: In patients at early disease, the presence of orthostatic hypotension (OR 6.50, 1.6–26.7 95% CI, p = 0.009), urinary disturbances (OR 22.1, 3.7–150.9 95% CI, p = 0.002) and postural instability (OR 27.9, 2.9–269.4 95% CI, p = 0.004) predicted multiple system atrophy at last-available visit. By assigning 1 point per above-mentioned clinical feature, a cumulative probability score ≥ 2 (score range 0–3) showed a 74.1% sensitivity and 90.1% specificity for a final diagnosis of multiple system atrophy—Parkinsonian. At advanced disease, the presence of urinary disturbances (OR 3.0, 1.0–8.7 95% CI, p = 0.05), but not of orthostatic hypotension, was distinctive of multiple system atrophy.
Interpretation: Autonomic failure featured both in Parkinson's disease and multiple system atrophy, but its early development anticipated a diagnosis of multiple system atrophy at follow-up. Parkinsonian patients presenting with 2 or more clinical features out of urinary disturbances, orthostatic hypotension or postural instability within the first 2 years of disease, have a high probability of suffering from the parkinsonian variant of multiple system atrophy.
Funding: Academic study, no external financial support allotted.

Poster #6

Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS)

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Purpose: Patients suffering from cardiovascular autonomic failure often develop neurogenic supine hypertension (nSH), which is high blood pressure (BP) in the supine position, which falls when upright owing to impaired autonomic regulation. A committee was formed to reach consensus among experts on the definition and diagnosis of nSH in the context of cardiovascular autonomic failure.
Methods: A systematic search of PubMed-indexed literature on nSH up to January 2017 was performed in a preparatory work. Available evidence was discussed in a consensus panel round table in Innsbruck on February 16th 2017. Derived statements were further discussed by representatives of the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS) and summarized in the final version of the consensus document, which received the endorsement of the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH).
Results: In patients with proven neurogenic orthostatic hypotension, nSH is defined as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg, measured after at least 5 min of rest in the supine position. Three severity degrees are recommended: mild, moderate and severe. nSH may be present also during nocturnal sleep, with reduced-dipping, non-dipping or rising nocturnal BP profiles with respect to daytime. Home BP monitoring and 24 h-ambulatory BP monitoring provide relevant information for a customized clinical management.
Conclusions: The establishment of expert-based criteria to define nSH should standardize diagnosis and allow better understanding of its epidemiology, prognosis and ultimately treatment.

Poster #7

Unresponsiveness of baroreflex sympathetic regulation leads to orthostatic intolerance in a rat model of type 2 diabetes mellitus

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Introduction: Patients with diabetes mellitus often present autonomic neuropathy and manifest arterial pressure (AP) dysregulation such as orthostatic hypotension. Since arterial baroreflex is the central mechanism to stabilize AP via regulating sympathetic nerve activity (SNA), we investigated how diabetes mellitus impairs baroreflex function by using a baroreflex open-loop analysis.
Methods: We used ZDF-Lean rats as control (CNTL) and ZDF-Fatty rats (DM) as type-2 DM. Under general anesthesia, we vagotomized and isolated carotid sinuses from the systemic circulation. We changed intra-carotid sinus pressure (CSP) stepwise from 60 to 180 mmHg every 30 s, and recorded SNA, AP, and HR. We compared the CSP-SNA (neural arc), SNA-AP (peripheral arc), CSP-AP (total arc), and CSP-HR relationships between CNTL (n = 9) and DM (n = 6).
Results: Although the total arc gain ($\Delta AP/\Delta CSP$) at the operating point did not differ between the two, the gain in the low CSP range (60–120 mmHg) markedly decreased ($< 1/30$) in DM (0.95 ± 0.10

vs. 0.03 ± 0.01 mmHg/mmHg, $P < 0.01$). The neural arc showed the exaggerated trend as the total arc. In DM, increases in CSP below the threshold pressure (140.5 ± 0.8 mmHg) did not suppress SNA at all while markedly suppressed SNA above the threshold. The peripheral arc did not differ between the two. In the CSP-HR relationship, the gain in the low CSP range significantly reduced (< 1/10) in DM than in CNTL (0.43 ± 0.08 vs. 0.04 ± 0.04 bpm/mmHg, $P < 0.01$). In the simulation study, estimated pressure fall against a hypotensive stress (− 20 mmHg) increased in DM by nearly 80% (9.6 ± 1.0 vs. 16.9 ± 2.5 mmHg, $P < 0.05$) reflecting exacerbating orthostatic intolerance in DM.
Conclusions: DM virtually nullifies the baroreflex-mediated SNA response in the low CSP range and markedly reduces the gain of baroreflex total arc. The baroreflex dysfunction may play a significant role in the pathogenesis of orthostatic intolerance in DM.
Funding: Omron Healthcare.

Poster #8

Human deep brain stimulation as a tool to study the neural control of blood pressure and heart rate

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Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established and effective therapy to improve motor dysfunction in selected patients with Parkinson's disease. Stereotactic neurosurgical implantation of the DBS electrode allows for intraoperative registration/stimulation of neuronal areas, useful to identify cerebral structures. We aimed to identify deep brain control sites for human blood pressure regulation.
Methods: Patients with Parkinson's disease undergoing STN DBS surgery at New York University School of Medicine were potential candidates for this study. During the DBS electrode implantation surgery, we recorded changes in continuous, noninvasive, beat-by-beat blood pressure parameter responses from the deep brain areas in the trajectory of the implantation electrode, through the thalamus, zona incerta, STN and substantia nigra. Electrocardiogram and arterial oxygen saturation were monitored as well.
Results: Two men (aged 60 and 74 years old; disease duration 4 and 8 years, respectively) were studied. Patient 1 underwent DBS implantation into the right STN and Patient 2 underwent implantation into the left STN. Baseline blood pressure and heart rate were 89/64 mmHg 68 bpm in Patient 1 and 81/74 mmHg 90 bpm in Patient 2. In both cases there was a striking, sudden increase in blood pressure of + 30 mmHg and heart rate when the registering electrodes had just left the terminal end of the thalamus, before entering the STN. Blood pressure and heart rate increased to 123/93 mmHg 99 bpm in Patient 1 and to 127/105 mmHg 128 bpm in Patient 2. In both cases, the blood pressure and heart rate returned to baseline numbers as the electrodes were further inserted into the STN. No other stimulated structure produced significant blood pressure or heart rate changes.
Conclusion: These findings suggest that the area between the thalamus and the STN, traditionally referred to as zona incerta, could have a role in increasing blood pressure and heart rate in humans. Further studies are warranted.
Funding: Dysautonomia Foundation, Inc.

Poster #9

Susceptibility to cardiac arrhythmia increases with sympathetic stimulation in rodents with high-thoracic spinal cord injury

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Introduction: Autonomic dysfunction (due to injury to descending sympathetic pathways) is common in individuals with high-level spinal cord injury (SCI) and associated with abnormal control of blood pressure and heart rate. Periods of sympathetic stimulation are thought to be proarrhythmogenic and this has important implications for individuals with high-level SCI who experience paroxysmal increases in sympathetic tone during episodes of autonomic dysreflexia (profound hypertension provoked by sensory stimuli below the injury level). Dobutamine (DOB) is a cardiac inotrope that mimics cardiac sympathetic stimulation. We aimed to evaluate whether: (i) susceptibility to arrhythmia increases in a rodent-model of SCI; (ii) the impact of cardiac sympathetic stimulation (DOB) on arrhythmia risk.
Methods: Experiments were conducted in 14 Wistar rats: sham-injured controls (SHAM, n = 7); and second thoracic level contusive SCI (T2, n = 7). Electrocardiogram (ECG) data were evaluated before (PRE), 1-week (POST) and 5-weeks post-SCI (TERM). At each time point, animals were infused with 30 μg/min/kg of DOB. ECG indices of atrial (P-wave duration [PWD] variability) and ventricular (Tpeak-Tend variability, QT interval corrected for heart rate [QTc], and QT variability index [QTVI]) arrhythmia risk were determined at baseline and during DOB. R-R interval (RRI) was determined.
Results: At PRE, RRI decreased in both groups (both p 0.05). Tpeak-Tend and PWD variabilities increased in T2 compared to SHAM at POST ($p = 0.033$, $p = 0.058$) and TERM ($p < 0.001$, $p = 0.004$). On average, QTVI worsened with DOB infusion ($p < 0.001$). In the presence of sympathetic stimulation (DOB) Tpeak-Tend, PWD and QTc variabilities, and QTVI all increased over time in T2 ($p < 0.001$, $p = 0.044$, $p < 0.001$, $p = 0.026$) but not in SHAM ($p = 0.115$, $p = 0.929$, $p = 0.21$, $p = 0.115$).
Conclusion: Susceptibility to cardiac arrhythmia is increased in a rodent-model of high-level SCI. Cardiac sympathetic stimulation further increases susceptibility to arrhythmia in high-level SCI. These data explain the high susceptibility to arrhythmia in individuals with SCI, particularly during sympathetic stimulation associated with autonomic dysreflexia.

Poster #10

Heart rate variability and gastric myoelectric activity in women with chronic pelvic pain: a pilot study

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Research has shown that factors that impact parasympathetic (PSNS) activity systematically impact gastric myoelectrical activity. We recently showed poorer PSNS function in individuals with chronic

pelvic pain (CPP) disorders from a supine to upright position. The following pilot study sought to examine if poorer autonomic function, marked by maladaptive patterns in PSNS activity, is accompanied by maladaptive gastric myoelectric activity in those with CPP. A sample of 111 women (36 health controls (HC); 75 CPP) were placed in supine (10 min), upright (tilted 70° head up; 30 min), and back to supine (10 min) positions. High-frequency heart rate variability (HF-HRV; 0.15–0.4 Hz) was measured at each time point as an index of PSNS activity. Electrogastrography (EGG) was used to assess gastric myoelectric activity pre- and post-upright tilt. EGG measures from 47 women (16 healthy; 31 CPP patients) were available for analysis and included relative percentage of gastric activity within the normal (2–4 cpm) and tachygastria (4–10 cpm) ranges, in addition to a ratio between the two (normal/tachy). HF-HRV was lower in CPP individuals at all time points (each $p < 0.05$). CPP individuals also showed a lesser decrease in HF-HRV from supine to upright, and poorer HF-HRV recovery from upright back to supine, as compared to HC ($F(1,106) = 4.62$, $p = 0.034$). The CPP group showed no change in tachygastria activity from pre-upright to post-upright ($t(30) = -0.62$, $p = 0.537$), whereas HC showed an increase in tachygastria activity ($t(15) = -2.09$, $p = 0.054$). No pre-post differences were found for either group in normal gastria or the normal/tachy ratio. Overall, as tachygastria should increase along with decrements in HRV from supine to upright, our results suggest poorer physiological activity in CPP individuals from both a cardiovascular and gastric standpoint. Implications, limitations, and future directions will be discussed.

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Poster #11

The association between cardiac parasympathetic activity and the lipid accumulation product

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Body mass index (BMI) serves as a modest predictor of cardiovascular disease (CVD). In contrast, the lipid accumulation product (LAP), calculated using both waist circumference (WC) and triglyceride (TG) fasting concentration, better predicts CVD risk compared to BMI. Interestingly, lower vagally mediated heart rate variability (vmHRV), an index of parasympathetic activity and overall health, is associated with both higher BMI and greater CVD risk. Yet, research has not shown a relationship between vmHRV and LAP; the following study investigated this in a sample of 641 individuals (70 females, mean age of 42 years, standard deviation of 12 years). Continuous heart rate data was recorded for a typical work day. The root mean square of successive differences was used as the measure of vmHRV for the full day (total vmHRV). LAP was calculated as: LAP (men) = (WC [cm] − (65) × (TG concentration [mmol/L]); LAP (women) = (WC [cm] − 58) × (TG concentration [mmol/L]). Zero-order correlations results showed total vmHRV to be significantly negatively associated with BMI ($r = -0.134$, $p = 0.001$), WC ($r = -0.160$, $p < 0.001$), TG concentration ($r = -0.108$, $p = 0.006$), and LAP ($r = -0.205$, p 0.05). These data are the first to show a significant association between vmHRV and LAP, but not BMI, independent of age and sex. Overall, these data highlight the strong influence of autonomic activity—particularly PSNS activity—in regulating deleterious excess-weight.

Poster #12

Determining sex-specific waist circumference cut-off values for cardiovascular disease risk in individuals with spinal cord injury

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Introduction: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with spinal cord injury (SCI). Anthropometric markers of obesity provide convenient CVD risk prediction, but proposed cut-offs for able-bodied individuals underestimate CVD risk in individuals with SCI. We aimed to evaluate use of waist circumference (WC) as a proxy for CVD risk and determine sex-specific cut-off values for individuals with SCI.

Methods: We performed a multicentre cross-sectional study of individuals with traumatic SCI (n = 257, 61 females, aged 47 ± 9 years, duration of injury 23 ± 9 years). Three anthropometric measures were compared: body mass index (BMI); WC; and waist-to-height ratio (WHtR). CVD risk was determined from the 10 and 30 years Framingham risk score (FRS). Cut-off criteria were determined using receiver operator characteristic curves (Euclidean Index).

Results: WC, WHtR, and BMI were significantly correlated (all $p < 0.00001$) with 10 and 30 years FRS in all participants (r 0.34–0.48) and males (r 0.32–0.46); in females only WC and WHtR were significantly correlated with 10 and 30 years risk (all $p < 0.05$; r 0.29–0.38). The optimal cut-off for WC (the most highly correlated anthropometric variable) was 96 cm for 10 and 30 years FRS for all participants. Sex specific cut-offs were 96 cm for 10 years and 95 cm for 30 years FRS for males, and 93 cm for 10 years and 84 cm for 30 yearss FRS for females.

Conclusion: WC is a practical measure of obesity and CVD risk for individuals with SCI. The WC cut-off for an adverse CVD risk profile is lower for individuals with SCI compared to established able-bodied criteria. Use of WC with sex and SCI-specific cut-offs should guide risk management decisions, and provide target criteria for individuals with SCI to maintain a healthy body composition.

Poster #13

Arterial stiffness and spontaneous baroreflex sensitivity in African American women

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Introduction: African American women (AAW) are at greater risk for cardiovascular disease (CVD) versus Caucasian women (CW). Decreased spontaneous baroreflex sensitivity (sBRS) is associated with negative cardiovascular outcomes and AAW have been found to have significantly lower sBRS versus CW. Increased arterial stiffness (AS) is associated with reduced sBRS particularly in older individuals, while increased cardiorespiratory fitness (CRF) is associated with increased sBRS and improved cardiovascular health. Although AAW have lower baroreflex sensitivity and are at greater risk for CVD, there is a paucity of research examining how much of the variation in sBRS is explained by AS and CRF in young, healthy, normotensive AAW and CW. Therefore, the aim of this study was to determine how much of the variation in sBRS is explained by AS and CRF in young, healthy, normotensive AAW and CW.
Methods: Thirty-seven (AAW-13; CW-24) healthy, age, height, and weight-matched college-aged women were examined for AS, CRF, and sBRS. AS was determined by pulse wave velocity (PWV), and CRF by maximal oxygen consumption (VO_2 max), while sBRS was determined by the alpha-index.
Results: Multiple regression analysis with sBRS as the dependent variable and AS and CRF as predictors indicated that in AAM, AS and CRF explained 11% of the variation in sBRS and 10% in CW. ANOVA demonstrated that neither model was significant: AAW ($P = 0.55$) and CW ($P = 0.31$).
Conclusion: Preliminary data suggest that AS and CRF are not significant predictors of sBRS in young, healthy, normotensive AAW or CW.
Funding: This study was partially supported by a grant from the Connecticut State University System.

Poster #14

Significance of efferent autonomic innervation and reactivity of arterial pressure in prognosis of patients with arterial hypertension

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Introduction: Arterial hypertension (AH) is the most important factor of cardiovascular mortality but its impact is varying for different patients.
Objective: To estimate the influence of blood-circulation autonomic regulation on the course disease in patients with AH.
Methods: We studied 56 patients with AH (59 ± 12 years) with target organ damage, among them 28 patients were with associated clinical conditions. Autonomic regulation was assessed by applying sequence of tests including tilt test, Valsalva maneuver, handgrip test, cold stress vasoconstriction test (CVC). In addition, arterial baroreflex and power spectrum of variability of both the heart rate and blood pressure (BPV) were calculated. Hemodynamic parameters were measured by using noninvasive continuous blood pressure (BP) monitor, electrocardiogram, and air-cuff occlusion plethysmograph. Repeated clinical and laboratory examinations were performed after a lapse of 5.5 to 7.9 years.
Results: Valsalva index (VI) and CVC in the group of deceased patients ($n = 5$) were smaller than in the group of survivors: 1.4 ± 0.2 vs. 1.6 ± 0.4 a.u., $p < 0.05$ and 0.20 ± 0.02 vs. $0.39 \pm 0.16\%$, $p < 0.05$, respectively, whereas total peripheral resistance and BPV in the respiratory range were larger: 1.4 ± 0.2 vs. 0.9 ± 0.3 a.u., $p < 0.001$ and 18 ± 14 vs. 6 ± 4 $mmHg^2$, $p < 0.001$, respectively. Patients, who suffered a stroke ($n = 5$) had higher total BPV 114 ± 49 vs. 66 ± 40 $mmHg^2$, $p < 0.05$, and a tendency to increase of systolic BP in orthostasis: 4 ± 15 vs. -8 ± 13 mmHg, $p = 0.06$. Patients who underwent revascularization ($n = 7$) showed orthostatic hypotension: -15.8 ± 8.8 vs. 3.6 ± 12.9 mmHg, $p < 0.05$ and tendency of decreased VI: 1.5 ± 0.1 vs. 1.8 ± 0.5, $p = 0.07$. Patients with newly developed associated clinical conditions showed orthostatic hypertension: 15 ± 6 vs. -10 ± 13 mmHg, $p < 0.005$ but decreased VI: 1.41 ± 0.08 vs. 1.99 ± 0.55 a.u., $p < 0.05$.
Conclusion: The parameters of cardiac and vasomotor reactivity, such as Valsalva index, cold-stress vasoconstriction, inadequate BP dynamics in orthostasis, and beat-to-beat BP variability are important markers for prognosis of the disease progression in patients with arterial hypertension.

Poster #15

Assessing individual human baroreflex-chemoreflex interactions using an n-of-1 trial design

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Introduction: Baroreflexes and peripheral chemoreflexes have a powerful effect on efferent autonomic activity making them prime suspects in the pathogenesis of cardiovascular disease and attractive treatment targets. However, the literature on their interaction is controversial, likely through inter- and intraindividual variability in cardiovascular reflex regulation. Therefore, we applied an n-of-1 trial design to elucidate individual baroreflex-chemoreflex interactions.
Methods: We studied 10 healthy men (18–40 years, BMI 18–28 kg/m^2) breathing either normal air or an air-nitrogen-carbon dioxide mixture for 90 min each in randomized order. We applied 20 phenylephrine boli per subject and condition to raise blood pressure (one every 4 min). To limit variability, we utilized an automated injector providing standardized boli. We determined the pressor response to phenylephrine as estimate of baroreflex blood pressure buffering capacity and baroreflex sensitivity (BRS).
Results: Hypoxia reduced arterial oxygen saturation from 98.0 ± 1.0 to $80.8 \pm 1.3\%$ ($p < 0.0001$), raised heart rate from 63.6 ± 6.5 to 75.6 ± 10.2 bpm ($p = 0.004$), but did not change systolic blood pressure (132.1 ± 10 vs. 133.8 ± 8.9 mmHg; $p = 0.404$). 5 out of 10 subjects had significantly lower BRS with hypoxia ($p < 0.05$). 5 out of 9 subjects showed a significantly increased pressor response to phenylephrine during hypoxia likely through impaired baroreflex buffering ($p < 0.05$). One subject presented a reverse response,

namely significant increases in BRS and baroreflex buffering function under hypoxic conditions. On average, hypoxia decreased BRS by 5.6 ± 6.3 ms/mmHg (20.1 ± 6.4 vs 14.6 ± 6.9 ms/mmHg, p = 0.021) but did not change the phenylephrine pressor response (p = 0.769).
Conclusion: An n-of-1 trial design can be applied to assess individual baroreflex-chemoreflex interactions in human subjects. Indeed, we identified a subgroup of persons exhibiting significant impairments in baroreflex blood pressure buffering and BRS with peripheral chemoreflex activation. The approach may have utility in elucidating individual pathophysiology and in targeting treatments modulating baroreflex or chemoreflex function.

Poster #16

Stress response and role of autonomic nervous system in Takotsubo cardiomyopathy

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Introduction: Takotsubo cardiomyopathy (TCM) is a disease typically characterized by transient left ventricular dysfunction with apical ballooning. The clinical presentation is often similar to those of an acute myocardial infarction. Although the cause of TCM remains unknown, the emotional and physical stress and exaggerated sympathetic nerve activity plays a key role.
Methods: We studied psychological stress response of plasma catecholamine in 8 TCM patients (72 years old, 11 female) and 3 healthy subjects (39 years old, 3 female). The mean onset age to develop TCM was 70. All the subjects were asked to finish 3 min mental calculation (MC) task and 3 min public presentation (PP) task (stress test). The order of MC and PP task were randomly assigned. Plasma epinephrine, norepinephrine, dopamine, renin, and aldosterone were measured before and after the series of two procedures. Autonomic function tests were performed to assess cardiovascular sympathetic indices and cardio-vagal indices.
Results: TCM patients had reduced sinus arrhythmia ratio (1.2 vs. 1.6, p = 0.004) and Valsalva ratio than the healthy subjects (1.2 vs. 1.8, p = 0.02). The incremental change of systolic blood pressure during cold pressor, hand grip, and hyperventilation test were comparable to those of the healthy subjects. Plasma norepinephrine (74.7 pg/ml vs. 167.2 pg/ml, p = 0.004) and epinephrine (16.3 pg/ml vs. 13.2 pg/ml, p = 0.03) were significantly increased in TCM patients than the healthy subjects after the series of stress tests. However, incremental change of plasma aldosterone was lower in TCM patients (25.6 pg/ml vs. 40.2 pg/ml).
Conclusion: Gene polymorphisms of alpha-adrenergic receptors, beta-adrenergic receptors, and dopamine receptors were evaluated. ADRA1A, ADRA2B, ADRB1, DRD2, DRD4 gene variants were found in TCM patients. Further evaluation of the genotypes combined with clinical presentation is currently proceeding.
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Poster #17

Attention and information processing impairment in individuals with chronic SCI: role of autonomic dysfunction

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Objective: Cognitive deficits in persons with spinal cord injury (SCI) are often attributed to concomitant traumatic brain injury (TBI); however, emerging evidence supports potential association with cardiovascular autonomic (CardioAuto) dysfunction. Analysis of heart rate variability (HRV) in the mid-frequency range (MF: 0.07–0.14 Hz) during cognitive testing may provide insight regarding the contribution of both sympathetic and vagal influences to performance.
Participants: Subjects included 30 controls and 60 individuals with chronic (10 ± 7 years) SCI (C3-T12). The participants were age-matched and none had a documented history of TBI.
Methods: The Paced Auditory Serial Addition Task (PASAT) evaluates information processing and sustained and divided attention. Participants were presented with a number every 1.2 to 2.4 s, in 4 sets, at an accelerated rate of presentation, and were asked to add the preceding number to each new number. Beat-to-beat HR was assessed at rest and continuously during the PASAT. Frequency analysis was used to determine change in power spectral density (ms/Hz) from rest to during the PASAT within the MF bandwidth of HRV as an indicator of CardioAuto function.
Results: Scores on the PASAT were significantly lower in participants with SCI (102.6 ± 47.2) compared to the controls (130.2 ± 38.1; $p < 0.01$). MF amplitude during the PASAT was significantly lower in participants with SCI compared to the controls (1012.2 ± 1132.2 vs. 1759.5 ± 1938.3, respectively; $p < 0.05$). Change in MF was significantly correlated with PASAT scores in the controls ($r^2 = 0.468$; $p < 0.01$) but not in the SCI group.
Conclusion: Diminished performance on the PASAT in the SCI group, in the absence of documented TBI, suggests an alternative etiology may be responsible for the reported cognitive dysfunction in the SCI population. Furthermore, lower MF amplitudes and the lack of an association between changes in MF and PASAT scores in persons with SCI suggests that CardioAuto impairment may contribute to the observed cognitive dysfunction.
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Poster #18

Sudomotor dysfunction in diabetic autonomic neuropathy is not a frequent finding

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Introduction: Timely diagnosis of diabetic autonomic neuropathy (DAN) should allow for an early intervention so as to prevent complications. Literature review reveals that the most common pattern of involvement is cardiac vagal and distal sudomotor dysfunction occurring in equal frequency. We performed a retrospective review of a cohort of patients with DAN of various severity who had autonomic reflex testing in our laboratory. As part of quality improvement, we

wanted to see if published autonomic reflex screen abnormalities can be reproduced in our population
Methods: All consecutive patients, men, and women regardless of age, diagnosed as DAN after autonomic reflex screen testing in the NorthShore autonomic laboratory between 2014 and 2018 were included. The patients had DM and had no other identified etiology for their autonomic symptoms. All patients underwent autonomic reflex screen testing and some also had quantitative pupillometry. Potential pharmacological interfering agents, including eye drops, were stopped before testing as per laboratory protocol. Age appropriate cardiovagal and sex-appropriate sudomotor normative data were used.
Results: 100 patients were studied. 38 of subjects had CV dysfunction in isolation. 62 subjects had combined CV and SD: 29 length dependent SD, 14 non-length dependent SD (> 2 sites), 16 with single site sweat abnormality (6 at the foot and 10 at various other sites). Only 3 subjects had normal CV function but had SD dysfunction (1 length dependent and one patchy).
Conclusions: Most common autonomic reflex testing abnormality in DAN is CV dysfunction: 97%. Little over 50% of subjects with abnormal CV also have SD: roughly half-length dependent and half patchy or single site SD pattern. We believe that pseudo normalization or even excessive sweat volumes may also be a manifestation of DAN, suggestive of denervation hypersensitivity.

Poster #19

Fingolimod does not seem to affect autonomic bladder function in patients with relapsing–remitting multiple sclerosis

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Background: Fingolimod, an oral medication for relapsing–remitting multiple sclerosis (RRMS), alters cardiovascular-autonomic modulation due to its vagomimetic effects on S1P1-receptors of cardiomyocytes. S1P1-receptors occur ubiquitously and might present within the bladder wall and sphincters. We hypothesize that Fingolimod affects these receptors and alters autonomic bladder-function due to direct parasympathomimetic or secondary autonomic influences.
Objective: To determine whether Fingolimod alters bladder-function in RRMS-patients without clinically evident bladder dysfunction prior to Fingolimod-treatment.
Methods: In 24 RRMS-patients (mean age 39 ± 11 years, 17 women), we performed uroflowmetry to determine voided-urine-volume, maximum-flow-rate, average-flow-rate, flow-time, time-to-maximum flow, and bladder ultrasonography (Solar-Uroflow™, Scanmaster™, MMS, Germany) to assess pre-voiding urine-volume and post-voiding residual urine-volume. Measurements were taken upon Fingolimod-initiation and after one year of Fingolimod-therapy (0.5 mg/day), and were compared to values assessed in 25 age- and sex-matched healthy controls (mean age 32 ± 10 years, 13 women). Parameters measured in patients at the two time-points and in controls were compared by ANOVA and post hoc analysis, using t-tests for normally distributed data and Mann–Whitney-*U*-tests or Wilcoxon-tests for non-normally distributed data. Significance was assumed for $p < 0.05$.
Results: Voided-urine-volume, maximum-flow-rate, average-flow-rate, flow-time, and time-to-maximum flow, as well as pre-voiding urine-volume did not differ between controls and patients at the two measurement dates. Only post-voiding residual urine-volume was higher in patients than controls, but again did not differ within the patient-group at the two measurement dates.
Conclusion: Our findings showed slightly elevated post-voiding residual urine-volume which is common among RRMS patients. The results otherwise confirmed that the assessed parameters of bladder-function were similar between controls and patients at Fingolimod-initiation, a requirement to assure that possible changes in bladder-function are most likely not related to the RRMS but to Fingolimod. Yet, parameters remained unchanged in the RRMS-patients after 1 year of Fingolimod-treatment, suggesting that Fingolimod itself does not have any clinically relevant effects on bladder-function.
Funding: The authors received a travel grant from Novartis Pharma Germany.

Poster #20

Uroflowmetry and bladder ultrasonography non-invasively quantify slightly impaired autonomic bladder function in patients with relapsing–remitting multiple sclerosis

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Background: Although lower-urinary-tract symptoms are common in relapsing–remitting multiple sclerosis (RRMS), correlation between voiding parameters and disease-severity or -duration has not yet been assessed. In this study, we evaluated voiding parameters of RRMS-patients using non-invasive uroflowmetry and bladder-sonography to correlate these parameters with disease-duration and -severity, and to compare parameters between RRMS-patients and healthy persons.
Methods: 50 RRMS-patients (mean age 35.1 ± 8.7 years, 31 women) and 25 age- and gender-matched healthy participants participated in uroflowmetry (Solar-Uroflow™, MMS, Germany) to determine voided-urine-volume, maximum-flow-rate, average-flow-rate, flow-time, time-to-maximum flow. Bladder ultrasonography (Scanmaster™, MMS, Germany) was used to assess pre-voiding urine-volume and post-voiding residual urine-volume. Parameters were compared between patients and controls using Student's-t-tests for normally distributed data and Mann–Whitney-U-tests for non-normally distributed data. Uroflowmetry and ultrasound values were correlated with MS-duration and MS-severity, assessed as Expanded-Disability-Status-Scale (EDSS) scores and Multiple-Sclerosis-Functional-Composite (MSFC) scores, using Spearman's rank-correlation-tests for non-normally distributed data and Pearson-tests for normally distributed data. Significance was assumed for $p < 0.05$.
Results: In the patients, EDSS-scores ranged from 1.0 to 7.5 (median 2.0; interquartile range (IQR) 1.5–3.0, MSFC was − 0.07 ± 0.96, disease duration was 88.7 ± 84.5 months. Average-flow-rate tended to be lower in patients than controls (11.2 ± 4.2 ml/s vs. 13.9 ± 5.7 ml/s, $p = 0.052$). Flow-time was longer in patients than controls (31.9 ± 15.9 s vs. 24.2 ± 12.9 s, $p = 0.012$). Post-voiding residual urine-volume was higher in patients than controls (56.0 ± 61.5 ml vs. 28.2 ± 14.4 ml, $p = 0.003$). Other uroflow-parameters were similar in both groups. In the RRMS-patients, average-flow-rate correlated negatively with disease-duration (Spearman's rho = − 0.331, $p = 0.019$) and EDSS-scores (Spearman's rho = −

0.360, p = 0.010). Voided-urine-volume correlated positively with MSFC-scores (Spearman's rho = 0.314, p = 0.026).
Conclusion: In our RRMS-patients, non-invasive uroflowmetry and bladder ultrasonography non-invasively unveiled mild autonomic bladder dysfunction which is associated with longer disease-duration and higher disease-severity.
Funding: The authors received a travel grant from Novartis Pharma Germany.

Poster #21

Persistent baroreflex dysfunction in patients with a history of moderate or severe traumatic brain injury

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Background: In a previous study of patients with a history of mild traumatic brain injury (post-mTBI patients), we found a delay in blood pressure (BP) decrease upon Valsalva maneuver (VM)-induced baroreceptor-loading, indicating a compromised baroreflex-mediated sympathetic withdrawal. Given the more severe cerebral lesions in patients with a history of moderate or severe TBI, we hypothesize that these patients also have persistent baroreflex-mediated autonomic dysfunction.
Methods: In 17 patients with a history of moderate or severe TBI, defined by Glasgow Coma Scale (GCS) scores below 13 (aged 32.2 ± 10.5 years; 9 women, GCS of 6.4 ± 2.5, interval since TBI 43.1 ± 33.4 months), and 29 healthy controls (aged 31.3 ± 12.2 years; 9 women), we performed 3 VMs from which we calculated Valsalva ratios (VRs) and intervals from the highest systolic BP (BPsys)-value after strain-release to the time when BPsys had fallen by 90% of the difference between peak-phase-IV-BPsys and baseline-BPsys (90%-BPsys-normalization-times), and velocities of BPsys-normalization, defined as change in BPsys related to the 90%-BPsys-normalization-time (90%-BP-normalization-velocities) as indices of sympathetic withdrawal. We used the Kolmogorov–Smirnov-test to evaluate normal distribution of data. To compare patient and control data, we used independent t-tests for normally distributed data and Mann–Whitney-U-tests for non-normally distributed data. (significance: $p < 0.05$).
Results: VR did not differ significantly between patients (1.85 ± 0.4) and controls (2.0 ± 0.6; p = 0.3). 90%-BP-normalization-times were longer in patients than controls (22.2 ± 14.5 ms vs. 12.6 ± 4.8 ms; p = 0.02), 90%-BP-normalization-velocities were lower in patients than controls (2.3 ± 2.4 mmHg/s vs. 3.7 ± 1.1 mmHg/s; p = 0.003).
Conclusion: While autonomic dysfunction is known to be common after acute TBI, our data show that baroreflex-mediated sympathetic withdrawal after VM remains compromised for extended periods of time after moderate or severe TBI, and thus confirm our previous findings in post-mTBI patients.

Poster #22

Psychological and physiological effects of 12 weeks of slow breathing exercise on healthy subjects

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Introduction: Slow breathing exercises (less than 10 breaths/min) are an integral part of different mind–body practices, and they might reduce both psychological and physiological stress. Yoga practitioners modify the ratio of inhalation and exhalation to enhance relaxation. It is unknown, if extended exhalation technique (Exhale longer than Inhale, E > I) applied over longer time will have different effects than common slow breathing (Exhale equal to Inhale, E = I).
Purpose: We hypothesize that E > I will enhance of vagal autonomic function and reduce of stress more than E = I.
Methods: We studied 94 healthy subjects (41 years old, 79% females), randomly assigned to either E > I (n = 48) or E = I (n = 46) daily exercise guided by Yoga teachers over 12 weeks. We measured autonomic modulation by spectral analysis of heart rate and blood pressure variability, cardio-vagal baroreflex sensitivity by spontaneous sequence technique (BRS), and recorded self-reported stress scales (PROMIS Anxiety).
Results: We found that both groups decreased anxiety from baseline to 12 weeks significantly (E > I: − 5.365 ± 0.93, pI: − 3.5 ± 0.9 mmHg, E = I: − 2.3 ± 1.0 mmHg, p(time) = 0.028). BRS changed differently by time and group with increase in E > I (E > I: 3.07 ± 1.2 ms/mmHg, E = I: − 0.24 ± 0.8 ms/mmHg, p(time) = 0.013, p(timeXgroup) = 0.019 (rmANOVA).
Conclusion: 12 weeks of slow breathing exercises resulted in reduction of self-reported anxiety and blood pressure in both groups. Additionally, E > I increases cardio-vagal BRS.

Poster #23

Prediction of systolic blood pressure responses to orthostasis in persons with spinal cord injury

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Persons with spinal cord injury (SCI) often have exaggerated systolic blood pressure (SBP) responses to orthostasis that may present as hypotension (HYPO: SBP declines ≥ 20 mmHg) or hypertension (HYPER: SBP increases ≥ 20 mmHg). However, there remains uncertainty as to the specific mechanisms that contribute to the observed orthostatic BP responses in persons with SCI, which may relate to autonomic nervous system impairment and diminished sympathetic vasomotor tone. One hundred fifty-seven persons with SCI [age (years): 45 ± 14] performed a sit-up test (e.g., 5-min of supine followed by 4-mins in seated upright position) while continuous 3-lead electrocardiogram and beat-to-beat SBP was performed. Fast-fourier transform algorithms were used to calculate the high (HF), low (LF), and very low frequency (vLF) components of the SBP and heart rate (HR) signals; each variable was log10 transformed. A change score between supine and seated positions was calculated and stepwise regression analyses were performed to identify independent

variables with significant contribution to the observed changes in SBP (delta_SBP) during the sit-up test. Age, supine SBP, delta_vLF and grouping based on orthostatic response [e.g., HYPO, HYPER, or normal (NORM: SBP − 19 ≤ 19 mmHg)] were identified as significant contributors to delta_SBP. This combination created a significant prediction equation ($p < 0.0001$) that accounted for 93% of the variance delta_SBP (r^2: 0.925); delta_vLF contributing 64% (r^2 change: 0.639). Follow-up analyses on delta_vLF identified a significant group main effect ($P < 0.0001$) between the HYPO, HYPER and NORM groups, such that delta_vLF was significantly different for each group in response to orthostasis: HYPER: 0.28 ± 0.12; NORM: 0.00 ± 0.09; and HYPO: − 0.30 ± 0.16. ($p < 0.0001$). The vLF component, which has been demonstrated to reflect myogenic vascular mechanisms that are influenced by circulating catecholamines and angiotensin II, is a robust contributor to the prediction of orthostatic SBP responses and may be a sensitive marker for determination of orthostatic tolerance in persons with SCI.
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Poster #24

Optimization of heart rate variability testing

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Background: Heart variability is assessed clinically by a variety of methods, but it is often difficult to determine if abnormal results reflect a pathologic process, or suboptimal effort. This may be particularly problematic in older or frail individuals where sustained respiratory effort may be compromised.
Objective: To modify aspects of clinical heart rate variability testing in an effort to increase sensitivity and specificity.
Methods: We altered our autonomic testing protocol by including a single supra-maximal breathing cycle over 10 s after a baseline period of rest. Subjects also underwent standard heart rate variability testing, a Valsalva maneuver, 45 min tilt table testing and a 5 min active stand. Continuous heart rate and beat-to-beat blood pressures were recorded throughout. We tested 50 subjects (mean age 53, range 17–85) with a range of autonomic dysfunction from healthy to severe dysautonomia undergoing clinical autonomic testing and compared the results of the single supra-maximal breath to other measures of heart rate variability.
Results: There was a strong correlation between heart rate variability measured by single supramaximal breath compared to 10 cycles of breathing by E:I ratio ($R^2 = 0.72$, $P < 0.001$), or maximum-to-minimum heart rate variability ($R^2 = 0.70$, $P < 0.001$). However, in a significant number of cases the single supramaximal breath suggested routine HRV testing could be improved by better effort, and in some cases identified 'abnormal' results that were simply due to poor effort.
Discussion: The single supra-maximal breath provides a valuable insight into effort related variation in parasympathetic function, and may improve the ability to interpret clinical testing results. The use of a single supramaximal breath in large clinical trials where 10 s electrocardiogram tracings are routinely utilized could offer a powerful insight into parasympathetic function that might not otherwise be obtained. We plan to evaluate this technique in a large number of subjects across a range of age, gender and disease severity.

Poster #25

Reproducibility of Valsalva maneuver–derived baroreflex parameters

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Background: The Valsalva maneuver (VM) can provide estimates of both vagal and sympathetic baroreflex sensitivity (BRS).
Objective: To determine the intra-subject variability of VM-derived baroreflex parameters.
Methods: Subjects in the IRB-approved ICECAN trial return 5 times in 6 months for a series of 4 Valsalva maneuvers, using 15″ and 40 mmHg supine and at 30° until good recordings were obtained. As per Singer et al., the vagal baroreflex component (BRS_v) constitutes the RR interval response to a preceding change in BP, either during vagal excitation (BRS_vup, from Phase IV), or vagal inhibition (BRS_vdown, from Phase II early) while Pressure Recovery Time (PRT) to baseline during phase IV reflects adrenergic baroreflex. A custom MATLAB script selected the BP and RR interval correlation with the best R2 among 0, 1 and 2 beat delays, and calculated BRS_v as the linear regression slope. We examined 4 VMs collected from 4 subjects over 2 visits and selected the highest quality VM for analysis based on the best R2 and absence of artifact. The spread of BRS values was also assessed in 3 subjects using all 4 VMs in each visit.
Results: The BRS_vdown and the BRS_vup were highly reproducible with Pearson correlations of 0.99 and 0.69, respectively. BRS_vdown did not correlate with BRS_vup. Except for 2 trials, the R2 for selected trials ranged from 0.88 to 0.96. Values for BRS_vup: S1: 0.002 ± 0.001, S2: 0.002 ± 0.0009, S3: 0.005 ± 0.006; for BRS_vdown S1: 0.005 ± 0.003, S2: 0.002 ± 0.0008, S3: 0.009 ± 0.008. The PRT clustered nicely for each subject across the 2 trials, S1: 5.7 ± 2.91 s, S2: 2.67 ± 0.92 s, S3: 1.13 ± 0.33 s, S4: 2.44 ± 0.75 s.
Discussion: The VM baroreflex parameters show robust intra-subject reproducibility in this small sample, including BRS_vup, BRS_vdown, and PRT. There was little correlation between any of these paramenters.
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Poster #26

Ventilatory and cerebrovascular response to metaboreflex activation while supine or upright in men and women

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Men have an enhanced metaboreflex compared to women [as measured by blood pressure and sympathetic nerve activity (Jarvis et al., 2011)]; however, sex differences in the ventilatory and cerebrovascular response to metaboreflex activation have never been determined. Since it has been previously shown in men that the chemoreflex is activated subsequent to metaboreflex activation (Edgell et al., 2014), we hypothesized that there would be reduced ventilation in women leading to higher end-tidal CO_2 and greater cerebrovascular conductance. Men (n = 14; age: 21 ± 1) and women (n = 11; age: 19 ± 1) performed 40% maximal voluntary contraction handgrip exercise (HG) for 2 min followed by 3 min of post-exercise circulatory occlusion (PECO) in supine and 70° head-up tilted

postures. Supine: 1) During HG and PECO men increased ventilation, but women did not (Men: Baseline: 12.5 ± 0.5 L/min, HG: 18.6 ± 1.5 L/min, PECO: 17.7 ± 2.8 L/min; Women: Baseline: 12.0 ± 0.4 L/min, HG: 12.4 ± 0.4 L/min, PECO: 11.5 ± 0.4 L/min; Sex × Time interaction P = 0.037), 2) During PECO both sexes had a similar reduction of end-tidal CO_2 (Men: Baseline: 38.6 ± 0.9 mmHg, PECO: 35.3 ± 1.6 mmHg; Women: Baseline: 33.5 ± 0.9 mmHg, PECO: 32.2 ± 1.0 mmHg; Main effect of Time P < 0.001), and 3) During HG and PECO men and women decreased cerebrovascular conductance equally (Men: Baseline: 0.79 ± 0.04 cm/s/mmHg, HG: 0.68 ± 0.05 cm/s/mmHg, PECO: 0.61 ± 0.05 cm/s/mmHg; Women: Baseline: 0.87 ± 0.04 cm/s/mmHg, HG: 0.83 ± 0.04 cm/s/mmHg, PECO: 0.75 ± 0.05 cm/s/mmHg; Main effect of Time P < 0.015). Upright: The increase of mean arterial pressure due to PECO was significantly smaller in the upright position compared to the response while supine in both men and women (Supine posture: Men: + 23.3 ± 4.0 mmHg, Women: + 12.0 ± 7.7 mmHg; Upright posture: Men: + 15.7 ± 3.9 mmHg, Women: + 7.7 ± 2.0 mmHg; Main effect of sex P = 0.042, Main effect of posture P < 0.001). Our results indicate that women do not increase ventilation during metaboreflex activation which may be due to an absence of chemoreflex activation. However, the reduction of cerebrovascular conductance was similar between the sexes likely due to similar reductions of end-tidal CO_2.

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Poster #27

The effect of habitual physical activity on sympathetic vascular transduction

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Purpose: Physical activity (PA) positively influences cardiovascular (CV) health. Increasing PA reduces muscle sympathetic nerve activity (MSNA) in elevated CV risk populations, but not in healthy adults. Sympathetic vascular transduction represents SNA-induced changes in beat-to-beat blood pressure (BP) and vascular conductance (flow ÷ mean BP). Importantly, groups with heightened CV risk exhibit augmented transduction, however, the influence of PA on transduction is unknown. Therefore, the purpose of this investigation was to determine the influence of PA on sympathetic vascular transduction.
Methods: Seventeen healthy adults (7F/10M; age: 24 ± 1 years; BMI: 25 ± 1 kg/m^2; BP: 114 ± 3/65 ± 2 mmHg, mean ± SEM) underwent MSNA (microneurography), beat-by-beat BP (finger photoplethysmography), and femoral artery blood flow (ultrasound) measurements throughout 10 min of rest. Femoral blood flow was used to derive leg vascular conductance (LVC). Each cardiac cycle containing burst(s) of MSNA was identified and the absolute change in mean BP and %ΔLVC were determined over 10 subsequent cardiac cycles. Changes after each burst were averaged to quantify transduction. Habitual PA was assessed via 7 days of accelerometry. A median split was performed to divide participants into less- and more-active groups based on their average daily steps and moderate to vigorous PA (MVPA).
Results: Data are presented as less active (n = 8) vs. more active (n = 9). There was a significant difference between groups for daily step count (6788 ± 693 vs. 12,233 ± 929, p < 0.01) and MVPA (74 ± 7 vs. 124 ± 7 min/day, p < 0.01). MSNA was similar between groups (Burst freq: 14 ± 3 vs. 14 ± 2 burst/min, p = 0.96). There was an interaction (time × group) on %ΔLVC transduction for step count (p 0.05, for both step count and MVPA). There was a significant unexpected correlation between negative peak %ΔLVC and MVPA (r = − 0.59, p = 0.02).
Conclusion: These preliminary data suggest habitual physical activity may influence sympathetic vascular transduction in young healthy adults.

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Poster #28

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

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Background: The cell bodies of afferent nerves that pass from the periphery to the spinal cord are housed in the dorsal root ganglion (DRG), a swelling in the nerve just before it enters the spine. In pain processing, the DRG is hypothesized to be an important site in the induction of neuropathic pain, with alterations in neurotransmitters, genetic markers, and neurophysiological characteristics having been demonstrated. However, the role of the DRG in sympathetic regulation is yet to be elucidated and there have been no human neurophysiological studies due to the inaccessibility of the DRG to manipulation. Lesion to a peripheral nerve may result in chronic pain syndromes, hypothesized to be relieved only 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.
Methods: 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.
Results: 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.

Conclusion: 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.
Funding: British Heart Foundation, Saint Jude Medical.

Poster #29

Heightened sympathetic neural and blood pressure responses to cold pressor test in women with post-traumatic stress disorder

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Post-traumatic stress disorder (PTSD) is a psychiatric illness that is more common in women compared to men, and there is growing evidence suggesting a close link between PTSD and future development of hypertension and cardiovascular disease. The underlying mechanisms are unclear, but increased sympathetic reactivity to stressors may be involved. We hypothesized that women with PTSD would have an augmented sympathetic neural response to the cold pressor test (CPT). Heart rate (HR, ECG), blood pressure (BP, SunTech) and muscle sympathetic nerve activity (MSNA, microneurography) were measured in 16 women with PTSD and 9 healthy female controls [age: 43 ± 3 (SE) vs. 41 ± 3 years] during supine baseline, 2-min CPT, and 3-min recovery. Data were averaged for every 30 s. At the baseline, mean arterial pressure (MAP) and HR were not different between groups; however, MSNA burst frequency (BF) was greater in women with PTSD (30 ± 3 vs. 13 ± 3 bursts/min; P = 0.002). MAP and MSNA increased during CPT in both groups. The CPT-evoked MSNA BF response was greater in women with PTSD compared with healthy controls (Group × time interaction P = 0.039, Group P = 0.001, Time P = 0.0001). Similarly, the CPT-induced BP (pressor) response was also greater in women with PTSD (MAP; Group × time interaction P = 0.001, Group P = 0.04, Time P = 0.0001). The changes in MSNA BF and MAP during CPT were strongly correlated in the PTSD group (1 min CPT: P = 0.01 r = 0.63; 2 min CPT: P = 0.02, r = 0.61). We found women with PTSD have augmented sympathetic neural and pressor responses to cold (painful) stimuli which may, in part, explain the propensity toward developing hypertension and cardiovascular disease in this population.
Funding: Supported by the Harry S. Moss Heart Trust Medical Research Grant.

Poster #30

Resting state fMRI functional connectivity of the PAG in healthy adolescents and adolescents with functional gastrointestinal disorder

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Background: The midbrain periaqueductal gray region (PAG) modulates both pain and cardiac vagal outflow. Few neuroimaging studies have investigated the PAG's functional connectivity with the rest of the brain or its role in pain, anxiety, stress or autonomic regulation in patients with functional gastrointestinal disorders (FGID).
Methods: High resolution anatomical and resting-state fMRI images were acquired from 11 healthy controls (HC) and 9 FGID patients on a GE 3T scanner. 1 HC excluded from fMRI analyses due to excessive motion. The PAG boundary was hand traced and the structural image was segmented into CSF, white matter and grey matter using FSL. The tissue volumes were compared across groups. We collected two 6-min runs of resting-state fMRI data (TR = 2000 ms; TE = 24 ms; FOV = 240 mm, matrix size = 64 × 64; slice thickness = 3.5 mm). Time-series data were extracted from the PAG mask and correlated with the data from 14 target ROIs in the subject space. Statistical analysis was performed on the Fisher z transformed correlation scores.
Results: There were no significant age (p = 0.341) or gender differences (p = 0.094) between groups (HC: 7 females, age range 12–17 years, mean 14.72 ± 1.35; FGID: 9 females, age range 14–17 years, mean 15.33 ± 1.41). Volumetric analyses showed no group differences. Significant group connectivity differences of the PAG occurred with the L insula (HC mean − 0.11 ± 0.25; FGID mean 0.28 ± 0.27; p = 0.017), with trends for the R insula (HC mean − 0.009 ± 0.26; FGID 0.22 ± 0.27; p = 0.070) and R hypothalamus (HC mean 0.21 ± 0.33; FGID 0.51 ± 0.41; p = 0.096).
Discussion: The PAG in adolescents with FGID demonstrates increased connectivity with the insular cortex. This may reflect an attempt by the insula to restore impaired autonomic and pain modulation at the level of the PAG, or greater afferent information flow from the PAG to the insular cortex, leading to conscious perception of the subject's symptom experience.
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Poster #31

Distinguishing multiple system atrophy and Parkinson's disease using resting state functional MRI: a pilot study

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Background: Multiple system atrophy parkinsonian subtype (MSA-P) and Parkinson's disease (PD) can be difficult to distinguish clinically. A common feature among PD patients misdiagnosed with MSA-P is autonomic dysfunction. Though the central nervous system (CNS) contributions to autonomic dysfunction in MSA and PD are incompletely understood, several brain regions are strongly implicated. Particularly, there is evidence of involvement of the hypothalamus (HTH) in both diseases. We collected pilot data to investigate the role of intrinsic interactions within large scale brain systems, as measured using resting state functional magnetic resonance imaging (rs-fMRI), in distinguishing MSA-P from PD, focusing on CNS autonomic structures, specifically the HTH given its role in both diseases.
Methods: We enrolled 5 subjects with MSA-P from among patients at the UNC Neurology clinic. rs-fMRI data for 10 age and disease duration matched PD subjects were obtained from the Parkinson's Progression Markers Initiative (PPMI) database, an open-access database for PD patients. We used seed-to-voxel analysis, placing

seeds in the left and right HTH, to investigate patterns of functional connectivity between the HTH and cortical and subcortical structures, with correction for multiple comparisons.
Results: Mean age of MSA and PD subjects was 65.2 and 63.4 years, respectively. Mean disease duration for MSA and PD subjects was 5.4 and 5.9 years, respectively. PD subjects had significant differences in functional connectivity between the HTH and cortical and subcortical structures ($p < 0.001$) compared to MSA subjects.
Discussion: Preliminary analysis of functional connectivity of the HTH from the first 5 MSA subjects recruited to this study demonstrates robust differences distinguishing them from 10 age and disease duration matched PD subjects. Using autonomic central nervous system structures as a candidate system, rs-fMRI may prove to be an important clinical and research tool for PD and MSA. Further investigation is warranted, and our data collection continues.
Funding: UNC Department of Neurology - Soo Neuroimaging Research Fund, Parkinson Foundation travel awards.

Poster #32

Evidence of cortical autonomic impairment in the pathophysiology of neurogenic orthostatic hypotension associated with peripheral autonomic dysfunction

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Background: Neurogenic orthostatic hypotension (NOH), defined as a drop in systolic blood pressure (SBP) $\geq$ 30 mmHg on standing or head-up tilt, is associated with autonomic dysfunction. The cortical autonomic network (CAN) is a network of brain regions associated with autonomic function. Our aim was to investigate CAN activation patterns in NOH patients during autonomic testing.
Methods: Fifteen controls (63 $\pm$ 13 years) and fifteen NOH patients (67 $\pm$ 6 years; $p = 0.2$) with peripheral autonomic dysfunction completed: (1) deep breathing (DB), (2) Valsalva maneuver (VM) and (3) lower-body negative pressure (LBNP) during a functional MRI. Blood-oxygen level dependent contrasts were obtained and contrasted.
Results: Hemodynamics: Compared to controls, patients had significantly smaller heart rate responses to DB (C: 15.23 $\pm$ 9.6 vs. NOH: 5.7 $\pm$ 2.1) and Valsalva ratios (C: 2.1 $\pm$ 0.47 vs. NOH: 1.2 $\pm$ 0.1; $p < 0.001$). NOH patients had absent adrenergic phases (late phase II and phase IV) during VM as per a qualitative analysis. Patients had significantly larger BP drops during LBNP ($p < 0.001$). Function Imaging: During VM, controls had greater activation in the right hippocampus (TR-value: 8.03), left posterior cingulate (TL: 7.6) and bilateral thalamus (TR: 7.41, TL: 8.45; $p < 0.05$). During phase IV, controls had greater activation in the right hippocampus (TR: 5.78; $p < 0.05$). Following subtraction analysis, no significant differences were evident during DB. Compared to controls, NOH patients had significantly less activation within the cerebellum during both LBNP and VM.
Conclusion: NOH patients have significantly less CAN activation during tests of sympathetic, but not parasympathetic, activation. Furthermore, the cerebellum, which plays an important role in orthostatic reflexes such as the vestibulo-sympathetic reflex, may be impaired in NOH patients. Overall, impaired cortical autonomic networks appear involved in the pathophysiology of NOH.

Poster #33

The Orthostatic Discriminate and Severity Scale (ODSS): a tool to discriminate orthostatic from non-orthostatic symptomatology

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Objective: In the present prospective study, we aimed to assess the ability of Orthostatic Discriminate and Severity Scale (ODSS) to distinguish symptoms of orthostatic intolerance from non-orthostatic symptoms.
Methods: Clinical evaluations and questionnaire responses were collected in 73 healthy controls and 132 patients referred to the Autonomic Disorders Clinic for queries surrounding autonomic dysfunction. A receiver operating characteristic (ROC) curve analysis was used to interpret sensitivity and specificity and to determine cut-off scores for symptom assessment. Inter-item reliability was assessed using Cronbach's alpha. To calculate positive and negative predictive powers, patient data was collected in a single-blinded fashion where the researcher collecting questionnaire data was blinded to the clinical evaluation and diagnosis. Predictive powers were calculated using a Chi square cross-tabulation.
Results: The orthostatic and non-orthostatic symptoms scores produced ROC curves with an area under the curve of 0.89 and 0.79, respectively. The orthostatic scores yielded a positive and negative predictive power value of 73% and 81%, respectively. Combined, the ODSS identified patients with and without orthostatic symptoms with an overall accuracy of 76%. The reliability of the ODSS was significant with a Cronbach's alpha of 0.88 and all dichotomous items were deemed worthy of retention following an inter-item reliability assessment.
Conclusion: The ODSS demonstrates a strong ability to distinguish patients with and without orthostatic intolerance and demonstrates a sensitivity and specificity equivalent to that of other standardized measures. Overall, the ODSS produces symptom scores that are both reliable and useful for both research and clinical practice.

Poster #34

Can head-up tilt (HUT) be used to distinguish between clinical sub-groups of vasovagal syncope (VVS): the Heisenberg principle at play

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VVS is triggered by emotive, orthostatic or both (mixed) stressors. The initial blood pressure (BP) collapse during HUT-induced VVS in VVS patients is unique and due either to a decrease in heart rate, stroke volume or total peripheral resistance. These hemodynamic patterns are largely exclusive of age, gender or clinical subtype of VVS. Many patients with identical clinical patterns of VVS, however, do not faint during HUT. To determine whether HUT, an "orthostatic stressor", selectively uncovers "orthostatic" phenotypes of VVS we evaluated the response of 144 healthy [age 17–62 (31.5 $\pm$ 1 year, 43 men)] VVS patients. 76 had HUT-induced VVS (Reactors) 68 did not (HUT duration (38.4 + 4.0 min). Strict inclusion criteria eliminated

patients who took medications or had any medical condition. Finger BP and EKG were continuously recorded. We averaged the first six 20 s data segments of the cardiovascular responses to HUT. The time to HUT-induced VVS was not significantly different for the 3 groups of VVS patients (overall 13.8 + 9.0 min). The distribution of clinical VVS groups was identical between Reactors vs. Non-Reactors (Orthostatic 33 vs. 37; Emotive 13 vs. 11; Mixed 30 vs. 20; X^2 (2) = 2.0, p = 0.38.). Any of the 3 groups were equally likely to have or not have HUT-induced VVS. Group (Reactor/Non-reactor) X 6 Time averages of the initial cardiovascular responses of Reactors to HUT were indistinguishable from Non-Reactors. Although HUT testing is considered an "orthostatic stress test", it is just as likely to lead to a presyncopal reaction in those with a purely emotive (24/144) or mixed orthostatic-emotive (50/144) history of VVS. The very act of laboratory testing imposes measurement error and unanticipated stressors. Further research is needed to help elucidate the potentially psychological components of HUT testing, or other factors contributing to VVS during HUT.

Funding: Fonds de Recherche Sante Quebec (FRSQ) - Programme de bourses de formation de doctorat (FF11-24D).

Poster #35

Effects of droxidopa treatment for neurogenic orthostatic hypotension in patients concomitantly on dopa decarboxylase inhibitors

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Objective: To assess the long-term efficacy of droxidopa for treatment of neurogenic orthostatic hypotension (nOH) in patients concomitantly on dopa decarboxylase (DDC) inhibitors (DDCIs).
Background: nOH is a non-motor symptom of Parkinson's disease (PD). Treatment of PD frequently includes DDCIs. Droxidopa, a treatment for symptomatic nOH, is converted to norepinephrine by DDC.
Methods: Patients were enrolled in a prospective cohort study comparing outcomes before initiation of droxidopa and after 1, 3, and 6 months of treatment. Patients recorded monthly number of falls using a questionnaire and dizziness/lightheadedness using the Orthostatic Hypotension Symptom Assessment, Item 1 (OHSA-1). A post hoc analysis compared outcomes in patients on DDCIs vs. without DDCIs. "DDCI treatment" was defined as receiving carbidopa/levodopa, with or without entacapone. The influence of DDCIs was compared across time points using generalized linear mixed models adjusting for repeated measures within individuals.
Results: 168 patients were included (PD: 32.1%, autonomic failure: 66.1%, other: 1.8%). 61.8% of patients on DDCIs (n = 55) reported $\geq$ 1 fall at baseline vs. 46.9% of patients not on DDCIs (n = 113). Patients on DDCIs experienced a significant reduction in fall rate (30.1%, 36.4 point reduction) and improvement in OHSA-1 scores (− 1.8) from baseline to 6 months ($P < 0.05$ for both). Patients not on DDCIs also experienced significant improvement in OHSA-1 scores (− 1.9, $P < 0.05$), but the reduction in fall rate was not significant (39.8%, 6.2 point reduction, P = 0.49). The differences in change from baseline to 6 months for fall risk and OHSA-1 score were not significant between groups (P = 0.15, P = 0.96, respectively).
Conclusions: These post hoc analyses suggest that both DDCI users and nonusers experienced reductions in fall rate and dizziness/lightheadedness with droxidopa treatment. Additional studies are needed to examine the impact of DDCIs on droxidopa because the current study was not powered for subgroup analyses and data were self-reported by patients.
Funding: This work was supported by Lundbeck.

Poster #36

Diagnosis of orthostatic hypotension: contribution of diastolic blood pressure

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Background: Orthostatic hypotension (OH) is defined as a drop in systolic blood pressure (SBP) of $\geq$ 20 mmHg or diastolic blood pressure (DBP) of $\geq$ 10 mmHg within 3 min of upright tilt table testing or active standing.
Objective: To determine the role of DBP on the diagnosis of OH.
Methods: We tested 50 subjects (mean age 53, range 17–85 years) ranging from healthy to severe dysautonomia. Subjects underwent heart rate variability to paced breathing, Valsalva maneuver, a 45 min tilt table test and a 5 min active stand. Automated sphygmomanometer recordings each minute of testing and continuous heart rate and beat-to-beat blood pressures were monitored. SBP and DBP results were compared to overall diagnosis and correlated with other autonomic function testing.
Results: There was poor agreement between orthostatic drops in SBP and DBP that met criteria for OH across any disease state with the exception of severe OH (where it was consistent) ($P < 0.01$, X2). Intermittent (non-sustained) drops in DBP were more than twice as common as non-stained drops in SBP ($P < 0.01$). When the diagnosis of OH was made by SBP criteria, the mean drop was 32 ± 18 mmHg, the corresponding DBP fall was 12 ± 12 mmHg. When the diagnosis of OH was made by diastolic blood pressure, the mean diastolic drop was 17 ± 7 mmHg and the corresponding drop in SBP was 10 ± 18 mmHg.
Discussion: Although a diagnosis of OH can be made with both SBP and DBP criteria, we found little agreement between the two methods in the routine analysis of blood pressures across a range of disease states. DBP was frequently abnormal without a corresponding change in SBP. In contrast, abnormal drops in SBP were frequently accompanied by corresponding drops in DBP. Our findings suggest that a diagnosis of OH using only DBP criteria should only be made with caution.

Poster #37

Can the Valsalva maneuver serve as a biomarker for syncope diagnoses?

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Introduction: Syncope or fainting is ultimately caused by a reduction in cerebral blood flow. Previous research identified that impaired cerebral autoregulation contributes to increased fainting

susceptibility. The Valsalva maneuver (VM) challenges cerebral autoregulation and may reveal impairments in individuals who are susceptible to syncope. Seated VM elicit exaggerated blood pressure responses, and may further unmask cerebrovascular impairments, and better identify syncope disorders, in susceptible individuals. We hypothesized that both cardiovascular and cerebrovascular responses to the VM would be exaggerated in the seated position and would serve as a biomarker for syncope susceptibility.
Methods: In a randomized order, healthy participants (N = 15; 8 males; 26.5 ± 1.2 years) performed a standard 40 mmHg, 20 s VM in both a supine and seated position. This was followed by a graded 60° head-up-tilt test with combined lower body negative pressure continued to pre-syncope, to determine orthostatic tolerance (OT) in minutes. Beat-to-beat cardiovascular responses were determined using finger plethysmography and transcranial Dopper ultrasound was used to measure cerebral blood flow velocity (CBFv).
Results: Mean arterial pressure (MAP) responses were greater in the seated position in phases 2A ($p = 0.023$), 2B ($p < 0.001$) and 4 ($p = 0.031$) compared to supine. Similarly, the magnitude of the phase 2B CBFv recovery ($p = 0.026$) and phase 4 overshoot ($p = 0.065$) were greater in the seated position, compared to supine. The area under the curve from the phase 4 peak, until CBFv returned to baseline values was used as a measure of autoregulatory integrity, and in seated VM this measure was predictive of OT (seated: $R = -0.637$, $p = 0.048$). Interestingly, the max systolic arterial pressure achieved during phase 4 of a seated VM was strongly related to OT ($R = -0.785$; $p = 0.0025$), this relationship was not seen in supine VM.
Conclusion: Cardiovascular and cerebrovascular responses to seated VM may provide attractive biomarkers for susceptibility to syncope.

Poster #38

The relationship between changes in orthostatic blood pressure and symptoms in patients with orthostatic hypotension

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Background: Orthostatic hypotension (OH) is a common feature of many neurological disorders. Patients with OH can present with a wide range of symptoms. The relationship of symptoms to blood pressure (BP) is not known.
Objective: To define the relationship between changes in orthostatic BP and symptoms in patients with OH.
Methods: In this retrospective study, 1037 charts of patients referred for autonomic testing from January 2016 to March 2018 were reviewed. Systolic, diastolic and mean BPs were recorded continuously and every minute of testing using an automated, oscillometric, cuff sphygmomanometer. Orthostatic BP falls were compared to baseline supine values. Symptoms were acquired at baseline and during the first 3 min of upright tilt using a 0 to 10 scale.
Results: Eighty-nine patients (57% male, mean age 69 years) with OH were included in the final analysis. The majority (78/89) had OH related to neurodegenerative disease or a peripheral neuropathy. Lightheadedness and dizziness were the most common symptoms. Thirty-two (36%) patients had orthostatic systolic BPs of < 90 mmHg. Of those, 16% were asymptomatic and only 47% rated symptoms as 4/10 or more. Thirty-eight (43%) patients had systolic BP falls of ≥ 50 mmHg. Of these 39% were asymptomatic and only 39% rated symptoms as 4/10 or more. There was no relationship between magnitude of BP fall and individual orthostatic symptoms ($R^2 = 0.0$, P = NS) or total symptom score ($R^2 = 0.04$, P = NS). There was no relationship between absolute lowest BP and maximum symptoms ($R^2 = 0.02$, P = NS) or total symptom score ($R^2 = 0.05$, P = NS).
Conclusions: These results suggest a poor relationship between the magnitude of the orthostatic BP fall, the absolute orthostatic BP and symptoms. Many patients are asymptomatic or mildly symptomatic despite substantial BP falls and low orthostatic BPs. These findings have implications for clinical care of patients with OH and clinical trials to treat patients with OH.

Poster #39

Validation of finger blood pressure monitoring in children

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Continuous beat-to-beat blood pressure monitoring permits the rapid detection of blood pressure fluctuations for cardiovascular reflex testing and clinical hemodynamic monitoring. In adults, this can be achieved non-invasively with high accuracy, using finger blood pressure monitoring with volume clamp photoplethysmography. However, data are lacking on the validity of finger blood pressure monitoring in children compared to the gold standard—invasive intra-arterial blood pressure monitoring. We aimed to evaluate the accuracy of novel non-invasive index and middle finger arterial pressure measurements in children. Using prototype pediatric finger cuffs, we compared: mean differences, bias and limits of agreement (Bland–Altman analyses); cumulative percentage differences [clinical grade A–D (based on the percentage of heart beats in agreement with the standard)]; and waveform morphology (regression analysis and smoothing) between both raw finger arterial pressure (FinAP; Finapres NOVA) and reconstructed finger-brachial arterial pressure (reBAP) compared to intra-arterial blood pressure measurements. We tested 18 children [aged 7 ± 3 standard deviation (SD) years (range 3–13 years); 12 male]. The bias for all conditions of reBAP fell within 3 ± 9 mmHg, while accuracy of systolic, diastolic and mean arterial pressure met clinical grades of C, B and A, respectively. reBAP improved numerical accuracy, but reduced waveform morphological agreement. Finger arterial measurements are an acceptable surrogate for invasive intra-arterial recording in children, with accuracy at, or close to (within 0.5 mmHg) clinical guidelines. Finger arterial pressure monitoring is a novel, comfortable, convenient, and accurate alternative approach for non-invasive beat-to-beat blood pressure monitoring in children.
Funding: Heart and Stroke Foundation of Canada.

Poster #40

Menstrual irregularities in pediatric postural orthostatic tachycardia syndrome

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Postural orthostatic tachycardia syndrome (POTS) is a chronic condition involving orthostatic intolerance and tachycardia upon standing in the absence of hypotension. While multiple comorbid disorders have been documented and studied, a relationship between menstrual disorders and adolescent POTS has not been well described. To better educate patients on their syndrome and to better guide providers on how to counsel their patients, a retrospective cohort study of pediatric patients seen at the Mayo Clinic explored this relationship. This study aimed to explore menstrual disorders and dysfunction among pediatric patients with postural orthostatic tachycardia syndrome, as well as characterize the pharmaceutical contraceptive agents used by this population. The results were analyzed with the Fisher exact test. 149 POTS patients (age 12–18, mean 15.4) and 226 healthy controls (age 12–18, mean 14.6) were reviewed. In the POTS patients, 67% reported at least one menstrual irregularity as compared to 42% in the control group ($p < 0.0001$). Of POTS patients reporting menstrual irregularities, 80% reported cramping, 47% reported irregular periods, 36% reported abnormal flow, and 17% reported vaginal discharge. 8% of POTS patients reported POTS symptoms worsening with menstruation. Significantly more POTS patients were on hormonal birth control than their healthy peers (36% versus 14%, $p < 0.0001$). In patients with POTS, combined oral contraceptive pills were the most prevalent birth control used (72%), followed by the mini pill (7%) and Depo-Provera shot (7%), IUD (6%), patch (2%), and implant (2%). Adolescent patients with POTS are more likely to report menstrual irregularities than their healthy peers and are also more likely to be prescribed a hormonal birth control agent. Providers caring for adolescent patients with POTS should consider taking a thorough menstrual history to identify menstrual irregularities and address the concerns of this patient population.

Poster #41

Silicone breast implant rupture as a cause of postural orthostatic tachycardia syndrome (POTS)

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Introduction: Postural orthostatic tachycardia syndrome (POTS) is a heterogenous group of disorders that has been associated with multiple etiologies. We hereby present a case of POTS most probably caused by rupture of breast implants.
History: A 41-year-old female presented with an acute onset of symptoms of dizziness, lightheadedness, and syncope after her colonoscopy. A detailed workup revealed joint hypermobility, evidence of exaggerated heart rate response to tilt test that was consistent with postural tachycardia, normal heart rate with deep breathing, normal Valsalva maneuver and no evidence of small fiber neuropathy in Q-SWEAT. A complete diagnostic workup including abdominal ultrasound and referral to an immunologist was done. No definite cause of her symptoms was established and she was stabilized on Florinef and IV fluids. The patient was barely able to get back to work. During one of her incidental self-exams, she found an asymmetric breast. She consulted the plastic surgeon who had performed her breast implant surgery, and was told follow up after an MRI was done. An MRI scan of the breasts showed rupture of the right breast implant. The area on the right side was found to have gross ecchymosis with inflammation of the right breast. Surgical removal of both breast implants was done and resulted in almost immediate improvement in the patient's symptoms of orthostatic intolerance. A repeat tilt that was done post breast implant removal showed exaggerated heart rate response to tilt that was less than the original tilt table test.
Conclusion: We conclude that in this particular case for a patient with joint hypermobility, breast implant rupture was associated with acute onset of orthostatic symptoms that coincided with a colonoscopy. There was a strong relationship with resolution of the patient's symptoms and removal of the breast implants. It has resulted in significant improvement in the quality of life and the patient is able to return back to work and back to her baseline. We still suspect that because of her joint hypermobility, she may still be prone to developing postural tachycardia from another cause. The patient has been taken off her medications. We recommend that in appropriate subjects, breast implant rupture should be considered as a potential cause of postural orthostatic tachycardia syndrome, especially in the group of patients with joint hypermobility. MRI of the breast or self-examinations may aid in the diagnosis.

Poster #42

Postural tachycardia syndrome and pregnancy: insights from a cross-sectional community based survey

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Background: Postural tachycardia syndrome (POTS) is a common form of orthostatic intolerance. Despite the primarily female demographic, there is little research investigating the impact of pregnancy in POTS. This study sought to investigate the impact of pregnancy on POTS symptoms using large cohort data.
Methods: The "Diagnosis and Impact of POTS" is a structured patient-community based online survey approved by the Vanderbilt University IRB. Between July 2015 and February 2018, 5811 patients (or their parents) with a physician-diagnosis of POTS completed the survey. This analysis was restricted to females who have been pregnant at least once (n = 2151).
Results: During the first trimester of pregnancy, 62% of POTS patients reported that their POTS symptoms worsened compared to baseline ($p < 0.001$ vs. improved or no change). During the second trimester, 47% reported their symptoms worsened ($p < 0.001$), but 36% reported improved symptoms. In the third trimester, 58% reported worsened symptoms ($P < 0.001$), with improved symptoms in 27%. After delivery, 61% reported worsened symptoms ($p < 0.001$), while 23% reported improvement compared to baseline. Patients who had worsening POTS symptoms in their first trimester were more likely to have worsening symptoms than better symptoms or no change in the second (38% vs. 24%, $p < 0.001$) and third trimesters (43% vs. 19%, $p < 0.001$). Cesarean sections occurred in 29% of patients. Miscarriages occurred in 29% of total pregnancies, and 45% of POTS patients experienced at least one miscarriage. A pregnancy complication was reported in 65% of patients, although the details are not known. Patients with Ehlers-Danlos syndrome (EDS) were more likely to experience a pregnancy complication (74% vs. 61%, $p < 0.001$) than patients without EDS.
Conclusions: In this large cross-sectional study, individuals with POTS experience a worsening of baseline symptoms during and after pregnancy. Worsening symptoms in the first trimester may be predictive of POTS symptoms in later stages of pregnancy.

Poster #43

Small fiber neuropathies and related autoimmunity in postural orthostatic tachycardia syndrome

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Objective: Describe rates of small fiber neuropathy findings and autoimmune disorders associated with postural orthostatic tachycardia syndrome (POTS) in a Military Health System autonomic disorders referral clinic.
Background: The Military Health System (MHS) provides medical care to active duty military personnel, their family members, and retirees and their spouses. POTS comprises a significant portion of patients seen in the MHS Autonomic Disorders Clinic.
Methods: Clinical and diagnostic information was obtained both retrospectively (through May 31, 2017) and prospectively (beginning June 1, 2017) on patients diagnosed with POTS seen in the Clinic. Results of sudomotor testing, epidermal nerve fiber density (ENFD), sensory abnormalities, and associated autoimmune disorders (including post-infectious onset) were analyzed.
Results: Of 215 patients, 68 (32%) were diagnosed with POTS. Of the POTS patients, 53 (78%) were female. Thirty-seven (54%) of POTS patients were classified as having neuropathic POTS. Of those classified as neuropathic POTS, 4 had abnormal sudomotor testing and abnormal ENFD, 2 had abnormal sudomotor testing and normal ENFD, 13 had abnormal sudomotor testing with no skin biopsy performed, and 11 had abnormal ENFD with normal sudomotor testing. Six patients were diagnosed as having neuropathic POTS based on small fiber sensory abnormalities. Of these, four had normal sudomotor testing without skin biopsy and one had normal sudomotor testing and normal ENFD. Of the neuropathic POTS, 11 (30%) were classified as having a possible or probable autoimmune cause (including post-infectious onset). Only 2 of the non-neuropathic POTS patients were designated as having possible or probable autoimmune cause to their POTS.
Conclusions: Based on abnormal sudomotor testing or abnormal ENFD on skin biopsy, neuropathic POTS is quite common. The possibility of false positive results on both these tests limits the widespread applicability of this finding. Possible or probable autoimmune disorders may be more common in neuropathic POTS as opposed to non-neuropathic POTS subtypes.
Funding: 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. I am a military service member. This work was prepared as part of my official duties. Title 17 U.S.C. 105 provides that 'Copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member or employee of the United States Government as part of that person's official duties. The study protocols were approved by the Naval Medical Center Portsmouth Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects. Research data derived from Naval Medical Center Portsmouth, Virginia, IRB protocol numbers NMCP.2016.0035 and NMCP.2017.0054.

Poster #44

POTS patients vs. healthy controls: similar postural tachycardia, different symptom burden

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Background: Postural orthostatic tachycardia syndrome (POTS) is a condition of orthostatic intolerance diagnosed in symptomatic individuals with an excessive rise in orthostatic heart rate (HR) without orthostatic hypotension. Patients complain not only of orthostatic symptoms such as dizziness, palpitations, and tremulousness, but also of pervasive symptoms including fatigue, sleep disturbance, headache, and gastrointestinal dysfunction. Previous studies of POTS patients have described both improvement in symptoms with persistent postural tachycardia, and persistent symptoms despite improvement in postural tachycardia.
Objective: To describe orthostatic vital signs in a cohort of POTS patients and healthy controls, and to compare these to symptom profiles (both acute orthostatic symptoms and pervasive symptoms).
Methods: POTS patients and healthy controls (both by self-report) participated in 10-min stand testing and symptom surveys as part of the 2016 Dysautonomia International conference research project.
Results: 142 POTS patients and 14 healthy controls participated. Mean orthostatic HR increments were similar between the two groups: 21.7 beats per minute (bpm) for POTS patients and 19 bpm for healthy controls. 26.8% of POTS patients and 28.6% of healthy controls had orthostatic HR increase $\geq$ 30 bpm. After accounting for age and presence of orthostatic hypotension, 18.3% of POTS patients and 21.4% of healthy controls met formal hemodynamic criteria for POTS (2011 consensus definition). Despite the similarity in orthostatic tachycardia, POTS patients reported higher symptom burden during the stand test (Vanderbilt Orthostatic Symptom Scale average 24.8 in POTS vs. 4.2 in healthy controls), worse orthostatic symptoms over the past year (COMPASS-31 orthostatic intolerance score average 23.3 vs. 3.3), and more general autonomic symptoms (COMPASS-31 total score average 45.3 vs. 11.7).
Conclusions: In a sample of self-reported healthy controls and POTS patients, orthostatic HR increment was similar between the two groups, despite significantly higher orthostatic and general autonomic symptom burden in the POTS group.
Funding: Dysautonomia International.

Poster #45

Is pseudobulbar affect unique to PoTS? Emotional lability in orthostatic intolerance

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Background: Our previous report identified pseudobulbar affect (PBA) and emotional lability (EL) as distinctive features of postural tachycardia syndrome (PoTS). Crying predominance suggested depression as a possible co-factor.
Objectives: To compare 1. EL symptoms between controls and three forms of OI: PoTS, neurally mediated hypotension (NMH), and symptomatic nonspecific (SN) type. 2. Overt occurrence of PBA during head-up tilt (HUT) among OI groups. 3. Depression between controls and OI groups.

Methods: Institutional review board approved the study. Participants were 90 OI patients (symptoms > 6 months): PoTS 47, NMH 16, SN 27; normal controls 12. OI types were documented with HUT, heart rate response to deep breathing, and Valsalva maneuver. Center for Neurologic Study-Lability Scale (CNS-LS) assessed EL symptom severity; score ≥ 13 predicts EL in amyotrophic lateral sclerosis patients. Patients Health Questionnaire 9 (PHQ-9) score of ≥ 10 indicated depression. Questionnaires were completed before the author performed HUT. ANOVA and Fisher exact test were employed.
Results: Subclinical EL was found in 43% PoTS, 31% NMH, 41% SN, and 0% controls (P = 0.03). CNS-LS score was higher in PoTS compared with controls (12.2 ± 4.2 versus 8.4 ± 1.7; P = 0.04) but not between other OI groups and controls (P > 0.05). Overt PBA was observed in 19% PoTS, 0% NMH, 4% SN, and 0% controls (P = 0.02). PHQ-9 score was higher in all OI groups versus controls (PoTS 10.6 ± 5.1, NMH 9.5 ± 5.5, SN 10.0 ± 6.1, controls 1.8 ± 1.8; P = 0.001). Depression scores did not differ among the OI groups (P = 1.00) or between PoTS patients with CNS-LS score ≥ 13 versus < 13 (12.1 ± 3.7 versus 9.7 ± 5.7; P = 0.16).
Conclusions: Subclinical emotional lability afflicts all OI types. Despite EL predisposition in all OI types, HUT precipitated overt PBA mostly in PoTS. Orthostatic stress mediated central catecholaminergic dysregulation may predispose PoTS patients to overt occurrence of reversible PBA. Depression, although co-morbid, does not contribute to emotional lability.

Poster #46

Antimuscarinic autoimmunity in postural tachycardia syndrome

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Background: Postural tachycardia syndrome (POTS) is characterized by an exaggerated heart rate increase during orthostasis and a wide spectrum of adrenergic-related symptoms. Activating autoantibodies to the alpha1- adrenergic and beta1/2- adrenergic receptors have previously been found in sera from patients with POTS. We hypothesized that patients with POTS might also harbor activating autoantibodies to M2 muscarinic receptor (M2R). This study examines a possible pathophysiological role for M2R autoantibodies in POTS.
Methods and Results: Serum from 11 patients with POTS and 5 healthy controls was analyzed for the ability to activate M2R and alter M2R orthosteric ligand responsiveness in M2R-transfected cells using the GPCR assay kit (DiscoveRx). Of the 11 subjects with POTS, 6 demonstrated significant M2R-activating antibody activity from their serum. No significant M2R antibody activity was found in the healthy subjects. IgG from 3 of the POTS subjects was tested at 4 different concentrations. There was a significant dose effect of IgG on M2R activation, and the maximal effect appeared to occur at 0.2 mg/mL of IgG. M2R activation by POTS IgG was blocked by the muscarinic blocker atropine (1 mM). Moreover, POTS IgG significantly shifted the selective M2R agonist oxotremorine dosage response curve to the right, indicating an inhibitory allosteric effect of M2R antibodies. This would exaggerate the effect of vagal withdrawal on the heart rate during upright posture in POTS.
Conclusions: Over half of the subjects with POTS harbor M2R autoantibody activity. This supports the concept that a negative allosteric effect of these M2R autoantibodies may exert a significant impact on the cardiovascular pathophysiological characteristics in POTS.

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Poster #47

Impaired glucose homeostasis in lean women with postural tachycardia syndrome

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The autonomic nervous system is a key regulator of metabolic function. The sympathetic nervous system (SNS) promotes hyperglycemia by inhibiting insulin secretion, stimulating hepatic glucose production and lipolysis and by decreasing whole-body insulin sensitivity. The parasympathetic nervous system (PSNS) opposes these actions and maintains glucose homeostasis. We previously reported an abnormal increase in SNS activity in obese subjects, which reduces insulin sensitivity. Similarly, patients with postural tachycardia syndrome (POTS) are characterized by increased SNS activity; however, the metabolic effects of this hyperadrenergic state are unknown. We hypothesized that similar to the obese subjects, the increased SNS activity in POTS patients results in impaired glucose homeostasis. We recruited 14 women with POTS (37 ± 11 years, BMI 25 ± 5 kg/m^2) and 12 obese women (37 ± 9 years, BMI 35 ± 5 kg/m^2) as positive controls. All subjects received 75 grams oral glucose tolerance, plasma samples were obtained at baseline, 30, 60, 90 and 120 min post-administration. Our results showed that fasting glucose levels were significantly elevated in obese subjects when compared to POTS women (93 ± 8.7 vs. 84 ± 7.6 mg/dL, p = 0.018). However, 50% of POTS women had impaired glucose tolerance defined as glucose level above 140 mg/dL between 90 and 120 min post-ingestion. The blood glucose at 120 min was similar between POTS and obese subjects (126 ± 8.4 vs. 126 ± 8.7, P = 0.96). We concluded that despite normal BMI, POTS patients have impaired glucose tolerance, which dramatically increases their risk to develop type 2 diabetes mellitus. Further studies are needed to evaluate differences in insulin sensitivity or beta cell function in this population.
Funding: Dysautonomia International.

Poster #48

Prevalence and treatment of small intestinal bacterial overgrowth (SIBO) in patients with postural orthostatic tachycardia syndrome (POTS)

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Background: POTS is a form of orthostatic intolerance characterized by a myriad of symptoms including syncope, dizziness, poor concentration, exaggerated heart rate response (palpitations) upon postural changes, fatigue, and nausea. Patients with autonomic dysfunction, such as POTS, often present with GI motility issues. SIBO refers to a condition in which large amounts of bacteria are present in the small intestine. The two processes that most commonly predispose to bacterial overgrowth are diminished gastric acid secretion and small intestine dysmotility.

Objective: We aim to study the prevalence of small intestinal bacterial overgrowth in POTS patients. We also aim to analyze the improvement of POTS symptoms by treating SIBO in POTS patients.
Method: We did a retrospective study of 876 patients randomly selected from our pool of POTS patients. Their electronic medical records were reviewed and the SIBO tests were evaluated to determine their diagnosis.
Results: 67 (7.65%) out of 876 POTS patients (age = 32.94 ± 12.21) had SIBO testing for clinically unexplained or unresolved nausea, vomiting, and bloating. 39 of 67 patients (58.21%) tested positive whereas 28 of 67 patients (41.79%) tested negative for SIBO. Out of the 39 patients that tested positive for SIBO, 6 (15.38%) were male (age 28 ± 9.34) whereas 33 (84.62%) were female (ages 26.69 ± 10.08). 14 of 39 SIBO (+) patients were prescribed antibiotics (rifaximin or metronidazole) to alleviate associated symptoms out of which 4 patients were available for follow-up results. 2 patients treated with rifaximin (200 mg BID) reported improvement in abdominal pain, sleep, dizziness and chest pain. The other 2 patients treated with metronidazole denied improvement in GI symptoms and/or had no change in symptoms.
Conclusion: Our study reports show that out of 67 POTS patients that had SIBO testing, approximately 58.21% tested positive and those that were treated with rifaximin reported an improvement in their POTS and GI symptoms. It has been clinically observed that POTS patients respond to lower doses of medication than the general population. Our study shows that SIBO is a pathology that can be associated with POTS and must be acknowledged for more comprehensive treatment. Further studies must be conducted in order to better understand this relationship.

Poster #49

Postural hyperventilation as a cause of POTS

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Background: Postural tachycardia syndrome (POTS) is a heterogeneous condition. We stratified patients previously evaluated for POTS on the basis of supine resting cardiac output (CO) or with the complaint of platypnea or "shortness of breath" during orthostasis. We hypothesize that postural hyperventilation is one cause of POTS, and that hyperventilation-associated POTS occurs when initial reduction in CO is sufficiently large. We also propose that circulatory abnormalities normalize with restoration of CO_2.
Methods and Results: Fifty-eight POTS enrollees were compared to 16 healthy volunteer controls. Low CO in POTS was defined by a resting supine CO < 4 L/min. Patients with shortness of breath had hyperventilation (designated HV) with end tidal CO_2 ($ETCO_2$) < 30 Torr during head-up tilt table testing (HUT). There were no differences in height or weight between control and POTS patients or differences between the POTS groups. Beat-to-beat blood pressure (BP) was measured by photoplethysmography and CO by ModelFlow. Systemic vascular resistance (SVR) was defined as mean arterial blood pressure (MAP)/CO. $ETCO_2$ and cerebral blood flow velocity of the middle cerebral artery were only reduced during HUT in the HV group, while BP was increased compared to control. We corrected the reduced $ETCO_2$ in HV by addition of exogenous CO_2 into a re-breathing apparatus. With added CO_2, HR, BP, CO and SVR in HV became similar to control.
Conclusions: We conclude that all POTS is related to decreased CO, decreased central blood volume, and increased SVR and that a variant of POTS is consequent to postural hyperventilation.
Funding: Funding for this project was provided by Grants R01 HL 134674 and R01 HL 112736 from the National Heart Lung and Blood Institute.

Poster #50

A rabbit model of autoimmune postural tachycardia syndrome

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Background: Previous studies have demonstrated that functional autoantibodies to adrenergic receptors may be involved in the pathogenesis of postural tachycardia syndrome (POTS). The objective of this study was to develop an animal model to examine the impact of these autoantibodies on cardiovascular responses to postural changes and adrenergic orthosteric ligand infusions.
Methods: Eight New Zealand white rabbits were coimmunized with peptides from the first and second extracellular loops of alpha1-adrenergic receptor (alpha1AR) and the second extracellular loop of beta1-adrenergic receptor (beta1AR) to produce sympathomimetic antibodies. Tilt test using a custom-made device and separate agonist-infusion studies in the ventral recumbent position were performed on conscious animals before and after immunization and subsequent treatment with epitope-mimetic peptide inhibitors.
Results: All immunized animals produced high alpha1AR and beta1AR antibody titers. At 6 weeks after immunization, there was a greater percent increase in heart rate upon tilting compared to preimmune baseline (28 ± 8% vs. 18 ± 4%, P = 0.02). No significant difference in blood pressure response to tilting was observed between preimmune and postimmune animals. The heart rate response to infusion of the beta1AR agonist isoproterenol (0.1–2 μg/kg) was significantly enhanced in immunized animals, suggesting a hyperadrenergic state and/or a positive allosteric effect of beta1AR antibodies. In contrast, the blood pressure response to infusion of the alpha1AR agonist phenylephrine (5–30 μg/kg) was attenuated in immunized animals, indicating a negative allosteric effect of alpha1AR antibodies. A single intravenous injection of the antibody-neutralizing peptides (1 mg/kg) into immunized animals suppressed the postural tachycardia and reversed the altered heart rate and blood pressure responses to orthosteric ligand infusions.
Conclusions: The differential allosteric effect of alpha1AR and beta1AR autoantibodies would lead to compensatory increase in norepinephrine and overstimulation of cardiac beta1AR. These data support evidence for an autoimmune basis for increased upright plasma norepinephrine and tachycardia that characterize POTS.
Funding: NIH HL128393.

THURSDAY, OCTOBER 25, 2018

POSTER SESSION II

Poster #51

Inter-rater agreement of thermoregulatory sweat testing (TST)

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Introduction: TST is a clinical test for evaluating sudomotor function in central or peripheral disorders of autonomic nervous system such as multiple system atrophy and small fiber neuropathy. The TST evaluates the distribution of sweating by a change in color of an indicator powder, Alizarin Red.
Design: Retrospective.
Methods: TST was done at 50 °C heat and 50% humidity and multiple photos was taken at the end of 30 min cycle. Each subject's digital photographic pictures were reviewed by two reviewers (neuromuscular specialist with experience on reporting TST) separately and rated four body locations—dorsum of hand, forearm, proximal leg (neck of fibula) and dorsum of foot (on extensor digitorum brevis) on two ordinal scales: 1-normal/reduced/absent, 2-present/absent. Reviewers were blind to other clinical data of the patient including quantitative sweat collection by Q-sweat machine. Cohen's kappa was used for measuring inter rater agreement.
Results: 81 subjects (female 57%) with mean age of 41 years (SD: 20, range 14–85) were included. Three level ordinal rating showed moderate agreement for all the testing locations (kappa for foot, proximal leg, hand and forearm: 0.57, 0.57, 0.50, 0.51). However, two level ordinal rating of sweat present/sweat absent showed strong inter-rater agreements (kappa for foot, proximal leg, hand and forearm: 0.80, 0.77, 0.78, 0.72). The agreement between reviewers was higher in male subjects (highest agreement: 0.87 for proximal leg of male subjects).
Conclusion: Photographic review of TST by two reviewers showed strong agreement between reviewers on a two level scale (sweat present/sweat absent) for detecting local anhidrosis. The reviewers' agreement on a three level scale (normal, reduced, absent) was modest.

Poster #52

Quantification of thermoregulatory sweat testing (TST)

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Introduction: TST evaluates the distribution of sweating by a change in color of an indicator powder (Alizarin Red) from orange to purple. Uniform Spreading of the powder over different body parts is technically challenging and may cause false readings. The amount of sweat volume required per cm^2 to change the color of powder to purple has not been studied.
Objective: To quantify minimum amount of sweat volume required for changing the Alizaren red mix to purple.
Design: Retrospective.
Methods: TST was done at 50 °C heat and 50% humidity and multiple photos was taken at the end of 30-min cycle. A Q-Sweat device was used to collect sweat from foot, proximal leg, hand and forearm with 0.79 cm^2 capsules. Digital photographic pictures were reviewed by two reviewers who were blind to clinical situation and quantitative sweat collection on two level scale (sweat present/sweat absent) for the areas around the Q-Sweat capsules.
Results: 80 patients (44 females) were included. Mean and 95% confidence interval of sweat outputs (μl/0.79 cm^2 square) in patients who were rated as "Anhidrosis" were: foot 15.1 (11.2–20.3), proximal leg 25.2 (17.1–2.71), hand 32.3 (13.9–50.7) forearm 18.3 (12.1–24.5). In the group rated as "Sweat present" by reviewers, mean and 95% confidence interval were: foot 45.7 (23.8–67.6), calf 62.5 (50.3–84.8), hand 75.2 (61–89.5) and forearm (52.4–71.2).
Conclusion: Visually-rated anhidrosis is sometimes misjudged with values as high as 50 μl per 0.79 cm^2 while sweat output as low as 24 were considered normal in other subjects. Uneven spreading of the indicator powder on different body parts may be one of the contributing factors. Simultaneous collection of sweat output by Q-Sweat device may reduce misinterpretation of TST.

Poster #53

Neurogenic orthostatic hypotension unawareness in multiple system atrophy compared to peripheral autonomic neuropathy

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Objective: To assess whether multiple system atrophy (MSA) patients' inability to recognize symptoms of orthostatic hypotension (OH) is specific to the disease or a phenomenon of cerebral hypoperfusion.
Background: Despite OH being one of the most disabling manifestations of MSA, patients frequently do not express symptoms during even large falls in blood pressure (BP). Unawareness of OH might be explained by degeneration of central afferent systems, such as cortical processing units that attend to changing stimuli and are subject to noradrenergic influence by the locus ceruleus, or it might be a general phenomenon caused by global cerebral hypoperfusion.
Methods: Orthostatic symptoms and beat-to-beat BP responses to the Valsalva maneuver and tilt table testing were undertaken in 50 patients (64.4 ± 10.6 years M/F 1.9) clinically diagnosed with MSA (35 MSA-C, 15 MSA-P) who, therefore, had central autonomic failure. Findings were compared to those in a cohort of 50 patients (67.0 ± 12.2 years, M/F 1.8) with neurogenic OH caused by peripheral autonomic neuropathy (PN) due to diabetes (N = 43), amyloidosis (N = 6), or autoimmune autonomic ganglionopathy (N = 1).
Results: 20.0% of MSA patients (14.3% of MSA-C and 33.3% of MSA-P) and 32.0% of PN patients reported symptoms during head-up tilt. The difference did not reach statistical significance ($p = 0.17$). Presence of symptoms correlated with lowest systolic BP ($p = 0.016$) but not with lowest diastolic BP, magnitude of BP drop, heart rate, pressure recovery time, adrenergic score, age, or duration of disease.
Conclusions: Failure of recognition of symptoms of OH in MSA did not differ significantly in comparison to PN causing comparable OH severity. Therefore, OH symptom unawareness is most likely explained by cerebral ischemia rather than by degeneration of central afferent systems. Measuring standing BP rather than relying on symptoms alone is indispensable to the evaluation of the patient with MSA.

Poster #54

Symptom burden within 1 year differentiates rapidly progressive multiple system atrophy

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Objective: To evaluate demographic and clinical features which may differentiate multiple system atrophy (MSA) patients who have a rapidly progressive disease course.
Background: Median survival time in multiple system atrophy (MSA) is around 7.5 years; however, some patients have a rapidly progressive course. Demographic and clinical features differentiating rapidly progressive MSA are uncertain.
Methods: We performed a retrospective review of all patients diagnosed with MSA between 1998 and 2012 with autonomic function testing. Living patients were called to assess development of symptoms. Survival data was obtained from the clinical record and social security data base. Short duration MSA patients were defined as those less than the 5th percentile of overall disease duration in the entire cohort. Patients lost to follow-up or with unknown death date were excluded.
Results: Of 669 MSA patients included in the survival analysis, 33 patients were short duration of disease patients with survival ranging from 1.13 to 3.21 years. When comparing short duration patients to the main cohort, there were no significant demographic or clinical differences at the time of assessment, when adjusting for multiple comparisons. However, when focusing on the first year of symptom onset, short duration patients were more likely to have motor symptoms ($p = 0.0002$), falls ($p = 0.0007$), orthostatic intolerance ($p = 0.0001$) and bladder symptoms ($p < 0.0001$). Odds ratios for short duration of MSA with development of specific symptoms within 1 year of onset were: bladder symptoms 5.41, orthostatic intolerance 4.04 and falls 3.42. Those clinical features were often coexistent with most short duration MSA patients having 3 factors.
Conclusions: Our data suggests that demographic and baseline clinical features do not readily differentiate MSA patients with short duration of disease; however, symptom burden within 1 year from the onset of symptoms may be indicative of rapid progression to death.

Poster #55

Pure autonomic failure with sick sinus syndrome of reduced striatal DAT binding

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Pure autonomic failure (PAF) is a rare neurodegenerative disorder of the autonomic nervous system which is caused by pathological accumulation of misfolded alpha-synuclein. We experienced two cases of PAF with sick sinus syndrome (SSS) who had frequent episodes of syncope. Neither of them had any neurological abnormal findings including tremor, bradykinesia nor rigidity. However, the Odor Stick Identification Test for Japanese score was low in both patients. One of them also had REM sleep behavior disorder in the past. Moreover, dopamine transporter (DAT) single photon emission computed tomography imaging revealed that striatal DAT binding was reduced. Kaufmann et al. reported that olfactory dysfunction is one of the prognostic predictors of these patients. A recent study showed that the cumulative incidence of phenoconversion from PAF to synucleinopathy of the central nervous system was 34% during the 4-year follow-up. We have anticipated the high risk of phenoconversion in these patients from these findings. Their electrophysiological evaluation showed prolonged sinoatrial node recovery time but had no evidence of the atrioventricular node conduction time and His-Purkinje conduction time prolongation in both patients. Based on these results, we confirmed their diagnosis as SSS. After their pacemaker implantations, they have not experienced any syncope episodes. SSS is caused by the sinoatrial node dysfunction which is possibly caused by the degeneration of the SA node cells. However, its pathophysiology is not well elucidated. Alpha-synuclein is abundant in the brain while smaller amounts are found in the heart, muscles, and other tissues. On the other hand, cardiac sympathetic denervation is well known in PAF. Taken together, the alpha synucleinopathy may have some role of the etiology, severity, and prognosis of our patients. This is the first report of PAF patients with severely affected sinoatrial node function and reduced striatal DAT binding without any apparent neurological findings.

Poster #56

Neuroimaging evidence for decreased cardiac sympathetic innervation and a vesicular storage defect in residual nerves in Lewy body forms of neurogenic orthostatic hypotension

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Background: Pure autonomic failure (PAF) and Parkinson's disease with orthostatic hypotension (PD + OH) are Lewy body diseases characterized by neurogenic orthostatic hypotension (nOH) and myocardial norepinephrine depletion. Since norepinephrine is synthesized in vesicles, decreased vesicular uptake might contribute to sympathetic neurocirculatory failure in these disorders. To explore this we conducted positron emission tomographic scanning after administration of 18F-dopamine (18F-DA) and on a separate day 11C-methylreboxetine (11C-MRB). Both are radioligands for the cell membrane norepinephrine transporter (NET), but after neuronal uptake 18F-DA is stored in vesicles, whereas 11C-MRB does not enter neurons. A vesicular storage defect would produce a greater fall in 18F-DA-derived than in 11C-MRB-derived radioactivity.
Methods: Nine patients with nOH from PAF or PD + OH and 6 control subjects without evidence of central neurodegeneration or nOH underwent 18F-DA- and 11C-MRB scanning. Two other subjects with cardiac transplants were studied, to adjust for non-specific binding of 11C-MRB.
Results: In the Lewy body group the mean values for 18F-DA- and 11C-MRB-derived radioactivity (4200 ± (SEM) 23 and 4075 ± 22 nCi-kg/cc-mCi) were lower than those in the controls (10,820 ± 1046 and 6012 ± 426 nCi-kg/cc-mCi; $p = 0.0002$, 0.0122). After adjustment for non-specific binding the mean 18F-DA/11C -MRB ratio was also lower in the Lewy body group (1.88 ± 0.43 vs. 3.30 ± 0.31, $p = 0.0005$).
Conclusions: Lewy body forms of nOH are associated with neuroimaging evidence for both decreased cardiac sympathetic innervation and a vesicular storage defect in the residual nerves, indicating populations of catecholaminergic neurons are "sick but not dead" in these diseases.
Funding: Division of Intramural Research, NINDS, NIH.

Poster #57

Effects of different classroom temperatures on cardiac autonomic control and cognitive performance in students

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Background: Indoor microclimate may affect students' wellbeing, cardiac autonomic control and cognitive performance with potential impact on learning capabilities.
Aim: To assess the effects of classroom temperature variations on the autonomic profile and student's learning capabilities.
Methods: Thirty-four students attending Humanitas University School of Physiotherapy (15 F, age 20 ± 1 yrs) underwent a single lead ECG continuous recording by a portable device (MR&D Pulse, Italy) during a 2-h lecture both when classroom temperature was set "neutral" (22 °C, Day 1) and in a different day (Day 2), when classroom temperature was increased up to 26 °C. Data were sent by telemetry (HP Mobile H&S) to a server for off-line analysis. Symbolic analysis of heart rate (HR) variability provided the percentage of sequences of three heart periods with no significant change in RR interval (0 V%) and with two significant unlike variations (2 UV%) reflecting cardiac sympathetic and vagal modulation, respectively. Students' cognitive performance (memory, verbal comprehension and reasoning) was assessed at the end of the lecture using the online Cambridge Brain Science cognitive evaluation tool, developed by Cambridge University (https://www.cambridgebrainsciences.com/science/tests). Classroom temperature was remotely assessed every 5 min.
Results: Classroom actual temperatures were 22.4 ± 0.1 °C (Day 1) and 26.2 ± 0.1 °C (Day 2). HR and 0 V % were greater ($p < 0.04$) during Day 2 (80 ± 13 bpm and 74.6 ± 6.5%, respectively) than during Day 1 (73 ± 12 bpm and 69.9 ± 6.2%, respectively). Conversely, 2 UV% was lower ($p = 0.009$) during Day 2 (7.9 ± 3.9%) than during Day 1 (10.9 ± 5.4%). Memory and verbal comprehension scores were lower ($p = 0.03$) during Day 2 (10.3 ± 0.3 and 8.2 ± 0.4, respectively) compared to Day 1 (11.3 ± 0.5 and 10.6 ± 0.3, respectively). Reasoning score was unchanged. In Day 2 the overall cognitive c-score (10.7 ± 0.4) was lower ($p = 0.001$) compared to Day 1 (12.2 ± 0.4).
Conclusions: During Day 2, the greater HR and 0 V% index are likely to indicate a cardiac sympathetic over-activity counteracting the potential vasodilation due to enhanced environmental temperature. This autonomic response was, however, associated with a global reduced student's cognitive performance.
Funding: Funded by Fondazione Humanitas per la Ricerca.

Poster #58

Central acetylcholinesterase inhibitor, galantamine, prevents lipid-induced oxidative stress in African Americans

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African American women (AAW) have one of the highest prevalence of hypertension in the US. Obese AAW have decreased parasympathetic (PSNS) activity compared to whites. Continuous lipid infusion that causes cardiovascular autonomic imbalance (decrease in PNS and increase in sympathetic activity) induces a greater increase in oxidative stress in AA compared to whites. Considering that PSNS protects against oxidation and that central acetylcholinesterase inhibitors have been shown to suppress oxidative stress in animal models. We tested the hypothesis that the central acetylcholinesterase inhibitor, galantamine attenuates oxidation in response to lipid infusion in obese AAW compared to white women. We randomized 14 healthy obese AA (39.5 ± 10.7 yo, BMI 38.8 ± 3.4) and 10 (35.9 ± 8.3 yo, BMI 36.3 ± 2.1) white women. All subjects underwent 4-h infusions of Intralipids and heparin. On separate days subjects received either 16 mg galantamine or placebo in a crossover fashion. Lipid-induced oxidative stress and inflammation were assessed with plasma F2-isoprostanes and cytokines at baseline, 2 and 4-h post-intralipid infusion. In AA, 16 mg of galantamine significantly suppressed the increase in lipid-induced oxidative stress (10 ± 18 vs. − 3.0 ± 12 pg/mL with galantamine, $P = 0.014$). No effect was noted in whites. Galantamine tended to increase IL10 (4.8 ± 7.58 vs. 17.3 ± 20.7 pg/mL with galantamine, $P = 0.06$). We did not observe any effect on blood pressure or heart rate. In conclusion, increased parasympathetic tone with central acetylcholinesterase inhibitor, galantamine, suppressed lipid-induced oxidative stress in African American women.
Funding: Doris Duke Foundation Career Development Award.

Poster #59

Comparison of cerebral oxygen saturation patterns in adolescents with autonomic dysfunction who experience syncope versus convulsive syncope during head up tilt testing

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Introduction: The autonomic nervous system is composed of the parasympathetic and sympathetic nervous systems which are typically in balance and achieve normal vascular flow throughout the body. Autonomic dysfunction implies an imbalance of these systems and symptoms may be revealed during times of stress. One symptom is syncope defined as a transient loss of consciousness resulting from reduced cerebral blood flow precipitated by standing. Convulsive syncope, syncope that is accompanied by seizure-like activity, may have a more severe cerebral blood flow disruption leading to a more severe clinical symptomatology. At our institution, we sought to further understand the differences in cerebral blood flow changes

between patients with syncope and convulsive syncope during head-up tilt testing (HUTT) utilizing near-infrared spectroscopy.
Methods: Near-infrared spectroscopy was used to estimate bilateral cerebral perfusion patterns during HUTT in 23 adolescents with a diagnosis of autonomic dysfunction. The resulting waveforms of cerebral regional oxygen saturation (rSO_2) were analyzed visually and a Stata algorithm for data point identification was generated and compared to the visual analysis for more objective and efficient analysis of the waveforms. Parameters of absolute changes and rates of change in rSO_2 during HUTT were calculated and compared for adolescents who experienced syncope versus convulsive syncope.
Results: The Stata program identified key data points in the rSO_2 waveforms that were similar to those identified by visual analysis. Absolute changes and rates of change in the rSO_2 waveforms during three phases of HUTT were described numerically for patients who experienced syncope and convulsive syncope. No significant difference was identified in the cerebral oxygen patterns between the two groups.
Conclusion: These results suggest that cerebral oxygenation patterns may not differ significantly between patients who experience syncope versus convulsive syncope. However, the Stata program for analyzing NIRS data contour changes may enable further analysis for a larger patient population.

Poster #60

Hypocapnic cerebral hypoperfusion: a biomarker of orthostatic intolerance

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The objective of the study was to assess the presence of hypocapnic cerebral hypoperfusion (HYCH) in patients with orthostatic intolerance (OI) without tachycardia and without orthostatic hypotension. This single center, retrospective study included OI patients referred for autonomic evaluation which included the 10 min tilt test. Heart rate, end-tidal CO_2 (ET-CO_2), blood pressure, and cerebral blood flow velocity (CBFv) from middle cerebral artery were monitored. HYCH was defined by: (1) symptoms of OI; (2) orthostatic hypocapnia (low ET-CO_2); (3) abnormal decline in orthostatic CBFv due to hypocapnia; (4) absence of tachycardia, orthostatic hypotension, or other causes of low CBFv or hypocapnia. Sixteen subjects met HYCH criteria (15/1 women/men, age 38.5 ± 8.0 years) and were matched by age and gender to postural tachycardia patients (POTS, $n = 16$) and healthy controls ($n = 16$). During the tilt, CBFv decreased more in HYCH ($-22.4 \pm 7.7\%$, $p < 0.0001$) and POTS ($-19.0 \pm 10.3\%$, $p < 0.0001$) compared to controls ($-3.0 \pm 5.0\%$). Orthostatic ET-CO_2 was lower in HYCH [26.4 ± 4.2 (mmHg), $p < 0.0001$] and POTS (28.6 ± 4.3, $p < 0.0001$) compared to controls (36.9 ± 2.1 mmHg). Orthostatic heart rate was normal in HYCH (89.0 ± 10.9 (BPM), $p < 0.08$) and controls (80.8 ± 11.2), but was higher in POTS (123.7 ± 11.2, $p < 0.0001$). Blood pressure was normal and similar in all groups. In conclusion, both HYCH and POTS patients have comparable decrease in CBFv which is due to vasoconstrictive effect of hypocapnia. CBFv monitoring can serve as an objective biomarker for HYCH in OI patients without tachycardia.

Poster #61

Prevalence of convulsions in the pediatric population with orthostatic intolerance and neuro-cardiogenic syncope

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Introduction: Neurocardiogenic syncope (NCS) results from decompensated vascular mechanisms that maintain postural brain perfusion, usually preceded by prodromal symptoms. Convulsive disorders have been considered in the differential diagnosis of such patients that necessitate electroencephalograms (EEG) and brain imaging in most of these patients. The mechanism of convulsions in the two clinical entities is different. The presence of generalized tonic movements during NCS adds to such diagnostic confusion. Our aim of this study is to evaluate the prevalence of convulsions in pediatric patients with NCS during head up tilt table test (HUTT), determine their physiological parameters and evaluate their brain imaging and EEG.
Methods: This is a retrospective cohort study of pediatric and young adult population who underwent HUTT evaluation for their orthostatic intolerance (OI) symptoms (such as dizziness, blurry vision, nausea, palpitations and syncope) between 2013 until December 2017. HUTT consisted of 10 min of supine baseline phase, 30 min of head up tilt at 70° followed by 10 min of recovery supine phase. Physiological parameters collected included continuous heart rate and blood pressure, cardiac stroke volume, bilateral cerebral near infrared spectroscopy (NIRS) and sympathetic/parasympathetic tone. All HUTT procedures were performed by an attending physician. Subjects who developed NCS during HUTT were further categorized as to the presence of tonic–clonic movements of one or more extremities during their unconscious state. Physiological parameters were evaluated for differences in those specific groups.
Results: During the study period, 616 patients underwent HUTT evaluation for their OI symptoms (492 subjects were female) with median age of 16 years (range 8–24 years). Of those subjects 240 developed NCS during HUTT ($\sim$ 39% of the study group). Females comprised 178 of the 240 NCS group (74%). Upon further evaluation of the NCS group, there were 68 subjects who developed convulsions during HUTT with 55 being females (81%). There was a significant gender difference between the NCS-none convulsion group and the convulsion group with a predominance of females in the convulsion group ($p = 0.04$). The degree of decrement in blood pressure was not significantly different between the two groups whereas the cerebral perfusion pattern was unique in that there was a sharp sudden decrease in NCS non-convulsion and convulsion groups compared to the OI group. Among the 68 subjects who developed convulsions, EEGs and/or MRIs were performed in 59 patients and both were reportedly normal per the neurologist. Cardiac asystole for ≥ 3 s was present in 42/68 in the convulsion group compared to 24/172 the NCS non-convulsion group ($p < 0.01$).
Conclusion: Convulsions in NCS are not uncommon with a prevalence of 28% in our study group. Female gender carries a higher risk of developing convulsions during NCS. Cardiac asystole is significantly more common in the convulsion group. Cerebral NIRS add a significant diagnostic value in evaluating this specific population.

Poster #62

What chronic disorders overlap with the migraine complex?

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Introduction: Pediatric migraine headache frequently clusters with other chronic overlapping pain disorders such as, chronic nausea, irritable bowel syndrome and fibromyalgia. We reasoned that if a condition responded to dihydroergotamine (DHE), it may arise from migraine neural generators.
Methods: This prospective IRB-approved study included 18 patients receiving the 4-day inpatient DHE (10 mg total) Raskin protocol for chronic migraine headache. The "improvers" group was defined as $\geq$ 20/100 headache amelioration at 4 weeks after discharge. Pre-hospitalization, daily inpatient, and weekly post-hospitalization 100-point symptom severity scores included: headache, nausea, vomiting, abdominal pain, sound sensitivity, light sensitivity and restedness. Group differences were tested using non-parametric Mann–Whitney and Kruskal–Wallis tests. Pearson correlations among symptom groups were calculated.
Results: 18 female patients aged 12–21, did not differ in age between the 8 improvers and 10 non-improvers ($p = 0.46$). Improvers had significantly worse headache ($p = 0.027$) and sound sensitivity ($p = 0.015$) at baseline. At four-week follow up, improver headaches dropped from 61.754.85 to 14.255.98 ($p = 0.001$) compared to 25.609.60 to 29.909.78 ($p = 0.676$) in non-improvers. Abdominal pain in improvers dropped from 42.569.72 to 29.6310.71 ($p = 0.344$) and in non improvers 28.309.87 to 25.8010.88 ($p = 0.815$). Between baseline and 2-week follow up, nausea correlated strongly with abdominal pain ($R = 0.84$, $p < 0.01$), as did headache with photophobia ($R = 0.75$, $p < 0.01$).
Discussion: Baseline predictors of DHE responsiveness included higher headache scores, and light and sound sensitivity, typical features of "true" migraine headache. No other symptom was as clearly responsive to DHE, and these may therefore not share the same neural generators. Nausea and abdominal pain correlate with one another and could reflect a different symptom mechanism.
Funding: Advancing a Healthier Wisconsin Grant #5520298.

Poster #63

Quality improvement and practice-based research in autonomic neuropathy using the electronic medical record

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Objectives: (1) To develop a structured clinical documentation support (SCDS) toolkit within the electronic medical record (EMR) that navigates care, writes notes, and captures data at office visits; (2) to share the toolkit with neuromuscular and autonomic specialists using the Epic EMR platform, as part of a Neurology Practice-Based Research Network (NPBRN).
Background: We developed a seven-stage process for quality improvement and practice-based research in Neurology using the EMR: (1) SCDS toolkits (custom navigators, electronic forms, smart data elements); (2) enrollment reports; (3) data quality reports; (4) descriptive cohort reports; (5) quality improvement dashboards; (6) clinical decision support; (7) sharing of toolkits and data (NPBRN).
Methods: We met every 2 weeks for 3 months to develop content: define the cohort, select outcome measures, and delineate factors known to modify disease progression. We assigned tasks to the care team and mapped data elements to the progress note. We then met every 2 weeks for 3 more months with programmer analysts to build and test the SCDS toolkit. Auto scored and interpreted tests included the Center for Epidemiological Studies-Depression (CES-D) scale, Fatigue Severity Scale (FSS), Survey of Autonomic Symptoms (SAS), Insomnia Severity Index (ISI), modified Rankin scale (mRankin), timed 25 foot walk (T25-W) and newly created North Shore Neuropathy Impairment Score (NS-NIS).
Results: Our toolkit captures 745 fields of data per office visit. We have used the toolkits 1087 times to assess patients at initial visits for possible neuropathy, finding autonomic polyneuropathy in 280 of those patients. We present screenshots of our SCDS toolkit and descriptive data, pairwise correlations principal component analyses of score test measures at initial visit from 280 patients in our autonomic neuropathy cohort.
Conclusions: The EMR can be effectively structured to standardize autonomic neuropathy office visits, capture data, and support multicenter quality improvement and practice-based research initiatives
Funding: Agency for Healthcare Research and Quality Grant 5R01HS024057-03 'Quality Improvement and Practice-Based Research in Neurology Using the EMR'.

Poster #64

Autoimmune component of diabetic autonomic gastroparesis

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Background: Diabetic gastroparesis is characterized by stomach pump failure. Although its etiology is still unknown, its association with other manifestations of autonomic neuropathy has led to the presumption that autonomic nerve dysfunction is a primary issue. There is indirect evidence that autoantibodies directed toward the autonomic receptors may alter nerve function.
Methods and Results: Sera from 25 DG subjects and 20 healthy controls were screened by ELISA for autoantibodies to the second extracellular loops of the M2 and M3 muscarinic cholinergic receptors (M2R and M3R). Out of the 25 DG subjects, 12 and 10 were positive for autoantibodies to M2R and M3R, respectively, while only 1 of the 20 controls was antibody positive for M2R and M3R. Nine DG subjects and 1 control subject harbored both autoantibodies (9/25 vs. 1/20, $P < 0.05$). Sera from 4 DG subjects and 2 controls were tested to examine the impact of these autoantibodies on gastric motor activity using rat gastric fundus strips. The DG sera significantly reduced the contractile responses to the cholinergic agonist acetylcholine (0.1–10 μM) compared to control sera (fold over baseline at maximal concentration of acetylcholine: 0.5 ± 0.2 vs. 2.0 ± 0.5, $P < 0.01$). The control sera did not show any significant effect on the contractile responses to acetylcholine. These data are similar to those obtained with purified serum IgG.
Conclusions: M2R and M3R are both involved in gastric motility. Our study demonstrates that circulating autoantibodies to these receptors alter gastric contractility in vitro. These data support the hypothesis that autoantibody-mediated changes in gastric motility may contribute to abnormal gastric emptying. If these data are confirmed, future diagnostic and specific therapeutic interventions may provide relief.

Poster #65

A new approach in assessing vasomotor reactivity in response to cold stress using non-contact optical technology

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Introduction: Cold stress vasoconstriction reflects general sympathetic reactivity, and it is an important indicator of autonomic regulation wellness. Vasomotor components are typically measured by contact plethysmographs, the use of which is inconvenient and limited in areas of application.
Aim: To compare the blood flow reactivity in response to the cold stress estimated by the classical Dohn occlusion plethysmography and novel imaging photoplethysmography (iPPG) systems during venous occlusion.
Methods: The group of seven volunteers with age of 41 ± 15 years participated in the experiment for assessing the forearm blood flow by two methods. Musculocutaneous blood flow was measured by Dohn occlusion plethysmography simultaneously with the cutaneous blood flow estimations by green-light iPPG system. Reaction of blood flow on three sequential venous occlusion was compared at rest and during the cold stress that was induced by placing an ice package on the chest.
Results: After venous occlusion, the linear increase of the forearm volume accompanied by the linear decrease of the PPG signal was observed, registered by air-plethysmography and iPPG system, respectively. Cold stress resulted in decrease of the slope in both curves. The relative changes of the curve inclination measured by air-plethysmography optical system were comparable: 40 ± 17 vs. 36 ± 12%, $p = 0.60$ (Wilcoxon test). Moreover, individual values of the relative change in the angle of inclination obtained by different methods correlated with each other: $r = 0.82$, $p = 0.023$ (Spearman rank correlation).
Conclusion: The classical and novel optical methods of occlusion plethysmography gave a similar assessment of blood flow changes in response to the cold stress. Therefore, the use of iPPG system simplifies and expands the research capabilities allowing study of vasomotor reactivity in different regions of the body.
Funding: Russian Science Foundation Grant 15-15-20012.

Poster #66

Impaired sensorimotor control of the hand in congenital absence of functional muscle spindles

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Patients with hereditary sensory and autonomic neuropathy type III (HSAN III) exhibit marked gait disturbances. The cause of the gait ataxia is not known, but we recently showed that functional muscle spindle afferents in the leg, recorded via intraneural microelectrodes inserted into the peroneal nerve, are absent in HSAN III, although large-diameter cutaneous afferents are intact. Moreover, there is a tight correlation between loss of proprioceptive acuity at the knee and the severity of gait impairment. Here we tested the hypothesis that manual motor performance is also compromised in HSAN III, attributed to the predicted absence of muscle spindles in the intrinsic muscles of the hand. Manual performance in the Purdue pegboard task was assessed in 12 individuals with HSAN III and 12 age-matched healthy controls. The mean (± SD) pegboard score (number of pins inserted in 30 s) was 8.1 ± 1.9 and 8.6 ± 1.8 for the left and right hand respectively, significantly lower than the scores for the controls (14.3 ± 2.9 and 15.5 ± 2.0; $p < 0.0001$). In five patients we inserted a tungsten microelectrode into the ulnar nerve at the wrist. No spontaneous or stretch-evoked muscle afferent activity could be identified in any of the 11 fascicles supplying intrinsic muscles of the hand, whereas rich tactile afferent activity could be recorded from 4 cutaneous fascicles. We conclude that functional muscle spindles are absent in the hand, and likely absent in the long finger flexors and extensors, and that this largely accounts for the poor manual motor performance in HSAN III.

Poster #67

Disturbed proprioception at the knee but not the elbow in hereditary sensory and autonomic neuropathy type III

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Hereditary sensory and autonomic neuropathy type III (HSAN III) features a marked ataxic gait that progressively worsens over time. We recently assessed whether proprioceptive disturbances can explain the ataxia. Proprioception at the knee joint was assessed using passive joint angle matching in 18 patients and 14 age-matched controls; five patients with cerebellar ataxia were also studied. Ataxia was quantified using the Brief Ataxia Rating Score, which ranged from 7 to 26/30. Patients with HSAN III performed poorly in judging joint position at the knee: mean (± SE) absolute error was 8.7° ± 1.0° and the range was very wide (2.8°–18.1°); conversely, absolute error was only 2.7° ± 0.3° (1.6°–5.5°) in the controls and 3.0° ± 0.2° (2.1°–3.4°) in the cerebellar patients. This error was positively correlated to the degree of ataxia in patients with HSAN III but not in patients with cerebellar ataxia. However, using the same approach at the elbow revealed no significant differences in mean error in 12 patients with HSAN III (4.8° ± 1.2°; 3.0°–7.2°) and 12 age-matched controls (4.1° ± 1.1°; 2.1°–5.5°). Interestingly, microelectrode recordings from the peroneal nerve showed a complete absence of spontaneous or stretch-evoked muscle afferent activity, confirmed in the ulnar nerve. Clearly, the lack of muscle spindles compromised proprioception at the knee but not at the elbow, and we suggest that patients with HSAN III have learned to rely more on proprioceptive signals from the skin around the elbow. Indeed, applying longitudinal strips of elastic tape around the joint to increase tensile strain in the skin improved proprioception at the knee but not the elbow.
Funding: Dysautonomia Foundation.

Poster #68

Transdermal vagal stimulation in postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) is a clinical syndrome characterized by an excessive increase in heart rate ($\geq$ 30 bpm) on standing in the absence of orthostatic hypotension, and frequent orthostatic symptoms for more than 6 months. While most researchers focus on the hyperadrenergic features of POTS, these patients also have significant cardio-vagal (parasympathetic) impairment. We tested the hypothesis that transdermal electrical stimulation of the auricular branch of the vagus nerve will enhance cardio-vagal modulation, reduce heart rate, upright symptoms, and improve orthostatic tolerance. We studied 14 patients with POTS (31.5 $\pm$ 11.7 years, BMI 22.6 $\pm$ 3.9 kg/m^2). Sham or transdermal electrical vagal stimulation below perception threshold was applied in random order to the auricular branch in the right ear in supine and during graded tilt maneuver. Patients with low vagal modulation (low high frequency HF $<$ 200 ms^2) responded to vagal stimulation (Kruskal–Wallis p = 0.01, n = 7) with significant increase in HF power (e.g., @50 Hz: + 51 $\pm$ 10 ms^2, p = 0.0032). Vagal stimulation during upright tilt tended to reduce orthostatic tachycardia and overall orthostatic symptom score. It improved significantly tilt time (+ 5.3 $\pm$ 2.6 min, p = 0.0156). Patients with higher baseline vagal modulation (HF $\geq$ 200 ms^2) did not response to vagal stimulation (interaction p = 0.41). This proof of concept study indicates that auricular transdermal vagal stimulation improves supine cardio-vagal function in POTS patients with low vagal modulation. Further research will determine if this approach can be used therapeutically, alone or in combination with other therapies.

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Poster #69

Non-invasive intervention for trigeminal neuropathy pain through mechanical modulation of pterygopalatine ganglia and trigeminal afferents

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Chronic trigeminal neuropathic pain is frequently inadequately managed by classic pain medications. We used mechanical vibratory neuro-modulation techniques to affect trigeminal nerve branches to relieve chronic pain and accompanying autonomic symptoms from oral, intranasal, and facial regions. One device consisted of a small magnetized vibratory motor latched to an opposite-polarity disc magnet fused to adhesive tape. A second device used a customized silicon impression for one nasal cavity with an embedded magnet for attachment of a magnetized vibratory motor. Device 1 was placed on the skin overlying trigeminal nerve branch exits. Device 2 was inserted into one nasal cavity to modulate branches of the second trigeminal division (V2; internal nasal; lateral nasal; nasopalatine), some of which connect to the pterygopalatine ganglion. The vibrations also affected branches of the first trigeminal division (V1, medial and lateral internal nasal; anterior ethmoidal, supplying posterior orbit contents). Parasympathetic fibers arising from the pterygopalatine ganglion were also affected, as were sympathetic fibers accompanying nasal blood vessels. The intervention reduced concurrent autonomic deficits, e.g., xerostomia, accompanying pain. Fifteen subjects with varying symptoms, including burning mouth syndrome, localized facial pain, and retroorbital pain were recorded during a 10-min baseline, 25-min stimulation, and 10-min post-stimulation period; pain levels were obtained at onset and offset of sessions, and declined by 3.25 $\pm$ 2.54 sd perceived units ($p < 0.01$, ANOVA). The mechanical vibration provides a rapid-acting (within minutes), drug-free, low-cost, non-invasive means to reduce chronic trigeminal pain without electrical stimulation to the skin or nasal mucosa, and with few side effects. The mechanisms of action are likely multi-fold, and presumably include massive disruption of existing neural circuitry for pain in the descending nucleus of V, as well as interruption of mechanoreception and pain circuitry in the thalamus, basal ganglia, insula, and cingulate cortices.

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Poster #70

The diagnostic yield and accuracy of a tertiary Syncope Unit; the Fainting Assessment Study II (FAST II)

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Background: Diagnosing patients with transient loss of consciousness (T-LOC) is a challenge, as patients are often asymptomatic upon presentation. The hospital-wide diagnostic yield ranges from 31 to 64%. The diagnostic yield of a tertiary Syncope Unit (SU), with complex patients and often thorough testing prior to the consult, has never been assessed.

Methods: Consecutive patients $\geq$ 18 y with T-LOC were eligible for inclusion. Patients underwent the Initial Syncope Evaluation combined with autonomic testing according to the ESC guidelines. The physician also reported if the diagnosis was certain, highly likely, likely, or unknown. Critical follow-up was applied after 1–1.5 years by an expert committee who established the definitive diagnosis. We identified the yield, accuracy, and safety (adverse events or unexpected diagnosis of epilepsy or cardiac syncope).

Results: 264 patients were included [median age 51, IQR: (34–64)]. A tilt-table test was performed in 59%. A certain diagnosis was made in 42% and a highly likely diagnosis in 39.8% patients, resulting in a diagnostic yield of 81.8%. A likely diagnosis was made in 15.2%. T-LOC remained unexplained in 3%. The diagnostic accuracy was 99% for certain diagnoses, 92% for highly likely diagnoses and 64% for likely diagnoses. Some patients with a likely or no diagnosis were referred to a neurologist specialized in epilepsy for a third opinion initiated by the SU. Three patients died. In one patient the expert committee deemed the cause of T-LOC as the suspected cause of death, although they made no diagnosis.

Discussion and Conclusion: The diagnostic yield of a tertiary SU was high, at 81.8%, with a high accuracy. The SU was safe, as no dangerous diagnoses were missed. The use of a tertiary Syncope Unit ran by a syncope expert provides a huge benefit in safely diagnosing and treating patients with unexplained T-LOC.

Poster #71

Patient-reported falls and fear of falling in a prospective study of droxidopa for treatment of neurogenic orthostatic hypotension

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Objective: To assess the long-term effectiveness of droxidopa in reducing the risk of falling and fear of falling (FoF) in patients with neurogenic orthostatic hypotension (nOH).
Background: nOH, a sustained blood pressure drop upon standing may increase fall incidence, which can trigger FoF and future fall risk. Droxidopa is approved to treat nOH symptoms; fall benefits were suggested in pivotal trials.
Methods: Patients newly initiating droxidopa enrolled in an open-label, prospective cohort study. The number of falls in the past month and FoF were recorded at baseline, 1, 3, and 6 months using a falls questionnaire and the Short Falls Efficacy Scale-International, respectively. P values were calculated using paired t test for continuous measures and generalized estimating equations with multinomial distributions for categorical measures.
Results: 179 patients were enrolled (Parkinson's disease: 33%, pure autonomic failure: 65%, other: 2%). Patients reported fewer falls in the previous month compared with baseline at 1, 3, and 6 months ($n = 135$, $n = 119$, and $n = 105$, respectively; all $P < 0.05$). Among those who fell ≥ 1 time, patients reported fewer falls during droxidopa treatment. At baseline, 57% of patients with ≥ 1 fall fell ≥ 3 times; at 6 months, only 35% fell ≥ 3 times. At 1, 3, and 6 months, patients reported significantly less concern about falling than at baseline ($n = 126$, $n = 112$, and $n = 98$; all $P < 0.0001$). The level of concern about falling was significantly decreased at 1, 3, and 6 months (all $P < 0.01$).
Conclusions: In this "real-world" study patients taking droxidopa were at significantly lower risk of falling after 1, 3, and 6 months of treatment and those falling ≥ 1 time in the prior month reported fewer falls/month compared with baseline. Patients reported reduced FoF during treatment. These results suggest persistence of beneficial effects at 6 months of treatment, but conclusions are limited by the lack of a control cohort.
Funding: This work was supported by Lundbeck.

Poster #72

Diagnosis and treatment of neurogenic orthostatic hypotension: online, case-based education successfully improved knowledge and competence of cardiologists and neurologists

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Introduction: Neurogenic orthostatic hypotension (NOH) is a common feature of conditions that are associated with autonomic dysfunction, including Parkinson's disease (PD). Clinicians may misdiagnose NOH and there is evidence that overall management is suboptimal. To address this, we investigated whether a case-based educational activity was able to improve the knowledge and competence of specialists regarding both the diagnosis and management of NOH.
Methods: An online, text-based educational intervention comprising 2 patient case scenarios was developed. Using a "test and teach" approach, clinicians were presented with multiple-choice questions to evaluate their application of evidence-based recommendations. Each response was followed by detailed, referenced, feedback to teach. Educational effect was evaluated with a repeated-pairs pre- to post-assessment study design in which each individual learner acts as his/her own control. A paired 2-tailed *t* test evaluated whether the mean pre- and post-assessment scores significantly differed from one another. Cramer's V was used to calculate the effect size of the intervention. Data were collected between March 28, 2018 and May 02, 2018.
Results: The education resulted in an extensive educational effect for both cardiologists ($n = 437$; $V = 0.456$; $P < 0.05$) neurologists ($n = 333$; $V = 0.411$; $P < 0.05$). Significant improvements were observed in several areas for both groups ($P < 0.05$ for all comparisons) including: the blood pressure reading after standing indicative of NOH; selection of non-pharmacologic treatments for NOH; the role of dopamine on blood pressure regulation and; pharmacotherapy for the management of NOH in patients with PD and comorbidities.
Conclusion: This study demonstrated the success of a targeted, online, interactive, case-based educational intervention on improving the knowledge and competence of both cardiologists and neurologists regarding the care of patients with NOH. Both clinician groups would benefit from continued education on the clinical recognition and management of NOH based on the magnitude of the educational effect.
Funding: The education and outcomes analysis were funded through an unrestricted educational grant from Lundbeck.

Poster #73

Polymorphic ventricular tachycardia associated with an episode of reflex syncope: is this the needle in the haystack?

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We present an unusual case of seemingly typical reflex syncope, in the form of defecation syncope, in a 17-year-old female with a pacemaker in situ for congenital heart block. Device interrogation demonstrated normal pacemaker function with a short run of polymorphic ventricular tachycardia (PVT) coinciding with the syncope. The patient was upgraded to an implantable defibrillator and underwent subsequent echocardiography and stress testing which were both normal, with no evidence of cardiomyopathy and no induced arrythmia. There is no family history of sudden cardiac arrest (SCA) or suspicious deaths. Screening for genetic causes of arrhythmia was negative. Given the autonomic trigger for her event, she was referred for autonomic function testing with non-invasive beat-to-beat blood pressure (BP) and electrocardiographic monitoring (Finometer ProTM). Her supine heart rate (HR) variability was reduced in the very low (1798 ms^2), low (LF: 672 ms^2) and high (HF: 107 ms^2) frequency ranges, but with a normal LF:HF ratio (6.3). Vagal baroreflex control (cross-spectral analysis) was impaired, with normal delay (2.2 s) but low sensitivity (3.8 ms $mmHg^{-1}$); HR responses to deep breathing were also small ($\pm$ 16 bpm). An active stand from the supine position revealed a borderline abnormal initial BP decrease (−

38/− 19 mmHg) that was associated with light-headedness and accompanied by an excessive HR response (+ 50 bpm). The BP decline was well recovered within 3 min of standing, but the HR remained excessive (+ 40 bpm). Her QT variability index was − 0.325, which reflects high susceptibility to ventricular arrhythmia. HR and BP responses to the Valsalva maneuver were normal, but in each of four repetitions there were associated non-conducted atrial ectopics and ventricular ectopy, consistently triggered during phase 2A. In susceptible individuals, autonomic stimuli may trigger significant arrhythmia, with the potential of progressing into a SCA. This case may provide insight into the 50% of individuals who experience SCA with no identifiable cause.

Poster #74

Droxidopa and midodrine treatment persistence in patients with orthostatic hypotension

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Objective: Determine the treatment persistence of no-cost droxidopa and midodrine in patients with orthostatic hypotension (OH) or neurogenic orthostatic hypotension (nOH).
Background: nOH is a sustained drop in blood pressure upon standing that can lead to falls and other poor outcomes. Droxidopa and midodrine are approved to treat symptomatic nOH and symptomatic OH, respectively. We compared treatment persistence over 1 year in patients taking droxidopa or midodrine with no copay.
Methods: Retrospective data were collected from Symphony Health Solutions Database (Symphony Health; Conshohocken, PA, USA). Inclusion criteria were continuous healthcare coverage from Sept 1 2014, to June 30 2017, an active prescription for droxidopa or midodrine of $\geq$ 30 days during that window, and no copay for the medications. Persistence was capped at 365 days for an unbiased comparison between midodrine (introduced in 1996) and droxidopa (introduced in 2014). The difference between estimated survival curves for droxidopa and midodrine was calculated using a log-rank test and a multivariable Cox regression analysis.
Results: Data from 688 patients on droxidopa (mean ± SD age, 63.8 ± 16 years; 48% women) and 1888 patients on midodrine (55.2 ± 16 years; 62% women) were included. Of patients on droxidopa, 12% had a diagnosis of Parkinson disease (PD), 34% cardiovascular disease (CVD), 18% both PD and CVD, and 35% unknown. Of patients on midodrine, 1% had a diagnosis of PD, 69% CVD, 3% both PD and CVD, and 26% unknown. Median persistence was significantly longer for droxidopa [240 days; 95% confidence interval (CI), 210–299] versus midodrine (180 days; 95% CI, 160–183; $P < 0.0001$). Patients on midodrine were 27.4% more likely to discontinue than those on droxidopa ($P = 0.002$).
Conclusions: When insurance covered medication cost, patients were more likely to remain on droxidopa than on midodrine. Possible reasons for this could be enhanced efficacy or fewer side effects.
Funding: This work was supported by Lundbeck.

Poster #75

Why do syncope patients go to the Emergency Department? … Or not?

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Background: Syncope causes 1–3% of emergency department (ED) admissions with 65% of syncope patients seen in ED arriving by ambulance. Little is known about the motivations prompting syncope patients to access emergency services (ES).
Objective: Exploratory qualitative research identified the factors prompting syncope patients to access ES. Results informed development of a paramedic-run ED "treat and refer" (T + R) for syncope patients, whereby they will receive assessment, education and follow-up facilitated by paramedic services.
Methods: A convenience snowball sample of self-identified "repeat fainters" (aged 18–67 years) were interviewed. Participants were asked to discuss their reasons for contacting or not contacting ES and their perception of the process in terms of meeting needs and expectations. Participants were then asked to discuss the potential for a T + R program administered by paramedic services.
Results: Patients who accessed emergency services expressed fear that their faint was a symptom of graver illness, fear due to ambiguity of symptoms, had been injured during fall, were seen because a bystander or family member called ES, or accessed care as a way to facilitate assessment. Also expressed was a sense of embarrassment and frustration over paramedics being called given that symptoms were generally resolved by the time they were seen. A paramedic-run T + R program was a supported concept, although patients expressed the need for referring paramedics to communicate the diversion as a completed assessment with protocols for follow-up care as many felt patients would see the decision not to transport to the ED as invalidating of their initial decision to seek ES care. Patients identified the need for decision matrices, accurate information for themselves and bystanders, and patient support resources.
Conclusions: Syncope patients contacted paramedics or attend the ED due to fear, injury, bystander concern or with hope of documenting symptoms to facilitate diagnosis. Patients are supportive of a T + R program that provides education, assessment and follow-up in the absence of an ED visit.
Funding: Cardiac Arrhythmia Network of Canada (CANet).

Poster #76

Orthostatic intolerance syndrome after bariatric surgery

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Background: This year over 200,000 individuals in the U.S. will likely undergo bariatric surgery for the treatment of morbid obesity. Several small case series and retrospective studies describe the occurrence of an orthostatic intolerance (OI) syndrome after bariatric surgery. However, the incidence of this syndrome remains unknown.
Methods: We used the Vanderbilt Metabolic and Bariatric Surgery Quality, Efficacy, and Safety Database (VMBSD), a prospective, de-identified registry of 4547 patients who have undergone bariatric surgery at Vanderbilt, to identify cases of post-bariatric surgery OI

syndrome. Chart review was conducted for all subjects who reported OI symptoms. Cases of OI were confirmed using a protocol developed by the Vanderbilt Autonomic Dysfunction Center, and data from available autonomic function tests were extracted from medical records for evidence of impaired autonomic function. The cumulative incidence of post-bariatric surgery OI syndrome was estimated using a life table.
Results: Of 4547 bariatric surgery patients, 741 patients reported OI symptoms. We confirmed the presence of post-bariatric surgery OI syndrome in 85 patients, including 14 with severe OI requiring pressor agents. By the end of 5 years post-operation, the estimated cumulative incidence of OI syndrome was 4.2%, after accounting for loss to follow-up. The majority of OI cases occurred after weight reductions post-operation, during relatively weight-stable months. At the time of identification, 52% of OI cases with available autonomic function test data (11 of 21) showed evidence of impaired sympathetic vasoconstrictor activity. The baseline pre-operation prevalence of neuropathy, coronary artery disease, and arrhythmias were significantly higher among patients who developed OI syndrome than among those who did not.
Conclusion: Orthostatic intolerance is relatively frequent in the bariatric surgery population, affecting 4.2% of patients within the first 5 years after their operation. Some patients with OI exhibit evidence of impaired sympathetic vasoconstriction activity.
Funding: C.A.S. was supported by National Institute of Health (NIH) Grant K23 HL103976-02 and by PHRMA Foundation Career Development Award, and Doris Duke Foundation Career Development Award. R.A.T. was supported by NIH Grant R01 DK100431. V.L.A. was supported by F32DK103474. The dataset(s) used for the analyses described were obtained from Vanderbilt University Medical Center's Synthetic Derivative which is supported by institutional funding and by the Vanderbilt CTSA Grant ULTR000445 from NCATS/NIH.

Poster #77

The impact of nausea in pediatric patients with chronic overlapping pain conditions

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Introduction: Despite its frequency in chronic overlapping pain conditions (COPC), nausea is rarely studied, particularly regarding triggers and co-morbid symptoms.
Methods: Retrospective chart review of pediatric patients in the Autonomic Registry who had filled out a questionnaire regarding symptoms, family history, and co-morbidities. Patients with and without nausea were included for comparison. The two groups were separated and compared using a pooled t-test.
Results: Of 39 patients, 25 identified nausea as a symptom. The mean functional disability inventory (FDI, range limits 0–60) was significantly higher in patients with nausea with a median 29 (range 16–54) vs. 13.5 (0–33) ($p < 0.01$). The nausea group had more frequent headache ($p = 0.01$), sleep disruption ($p = 0.03$), and aches and pains ($p = 0.02$). Interestingly, mental health conditions such as depression, anxiety, and PTSD did not differ between groups, nor did hypermobility or joint dislocation. Family history was only significant for gastroesophageal reflux disease in the nausea group ($p = 0.02$), and specifically there was no difference for migraine.
Conclusion: When nausea is present, children with COPC have greater disability, suggesting a high impact on their daily function. COPC with nausea also has more headaches, sleep issues, and aches and pains. Interestingly, nausea was not associated with higher prevalence of migraine in the family.

Poster #78

Reduced heart rate variability at the time of PICU admission improves with recovery from critical illness

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Background: Autonomic nervous system dysregulation (ANSD) is common in critical illness. Changes in heart rate variability (HRV) reflect ANSD, often precede clinical deterioration, and are associated with poor outcomes. However, data associating HRV with recovery from critical illness in children are lacking.
Objective: HRV derived from electrocardiogram (ECG) data from bedside monitors can be calculated in children using an automated, streaming analytics platform. Determine if changes in HRV can be detected with recovery from critical illness by comparing HRV from the time of pediatric intensive care unit (PICU) admission with HRV immediately prior to discharge.
Methods: Retrospective, observational pilot study examining HRV in 17 patients ages 0 to 18 years admitted to the PICU at a tertiary-care children's hospital. Three time-domain measures of HRV were calculated in real-time from bedside monitor ECG data and stored for analysis. Measures included: root mean square of successive differences between NN intervals (rMSSD), % of successive NN interval differences over 50 ms (pNN50), and standard deviation of NN intervals (SDNN). Values from the first and last 24 h of PICU stay were analyzed.
Results: Mixed models demonstrated that all three measures of HRV were significantly lower during the first 24 h compared to the last 24 h of PICU admission ($p < 0.001$ for all three measures). In models exploring the relationship between time from admission and log HRV values, the predicted average HRV remained consistently higher in the last 24 h of PICU stay compared to the first 24 h.
Conclusion: HRV was significantly lower in the first 24 h compared to the 24 h preceding PICU discharge, after resolution of critical illness. This demonstrates that it is feasible to detect changes in HRV using an automated, streaming analytics platform. Continuous tracking of HRV may serve as a biomarker of recovery in critically-ill children.
Funding: Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Ruth D. and Ken M. Davee Pediatric Neurocritical Care Program.

Poster #79

NIH Toolbox application of cognition assessment in congenital central hypoventilation syndrome

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Introduction: Congenital central hypoventilation syndrome (CCHS) is a neurocristopathy characterized by autonomic nervous system dysregulation, including a control of breathing deficit and risk of repeated hypoxic exposure. Formal neurocognitive testing indicates mid-average or better development in a subset of preschool-age CCHS children, and low-average results in most school-age children. The NIH Toolbox Cognition Battery (NTCB) is a highly portable validated tool that measures six cognitive domains (executive function, attention, episodic memory, language, processing speed, working memory), with application across a broad age range for longitudinal purposes. NTCB summary scores are generated for overall cognitive total composite based on fluid (measures cognitive abilities related to capacity for new learning and information processing in novel situations) and crystallized (measures cognitive abilities dependent upon past learning experiences) composite scores.
Methods: 62 CCHS subjects (35 females; mean age 15.7 $\pm$ 10 years) were recruited and administered NTCB via an iPad. Two-sided one-sample t-tests were performed on age-corrected standard scores compared to the population mean (100 $\pm$ 15), and a fully-corrected T-score compared to a population mean (50 $\pm$ 10). Significance was applied to $p \leq 0.05$.
Results: Age-corrected standard scores and fully-corrected T-scores were frequently reduced in CCHS (fluid composite scores for both and cognition total composite score for fully-corrected are $\geq$ 1 SD below the population mean). However, the crystallized fluid composite did not differ from the population mean.
Conclusions: The NIH Toolbox Cognition Battery effectively and objectively measures neurocognition in CCHS. Crystallized composite scores indicate normal mean values in CCHS. However, fluid composite scores are significantly below normative values, as are overall fully-corrected cognition total composite scores. These NTCB results within the largest CCHS cohort reported to date for neurocognitive testing support previously published formal neurocognitive testing results. This suggests that the NTCB has utility in longitudinal testing and determination of specific modifiers of neurocognitive development before and after intervention strategies.
Funding: National Institutes of Health's National Center for Advancing Translational Sciences, Grant Number UL1TR001422; PHOX2B Patent Fund at Chicago Community Trust Foundation.

Poster #80

Case report of uccessful May-Thurner syndrome (MTS) surgery in postural orthostatic tachycardia syndrome (POTS)

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Background: POTS is a condition characterized by an abnormal increase in heart rate upon changes in posture and presents with an array of symptoms like headache, dizziness, syncope, palpitations, nausea, abdominal discomfort, fatigue, and blood pooling of hands and feet. MTS is a compression of the left common iliac vein (LCIV) by the right common iliac artery (RCIA) and may present with DVT, leg swelling, varicose veins. Theoretically, treating MTS will improve venous flow back to the heart, which will reduce the POTS symptoms. Previously, a case report was presented of a patient who reported no improvement of their POTS symptoms after MTS surgery without a hemodynamic study prior to the procedure.
Method: A case of a 38-year-old female with POTS and MTS symptoms with failure of medical management is presented. Imaging studies such as mesenteric and renal doppler, and magnetic resonance venogram-abdomen and pelvis (MRV-AP) were performed prior to the surgery. Patient proceeded with MTS surgery done through stenting of LCIV and RCIA known as "kissing stents".
Results: Celiac and renal doppler were normal. MRV-AP showed narrowing of the proximal LCIV distal to the bifurcation of the inferior vena cava as it coursed between the lumbar vertebral body and the RCIA. Significant short-term improvement of the patient's symptoms after MTS surgery were noted. She reported a significant decrease in her fluctuating heart rate, she was able to stop taking the prescribed Ivabradine; significant decrease in symptoms of dizziness, chest pressure, and palpitations from postural/positional changes. A significant decrease in swelling and discoloration of her lower extremities and slight-moderate increase in her energy levels were also noted.
Conclusion: MTS surgery using two stents, with prior hemodynamic study, was found to be beneficial in relieving the POTS symptoms in this patient. We are currently studying the long term benefits and management of MTS surgery in POTS patients, while using hemodynamic studies to guide us.

Poster #81

Abdominal binder with insulin therapy for better glycemic control in a patient with POTS and DM-Type 1

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Introduction: Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous group of disorders and a form of autonomic dysfunction that could be associated with other comorbidities. We hereby present a case of POTS and diabetes mellitus type 1 treated with subcutaneous insulin injections, and abdominal binder for better glycemic control.
History: An 18-year-old female with diabetes mellitus type 1 and postural orthostatic tachycardia syndrome (POTS) presented with longstanding symptoms of dizziness, lightheadedness, palpitations and syncope. A detailed workup also revealed a moderate form of hypermobility. Patient complained of having difficulty in controlling her blood sugar levels with the use of subcutaneous insulin Lispro injections after meals, and subcutaneous insulin glargine injections before going to bed. She used continuous glucose monitoring to check random blood glucose levels that ranged between 300 and 500 mg/Dl. A therapeutic trial of using an abdominal binder with insulin injections for 1 week was suggested to see if this could help in achieving better glycemic control. Theoretically, the abdominal binder should help with improving circulation and decreasing the effect of blood pooling associated with POTS, and possibly improving absorption of insulin to the circulatory system. During the therapeutic trial, the patient used an elastic abdominal binder during the day, Lispro insulin was injected after meals, and Glargine insulin was injected before bed time. On day 4 post treatment, normalization in blood glucose levels were appreciated using a continuous glucose monitoring device. The patient continued using the abdominal binder with her insulin therapy, and her average random blood glucose level was 170 mg/DL post treatment.
Conclusion: In patients with POTS and DM type 1, the use of an abdominal binder along with insulin injections may help in achieving better glycemic control. This could be explained by increasing circulation in POTS patients, which may facilitate the absorption of insulin subcutaneously injected in the abdominal area. Therefore, we suggest that patients with POTS and signs of blood pooling may benefit from the use of abdominal binder in combination with the insulin therapy to achieve a tighter blood glucose control. Further

studies should be conducted in order to better understand this implementation.

Poster #82

Ehlers-Danlos syndrome and mast cell activation syndrome in postural tachycardia syndrome: contributions to a sicker phenotype?

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Background: Postural tachycardia syndrome (POTS) is a common form of orthostatic intolerance. Some POTS patients also have Ehlers-Danlos syndrome (EDS), a heritable connective tissue disorder, and/or a mast cell activation syndrome (MCAS), an allergy spectrum disorder with gastrointestinal and neurological involvement. This relationship is not well understood and we hypothesize the presence of EDS and/or MCAS is associated with greater symptom burden.
Methods: The "Diagnosis and Impact of POTS" is an IRB approved, patient-community based online self-reported survey. Surveyed between Jul2015 and Feb2018, 4740 patients with physician-diagnosed POTS were included.
Results: Four groups: 289 (6%) diagnosed with both EDS and MCAS (POTS + EDS + MCAS), 918 (19%) with EDS but not MCAS (POTS + EDS), 174 (4%) with MCAS but not EDS (POTS + MCAS) and 3359 (71%) with POTS alone (POTS). Classic POTS symptoms including lightheadedness, chest pain, tachycardia and palpitations were not different between the 4 groups. Presyncope was significantly higher in POTS + EDS than POTS (96% vs. 93%, $p = 0.004$). Allergic symptoms including skin flushing and hives were higher in POTS + EDS + MCAS and POTS + MCAS when compared to both POTS and POTS + EDS ($p < 0.001$). Skin flushing was also significantly higher in the POTS + EDS group when compared to POTS (74% vs. 66%, $p < 0.001$). Gastrointestinal symptoms were most common in POTS + EDS + MCAS including nausea (97%), vomiting (46%), and diarrhea (81%), and significantly higher than POTS ($p < 0.001$ for each). Neurological symptoms including tingling (82%) and numbness (73%) in the feet were most common in the POTS + EDS + MCAS group, significantly higher than POTS (65% and 56%, $p < 0.001$), POTS + EDS (73%, $p = 0.001$ and 64%, $p = 0.005$), and POTS + MCAS (71% and 60%, $p = 0.003$).
Conclusions: MCAS was seen in 10% of the POTS population, and the majority of this subgroup also reported EDS. MCAS + EDS patients reported a higher rate of allergic, gastrointestinal, and neurological symptoms than those patients with POTS alone. Future mechanistic studies are needed to better understand pathophysiology.

Poster #83

Sensory functioning in postural orthostatic tachycardia syndrome and the relationship with autonomic symptom burden

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The purposes of this study were to form a comprehensive, foundational understanding of sensory functioning, specifically sensitivity to sensory stimulation, in adults with postural orthostatic tachycardia syndrome (POTS) and identify if there is a relationship between individual's sensory functioning and severity of autonomic symptoms. Adults diagnosed with POTS were surveyed on autonomic symptom severity using the Composite Autonomic Symptom Score 31 (COMPASS-31) and sensory functioning using the Sensory Perception Quotient (SPQ). Spearman's correlations were performed to analyze the relationship between the measures. 756 participants completed the survey. Of these, 2.6% had autism spectrum disorder, all of whom were female. Sensory hypersensitivities were identified in all senses. Touch was the most hypersensitive sense and hearing was the least sensitive. All correlations between COMPASS-31 and SPQ scores were weak despite reaching statistical significance provided the large sample size, however, several trends emerged from the data. Pupliomotor was the COMPASS-31 domain with the highest number of statistically significant correlations with sense subcategories. Touch and vision were the senses with the highest number of statistically significant correlations with COMPASS-31 domains. This study provides preliminary evidence of sensory hypersensitivities in individuals with POTS across all five major senses.
Funding: Research completed as part of doctoral work in the School of Occupational Therapy, Belmont University, Nashville, TN, USA.

Poster #84

Small vessel vasculitis associated with small fiber neuropathy featuring worsening of postural orthostatic tachycardia syndrome

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Introduction: The prevalence of postural orthostatic tachycardia syndrome (POTS) is estimated to be 0.1–1%. About 50% of POTS patients were found to be of the neuropathic type. The estimated sensitivity of sural nerve and combined superficial peroneal nerve and peroneus brevis muscle biopsies in diagnosing non-systemic vasculitic neuropathy is 50%.
Objective: To report subacute worsening of manifestations of POTS in the setting of non-systemic small vessel vasculitis associated with small fiber neuropathy.
Methods: Case report.
Results: A 45-year-old woman with remote history of POTS as a teenager who presented with subacute recurrence of her orthostatic symptoms and new onset diffuse neuropathic pain in 2015. The onset was associated with new complaints of dry eyes, early satiety, and several weeks of night sweats. Her neurologic examination was remarkable for decreased temperature sensation up to ankles bilaterally. Laboratory workup for causes of acquired neuropathy including vitamin B complex levels, heavy metal screen, inflammatory markers, and paraneoplastic panel were unremarkable. Nerve conduction studies and electromyography were normal. Quantitative sudomotor axonal reflex testing showed reduced sweat output on the forearm. Head up tilt table test showed reproduction of some of her symptoms with rise of heart rate from 80 (baseline supine) to 124 bpm after 9 min of tilt with no significant change in blood pressure. Thermoregulatory sweat test showed symmetric areas of anhidrosis over the forearms and toes. Skin punch biopsy showed reduced epidermal nerve fiber density in a non-length dependent manner. There were multiple moderate inflammatory mononuclear cellular collections surrounding and invading small dermal blood vessels.
Conclusion: This case highlights the importance of pathologic evaluation of POTS patients, especially the neuropathic type, via skin punch biopsy. Clues for more aggressive search for an underlying

cause could include subacute onset, non-length dependent distribution of neuropathic manifestations, and presence of systemic symptoms at time of onset.

Poster #85

Incidence of May-Thurner syndrome in postural orthostatic tachycardia syndrome (POTS) patients

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Background: Patients with autonomic dysfunction, such as POTS, often have co-existing vascular disorders. May-Thurner syndrome refers to a condition where the left iliac vein is compressed by the right iliac artery, which increases the risk of deep vein thrombosis (DVT) in the left extremity. Often, the syndrome acts as a permissive lesion and becomes symptomatic when something else happens such as, following trauma or a change in functional status. An incidental compression of 50% or more in the left iliac vein is seen in about a quarter of the general population.
Objective: We aim to study the prevalence of May-Thurner syndrome in POTS patients.
Method: We did a retrospective study of 876 patients randomly selected from our pool of POTS patients. Their electronic medical records were reviewed and the CT angiogram abdomen and pelvis were evaluated for their diagnosis. Patients were diagnosed based on a compression of 50% or more of the left iliac vein.
Results: 209 (23.74%) out of 876 POTS patients (age = 32.94 ± 12.21) were tested for May-Thurner syndrome. 33 of 209 (15.79%) tested positive whereas 176 of 209 patients (84.21%) tested negative for May-Thurner. Out of the 33 patients that tested positive for May-Thurner; 2 (6.06%) were male (age 31.5 ± 4.95) whereas 31 (93.94%) were female (ages 30.97 ± 11.11). 2 out of 33 (6.06%) had leg edema and 0 out of 33 (0.00%) had a DVT.
Conclusion: Our study reports show that out of 209 POTS patients that had CT abdomen and pelvis for May-Thurner testing, approximately 15.79% tested positive. Therefore, we do not see an increased incidence of May-Thurner syndrome in POTS patients compared to the general population. Further studies must be conducted in order to better understand this relationship.

Poster #86

A comparison study of heart rate with deep breathing variability (HRVdb) in female patients with intermediate tilt table test results vs. postural orthostatic tachycardia syndrome patients

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Background: Often, patients with orthostatic intolerance (OI) do not meet criteria for postural orthostatic tachycardia syndrome (POTS) or orthostatic hypotension. There was one previous study that showed relative inability to increase HR upon posture changes. This was attributed to enhanced vagal tone. That study used frequency domain analysis for HRVdb. HRVdb is a non-specific but reproducible marker to check for parasympathetic cardiac function.
Objective: We aim to study whether time-domain analysis for HRVdb also shows enhanced cardiovagal tone in female patients who have intermediate tilt test response, compared to female POTS patients.
Methods: A retrospective study was performed by randomly selecting 41 OI female patients using the intermediate tilt table test criteria (HR increase between 15 and 30 bpm within 10 min of tilt) as our case group. We selected our control group as 50 POTS female patients (HR increase > 30 bpm or exceeds > 120 bpm within 10 min of tilt) minimizing the confounders like age and gender. We utilized time-domain analysis for HRVdb results and performed a Chi square test to see if there are any significant differences between case and control group.
Results: Our study identified a total of 41 female OI patients (age = 36.5 years + 10.4). Their tilt table test results had: mean HR change = 24.225 bpm + 4.393, SEM = 0.694, and HRVdb mean = 19.014 + 8.633, SEM = 1.365. The study had a total of 50 female POTS patients (age = 31.372 years + 11.549). Tilt table test results had: mean HR change = 45.725 bpm + 13.523, SEM = 1.893 and HRVdb mean = 21.675 + 8.175, SEM = 1.144. Comparing HRVdb among these two groups showed Chi square statistic of 1.7144 and p-value of 0.190412.
Conclusion: Our study showed that there was no statistically significant difference in the case group vs. control group and did not show there was enhanced vagal tone in patients with OI symptoms (non-POTS patients). This is a preliminary study and further studies need to be conducted for better understanding.

Poster #87

Compression and velocity of the left renal vein as a measure of severity of Nutcracker syndrome in postural orthostatic tachycardia syndrome (POTS) patients

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Background: Previously, we have seen a relationship between Nutcracker syndrome and POTS. Nutcracker syndrome is the compression of left renal vein between the abdominal aorta (AA) and superior mesenteric artery (SMA) causing symptoms such as flank pain, lower abdominal pain, hematuria, pelvic congestion, varicocele and varicose veins due to the disturbance of blood flow from the left renal vein (LRV) into the inferior vena cava.
Objective: We aim to study the compression and velocity of the left renal vein in POTS patients as a possible indicator of the severity of Nutcracker syndrome based on prevalence of symptoms.
Methods: We did a retrospective study of 876 POTS patients referred to our clinic. Electronic medical records were reviewed and the CT angiograms of abdomen (w/and w/o contrast) evaluated for Nutcracker syndrome and its respective symptoms. Renal dopplers were assessed and left renal vein velocities were collected. The findings from both tests were compared to each other.
Results: 208 (23.74%) out of 876 POTS patients were tested for Nutcracker syndrome. 24 of 208 (11.54%) Patients were diagnosed with Nutcracker syndrome and had data on their systolic velocity. Out of the 24 patients that had Nutcracker syndrome; 1 (4.17%) was male (age 37) whereas 23 (95.83%) were female (ages 28.96 ± 10.59). Our findings showed that 5 out of 24 patients suffered from lower abdominal pain (20.83%); 6 out of 24 patients suffered from leg pain [(25%) 3 in only the left leg and 3 in both legs]; 6 out of 24 patients showed pelvic congestion (25%); 4 out of 24 patients had flank pain [(16.67%) 3-left flank and 1-right flank]; 3 out of 24 patients had

varicose veins (12.50%); and 2 out of 24 patients suffered from hematuria (8.33%). 7 out of 24 (29.17%) patients had mild compression; 17 out of 24 (70.83%) patients had 50% or more compression. Mean systolic LRV velocity = (31.33); No correlation was observed between degree of compression and LRV/RRV velocity ratio ($R^2 = 0.053$); No correlation was observed between degree of compression and LRV systolic velocity ($R^2 = 0.021$) and a Pearson correlation coefficient (R Value = − 0.145) was obtained for the same.
Conclusion: Our study showed that there is no correlation between the compression and velocity of the left renal vein and symptoms of Nutcracker syndrome. This is a preliminary study and further studies need to be conducted for a better understanding.

Poster #88

Validation of the German version of the Composite Autonomic Symptom Score 31

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Background: The Composite Autonomic Symptom Score 31 (COMPASS 31) is a validated, 31 item self-assessment questionnaire, developed by the Mayo Clinic autonomic group from their more time-consuming 169-item Autonomic Symptom Profile and 72-item COMPASS questionnaires. The 31 items assess autonomic symptoms in 6 domains, orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor functions. So far, there is no validated German version of the Compass 31.
Objective: To establish a validated German version of the COMPASS 31.
Methods: Two neurologists with autonomic expertise (WS and MJH) independently translated the original questionnaire into German; then, this version was translated back into English to assure conformity of the German with the original version. 20 patients with autonomic dysfunction and 20 age- and gender-matched healthy controls completed the COMPASS 31 twice, 4 weeks ± 1 week apart, once in German and once in English. The order was randomized at the Mayo Clinic, Rochester, MN. The validation of the German version of COMPASS 31 was evaluated by correlating its total and sub-scores with those of the original English COMPASS 31 using Pearson's correlation test. Significance was set as p-value < 0.05.
Results: The German version of COMPASS 31 significantly and positively correlated with the English version of COMPASS 31 in scores of orthostatic intolerance (coefficient = 0.919, $p < 0.001$), vasomotor function (coefficient = 0.934, $p < 0.001$), secretomotor function (coefficient = 0.741, $p < 0.001$), gastrointestinal function (coefficient = 0.896, $p < 0.001$), bladder function (coefficient = 0.864, $p < 0.001$), pupillomotor function (coefficient = 0.776, $p < 0.001$), and total scores (coefficient = 0.934, $p < 0.001$).
Conclusions: Total- and sub-scores of the German Version of COMPASS 31 correlated well with those of the original English version of COMPASS 31. These data indicate that the German version of COMPASS 31 is a validated tool to assess autonomic involvement in both clinical and research applications.

Poster #89

Assessment of postural orthostatic tachycardia syndrome (POTS) in adolescents and young adults using pupillometric parameters: a pilot study

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Purpose: To observe differences in 8 pupillometry variables before and after orthostatic stress in adolescents and young adults with a diagnosis of POTS in comparison to control subjects without a diagnosis of dysautonomia.
Methods: Pupillometry data were collected using an infrared pupillometer (Neuroptics PLR-200) in 20 adolescents and young adult subjects with a diagnosis of POTS and 20 similarly aged controls. Pupillometry data for each participant were recorded at three time points: lying supine for 10 min for a baseline measurement, and then documented at 5 and 10 min under orthostatic stress in the standing position. The 8 pupillometry parameters collected were: the initial pupil diameter (MAX), the smallest diameter of pupillary constriction (MIN), the amplitude of constriction as a percent (CON), the latency of the pupil to constrict (LAT), the maximum speed of pupillary constriction (MCV), the average velocity of pupillary constriction (ACV), the average velocity of pupillary re-dilation (ADV) and the time to re-dilate 75% (T75).
Results: This study was analyzed using SAS 9.4 with a significance level of $p < 0.05$. A total of 40 subjects (65% female, ages 12–22) were enrolled in the study. After adjusting for age and gender, there were significant differences between the POTS and control groups in 3 pupillometry outcomes. The CON for POTS subjects was significantly smaller at each time point. The MIN was significantly larger at 5 and 10 min post orthostatic stress. LAT was significantly higher in POTS than controls at 10 min after orthostatic stress.
Conclusion: Based on the results of this pilot study, pupillometry has potential as a tool to screen for autonomic nervous system disorders such as POTS in adolescents. Further research is required to develop an algorithm based on pupillometry parameters that can be utilized in assessing patients with signs of dysautonomia.

Poster #90

Healthcare related costs of autonomic disorders in MHS beneficiaries

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Objective: Describe healthcare related costs in Military Healthcare System (MHS) beneficiaries diagnosed with various autonomic disorders.
Background: The MHS has one of the largest cradle-to-grave health systems in the United States with over 9.7 million patients. Healthcare related costs in individuals diagnosed with autonomic disorders in the MHS have not been explored.
Methods: The MHS Data Repository (MDR) was queried for patients with at least two ICD-9 diagnostic codes for autonomic disorders between the dates of January 1, 2009 and September 30, 2015. Individuals with any diagnosis of diabetes mellitus were excluded.

Results: Diagnosis of tachycardia, unspecified, was most common, with 165,484 cases over the period with total healthcare costs of $14.8 billion, or $15,066 per beneficiary per year. Number of cases of other autonomic disorders, total costs, and beneficiary per year costs were: orthostatic hypotension, 54,642, $3.95 billion, $11,752; idiopathic peripheral autonomic neuropathy, 8314, $661 million, $12,087; autonomic neuropathy in diseases classified elsewhere, 3470, $313 million, $14,082; disorder of the ANS, unspecified, 7145, $699 million, $15,644; other degenerative changes of the basal ganglia/MSA, 3619, $262 million, $12,556; and hereditary sensory neuropathy 2463, $200 million, $12,533. Costs for encounters directly related to autonomic disorders were, respectively (in millions), $761, $214, $21.1, $12.2, $67.1, $21.3, and $5.5.
Conclusions: Disorders of the autonomic nervous system are prevalent among MHS beneficiaries and reflect substantial cost. Costs directly related to autonomic disorders are lower than overall costs.
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Poster #91

Sudoscan utility in sudomotor function assessment in patients referred for autonomic evaluation in a Chilean neurology clinic

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Introduction: Sudoscan is a noninvasive sudomotor test based on electrochemical skin conductance (ESC) measurement. The aim of this observational study was to describe ECS testing utility in patients referred for autonomic function evaluation.
Patients and Methods: 46 consecutive patients, grouped in: syncope (21), peripheral neuropathy (PN) (8), Parkinson's disease (PD) (13), multiple system atrophy (MSA) (4). Autonomic tests: Blood pressure (BP) and heart rate (HR) change on standing, Cardiovagal: Valsalva ratio (VR), HR change on deep breathing (HRDB), sympathetic skin responses (SSR) and ESC in palm (P) and sole (S). Data: Mean $\pm$ SEM, One-way Anova followed by Dunnet multiple comparisons.
Results: Mean P-ESC and S-ESC were different among groups ($p < 0.01$), in PN mean P-ESC = 45.6 $\pm$ 19 uS was lower than in syncope = 67.9 $\pm$ 16 uS. In PN mean S-ESC = 51.8 $\pm$ 18 uS was lower than in syncope = 83.6 $\pm$ 7.2 uS, PD = 77.4 $\pm$ 9 uS and MSA 73.8 $\pm$ 11 uS. Mean P-ESC and S-ESC in PD and MSA did not show significant difference. In PN mean P-SSR = 1.6 $\pm$ 2.3 mV and mean S-SSR = 1.4 $\pm$ 2 mV did not differ significantly from syncope, PD and MSA. Number of patients with orthostatic systolic BP fall $\geq$ 20 mmHg: syncope n = 0, PN n = 4, PD n = 0, MSA n = 2. In PN the VR and HRDB were lower than in syncope and PD.
Conclusions: This study shows that S-ESC assessment is more sensitive than SSR and useful to detect sudomotor dysfunction in patients with peripheral neuropathies.