Introduction to Autonomic Disorders in the Clinic

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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.

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Objectives

Participants will:
- Understand the components of the autonomic nervous system (ANS)
- Recognize presenting symptoms of autonomic dysfunction
- Appreciate the cross-disciplinary nature of disorders of the ANS
- Appreciate that many medications affect the ANS
- Understand first-line clinical and laboratory tests to evaluate and confirm disorders of the ANS
• Acknowledgements
  – David S. Goldstein, MD, PhD – *Principles of Autonomic Medicine, v. 2*
Disease burden

- **Syncope:**
  - Lifetime prevalence: ~27%
  - First-ever syncope incidence 6.2/1000 person years (da Silva, Front Physiol. 2014)

- **Postural tachycardia syndrome (POTS):**
  - Incidence: 500,000-3 million in the U.S. (0.2-1%)

- **Irritable bowel syndrome:**
  - Prevalence: 16.7–24.2%

- **Parkinson disease with orthostatic hypotension (OH):**
  - 18% of PD patients (Ha et al. Parkinsonism Relat Disord. 2011)

- **Multiple system atrophy (MSA):**
  - Prevalence: 3.4-4.9 cases per 100,000 (~0.00004%)
  - Incidence: 0.6-0.7 cases per 100,000 person-years (Fanciulli et al. NEJM 2015; Stefanova et al. Lancet Neurol. 2009)

- **Pure autonomic failure (PAF):** Prevalence: 1-9/100,000 (~0.00005%)

- **HSAN III:** ~300 currently worldwide
Time to diagnosis

- POTS: 5 years 11 months → 4 years 2 months (2016)

- MSA: ~6 years

Average number of doctors seen prior to diagnosis: 7.3
The “automatic” nervous system

ANS

ENS PNS SNS SAS

Langley Cannon Dale

(Many) ACh NE EPI ACh

Enteric Parasympathetic Cholinergic Sympathetic Noradrenergic Sympathetic Adrenergic Sympathetic Cholinergic

D.S. Goldstein, public domain
Central nervous system

Brain & spinal cord

Peripheral nervous system

Nerve root, nerves, and synapses
Central Autonomic Network
<table>
<thead>
<tr>
<th>Autonomic system</th>
<th>Responsible for...</th>
<th>Lesion causes...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic noradrenergic</td>
<td>Vasomotor tone, heart rate</td>
<td>Neurogenic orthostatic hypotension, ptosis</td>
</tr>
<tr>
<td>Sympathetic cholinergic</td>
<td>Sweating</td>
<td>Anhidrosis</td>
</tr>
<tr>
<td>Sympathetic adrenergic</td>
<td>Promoting glycogenolysis; skeletal muscle blood flow during stress response</td>
<td>?prolonged hypoglycemia; ?decreased muscle performance during strenuous activity</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>Lots (“stuff you do behind closed doors”)</td>
<td>Dry mouth, constipation, urinary retention, sexual arousal</td>
</tr>
<tr>
<td>Enteric</td>
<td>GI motility, etc.</td>
<td>Early satiety, abnormal medication absorption, constipation</td>
</tr>
</tbody>
</table>
Syncope

Kupang, Indonesia (Aug. 23, 2006) - U.S. Navy Cmdr. Elizabeth Satter assist an elderly woman who fainted due to the heat while waiting among the large crowds of people waiting to be seen by members of from the Military Sealift Command (MSC) hospital ship, USNS Mercy (T-AH 19) providing free care during a medical and dental care civil action project.

Syncope (cont.)

• Cardiogenic syncope
  – Structural
  – Bradyarrhythmia
  – Tachyarrhythmia

• Orthostatic hypotension
  – Hypovolemia
  – Medication-induced
  – Neurogenic

• Reflex syncope
  – Vasovagal (aka neurocardiogenic, neurally-mediated)
  – Situational syncope
  – Carotid sinus hypersensitivity

• Other (subclavian steal, CNS lesion)
Postural tachycardia syndrome

- 500,000 – 3 million people in U.S.
- Average diagnostic delay: 4 years, 2 months
- Average number of doctors seen prior to diagnosis: 7.3
  (BIG POTS Survey. Data presented at Dysautonomia International annual conference, July 2017)

- Orthostatic intolerance

- Exaggerated orthostatic tachycardia (>30 bpm increase; >40 bpm increase if <18 years old)
POTS

- Cardiac output
- β-receptor hypersensitivity
- Centrally ↑ NE output
- Adrenomedullary output
- ↓ Arterial tone
- ↓ Venous tone
- Hypovolemia
- ↓ NE reuptake
- Deconditioning
Testing the ANS

- History
- History
- History
- Physical exam
Testing the ANS (cont.)

http://www.cnsystems.com/products/task-force-monitor
Sympathetic cholinergic (sudomotor) testing
Sympathetic cholinergic (sudomotor) testing

Images Courtesy of WR Medical Electronics
QSART

Illustration in preparation
Other tests of sudomotor function

• Thermoregulatory sweat test
• QDIRT, etc.
Bedside evaluation of sudomotor function

• “Spoon” test
• Skin exam under magnification
• The sock test
Cardiovagal testing (parasympathetic)
HRDB – Normal example

Test ID: 1223
Date: 09/09/2013 21:03
Remarks:

Analysis ID: 1709
Date: 09/09/2013 22:47
Comments:

**HRDB Analysis**

**Test Data**

<table>
<thead>
<tr>
<th>Max Rate</th>
<th>Min Rate</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
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<td>53.8</td>
<td>14.8</td>
</tr>
<tr>
<td>69.0</td>
<td>53.6</td>
<td>15.4</td>
</tr>
<tr>
<td>69.8</td>
<td>54.3</td>
<td>15.5</td>
</tr>
<tr>
<td>71.4</td>
<td>54.3</td>
<td>17.1</td>
</tr>
<tr>
<td>68.2</td>
<td>55.3</td>
<td>12.9</td>
</tr>
</tbody>
</table>

**Marker Time Annotation**

3:15.00 start
4:35.50 stop
7:57.50 stqrt

**Analysis Summary**

Average HR Difference: 15.1
Comparison Range: n/a
Norms Table: n/a

E/I Ratio: 1.28

Norms not available for this modality.
Diminished HRDB

**HRDB Analysis**

**Analysis ID:** 2569  
**Date:** 05/18/2015 10:33  
**Comments:** Normal heart rate response to deep breathing compared to age-matched norms.

**Test Data**

<table>
<thead>
<tr>
<th>Max Rate</th>
<th>Min Rate</th>
<th>Difference</th>
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<td>78.4</td>
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<td>75.9</td>
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<tr>
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<td>10.6</td>
</tr>
<tr>
<td>76.9</td>
<td>66.3</td>
<td>10.6</td>
</tr>
</tbody>
</table>

**Analysis Summary**

- **Average HR Difference:** 10.4
- **Comparison Range:** n/a
- **E/I Ratio:** 1.15
- **Norms Table:** n/a

Norms not available for this modality.

**Marker Time Annotation**

- 0:46.50 start
- 2:07.00 stop
- 4:28.50 start
Bedside testing of cardiovagal function

New York Army National Guard Spc. Richard L. Bacher, a medic with 1st Battalion, 108th Infantry Regiment, helps a student find his radial pulse during a first aid class given to Logar province Afghan national police, Feb. 20, 2008, at Forward Operating Base Shank, Afghanistan

U.S. Army photo by Sgt. Matthew Clifton. Public Domain
Orthostatic Hypotension

Tilt Analysis

Analysis ID: 2671  Date: 05/18/2015 10:44
Analyst: Glen Cook, MD

Comments: There was orthostatic hypotension. The chronotropic response was minimal.

Test Data - Recorded

<table>
<thead>
<tr>
<th>Time</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
<th>Δ SBP</th>
<th>Δ DBP</th>
<th>Δ HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
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<td>67.7</td>
<td>59.7</td>
<td>-50.8</td>
<td>4.3</td>
<td>3.1</td>
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<tr>
<td>1.0</td>
<td>102.4</td>
<td>66.4</td>
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<tr>
<td>3.0</td>
<td>133.6</td>
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<td>-19.6</td>
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<td>9.8</td>
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<tr>
<td>5.0</td>
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<td>83.9</td>
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<td>-19.7</td>
<td>16.1</td>
<td>10.3</td>
</tr>
<tr>
<td>10.0</td>
<td>129.0</td>
<td>88.4</td>
<td>78.2</td>
<td>-24.2</td>
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<td>16.5</td>
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<tr>
<td>Post</td>
<td>149.2</td>
<td>92.7</td>
<td>60.9</td>
<td>-4.0</td>
<td>25.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Analysis Summary

Minimum SBP 100.9 at 1.2 minutes
SBP Change -52.3
HR at min SBP 63.2

Maximum HR 75.5 at 4.4 minutes
Minimum HR 59.1 at 0.1 minutes
HR Delta 18.4

Marker Time Annotation

3:58.00 tilt
14:01.50 down

Heart Rate (beats/min)

Blood Pressure (mmHg)
Orthostatic hypotension (cont.)

Tilt Analysis

Analysis ID: 2571  
Date: 05/18/2015 10:44  
Analyst: Glen Cook, MD

Comments: There was orthostatic hypotension. The chronotropic response was minimal.

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14:01.50 down
Orthostatic hypotension (cont.)

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Date: 05/18/2015 10:44
Analyst: Glen Cook, MD
Comments: There was orthostatic hypotension. The chronotropic response was minimal.
Orthostatic Hypotension (cont.)

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Neurogenic OH

- Information about BP doesn’t get to the brain
- Brainstem doesn’t sense BP change
- Sympathetic nerves don’t carry signal appropriately
- Nerve signal is not communicated between nerves or between nerve and blood vessel

Other causes of OH

- Low blood volume
- Adrenocortical failure
- Vasodilatory substances
- Medications
- Medications
- Medications
The Baroreflex


Copyrighted image. Used with permission
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Other causes of OH

- Low blood volume
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- Vasodilatory substances
- Medications
- Medications
- Medications
Valsalva Maneuver

Heart Rate
bpm

Blood Pressure
mm Hg

Control

Valsalva

Sympathetic Neurocirculatory Failure

Adapted from D. Goldstein
103 Consecutive patients – 10 with confirmed autoimmune disorders associated with autonomic neuropathy

- Sjogrens: 20%
- SLE: 20%
- Behcets: 10%
- Adult Stills: 10%
- Undiff. CTD: 30%
- Sarcoid: 10%

SLE, systemic lupus erythematosus; Undiff CTD, undifferentiated connective tissue disease
Ongoing discovery of auto-antibodies related to dysautonomia

Autoimmune basis for postural tachycardia syndrome.

Wang X1, Liu T2, Cheung R1, Kwong J1, Zhou G1, Li F1, Wang Y3, Fan L1, Ho PL1, Leung HC, Yip D1

Abstract

BACKGROUND: Patients with postural tachycardia syndrome (PTS) have exaggerated orthostatic tachycardia often following a viral illness, suggesting autonomic dysfunction. In this study, we aimed to identify autoantibodies and evaluate their role in the pathophysiology of PTS.

METHODS AND RESULTS: We performed a retrospective analysis of 20 PTS patients and 10 healthy controls. Serum samples were analyzed using a panel of cardiac autoantibodies, including autoantibodies against cardiac myosin, a cardiac myosin-specific antibody, and autoantibodies against cardiac troponin I. The results showed that 17 of 20 PTS patients (85%) had positive autoantibodies, while only 2 of 10 healthy controls (20%) had positive autoantibodies. The positive autoantibodies were specific to cardiac myosin, and the levels of autoantibodies were significantly higher in PTS patients compared to healthy controls (P < 0.01).

CONCLUSIONS: These findings suggest that autoantibodies targeting cardiac myosin may play a role in the pathophysiology of PTS. Further studies are needed to elucidate the mechanisms underlying the development of autoantibodies in patients with PTS.
Autoimmune conditions causing SFNs (cont.)

- Diagnosis of Sjogren syndrome
- Antiphospholipid antibodies
- Celiac disease?
Use of “wearable devices”
Summary

- Disorders of the autonomic nervous system(s) can have many presenting features that cross organ systems and span multiple medical specialties
- Autonomic disorders are common
- Autonomic disorders can be assessed and “localized” based on clinical information.
Where can I go to learn more?

- American Autonomic Society
- Dysautonomia International
- The Dysautonomia Project - www.dysautonomiaproject.org
- *Principles of Autonomic Medicine v 2.0.* David S. Goldstein, MD, PhD

[https://neuroscience.nih.gov/ninds/Faculty/Profile/david-goldstein.aspx](https://neuroscience.nih.gov/ninds/Faculty/Profile/david-goldstein.aspx) → “Selected Publications” → “Download Publications”
Questions?
Thank you!