Disorders of the Autonomic Nervous System

3 Syndromes of Orthostatic Intolerance
Common practice encounters
The Autonomic Nervous System
General Role and Prominence

Three output systems govern behavior:

Somatomotor
  •  Full range of motor, sensory experience

Autonomic
  •  Moment to moment adaptations

Neurohumoral
  •  Sustained changes of state
CNS: Integration of Three Output System

Jaenig, W, 2006 The Integrative Action of The Autonomic Nervous System
Autonomic Nervous System

- Efferent and Afferent relationships with every organ system including hematological and immune systems

- Modulates or directs in some way every aspect of normal human behavior

- It is involved at some level in every human disease or disorder

- Essentially all medications used in neurology and psychiatry work exclusively by modulating autonomic functions or functions that are shared by autonomic and the other efferent systems
Specialized functions by region

Forebrain (Limbic System - cingulum, stria terminalis, amygdala, insula):
• Mood, anxiety, pain, fear, initiates actions at lower levels

Diencephalon (hypothalamus and preoptic area):
• Sleep, neuroendocrine control, homeostasis temp, osmoregulation, nutrition stress reaction, reproduction

Brain Stem:
• Cardiovascular, antinociceptive, respiratory, GI

Segmental Cord and Rhombencephalon all efferent and afferent links with organ systems of the body.
• Parasympathetic Brain Stem and S1-3
• Sympathetic: T1-L3
Peripheral Autonomic nervous system
Structure of Enteric Nervous System

Furness, J 2012 Nat Rev Gastroentero Hepatol
## Peripheral Nerve Fiber Classification

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Subtype</th>
<th>Diameter (microns)</th>
<th>Myelin</th>
<th>System</th>
<th>Function</th>
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<tbody>
<tr>
<td>A</td>
<td>alpha</td>
<td>6 to 22</td>
<td>Yes</td>
<td>Som-mot</td>
<td>Motor</td>
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<tr>
<td>A</td>
<td>beta</td>
<td>6 to 22</td>
<td>yes</td>
<td>Som-Sens</td>
<td>Proprioception</td>
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<tr>
<td>A</td>
<td>gamma</td>
<td>3 to 6</td>
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<td>Som-mot</td>
<td>Muscle tone</td>
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<tr>
<td>A</td>
<td>delta</td>
<td>1 to 4</td>
<td>Yes</td>
<td>Som-Sen</td>
<td>Pain, Temp</td>
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<tr>
<td>B</td>
<td>D</td>
<td>&gt; 3</td>
<td>Yes</td>
<td>Symp - Preg</td>
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<tr>
<td>C</td>
<td>a</td>
<td>.1 to 1.3</td>
<td>No</td>
<td>Aut-Postg</td>
<td>Aut Efferent</td>
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<tr>
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<td>b</td>
<td>.4 to 1.4</td>
<td>No</td>
<td>Aut-Eff</td>
<td>Aut-Afferent</td>
</tr>
</tbody>
</table>

Adapted from: Barde et al., Local Anesthesia, in Miller’s Anesthesia, Elsevier 7th edition 2009.
Etiologies of autonomic neuropathy

Acute
- Autoimmune ganglionopathy
- Paraneoplastic
  - Ganglionic AChR antibodies
  - Hu, CRMP5, VGKC, P/Q Ca++, PCA-2

Chronic
- Sensorimotor neuropathy (diabetes)
- Sjogren’s, SLE, RA
- Primary amyloidosis
  - TSH, B12, HgbA1c, EMG
  - ANA, Ro/La, dsDNA, RF
  - SPEP with IFE

Inherited
- Familial amyloidosis
  - Transthyretin sequencing, fat pad biopsy
- Fabry disease
  - β-galactosidase A assay
- HSAN
  - Genetic testing

Neurodegenerative
- Synucleinopathies (MSA, PD, PAF)
  - Parkinsonian features, neuroimaging

Toxic/infectious
- HIV, leprosy, Chagas disease
  - HIV, exposure history
- Medications, heavy metals
  - Drug history, heavy metal screen
1. **Neurocardiogenic (vasovagal syncope, faint):** Complete loss of consciousness due to transient global cerebral hypoperfusion of rapid onset, short duration and spontaneous complete recovery. (Stewart Pediatrics 2013; 131:968-980.)

2. **Postural Orthostatic Tachycardia Syndrome (POTS):** Chronic symptoms of orthostatic intolerance with tachycardia but not hypotension when upright. (Shondorf and Low Neurology 1993; 43 132-137).

3. **Orthostatic hypotension (OH):** Sustained reduction of systolic BP > 20mmHg or diastolic BP > 10 mmHG within 3 minutes of standing or HUT. (Freeman .et al Clin Auton Res 2011; 21: 69-72)
Normal Blood Volume Distribution

- Heart: 8%
- Pulmonary: 12%
- Capillaries: 5%
- Arterial System: 15%
- Venous System: 60%

Grubb, 2005 Circulation 111: 2997-3006
Postural Volume Stress

- Recumbent to orthostatic volume shift ~ 25%
- Arterial Resistance System
- Venous Compliance System

Grubb, 2005 Circulation 111: 2997-3006
Normal Response to Head Up Tilt

Figure 1
IOH upon standing. There is a short-lived decrease in BP (upper panel) and increase in HR (lower panel). The fall in BP is resolved within ~20 seconds. The patient experienced transient lightheadedness.
Syndrome 1: SYNCOPE

Transient self limited loss of consciousness, usually with fall, onset rapid, recovery spontaneous and complete, prompt, due to transient global cerebral hypoperfusion due to blood pressure control

GENERAL MECHANISMS

- Cardiac Rhythm
- Cardiac structure
- Neurally mediated: Aortic, Carotid Baroreceptor Surge
Head Up Tilt with Syncope

**Fig 1.** Responses of heart rate (left panels) and systolic blood pressure (right panels) to HUT in representative control subjects and patients with syncope. Onset of HUT is indicated by an arrow, as is the time that the patient is made supine. The abscissa has units of heart beats, which can be converted to absolute time by multiplying by local mean heart rate. **Upper panels** show response of a representative healthy control subject who did not faint during tilt. There is a modest increase in heart rate by approximately 20 beats/min and essentially no change in systolic blood pressure throughout HUT. **Lower panels** show response of a representative control patient with syncope who experienced a simple faint during tilt testing. Initial blood pressure and heart rate are similar to those of a healthy control subject but fall abruptly and in near synchrony many minutes into the study and are restored by recumbency. Healthy control subjects who fainted during HUT had patterns indistinguishable from those of patients with syncope who fainted during HUT.

Syncope and Medical Resources

- 1-2 million per year
- 1% EW visits, 30-60% of these admitted. 1.3% of all hospitalizations in US.
- Annual Costs 24 billion dollars: enormous drain on resources and finance for utilization.
On the Spot Management Decisions

- Potential life threatening causes
- Not symptomatic when seen
- No evidence that admission influences outcome
- Rx generally follows from sorting out mechanism
Prevalence and triggers of syncope in medical students

- Pediatric age group: strongly weighted to reflex syncope
- 40-50 per female med students
- Peak incidence about 15 years old
- Family hx strong
- Seizures less than 1% and cardiac even less than seizure

Ganzeboom et al 2003 Am J Cardio 91:1006-1008
Syncope as CC in Office of Dutch General Practitioner

Table 1  Typical reflex syncope triggers

- Prolonged standing, especially in combination with warm temperature, confined spaces, or crowding (“church syncope”)
- Emotional circumstances, pain (for example, venepunctures, immunisation, sight of blood)
- Fasting, lack of sleep, fatigue, menstruation, illness with fever
- Micturition
- Early after intense exercise
- Hyperventilation and straining (self induced syncope)
- Stretching, coughing
- Standing quickly, arising from squat
- Rapid weight loss
- Certain medications, alcohol, and illicit drugs (must be distinguished from intoxication)

Wieling et al., Heart 2004;90:1094–1100
Management of Syncope

- Sensible Precautions in activities
- Salt tablets and or intake with salt
- Generous fluid intake
- Florinef: 0.1- 0.3 mgm/day
Orthostatic Intolerance Presenting as Chronic Fatigue Syndrome

Definition and Features of CFS

- A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest

- Postexertional malaise*

- Unrefreshing sleep*

- Cognitive impairment* OR Orthostatic intolerance

*Patients should have symptoms at least half of the time with moderate, substantial, or severe intensity.

Chronic Fatigue Syndrome

30-40 %: underlying POTS

10-20 %: Underlying ANS PNS or rhombencephalic disorder or renin deficit

SYNDROME 2: POTS: Children and Adolescents

Chronic symptoms of orthostatic intolerance with tachycardia but not hypotension when upright

- Must have OI SYMPTOMS at least 50% of time standing up

- HR with HUT: = or >

- 130 BPM age 13 or younger

- 120 BPM for 14 or older

Singer et al., 2012 J Peds 160: 222-6
Postural Orthostatic Tachycardia Syndrome

Response to HUT

Transcranial Doppler

Day-to-Day Symptoms of OI
+
Sustained Excessive Tachycardia
(without Hypotension)
Adults $\Delta > 30$ or HR $> 120$ beats per minute
within 10 minutes Adolescent $\Delta > 43$
+
Concurrent Symptoms of OI
during testing

Improved by Recumbence

![Graphs showing heart rate (HR) and mean arterial pressure (MAP) during postural tilt test.](image)

FIGURE 4
A representative POTS patient's data. HR (top panel) increases excessively without significant change in mean arterial pressure (MAP, bottom panel) change during a tilt test.

![Graphs showing cerebral blood flow (CBF) during postural tilt test.](image)

FIGURE 2
Decreased CBF measured by transcranial Doppler ultrasound occurs during a VVS (shown in the upper panel) and in POTS (shown in the bottom panel). During VVS, CBF declines gradually at first and then more abruptly as the patient acutely loses consciousness. In POTS, CBF is fairly uniformly reduced; there is no loss of consciousness, although lightheadedness is typical.

Stewart. Pediatrics 2013;131:968–980
Background Symptoms

- Fatigue, some w/u mitochondrial disorder. Rarely indication of such.
- Sleep disorder
- GI dysmotility
- Mood, anxiety as background for profound disability
Management

- Compression stockings, exercise
- Midodrine, Florinef, Salt
Syndrome 3: Orthostatic Hypotension

Sustained reduction of systolic BP > 20mmHg or diastolic BP > 10 mmHG within 3 minutes of standing or HUT
AAG: Acute panautonomic neuropath + acute pandysautonomia = autoimmune autonomic neuropathy

- Acute or subacute (peak by 3 months)
- Widespread spread autonomic failure
- Relative or complete sparing of somatic functions
Clinical Profile

- Young previously healthy
- Female 65%
- 75 % combination Psymp and symp
- Enteric dysfunction
- Variants: primarily cholinergic without OH; only GI in minority.
- Antecedent viral > 50% Also HSV, EBV
- Usual peaks days acute or 3-4 weeks subacute though some reported more gradual

Presentation

- OH, GI each > 70%

- Impaired erection, voiding

- Fixed heart rate with OH, decreased BP > 40% and loss of Valsalva phase II and IV i.e. components that strongly reflect symptoms on resistance vessels

- Plasma NE generally decreased

- About 50% AAG have AChR α3-subunit ab – nicotinic

- Level correlates with severity and improvement.
Orthostatic Hypotension

Figure 3
NOH: mean arterial pressure (MAP, top panel) and HR (bottom panel) are shown during a standing test. The BP begins to decrease immediately upon standing and continues to decrease until the patient is supine. HR increases by only a small amount despite hypotension.

Stewart. Pediatrics 2013;131:968–980
Treatment

- Mestinon
- IVIG
- Plasma exchange
- Immune suppression
- Steroids
Dopamine β-hydroxylase Mutation
Norepinephrine Transporter Defect

• Failure of NE mediated transmission

• Intractable postural hypotension

Robertson et al., Hypertension 1991;18:1-8
The opposing coach gave him the game ball today despite losing. Below is a picture of him holding his home run baseball. He also singled in the game.
Bibliography