Orthostatic Intolerance (OI) 
In the Young 
(orthostasis = standing) 
(OI = Can’t remain standing)
Gravitational Blood Distribution in Man and Beast

Unconstrained Pooling Causes Rapid Loss of BP
Circulatory Responses to Orthostasis

- Physical forces (muscle/abd – resp pump)
- Vascular structure and Blood volume
- Vascular regulation of O₂ Delivery
  - **Rapid**
    - ANS–Sympathetic/Parasymp
    - Myogenic
    - Flow Mediated
  - **Slower**
    - Setting the tonic milieu – NO/Ang
    - autocrine, paracrine, endocrine
    - Metabolic
    - Gene expression -> Epigenetics

Most of OI=
Abnormalities in adrenergic regulation and the modulation of adrenergic vasoconstriction in humans
Normal Circulatory Response to Orthostasis

![Graph showing the normal circulatory response to orthostasis. The graph illustrates changes in heart rate, relative stroke volume, relative cardiac output, blood pressure, and relative total peripheral resistance over time. The x-axis represents time in minutes (0 to 40), and the y-axis represents various quantitative measures.](image-url)
Impose Orthostatic Stress

~Model for Standing
↓Skeletal Muscle Pump ≠ 100% Syncope in Syncopizers

http://www.standingwave.ca/Support.html

LBNP=Surrogate Hemorrhage
Orthostatic Intolerance: defined by inability to tolerate the upright posture relieved by recumbence

- Loss of Consciousness
- Lightheadedness-Dizziness
- Neurocognitive Deficit
- Headache
- Fatigue – worst post-ictal
- Orthostatic Hypotension/Hypertension
- Weakness – peripheral malperfusion?
- Nausea/abdominal pain
- Sweating, tremulousness
- Exercise Intolerance

Cerebral perfusion abnormalities despite cerebral autoregulation

↓↑ Adrenergic vasoconstriction

Parasympathetic

↓↑
Variants of Orthostatic Intolerance

• Initial Orthostatic Hypotension
• Gravitational Deconditioning
• Orthostatic Hypotension
• Chronic Orthostatic Intolerance
  Postural Tachycardia Syndrome (POTS)
• Other
• Postural Vasovagal Syncope
• Newer variants – Hyperpnea, Cerebral Dysreg
Initial Orthostatic Hypotension

Graph showing changes in arterial pressure (AP), heart rate (HR), blood pressure (BP), and total peripheral resistance (TPR) before and after standing. The graph illustrates the decrease in blood pressure and other cardiovascular variables during orthostatic hypotension.
Gravitational Deconditioning

- Reduced blood volume
- Cardiovascular remodeling
- Different Regional blood volume redistribution
- Reduction in the response to norepinephrine/MSNA (and other pressors)
Orthostatic Hypotension (OH)

• OH is defined as a sustained reduction of systolic BP > 20 mmHg or diastolic BP > 10 mmHg within 3 min of standing or head-up tilt to ≥60°

• Non-neurogenic OH Drugs,
  • hypovolemia (pheochromocytoma, Addison Disease)

• Neurogenic OH is identified with Autonomic vasoconstrictor failure due to inadequate release of norepinephrine from sympathetic vasomotor neurons.
Chronic Orthostatic Intolerance: Postural Tachycardia Syndrome (POTS)

Day-to-Day Symptoms of OI

- Excessive Tachycardia (without Hypotension)
  - Adults Δ>30 or HR>120bpm within 10min
  - Adolescent – Δ>43
    (IOH a confound)?

Concurrent Symptoms of OI during testing

Improved by Recumbence

What’s This?

Heart Rate (BPM)

Blood Pressure (bpm)

Tilt up
Tilt down

HR
BP

IOH
Well, so what! Maybe POTS patients Faint?

Incremental tilt

[Survival Plot Image]
The Tachycardia of POTS

• Sinoatrial Node Tachycardia
  • Hypovagal POTS Parasympathetic due to cholinergic and nitrergic (NO) mechanisms. Channelopathy.
  • “Hyperadrenergic POTS” (↑adrenergic activity)
    • Increased sympathetic nerve activity
    • Increased peripheral transduction (NET, NPY, receptors, β-1 receptors, Ang, NO deficit)
    • Postural Hyperpnea – Hypocapnic sympathoexcitation
The Tachycardia of POTS

- **Reflex (Neuropathic)** Central Hypovolemia with baroreflex mediated tachycardia (intact cardiac ANS)
  - Absolute Hypovolemia
  - Regional Redistribution “Neuropathic POTS”
    - ↓ regional adrenergic vasoconstriction
      - Legs
      - Splanchnic
Neuropathic - Splanchnic Blood Pooling

Control

POTS

Percent Change in Computed Blood Volume

Thorax

Splanchnic

Pelvic

Leg

*
# POTS Factoids

<table>
<thead>
<tr>
<th>Female</th>
<th>Rx Beta Blocker? $\alpha_1$ agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Inflammation</td>
<td>Volume load, fludrocortisone</td>
</tr>
<tr>
<td>EDS</td>
<td>Acetylcholinesterase Inhibitors</td>
</tr>
<tr>
<td>Defects in Cerebral Autoregulation</td>
<td>AT1R antagonists</td>
</tr>
<tr>
<td>Cognitive Deficits/Exercise Intolerance</td>
<td>Statin drugs</td>
</tr>
<tr>
<td>Association with low BMI</td>
<td>Water Palliation</td>
</tr>
<tr>
<td>BP maintained</td>
<td>Salt? – in very large amounts</td>
</tr>
<tr>
<td>Variable pale appearance</td>
<td>IV saline/oral rehydration – yes</td>
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Syncope

Transient loss of consciousness and postural tone due to global cerebral hypoperfusion and characterized by rapid onset, short duration, and spontaneous recovery.

Often the result of systemic hypotension

Very Common (~40%)
**Syncope due to orthostatic hypotension**

Primary autonomic failure:
- pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia

Secondary autonomic failure:
- diabetes, amyloidosis, uraemia, spinal cord injuries

Drug-induced orthostatic hypotension:
- alcohol, vasodilators, diuretics, phenothiazines, antidepressants

Volume depletion:
- haemorrhage, diarrhoea, vomiting, etc

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**Cardiac syncope (cardiovascular)**

Arrhythmia as primary cause:

Bradycardia:
- sinus node dysfunction (including bradycardia/tachycardia syndrome)
- atrioventricular conduction system disease
- implanted device malfunction,

Tachycardia:
- supraventricular
- ventricular (idiopathic, secondary to structural heart disease or to channelopathies)

Drug induced bradycardia and tachyarrhythmias

Structural disease:
Cardiac: cardiac valvular disease, acute myocardial infarction/ischaemia, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors, etc.), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valves dysfunction

Others: pulmonary embolus, acute aortic dissection, pulmonary hypertension
Syncope (not so nasty?)

**Reflex (neurally-mediated) syncope**

Vasovagal:
- mediated by emotional distress: fear, pain, instrumentation, blood phobia
- mediated by orthostatic stress

Situational:
- cough, sneeze
- gastrointestinal stimulation (swallow, defaecation, visceral pain)
- micturition (post-micturition)
- post-exercise
- post-prandial
- others (e.g., laught, brass instrument playing, weightlifting)

Carotid sinus syncope

Atypical forms (without apparent triggers and/or atypical presentation)

But then there is asystolic syncope.

**EKG**

**AP**

And being in harm’s way.
Postural Vasovagal Syncope in the Young

Mechanism Remains Elusive

Heart Rate (bpm)

Tilt Up

Tilt Down

MAP (mmHg)

Slow ↓ BP

Rapid ↓ BP
Hemodynamics are Similar to Hemorrhage with impaired Adrenergic Vasoconstriction


Reduced response to NE reversed with NOS inhibitors


![Graph showing hemodynamic changes during hemorrhage](image-url)
How do you explain Stage 2 gradual hypotension

MAP = CO x SVR
VVS in the Old vs Young: ↓CO vs ↓TPR
Excessive ↓ Central Blood Volume ↑ Splanchnic Blood Volume

**Thorax**
- Fainters
- Healthy

**Splanchnic**
- Fainters
- Healthy

**Pelvic**
- Fainters
- Healthy

**Leg**
- Fainters
- Healthy
Or even
How do you explain Hypotension-Bradycardia?

Hyperpneic Hyperventilation
Loss of Cerebral Autoregulation
Baroreflex Failure

We do not know the mechanism
### VVS Factoids

| Female 2:1 | Adult studies of beta blocker, fludrocortisone not work |
| Must R/O Cardiogenic (is not OI) but most exercise syncope is VVS. ?seizure | Volume load needs to be huge |
| VVS is not deadly unless in harm’s way | If non-asystolic use physical countermeasures + water |
| Iron/ferritin contribution | These require recognition of immanent faint. |
| Athlete > Sedentary | Don’t stand! |
| Diagnosis by characteristic features: prodromal, ictal, post | No prodrome/injury cardiogenic or asystolic VVS. |
| Tilt ?correlation with real life? | Prolonged or very frequent |
| Variable pale appearance | |
Arterial Resistance first↑, then↓ in VVS

TPR

Splanchnic

Pelvic

Leg

Arterial resistance trunk (mm Hg)

Arterial resistance splanchnic (mm Hg)

Arterial resistance pelvic (mm Hg)

Arterial resistance leg (mm Hg)
Reflexes from Hypercontractile Underfilled Heart?


- This mechanism was proposed despite the fact that any stimulus could only be short lived and baroreceptors would immediately be unloaded. Hainsworth R. Syncope: what is the trigger? Heart. 2003;89:123-124.

- Relatively few afferent nerves were excited in the original Oberg and Thoren hemorrhaged cat model. Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of the caval veins in the cat. A possible cause of the vasovagal reaction. Acta Physiol Scand 1972;85:164–73.


Sympathetic Withdrawal:
↓ MSNA at Faint Sufficient but not Necessary

**Decreased MSNA in Syncope**


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**Fig. 1.** Mean blood pressure (MBP) (A), heart rate (HR) (B), and muscle sympathetic nerve activity (MSNA) (C) during head-up tilt in tilt-tolerant (TT) and tilt-syncope (TS) patients. Mean time to syncope was 15.4 ± 2 min. In TT patients, MSNA increased for the duration of tilt and MBP did not fall below baseline levels until 20 min of tilt. In TS patients, MSNA initially increased during the first minute of tilt, but decreased to baseline levels at least 7 min before syncope. Values for MBP, HR, and MSNA from 7 min before syncope are plotted retrogradely from 15-min tilt time. bpm, Beats per minute; bs/min, bursts per minute. *Differences from baseline in TS group; #differences from baseline in TT group.