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Hardware Vs Software?

**Autonomic Failure**
- Orthostatic hypotension
- Heat intolerance with lack of sweating
- Dizziness/Lightheadedness while upright
- Syncope
- Urinary incontinence
- Constipation
- Nausea/bloating
- Difficulty concentrating while upright

**Autonomic Dysregulation**
- Tachycardia/palpitations with upright posture
- Heat intolerance
- Dizziness/Lightheadedness while upright
- Syncope
- Constipation or Diarrhea or both
- Nausea/bloating
- Difficulty concentrating while upright
Standing Involves Initial Reductions in BP

- Standing causes blood pooling in the lower part of the body\(^1,2\)
- Physiologically, standing is followed by a rapid, transient reduction in mean arterial pressure (MAP) (A), total peripheral resistance (TPR) (B), and cerebral perfusion (C)\(^3\)

BP = blood pressure; \(V_{\text{mean}}\) = mean flow velocity in middle cerebral artery.

Anatomy of Baroreflex

Low and Singer. Lancet 2008
Case 1

- 67 year old pastor with dizziness and constipation for 2 years. Dizziness improves on lying down.
- His voice has changed over time.
- He has worsened memory.
- He does not tolerate the heat.
- He has increased urinary frequency.
- He is noted to have decreased facial movement, increased muscle tone and rigidity without tremor.
- Orthostatic vital signs reveal a drop over 60 mm systolic when standing without significant heart rate increase.
Multiple System Atrophy (MSA)

- Degenerative disorder by definition, affecting at least 3 systems (autonomic, basal ganglia (producing Parkinsonian symptoms), ataxia (cerebellum) in any order.
- Cerebral peduncles causing spasticity, brisk reflexes can occur
- Lower motor neuron (ALS) involvement can also occur.
- May present with ataxia (olivopontocerebellar atrophy)
- Prognosis is poor: Most patients die within seven years of diagnosis
MSA

- Catecholamines typically normal supine, but do not show rise with standing
- Typically significantly orthostatic
- Bladder involvement almost always
- Parasympathetic/Cholinergic symptoms common
- QSART typically normal
- Parkinsonism typically does not respond to levodopa
Pure Autonomic Failure

- Originally described as Bradbury-Eggleston Syndrome in 1925
- A-Synuclein deposits found in autonomic ganglia
- Typically have history of REM-Behaviour Disorder
- Patients typically have low smell and peripheral autonomic deficits
- Increased risk of late development of PD and LBD
Parkinson’s Disease

- One of the most common causes of neurogenic orthostatic hypotension
- Can have autonomic symptoms prior to presentation or any time during course of disease
- Autonomic failure is due to peripheral autonomic nerve degeneration.
# Approach to Treat Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Step 1: Eliminate Iatrogenic Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-hypertensives during the day</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Alpha-blockers for BPH</td>
</tr>
<tr>
<td>Heavy Meals</td>
</tr>
</tbody>
</table>
## Approach to Treat Orthostatic Hypotension

### Step 2: Nonpharmacological Measures

<table>
<thead>
<tr>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Fluid Intake, 16 oz. tap water</td>
</tr>
<tr>
<td>Avoid standing quickly or standing motionless</td>
</tr>
<tr>
<td>Abdominal binder or waist-high pressure stockings</td>
</tr>
<tr>
<td>Avoid supine position during the daytime</td>
</tr>
</tbody>
</table>
Hemodynamic Effects of 16oz of Water
## Approach to Treat Orthostatic Hypotension

### Step 3: Improve Central Volume

- **Treat anemia even if mild**
- **Fludrocortisone 0.1-0.3mg every day with increased salt intake**
- **Add NaCl tablets 1 gram with meals if necessary**
### Approach to treat orthostatic hypotension

**Step 4: Short acting pressor agents PRN**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midodrine</td>
<td>2.5-10mg TID</td>
<td>CC</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>30-60mg TID</td>
<td>CC</td>
</tr>
<tr>
<td>Droxidopa</td>
<td>100-600 TID</td>
<td>CC</td>
</tr>
</tbody>
</table>
Treatment of Orthostatic Hypotension

In the past 20 years, only two FDA approved drugs
“PRESSOR AGENTS”

- **Midodrine**, $\alpha$-1 adrenergic agonist. Direct vasoconstrictor
  
  In 2010, the FDA requested to remove it from the market because of lack of evidence supporting clinical benefit in post-marketing studies.

- **Droxidopa**, synthetic norepinephrine precursor
  
  Long-term efficacy and safety still under investigation.
  
  Limited use because of prohibited cost
  
  (~$5,000/30-day supply)
Pharmacologic effect of Atomoxetine Norepinephrine Transporter Inhibitor

Atomoxetine commercially available for the treatment of attention deficit hyperactivity disorder in children and adults.
Atomoxetine Increased Blood Pressure in Multiple System Atrophy

N=21 patients (10 MSA, 11 PAF)

2X2 crossover design

Intervention: 18 mg atomoxetine (single dose)

Endpoint: Seated blood pressure
What is the Most Appropriate Action to Improve Orthostatic Hypotension

A. Use an abdominal binder
B. Use a volume expander
C. Use a pressor agent
D. Use a combination of measures
• His supine blood pressure is 179/84
• Does that change your response?
• A. No it does not
• B. Yes it does
What Choice Would You Not Consider For This Patient

• A. Midodrine
• B. Fludrocortisone
• C. Pyridostigmine
• D. Droxidopa
• E. Atomoxetine
Supine Hypertension

• ~50% of patients with primary autonomic failure exhibit paradoxic supine hypertension
  o SBP≥150mmHg or DBP≥90mmHg
• Often goes undetected
  o BP measured in seated position
  o Automated 24hr BP monitoring helpful
• Increases end organ damage and risk of acute CV events
  o Limits pressor agents
  o Induces nocturnal diureses
Stepwise Approach to Supine Hypertension

**Step 1: Education and Avoidance**

<table>
<thead>
<tr>
<th>Instruct patients about OTC medications with pressor effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid fluid intake at bedtime</td>
</tr>
<tr>
<td>Avoid using elastic stockings when supine</td>
</tr>
<tr>
<td>Avoid pressor agents before bedtime</td>
</tr>
</tbody>
</table>
### Stepwise Approach to Supine Hypertension

#### Step 2: Nonpharmacologic measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raise the head of the bed up 6-9 inches</td>
<td></td>
</tr>
<tr>
<td>Rest on a semirecumbent chair with feet on the floor during the day</td>
<td></td>
</tr>
<tr>
<td>Encourage snack before bedtime</td>
<td></td>
</tr>
<tr>
<td>Allow minimal alcohol consumption before bedtime</td>
<td></td>
</tr>
</tbody>
</table>
Stepwise Approach to Supine Hypertension

**Step 3: Pharmacologic Measures**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates, transdermal nitroglycerin</td>
<td>(0.1-0.2mg/h, removed in the morning)</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>(50mg)</td>
</tr>
<tr>
<td>Short-acting calcium blocker, nifedipine</td>
<td>(30mg)</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>(2.5mg)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>(0.1mg), early in the evening</td>
</tr>
</tbody>
</table>
Case 2

• 25 year old female with history of headaches, presents with dizziness, lightheadedness while standing, numbness and tingling in fingers and feet
• History of irritable bowel syndrome, fibromyalgia, chronic fatigue
• Heart rate and palpitations when standing, notes on fitbit heart rate over 160 when standing
Postural Tachycardia Syndrome (POTS)

- Commonly affects young to middle aged women
- Multiple previous monikers including “soldier’s heart”, “mitral valve prolapse”, etc.
- No defined cause
- By definition require a significant heart rate elevation of at least 30 bpm on standing without hypotension
- Orthostatic symptoms of dizziness, palpitations, fatigue, “brain fog” and difficulty concentrating when standing present
- Often have mild GI symptoms and frequent diagnosis of irritable bowel syndrome, fibromyalgia, and other “software” diagnoses
POTS: Treatment Approaches

• Increase Blood Volume
  o Oral Water
  o Increase Salt (diet vs. tablets)
  o Fludrocortisone
  o IV Saline
  o Acute DDAVP-H₂O

• Hemodynamic Agents
  o Propranolol
  o Midodrine
  o Clonidine/α-Methyldopa
  o NET Inhibitors…can be a double-edged sword

• Exercise
IV Saline (1L) Acutely Decreases Orthostatic Tachycardia

G Jacob et al. Circulation 1997;96:575-580
Midodrine Decreases Orthostatic Tachycardia...a little bit.

Beta-Blockers in POTS

• PRO
  o Intuitively appealing
    • High HR -> Lower it

• CON
  o Stewart et al. studied IV esmolol and found that it DID NOT improve orthostatic tolerance
  o Many patients report “intolerance to beta-blockers”
Propranolol 20mg lowers Orthostatic Tachycardia

SR Raj et al. Circulation 2009;120:725-734
Propranolol Improves Symptoms…

Symptoms

Propranolol Improves Symptoms…

Propranolol
Placebo

Time Post Dose

Symptoms (a.u.)

Prec Pre 2H 4H

P_{int} = 0.04

SR Raj et al. Circulation 2009;120:725-734
…but Less is More

SR Raj et al. Circulation 2009;120:725-734
Inhibition

• Pyridostigmine
  o Peripheral AChEI
  o Increases availability of synaptic ACh
  o Ganglionic Nicotinic Receptor
    • ↑ SNS & ↑ PNS
  o Postganglionic Muscarinic Receptor
    • ↑ PNS

• Might decrease tachycardia in POTS
**Acetylcholinesterase Inhibition**

### Standing Heart Rate

<table>
<thead>
<tr>
<th>Time Post Dose</th>
<th>Heart Rate (bpm)</th>
<th>Pyridostigmine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4H</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **P=0.001**
- **P=0.160**
- **P<0.001**

### Symptoms

<table>
<thead>
<tr>
<th>Change in Symptom Score (au)</th>
<th>Pyridostigmine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.025</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SR Raj et al., Circulation 2005;111:2734-2740
Norepinephrine Transporter Inhibition in POTS

SR Raj et al., AAS Presentation (2010)
Norepinephrine Transporter Inhibition

Orthostatic Change

Symptoms: 0 to 2h

Δ Heart Rate (bpm)

Δ Symptoms Score (a.u.)

Pre 1H 2H 3H 4H

Atomoxetine Placebo

P_int = 0.001

P = 0.028

SR Raj et al., AAS Presentation (2010)
POTS: Treatment Approaches

• Increase Blood Volume
  o Oral Water
  o Increase Salt (diet vs. tablets)
  o Fludrocortisone
  o IV Saline
  o Acute DDAVP-H₂O

• Hemodynamic Agents
  o Midodrine
  o Propranolol
  o Pyridostigmine
  o Clonidine/α-Methyldopa
  o NET Inhibitors…can be evil

• Exercise
Exercise in POTS

• Historically
  o “good thing to do”
  o Many patients could not/would not
    • excessive fatigue (~days) and intolerance
  o Anecdotally, those patients that did exercise did better over time
    • Cause/effect vs. selection bias

• Now
  o Emerging data on effects of exercise training in POTS from Vienna, Dallas & Mayo…
Exercise Study in POTS - Design

3 months of exercise training

- Cardiac MRI
- Maximal Exercise Test
- Blood Volume Measurement
- 45-min 60° Upright Tilt
- 3 months of exercise training
Exercise in POTS - Summary

• Short-term exercise training in POTS
  o Increases fitness levels
  o Increases blood volume
  o Cardiac Remodeling
  o Normalizes Sympathetic Activity
  o Decreases Orthostatic Tachycardia

Qi Fu et al., JACC 2010;55:2858-68
Case 2:

• What would be your first treatment option?
• A. Midodrine
• B. Exercise
• C. Propanolol
• D. Fludrocortisone
• E. Two of the above
• F. None of the above
Case 2:

• Answer:

• F. None of the Above: First identify medications which could worsen POTS, increase volume with oral hydration and salt

• A second step would be adding low dose propranolol and encouraging exercise. We typically do this simultaneously.
Conclusions

• Start with non-pharmacologic interventions as needed.
• Multiple strategies may be needed for some patients.
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In MSA, Neurodegenerative Lesions are in Central Autonomic Pathways

Central Autonomic Failure (Multiple System Atrophy, MSA)
Normal Norepinephrine levels

Courtesy of Gamboa A.
Vanderbilt University Medical Center
In PAF, Lesions are in Peripheral Autonomic Pathways