Postural orthostatic tachycardia syndrome: diagnosis and Management

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POTS= Postural Orthostatic Tachycardia Syndrome

• Defined as:
  o presence of symptoms of orthostatic intolerance
  o Increase in heart rate (HR) of 30 points or absolute HR of over 120 bpm after standing less than 10 minutes or with head up tilt table testing
    • “Adolescent criteria” = 35-40 point increase?
  o Not associated with prolonged bed rest or with use of medications known to reduce vascular tone
POTS

- Note that definition does not include criteria involving blood pressure!!!
  - Variability in postural BP response observed in patients
- > 500,000 people affected by POTS in the U.S.
  - 25% are unable to work or attend school full time
  - Frequently misdiagnosed as anxiety or depression, conversion disorder
  - Onset in many patients is often after an acute event (mononucleosis, head trauma, etc.)
  - High frequency of symptoms in Ehlers-Danlos Syndrome and various metabolic diseases (more frequently one aspect of a pervasive dysautonomia syndrome)
What we see…

- Vital sign changes are a pathologic and **paradoxical neural reflex**
- Occurs in people of all ages, both healthy and chronically ill
- Can occur during either a sitting or standing position
  - In more severe cases of POTS associated with chronic disease states, blackouts and syncope can occur **lying down**
Features, cont.

• Blood pressure drops usually preceded by **prodromal symptoms:**
  o Weakness
  o Nausea
  o diaphoresis and flushing
  o light headedness
  o sense of impending darkness (“tunnel vision”)

• Followed by **signs/symptoms:**
  o tachycardia, pallor, abrupt bradycardia, diaphoresis, pupillary constriction
  o finally decreased cerebral perfusion resulting in **syncope.**
Normal Physiology

• Normally, from supine to upright position, up to one liter of venous blood is shifted from the thorax to the lower extremities.

• To preserve cerebral perfusion, baroreceptors in the carotid sinus and aortic arch reduce their inhibitory control of the vasomotor center of the medulla.

• Sympathetic tone is enhanced and parasympathetic tone is reduced (theoretically increasing vascular tone and increasing cardiac contractility).
Normal Physiology, cont.

• Reflexive increase in vasoactive substances such as catecholamines and vasopressin are released to increase cardiac contractility, heart rate, and vascular resistance.

• As a result, cerebral perfusion is maintained (and no one “blacks out”)

So what goes wrong???
What goes wrong???

- **Neuropathic POTS** = decreased vascular tone; impaired vasoconstriction causing compensatory tachycardia

- **Hyperadrenergic POTS** = Inappropriately elevated standing norepinephrine levels; tachycardia, hypertension, and hyperhidrosis
Abnormal Pathophysiology

• During the catecholamine state, with initial sympathetic discharge, there is increased cardiac contractility

• This, coupled with low ventricular volume from the decreased filling, triggers the cardiac mechanoreceptors
  o the cardiac mechanoreceptors are located in the base of both ventricles, especially the inferior wall
Pathophysiology, cont.

- Paradoxically and/or mistakenly, the mechanoreceptors and the receiving nuclei misinterpret this response to be a high volume/hypertensive state
  - this is thought to be the pathologic step in the vasovagal response
  - this has been confirmed with animal and human studies, and has been termed the “Bezold-Jarisch reflex”
  - CNS response to increase parasympathetic output, causing bradycardia and vasodilatation = SYNCOPE
POTS as a chronic state

- Additional symptoms seemingly unrelated to autonomic NS abnormalities
  - Anxiety and/or Depression
  - “Brain Fog”
  - Chronic Fatigue
  - Headaches
  - Exercise intolerance
  - Dysautonomia symptoms are increased in patients with autistic spectrum disorder
POTS as a chronic state

• Visceral pain and dysmotility:
  o 39% nausea
  o 18% Diarrhea, 15% Constipation, 15% abdominal pain
  o 9% Bladder symptoms (Mayo Clin Proc. 2007 Mar; 82(3):308-13.)

• Chronic fatigue and insomnia:
  o Chronic fatigue reported in 48%
  o Insomnia/Sleep disturbances in 36% (J Clin Sleep Med. 2011;7(2):204–210.)

• Headaches
  o Orthostatic headaches
  o Postural tachycardia in Chiari I malformation
Diagnostics

• Taking a good history → **review of systems** key to identify signs of pervasive autonomic dysfunction

• **Orthostatic BP and HR measurements**
  o Different methods—at least 3 measurements, 2 of which should be in upright position at different increments

• Examination findings:
  o Mydriasis
  o Evidence of venous congestion in extremities (Acral cyanosis)
  o Hypermobile joints
Tilt Table Testing

- Patient passively strapped to bed with several belts
- IV placed for fluid and medication access
- BP and ECG monitoring placed
- Room made to be warm and dark, low noise level (NOT play time!)

- Bed tilted to 60-70 degrees
  - Baseline monitoring x 20 minutes
  - Isuprel infusion started (0.5 micrograms/minute for 5-10 minutes, increase to 1 microgram/minute for another 5-10 minutes)
Tilt Table Testing

![Tilt Table Testing Image]

*Fig. 3 - Positive Tilt Table Test in patient with RVOT. BP: BP- blood pressure; HR: heart rate.*
Management: Conservative Measures

- **Hydration**
  - 80-100 ounces of fluid daily
  - General avoidance of caffeine
  - Caffeine may be useful for associated migraines, concentration problems

- **Sodium Intake**: 5-6 g of sodium daily

- **Dietary habits**
  - No skipping meals
  - Small, frequent meals to avoid pooling of blood in splanchnic vascular bed
  - Avoidance of high carbohydrate meals

- **Sleep**

- **Exercise:**
  - 30 minutes of aerobic activity 3 times per week
  - Daily resistance training, especially lower extremities
  - Water/Swimming
Conservative Management

• Stress management
  o Management of daily schedule to allow for rest periods
  o No “cramming” for exams, no pulling “all-nighters

• Management of provocative symptoms
  o PAIN
  o MIGRAINES
  o GASTROINTESTINAL DISTRESS PREVENTING ADEQUATE NUTRITION
  o HORMONAL DYSREGULATION
Management: Pharmacologic

• A large variety of drugs have been found to be “useful”
• Most are chosen based on the pathophysiology thought to be involved
• Overwhelming majority of agents came into popular use based on small studies, without placebo control, and had relatively short term follow-up
  o Anecdotal reports of success
  o “Off label” use of medications
Beta-Blockers

- **Beta-blockers:**
  - thought to block the early catecholamine induced inotropy in the presence of low ventricular filling volume, and decrease the stimulation of the mechanoreceptors
  - probably the most studied agent, although introduced as treatment in only 1989
  - data show conflicting results
  - Highest benefit is shown in patients with positive UTT only after isoproterenol provocation

  → Direct antagonism to catecholamine effect
Beta Blockers

• In patients not having UTT data, best response to beta blockers in my practice have had HR increases $\geq 30$ points with orthostatic testing with normal to borderline hypertensive postural blood pressure responses.
• Consider in comorbid migraines, anxiety states
• Agents used:
  o Metoprolol
  o Atenolol
  o Propranolol- crosses blood-brain barrier
  o Nadolol
  o Betaxolol- highest beta 1 selective activity
Fludrocortisone (Florinef)

- Mineralocorticoid analog (aldosterone): used in patients with adrenal insufficiency
- Acts on distal renal tubules to produce retention of sodium and excretion of potassium ions
- Low dose Fludrocortisone doses have powerful mineralocorticoid effects and minimize glucocorticoid effects
- Starting Dose: 0.1 mg PO daily, may increase to twice a day
Fludrocortisone (Florinef)

- Most effective in patients with baseline low blood pressures (SPB\(\leq 105\) mmHg), especially which drop with positional changes.
- Patient has failed to have signs of increased plasma volume despite salt supplementation.
- **Side effects:**
  - Headache
  - Swelling/edema
  - Hypokalemia
  - Hyperglycemia
  - Increased sweating
Midodrine (Proammatine)

• Oral vasopressor with short half life
  o Must be taken 3-4 times per day for sustained effect
  o Effects last only about 4 hours
  o Effects are improved with optimal intravascular volume status

• Directly impacts upright blood pressure with secondary effect on HR

• Side effects
  o Supine Hypertension (no doses given 3 hours before bed)
  o Scalp paresthesias (often diminish with time)
  o Pilomotor reactions--goosebumps
Midodrine (Proamatine)

- Best given in patients with evidence of neurogenic POTS, poor vascular tone
- Flushing in hot environments
- Flexibility of dosing: can give a “PRN” dose due to short acting properties
Pyridostigmine (Mestinon)

- Acetylcholinesterase inhibitor: inhibits the degradation of neurotransmitter acetylcholine
- Used in POTS with statistically significant improvement in HR and symptom burden in small series of 17 patients (Circulation. 2005 May 31;111(21):2734-40.)
- Study of 203 patients with POTS showed total of 43% with improved symptoms of orthostatic intolerance, including fatigue, palpitations and presyncope (Pacing Clin Electrophysiol. 2011 Jun;34(6):750-5)
Stimulants

• Similar Vasoconstrictive effects as Midodrine
• Elevation of BP, as well as HR!
• Added benefit of increased energy, concentration (treats “brain fog”)
• Negative effect on appetite
  o Ritalin
  o Adderall
  o Concerta
Management: SSRIs

- Selective serotonin reuptake inhibitors
  - Grubb et al. noticed through anecdotal observation that depressed patients with vasovagal syncope had substantial improvement of their syncope after SSRI Rx.
  - In animal models, has been shown to reduce CNS sympathetic activity and cause hypotension and bradycardia
  - There also may be suppression of the baroreceptor reflex
  - Theorized that SSRI’s blunt the cardiovascular response to changing serotonin levels by causing down regulation of receptors
Management: SSRIs

- Fluoxetine, sertraline, and nefazodone have been shown to improve symptoms in non-depressed patients in case controlled studies
  - Newer agents like Cymbalta are under investigation
  - Generally one of the least studied agents in this condition (off label use)
- Still used as 3rd or 4th line agent in pure POTS
  - May be used up front in chronic pain conditions associated with POTS
Influence of Hormones

- Irregular and painful menses are incredibly common in females with POTS, additional complications seen in female patients with EDS
- Pattern of worsening symptoms of dizziness and orthostatic intolerance with menses and breakthrough bleeding
  - Estrogens have effects on the renin-angiotensin system
  - Progesterone has smooth muscle relaxing effects, and is a natural diuretic!
Self-reported gynecologic abnormalities among patients with POTS and healthy controls.

Abbreviation: POTS, postural tachycardia syndrome.
Influence of Hormones

• GYN referrals often merited in young women with significant POTS and dysmenorrhea/metrorrhagia

• Goals:
  o Rule out underlying GYN pathology
  o Regulate hormonal fluctuations causing symptoms (dizziness, pain, nausea, migraines, etc.)

• Options:
  o Monophasic oral contraceptives
  o 3 month cycle oral contraceptives (e.g. Seasonale)
  o Depo-provera
  o Depo-provera + Progesterone supplement
Erythropoetin

- Used as a drug to augment red blood cell count
- Subcutaneous injection
- Found to be a potent vasoconstrictor in some patients
  - ONLY RECOMMENDED IN SEVERELY DEBILITATED PATIENTS
  - Risk of thrombosis/stroke with HCT > 50%
  - Risk of creating hypertension
  - OFF LABEL INDICATION ➔ OFTEN NOT COVERED BY INSURANCE PLANS
Overall Goals

• Get the day to day life habits solidified.
• Use orthostatic responses and items in the medical history to rule in/rule out potential pharmacologic therapies
• Understand (and be up front with patients) that your first agent may be: a.) the wrong choice, or b.) a partial solution due to multifactorial pathways causing POTS
• Be aware of other medical conditions which influence POTS and point your patients in the right directions!
Best Wishes, and
Thank you for coming!