Postural orthostatic tachycardia syndrome: diagnosis and Management

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POTS= Postural Orthostatic Tachycardia Syndrome

- Defined as:
  - presence of symptoms of orthostatic intolerance
  - **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?
  - 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**:
  - Weakness
  - Nausea
  - diaphoresis and flushing
  - light headedness
  - sense of impending darkness ("tunnel vision")
- Followed by **signs/symptoms:**
  - tachycardia, pallor, abrupt bradycardia, diaphoresis, pupillary constriction
  - 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???

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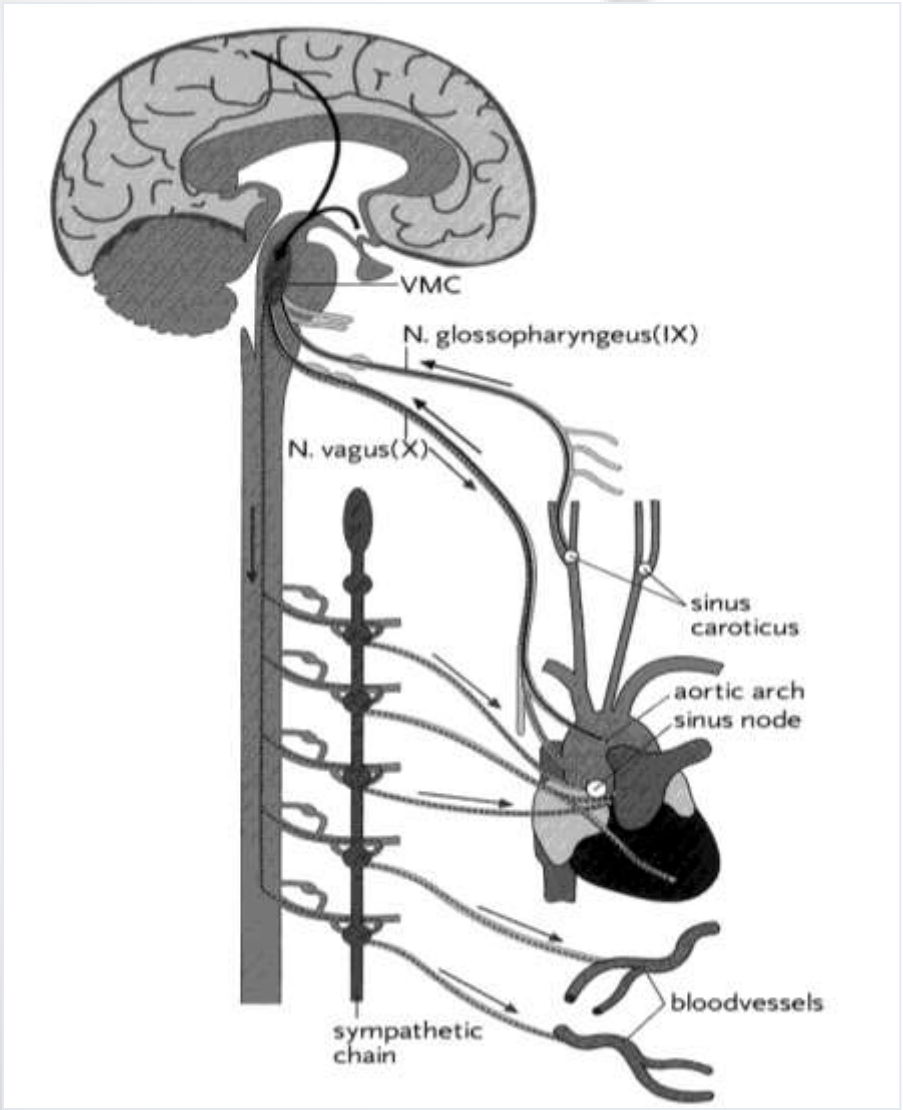


- **Neuropathic POTS**= decreased vascular tone; impaired vasoconstriction causing compensitory tachycardia
- **Hyperadrenergic POTS**= Inappropriately elevated standing norepinephrine levels; tachycardia, hypertension, and hyperhidrosis

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**
  - 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**:
  - 39% nausea
  - 18% Diarrhea, 15% Constipation, 15% abdominal pain
  - 9% Bladder symptoms (*Mayo Clin Proc. 2007 Mar; 82(3):308-13.)*
- **Chronic fatigue and insomnia**:
  - Chronic fatigue reported in 48%
  - Insomnia/Sleep disturbances in 36% (J Clin Sleep Med. 2011;7(2):204–210.)
- **Headaches**
  - Orthostatic headaches
  - 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**
  - Different methods—at least 3 measurements, 2 of which should be in upright position at different increments
- Examination findings:
  - Mydriasis
  - Evidence of venous congestion in extremities (Acral cyanosis)
  - 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

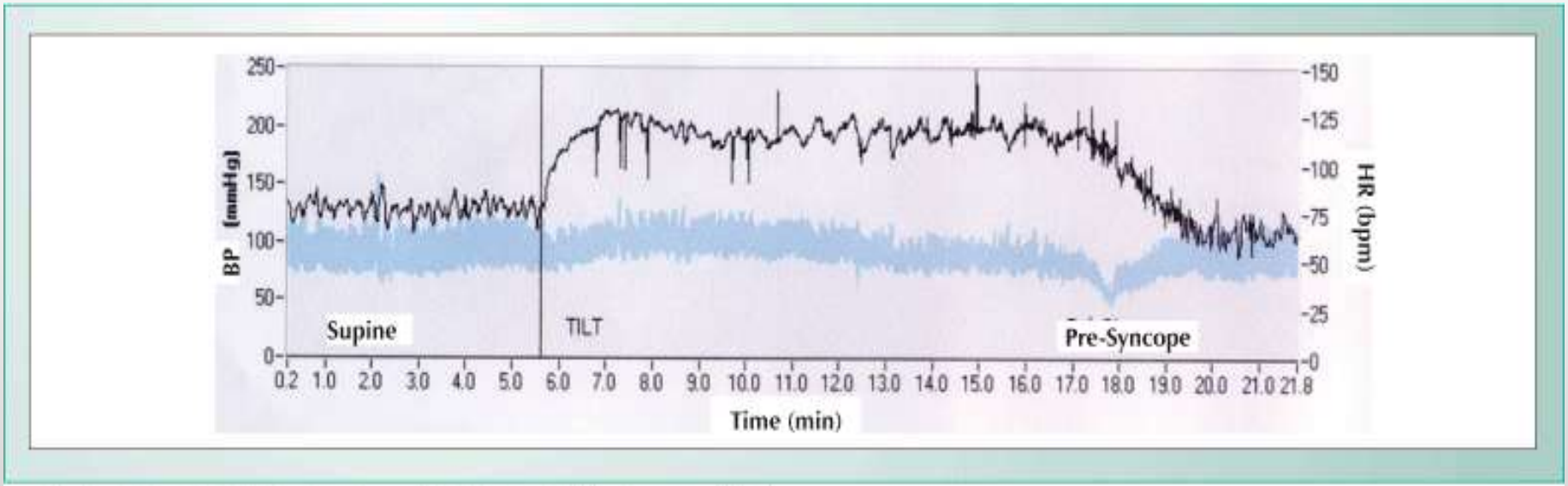


Fig. 3 - Positive Tilt Table Test in patient with RVOT PB. BP- blood pressure; HR- heart rate.

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
  - Management of daily schedule to allow for rest periods
  - No “cramming” for exams, no pulling “all-nighters
- Management of provocative symptoms
  - PAIN
  - MIGRAINES
  - GASTROINTESTINAL DISTRESS PREVENTING ADEQUATE NUTRITION
  - 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
  - Anecdotal reports of success
  - "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 >/= 30 points with orthostatic testing with normal to borderline hypertensive postural blood pressure responses.
- Consider in comorbid migraines, anxiety states
- Agents used:
  - Metoprolol
  - Atenolol
  - Propranolol- crosses blood-brain barrier
  - Nadolol
  - 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</= 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 (Proamatine)

- Oral vasopressor with short half life
  - Must be taken 3-4 times per day for sustained effect
  - Effects last only about 4 hours
  - Effects are improved with optimal intravascular volume status
- Directly impacts upright blood pressure with secondary effect on HR
- **Side effects**
  - **Supine Hypertension** (no doses given 3 hours before bed)
  - Scalp paresthesias (often diminish with time)
  - 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
  - Ritalin
  - Adderall
  - 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

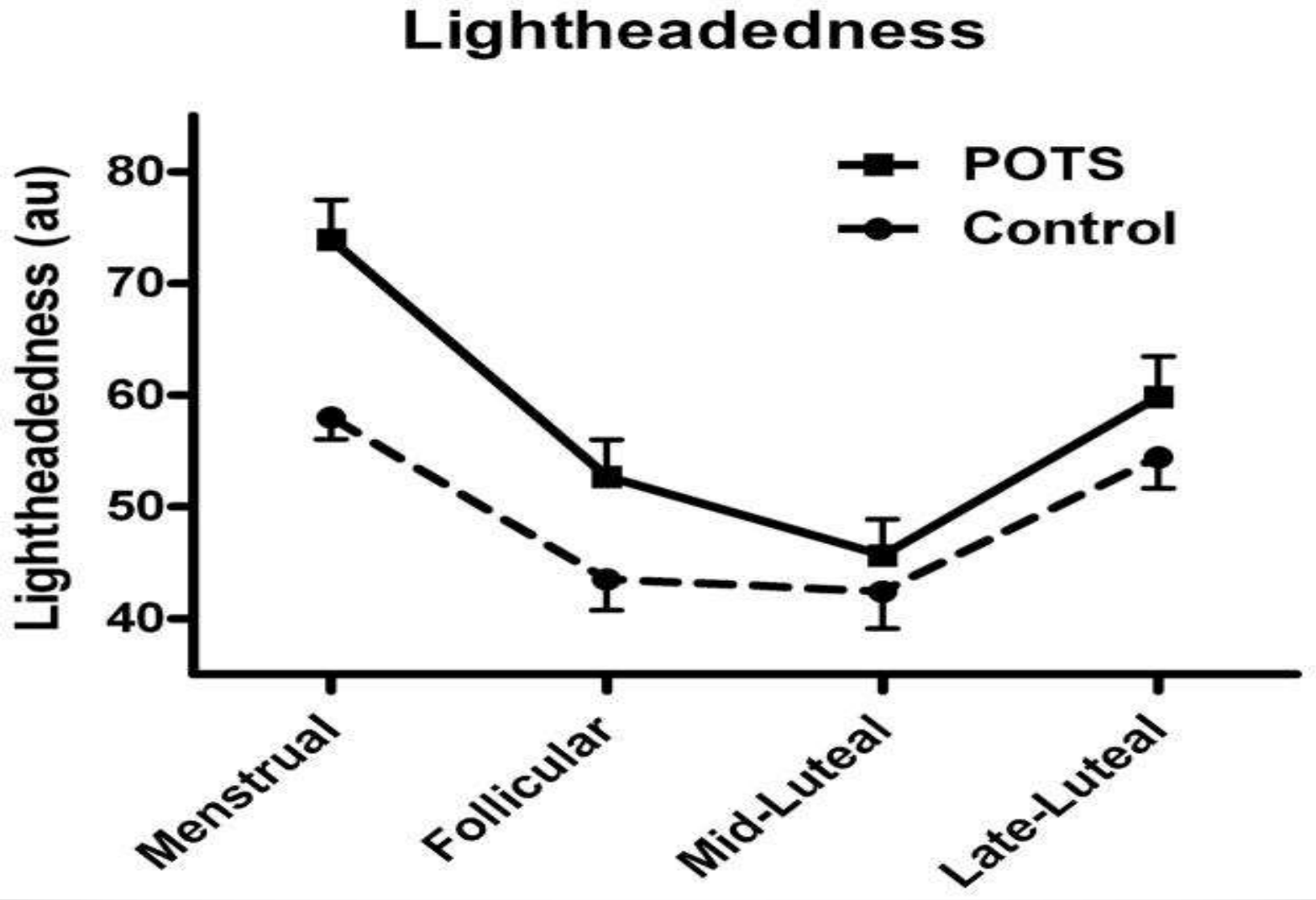
Management: SSRIs

- Fluoxetine, sertraline, and nefazedone 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!

Survey from Vanderbilt University Autonomic Dysfunction Center: Int J Gynaecol Obstet. Sep 2012; 118(3): 242–246.



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Gynecologic abnormality	POTS (n=65)	Controls (n=92)	*P* value (Mann–Whitney *U* test)
Anovulation [b]	3 (5)	2 (2)	0.401
Dysfunctional bleeding	9 (14)	4 (4)	0.042
Endometriosis	13 (20)	5 (5)	0.009
Uterine fibroids	16 (25)	9 (10)	0.015
Galactorrhea	6 (9)	0 (0.0)	0.004
Hirsutism	3 (5)	3 (3)	0.690
Hyperprolactinemia [b]	1 (2)	1 (1)	>0.999
Hypopituitarism	0 (0.0)	1 (1)	>0.999
Infertility [c]	2 (3)	3 (3)	>0.999
Ovarian cysts	28 (43)	12 (13)	<0.001
Polycystic ovarian syndrome	3 (5)	3 (3)	0.485
Premature menopause	3 (5)	1 (1)	0.307
Regular menopause	2 (3)	6 (7)	0.471

Self-reported gynecologic abnormalities among patients with POTS and healthy controls [a]
Abbreviation: POTS, postural tachycardia syndrome.

Influence of Hormones

- GYN referrals often merited in young women with significant POTS and dysmenorrhea/metrorrhagia
- Goals:
  - Rule out underlying GYN pathology
  - Regulate hormonal fluctuations causing symptoms (dizziness, pain, nausea, migraines, etc.)
- Options:
  - Monophasic oral contraceptives
  - 3 month cycle oral contraceptives (e.g. Seasonale)
  - Depo-provera
  - 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!

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