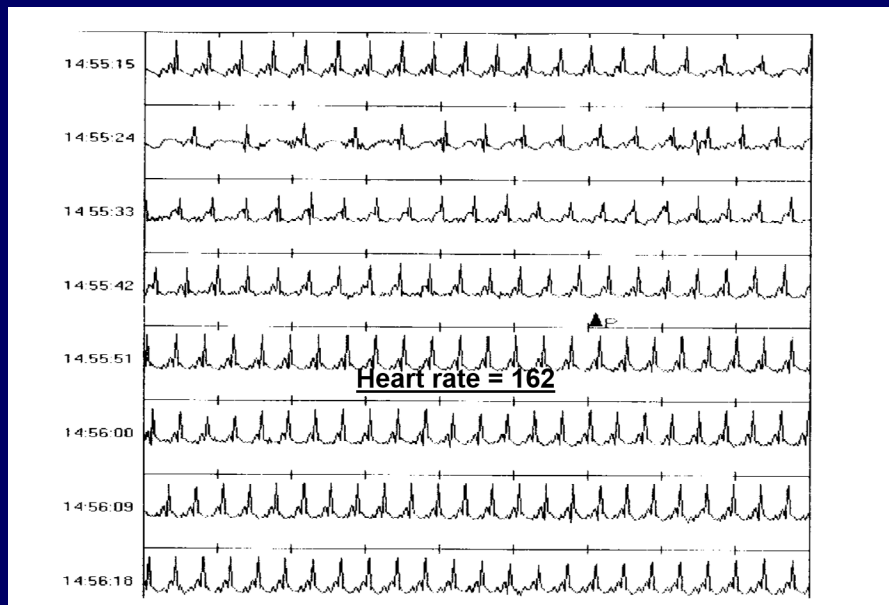


Postural Orthostatic Tachycardia Syndrome

Brian Olshansky MD
Professor Emeritus - University of Iowa
Adjunct Professor - Des Moines University
Electrophysiologist – Iowa and Illinois

1



2

One Day in Clinic

- Tilt table - heart rate >150 bpm
- Failed fluid and salt, stockings, β -blockers, citalopram, midodrine, fludrocortisone, oral contraceptives and in combination
- Minimal benefit from exercise
- Pyridostigmine 60 bid, glycopyrrolate 1 mg bid and midodrine 10 bid - long-term effective treatment

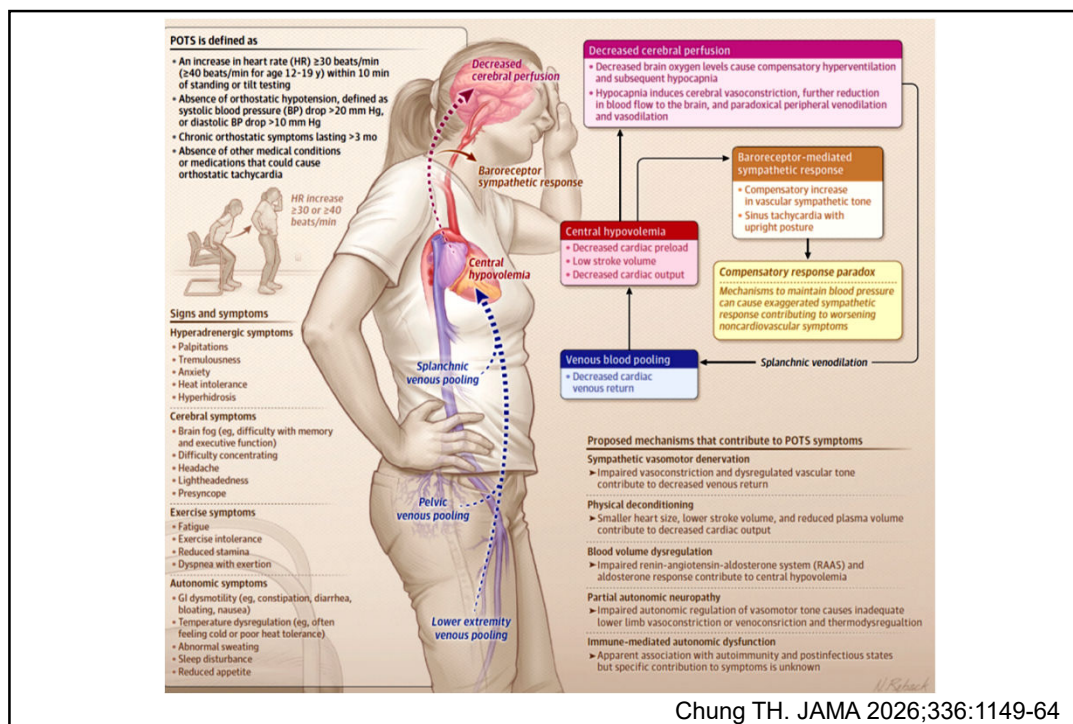
3

Postural Orthostatic Tachycardia Syndrome (POTS)

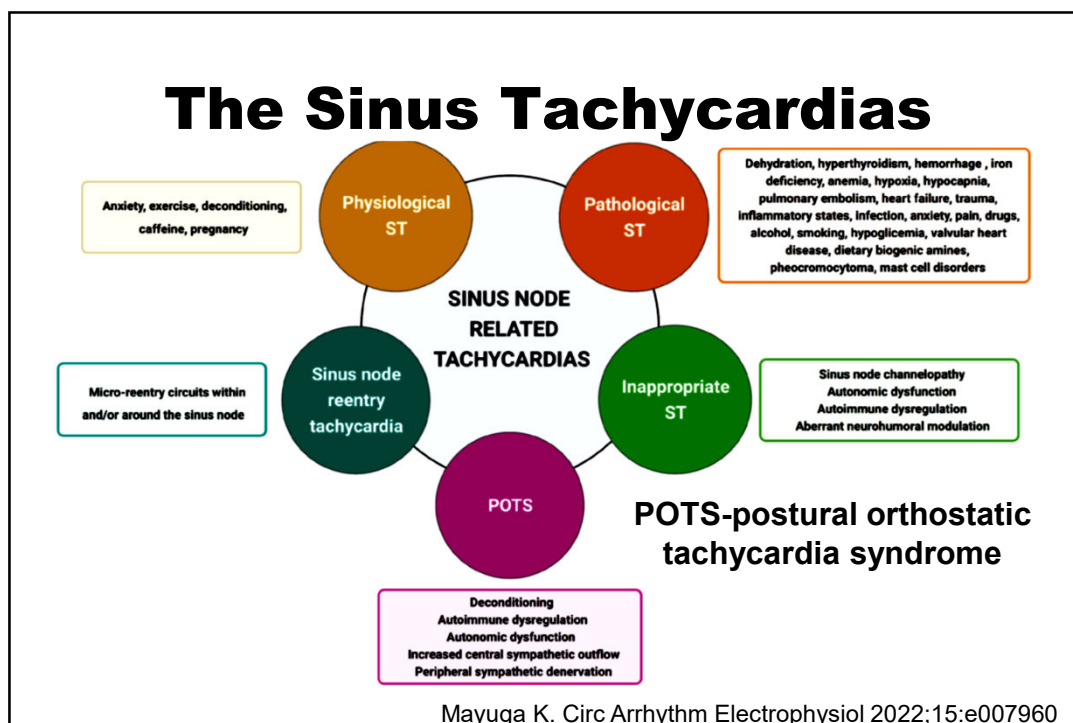
- Clinical syndrome - chronic postural, non-postural and systemic symptoms
- Orthostatic intolerance, positional tachycardia
- Reason to treat - symptoms
- No established medical treatment

A heterogenous condition

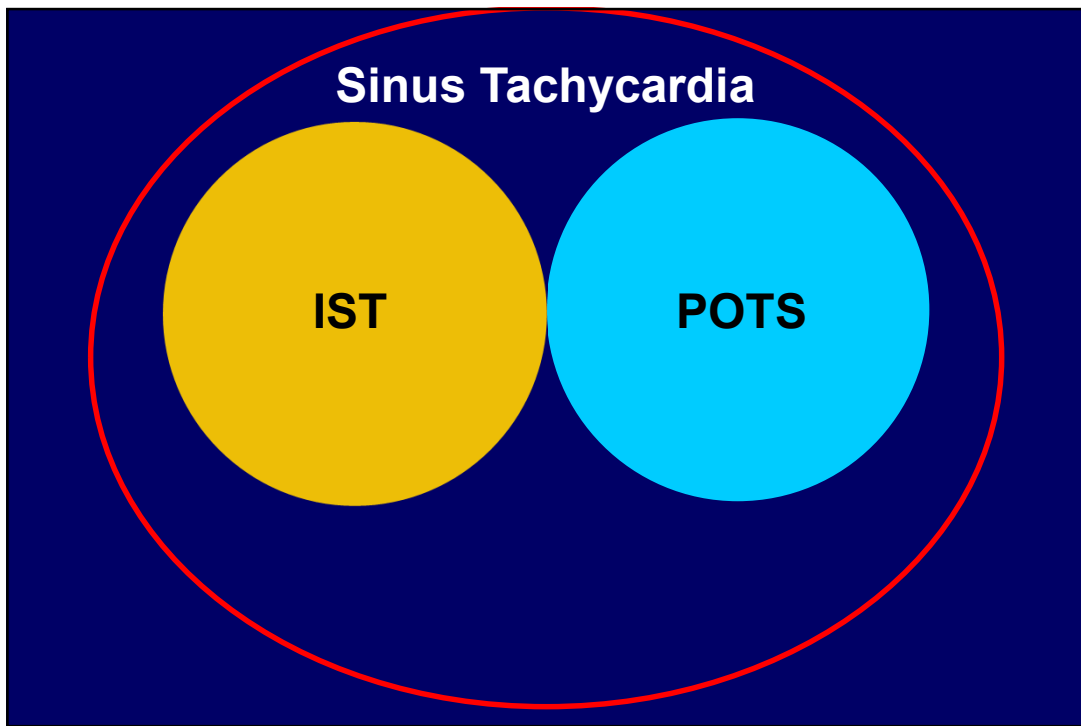
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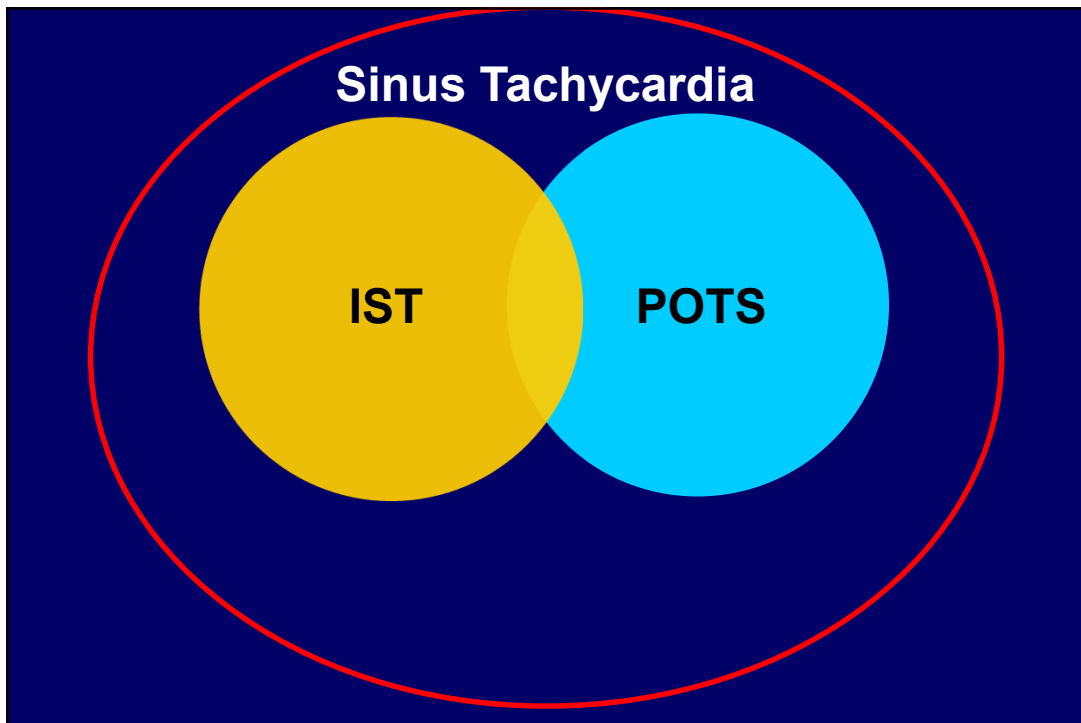
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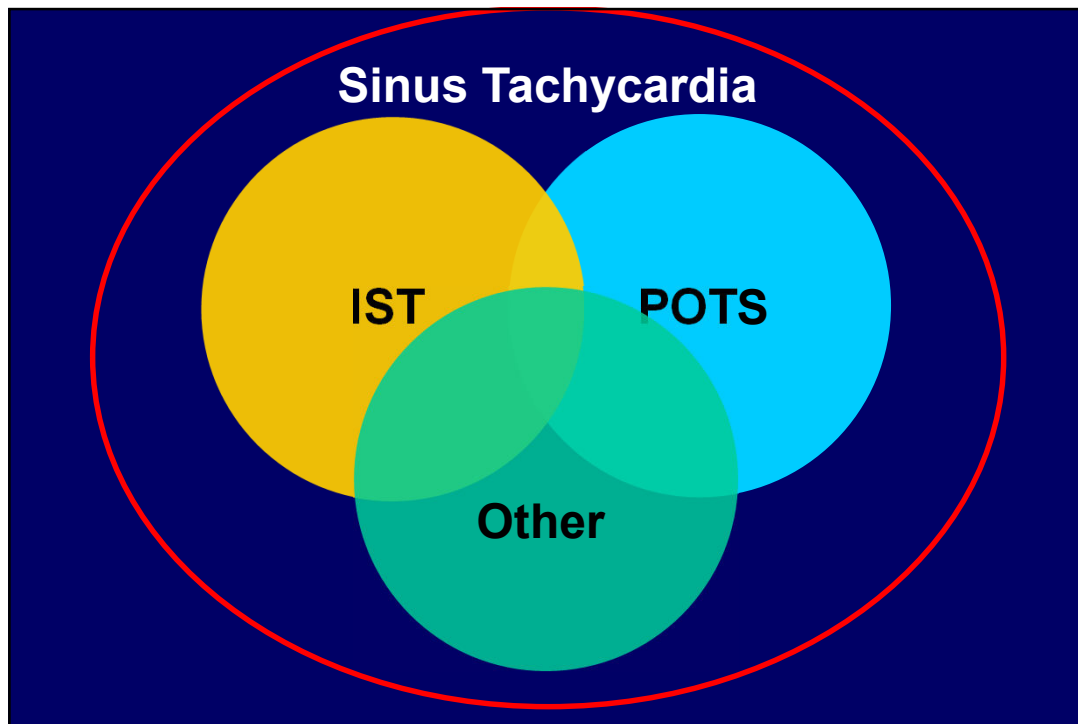
6



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9

Criteria for POTS

Reproducible orthostatic tachycardia (HR rise ≥ 30 bpm $>$ age 19 and ≥ 40 bpm age ≤ 19) with symptoms of orthostatic intolerance

- Orthostatic tachycardia 3-10 minutes on standing or on tilt-table
- No orthostatic hypotension
- "Secondary" orthostatic tachycardia is not POTS
- Symptoms present ≥ 6 months
- Symptoms alone do not make a diagnosis
- Syncope not a criterion

By consensus

Sheldon RS. Heart Rhythm 2015;12:e41-63

Olshansky B. Prog CV Dis 2020;63;263–270

10

POTS – Subtypes

- Partial Dysautonomic - inadequate vascular tone with orthostatic stress. females>males. Viral illness, pregnancy, surgery, sepsis, trauma. Acute onset.
- Hyperadrenergic – Excess norepinephrine spillover with sympathetic stimuli. Migraines common. Orthostatic hypertension. Family history. Gradual onset.

Olshansky B. Prog CV Dis 2020;63;263–270

11

POTS - Consensus Document

Clinical Syndrome Characterized as:

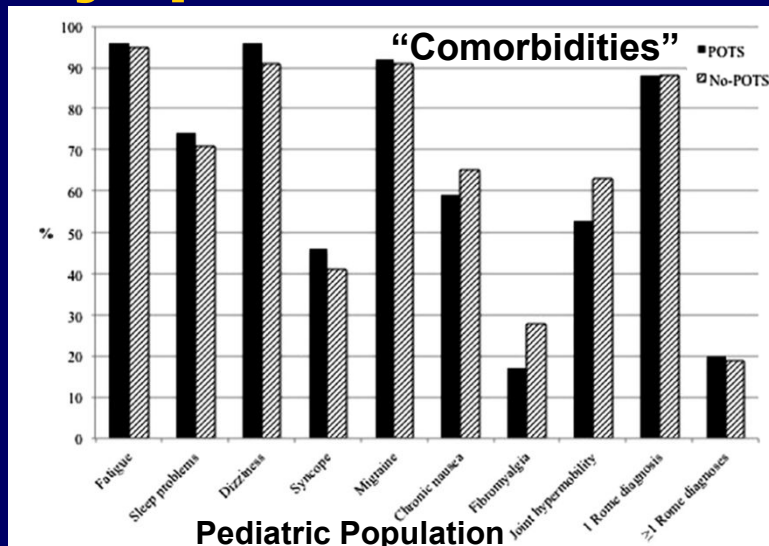
- Frequent symptoms with standing - light-headedness, palpitations, tremor, weakness, blurred vision, exercise intolerance
- Non-postural symptoms - bloating, nausea, diarrhea, abdominal pain
- Systemic symptoms - fatigue, sleep issues, migraines, “brain fog”

Chronic - symptoms linked to orthostatic intolerance

Sheldon RS. Heart Rhythm 2015;12:e41-63

12

Do Symptoms Tell the Story?



Chelmsky G. J Pediatr 2015;167:120-4

13

Symptoms – Due to POTS??

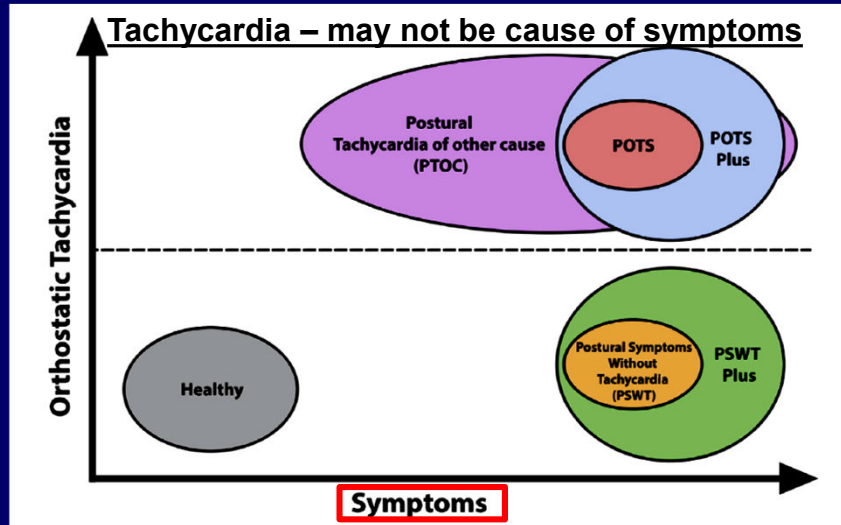
	HR upright 30-40 bpm	HR upright >40 bpm	P value
Total number of patients	302	338	
Abdominal pain	161 (53.3%)	195 (57.5%)	0.284
Blurred vision	119 (39.4%)	164 (48.4%)	0.022
Cognitive dysfunction	240 (79.5%)	267 (78.8%)	0.826
Chest pain	174 (57.6%)	182 (53.7%)	0.318
Cold intolerance	87 (28.8%)	110 (32.5%)	0.319
Constipation	142 (47.0%)	140 (41.3%)	0.145
Diaphoresis	157 (52.0%)	162 (47.8%)	0.289
Diarrhea	84 (27.8%)	101 (29.8%)	0.581
Dizziness	284 (94.0%)	329 (97.1%)	0.063
Dyspnea with activity	239 (79.1%)	255 (75.2%)	0.239
Early satiety	190 (62.9%)	208 (62.0%)	0.685
Exercise intolerance	215 (71.2%)	233 (68.7%)	0.498
Fatigue	278 (92.1%)	308 (90.9%)	0.589
Headache	281 (93.1%)	308 (90.9%)	0.311
Heat intolerance	214 (70.9%)	232 (68.4%)	0.505
Hypersensitivity	102 (33.8%)	128 (37.8%)	0.294
Insomnia	250 (82.8%)	245 (72.3%)	0.002
Joint hypermobility	159 (52.7%)	194 (57.2%)	0.245
Joint pain	127 (42.1%)	148 (43.7%)	0.682
Muscle pain	94 (31.1%)	114 (33.6%)	0.499
Nausea	222 (73.5%)	225 (66.4%)	0.0496
Numbness	98 (32.5%)	129 (38.1%)	0.139
Palpitations	219 (72.5%)	230 (67.9%)	0.198
Photophobia	134 (44.4%)	155 (45.7%)	0.731
Syncope	101 (33.4%)	123 (36.3%)	0.452
Tachycardia	131 (43.4%)	178 (52.5%)	0.021
Venous pooling	197 (65.2%)	220 (64.9%)	0.929
Vomiting	84 (27.8%)	75 (22.1%)	0.0959

Pediatric Population

Boris JR. Clin Auton Res 2020;30:19-28

14

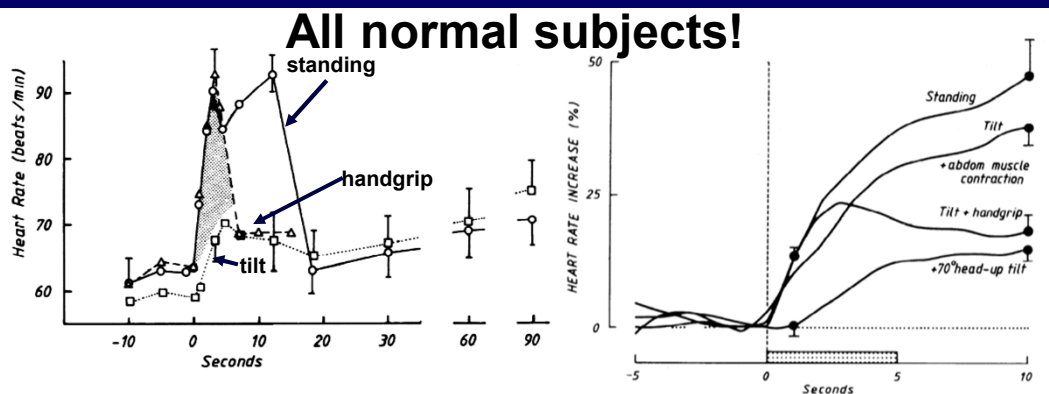
Canadian Position Statement



Raj S. Canadian J Cardiol 2020;36:357-372

15

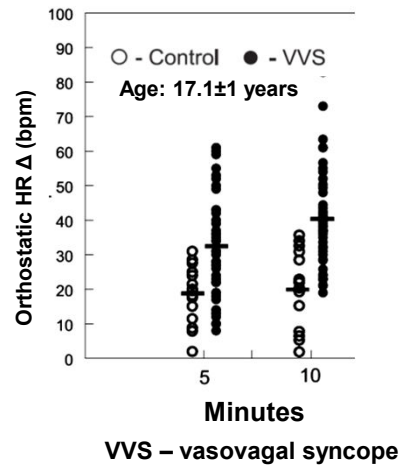
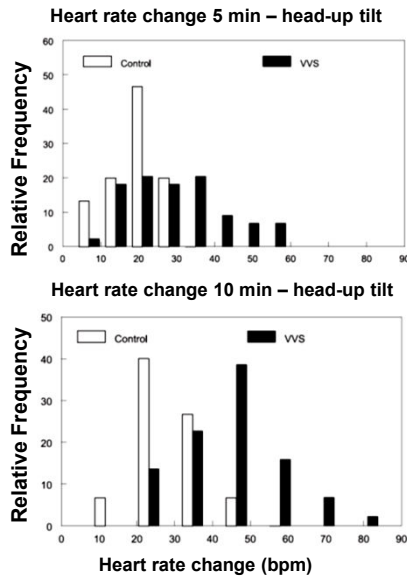
Orthostatic Tachycardia



Borst C. Am J Physiol 1982;243 (Heart Circ Physiol 12):H676-H681

16

What Is Normal?



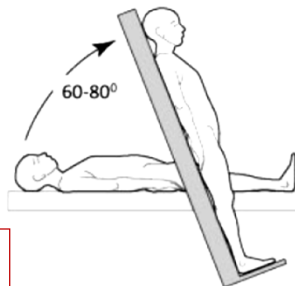
Medow MS. Pediatrics 2017;139:e20163189

17

Value of Tilt-Testing

Diagnostic Utility in VVS

1. Reproducing Spontaneous Symptoms
2. Identifying Haemodynamic Features
 - a. Mixed
 - b. Cardioinhibitory
 - c. Vasodepressor
3. Understanding Contributions of Brady/Asystole vs Vasodepression to loss of consciousness



Typical Tilt-Test Recordings

1. ECG
2. Beat-to-beat BP
3. Others on Selected Basis
 - a. EEG
 - b. Video
 - c. Measures of Cerebral Perfusion

Utility in Symptom Management

1. Warning Symptom Recognition
 - a. Understanding Importance and Nature of Prodromes
 - b. Initiate Protective Movement
2. Therapy Intervention
 - a. Reassurance
 - b. Counter-pressure Manoeuvres
 - c. Potential Pacing Utility

Sutton R. Eur Heart J 2021;42:1654-1660

18

Intra- and interindividual reproducibility of heart rate variations in the tilt-table test

Thomas Kaiser¹, Wolfgang H. Jost², Jochem König³, and Klaus Schimrigk¹

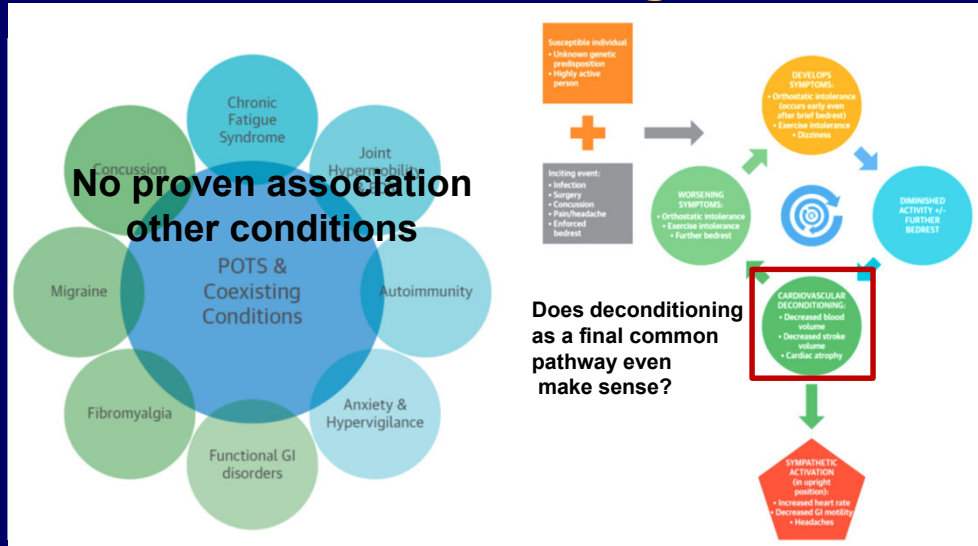
¹ Neurologische Klinik, ³ Institut für Medizinische Biometrie, Epidemiologie und Informatik, Universität des Saarlandes, Homburg, and ² Deutsche Klinik für Diagnostik, Wiesbaden, Federal Republic of Germany

“The tilt test was repeated 10 times in 40 subjects under standardized conditions. All subjects showed considerable variation in heart rate response within the 10 tilting maneuvers. Based on these results, we conclude that the initial heart rate response on the tilt table test is not suitable for routine diagnosis of autonomic regulation disorders.”

“I Have POTS!”

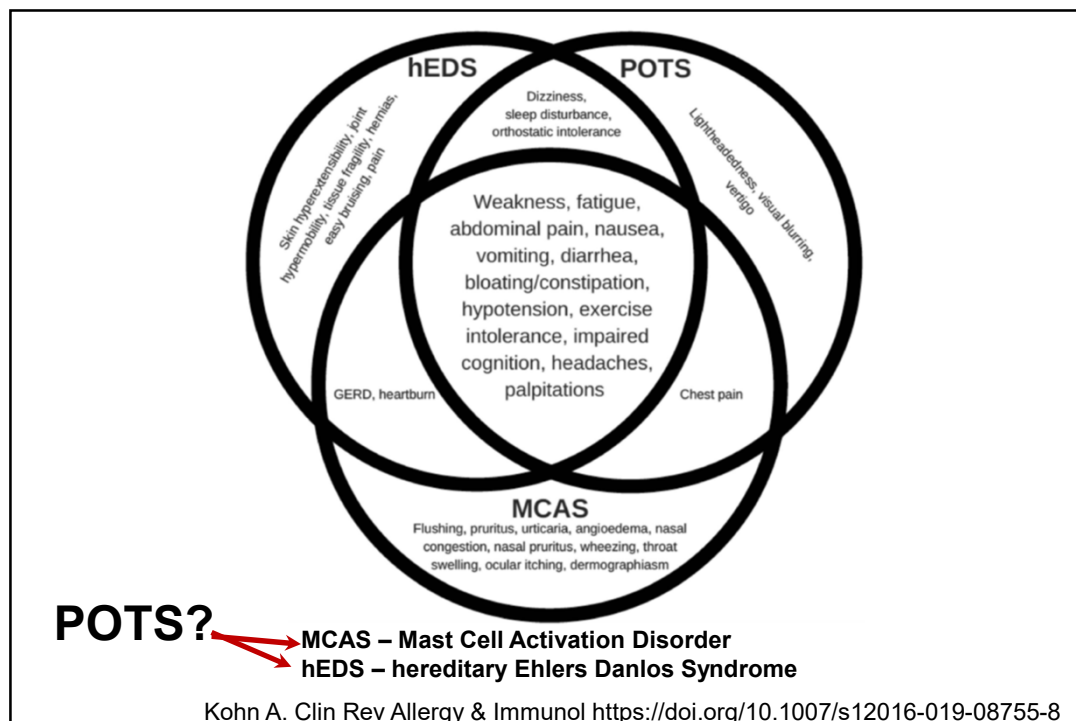
- A credible doctor told me after extensive testing.
- I have brain fog and am fatigued.
- I can't do anything.
- I need amphetamines for ADHD.
- I want ivabradine.
- How about IV saline? I'm allergic to water.

Does This Clarify POTS?



Bryarly M. J Am Coll Cardiol 2019;73:1207–28

21



22

ORIGINAL RESEARCH

Mast Cell Activation Disorder and Postural Orthostatic Tachycardia Syndrome: A Clinical Association

Ritsuko Kohno, MD, PhD; David S. Cannom, MD; Brian Olshansky , MD; Shijun Cindy Xi, MD; Darshan Krishnappa , MD; Wayne O. Adkisson, MD; Faye L. Norby , MS, MPH; Artur Fedorowski , MD, PhD; David G. Benditt , MD

BACKGROUND: Recently order and postural orth laboratory findings sug

What looks like POTS may be something else

cell activation (MCA) disorder with which symptoms and

METHODS AND RESULTS: Data were obtained from patients with orthostatic symptoms and orthostatic tachycardia consistent with a POTS diagnosis. Individuals with <4 months symptom duration, evident ongoing inflammatory disease, suspected volume depletion, or declined consent were excluded. All patients had typical POTS symptoms; some, however, had additional nonorthostatic complaints not usually associated with POTS. The latter patients underwent additional testing for known MCA biochemical mediators including prostaglandins, histamine, methylhistamine, and plasma tryptase. The study comprised 69 patients who met POTS diagnostic criteria. In 44 patients (44/69, 64%) additional nonorthostatic symptoms included migraine, allergic complaints, skin rash, or gastrointestinal symptoms. Of these 44 patients, 29 (66%) exhibited at least 1 laboratory abnormality suggesting MCA disorder, and 11/29 patients had 2 or more such abnormalities. Elevated prostaglandins (n=16) or plasma histamine markers (n=23) were the most frequent findings. Thus, 42% (29/69) of patients initially diagnosed with POTS exhibited both additional symptoms and at least 1 elevated biochemical marker suggesting MCA disorder.

CONCLUSIONS: Laboratory findings suggesting MCA disorder were relatively common in patients diagnosed with POTS and who present with additional nonorthostatic gastrointestinal, cutaneous, and allergic symptoms. While solitary abnormal laboratory findings are not definitive, they favor MCA disorder being considered in such cases.

Kohno R. J Am Heart Assoc 2021;10:e021002

23

Conditions Mimicking POTS

Mast cell activation syndrome (MCAS)
Ehlers Danlos syndrome (EDS)
Autoimmune disease: often positive ANA, but does not meet specific diagnosis
Sjögren's syndrome
Lupus erythematosus
Arthritis – rheumatoid, juvenile-onset rheumatoid arthritis
Autoimmune thyroid disease – Grave's disease and Hashimoto's thyroiditis
Gastroparesis and associated gastrointestinal diagnoses: small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome (IBS), median arcuate ligament syndrome (MALS)
Migraine headaches
Sinus node disease
Chronic immune deficiency
Chronic regional pain syndromes
Small fiber neuropathy
Raynaud's syndrome
Depression/anxiety
Urologic concerns: pelvic floor dysfunction, interstitial cystitis, endometriosis, polycystic ovary syndrome (PCOS)
Chiari malformation

Olshansky B. Prog CV Dis 2020;63:263-270

24

Pathophysiology of POTS

- Peripheral denervation with supersensitivity
- α -receptor hyposensitivity
- Acetylcholine receptor antibodies/inflammation/viral
- Central hyperadrenergic state
- Norepinephrine transporter deficiency
- Decreased baroreceptor gain
- Idiopathic hypovolemia - altered aldosterone, renin, nNOS and angiotensin II activity
- Mast cell activation
- Small left ventricle
- Deconditioning

Olshansky B. Prog CV Dis 2020;63;263–270

25

Autoimmune Basis for Postural Tachycardia Syndrome

Hongliang Li, MD, PhD; Xichun Yu, MD; Campbell Liles, BS; Muneer Khan, MD; Megan Vanderlinde-Wood, MD; Allison Galloway, MD; Caitlin Zillner, BS; Alexandria Benbrook, BS; Sean Reim, BS; Daniel Collier, BS; Michael A. Hill, PhD; Satish R. Raj, MD; Luis E. Okamoto, MD; Madeleine W. Cunningham, PhD; Christopher E. Aston, PhD; David C. Kem, MD

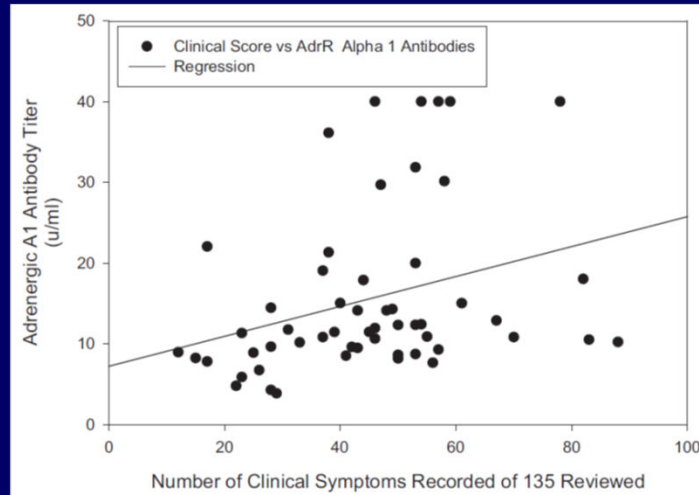
Background—Patients with postural tachycardia syndrome (POTS) have exaggerated orthostatic tachycardia often following a viral illness, suggesting autoimmunity may play a pathophysiological role in POTS. We tested the hypothesis that they harbor functional autoantibodies to adrenergic receptors (AR).

Methods and Results—Fourteen POTS patients (7 each from 2 institutions) and 10 healthy subjects were examined for α 1AR autoantibody-mediated contractility using a perfused rat cremaster arteriole assay. A receptor-transfected cell-based assay was used to detect the presence of β 1AR and β 2AR autoantibodies. Data were normalized and expressed as a percentage of baseline. The sera of all 14 POTS patients demonstrated significant arteriolar contractile activity ($69 \pm 3\%$ compared to $91 \pm 1\%$ of baseline for healthy controls, $P < 0.001$) when coexisting β 2AR dilative activity was blocked; and this was suppressed by α 1AR blockade with prazosin. POTS sera acted as a partial α 1AR antagonist significantly shifting phenylephrine contractility curves to the right. All POTS sera increased β 1AR activation ($130 \pm 3\%$ of baseline, $P < 0.01$) and a subset had increased β 2AR activity versus healthy subjects. POTS sera shifted isoproterenol cAMP response curves to the left, consistent with enhanced β 1AR and β 2AR agonist activity. Autoantibody-positive POTS sera demonstrated specific binding to β 1AR, β 2AR, and α 1AR in transfected cells.

Conclusions—POTS patients have elevated α 1AR autoantibodies exerting a partial peripheral antagonist effect resulting in a compensatory sympathoneural activation of α 1AR for vasoconstriction and concurrent β AR-mediated tachycardia. Coexisting β 1AR and β 2AR agonistic autoantibodies facilitate this tachycardia. These findings may explain the increased standing plasma norepinephrine and excessive tachycardia observed in many POTS patients. (*J Am Heart Assoc.* 2014;3:e000755 doi: 10.1161/JAHA.113.000755)

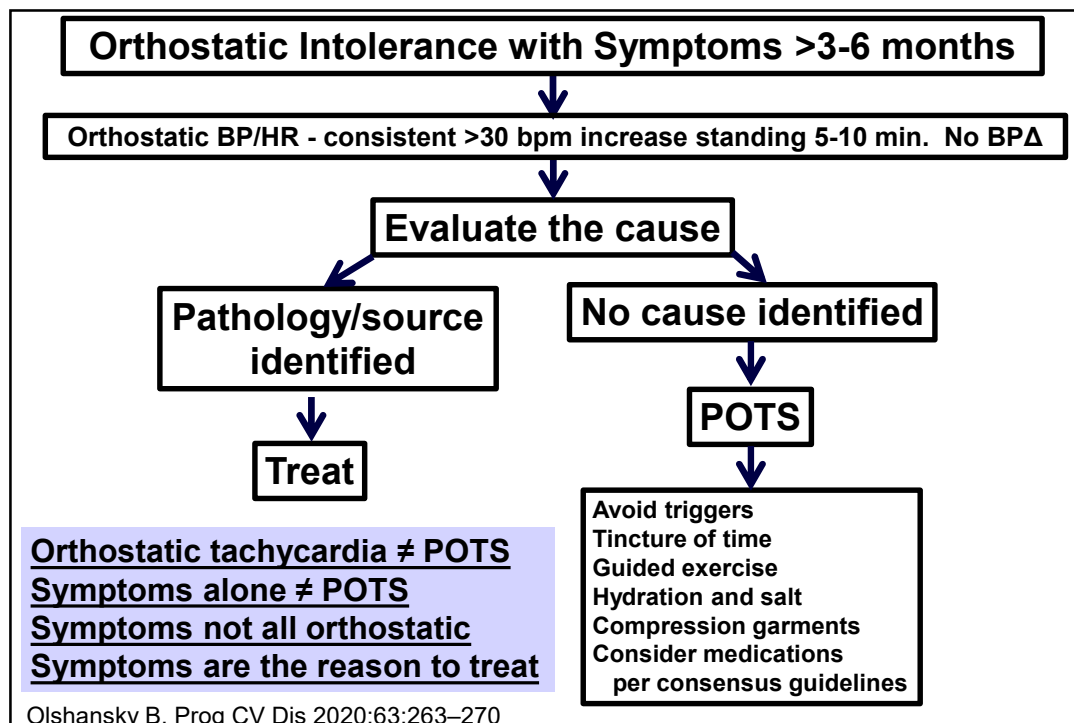
26

POTS - Autoimmune?



Gunning WT. J Am Heart Assoc 2019;8:e013602

27



28

Consensus Document - POTS

	Class	Level
A regular, structured, and progressive exercise program for patients with POTS can be effective.	IIa	B-R
It is reasonable to treat patients with POTS who have short-term clinical decompensations with an acute intravenous infusion of up to 2 L of saline.	IIa	C
Patients with POTS might be best managed with a multidisciplinary approach.	IIb	E
The consumption of up to 2–3 L of water and 10–12 g of NaCl daily by patients with POTS may be considered.	IIb	E
It seems reasonable to treat patients with POTS with fludrocortisone or pyridostigmine.	IIb	C
Treatment of patients with POTS with midodrine or low-dose propranolol may be considered.	IIb	B-R
It seems reasonable to treat patients with POTS who have prominent hyperadrenergic features with clonidine or alpha-methyldopa.	IIb	E
Drugs that block the norepinephrine reuptake transporter can worsen symptoms in patients with POTS and should not be administered.	III	B-R
Regular intravenous infusions of saline in patients with POTS are not recommended in the absence of evidence, and chronic or repeated intravenous cannulation is potentially harmful.	III	E
Radiofrequency sinus node modification, surgical correction of a Chiari malformation type I, and balloon dilation or stenting of the jugular vein are not recommended for routine use in patients with POTS and are potentially harmful.	III	B-NR

Heart Rhythm 2015;12:e41-e57

29

POTS “Treatments”

Giving unproven therapies is a concern

- Avoid triggers
- Tincture of time
- Exercise
- Water, salt loading
- Compression (TED) hose
- β-blockers (low dose)
- Fludrocortisone
- Midodrine
- Modafinil
- Vasopressin
- Serotonin reuptake inhibitors
- Yohimbine
- Methylphenidate
- Methyldopa
- Clonidine
- Phenobarbital
- Octreotide
- Ivabradine
- Droxidopa
- IVIG

30

Pharmacological Approach

No Drug Approved – Difficult to Prescribe

Some Evidence

- β -blocker (low dose)*
- Fludrocortisone*
- Midodrine*
- Ivabradine*
- Pyridostigmine*
- Methyldopa/Clonidine*

Little Evidence

- Modafinil*
- Droxidopa
- Desmopressin
- Methylphenidate
- Phenobarbital
- Octreotide
- Guanfacine
- Digoxin

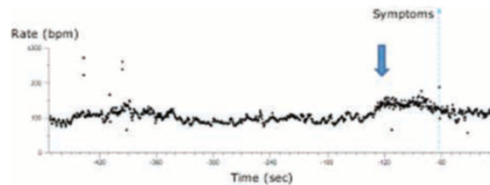
Other favorites used

Empiric combinations tried

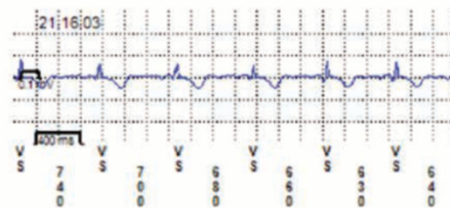
*Mentioned in 2015 Consensus Guidelines
Sheldon RS. Heart Rhythm 2015;12:e41

31

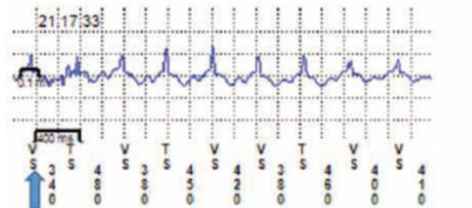
ILR Recording



Sitting



Standing

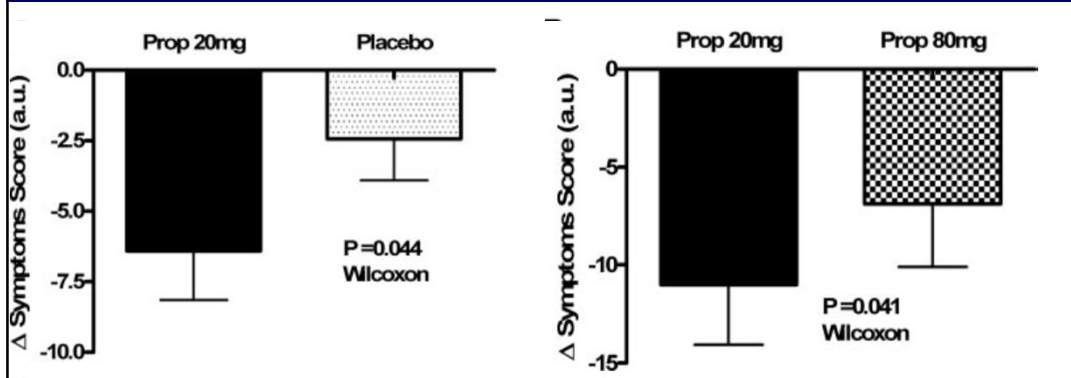


Zifra JB. J Innov Cardiac Rhythm Manage 2019;10:3541-3544

32

POTS and Propranolol

Less is More

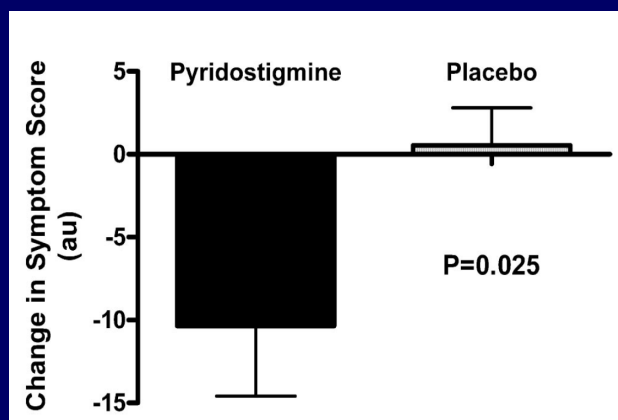


Symptoms: mental clouding, palpitations, dyspnea, visual change, lightheadedness, nausea, headache, tremulousness

Raj SR. Circulation 2009;120:725-34

33

Pyridostigmine Can Work



Raj SR. Circulation 2005;111:2734-2740

34

Single centre experience of ivabradine in postural orthostatic tachycardia syndrome

Claire McDonald, James Frith, and Julia L Newton*

Institute for Ageing and Health, FIV AHLD Biomedical Research Centre in Ageing and Associated Diseases, Newcastle University, Newcastle

Received 20 July 2011

What are we treating here? Is it even POTS?

Aims

ivabradine (a selective sinus node blocker, with no effect on blood pressure) may alleviate POTS-related symptoms. This is a retrospective case-series.

Methods and results

Postural orthostatic tachycardia syndrome patients prescribed ivabradine were identified from the pharmacy database. Case notes were reviewed and participants completed a symptom assessment tool. Twenty-two patients were identified. Data were available from 20. Eight patients reported reduced tachycardia and fatigue and four reported only reduced tachycardia. The most common reason for discontinuing ivabradine was lack of efficacy ($n = 6$). Five patients reported side-effects resulting in two discontinuing treatment.

Conclusion

This retrospective case series indicates that 60% of patients treated with ivabradine report a symptomatic improvement. A randomized controlled trial assessing the efficacy of ivabradine in POTS is indicated, particularly in patients resistant to, or intolerant of, conventional therapy.

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Randomized Trial of Ivabradine in Patients With Hyperadrenergic Postural Orthostatic Tachycardia Syndrome



Pam R. Taub, MD,^{a,*} Adena Zadourian, BS,^{a,*} Hannah C. Lo, BS,^a Cameron K. Ormiston, BS,^a Shahrokh Golshan, PhD,^b Jonathan C. Hsu, MD, MAS^a

ABSTRACT

BACKGROUND Postural orthostatic tachycardia syndrome (POTS) is a complex, multifaceted disorder that impairs functional status and quality of life. Current pharmacological treatments are limited.

OBJECTIVES This study investigated the effect of ivabradine (selective blocker of the $I_{\text{f}}/\text{H}_{\text{f}}$ channel in the sinoatrial node) on heart rate, quality of life (QOL), and plasma norepinephrine (NE) levels in patients with hyperadrenergic POTS defined by plasma NE > 600 pg/ml and abnormal tilt table test.

METHODS In total, 22 patients with hyperadrenergic POTS as the predominant subtype completed a randomized, double-blinded, placebo-controlled, crossover trial with ivabradine. Patients were randomized to start either ivabradine or placebo for 1 month, and then were crossed over to the other treatment for 1 month. Heart rate, QOL, and plasma NE levels were measured at baseline and at the end of each treatment month.

RESULTS The average age was 33.9 ± 11.7 years, 95.5% were women ($n = 21$), and 86.4% were White ($n = 23$). There was a significant reduction in heart rate between placebo and ivabradine ($p < 0.001$). Patients reported significant improvements in QOL with RAND 36-Item Health Survey 1.0 for physical functioning ($p = 0.008$) and social functioning ($p = 0.021$). There was a strong trend in reduction of NE levels upon standing with ivabradine ($p = 0.056$). Patients did not experience any significant side-effects, such as bradycardia or hypotension, with ivabradine.

CONCLUSION Ivabradine is safe and effective in significantly improving heart rate and QOL in patients with hyperadrenergic POTS as the predominant subtype. (J Am Coll Cardiol 2021;77:861–71) © 2021 by the American College of Cardiology Foundation.

36

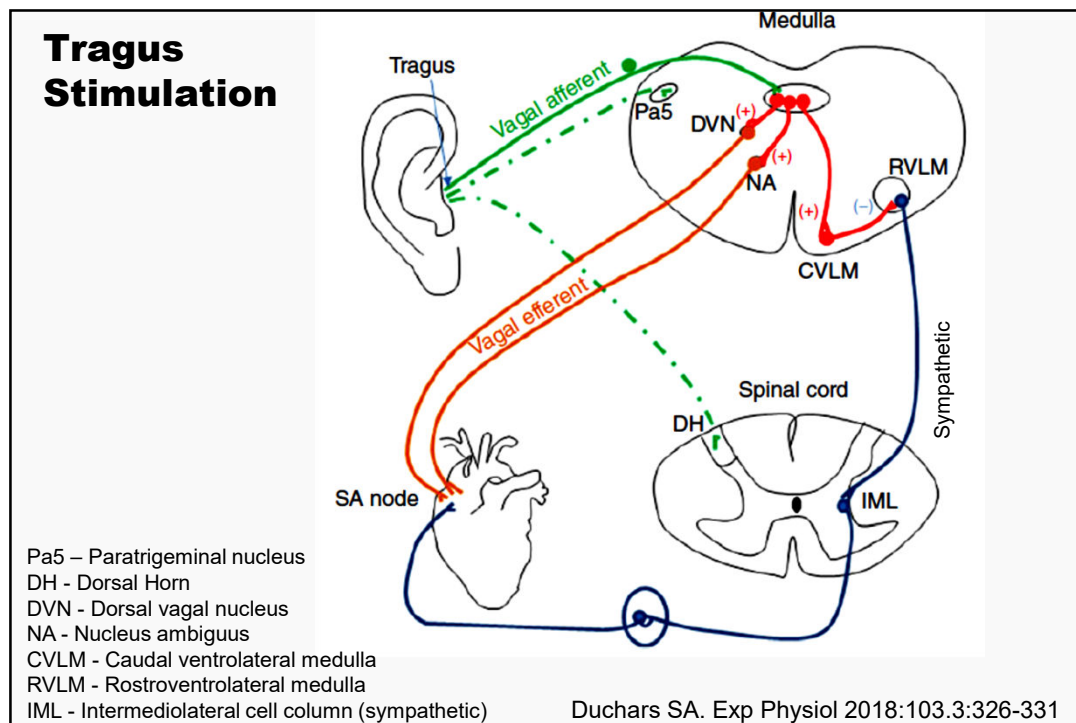
POTS - The Future??

Find the Cause

- Sinus node sparing epicardial ablation¹
- Intravenous immunoglobulin²
- Alternative therapy (α -lipoic acid, vitamin D, vitamin B12, iron, diet change)⁴⁻⁵
- Tragus stimulation⁶

1. De Asmundis C. Am J Cardiol 2022;183:24
2. Vernino S. Clin Auton Res. 2024;34:153-63
3. Wadhwan R. J Ped Neuro 2017;12:119
4. Ashangari C. Circ CV Qual Out 2015;8:A121
5. Öner T. Pediatrics 2014;133:e138
6. Stravakis S. JACC Clin Electrophys 2024;10:346-55

37



38

Take Home Messages

Postural Orthostatic Tachycardia Syndrome

- Determine if criteria for POTS are met
- Evaluate triggering causes
- Treat symptoms and underlying problems
- Use non-pharmacologic approach first
- Add medications only when necessary
- Engage a personalized, empathetic approach