Managing Orthostatic Intolerance in Adolescents

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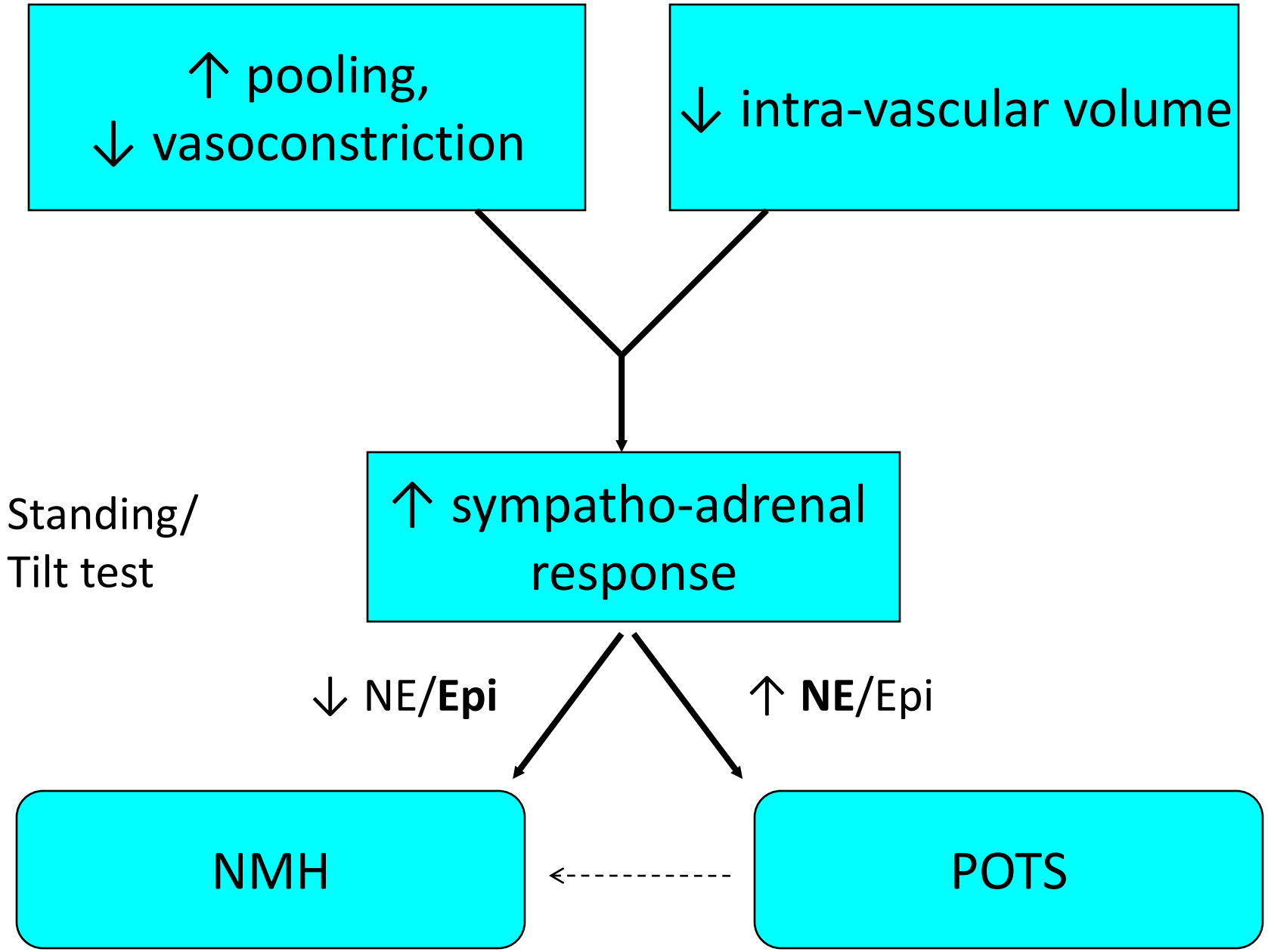
Abnormalities in the response to upright posture in those with orthostatic intolerance



Common Forms of OI

- Initial Orthostatic Hypotension (IOH):
  - transient ↓ of 40 mm Hg in SBP or 20 mm Hg DBP within 15 sec of standing (more common in adolescents)
- Orthostatic Hypotension (OH):
  - sustained ↓ of 20 mm Hg in SBP or 10 mm Hg in DBP within 3 min of standing or HUT (more common in older adults)
- Delayed OH
  - OH occurring after 3 minutes upright

Freeman R, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21:69-72;
Sheldon RS, et al. 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 2015;12:e41-63.

Common Forms of OI

- Postural tachycardia syndrome (POTS):
  - ≥ 40 bpm ↑ in HR in adolescents (≥ 30 bpm in adults) in first 10 min of standing or head-up tilt, with chronic OI symptoms, with no OH
- Neurally mediated hypotension (NMH):
  - ≥ 25 mm Hg drop in BP during standing or HUT, often associated with a reduction in HR
- Inappropriate sinus tachycardia (IST):
  - Sinus rhythm with a HR > 100 bpm at rest; similar symptoms to POTS
- Low orthostatic tolerance:
  - Orthostatic symptoms in the absence of HR and BP changes; preliminary evidence suggests many of these individuals have reduced cerebral blood flow.

Neurally Mediated Hypotension

also known as

Vasovagal syncope

Neurocardiogenic syncope

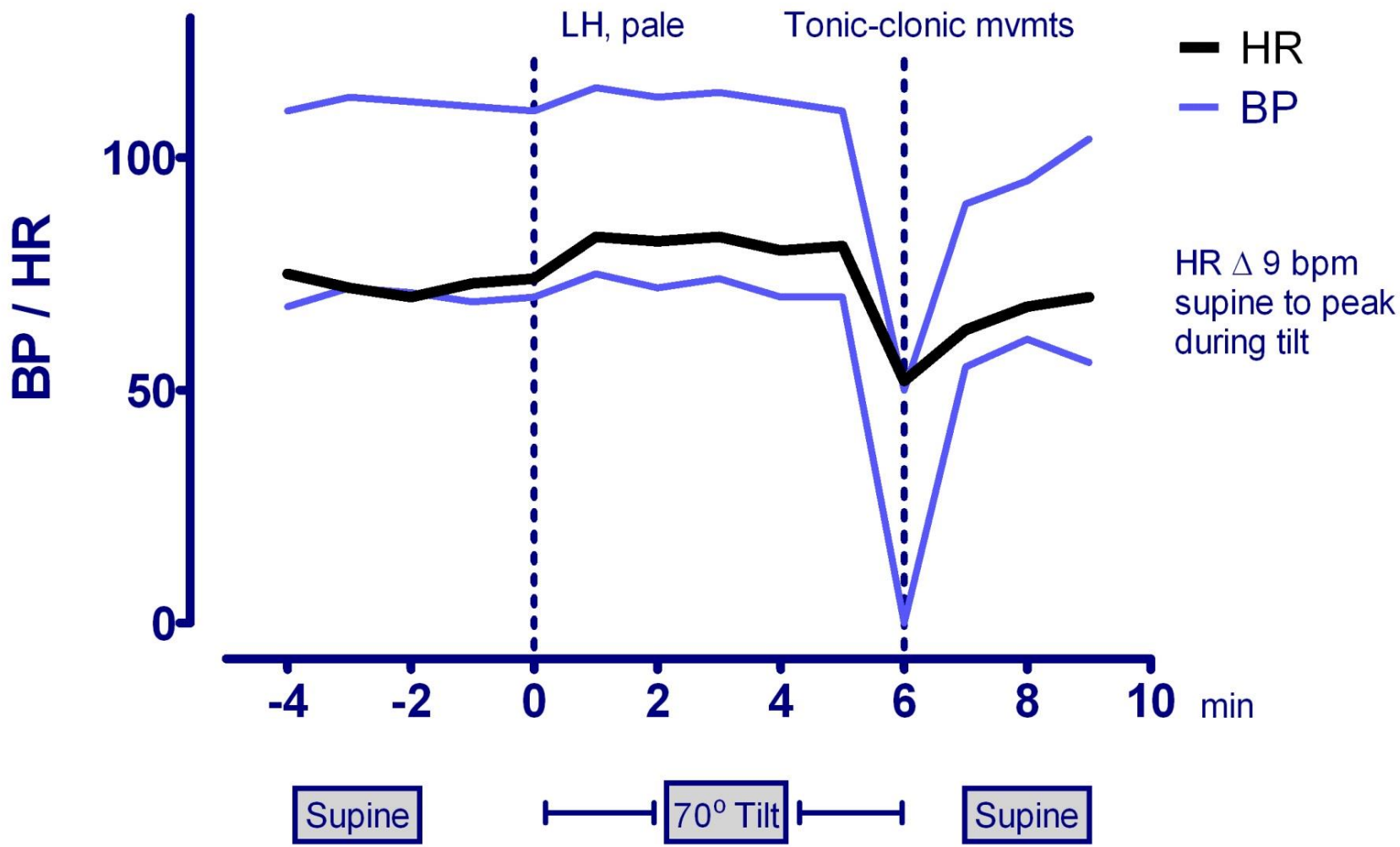
Vasodepressor syncope

Neurally mediated syncope

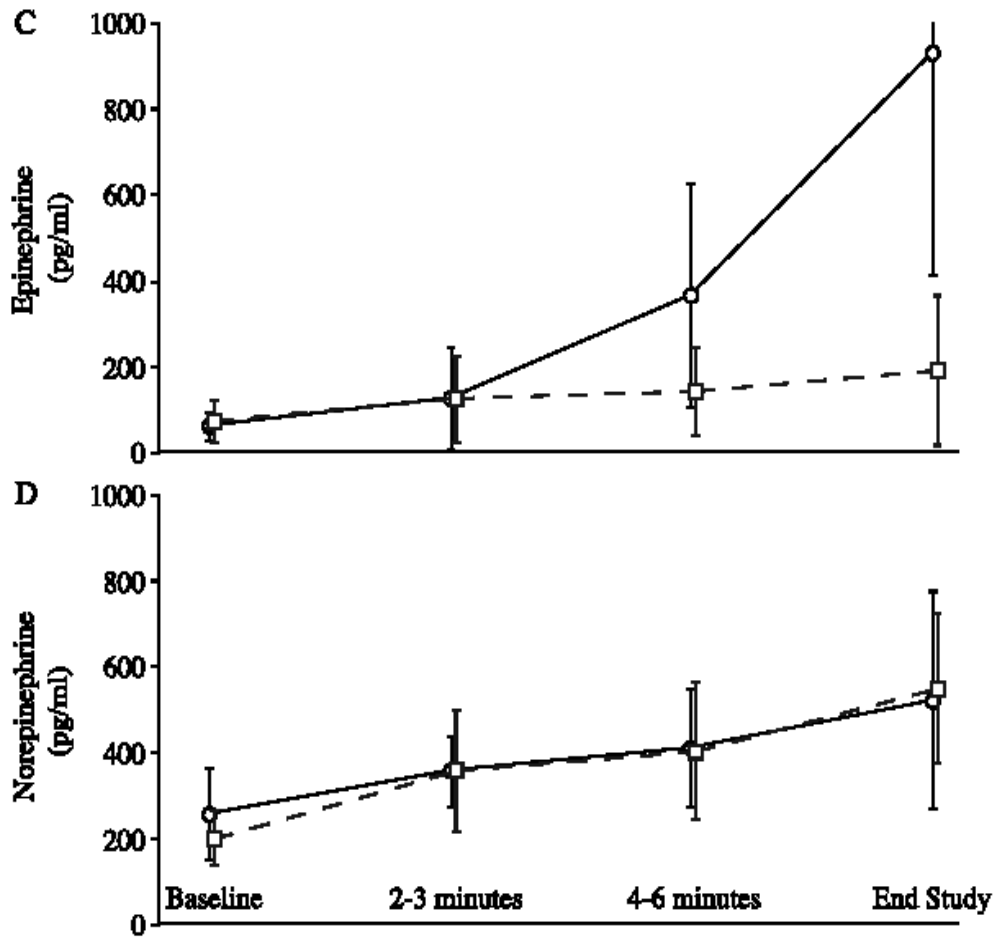
Neurally Mediated Hypotension

- The most common cause of recurrent syncope
- More common in women, the young, those with low normal or low BP
- Common following infection
- Family members often affected
- Routine physical and lab tests normal
- Hypotension not detected unless orthostatic stress is prolonged
- Fatigue common for hours after syncope

Neurally mediated hyptotension



Catecholamines during upright tilt in syncope patients (—) and controls (----)

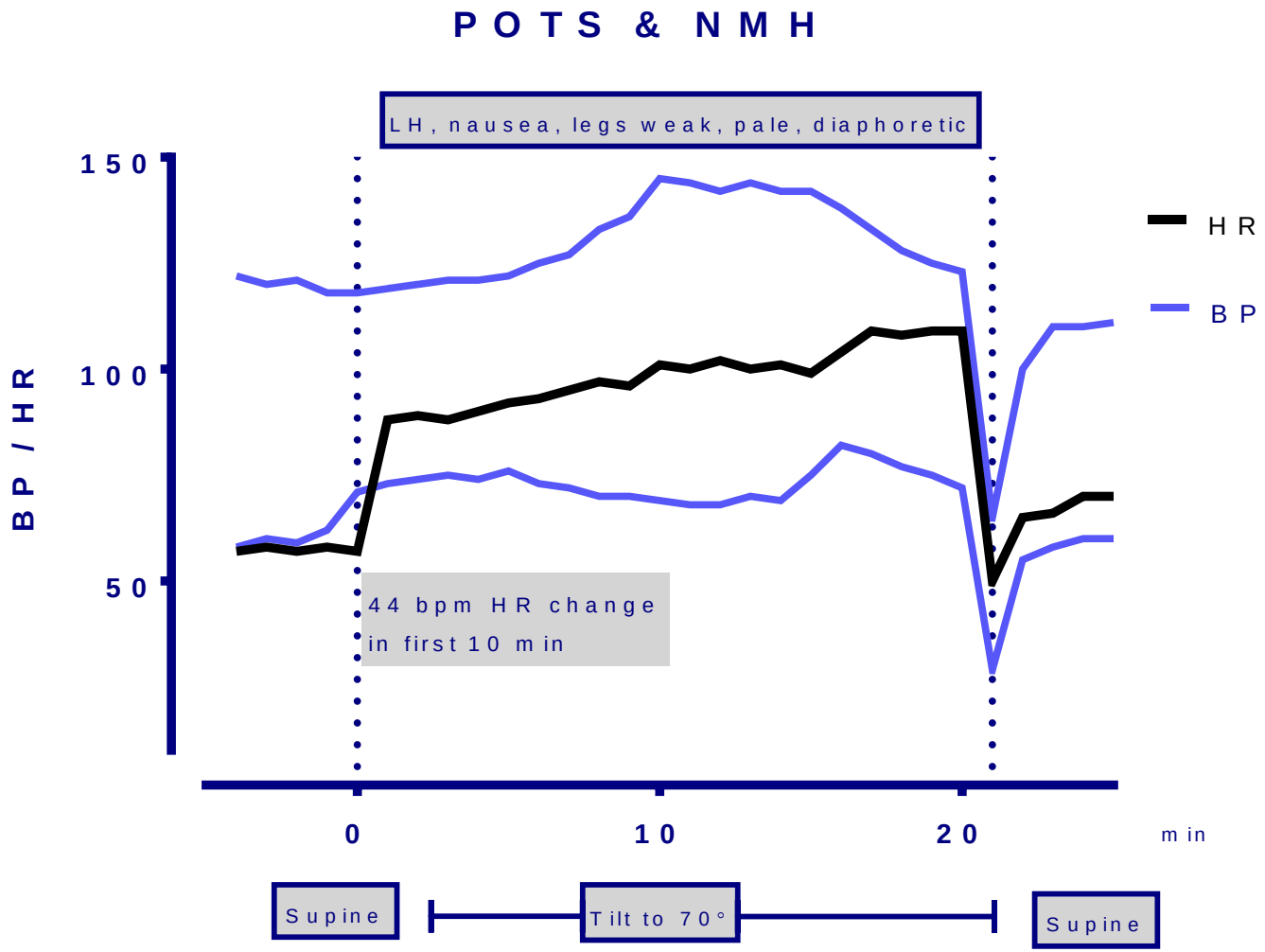


Benditt DG, Europace 2003;5:65-70.

Postural Tachycardia Syndrome (POTS)

- Described as early as the 1870s, termed irritable heart, effort syndrome, neurocirculatory asthenia.
- F:M ratio ~ 4:1, rare under age 10
- Insidious onset in some, often appears after infection, immunization, surgery, trauma
- Symptoms often disabling
- Marked increase in recognition and perhaps incidence in last 10-20 yrs

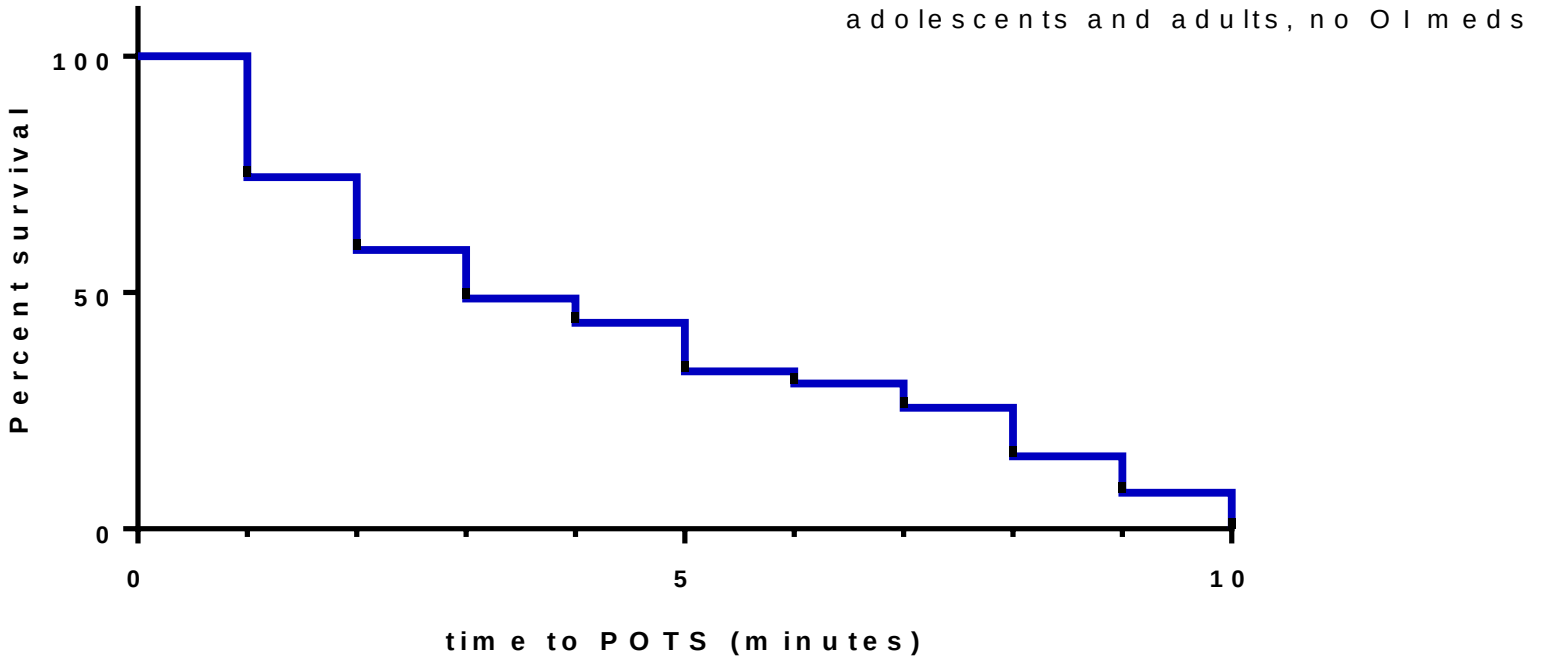
POTS and NMH can occur together



Historical questions with high yield in OI

- How long can you stand still before feeling unwell?
- How do you feel in the following settings:
  - Waiting in line, shopping?
  - Standing at a reception, in chorus, at a service?
  - After taking a hot shower, bath, or sauna?
  - In a warm environment (in a hot room, on a hot day)?
- Do you feel lightheaded or unwell …
  - when you stand for more than 5 minutes?
- Have you ever fainted?
- Do you study in a reclining position, with knees to chest, or feet under you?
- Do you fidget and move around when standing?

Orthostatic vitals for only 1-2 minutes misses 50-75% of those who develop POTS over 10 minutes of standing



FATIGUE: BIOMEDICINE, HEALTH & BEHAVIOR
2018, VOL. 6, NO. 4, 179–192
https://doi.org/10.1080/21641846.2018.1512836

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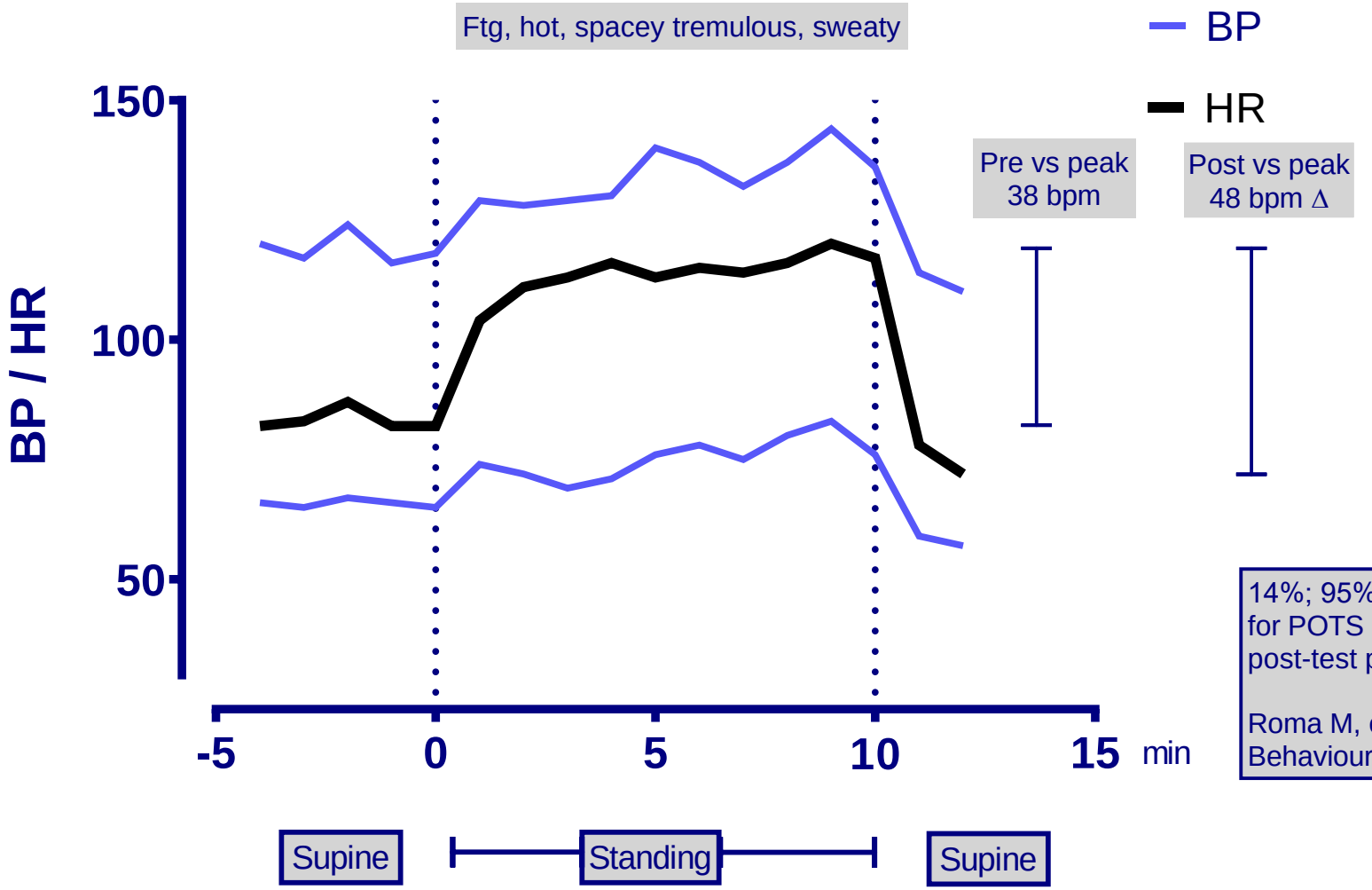
Passive standing tests for the office diagnosis of postural tachycardia syndrome: New methodological considerations

Maria Roma, Colleen L. Marden and Peter C. Rowe

Division of General Pediatrics and Adolescent Medicine, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

*POTS = >=40 bpm HR increase for <20 years of age; >=30 bpm HR increase for >=20 years of age

Value of post-test HR measurement



14%; 95% CI, 7–21%) satisfied HR criteria for POTS using the supine HR from only the post-test period

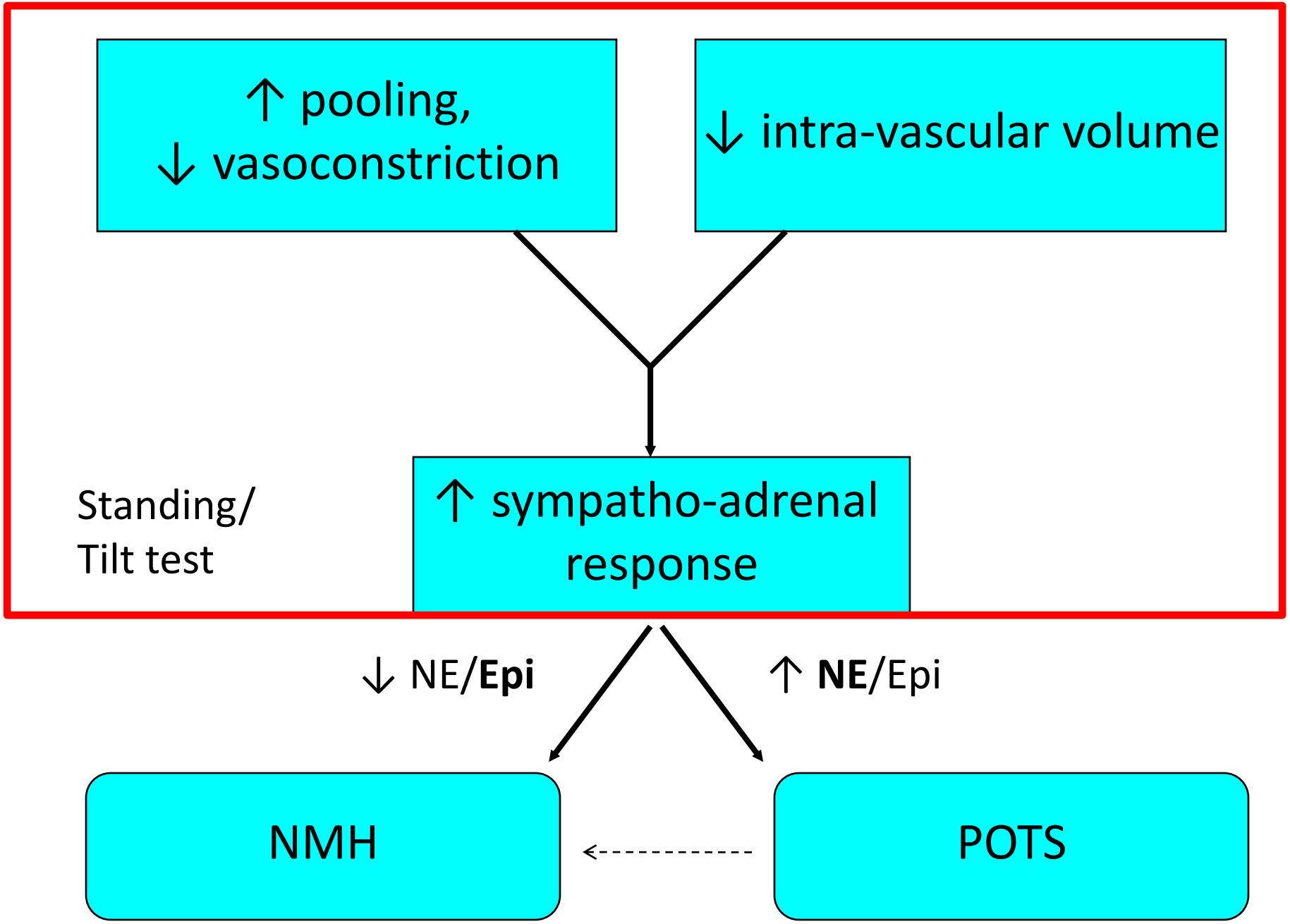
Roma M, et al. Fatigue Biomedicine, Health & Behaviour 2018; 6:179-192

Treatment of Orthostatic Intolerance

- Step 1: Non pharmacologic measures
- Step 2: Treat contributory conditions
- Step 3: Medications
  - Monotherapy
  - Rational polytherapy

Step 1: Non-pharmacologic measures

Where possible, avoid factors that precipitate symptoms.


↑ pooling,
↓ vasoconstriction
↓ intra-vascular volume
Standing/
Tilt test
↑ sympatho-adrenal response
↓ NE/**Epi**
↑ **NE**/Epi
NMH
POTS

Precipitating Factors For NMH & POTS

Increased pooling/decreased volume

- Prolonged sitting or standing
- Warm environment
- Sodium depletion
- Prolonged bed rest/deconditioning
- Varicose veins
- High carbohydrate meals
- Diuretics, vasodilators, alpha-blockers, anti-psychotics
- Alcohol

Precipitating Factors For NMH & POTS

Increased catecholamines

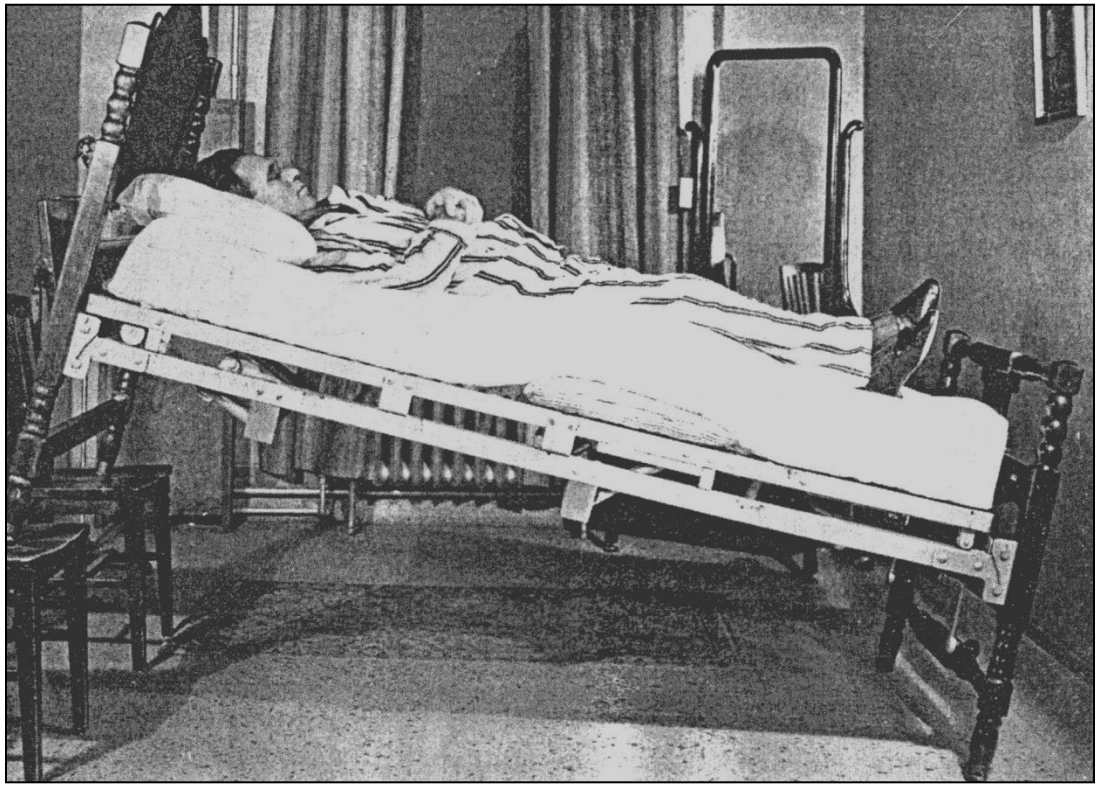
- Stress
- Exercise
- Pain
- Hypoglycemia
- Albuterol
- Epinephrine

Step 1: Non-pharmacologic measures

Raising the head of the bed has an anti-diuretic effect and preserves blood volume at night

MacLean AR, Allen EV. Am Heart J 1944; 27:145

Ten Harkel ADJ, et al. J Int Med 1992; 232:139-145.

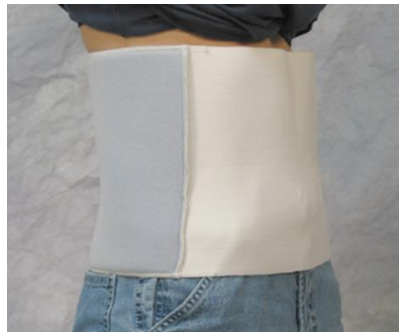


Step 1: Non-pharmacologic measures

Compression garments

- Support hose
  - (20-30 better tolerated than 30-40 mm Hg)
  - (waist high > thigh high > knee high)

- Body shaper garments
- Abdominal binders



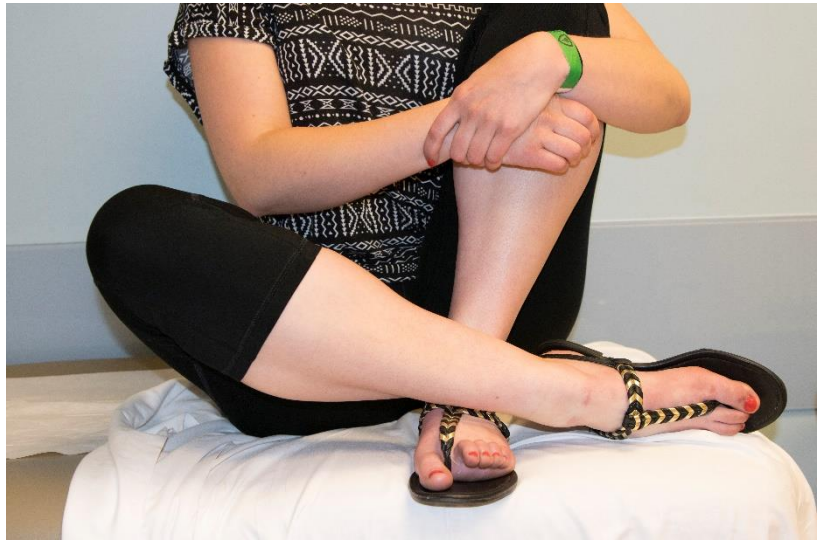
Step 1: Non-pharmacologic measures

Use postural counter-measures

- standing with legs crossed
- squatting
- knee-chest sitting
- leaning forward sitting
- elevate knees when sitting (foot rest)
- clench fists when standing up

[**Use the muscles as a pump**]

Postural countermaneuvers



Step 1: Non-pharmacologic measures

Fluids:	Minimally 2 L per day
	Drink at least every 2 hours
	Need access to fluids at school
	Avoid sleeping > 12 hrs/day
	Cooling garments in hot weather
Salt:	Increase according to taste
	Supplement with salt tablets, ORS

Step 1: Non-pharmacologic measures

Cooling garments

- Neck wraps
- Cooling hats
- Towels
- Vests

http://www.mscooling.com/

https://glaciertek.com/

http://www.mycoolingstore.com/

Oral rehydration products

Introducing Our **Hydration Multiplier**

Liquid I.V.'s Hydration Multiplier is a great-tasting, Non-GMO electrolyte drink mix that utilizes the breakthrough science of Cellular Transport Technology (CTT)™ to deliver hydration to your bloodstream faster and more efficiently than water alone. 1 Liquid I.V. can provide the same hydration as drinking 2-3 bottles of water.

VIEW PRODUCTS

Step 1: Non-pharmacologic measures: Activity

Avoid excessive bed rest/sleeping

For most impaired, start slowly, increase gradually

Recumbent exercise may help at outset

Beware rigid advancement of graded exercise

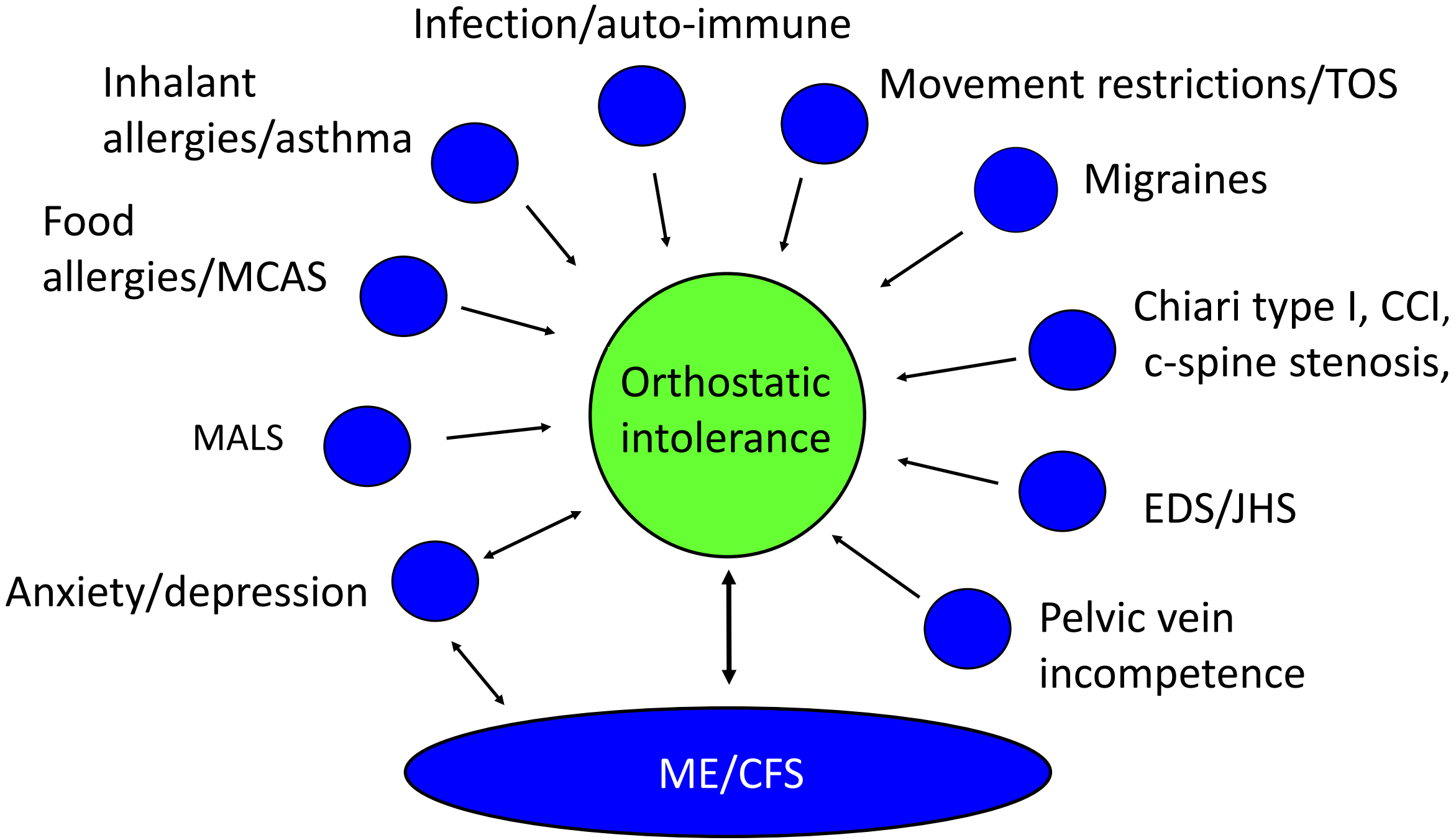
Exercise might not be tolerated before orthostatic intolerance is treated

Manual forms of PT may be a bridge to better tolerance of exercise

[**Complete inactivity is the enemy**]

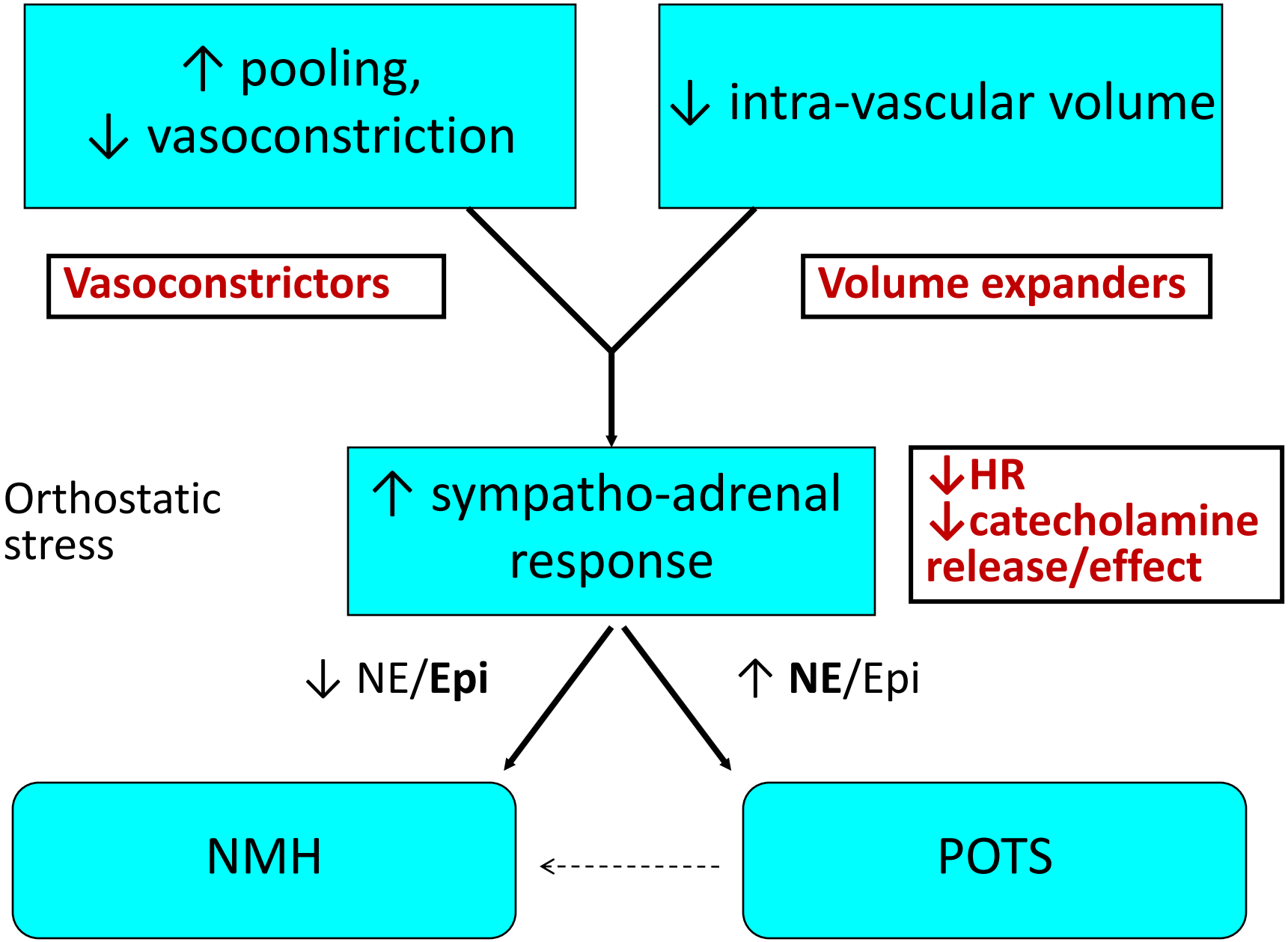
Treatment of Orthostatic Intolerance

- Step 1: Non pharmacologic measures
- Step 2: Treat contributory conditions
- Step 3: medications
  - Monotherapy
  - Rational polytherapy


Infection/auto-immune
Inhalant allergies/asthma
Movement restrictions/TOS
Migraines
Food allergies/MCAS
Chiari type I, CCI, c-spine stenosis,
Orthostatic intolerance
MALS
EDS/JHS
Anxiety/depression
Pelvic vein incompetence
ME/CFS

Treatment of Orthostatic Intolerance

- Step 1: Non pharmacologic measures
- Step 2: Treat contributory conditions
- Step 3: medications
  - Monotherapy
  - Rational polytherapy


↑ pooling,
↓ vasoconstriction
↓ intra-vascular volume
Vasoconstrictors
Volume expanders
Orthostatic stress
↑ sympatho-adrenal response
↓HR
↓catecholamine release/effect
↓ NE/Epi
↑ NE/Epi
NMH
POTS

Pharmacologic Therapy

Vasoconstrictors → Midodrine, dexedrine, methylphenidate, SSRIs, SNRIs; L-DOPS (Droxidopa)

Volume expanders → Sodium (PO & occasionally IV), fludrocortisone, clonidine, OCPs, desmopressin

↓ HR
↓Catecholamine release/effect → β-blockers, disopyramide, SSRIs, ACE inhibitor, ivabradine, methyldopa, pyridostigmine bromide

Fludrocortisone

- A synthetic mineralocorticoid used for the treatment of adrenal insufficiency and autonomic dysfunction
- Promotes reabsorption of sodium in distal tubule
- Pharmacologic effects: volume expansion, improved small vessel response to catecholamines
- Most common adverse effects: headache, swelling, hypertension, hypokalemia, depression
- Usual dose: 0.1 mg daily; doses above 0.2 mg daily often associated with hypokalemia
- Potassium chloride recommended at initiation of therapy (10 mEq per 0.1 mg fludrocortisone)

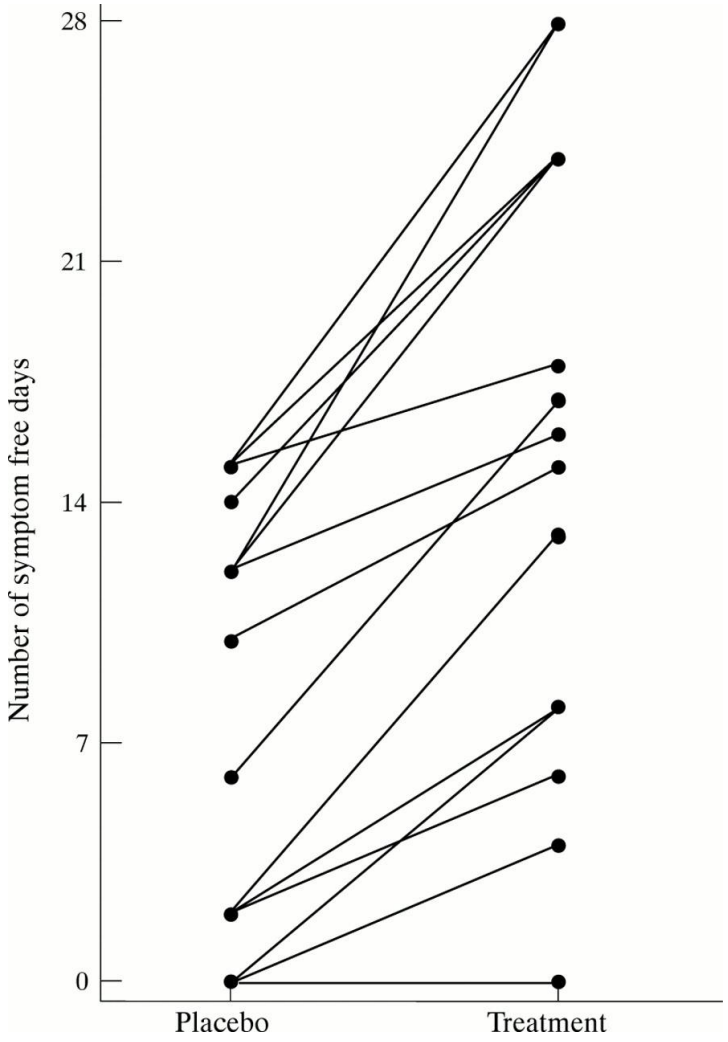
Beta blockers

- Interfere with catecholamine-mediated increases in heart rate (for POTS) and force of heart contraction (to block initiation of NMH reflex)
- May prevent epinephrine-induced vasodilation
- Most common adverse effects: fatigue, LH, decreased mood, cough/wheeze in asthmatics
- Usual dose for adolescents:
  - Atenolol 25 mg, increasing q3-7 days by 12.5 mg to 1 mg/kg (resting HR should be no lower than 50 bpm)
  - "Less is more" (Raj S, Circulation, 2009)

Midodrine

- Alpha-1 agonist vasoconstrictor; no CNS effect
- Duration of action only 4 hours
- Common adverse effects: scalp tingling, paresthesias, piloerection, hypertension
- Usual dose for adolescents/adults:
  - 2.5 mg q4h while awake for 3 days
  - Increase by 2.5 mg per dose q3-7 days until desired effect or to max of 10 mg per dose
  - 4^{th} dose OK if > 2 hours before bed; some need 10-15 mg/dose

Number of symptom free days during midodrine (treatment) or placebo study periods.



10/16 vs. 2/16 with syncope had normal HUT after 1 mo., and more symptom free days (P< .0001)

Ward C R et al. Heart 1998;79:45-49

Stimulants

- Vasoconstrictors with CNS effects
- Dosing similar to that for ADHD
- Most common adverse effects: insomnia, reduced appetite, moodiness, increased lightheadedness, agitation.
- Usual dose for adolescents:
  - Dextroamphetamine SR: start at 5 mg qAM, raise every 3-7 days by 5 mg as tolerated to 20-30 mg/day
  - Methylphenidate SR: start at 10 mg, increasing every 3-7 days by 10 mg as tolerated to 30-50 mg/day

Stimulants: references

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- Young J. Use of lisdexamfetamine dimesylate in treatment of executive functioning deficits and chronic fatigue syndrome: A double blind, placebo-controlled study. Psychiatry Res 2013; 207:127

SSRI/SNRI

- Inhibit the reuptake of serotonin (+/- NE) at nerve terminals, leaving ↑ serotonin (+/- NE) available.
- Serotonin can have a vasoconstricting effect. One RCT shows efficacy for paroxetine in NMH.
- Especially helpful in patients with co-morbid anxiety or depressed mood, or pain
- Adverse effects: occasionally worse LH or worse fatigue; bruising, sweating, reduced libido, diarrhea or nausea, or insomnia.
- Increased risk of suicide in the early phase of treatment, lower risk of suicide later in those with severe depression

Clonidine

- Alpha-2 adrenergic receptor agonist. Reduces sympathetic nervous system outflow; can lead to an expansion of blood volume in those with OI.
- Second line treatment for ADHD; can improve sleep when taken at night.
- Most common side effects: worse fatigue and lightheadedness (due to the anti-hypertensive effect), and dry mouth. Must wean off slowly to avoid rebound hypertension.
- Usual dose for adolescents: 0.05 mg at night for 3-7 days, then increase to 0.1 mg at night.

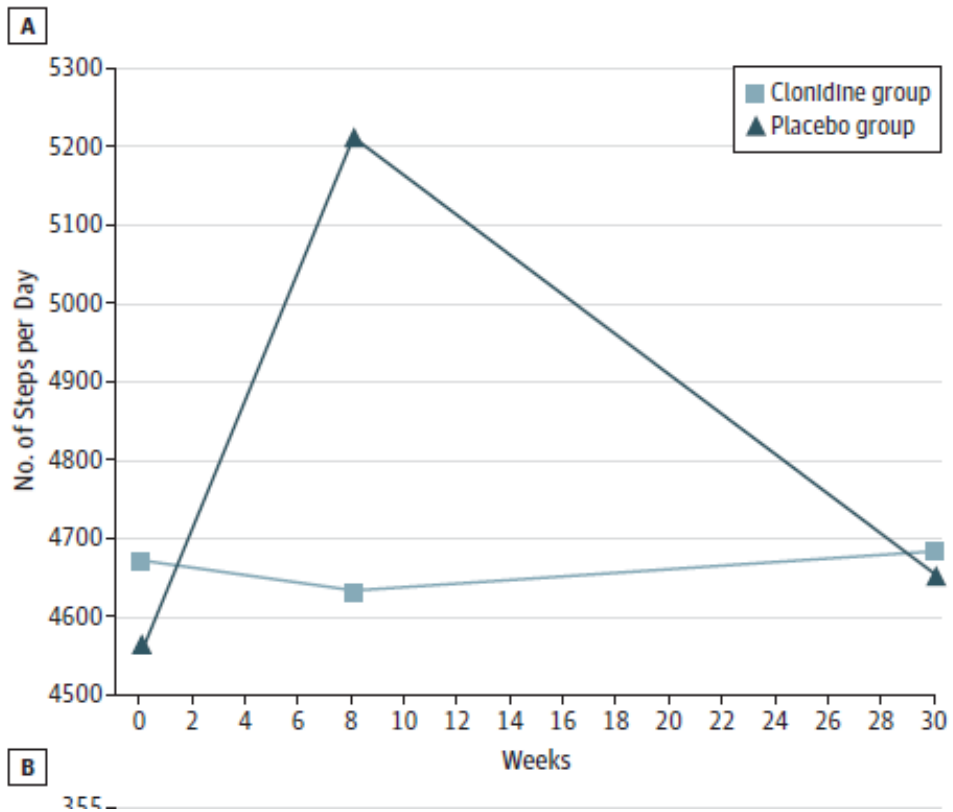
Original Investigation

Disease Mechanisms and Clonidine Treatment in Adolescent Chronic Fatigue Syndrome

A Combined Cross-sectional and Randomized Clinical Trial

Dag Sulheim, MD; Even Fagermoen, MD; Anette Winger, RN, MA; Anders Mikal Andersen, BSc; Kristin Godang, BSc; Fredrik Müller, MD, PhD; Peter C. Rowe, MD, PhD; J. Philip Saul, MD; Eva Skovlund, PhD; Merete Glenne Øie, PhD; Vegard Bruun Wyller, MD, PhD

JAMA Pediatr. doi:10.1001/jamapediatrics.2013.4647
Published online February 3, 2014.



Clonidine not effective for the entire group with ME/CFS, but can be helpful for selected patients.

Pyridostigmine bromide

- Acetylcholinesterase inhibitor
- Improves cardiovagal tone, lowering HR; other mechanisms may also play a role
- Typical doses:
  - Start with 30 mg twice/day- three times/day
  - Increase gradually to 60 mg 2-3 times daily
- Adverse effects: usually well tolerated, but can cause nervousness, muscle cramps or twitching, nausea, vomiting, diarrhea, stomach cramps, increased saliva, anxiety, and watering eyes.

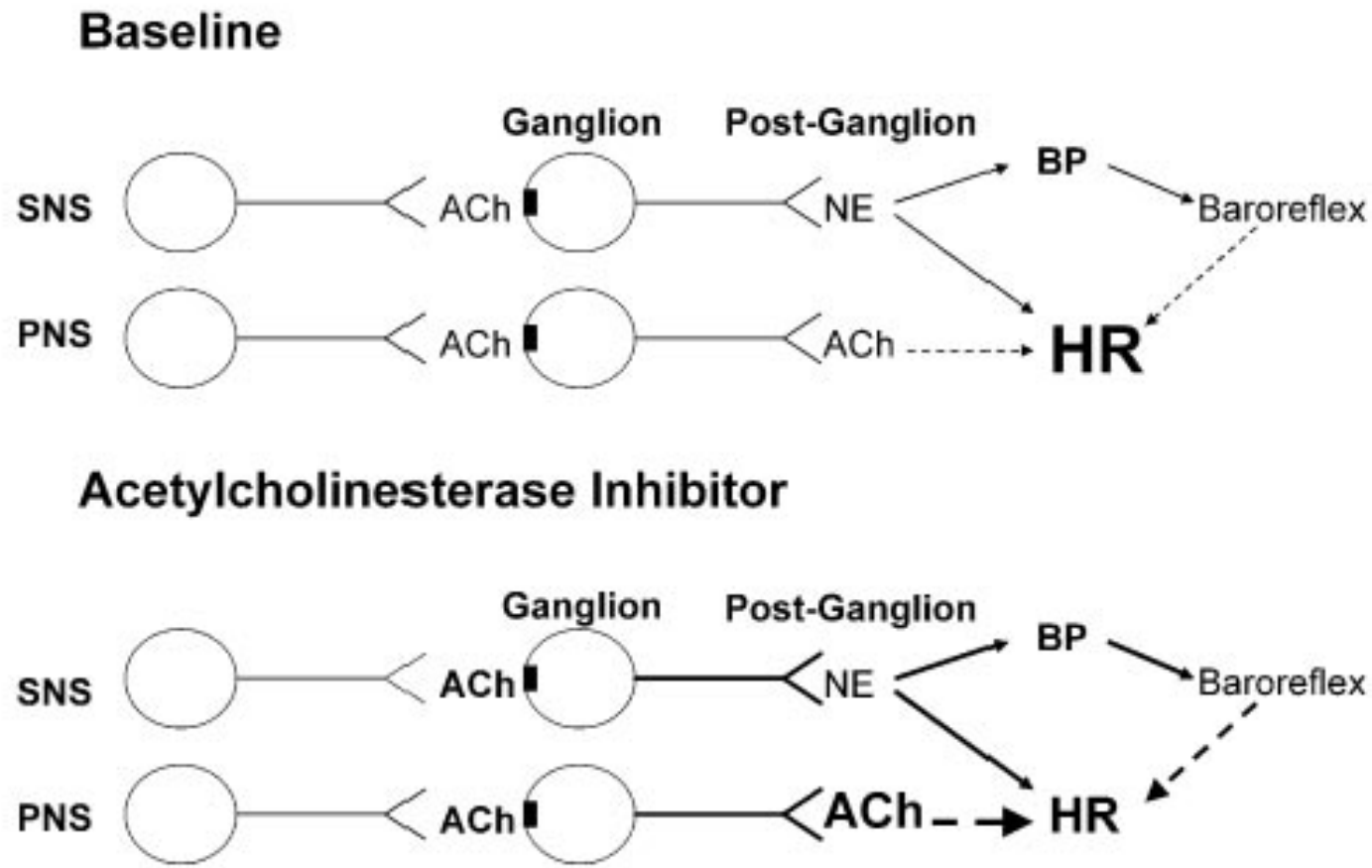


Figure 4. Role of acetylcholinesterase inhibition in heart rate and blood pressure control. See text for details. SNS indicates sympathetic nervous system; PNS, parasympathetic nervous system; ACh, acetylcholine; NE, norepinephrine; BP, blood pressure; and HR, heart rate.

Raj SR. Circ 2005;111;2734

Pyridostigmine in OI

(Singer W, et al. J Clin Neurophysiol, 2006:23;477-82)

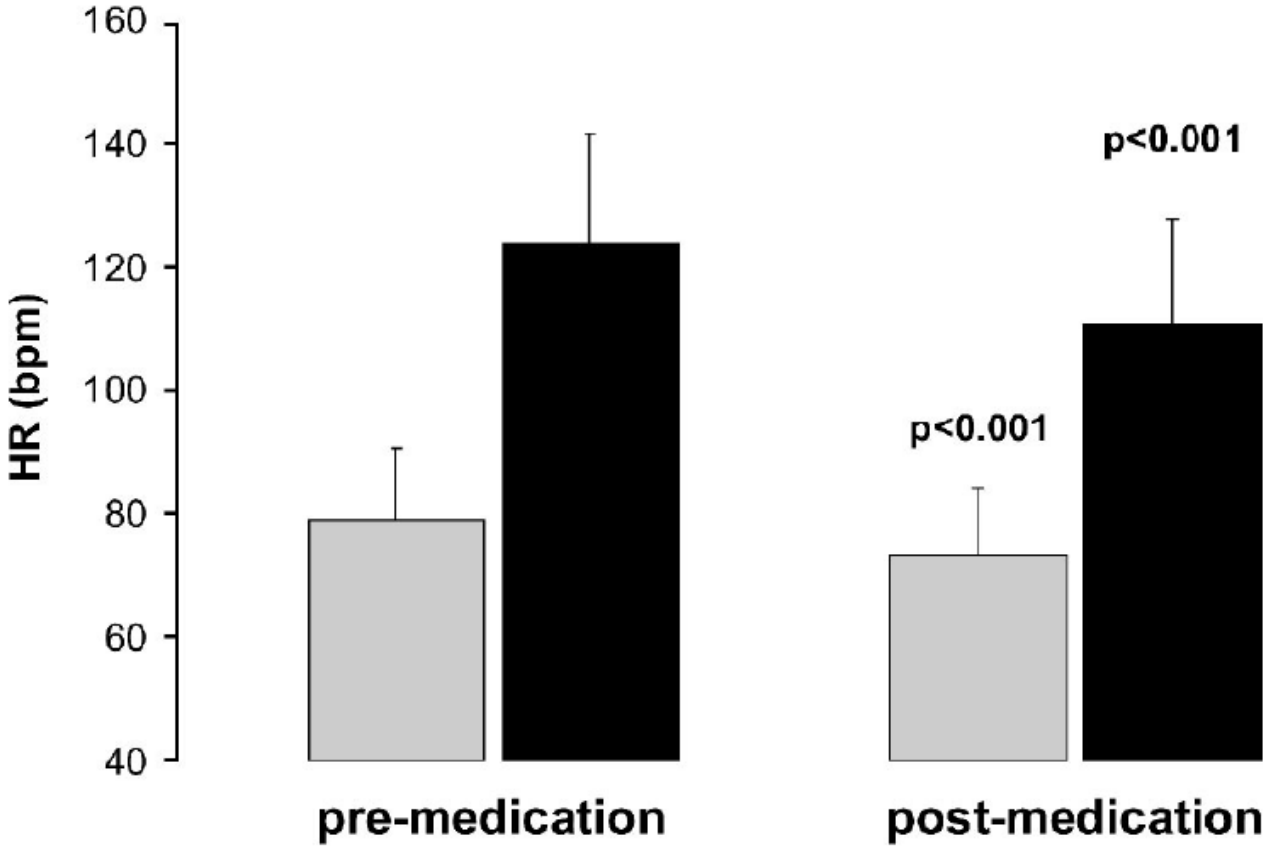


FIGURE 1. Heart rate in the supine position *(light bars)* and during head-up tilt *(dark bars)* before and after pyridostigmine.

Neurocardiogenic Syncope: Response to Hormonal Therapy

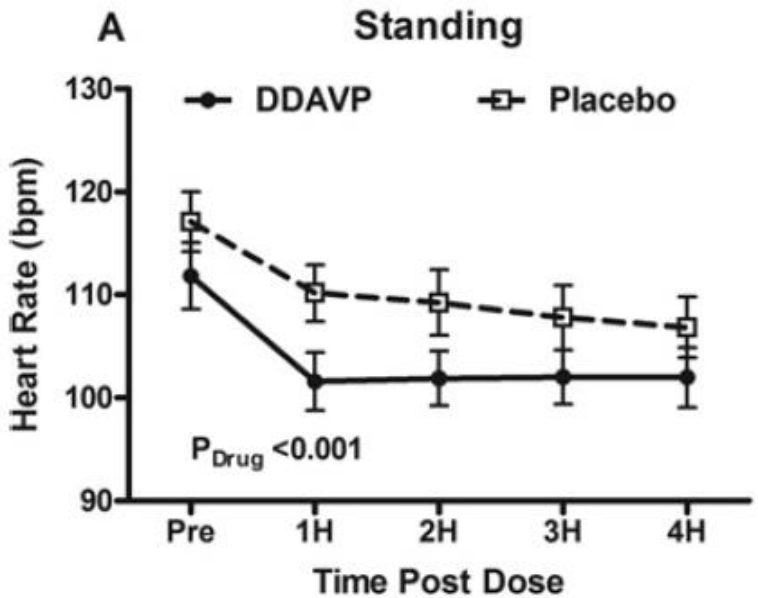
Boehm KE, Kip KP, Grubb BP, Kosinski D. Pediatrics 1997;99:623-5.

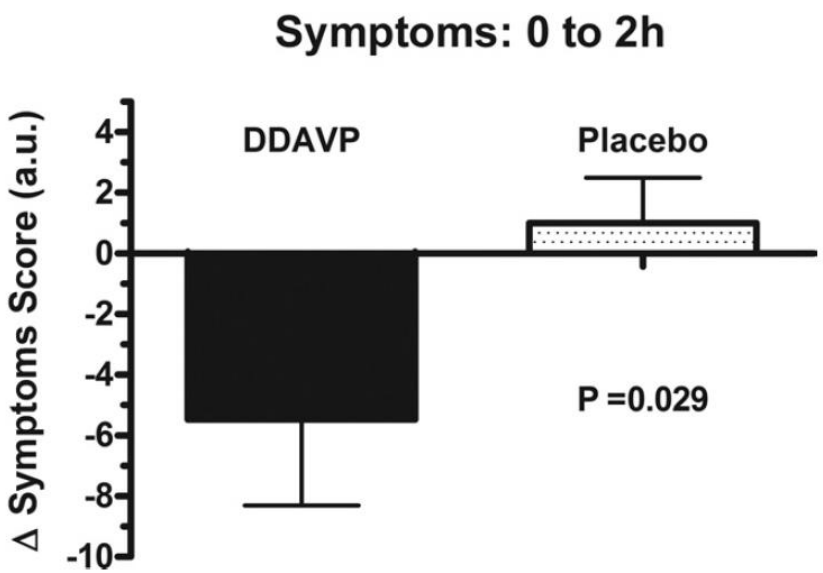
- Retrospective series of 15 females, age 14-39
- All had with POTS or NMH
- Sub-optimal responses to fludrocortisone, beta blockers, methylphenidate, SSRIs
- All had disturbances of the menstrual cycle (oligomenorrhea, metromenorrhagia, worsening of symptoms with periods)
- All improved with either OCPs or medroxy-progesterone acetate

Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome

Samuel T. Coffin, MD,* Bonnie K. Black, RN, CNP,* Italo Biaggioni, MD,*† Sachin Y. Paranjape, BS,* Carlos Orozco, BS,* Phillip W. Black, BS,* William D. Dupont, PhD,‡ David Robertson, MD,*†§ Satish R. Raj, MD, MSCI, FHRS*†

(Heart Rhythm 2012;9:1484–1490)





Ivabradine

- Slows HR by selectively blocking the hyper-polarization-activated, cyclic-nucleotide gated (HCN, or funny) channels in S-A node, w/o major effects on BP, or cardiac and autonomic function.
- Typical dose: 5 mg BID (range 2.5 mg-10 mg BID)
- Cautions:
  - do not use with other CYP3A4 inhibitors (itraconazole, clarithromycin, Ca-channel blockers, grapefruit juice)
  - Monitor HR if used in conjunction with beta-blockers. Do not increase dose if resting HR is below 60 bpm

Europace (2011) **13**, 427–430
doi:10.1093/europace/euq390

Single centre experience of ivabradine in postural orthostatic tachycardia syndrome

Claire McDonald, James Frith, and Julia L Newton*

- Retrospective case series, N=22
- Results:
  - 8 improved HR and fatigue
  - 3 improved HR only
  - 9 stopped (6 no effect, 3 AE, 1 other Rx better)
  - 2 lost to F/U

Ivabradine in children with postural orthostatic tachycardia syndrome: a retrospective study

Arooge Towheed[1], Zeid Nesheiwat[2], Muhammad A Mangi[1], Beverly Karabin[1] and Blair P Grubb[1]

[1]Department of Cardiovascular Disease, University of Toledo, Toledo, OH, USA and [2]Department of Internal Medicine, University of Toledo, Toledo, OH, USA

Cardiology in the Young

2020

doi: 10.1017/S1047951120001341

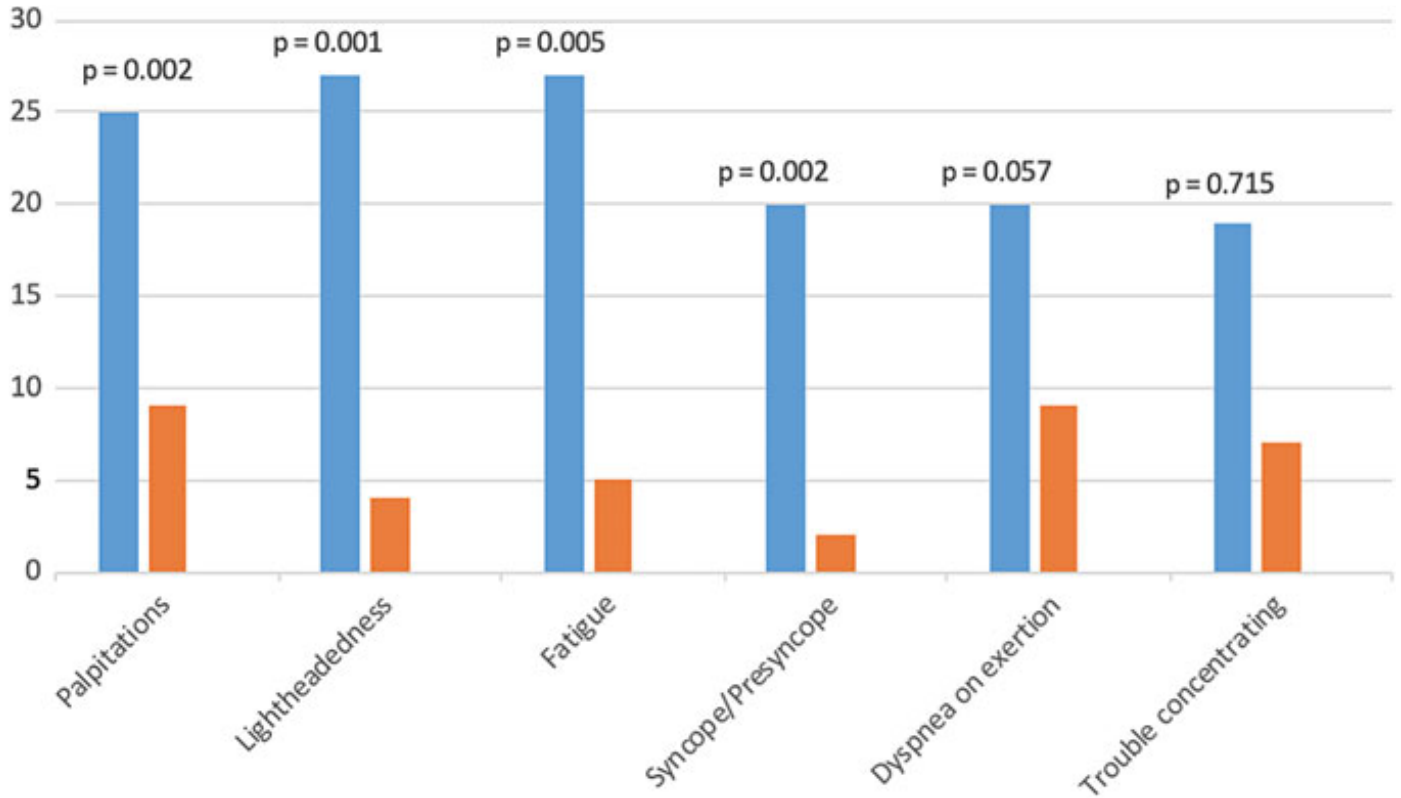


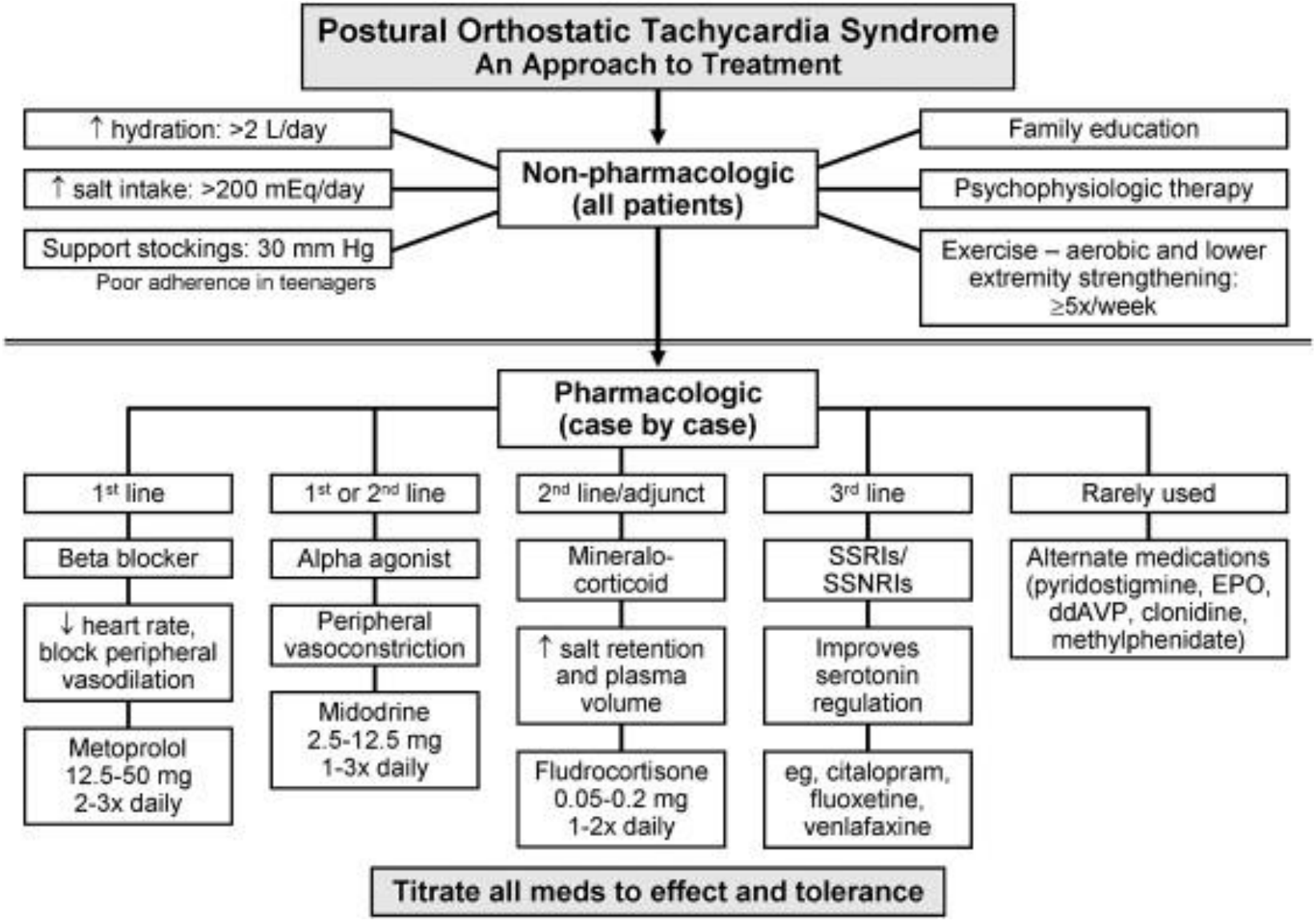
Figure 2. Number of patients reporting symptoms before (blue) and after treatment (orange).

How to select initial therapy?

Algorithm vs. individualized approaches

Caveat: *we have no clinical trial data to support the primacy of one therapy over another for managing OI. Most advice is based on the experience of individual clinicians.*

Algorithmic approach



Johnson JN, et al. Pediatr Neurology 2010; 42:77-85

Individualized approach

- SBP < 110: fludrocortisone, midodrine
- Increased HR at baseline: β-blocker, ivabradine if HR > 100 bpm
- Based on other clinical clues

  Increased salt appetite: fludrocortisone

  HA: β-blocker

  Dysmenorrhea/worse fatigue with menses: birth control pill or Depo-Provera

  Anxiety/low mood: SSRI, SNRI, clonidine

  Myalgias prominent: SNRI

  Hypermobility: stimulant, midodrine

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- Autonomic Neuroscience 2018 (entire issue on POTS)

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- Grants from NIAID, DoD, CFIDS Association of America
- Sunshine Natural Wellbeing Foundation (endowed Chair)
- Research Coordinator Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma)
- Many families and patients:
  - Special thanks to the following families:

    Boies, Bowen, Caldwell, Cornell, Ellen, Fox-Penner, Kelly, Kiely, Lauver, McFerron, Newbrand, Scheidlinger, Smith, and Vogel.