Managing Orthostatic Intolerance in Ehlers-Danlos Syndrome

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Presenter Disclosure Information

Peter C. Rowe, MD

- No relationships to disclose
- Off-label uses of several drugs will be discussed, where possible supplemented by short-term physiologic studies

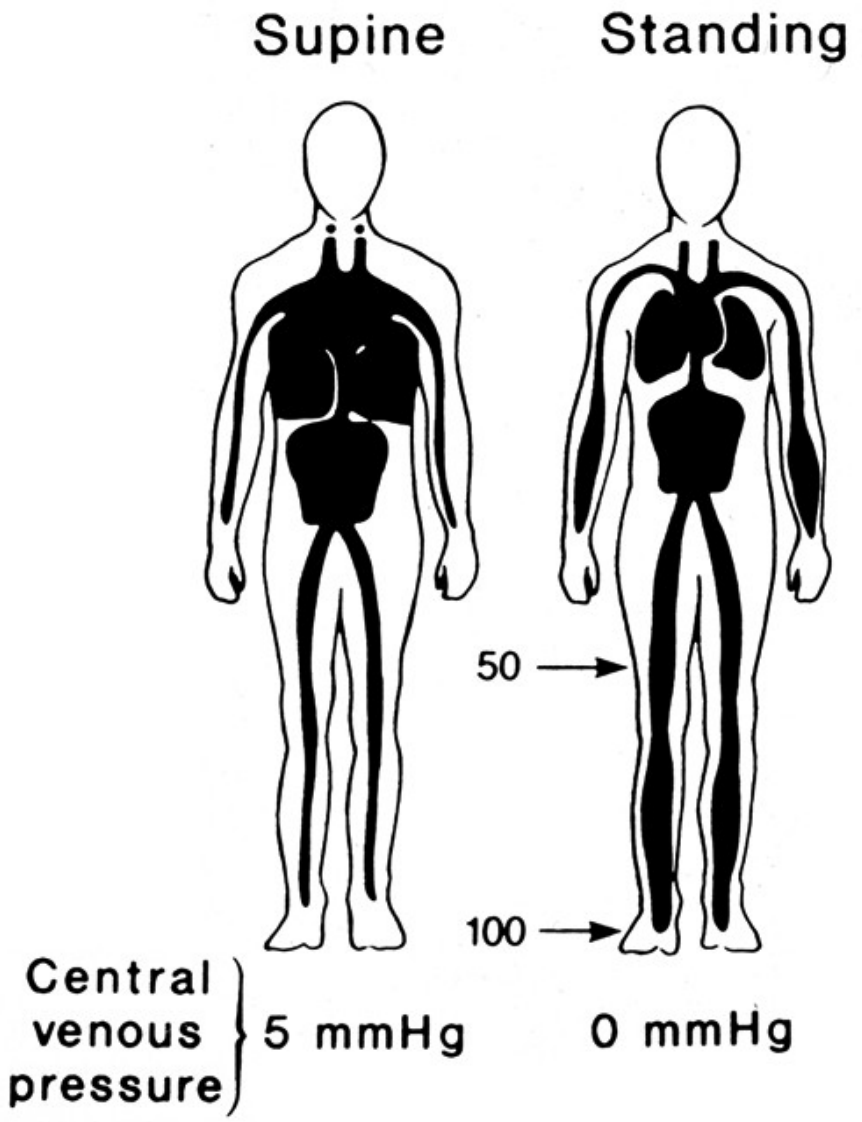
Managing Orthostatic Intolerance in Ehlers-Danlos Syndrome

- Definition and overview of the physiology
- Common forms of OI
- CFS, OI, and EDS
- Treatment of OI
  - Non-pharmacologic measures
  - Treating contributory conditions
  - Medications

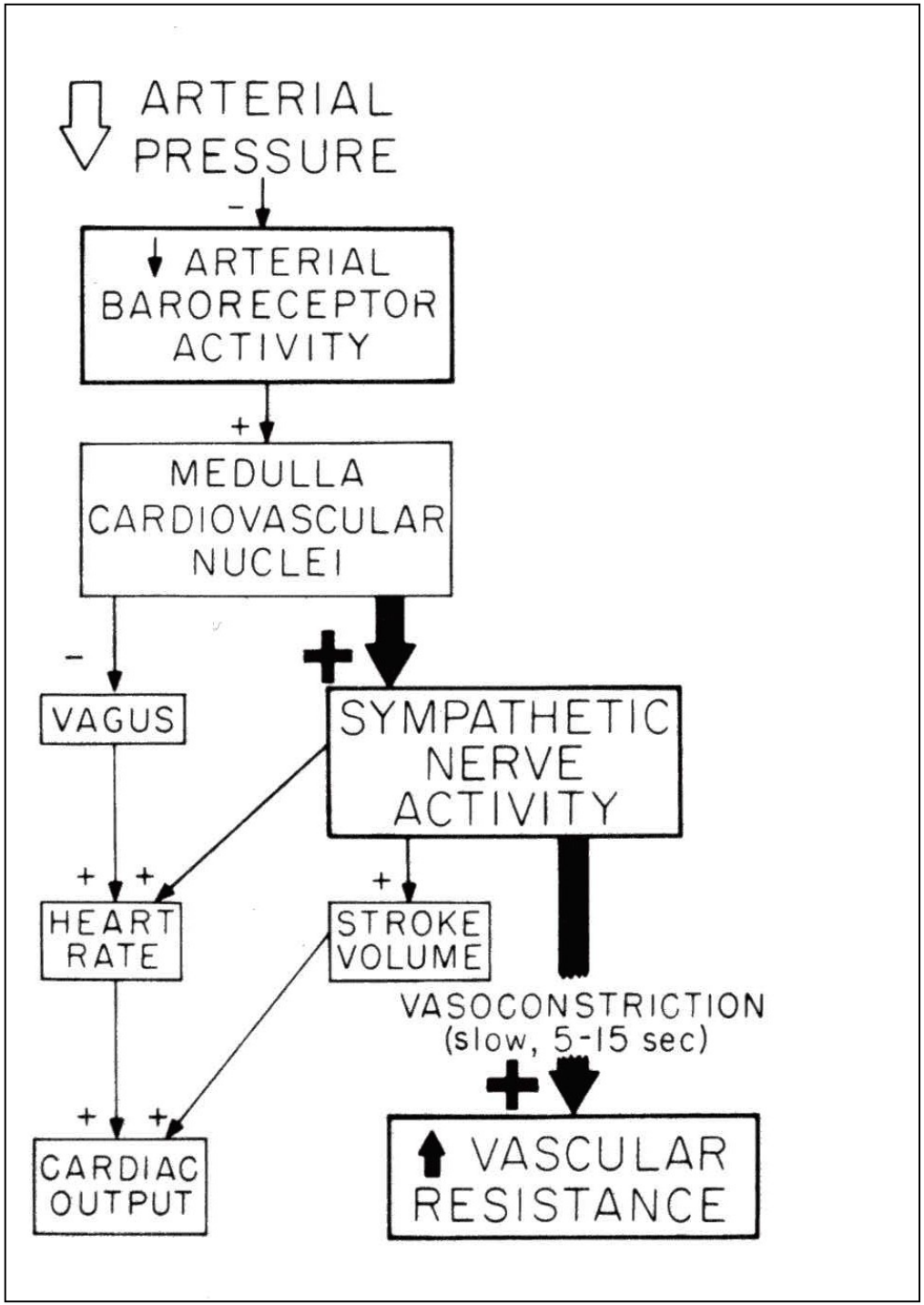
Orthostatic Intolerance

The term “orthostatic intolerance” refers to a group of clinical conditions in which symptoms worsen with quiet upright posture and are ameliorated (although not necessarily abolished) by recumbency.

Modified from: Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol 2009;20:352-8.


Supine
Standing
50
100
Central venous pressure
5 mmHg
0 mmHg

Low PA



Rowell LB

Human Cardiovascular Control, 1993

Symptoms of Orthostatic Intolerance

- Lightheadedness
- Syncope
- Diminished concentration
- Headache
- Blurred vision
- Fatigue
- Exercise intolerance
- Dyspnea
- Chest discomfort
- Palpitations
- Tremulousness
- Anxiety
- Nausea
- Nocturia

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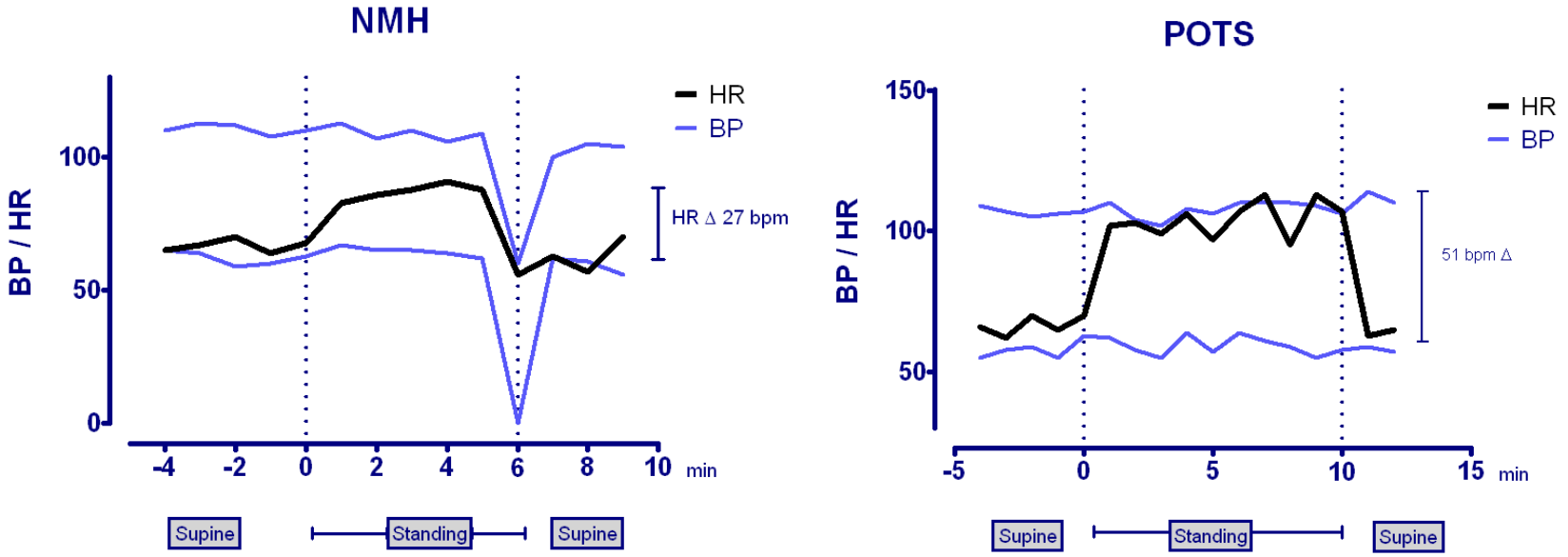
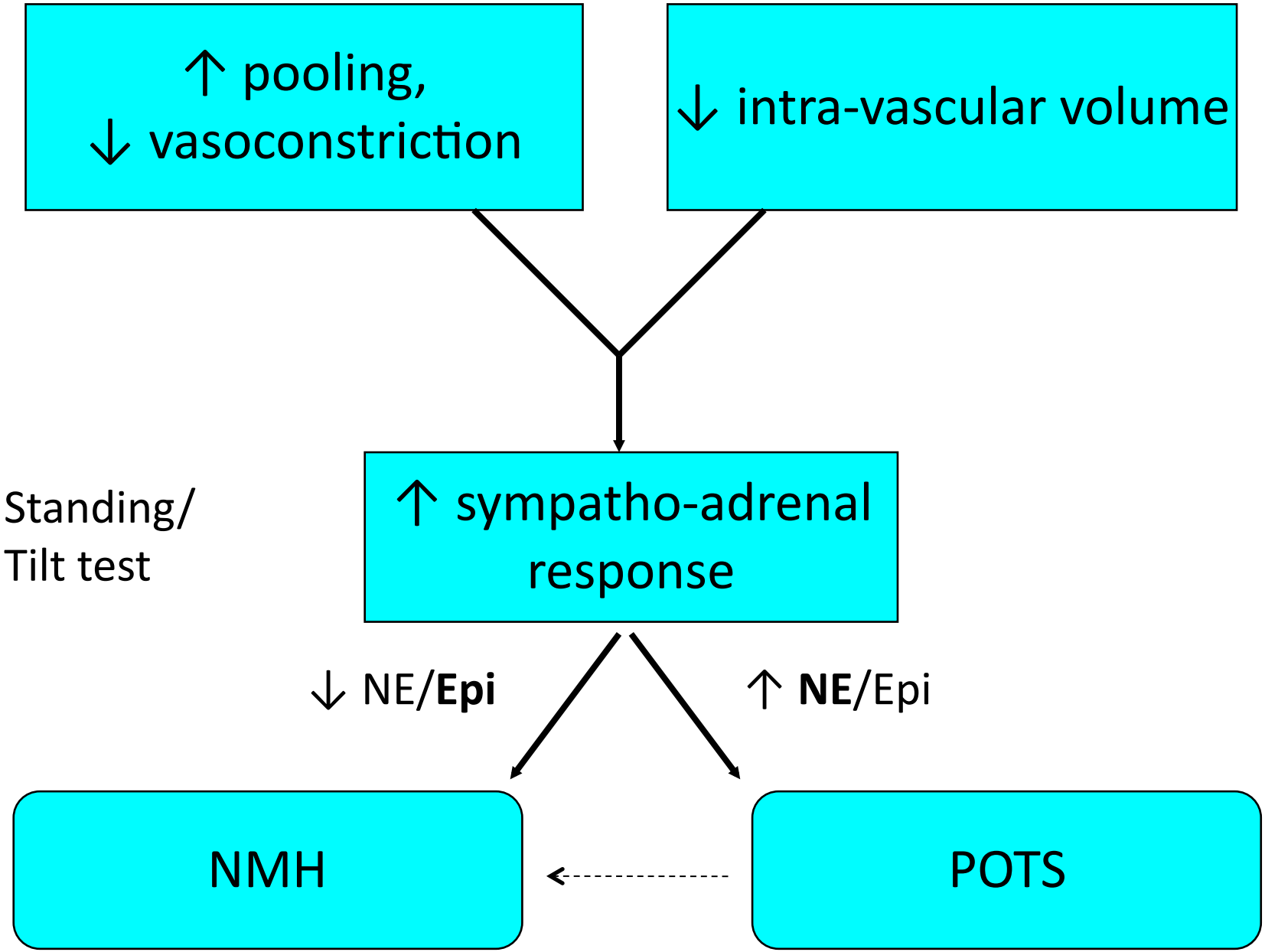
Common forms of orthostatic intolerance



POTS: 30 bpm increase (40 bpm in adolescents) in HR <u>with symptoms</u>, or HR > 120 bpm, in first 10 min of standing or HUT


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

Neurally Mediated Hypotension

also known as

Vasovagal syncope

Neurocardiogenic syncope

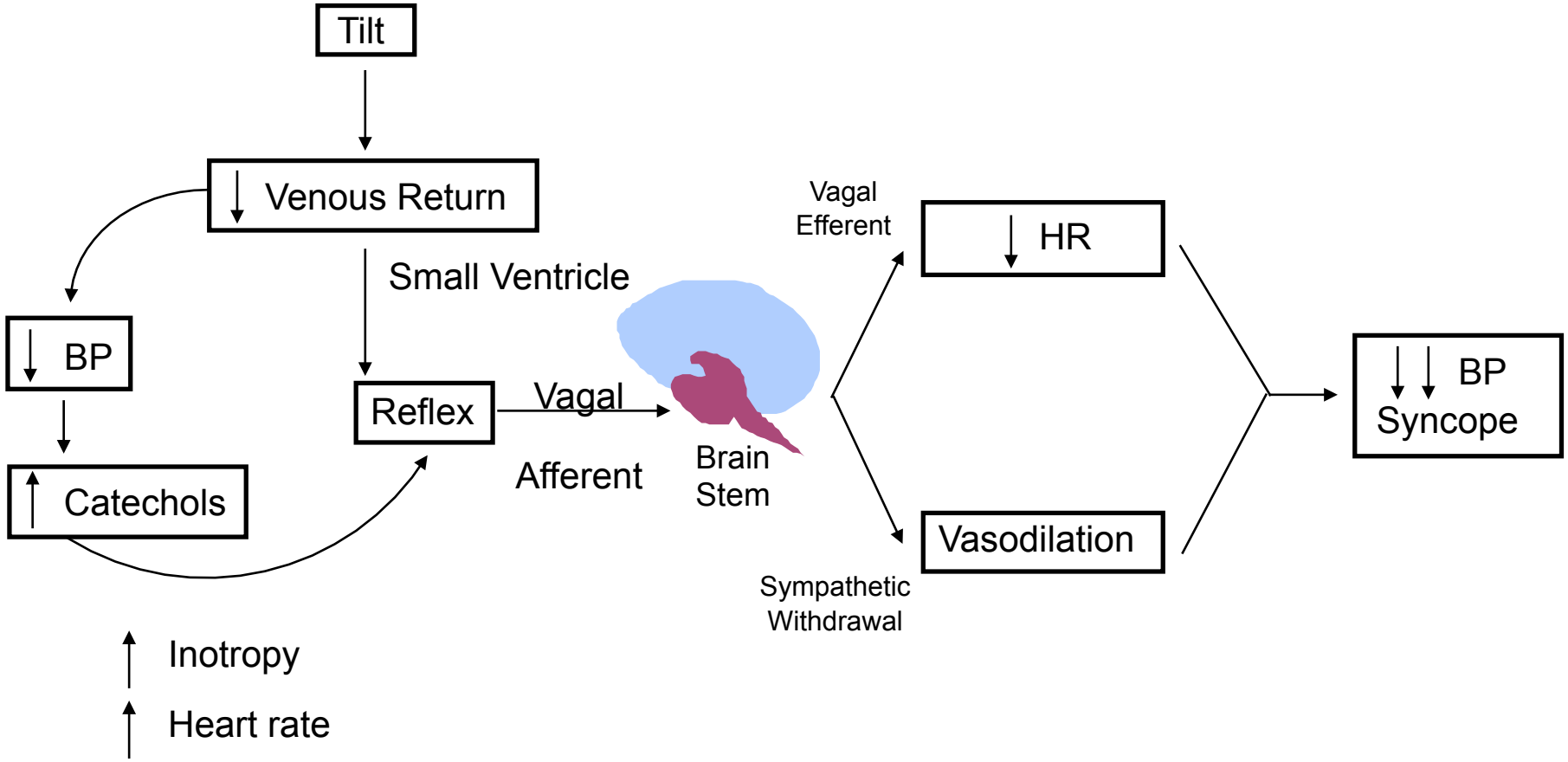
Vasodepressor syncope

Neurally mediated syncope

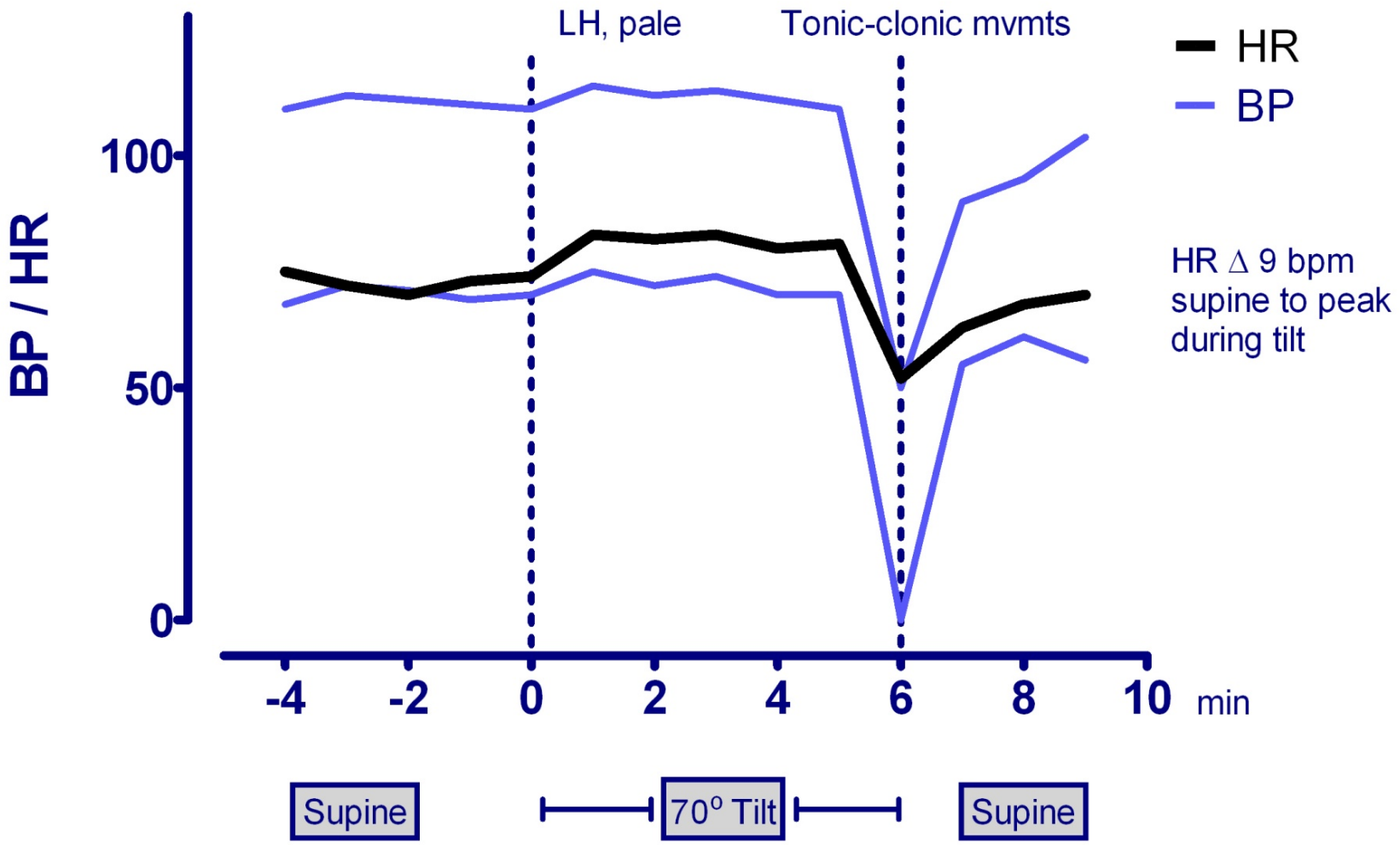
Delayed orthostatic hypotension

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



Chang-Sing P. Cardiol Clinics. 1991;9(4):641-651.


LH, pale
Tonic-clonic mvmts
HR
BP
BP / HR
100
50
0
HR Δ 9 bpm
supine to peak
during tilt
-4
-2
0
2
4
6
8
10
min
Supine
70° Tilt
Supine

Dependent acrocyanosis

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 Definitions

- ***Adults:***

  30 bpm increase in HR, with symptoms, or HR > 120 bpm, in first 10 minutes of standing or head-up tilt

- ***Adolescents:***

  40 bpm increase in HR, with symptoms, or HR > 120 bpm, in first 10 minutes of standing or head-up tilt

POTS: Heterogeneous pathophysiology

- Dysautonomic/neuropathic form (NE > 600; patchy denervation of SNS fibers in legs)
- Central hyperadrenergic form (NE > 1000 pg/mL)
- Hypovolemia common
- Elevated PRA/Aldosterone ratios
- Joint hypermobility common
- Deconditioning common
- Rare AChR ab, NET deficiency, mast cell disorder

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Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

Peter C Rowe, Issam Bou-Holaigah, Jean S Kan, Hugh Calkins

Lancet 1995; **345:** 623–24

The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome

Issam Bou-Holaigah, MD; Peter C. Rowe, MD; Jean Kan, MD; Hugh Calkins, MD

JAMA 1995;274:961-7

Features that Worsen Fatigue in 23 with CFS

	%
Physical exertion	100
Hot shower	78
Prolonged standing	78
Warm environment	74
Lightheaded episode	43

Bou-Holaigah I, Rowe PC, Kan J, Calkins H. JAMA 1995; 274:961-7.

Response To Upright Tilt: CFS

	Abnormal			Normal
	Stage of tilt			
	1	2	3	
CFS	16	3	3	1
CONTROL	0	1	3	10

P < .001; OR for abn. tilt in those with CFS: 55 (95% CI, 5.4-557)

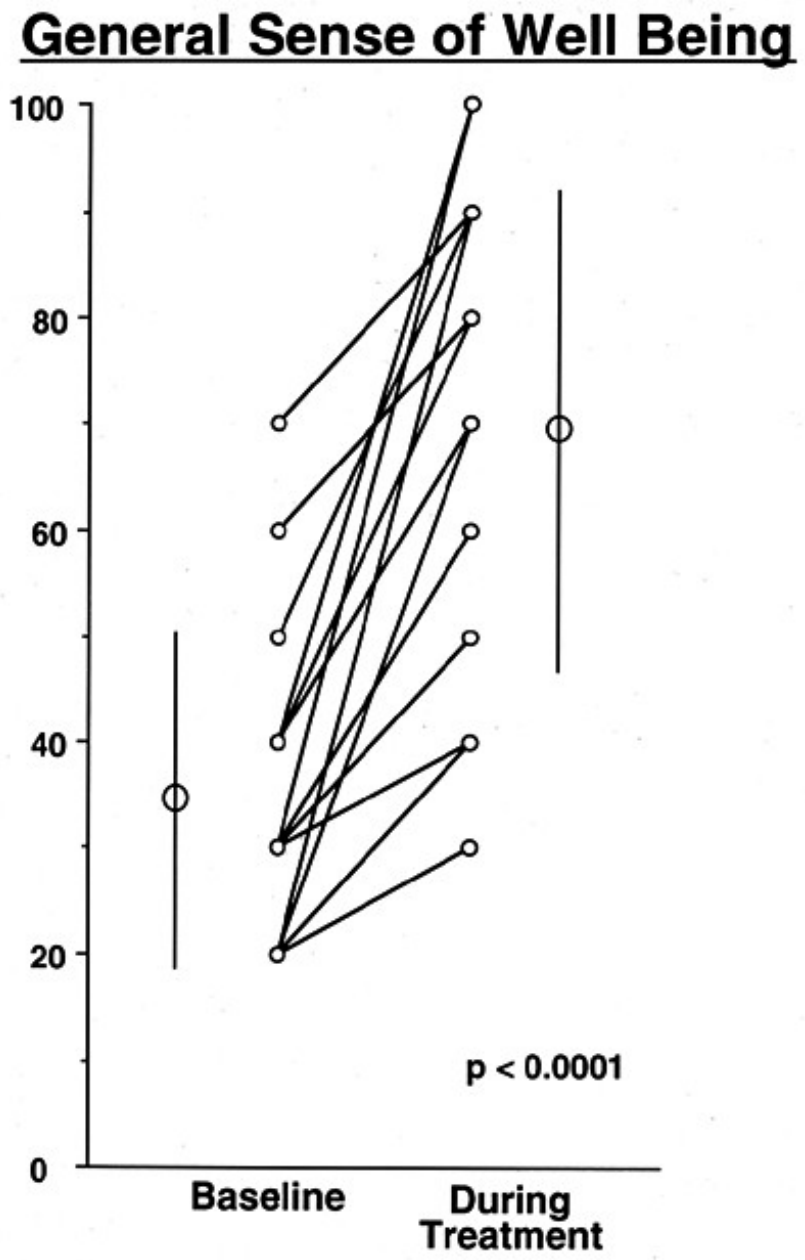
Bou-Holaigah, Rowe, Kan, Calkins. JAMA 1995;274:961-7.

Symptoms During Stage 1 Tilt

	CFS	CONT
Worse fatigue	23	n/a
Lightheadedness	20	0
Warmth	20	0
Nausea	16	0
Diaphoresis	4	0

Bou-Holaigah I, Rowe PC, Kan JS, Calkins H. JAMA 1995;274:961-7.

Response of CFS subjects to open treatment of orthostatic intolerance



JAMA
1995;274:961-7.

Evidence since 1995

- The majority of studies show that OI is strongly associated with CFS
- Upright posture consistently aggravates CFS symptoms, often long before changes in HR, BP
- In a subset with CFS, treatment of OI is associated with improvement in CFS symptoms and function
- Recognition and treatment of OI provides an avenue for pragmatic, individualized treatment of symptoms in those with CFS

What does this have to do with EDS?

What does this have to do with EDS?

Classical EDS: “Fatigue is a frequent complaint.”

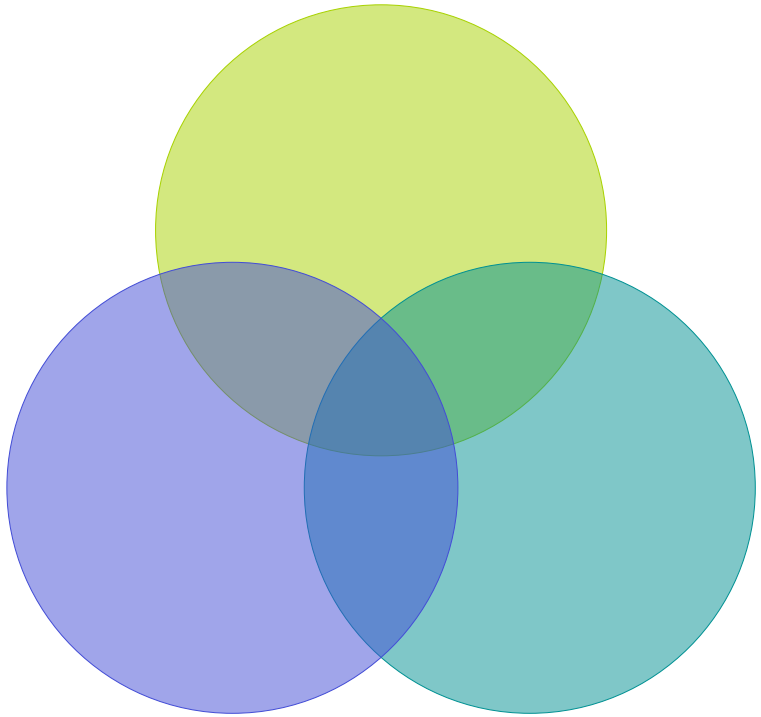
Beighton P, et al. Ehlers Danlos Syndromes: Revised nosology, Villefranche, 1997

Of 273 Dutch EDS subjects, 77% reported severe fatigue; for 57%, fatigue was 1 of the 3 most important symptoms

Severe fatigue was more common in hypermobile than classical EDS (84% vs. 69%; P=.032)

Voermans NC, et al. Fatigue is a frequent and clinically relevant problem in EDS
Semin Arth Rheum 2010; 40:267-74

EDS/
Joint hypermobility



Orthostatic Intolerance

CFS

Proposed mechanisms for the association of JH/EDS and OI syndromes

1. Connective tissue laxity in blood vessels allows increased vascular compliance, promotes excessive pooling during upright posture, leading to diminished blood return to the heart, and thus to OI symptoms. (Rowe PC, et al. J Pediatr 1999;135:494-9)
2. Physical inactivity as a result of joint dislocations and pain "may be disabling due to associated anxiety, depression, and a somatosensory amplification state; this may lead to secondary hypersympathetic responses triggered by fear of pain on standing." (Benarroch EE. Mayo Clin Proc 2012;87:1214-25)
3. Peripheral neuropathy (Gazit et al. Am J Med 2003;115:33-40)
4. Other shared factor
5. Could the excessive mobility of the cervical cord lead to transient, dynamic compression and autonomic symptoms?

(Holman AJ. Fibromyalgia Frontiers 2012)

Case presentation

24 yr old with fatigue, LH, warmth

L hip dislocation at birth; Rx Pavlik harness for 3 months

Active in gymnastics and dance

Headaches in early adolescence, q 2weeks in high school, typically worse through school day and better after nap

No difference with propranolol

24 yr old with fatigue, LH, warmth

HA less common in college on OCPs; daily during the week off active hormone pills

Aggravating factors for HA: any upright posture, inadequate hydration, skipping meals, warm environments, summer weather

LH since early HS years, especially after rising from seated position, standing in one place, anatomy lab in Physician Assistant school

24 yr old with fatigue, LH, warmth

No syncope, but vision goes black, hearing distant

Brings knees to chest when seated; studies lying down; stays in motion when standing

Hands and feet often appear purple

Sensation of warmth or heat when upright for long periods

24 yr old with fatigue, LH, warmth

Worried about having to stand for long periods of time for clinical rotations in PA school

Energy fairly good

Shoulders sublux easily

HR 60 supine in early AM, 90s during day

Normal mood; laid-back disposition

24 yr old with fatigue, LH, warmth

O/E: Tall, thin young woman

Wt 62 kg; ht 180.2 cm (>97th); BMI 19.1

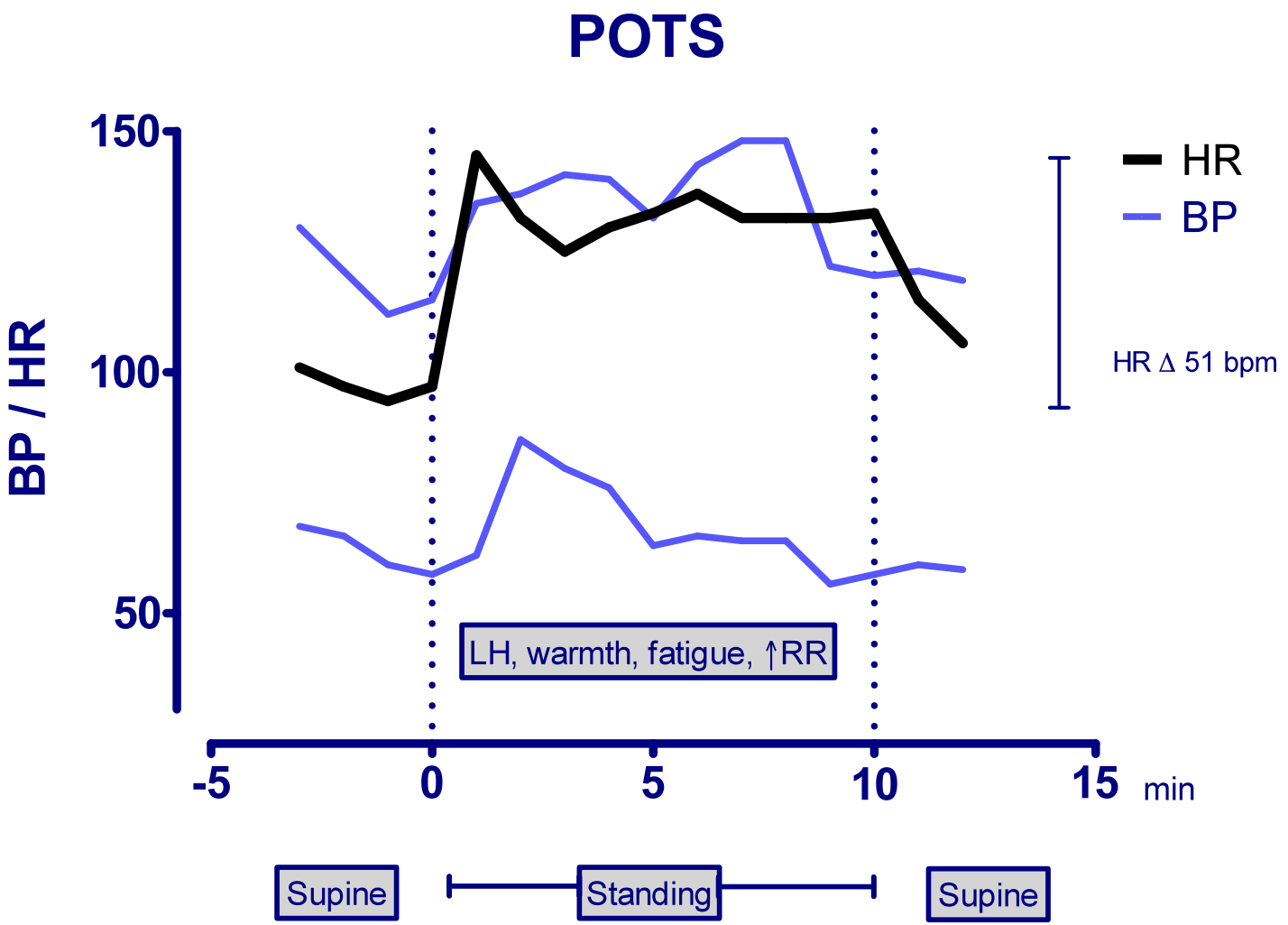
Easy eversion of lids; + Gorlin's sign; can touch tongue to elbow, place leg behind head

BS = 7/9; no arachnodactyly

Lordotic posture

Cardiac exam normal

Echo and labs normal


POTS
150
100
50
BP / HR
HR
BP
HR Δ 51 bpm
LH, warmth, fatigue, ↑RR
-5
0
5
10
15
min
Supine
Standing
Supine

Possible treatments

- Midodrine
- Methylphenidate
- Beta blocker
- Mestinon
- Resume oral contraceptives
- Desmopressin acetate
- ARB/ACE inhibitor

What we tried:

- Midodrine
- Methylphenidate
- Beta blocker
- Mestinon
- Resume oral contraceptives (stopping them associated with ↑symptoms)
- Desmopressin acetate
- ARB/ACE inhibitor

Course

"The atenolol at 12.5 mg seems to be working well. My upright HR has remained lower, ranging from 60-95. Hot flashes are significantly less frequent, no headaches, much easier time with exercising as well. My resting HR has usually been in the high 50s. No side effects. BP 105/70. Should I stay at 12.5 mg or is it OK to go to 25mg?"

Course

- Increased LH and fatigue as temperatures rise in the late spring
- Adds midodrine, with benefit for energy.
- Tries dexedrine as an alternative (sib on this)
- On dexedrine with atenolol, feels 100%.
- Appetite suppression on dexedrine; now uses it only on days when upright longer, taking midodrine on other days

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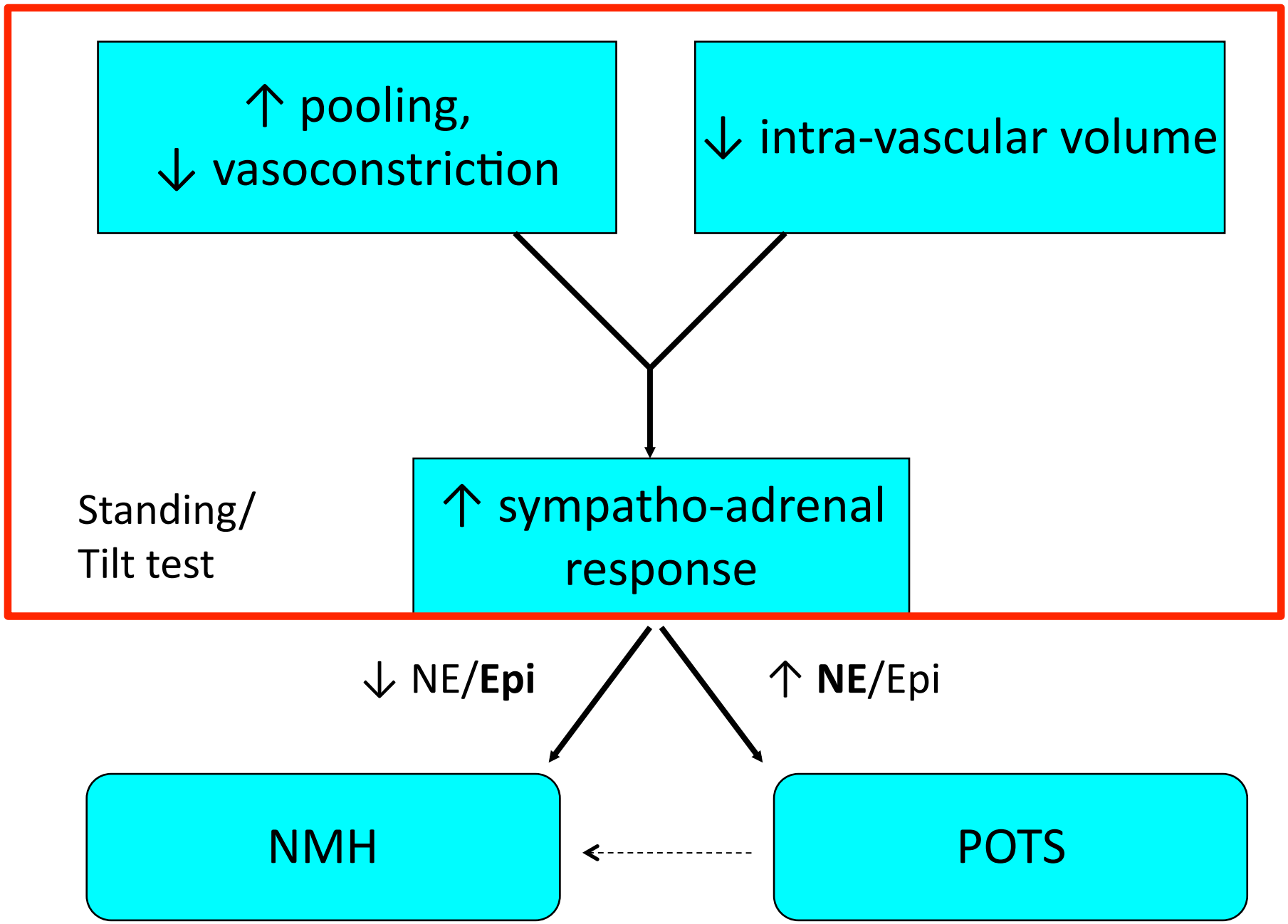
Treatment of OI

- Explanation and demystification
- Regular clinic visits for medical monitoring
- Provide guidance about new treatments
- Help with schooling/work
  - Letters for accommodations (fluids, extra time, flexibility with deadlines)
  - Home and hospital schooling when needed
  - Home tuition when part-time is impossible

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
  Alcohol

Precipitating Factors For NMH & POTS

- Increased catecholamines

  Stress

  Exercise

  Pain

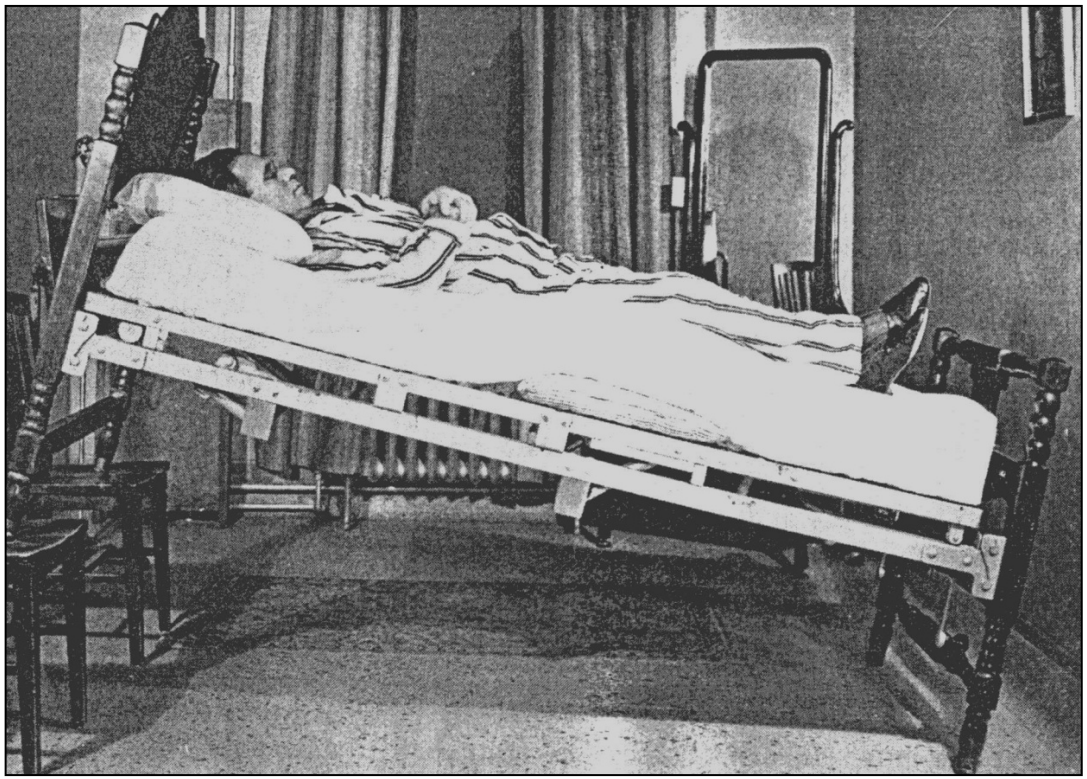
  Hypoglycemia

  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

Step 1: Non-pharmacologic measures

Compression garments

- Support hose (30-40 mm Hg)

  (waist high > thigh high > knee high)
- Body shaper garments
- Abdominal binders


TRAVELSOX
ALTA QUALITÀ
made in Italy


RECHARGE

Step 1: Non-pharmacologic measures

Use postural counter-measures

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

[Use the muscles as a pump]

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

Step 1: Non-pharmacologic measures

Exercise

- Avoid excessive bed rest/sleeping
- For most impaired, start exercise slowly, increase gradually
- Recumbent exercise may help at outset
- Manual forms of PT may be a bridge to better tolerance of exercise

[Inactivity is the enemy]

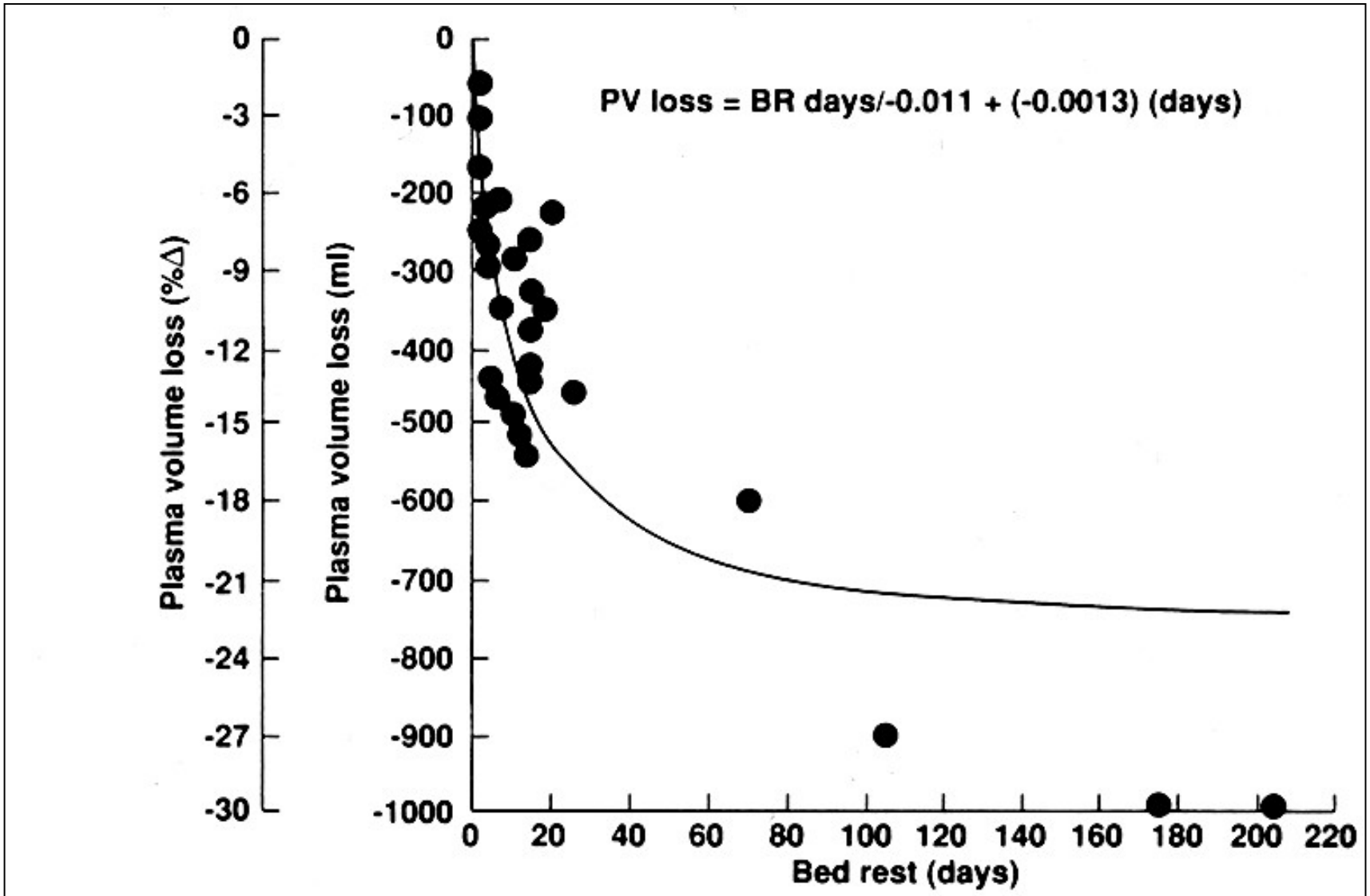
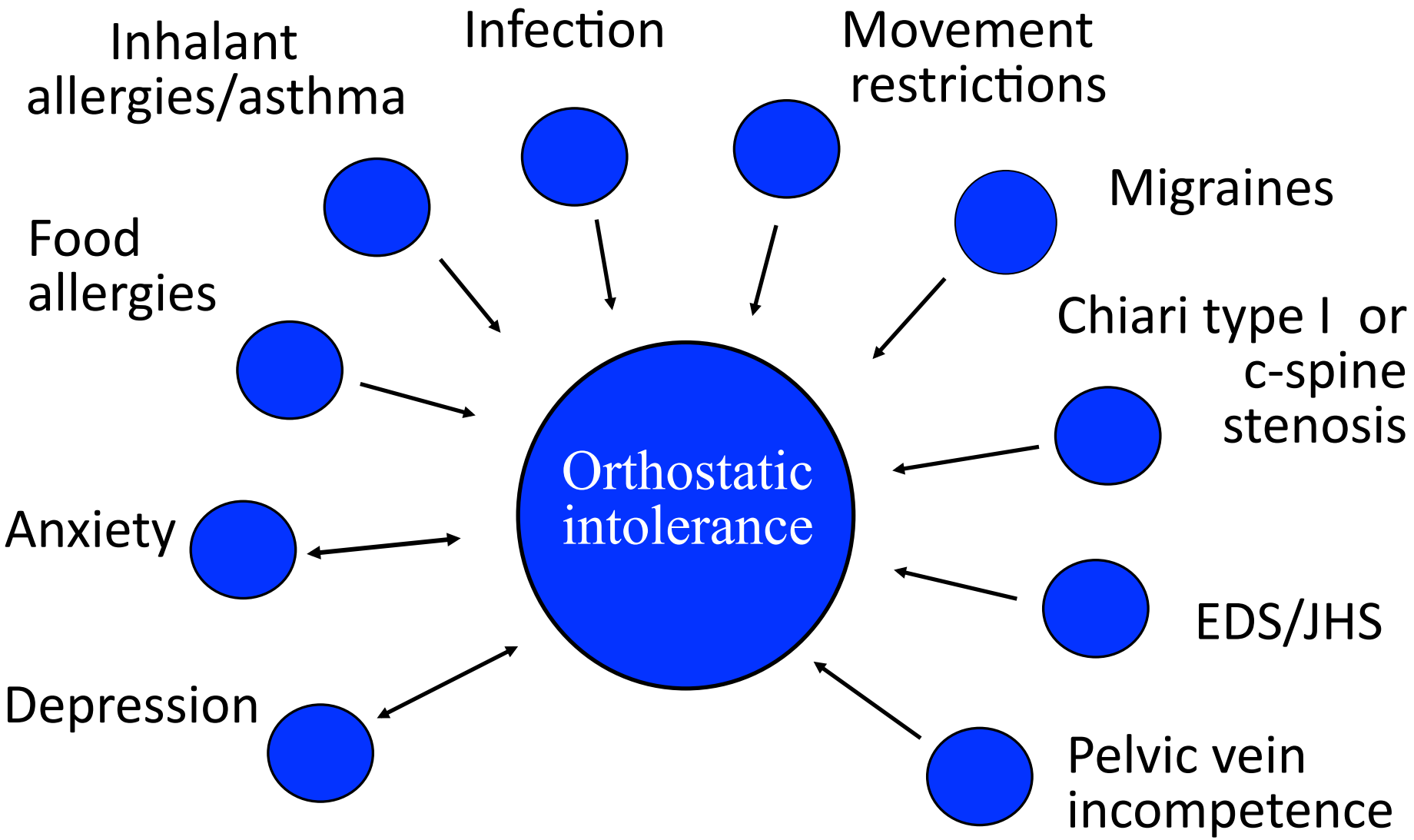


FIG. 39.3. Percent change in plasma volume with data from studies that utilized horizontal bed r
no remedial procedures. [From Greenleaf et al. (130) with permission.]

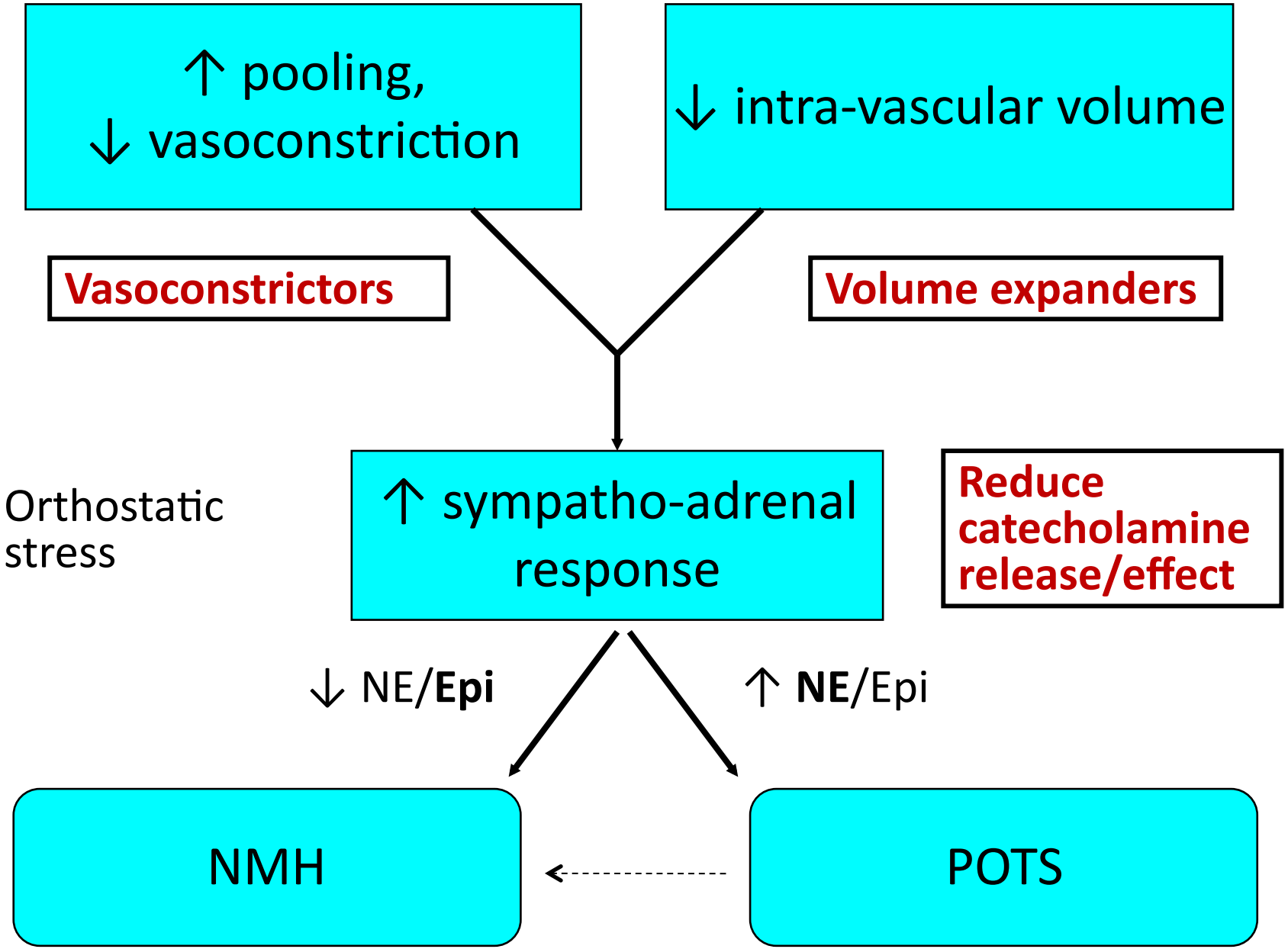
Treatment of Orthostatic Intolerance

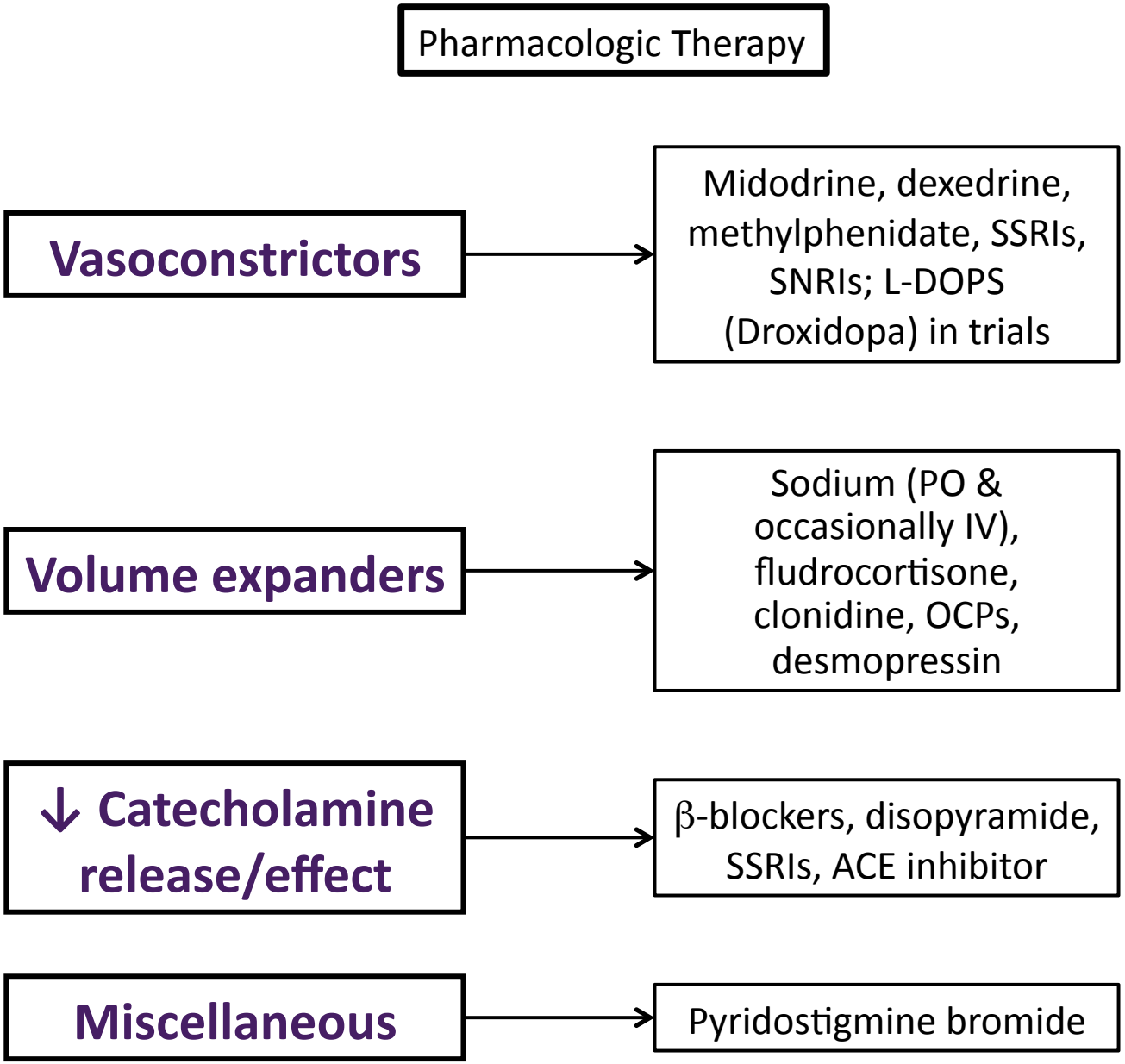
- Step 1: non pharmacologic measures
- Step 2: treating contributory conditions


Inhalant allergies/asthma
Infection
Movement restrictions
Migraines
Food allergies
Chiari type I or c-spine stenosis
Orthostatic intolerance
Anxiety
EDS/JHS
Depression
Pelvic vein incompetence

Treatment of Orthostatic Intolerance

- Step 1: non pharmacologic measures
- Step 2: treating contributory conditions
- Step 3: medications
  - Monotherapy
  - Rational polytherapy


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


Pharmacologic Therapy
Vasoconstrictors
Midodrine, dexedrine, methylphenidate, SSRIs, SNRIs; L-DOPS (Droxidopa) in trials
Volume expanders
Sodium (PO & occasionally IV), fludrocortisone, clonidine, OCPs, desmopressin
↓ Catecholamine release/effect
β-blockers, disopyramide, SSRIs, ACE inhibitor
Miscellaneous
Pyridostigmine bromide

Therapy For Orthostatic Intolerance

- **↑ blood volume**

  Sodium (PO & occasionally IV),

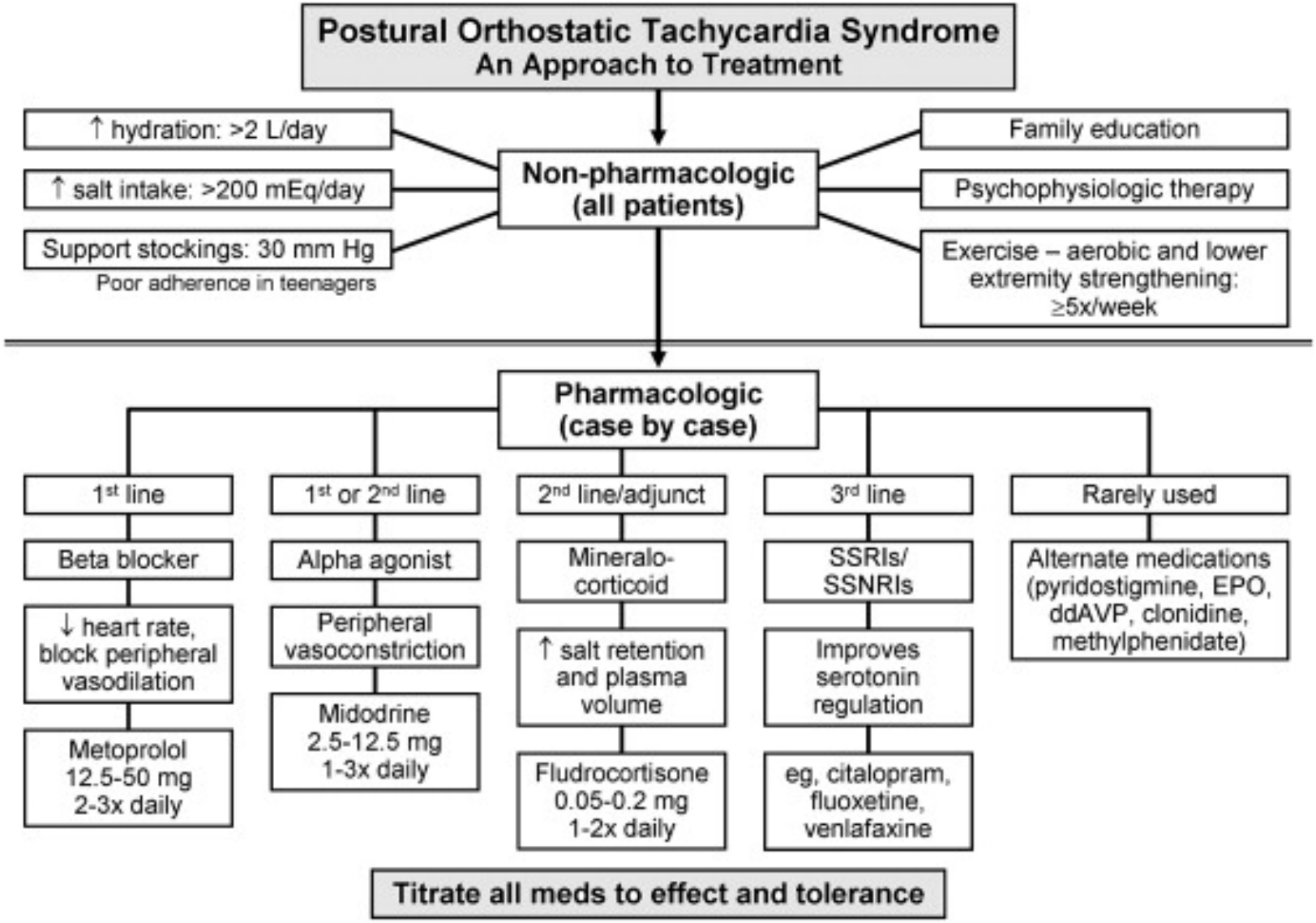
  fludrocortisone, clonidine, OCPs, desmopressin
- **↓ catecholamine release or effect**

  β-blockers, disopyramide, SSRIs, ACE inh.
- **Vasoconstriction**

  Midodrine, dexedrine, methylphenidate, SSRIs, SNRIs; L-DOPS (Droxidopa) in trials
- **Misc:** pyridostigmine bromide

How to select initial therapy?

Algorithm vs. individualized approaches



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

Individualized approach

- SBP < 110: fludrocortisone, midodrine
- Increased HR at baseline: β-blocker
- Based on other clinical clues

  Increased salt appetite: fludrocortisone

  HA: β-blocker

  Dysmenorrhea/worse ftg with menses: OCP, Depo

  Anxiety/low mood: SSRI, SNRI, clonidine

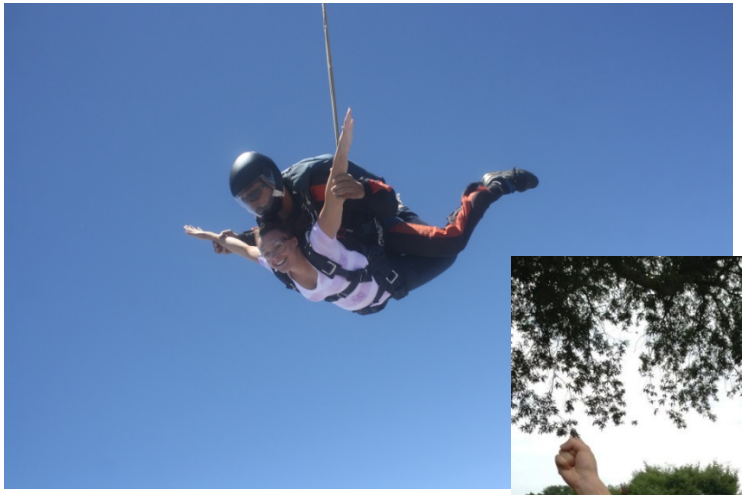
  Myalgias prominent: SNRI

  Hypermobility: stimulant, midodrine

  FH of ADHD: stimulant

Management of orthostatic intolerance

- requires careful attention by the patient and the practitioner to the factors that provoke symptoms
- requires a willingness to try several medications before a good fit is achieved
- requires a realization that meds often can treat symptoms but do not necessarily cure OI
- management of OI is one part of a comprehensive program of care

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RUN FOR THEIR LIVES
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- Volunteer RA Colleen Marden
- Summer students (Marissa Flaherty, Samantha Jasion, Erica Cranston, Jocelyn Ray, Andrew Marden)
- Sunshine Natural Wellbeing Foundation
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  - Boies, Bowen, Caldwell, Cornell, Kelly, Kiely, McFerron, Newbrand, Smith
  - Megan Lauver, Hannah Vogel