• Case presentation
• POTS definitions
• Pathophysiology of POTS
• Treatment of POTS
• Educational challenges and ways to improve transitions back to school
16 yr old with fatigue

Onset of knee pain 1 wk after visiting sister at college who was ill with sore throat, fatigue, myalgias
Fatigue and myalgias develop over the next month
Laboratory tests normal
Exam: Beighton score 4/9
Starts missing school, only attends 4 days in 3rd month
Unrefreshing sleep, losing focus in class, can’t read as before, myalgias worse post-exertion
Has to give up karate, violin lessons, scale back dancing
POTS

Standing

Supine

BP / HR

HR
BP

HR Δ 66 bpm

Supine
Standing
Supine

-5 0 5 10 15 min
Course

No response or adverse effects with 8 medications
School flexible, but only attending sporadically
Finishes 3 courses (independent study) in summer
1 year into illness, starts new school year attending half the days, able to do more, but still has increased fatigue for 3-4 days afterwards.
Gets through Sr. year (on fumes)
1.5 years later: Doing more, less payback; stops meds
2 years later: 95% of normal function; able to attend full-time college classes
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.

Postural Tachycardia Syndrome (POTS)

• Described as early as the 1870s, termed irritable heart, effort syndrome, neurocirculatory asthenia.
• F:M ratio $\sim$ 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*:
  35 bpm increase (Tanaka)
  40 bpm increase (Consensus statement, 2011)
106 healthy controls, mean age $14.5 \pm 3.3$ yrs

654 referred with OI sx

42% of normal controls had HR increment of $\geq 30$ bpm;

95th %ile for orthostatic HR increment in controls was 42.9 bpm

Caveats
Modified from Raj SR, Indian Pacing and EP J 2006; 6:84-99

• Orthostatic tachycardia by itself is not sufficient to make the diagnosis of POTS: orthostatic symptoms must be present (for months in most)

• POTS should only be diagnosed in the absence of other overt causes of orthostatic symptoms or tachycardia (active bleeding, acute dehydration)

• The focus on HR overlooks other autonomic problems (sweating, thermoregulation, bowel motility), and makes it easy to mislabel patients as POTS when they have other important problems (anorexia, panic)
POTS co-morbidities

Ojha, Chelimsky, Chelimsky. J Pediatr 2010
Beyond Postural Tachycardia Syndrome

“we should view the POTS diagnosis as a starting place for the discovery of the cause of the patient’s problem rather than a final answer as to what the patient actually has

… as a final common pathway by which a myriad of genetic and acquired pathophysiologys may present to the physician.”

Inhalant allergies/asthma
Food allergies
Anxiety
Depression
Infection
Movement restrictions
Migraines
Chiari type I or c-spine stenosis
EDS/JHS
Pelvic vein incompetence
Orthostatic intolerance
Health-related QOL: CFS vs. other pediatric chronic conditions

CFS data from Johns Hopkins Pediatric CFS Cohort Study; other conditions from Ingerski LM, et al., J Pediatrics 2010;156:639-44
POTS and the Medical Profession: Comments from a physician mother of POTS adolescent.

I get the feeling some cardiologists don't really buy into POTS, like the one at [Medical Center] who wanted my son to pass out and lose a tooth before she treated him with a “pill” because she didn't want him to think he was “sick.” Overall, my experience with most of my own colleagues has been disappointing, with some giving us a diagnosis of school phobia and Munchausen by Proxy (a personal favorite). I find most docs are so stressed with the time constraints and pressure to see enough pts that they no longer want to step up to the challenge of the patient who doesn't fit any mold.
Low PA
ARterial Pressure

- ARterial Baroreceptor Activity

+ Medulla Cardiovascular Nuclei

- Vagus

+ Heart Rate

+ + Cardiac Output

- + + Sympathetic Nerve Activity

+ Stroke Volume

Vasoconstriction (slow, 5-15 sec)

+ Vascular Resistance

Rowell LB
Human Cardiovascular Control, 1993
POTS symptoms

Lightheadedness
Syncope
Diminished concentration
Headache
Blurred vision
Fatigue
Exercise intolerance
Dyspnea
Chest Discomfort
Palpitations
Tremulousness
Anxiety
Nausea
Nocturia
Orthostatic stress

↑ sympatho-adrenal response

NMH

POTS

↑ pooling, ↓ vasoconstriction

↓ intra-vascular volume

↑NE/Epi

↓NE/Epi
POTS: causes

– Often follows common viral infections
– Can be associated with Lyme disease
– Joint hypermobility common
– Often runs in families
– Recent evidence suggests that it may be autoimmune in some instances
– Too much activity can make it worse
– But deconditioning and excessive bed rest can aggravate the problem as well
EDS/Joint hypermobility

Orthostatic Intolerance

CFS
Lessons from our understanding of CFS and POTS symptoms can help us understand fatigue and milder orthostatic intolerance in athletes and adolescents with other conditions (asthma, fatigue after cancer therapy)
16 year old swimmer with exertional symptoms

- Increasingly frequent episodes over 14 mo.
- Initially once per month, usually with URIs
- Gradually more frequent; twice weekly until daily in the last week; interferes with training
- During peak exercise in the pool, she describes a sensation of heaviness in the arms and legs, SOB, palpitations, exhaustion
- Episodes only occur with intense, extended practices in the pool
16 year old swimmer with exertional symptoms

- Heart rate at the time of the episodes is up to 192 bpm; usual peak exercise HR of 180 bpm
- Palpitations and increased HR resolve within 45 seconds of rest
- Slightly more common when pool temperature is warmer; never during running, gym exercises
- Other symptoms: no lightheadedness, occasional fatigue, no headache, no syncope, no reflux.
16 year old swimmer with exertional symptoms

Other history:

22 yr old sister is a triathlete who developed lightheadedness and exertional fatigue. Advised to increase salt intake.

No salt shaker on table, no added salt in food at home.
16 year old swimmer with exertional symptoms

Impression:
Dietary sodium deficiency, low blood volume

Course:
Added salt tablets 900 mg TID
Gradual reduction in frequency of episodes in next 2 weeks, then resolution. Able to swim for college team.
What are the initial steps in the management of POTS?
Step 1: Non-pharmacologic measures

Where possible, avoid factors that precipitate symptoms
Precipitating Factors For POTS

- Increased pooling/decreased volume
  - Prolonged sitting or standing
  - Warm environment
  - Sodium depletion
  - Prolonged bed rest
  - Varicose veins
  - High carbohydrate meals
  - Alcohol
Precipitating Factors For POTS

- Increased catecholamines
- Stress
- Exercise
- Pain
- Hypoglycemia
- Asthma medications (epinephrine, albuterol)
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

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 rest with no remedial procedures. [From Greenleaf et al. (130) with permission.]
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]
Step 1: Non-pharmacologic measures

Compression garments

- Support hose
  (waist high > thigh high > knee high)
- Body shaper garments
- Abdominal binders
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
What educational challenges arise for those with POTS?
I have been going to many doctors and have had symptoms for about three years. I'm in tenth grade. At first I missed a lot of school, but not enough to where I couldn't catch up. Then I started missing more as my symptoms got worse and my normally good grades started going way down. Now I barely ever make it in to school for one class in the afternoon and I am failing all my classes.

Question posted on POTS support web site
POTS: educational challenges

– Individuals feel worse in AM, when blood volume is lowest, and do better in PM
– Insomnia and disrupted sleep schedule common
– Symptoms wax and wane, often unpredictably, making planning and attendance a challenge
– Symptoms persist longer after URIs
– Symptoms worse in hot rooms, after gym class
– Cognitive problems can mimic ADD
– POTS symptoms worse with prolonged standing or longer periods of sitting
Mild-moderate POTS: accommodations

- Later start to day
- Reduction in course load
- Excuse from gym
- Salty snacks and water bottle in classroom
- Ability to get up and move around
- Permission to use common postural counter-maneuvers while seated
- Flexibility with assignments and deadlines
- Extended time for tests
- Access to extra-curricular activities
Moderate-severe POTS: accommodations

- Elevator privileges
- Extra set of books
- Taping of classes
- Place to rest at school
- Skipped day mid-week to rest/recover
- Half days
- Home and hospital teaching
Severe POTS: accommodations

- May need to withdraw from school entirely
- GED
- Start in community college classes part-time
- Increase course load gradually as tolerated
- Transition to full-time college
Helpful resources

- CFIDS Association: www.cfids.org
- Dysautonomia International: www.dysautonomiainternational.org
- The Dysautonomia Youth Network of America: www.dynainc.org
- Ehlers-Danlos National Foundation: www.ednf.org
- My webinar of September 2010 on “Managing Orthostatic Intolerance” is sometimes available as a download from the CFIDS Association web site, or on You Tube by searching under “Dr. Peter Rowe.”
Appendix

Slides on medical management of orthostatic intolerance
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

↑ sympatho-adrenal response

Orthostatic stress

↓ NE/Epi

↑ NE/Epi

NMH

POTS

Reduce catecholamine release/effect
Therapy For Orthostatic Intolerance

- **↑ blood volume**
  Sodium (PO & occasionally IV), fludrocortisone, clonidene, OCPs
- **↓ catecholamine release or effect**
  β-blockers, disopyramide, SSRIs, ACE inh.
- **Vasoconstriction**
  Midodrine, dexedrine, methylphenidate, SSRIs, SNRIs, aescin (horse chestnut seed extract)
- **Misc**
  pyridostigmine bromide; droxidopa (L-DOPS)
How to select initial therapy?

Algorithm vs. individualized approaches
Postural Orthostatic Tachycardia Syndrome
An Approach to Treatment

↑ hydration: >2 L/day
↑ salt intake: >200 mEq/day
Support stockings: 30 mm Hg
Poor adherence in teenagers

Non-pharmacologic
(all patients)

Family education
Psychophysiologic therapy
Exercise – aerobic and lower extremity strengthening:
≥5x/week

Pharmacologic
(case by case)

1st line
Beta blocker
↓ heart rate, block peripheral vasodilation
Metoprolol 12.5-50 mg 2-3x daily

1st or 2nd line
Alpha agonist
Peripheral vasoconstriction
Midodrine 2.5-12.5 mg 1-3x daily

2nd line/adjunct
Mineralocorticoid
↑ salt retention and plasma volume
Fludrocortisone 0.05-0.2 mg 1-2x daily

3rd line
SSRIs/SSNRI
Improves serotonin regulation
eg, citalopram, fluoxetine, venlafaxine

Rarely used
Alternate medications (pyridostigmine, EPO, ddAVP, clonidine, methylphenidate)

Tritrate all meds to effect and tolerance

Individualized approach

- **SBP < 110: fludrocortisone, midodrine**
- **Increased HR at baseline or when upright: β-blocker**

  (Modified from Bloomfield, Am J Cardiol 1999;84:33Q-39Q)

- **Based on other clinical clues**
  - Increased salt appetite: fludrocortisone
  - HA: β-blocker
  - Dysmenorrhea/worse fatigue with menses: OCP, Depo
  - Anxiety/low mood: SSRI, SNRI
  - Myalgias prominent: SNRI
  - FH of ADHD: stimulant
  - Hypermobility: stimulant, midodrine
**Fludrocortisone**

- A synthetic mineralocorticoid used for several decades 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 supplements recommended at initiation of therapy (10 mEq per 0.1 mg Florinef)
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
  – 4th 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 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
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)
Clonidine

• Alpha-2 adrenergic receptor antagonist. Reduces sympathetic nervous system outflow; can lead to an expansion of blood volume in those with orthostatic intolerance.

• 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.
SSRI/SNRI

• Inhibit the reuptake of serotonin (+/- norepinephrine) at nerve terminals, leaving more serotonin (+/- NE) available as a neurotransmitter.
• Serotonin can have a vasoconstricting effect on blood vessels. One RCT shows efficacy for paroxetine in NMH.
• Especially helpful in patients with co-morbid anxiety or depressed mood, or pain (duloxetine/Cymbalta)
• Adverse effects: occasionally worse lightheadedness 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
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.
FIGURE 1. Heart rate in the supine position (*light bars*) and during head-up tilt (*dark bars*) before and after pyridostigmine.