

# Postural Orthostatic Hypotension in Children & Adolescents

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*Hospital*



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**PEDI RHYTHM VII**

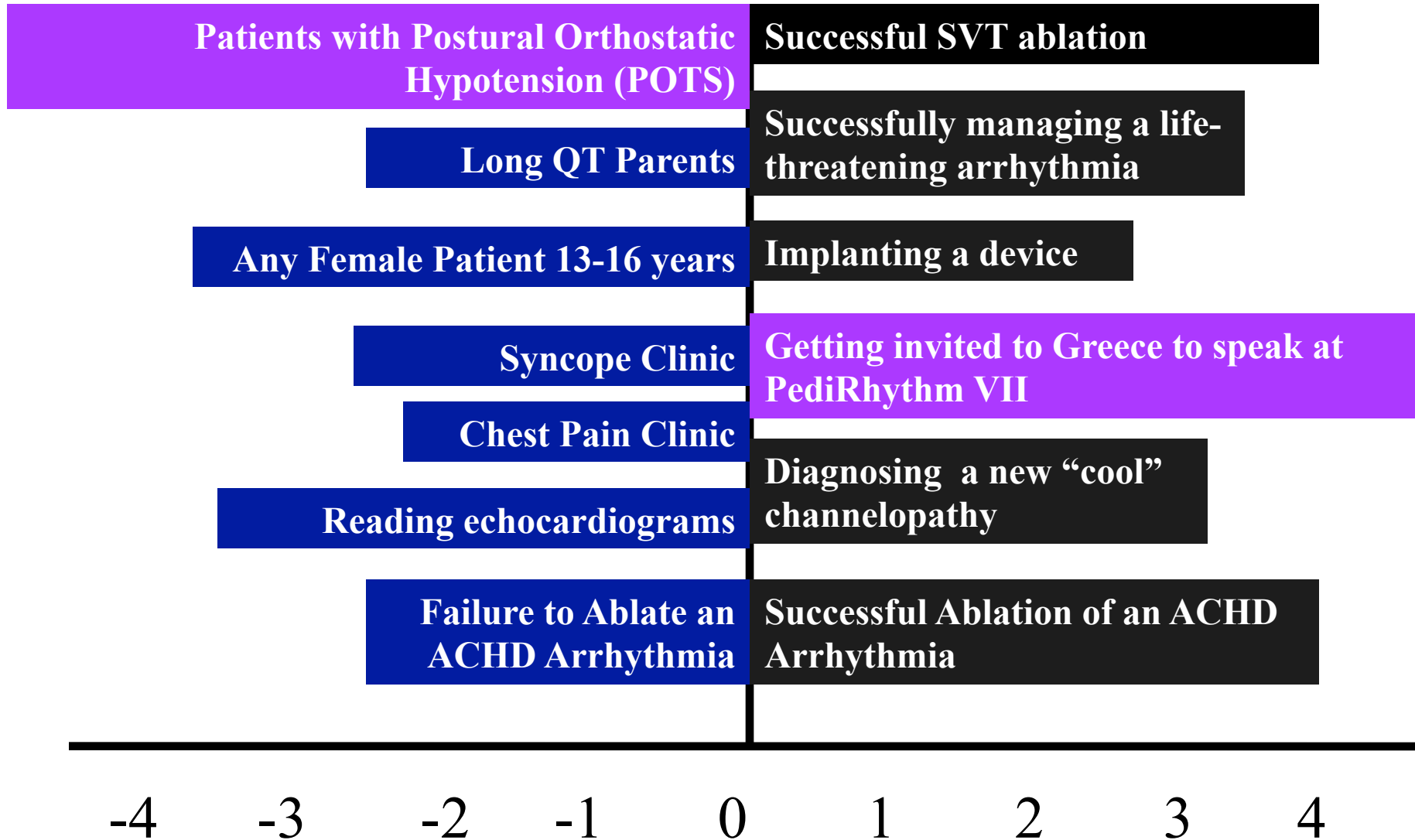


**Pediatric and Congenital  
Rhythm Congress VII**

4 - 7 February 2017 / Grand Hotel Palace - Thessaloniki, GREECE



# An Electrophysiology Happy Scale



# Goals of this Talk

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- Review the Definition of POTS
- Review the Demographics of POTS
- Review the Possible Pathophysiologic Explanations for POTS
- Think About Treatment Options in a New Paradigm of Personalized Medicine Using Biomarkers
- Future Areas of Research

# Postural Orthostatic Intolerance (POTS)

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- It is a syndrome in patients with orthostatic intolerance
- Heart Rate increase by 40 bpm within 10 minutes of standing (no significant BP change)
- Symptoms of cerebral hypoperfusion (lightheadedness, blurred vision, cognitive difficulties, weakness) **AND**
- Symptoms of sympathetic hyperactivity (palpitations, chest pain, tremulousness) that are relieved when placed supine.



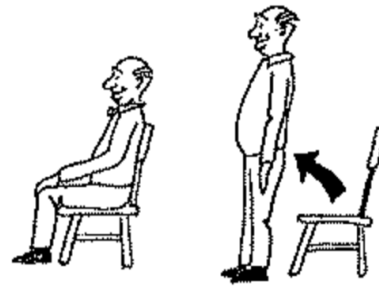
# Postural Orthostatic Intolerance (POTS)

## Demographics

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- More frequent in females
  - (female: male ratio 4.5:1)
- Most cases occur between 15-25 years of age
- Up to 50% of cases have an antecedent viral illness
- 25% have a family history with similar complaints

# Normal Response



Blood shifts from the chest to the lower abdomen, buttocks, and legs



Decreased venous return,  
transient decrease in  
cardiac output  
(HR increase by 10-30 bpm,  
negligible SBP, 5 mmHg  
increase in DBP)



Decreased circulating blood volume

Sympathetic  
Activation  
Increases HR

Venous Return &  
Cardiac Output  
Normalized



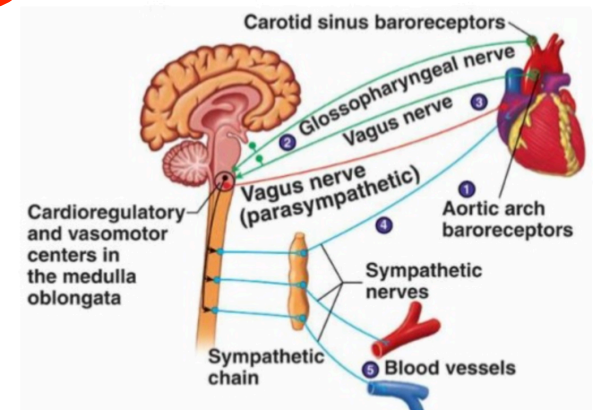
Baroreceptors  
Unloaded



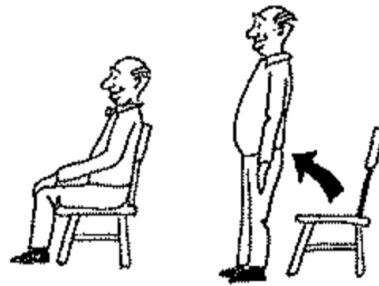
*Compensatory  
Mechanisms*

How the baroreceptor reflex works

Basic network



# POTS Response (Variable)



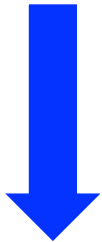
Blood shifts from the chest to the lower abdomen, buttocks, and legs



Venous Return  
Remains Decreased



Exaggerated orthostatic shift in blood  
volume



Stroke Volume  
and Cardiac  
Output are not  
Normalized



# Why Is POTS So Challenging or Why is POTS Like Donald Trump?

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We don't know how it  
happened?

We don't know how to  
deal with it?

We don't know how  
long it is going to last?

We get nauseous when  
we have to think about  
POTS and Trump

# Postural Orthostatic Intolerance (POTS)

## Potential Pathophysiologic Mechanisms

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- Low Blood Volume
- High Catecholamine Status
- Abnormal Local Vascular Tension
- Decreased Skeletal Muscle Pump Activity

The pathophysiology has tremendous heterogeneity and as such no single treatment option will consistently work

# #1: The Low Blood Volume

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- Up to 50% of patients have decreased blood volume or decreased red cell volume
- Up to 20% have been shown to have decreased left ventricular mass
- Up to 30% have low 24h-urinary sodium excretion

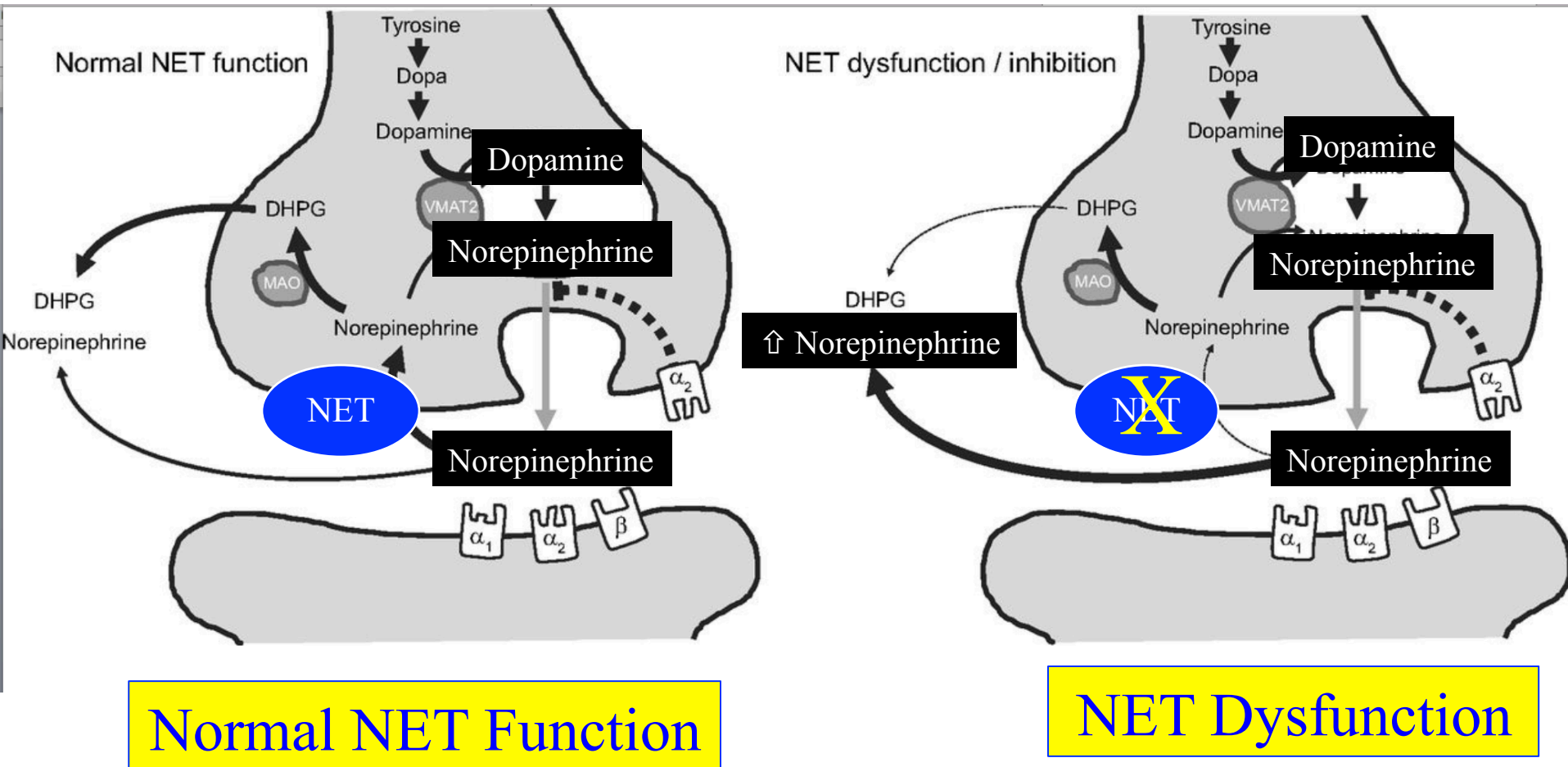
Supporting Data:  
Triggering events: diuretics, menses, dehydration

## #2: The High Catecholamine State

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- Between 30-60% of POTS patients can have increased sympathetic drive
- Plasma **norepinephrine** and **epinephrine** were significantly **elevated** in both supine and upright levels (>1000 pg/ml standing)
- ? Impairment of NET (norepinephrine transporter)
- Decreased expression of NET at sympathetic nerve

# The Norepinephrine Transmitter (NET)





# #3: The Abnormal Vascular Tension

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- Based on nuclear erythrocyte tagging studies, pooling in the lower extremities supports abnormal local vascular tension.
- Similarly NO (nitric oxide) and NO synthase as a systemic vasodilator was found to be elevated in POTS patients compared to healthy controls.
- Vascular endothelial dysfunction may also play in role in some of the abnormal POTS patients.

## #4: Decreased Skeletal Muscle Pump Activity

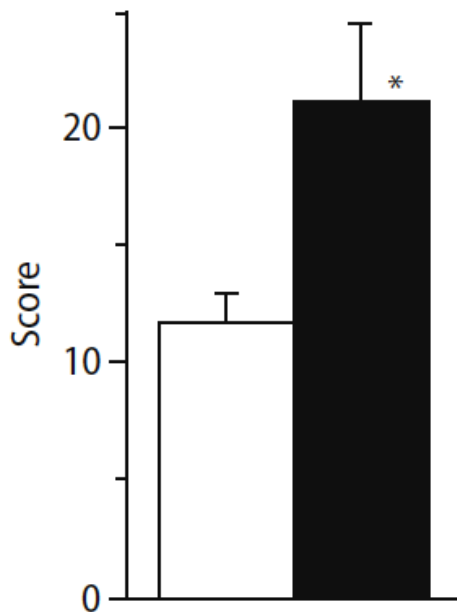
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- Some studies in adults have found decreased skeletal calf muscle in the lower extremities of patients with POTS
- May also reflect the decreased exercise performance and deconditioning in POTS patients

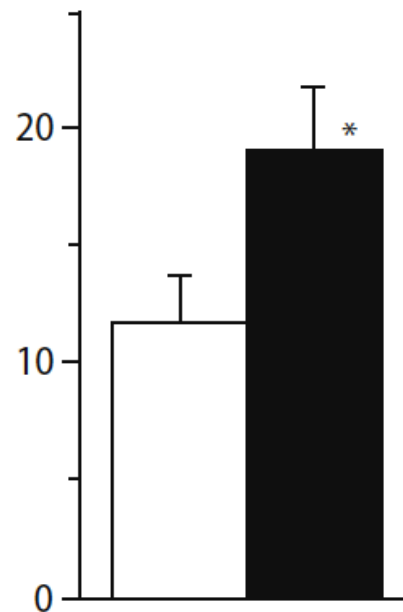
# #5: POTS & Somatic Hypervigilance (anxiety, depression, behavioral amplification)

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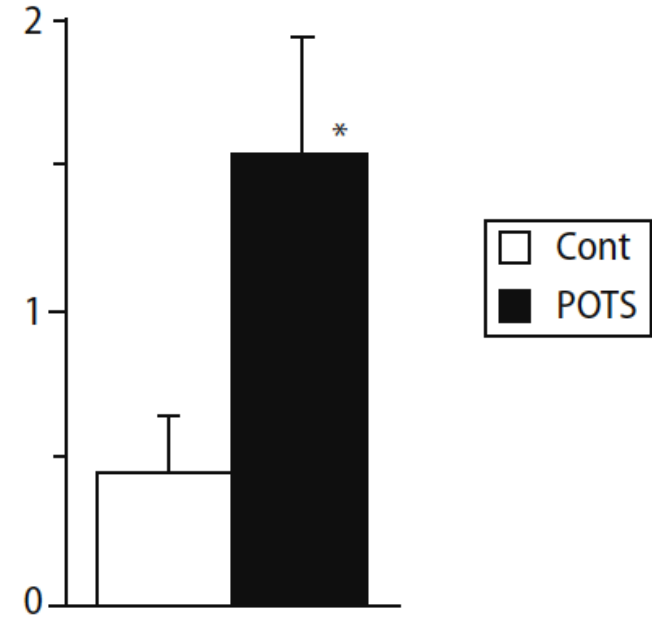
Anxiety Sensitivity Index



Body Vigilance Scale



Catastrophizing Scale



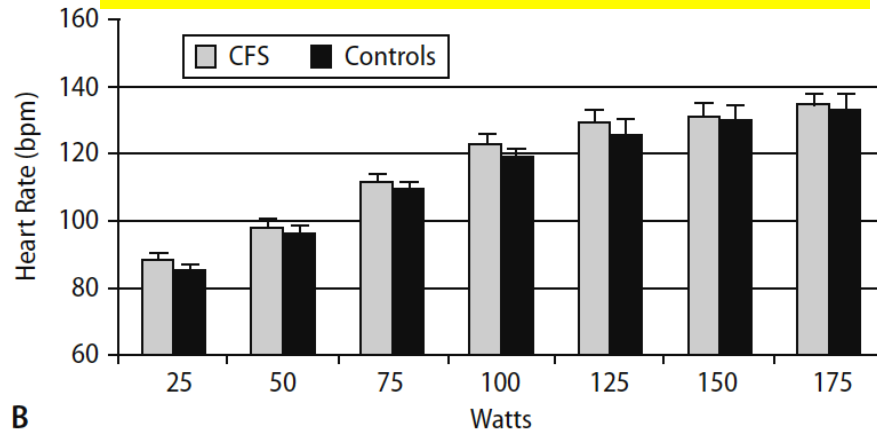
# POTS and Comorbidities

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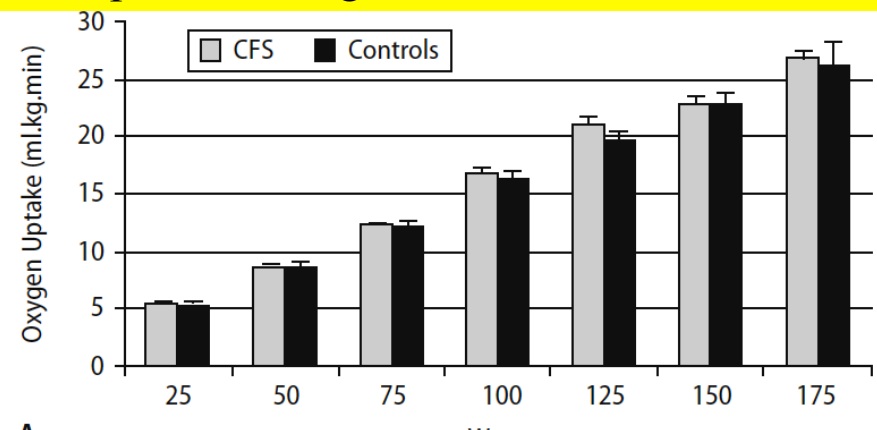
- Many patients with POTS complain about chronic symptoms that cannot be mechanistically explained by postural intolerance or excessive tachycardia.
- Visceral GI dysmotility (diarrhea, constipation, bloating, irritable bowel syndrome and GI dysmotility)
- Ehler-Danlos III: Joint hypermobility sequence variation in tenascin III (*?impaired vascular connective tissue limits venous return*)
- Chronic fatigue, irritable bowel syndrome, fibromyalgia and insomnia (POTS patients have higher laboratory markers of sympathetic drive than chronic fatigue patients) (16-48%)

# POTS & Similarities to Chronic Fatigue Syndrome

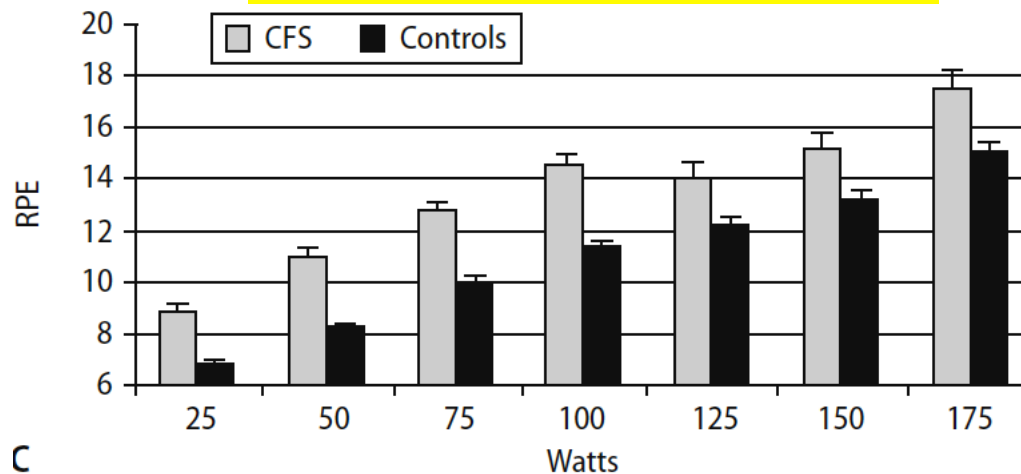
## HR During Incremental Exercise Test



## O2 Uptake During Incremental Exercise Test



## Ratings of Perceived Effort During Incremental Exercise Test



# The Individualized Treatment of POTS

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**Nonpharmacologic  
Treatment**

**Pharmacologic  
Treatment**

**Parent & Patient  
Expectations**

**Future Treatment  
Considerations**

# Non-Pharmacologic Treatment

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- Avoid Dehydration
  - Drink 2-3 liters a day
- Avoid Vasodilation medications
- Avoid Stress
  - Challenging cause adolescents are stressed
- Avoid Depression
- Physical Countermeasures
  - Recognize symptoms, leg crossing, bending forward, foot on chair etc.
- Must Create an Exercise Plan

# POTS & Physical Deconditioning

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## POTS Patients Compared to Controls

Persistent tachycardia

Decreased stroke volume

Decreased peak VO<sub>2</sub>

Reduced LV mass





# POTS & Physical Exercise (Stage I)

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Start slow (light strength training and aerobic exercise)

Aim for improvement over 8 weeks (5-6 days/week)

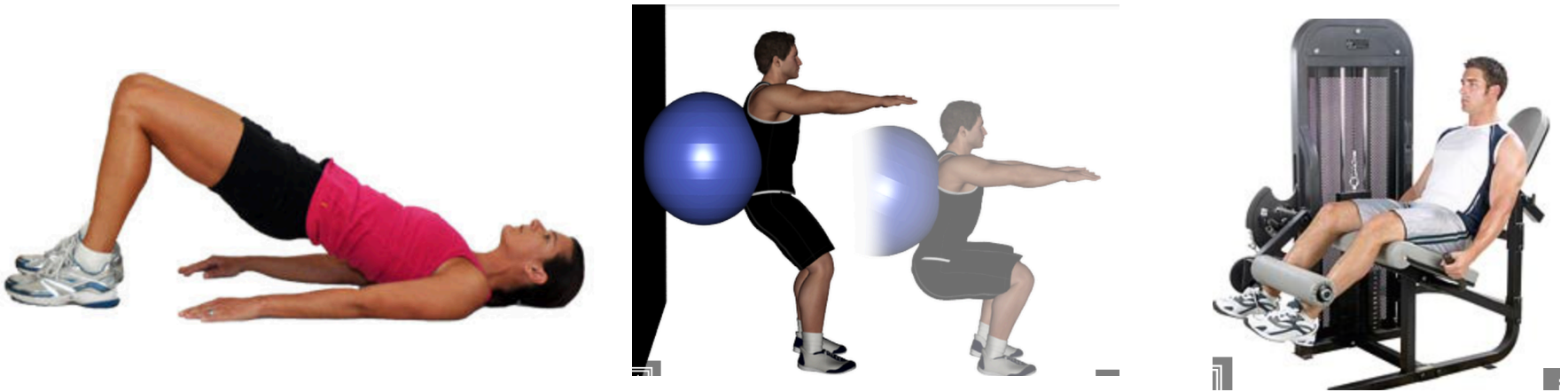


A structured and progressive exercise program is a HRS  
Class IIa recommendation

# POTS & Physical Exercise (Stage IA)

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Seated weight training is good  
Aim for improvement over 8 weeks



Picture I



Picture J



Picture K

# POTS & Physical Exercise (Stage II)

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Start slow

Aim for improvement over 8-16 weeks

If it gets worse or miss weeks go back to Stage I



# Treatment #1: Oral Rehydration Salts (ORS)

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- POTS patients have low blood volume and a shortage of water and salt intake
- In clinical settings there is a variable response to ORS
- Zhang compared 24-h urinary sodium level between POTS patients and healthy controls
  - **POTS Group:**  $117 \pm 58$  mmol/24 hours
  - **Control Group:**  $193 \pm 91$  mmol/24 hours
- **Results:** 24 hour/urinary sodium excretion  $< 124$  mmol/24h was an indicator of effectiveness of ORS
  - sensitivity: 77%; specificity: 93%

# Treatment #2:

## Norepinephrine Levels & Beta Blockers

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- Tachycardia associated with position change is the clinical feature of POTS
- Studies have shown that the higher the serum norepinephrine level the greater the symptoms

**Results:** A serum norepinephrine level  $> 3.59$  pg/yielded favorable response of beta-blocker suppression treating POTS (sensitivity: 77%; specificity: 91%)

- Not all beta-blockers are created equally.
- Beta-blockers have side effects of fatigue and depression which could make this worse
- Is there a role for Ivabradine?

# Single centre experience of ivabradine in postural orthostatic tachycardia syndrome

Claire McDonald, James Frith, and Julia L Newton\*

Institute for Ageing and Health, UK NIHR Biomedical Research Centre in Ageing and Age-related Diseases—Cardiovascular theme & Falls and Syncope Service, Newcastle University, Newcastle, UK

Received 20 July 2010; accepted after revision 24 September 2010; online publish-ahead-of-print 9 November 2010

## Aims

Postural orthostatic tachycardia syndrome (POTS) is associated with tachycardia on orthostasis. Patients frequently report palpitations, presyncope, and fatigue. Conventional therapy is effective in less than 60%. Case reports suggest ivabradine (a selective sinus node blocker, with no effect on blood pressure) may alleviate POTS-related symptoms.

## Methods and results

### Retrospective Review

20 patients (60% some improvement)

8 reduced tachycardia and fatigue

4 reported reduced tachycardia

## Conclusion

## Keywords

Postural orthostatic tachycardia syndrome • Ivabradine • Fatigue

pharmacy data-  
no patients  
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of efficacy

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in patients

# Treatment #3: Alpha-Adrenoreceptor Agonists

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Some POTS patients have abnormal limb vascular tension

- Midodrine can act as an  $\alpha$ 1-adrenoreceptor agonist
  - **Mid-region pro-adrenomedullin (MR-proADM)** is relatively stable and can reflect adrenomedullin (ADM) a vasoactive substance exerting vasodilation effects.
  - Some patients with POTS have higher MR-proADM than healthy controls.
- 
- A basal MR-proADM of 61.5 pg/ml yielded a sensitivity of 100% and a specificity of 72% in predicting efficacy of midodrine therapy on POTS patients



# Treatment #3: Alpha-Adrenoreceptor Agonists

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- Erythrocyte  $\text{H}_2\text{S}$  is a vasoreactant signaling molecule
- Can measurements of Erythrocyte  $\text{H}_2\text{S}$  predict effectiveness of midodrine in POTS patients?

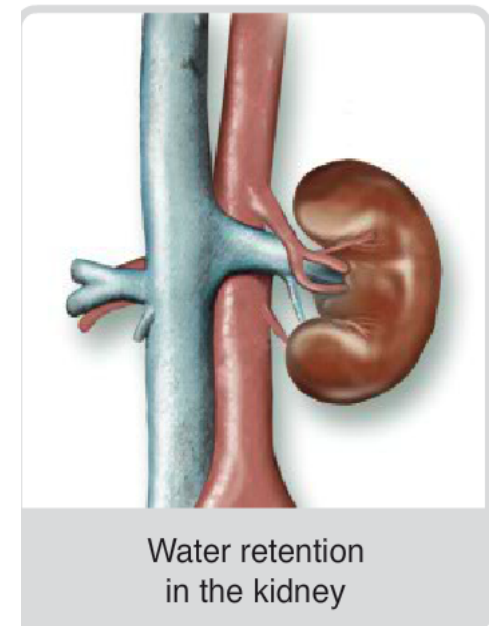
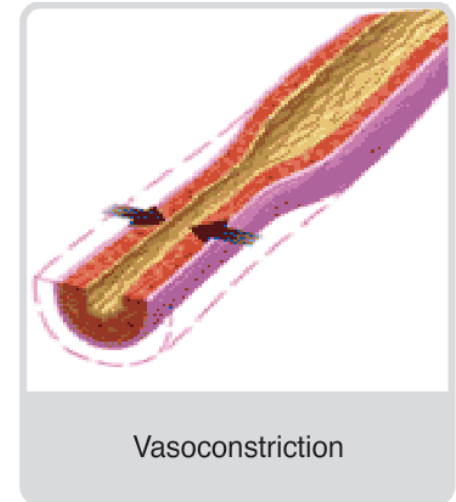
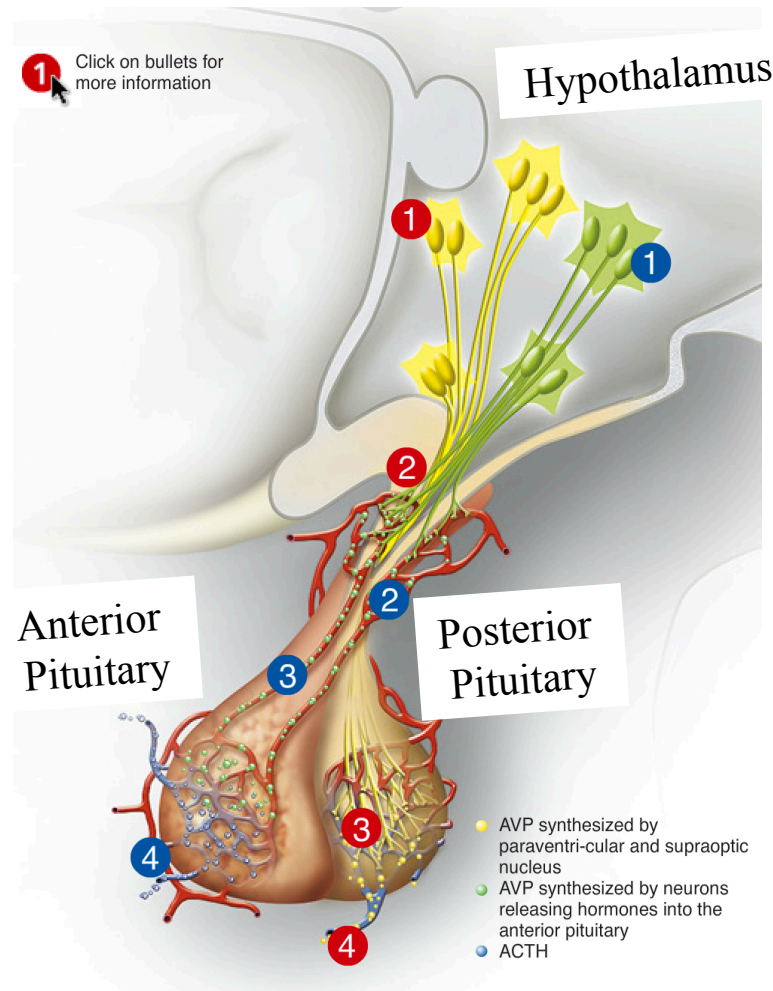
- Erythrocyte  $\text{H}_2\text{S}$  yielded a sensitivity of 78% and a specificity of 77% in predicting efficacy of midodrine therapy on POTS patients
- Receiver operator area under the curve 0.8



# Biomarkers to Guide Differential Therapy for POTS?

Volume depletion results in activation of AVP (arginine vasopressin) from the posterior pituitary which causes vasoconstriction and water retention

Catecholamines inhibit AVP release from the posterior pituitary



# Treatment #2 (Beta-Blockers) or #3 (Midodrine)?

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- In [some POTS patients](#) decreased central volume and stimulates the release of arginine vasopressin (AVP)
- In [other POTS patients](#) catecholamine release inhibits the release of AVP
- AVP cannot be used as a biomarker because it is unstable so it is impossible to measure in the laboratory
- Copeptin is a glycopeptide connected to precursor substrate of AVP and can be measured.

**ThermoFisher**  
SCIENTIFIC

[About Copeptin](#)

[Indications](#)

[Resources](#)



# Copeptin Levels for BB Recommendation

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- Zhao (*Am J Cardiol* 2014) compared serum copeptin between POTS patients and healthy controls at baseline.
  - **POTS Group (N=49)**:  $10.5 \pm 2$  pmol
  - **Control Group (N=25)**:  $8.75 \pm 1.4$  pmol

## Intervention: Metoprolol

Results after Treatment with Metoprolol

- **POTS Responders**:  $9.3 \pm 1.4$  pmol
- **POTS Nonresponders**:  $12.1 \pm 1.6$  pmol

- A basal plasma copeptin of 10.2 pmol could be used to predict the efficacy of Metoprolol in children
  - sensitivity: 91%; specificity: 79%

# The Value in a Multidisciplinary Approach

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Increase  
Fluid  
and Salt

Structured  
Aerobic  
Exercise

Increased  
Standing  
Tolerance

Personalized  
POTS  
Medical  
Regimen

Daily  
Group  
Based  
Therapy

Occupational  
Therapy

Recreational  
Therapy


Parents Learn to  
Support  
Adolescent Self-  
Awareness and  
Management

Biofeedback

Relaxation  
Strategies

Cognitive  
Strategies to  
Manage Stress

# Improvement in Functioning and Psychological Distress in Adolescents With Postural Orthostatic Tachycardia Syndrome Following Interdisciplinary Treatment

Clinical Pediatrics  
2016, Vol. 55(14) 1300–1304  
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sagepub.com/journalsPermissions.nav  
DOI: 10.1177/0009922816638663  
cpj.sagepub.com  


	Prerreatment, Mean (SD)	Posttreatment, Mean (SD)
Functional disability <sup>a</sup>	25.23 (11.22)	11.91 (10.04)
Depressive symptoms <sup>b</sup>	23.24 (13.15)	11.21 (10.47)
Catastrophizing <sup>c</sup>	22.70 (9.64)	11.48 (8.36)

Significant functional impairment and psychological distress have been observed in adolescent patients with postural orthostatic tachycardia syndrome (POTS). Interdisciplinary rehabilitation programs have been shown to be beneficial in the treatment of chronic pain in adults and adolescents. Only preliminary data have examined interdisciplinary rehabilitation efforts in patients with POTS. This study evaluated the impact of an interdisciplinary rehabilitation program on the functional impairment and psychological distress in 33 adolescents diagnosed with POTS. Patients included in the study were adolescents ages 11 to 18 diagnosed with POTS. Measures completed at admission and discharge from the program included the Functional Disability Index, Center for Epidemiological Studies–Depression–Child scale, and the Pain Catastrophizing Scale for Children. After participation in the 3-week program, adolescents with POTS demonstrated a significant increase in overall functional ability and significant reductions in depression and catastrophizing.

# Future Areas of Research

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- Prospective Study Comparing a Personalized Individualized Treatment Strategy that is Multidisciplinary with a Biomarker Guided Pharmacologic Approach Compared to a Multidisciplinary Random Pharmacologic Approach
- Are there noninvasive treatment measures that can be individualized and targeted based on neural imaging (functional MR)?



**WHEN THINGS DON'T HAPPEN  
RIGHT AWAY JUST REMEMBER IT  
TAKES 6 MONTHS TO BUILD A  
ROLLS-ROYCE AND 13 HOURS TO  
BUILD TOYOTA**

# Thank You

