Blood Pressure Regulation & the Postural Orthostatic Tachycardia Syndrome (POTS) Deconditioning, Pseudodeconditioning; Both or Neither?

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Mayo Clinic
Rochester, MN
Mayo Clinic

- Emerged in late 1800’s
- Practice, Research, Education
- Med school
- Training programs
- ~ 53,000 employees
- ~ 500 mil$ research budget

The Needs of the Patient Come First!
MAP = CO \times TPR

Feedback control by Baroreflexes
Arterial Pressure Regulation by Baroreflexes

Baroreceptors
Heart
Peripheral vessels
ACH-
NE+
Cardiovascular center
+
Integrated Baroreflex Response
Baroreflex Curve

www.rrk-berlin.de/fvkweb/nephrology/por1.html
Overview of Talk

• What happens when we stand up?
• Definition of POTS
• Is POTS “Psychogenic”?
• A baroreflex “problem”?
• POTS & deconditioning the same or different?
• The physiological evidence in “related syndromes”
• Ideas about how this might all fit together
• What should we do next?
What Happens When You Stand Up?

Supine          Standing

Central venous pressure

50 → 5 mmHg

100 → 0 mmHg

5 mmHg

0 mmHg
Definition of POTS

- Emerged as a recognized syndrome in the 1990s
- Baseline sinus rhythm with no evidence of cardiac disease
- Sustained HR $\uparrow$ 30 beats/min with 10 min of tilting
- Light-headedness, weakness, palpitations, blurred vision, breathing difficulties, nausea, or headache developing on standing or tilting and resolving with recumbency.
- No sustained or marked orthostatic hypotension
- No other explanation
David Streeten, MB, D Phil

- Native of Bloemfontein, South Africa
- Medical degree 1946, the University of the Witwatersrand in Johannesburg
- Doctorate in pharmacology from Oxford in 1951
- The main concern of his research was hypertension and orthostatic intolerance
- AAS President 1996

http://www.upstate.edu/library/history/portraitbiogs.shtml
Postural Orthostatic Tachycardia Syndrome (POTS)

- Dramatic increase in HR on standing
- Absence of orthostatic hypotension
Is POTS “Psychogenic”?

• Unusual presentations
• No obvious “cause” for the symptoms
• Some cross talk with CFS and/or Fibromyalgia etc
• Multiple encounters with the “Medical Industrial Complex”
• Psych drugs by the time they get to an “expert”
Hypothesis: Anxiety Plays a Key Role in the HR Responses in POTS?

POTS patients

- Increased HR during orthostatic stress is due to anxiety \textit{OR}
- Increased HR during orthostatic stress is a baroreflex mediated response to inadequate $\alpha$-adrenergic vasoconstriction
Will HR Rise During “Sham” Venous Pooling?

- “Sham” LBNP (Halliwill et al JAP, 1998)
- MAST pressure = 5 mmHg (relative to outside the LBNP box)
- Prevents venous pooling
- No sensation of severe pressure on legs
- Subject still feels “sucked” into box
Methods

Lower Body Negative Pressure (LBNP) with and without Medical Anti-Shock Trouser inflation

Measurements

- Arterial pressure: Finapres
- Heart rate: ECG
- Forearm blood flow: plethysmography
Individual Records

- **LBNP box or trouser pressure (mmHg)**
- **AP (mmHg)**
- **HR (beats/min)**
- **FBF (mL/100 mL/min)**

### No Inflation

#### Time (min)

-50 0 50 100 150

#### Control

#### POTS

### Trouser Inflation

- **LBNP box**

#### Time (min)

-50 0 50 100 150

#### Control

#### POTS

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**MAYO CLINIC**

CP1278619-16
Subject Characteristics

- N = 14* patients F/M = 12/2
  29 ± 2 yrs, 68 ± 2 kg, 170 ± 2 cm
- Drugs off for 5 ½ lives*
- N = 10 healthy controls
Group Responses to Real and Sham LBNP

**Control**

**POTS**

### Standard LBNP

- **HR (beats/min)**
- **MAP (mmHg)**

### MAST Inflation

- **HR (beats/min)**
- **MAP (mmHg)**

### Vacuum Sound

- **HR (beats/min)**
- **MAP (mmHg)**

**LBNP box**

**LBNP (mmHg)**

**baseline**
**Mental Stress Rationale**

- Increased HR during orthostatic stress is due to anxiety?

- Test HR response to non-orthostatic anxiety provoking stress
Responses to Mental Stress

- **HR** (beats/min)
  - Control
  - POTS

- **MAP** (mmHg)
  - Control
  - POTS

**Time (min)**
- Baseline
- Inst
- Mental stress

**Mental stress (min)**
- 1
- 2
- 3

**Graphs**
- HR and MAP trends over time for Control and POTS conditions.
- Bar graphs showing changes in HR and MAP at different mental stress intervals.
Somatic Hypervigilance

- Anxiety sensitivity index
- Body vigilance scale
- Catastrophizing scale

Comparison between Control and POTS groups:

- Anxiety sensitivity index: POTS group shows significantly higher scores compared to the Control group.
- Body vigilance scale: POTS group shows significantly higher scores compared to the Control group.
- Catastrophizing scale: POTS group shows significantly higher scores compared to the Control group.

* denotes statistical significance.
Physiology “Wins”

- HR response only happens with venous pooling
- HR response to mental stress “normal” in spite of increased hypervigilance
- Why?
  - Denervation
  - Hypovolemia
  - CNS
- Or, is there a deconditioning element and if so how big?
Is POTS a Baroreflex “Problem”? 

• Same subjects 
• Overnight hydration 
• Upright and supine exercise 
  Supine exercise and cardiac filling 
• Bolus doses of PE during exercise to raise BP and evoke reflex changes in HR
Same exercise protocol was repeated (no stand test)
Hemodynamic Responses to Exercise

<table>
<thead>
<tr>
<th>HR (beats/min)</th>
<th>Supine</th>
<th>Upright</th>
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<table>
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<tr>
<th>AP (mmHg)</th>
<th>Supine</th>
<th>Upright</th>
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<table>
<thead>
<tr>
<th>PP (mmHg)</th>
<th>Supine</th>
<th>Upright</th>
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<table>
<thead>
<tr>
<th>Workload (watts)</th>
<th>Rest</th>
<th>25</th>
<th>50</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POTS</td>
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</table>

*Significant difference
**Highly significant difference
SV Responses in POTS

Supine

Upright

CO (L/min)

SV (mL)

TPR (mmHg/L/min)

Rest 25 50 75

Workload (watts)

Control

POTS

*
Upright Exercise at 75W

Control

POTS

AP (mmHg)

1 sec
BP More Variable in POTS

Control

POTS

Distribution of PP (mmHg)

Frequency (%)

0 5 10 15 20

-40 -20 0 20 40

Control POTS

BP More Variable in POTS
Baroreflex Control of HR

Control

POTS

HR (beats/min)

SAP (mmHg)

Rest

25W

50W

75W

20

100

140

180

220

100

140

180

220

100

140

180

220
Baroreflex Control: Corrected for HR

Baroreflex sensitivity (beats/min/mmHg)

Heart Rate

Supine

Upright

Control

POTS
Change in SV vs HR

Rest

50W

Δ SV, upright — supine (mL)

Δ HR, upright — supine (beats/min)

R² = 0.35

R² = 0.60

Δ SV, upright — supine (mL)

Data for Control and POTS groups at rest and 50W exercise levels.
Exercise Studies

Physiology Wins Again

- Baroreflex control of HR is not fundamentally different
- Similar responses while supine
- Smaller SV while upright
- Responses are similar when SV is considered: cardiopulmonary interactions
- Small SV is a “hallmark” of deconditioning
Spaceflight & Regulation of MSNA
What Does It Tell Us About POTS?

- Cardiac atrophy
- Smaller stroke volume
- Reduced blood volume
- Can be simulated by bed-rest deconditioning
POTS Like Responses to Tilt After Spaceflight N=5

Levine et al J Phys 2002
MSNA Responses After Spaceflight

Preflight

Landing day

Supine

60° upright tilt

Muscle sympathetic nerve activity

Time

0 10 20 30 40

Levine et al J Phys 2002

Astronaut 3
Ventricular Volume & MSNA

Levine et al J Phys 2002

Muscle sympathetic nerve activity (bursts/min⁻¹)

Stroke volume (mL)

Preflight
Landing day
MSNA Responses to 45° HUT in POTS n=9

Baseline

30 degrees

45 degrees

Control 20 s

POTS 20 s

Swift et al 2005

*P=0.03

P=0.10

*P=0.02

P=0.03

*P=0.03

P=0.66

P=0.60

CP1278619-37
MSNA Responses to Nitroprusside in POTS

Bonyhay and Freeman 2004
Further Evidence from the Dallas Group
MSNA and SV Relationships in POTS

POTS

\[ r = 0.96 \pm 0.05 \]

Controls

\[ r = 0.87 \pm 0.15 \]

MSNA (bursts/min) vs. Stroke volume (mL)
Linear Correlation Between Total Peripheral Resistance and MSNA During Orthostasis in POTS Patients and Controls

 Stroke volume (mL)

Total peripheral resistance (dyne·sec·cm⁻⁵)

POTS

\[ r = 0.89 \pm 0.09 \]

Controls

\[ r = 0.81 \pm 0.19 \]
SV and HR in POTS

Stroke volume (mL)

- Group P < 0.001
- Protocol P < 0.001
- Group X Protocol P = 0.847

Heart rate (beats/min)

- Group P = 0.005
- Protocol P < 0.001
- Group X Protocol P = 0.015

Mean ± SD

POTS
Controls

Supine 30° tilt 60° tilt 60° tilt 5 min 10 min
LV Mass Increased After 3-Month of Exercise Training in POTS

Left ventricular mass (g)

Before training  | After training  | Healthy women

0  | 100  | 120
20 | 140  | +40%
40 |
60 |
80 |
100 |
120 |
140 |
Heart Rate Responses During 10-min Standing Before and After Exercise Training

1. Supine: 60 bpm, Stand 10 min: 97 bpm, +37 bpm
2. Supine: 59 bpm, Stand 10 min: 81 bpm, +22 bpm
POTS Interim Summary

- Physiological data looks like deconditioning
- Some evidence that training “works”
- Psych data suggests hypervigilance
- Is there a triggering “event” followed by prolonged inactivity
- Heterogeneous syndrome, what this might not explain
The Physiological Evidence & “Related Syndromes”

Is There a Similar Story for CFS and Fibromyalgia?
HR Responses Normal During Exercise in CFS n=31

Heart rate (bpm)

Wallman et al 2004
Oxygen Uptake Responses Normal During Exercise in CFS

Wallman et al 2004

Oxygen uptake (mL·kg·min)

Watts

CFS
Controls
Perception of Effort During Exercise Altered in CFS

Wallman et al 2004
Muscle Metabolism is Normal in CFS
NMR Measures of ADP n=19

- Quad exercise
- Cuffs to limit blood flow
- NMR measures of metabolism
- Doppler measures of flow

McCully et al J Appl Physiol 2003
Muscle Blood Flow Not Grossly Abnormal In CFS

McCully et al J Appl Physiol 2003
Does CFS Respond to Training?

82 volunteers

14 excluded for not meeting criteria

68 subject randomized

Exercise group (n=34)

Relaxation/flexibility group (n=34)

2 exercise subjects withdrew

4 weeks’ baseline testing

2 relaxation/flexibility subjects withdrew

12 weeks’ graded exercise with pacing (n=32)

12 weeks’ relaxation/flexibility (n=29)

4 weeks’ post-intervention testing
Wallman et al 2004

CFS Responds to Training

Self-rated clinical global impression change scores after completing treatment

<table>
<thead>
<tr>
<th>Rating</th>
<th>Graded exercise</th>
<th>Relaxation flexibility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Graded exercise</td>
<td>Relaxation flexibility</td>
</tr>
<tr>
<td>No. (%)</td>
<td>n=32</td>
<td>n=29</td>
</tr>
<tr>
<td>Very much better</td>
<td>5 (16)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Much better</td>
<td>14 (44)</td>
<td>10 (34%)</td>
</tr>
<tr>
<td>A little better</td>
<td>10 (31%)</td>
<td>10 (34%)</td>
</tr>
<tr>
<td>No change</td>
<td>3 (9%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>A little worse</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Much worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Very much worse</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are number (%) of people choosing each rating.

Changes (95% CIs) in selected physiological variables

- Power output (W/kg)
- RPE/power
- Activity level (kJ/week)

Graded exercise group (n=32) vs. Relaxation/flexibility group (n=29)
CFS
Interim Summary

• Physiological data looks “normal”
• Some evidence that training “works”
• Psych data suggests perception of effort is altered
• Is there a triggering “event” followed by prolonged inactivity
• Heterogeneous syndrome, what this might not explain
Same Story For Fibromyalgia

220 offered screening

196 screened
• Not fibromyalgia (n=29)
• Too mild (n=9)
• Fibromyalgia but ineligible (n=22)

Randomized (n=136)

Exercise group (n=69)

Adherence
No of classes attended:
0 11
1-8 16
9-16 23
17-24 19

Relaxation group (n=67)

Adherence
No of classes attended:
0 11
1-8 16
9-16 23
17-24 19

Richards and Scott 2002
## Exercise Improves Symptoms in Fibromyalgia

<table>
<thead>
<tr>
<th>Time</th>
<th>Relaxation group n=67</th>
<th>Exercise group n=69</th>
<th>Mean change between groups (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14.0 (13.4-14.6)</td>
<td>14.4 (13.7-15.1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 months</td>
<td>11.8 (10.9-2.8)</td>
<td>10.6 (9.2-12.0)</td>
<td>1.1 (-0.47-2.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>6 months</td>
<td>11.2 (10.0-12.3)</td>
<td>10.2 (8.9-11.5)</td>
<td>1.4 (-0.1-2.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>1 year</td>
<td>12.0 (10.8-13.0)</td>
<td>10.2 (8.8-11.6)</td>
<td>2.2 (0.63-3.7)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
Summary Thoughts

How This Might All Fit Together

• POTS, CFS and Fibromyalgia defy a clear physiological explanation

• Triggering event

• Perceptual “mismatch”?  

• Chronic deconditioning as a sustaining factor?

• “Medicalization” as a sustaining factor?
What To Do Next?

- Exercise based rehab
- Demedicalize
- Perceptual “retraining”
- Continued empathy for the patients with a firm consistent message
Acknowledgements

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C Hesse
T Pike
B Johnson
JT Shepherd
J Eisenach
W Schrage
K Krucker
D Wick
B Walker
B Wilkins
T Curry
D Proctor
A Reed
T Young
M Somanju
F Ramirez
B Welch
S Turner
BG Wallin
N Charkoudian
S Masuki
P Engrav
E Martin
E Snyder
N Nicholson
J Halliwill
L Sokolniki
M Ceridon
S Shastry
A Issa
P Krediet
P Sandroni
M Jensen
PA Low
If All You Have is a Hammer…
Everything Looks Like a Nail

Physician Perspective
• Cardiology
• Neurology
• Psych
If All You Have is a Hammer…
Everything Looks Like a Nail

Physician Perspective
Joyner & Levine Teams interested in exercise;
“Detraining” usually on the differential
MSNA Responses to HUT in POTS

Group P=0.198
Protocol P<0.001
Group x Protocol P<0.001

- POTS
- Controls
POTS Like Responses to 120 Days of HDT n=6

Changes in MBP (mmHg)

Pre-HDBR  HDBR60  HDBR120  Rec-HDBR (n=3)

Changes in total MSNA (arbitrary units/min)

Changes in heart rate (beats/min)

Kamiya et al Am J Physiol Regulatory Integrative Comp Physiol 2000
Baroflex sensitivity (beats/min/mmHg)

Workload

Control

POTS

Supine

Upright

Rest

25

50

75

-1.8

-1.2

-0.6

0

*