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Case Presentation - AP

ONSET
- Age 26 years; SWF; works in music industry
- Dx “Pneumonia” -> inhalers
- Developed “spells of tachycardia”
- Cardiologist #1 proposed EP Study/Ablation
- Cardiologist #2 -> Tilt Test

Associated Symptoms
- Lightheaded/presyncope (standing)
- Intermittent stabbing chest pains (standing)
- Mental clouding (“brain fog”)
- Severe fatigue

SR Raj, Circulation 2013
Case Presentation – AP (2)

Orthostatic Challenge

<table>
<thead>
<tr>
<th>Position</th>
<th>HR (bpm)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine – 15 min</td>
<td>73</td>
<td>103/72</td>
</tr>
<tr>
<td>Upright – 1 min</td>
<td>106</td>
<td>109/80</td>
</tr>
<tr>
<td>Upright – 3 min</td>
<td>105</td>
<td>106/83</td>
</tr>
<tr>
<td>Upright – 5 min</td>
<td>122</td>
<td>118/75</td>
</tr>
<tr>
<td>Upright – 10 min</td>
<td>121</td>
<td>118/78</td>
</tr>
</tbody>
</table>
WHAT is POTS?
Postural Tachycardia Syndrome - Common Criteria

- Orthostatic tachycardia > 30 bpm
  - >40 bpm required if <18 years
- No consistent orthostatic hypotension
  - ΔBP > 20/10 mmHg
- Symptoms of sympathetic activation
  - Worse upright; better recumbent
- Chronic symptoms > 6 months
POTS - Mimics & Associations

- **Mimics**
  - Acute infections
  - Multiple sclerosis
  - Sjogren’s syndrome

- **Associations**
  - Joint Hypermobility Syndrome
    - Ehlers Danlos Syndrome – Hypermobility
  - Fibromyalgia
  - Chronic Fatigue Syndrome
POTS - Common Symptoms

Cardiac
- Rapid Heartbeat
- Chest Discomfort
- Short of Breath
- Lightheaded
- Exercise Intolerance

Non-Cardiac
- Mental Clouding
- Headache
- Nausea
- Tremulousness
- Fatigue
- Sleep Complaints
Tilt Testing

SR Raj, Indian Pacing Electrophysiol J. 2006;6:84-99
POTS: Feel awful when upright

Symptoms Score (au)

Tilt (60°) Time

POTS vs. Control

POTS – Who is affected?

- Prevalence ½ million in USA
- Female (~80-85%)
- Typically aged 13-50 years
- Significant functional disability
Quality of Life in POTS
Health Related Quality of Life (SF-36) – Chronic Illnesses

SF36 Sub-Scores

- Physical
- Mental

Score

- Back Pain
- Dialysis

SF36 Sub-Scores
Health Related Quality of Life (SF-36) – Chronic Illnesses

SF36 Sub-Scores

POTS
Back Pain
Dialysis

Score

Physical
Mental

Modified from K Bagai et al., J Clin Sleep Med 2011
Sleep Problems Correlate with Poor HRQL

**Physical**

![Graph showing correlation between MOS Sleep Problems Index and SF36 Physical with R² = 0.62](image)

**Mental**

![Graph showing correlation between MOS Sleep Problems Index and SF36 Mental with R² = 0.60](image)

Modified from K Bagai et al., J Clin Sleep Med 2011
WHY do they have POTS?

... ‘final common pathway’ of hundreds of genetic and acquired autonomic and cardiovascular entities

- David Robertson
Pathophysiology of POTS –
The Challenge
Blind men and the Elephant

It was six men of Hindustan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind

They conclude that the elephant is like a
wall, snake, spear, tree, fan or rope,
depending upon where they touch.

Ancient Hindu Parable retold by John Godfrey Saxe (1816–1887)
Pathophysiology of POTS
POTS - Pathophysiology

- Mast Cell Activation
- Partial Autonomic Neuropathy
- Leg Blood Flow Abnormalities
- Hypovolemia
- Hyperadrenergic
  - Increased Release
  - Decreased Clearance
- Antibodies are Evil...
POTS and Mast Cells

- Spot (4 hour) urine collection
- If syncopal/flushing attack, 1-2 hour urine collection
- Mast cell activation disorder
- Often aspirin sensitivity
- Therapy:
  - H1 + H2 blockade
  - ASA
  - Alpha-methyldopa

C Shibao et al., Hypertension 2005
Neuropathic POTS

- Reduced NE Spillover in legs
- Abnormal sweat test (QSART) in legs

G Jacob et al., N Engl J Med. 2000;343:1008-14
Leg Blood Flow May Identify Different Subpopulations of POTS

Blood Volume & Renin-Angiotensin-Aldosterone System in POTS
Plasma Volume is Low in POTS

Adapted from SR Raj et al., Circulation 2005;111:1574-1582
Plasma Renin Activity & Aldosterone are inappropriately low in POTS... when one would expect them elevated

Adapted from SR Raj et al., Circulation 2005;111:1574-1582
RAAS Schema in POTS

- AGT → ANG I → ANG II
- PRA ↓
- ACE ↑
- ACE2 ↓
- AT1R ↓ Aldo
- ANG (1-7) ↓
- Blood Volume ↓

Adapted from HI Mustafa et al., Heart Rhythm. 2011;8:422-8.
Conclusions – RAAS in POTS

■ Things are screwy

■ Unusual RAAS profile in POTS
  ▶ Low blood volume
  ▶ Low plasma renin activity
  ▶ Low aldosterone

■ More work is needed to understand physiology
  ▶ Decreased ACE2 activity?
  ▶ Elevated ANG II due to less degradation?
  ▶ Why are aldosterone levels low?

■ Can the kidney not hold onto sodium in POTS?
  ▶ May explain the need for high sodium diets and low blood volume in POTS.
Hyperadrenergic POTS
– Increased SNS Nerve Firing
Hyperadrenergic POTS
– Decreased NE Clearance
A Norepinephrine Synapse

Slide courtesy of Alex Nackenoff (Vanderbilt)
ORTHOSTATIC INTOLERANCE AND TACHYCARDIA ASSOCIATED WITH NOREPINEPHRINE-TRANSPORTER DEFICIENCY

John R. Shannon, M.D., Nancy L. Flattem, B.S., Jens Jordan, M.D., Giris Jacob, M.D., D.Sc., Bonnie K. Black, B.S.N., Italo Biaggioni, M.D., Randy D. Blakely, Ph.D., and David Robertson, M.D.

Reaction at Vanderbilt

- Excitement

- The cause of POTS has been found!!!
POTS Patients with NET mutations: 2000-2010

No other patients had this mutation.

We had just about given up hope in NET defects as a cause of POTS...
Variable Expression of NET Protein in POTS

Courtesy of Murray Esler, Baker IDI (Melbourne, Australia)
Decreased NET Protein Expression in some POTS Patients
Role of Antibodies in POTS

1. AChR Antibody
2. Adrenergic Antibodies
Ganglionic Acetylcholine Receptor Ab

- Discovered at Mayo Clinic
  - Steve Vernino & Vanda Lennon
- Loss of function Ab at Autonomic Ganglia
- Prevalence in POTS
  - Mayo: ~7-14% of POTS patients
    - Now reportedly lower per Dr. P Low (Mayo)
  - Vanderbilt: 0% of POTS patients
- Presentation is usually Autonomic Failure
  - Orthostatic hypotension
  - Constipation, pupil findings

Schroeder C et al. NEJM 2005;353:1585-1590
POTS Patient serum stimulates adrenergic receptors

H Li et al., JAMA 2014; 3(1):e000755.
Beta-receptor activation from POTS sera

β2-AR mediated cAMP release

β1-AR mediated cAMP release

H Li et al., JAHA 2014; 3(1):e000755.
The Model

How could the Ab contribute to the POTS phenotype?

H Li et al., JAHA 2014; 3(1):e000755.
POTS – HOW to Manage?

Investigation & Treatment
POTS: Investigations

- History & Physical Examination
- Orthostatic Vital Signs
- CBC, BMP
- Autonomic Reflex Testing
- Echocardiogram
- Blood Volume Assessment
- Exercise Capacity Assessment
POTS: Treatment Approaches

- **Exercise**
- **Increase Blood Volume**
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - Octreotide
  - IV Saline
  - Acute DDAVP-H₂O
- **Hemodynamic Agents**
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Ivabradine (emerging)
- **Behavioral Therapies**
Exercise in POTS

Historically

- “good thing to do”
- Many patients could not/would not
  - excessive fatigue (~days) and intolerance
- Anecdotally, those patients that did exercise did better over time
  - Cause/effect vs. selection bias

Now

- Recent data on effects of exercise training in POTS from Dallas, Vienna, & Mayo...
Exercise Study in POTS - Design

- 3 months of exercise training
- 45-min 60° Upright Tilt
- Blood Volume Measurement
- Maximal Exercise Test
- Cardiac MRI
Exercise in POTS - Benefits

- Short-term exercise training in POTS
  - Increases fitness levels
  - Increases blood volume
  - Cardiac Remodeling
  - Normalizes Sympathetic Activity
  - Decreases Orthostatic Tachycardia

Qi Fu et al., JACC 2010;55:2858-68
Exercise in POTS – How To?

- Focus on Aerobic Activity
  - Some resistance training focused on thighs
- Must be Regular
  - Every other day (4/week)
- 30min/session -> 45-60min/session
- NO UPRIGHT EXERCISES
  - Rowing machines
  - Recumbent Cycles
  - Swimming
- Takes 4-5 weeks to start seeing benefits

Qi Fu et al., JACC 2010;55:2858-68
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IV Saline (1L) Acutely Decreases Orthostatic Tachycardia...a LOT!!

G Jacob et al. Circulation 1997;96:575-580
**DDAVP+H₂O reduces standing HR**

ST Coffin et al., Heart Rhythm. 2012;9:1484-90
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Midodrine Decreases Orthostatic Tachycardia...a little bit.

Beta-Blockers in POTS

- **PRO**
  - Intuitively appealing
    - High HR -> Lower it

- **CON**
  - Stewart et al. studied IV esmolol and found that it DID NOT improve orthostatic tolerance
  - Many patients report “intolerance to beta-blockers”
Propranolol 20mg lowers Orthostatic Tachycardia

SR Raj et al. Circulation 2009;120:725-734
Propranolol Improves Symptoms…

SR Raj et al. Circulation 2009;120:725-734
…but Less is More

Propranolol 20mg
Propranolol 80mg

Δ Symptoms Score (a.u.)

P = 0.041 Wilcoxon

SR Raj et al. Circulation 2009;120:725-734
Acetylcholinesterase Inhibition

- **Pyridostigmine**
  - Peripheral AChEI
  - Increases availability of synaptic ACh
  - Ganglionic Nicotinic Receptor
    - ↑ SNS & ↑ PNS
  - Postganglionic Muscarinic Receptor
    - ↑ PNS

- Might decrease tachycardia in POTS
Acetylcholinesterase Inhibition

Standing Heart Rate

Symptoms

SR Raj et al., Circulation 2005;111:2734-2740
Norepinephrine Transporter Inhibition

EA Green et al., JAHA 2013;2:e000395
Norepinephrine Transporter Inhibition

Orthostatic Change

Symptoms: 0 to 2h

EA Green et al., JAHA 2013;2:e000395
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What Type of POTS Do I Have?

Challenges:
1. Overlapping Subsets
2. Lost in Translation
What Type of POTS Do I Have?

Hyperadrenergic POTS

Neuropathic POTS

Hypovolemic POTS
What Type of POTS Do I Have?

Hyperadrenergic POTS

Neuropathic POTS

Hypovolemic POTS
Lost in Translation

Not my M-I-L
Prognosis of POTS

“Prediction is very difficult, especially about the future.”

Niels Bohr (1885-1962); Nobel Prize (Physics) 1922
POTS – Take Home Messages

POTS
- chronic disorder associated with significant disability
- Syndrome…not one disease
  - Multiple pathophysologies

Treatment
- Exercise
- Volume expansion
- Heart rate control
- Manage the “living with a chronic illness”
Questions?