A molecular cause for PoTS and vasovagal syncope – The Norepinephrine Transporter

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Postural Tachycardia Syndrome
- Common Criteria

- Orthostatic tachycardia > 30 bpm
  - >40 bpm required if <18 years
- No consistent orthostatic hypotension
  - $\Delta$BP > 20/10 mmHg
- Symptoms of sympathetic activation
  - Worse upright; better recumbent
- Chronic symptoms > 6 months
<table>
<thead>
<tr>
<th></th>
<th>POTS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Tilt Angle (deg)</td>
<td>0</td>
<td>60</td>
</tr>
</tbody>
</table>

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

SR Raj & RS Sheldon, *Tilt Table Testing* in
S Saksena & AJ Camm *Electrophysiological Disorders of the Heart* 2nd Ed. (2011)
POTS - Pathophysiology

- Mast Cell Activation
- Partial Autonomic Neuropathy
- Leg Blood Flow Abnormalities
- Hypovolemic
- Hyperadrenergic
  - Increased Release
  - Decreased Clearance
- Antibodies are Evil...
Hyperadrenergic POTS
– Increased SNS Nerve Firing

Normal

hPOTS
Hyperadrenergic POTS – Decreased NE Clearance
Patient with POTS led to a change in thinking....

- Palpitations
- Dizziness or lightheadedness
- Slowed thinking on standing
- Reduced exercise capacity
- Fatigue
- Near-fainting often and rarely fainting

Muscle Sympathetic Nerve Activity and Plasma NE

Electrochemical Dissociation

% of Supine Value

Supine
Upright

A Norepinephrine Synapse

Slide courtesy of
Alex Nackenoff
(Vanderbilt)
A Norepinephrine Synapse
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.

Heart Rate in A457P (NET KO) vs. Normal Subjects

Orthostatic Tachycardia in Affected Family Members but not Unaffected Members

Excitement

The cause of POTS has been found!!!
No other patients had this mutation.

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

“Cardiac Dropout” on MIBG Scan in some POTS patients

Haensch C et al. J Neurol Neurosurg Psychiatry 2010;81:339-343
NET Gene Silencing in POTS

Therapeutic Implication in POTS: Norepinephrine Transporter Inhibition

EA Green et al., JAHA (2014)
Therapeutic Implication in POTS: Norepinephrine Transporter Inhibition

Orthostatic Change

Symptoms: 0 to 2h

EA Green et al., JAHA (2014)
Syncope
Syncope Definition

— transient loss of consciousness with spontaneous recovery which does not require defibrillation
— “blackout, faint, spell, collapse”
— patient is unresponsive
— NOT
  ▪ coma, cardiac arrest, drowsiness, generalized seizure
Syncope: Basic Epidemiology

- **Common**
  - 40-50% lifetime prevalence
  - 0.5-1% incidence
  - 3-6% of emergency room visits
  - 1% of hospital admissions
  - 1 million Americans assessed/year

- **Expensive**
  - Case cost $500-25K
  - Falls, disability, lost productivity
### Causes of Syncope – Age and Risk Considerations

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td><strong>Vasovagal</strong></td>
<td><strong>Vasovagal</strong></td>
</tr>
<tr>
<td></td>
<td>Situational</td>
<td>Orthostatic</td>
</tr>
<tr>
<td></td>
<td>Psychogenic</td>
<td>Drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multifactorial</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td>Inherited</td>
<td><strong>Arrhythmias</strong></td>
</tr>
<tr>
<td></td>
<td>Electrical - LQT, BS, CPVT etc</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Mechanical - ARVC, HCM, DCM</td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>
The Sympathetic Nerve

With Heartfelt Sympathy

Neuron cell body
Axon
Myelin sheath
Nucleus
Dendrite
Tyrosine hydroxylase (TH) and norepinephrine transporter (NET) proteins in VVS patients

Gautam Vaddadi et al. Circ Arrhythm Electrophysiolog. 2011;4:711-718

↑ NET in VVS with normal BP

↓ TH in VVS with low BP
Novel Drug Therapy: Norepinephrine Transporter (NET) Inhibition
Norepinephrine Transporter Inhibition Prevents Tilt-Induced Pre-Syncope

Christoph Schroeder, MD,* Andreas L. Birkenfeld, MD,* Antje F. Mayer,* Jens Tank, MD,* Andre Diedrich, MD, PhD,† Friedrich C. Luft, MD,* Jens Jordan, MD*

“Meta-Analysis” of 3 studies of 2 different NET inhibitors

“Healthy” controls


Placebo – 9/18 fainted
Reboxetine – 1/18 fainted

Norepinephrine Transport Inhibition for VVS Treatment

- Sibutramine
- Open-label study
- “worst of the worst” fainters
- Marked reduction in fainting rates
- Sibutramine no longer on the Canadian Market
Assessment of Atomoxetine to Prevent Vasovagal Syncope
Assessment of Atomoxetine to Prevent Vasovagal Syncope

- Prospective placebo-controlled RCT; parallel design
- Acute NET blockade
  - atomoxetine 40 mg po bid x 2 doses
- N=74 vasovagal syncope patients
- GOAL: Prevent Tilt Table Test induced syncope
- Inclusion with fainting and Calgary S3 score
- 4 Canadian centres planned
  - Calgary
  - Winnipeg
  - Hamilton
  - Sherbrooke

- **Timeline: July 2015 – June 2017**
Study Design of Future Projects within the Program

- Multicentre placebo-controlled RCT
  - Outcomes driven by Patient Advisory Council

- Patient-driven research

- Phase 4 studies for impediments to uptake
Questions?
Physiologic model of VVS

Physiological Stress

Volume Depletion

Baroreceptor activation or inactivation

CNS Reflex

Vagal Stimulation

Sympathetic Withdrawal

Salt & Water
Fludrocortisone

Catecholamines

Beta-Blockers

POST 5

Pacemakers
Scopolamine

SSRI - Paroxetine

POST 4

Midodrine