Postural Tachycardia Syndrome (POTS) – What? Why? How?

Satish R Raj MD MSCI FACC FHRS FRCPC

Associate Professor of Cardiac Sciences
University of Calgary

Adjunct Associate Professor of Medicine
Autonomic Dysfunction Center
Vanderbilt University School of Medicine

October 2014

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

Position	HR (bpm)	BP (mmHg)
Supine – 15 min	73	103/72
Upright – 1 min	106	109/80
Upright – 3 min	105	106/83
Upright – 5 min	122	118/75
Upright – 10 min	121	118/78

WHAT is POTS?

Postural Tachycardia Syndrome - Common Criteria

Phillip Low MD
Mayo Clinic

- **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

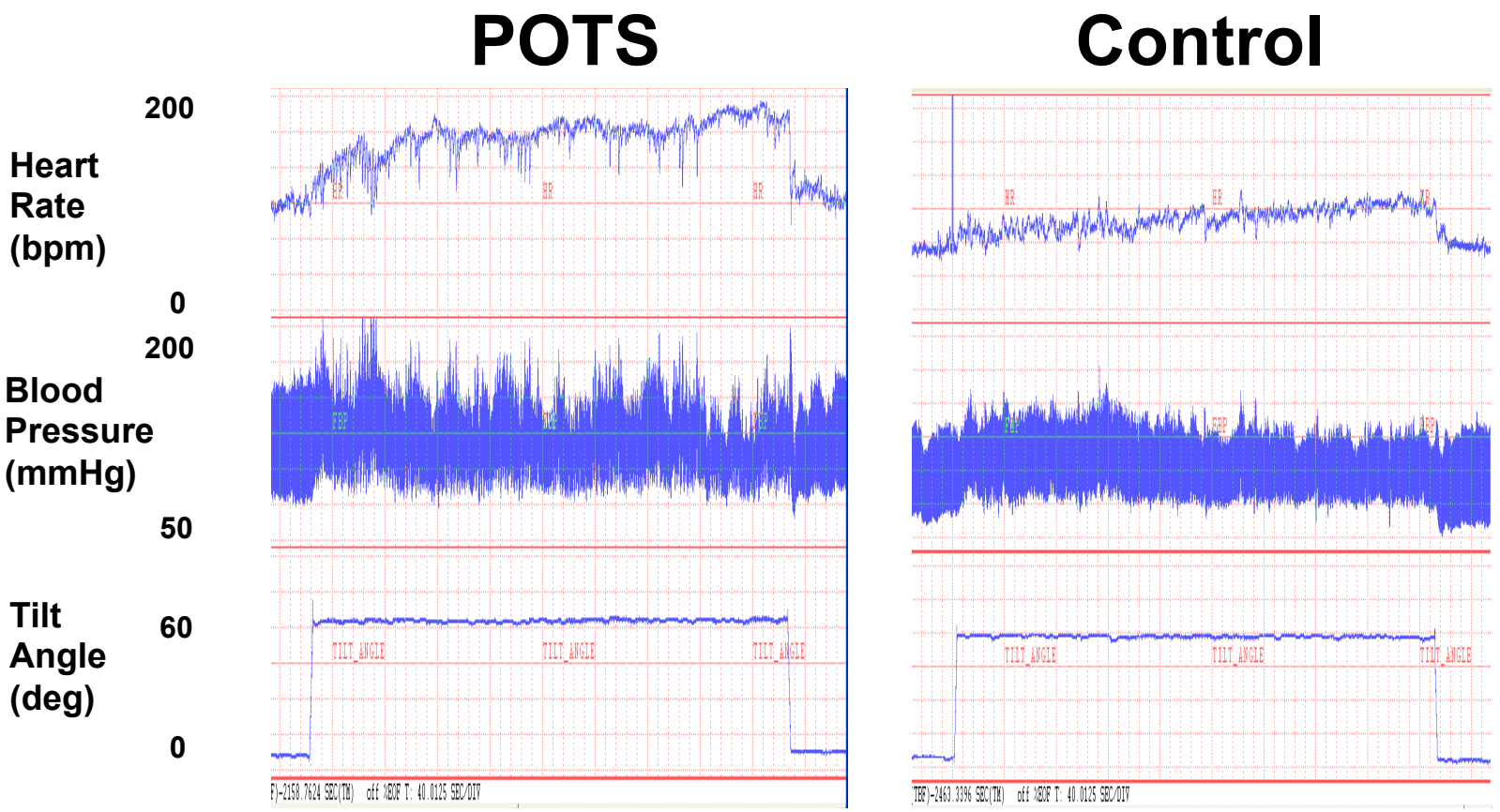
- Exercise Intolerance

Non-Cardiac

- Mental Clouding
- Headache
- Nausea
- Tremulousness

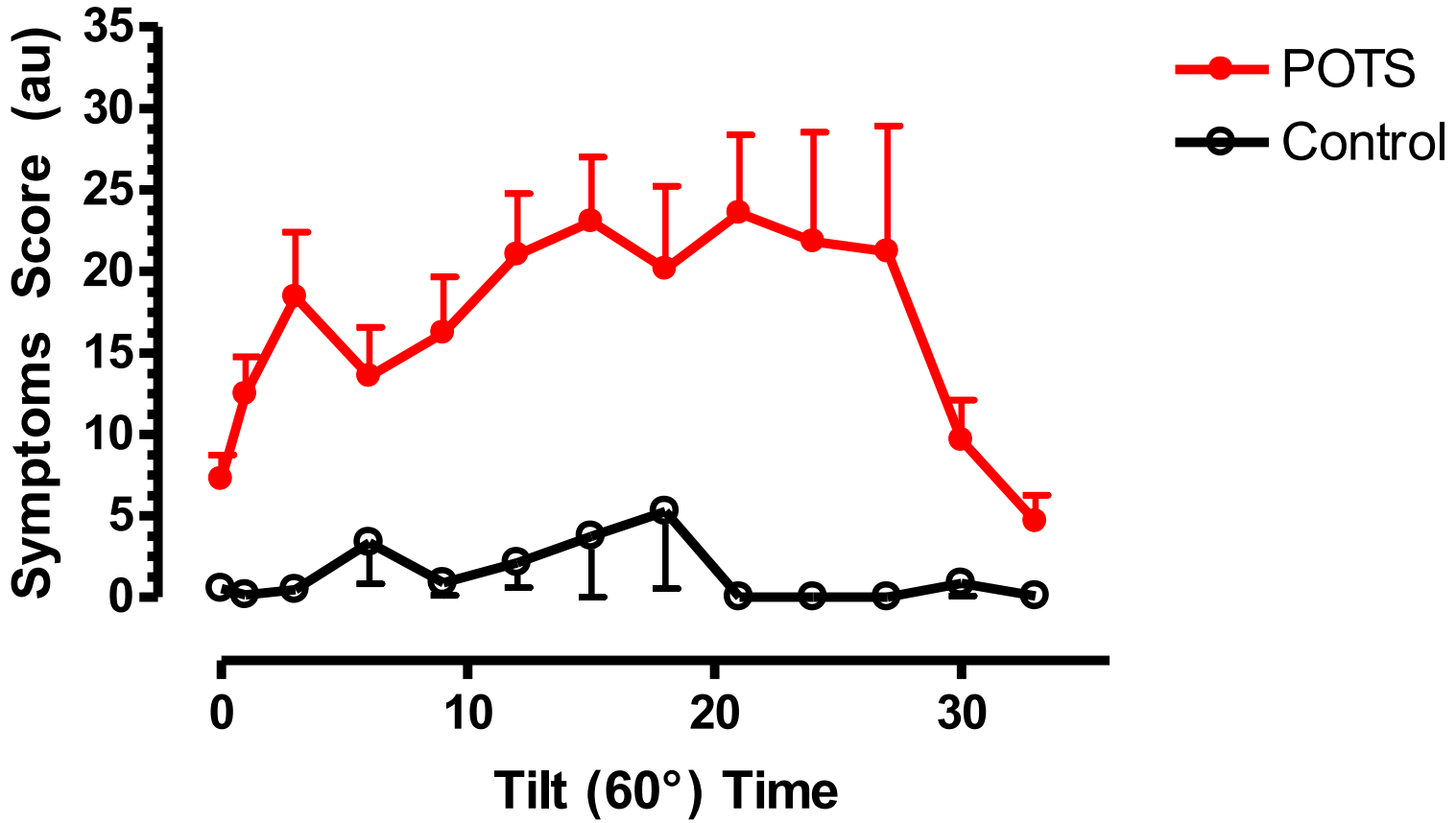
- Fatigue
- Sleep Complaints

Tilt Testing



SR Raj, Indian Pacing Electrophysiol J. 2006;6:84-99

POTS: Feel awful when upright



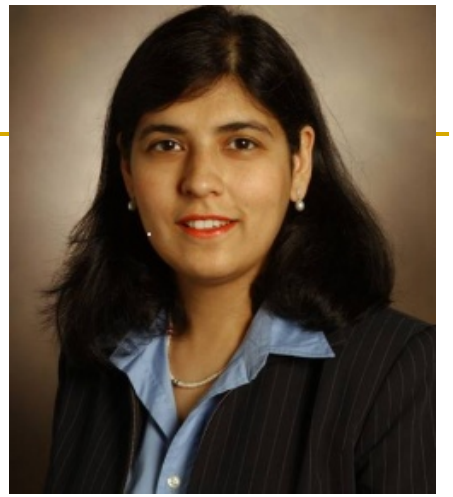
SR Raj & RS Sheldon, *Tilt Table Testing* in
S Saksena & AJ Camm Electrophysiological Disorders of the Heart 2nd Ed. (2011)

POTS – Who is affected?

- Prevalence ½ million in USA
- Female (~80-85%)
- Typically aged 13-50 years

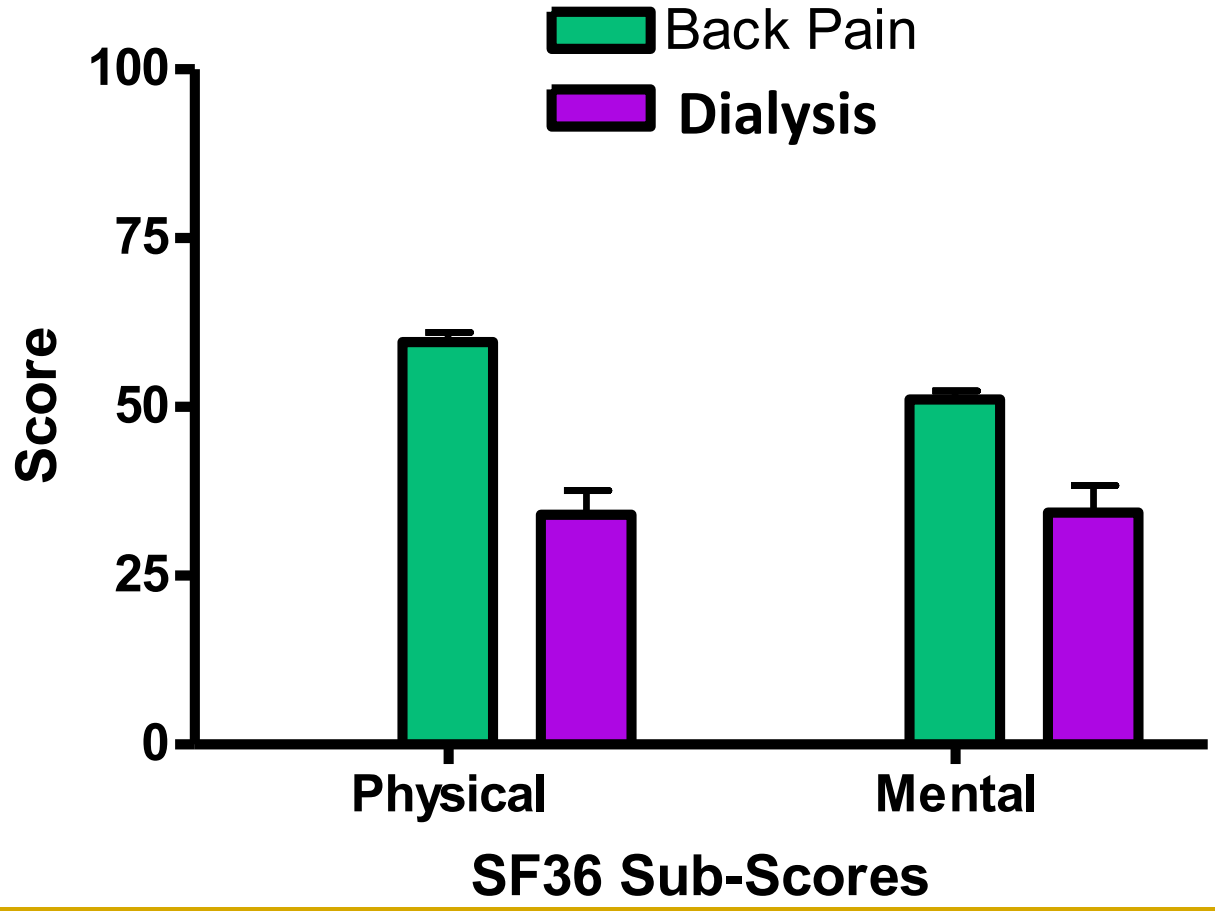
- Significant functional disability

Quality of Life in POTS

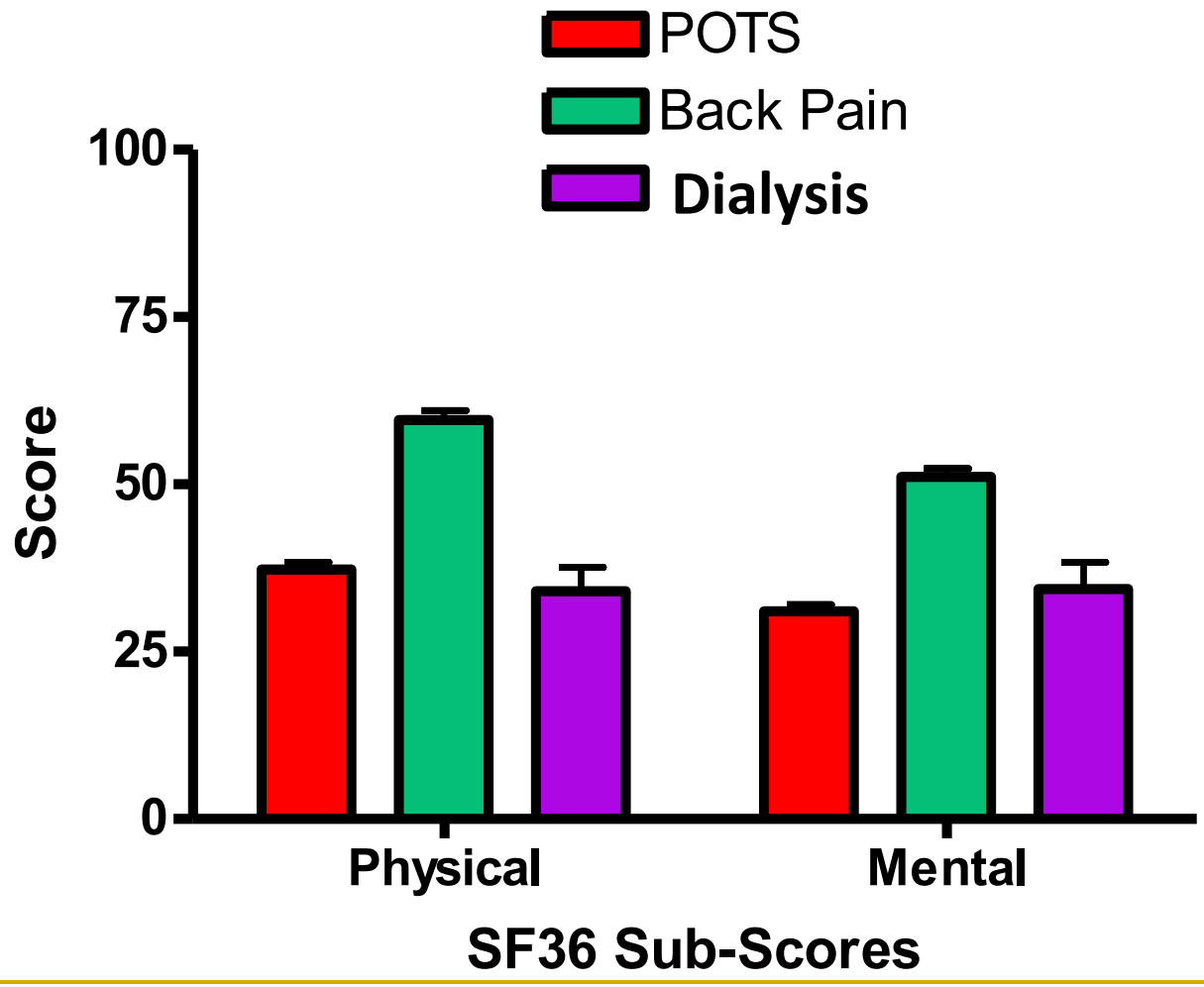


Kanika Bagai

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



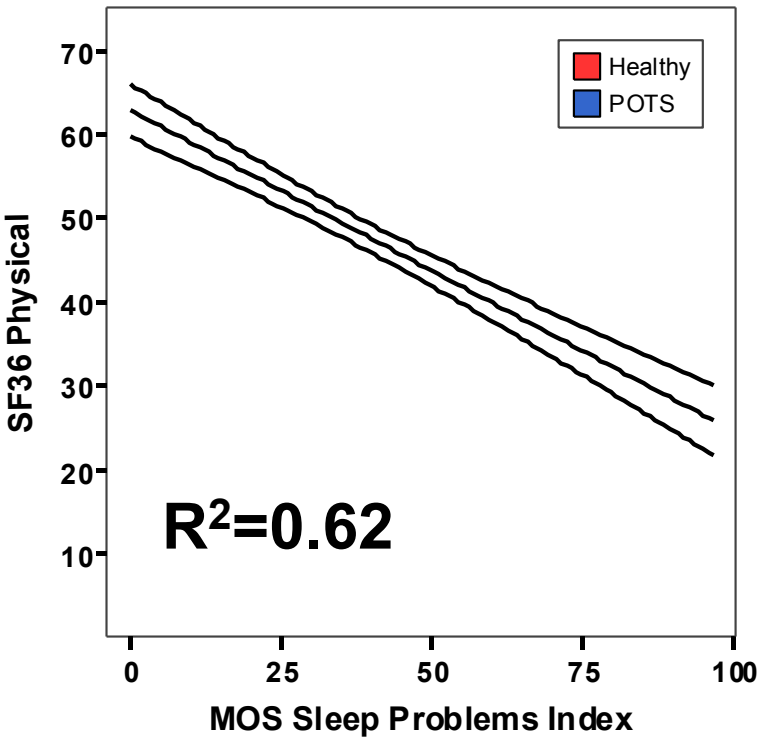
Health Related Quality of Life (SF-36) – Chronic Illnesses



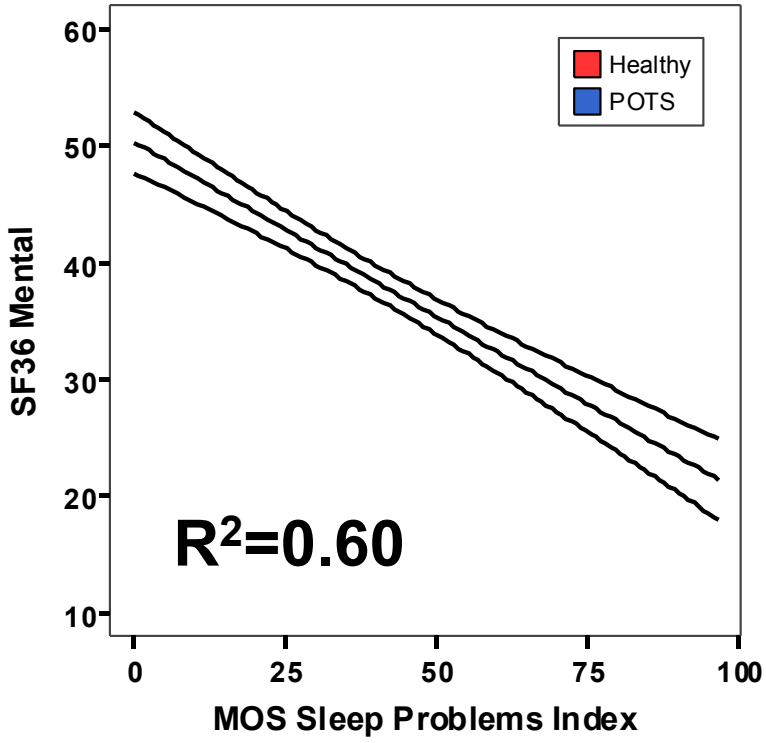
Modified from K Bagai et al., J Clin Sleep Med 2011

Sleep Problems Correlate with Poor HRQL

Physical



Mental



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

David Robertson

Pathophysiology of POTS – The Challenge

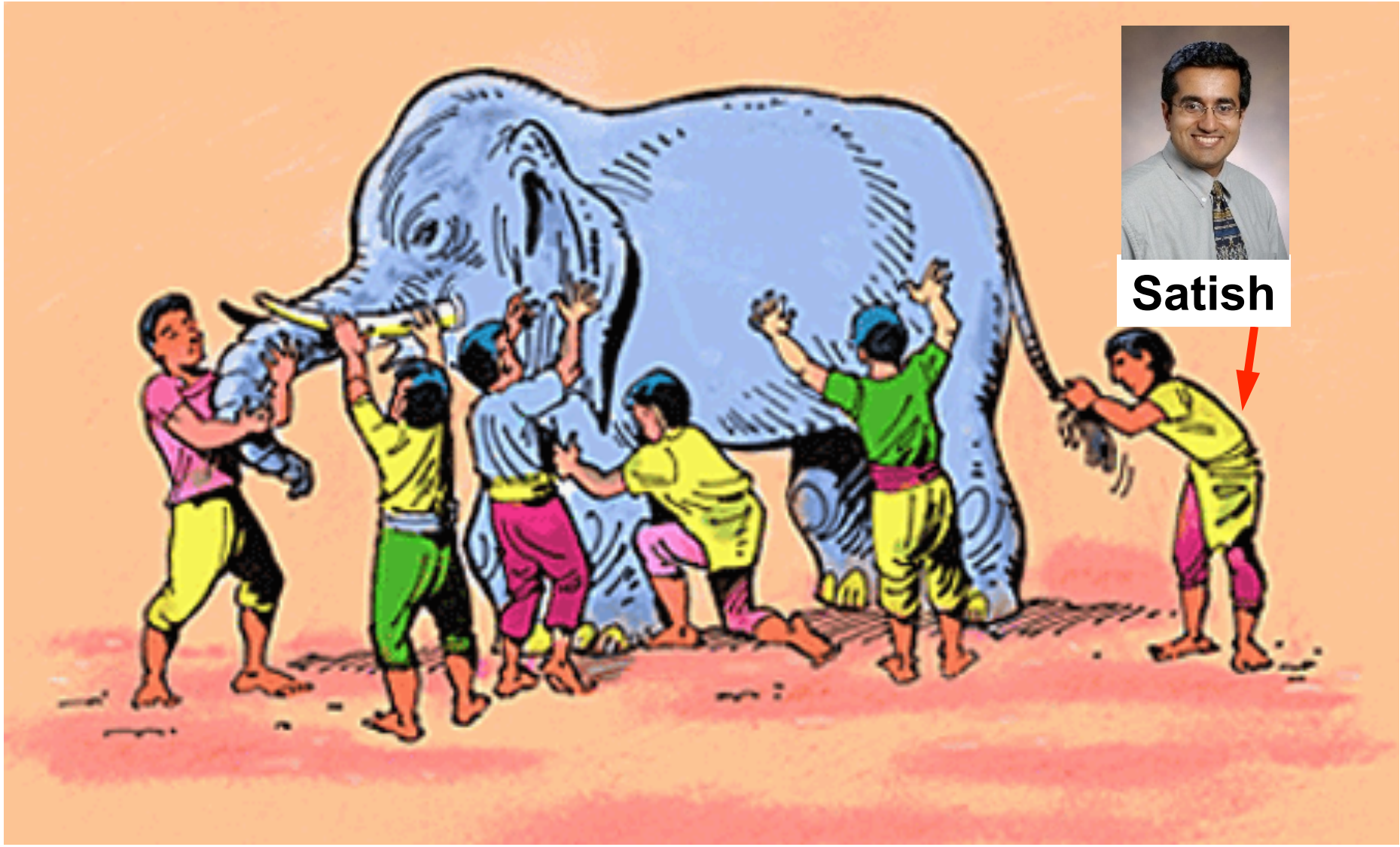
Blind men and the Elephant

- **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

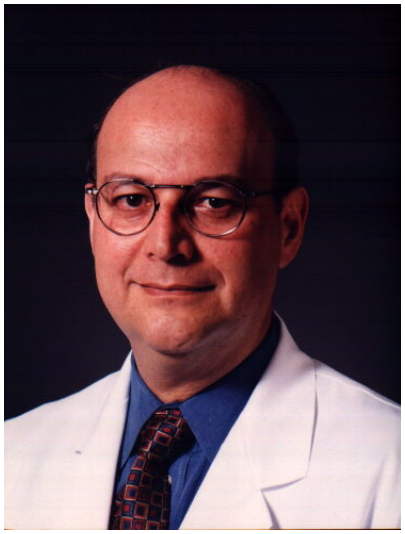


POTS - Pathophysiologies

- 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



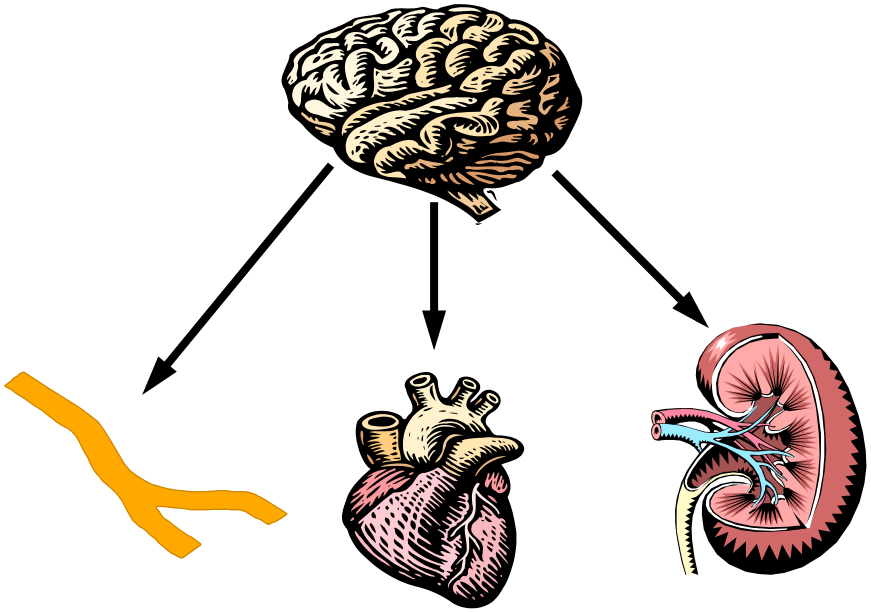
Italo Biaggioni

C Shibao et al., Hypertension 2005

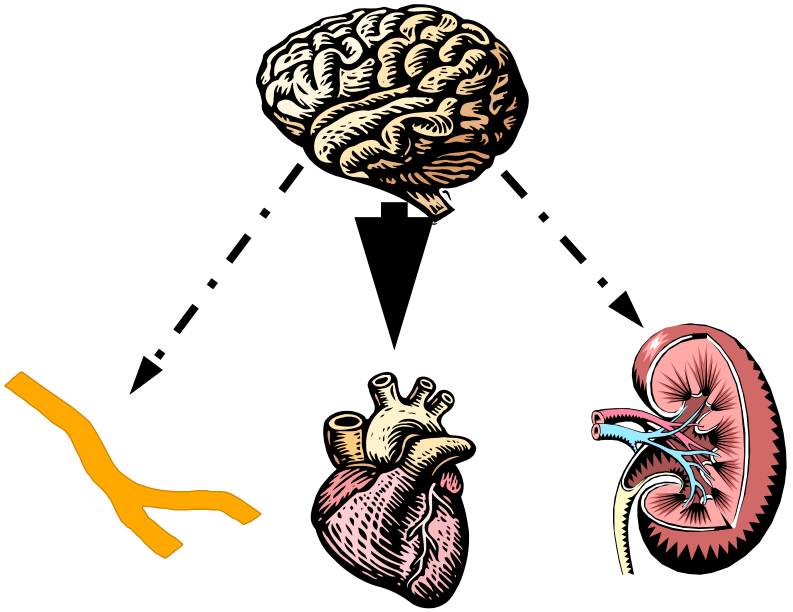
Neuropathic POTS

Giris Jacob

Normal



nPOTS

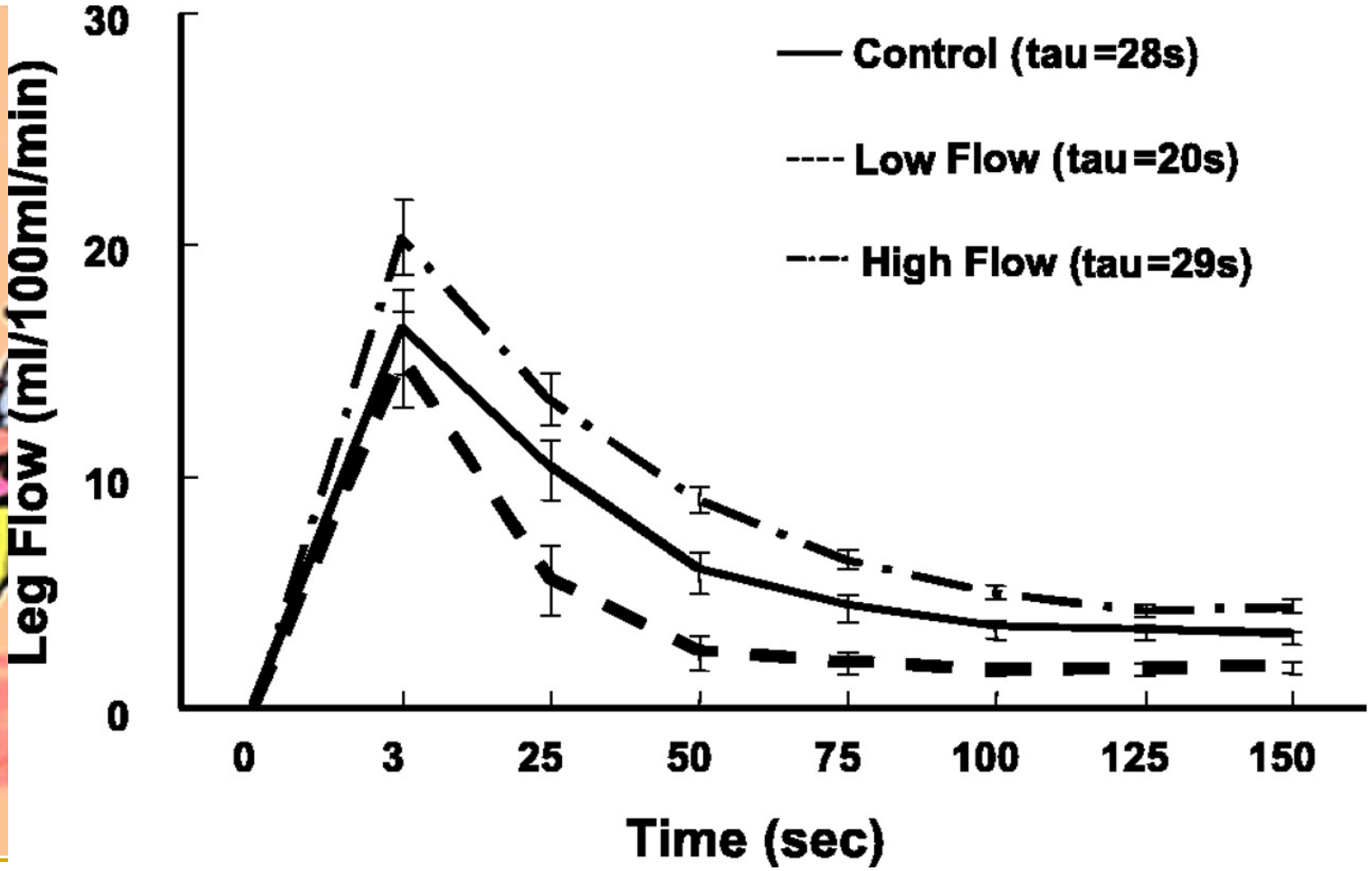


- Reduced NE Spillover in legs
- Abnormal sweat test (QSART) in legs

G Jacob et al., N Engl J Med. 2000;343:1008-14

Leg Blood Flow May Identify Different Subpopulations of POTS

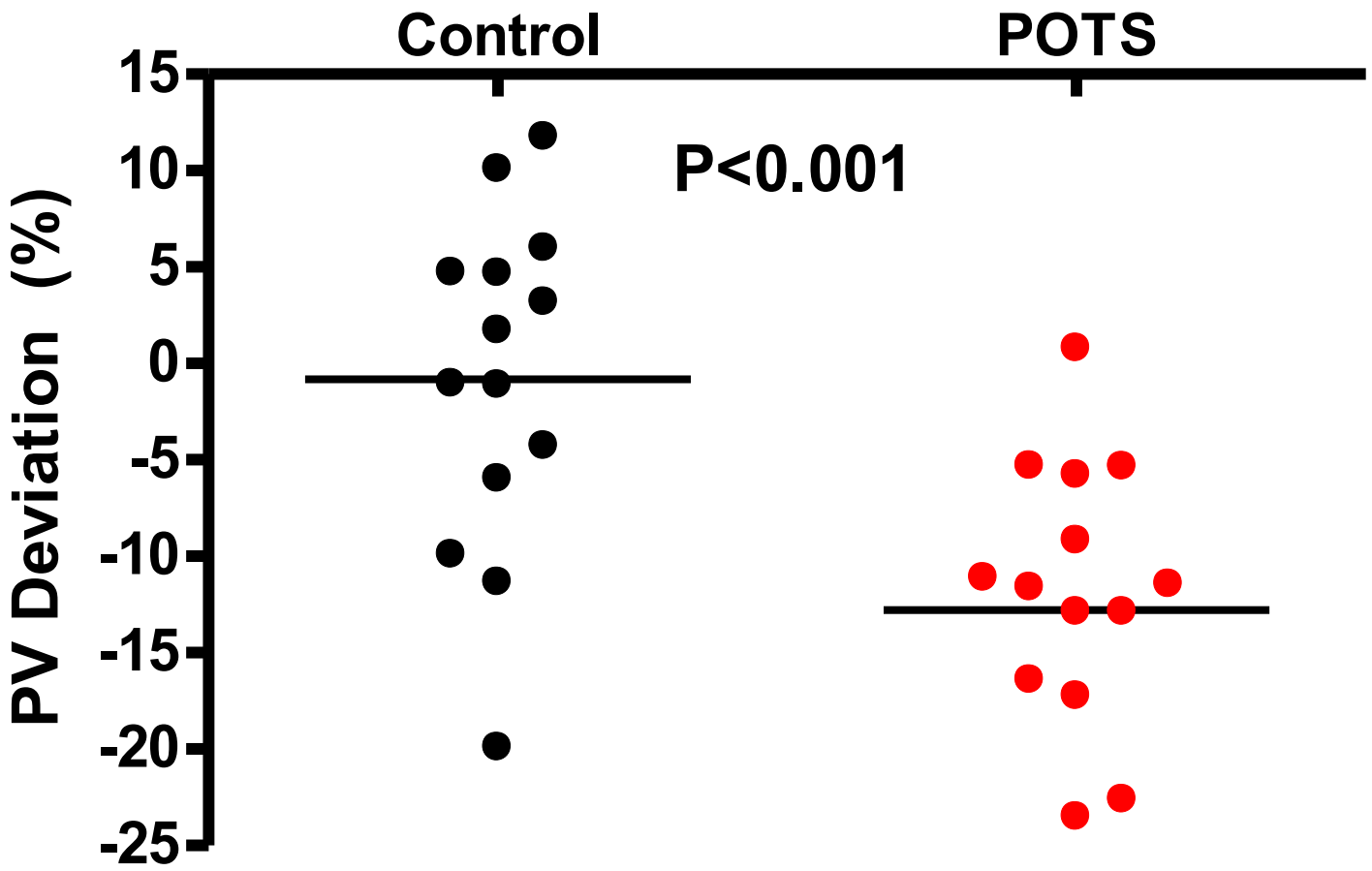
Julian Stewart



Stewart J M et al. AJP Heart Circ Physiol 2003;285:H2749-H2756

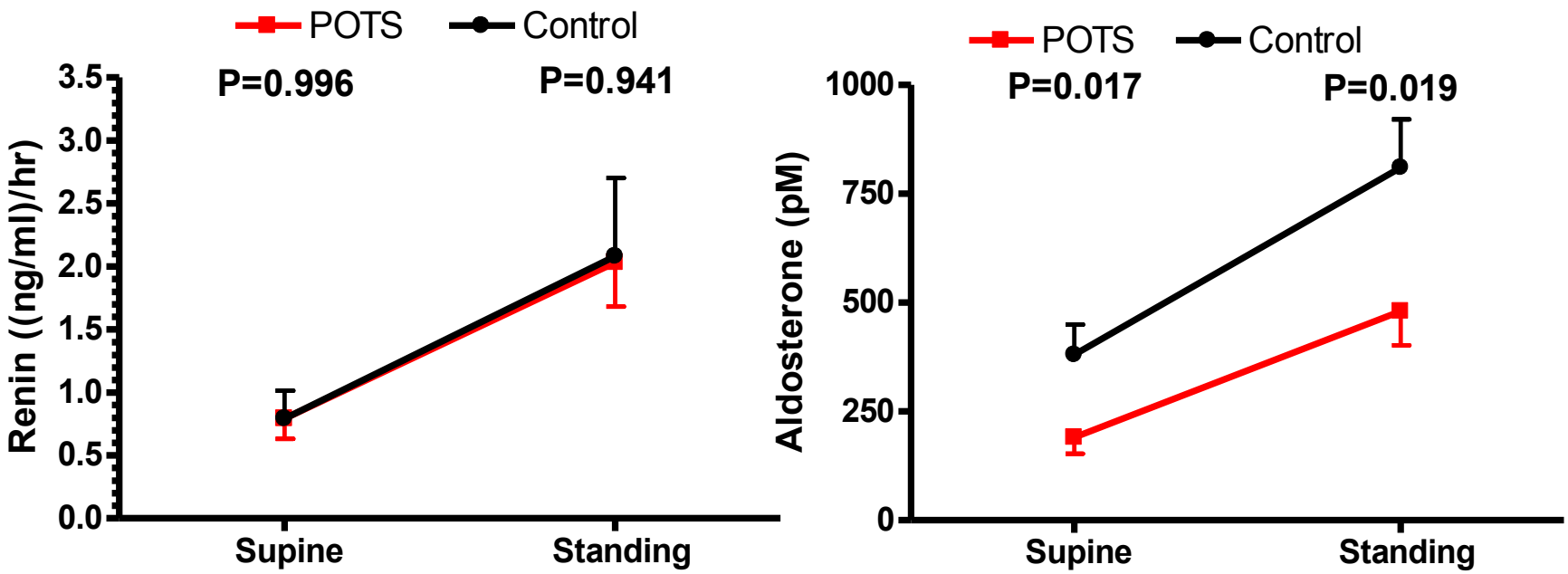
Blood Volume & Renin-Angiotensin-Aldosterone System in POTS

Plasma Volume is Low in POTS



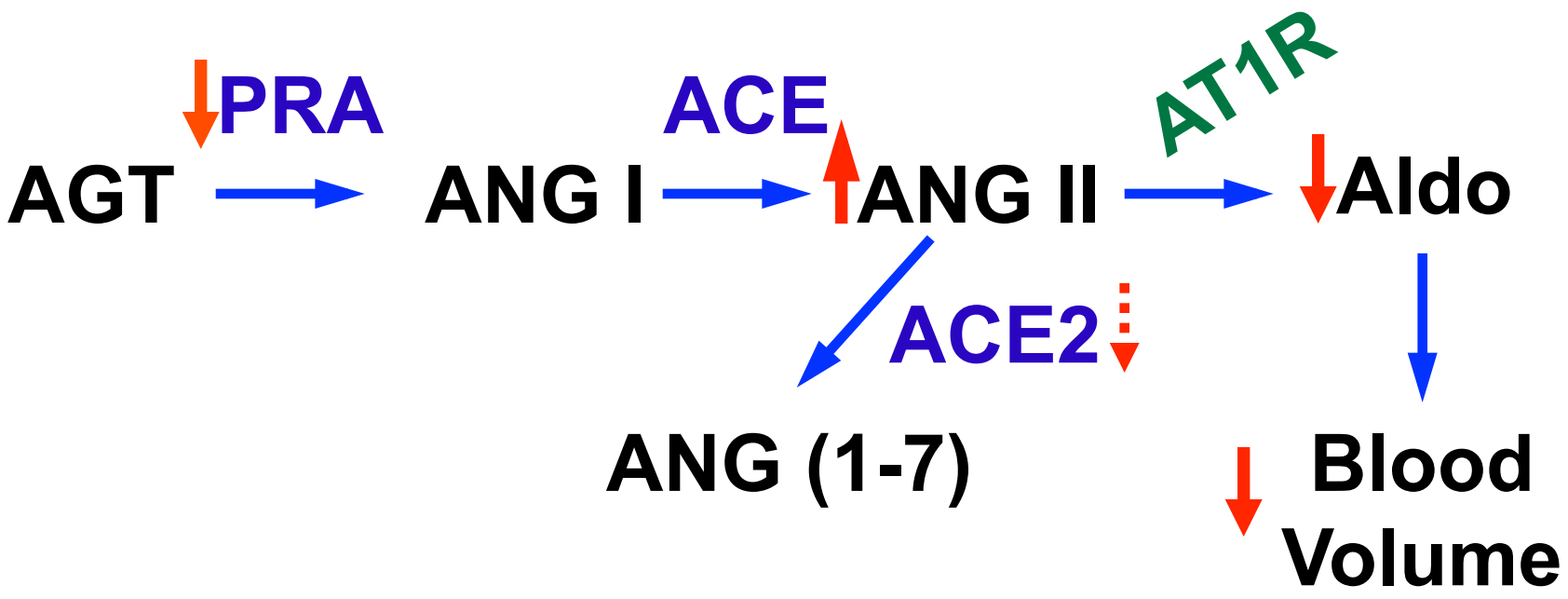
Adapted from SR Raj et al., Circulation 2005;111:1574-1582

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

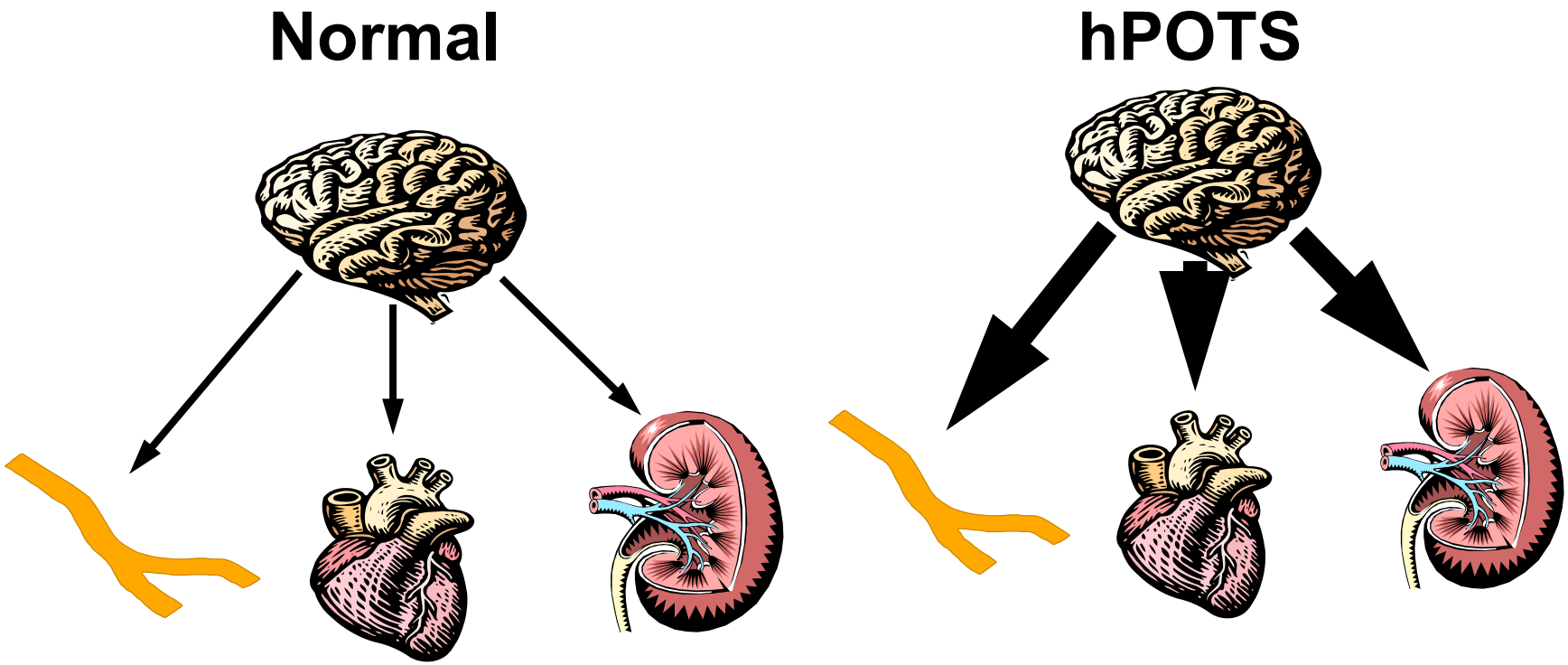


Adapted from HI Mustafa et al., Heart Rhythm. 2011;8:422-8.

Conclusions – RAAS in POTS

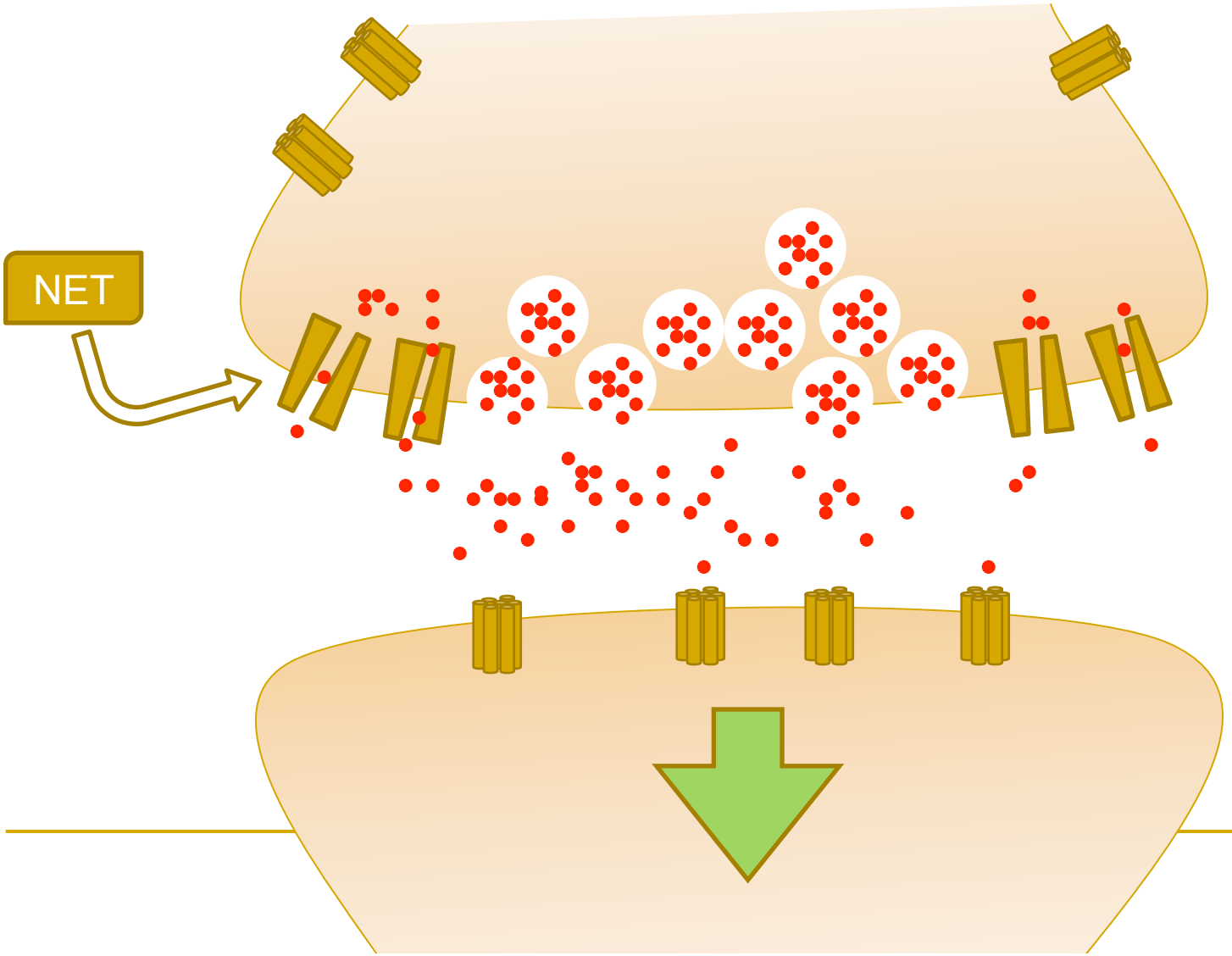
- Things are screwy
- Unusual RAAS profile in POTS
  - Low blood volume
  - Low plasma renin activity
  - Low aldosterone
- More work is needed to understand physiology
  - Decreased ACE2 activity?
  - Elevated ANG II due to less degradation?
  - Why are aldosterone levels low?
- Can the kidney not hold onto sodium in POTS?
  - May explain the need for high sodium diets and low blood volume in POTS.

Hyperadrenergic POTS – Increased SNS Nerve Firing



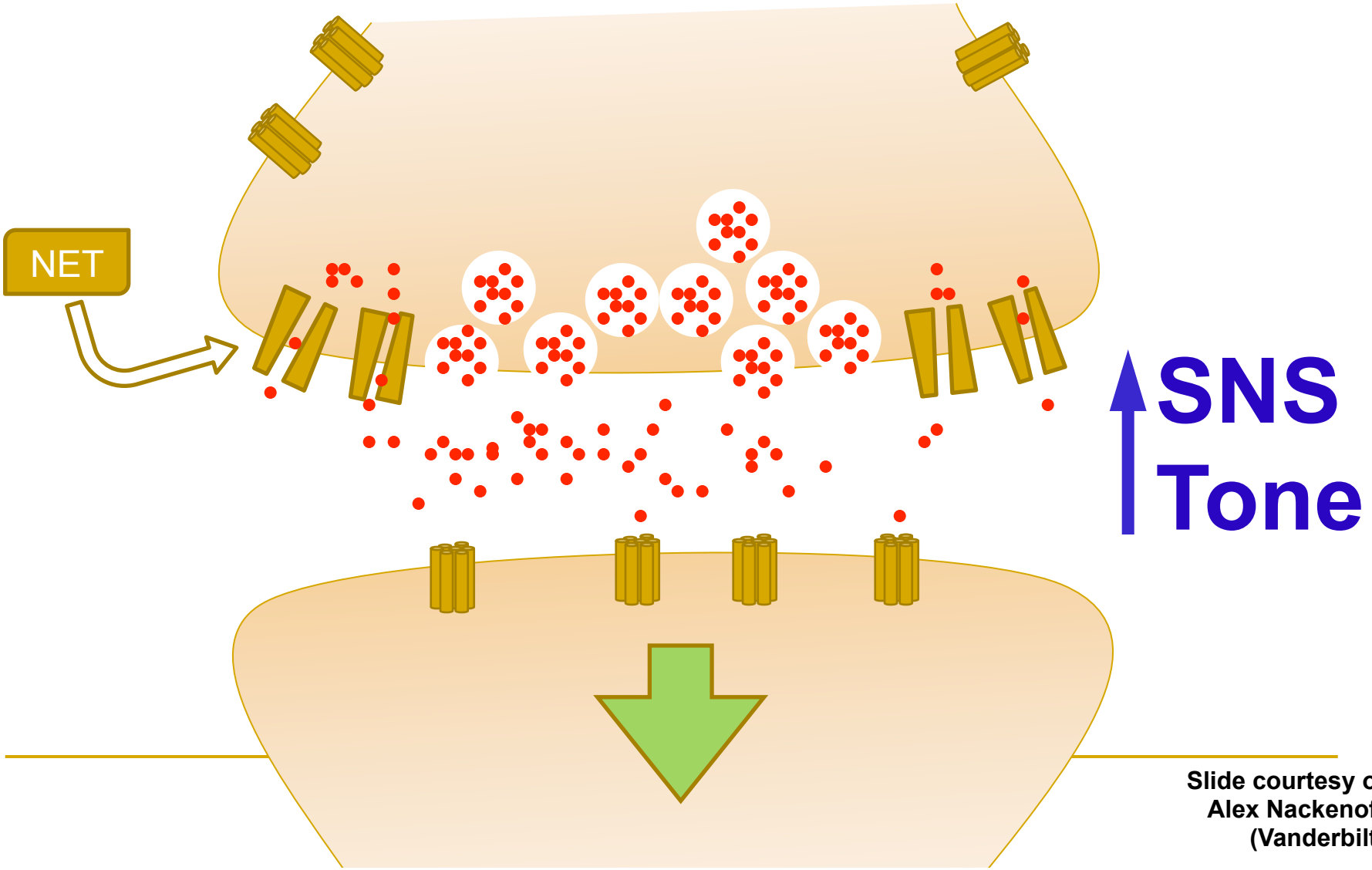
Hyperadrenergic POTS – Decreased NE Clearance

A Norepinephrine Synapse



Slide courtesy of
Alex Nackenoff
(Vanderbilt)

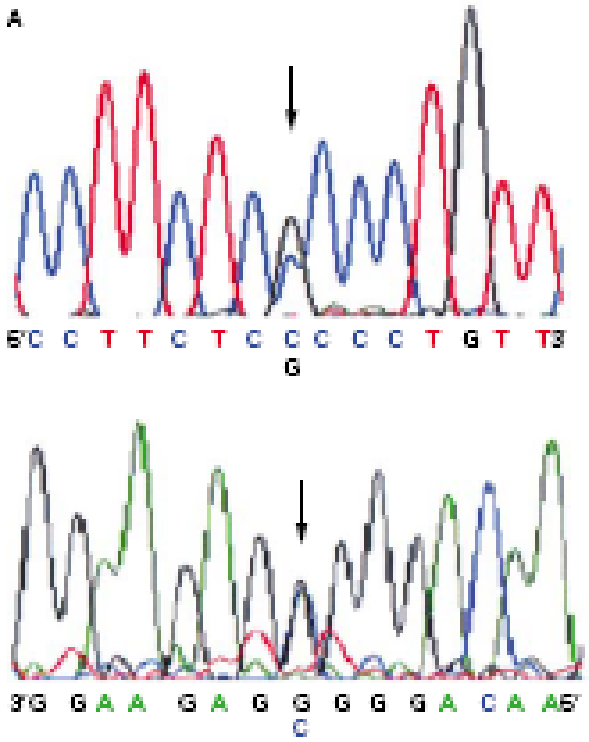
A Norepinephrine Synapse

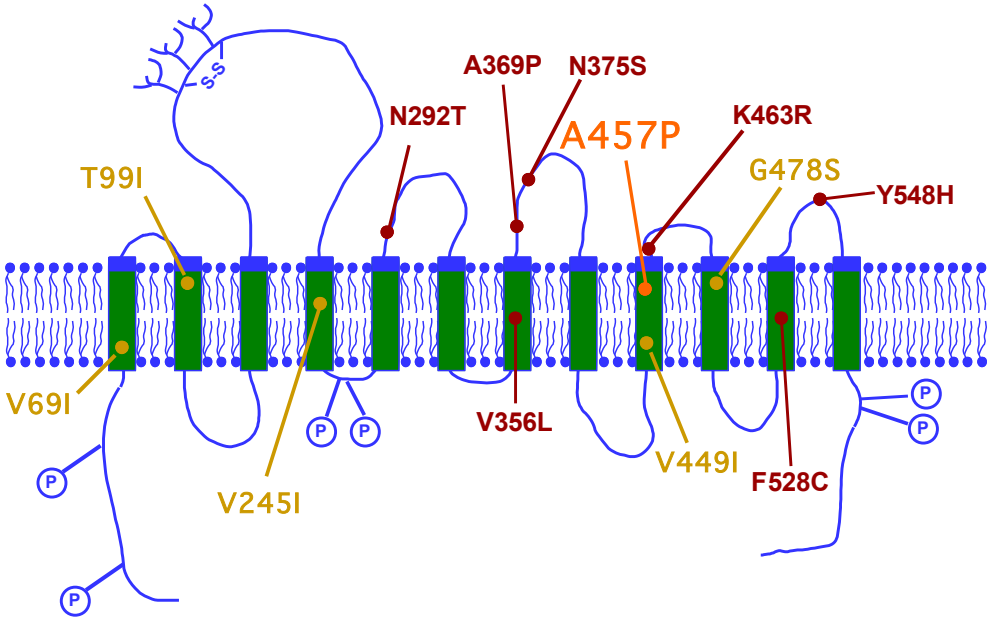


Slide courtesy of
Alex Nackenoff
(Vanderbilt)

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.





Shannon JR, NEJM 2000; 342:541-9.

Reaction at Vanderbilt

- Excitement
- The cause of POTS has been found!!!

POTS Patients with NET mutations: 2000-2010

-
-
-
-

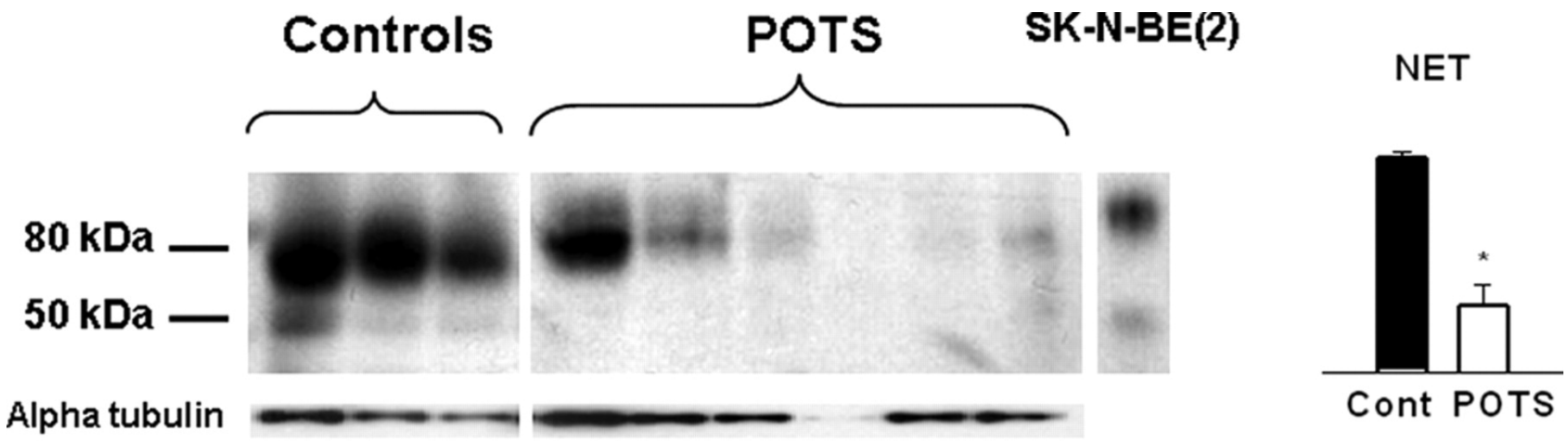
No other patients had this mutation.

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



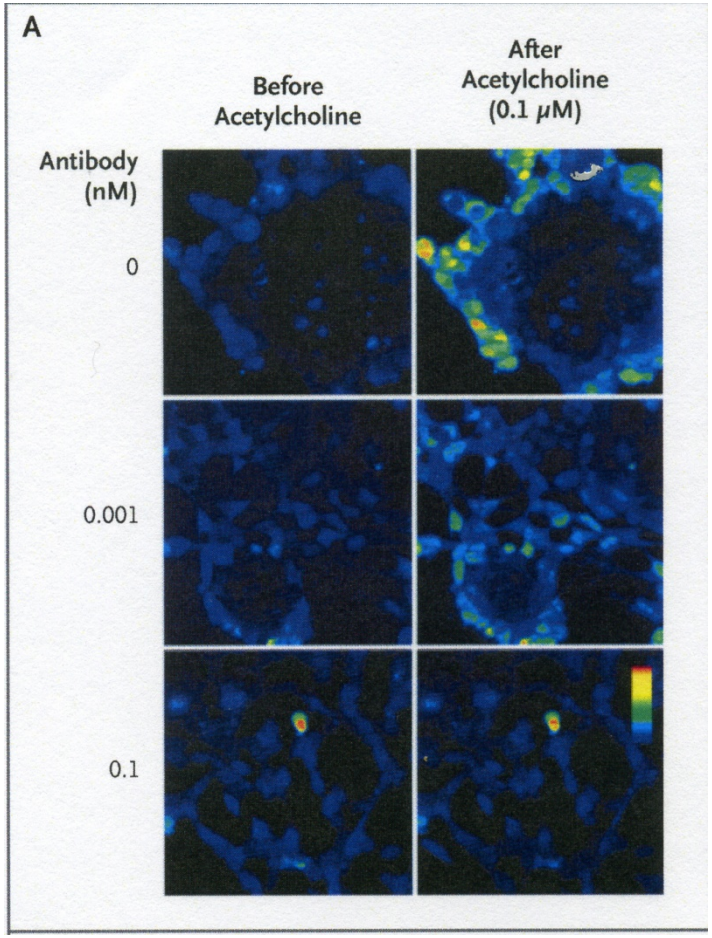
Lambert E et al. Circ Arrhythm Electrophysiol 2008;1:103-109

Role of Antibodies in POTS

1. AChR Antibody
2. Adrenergic Antibodies

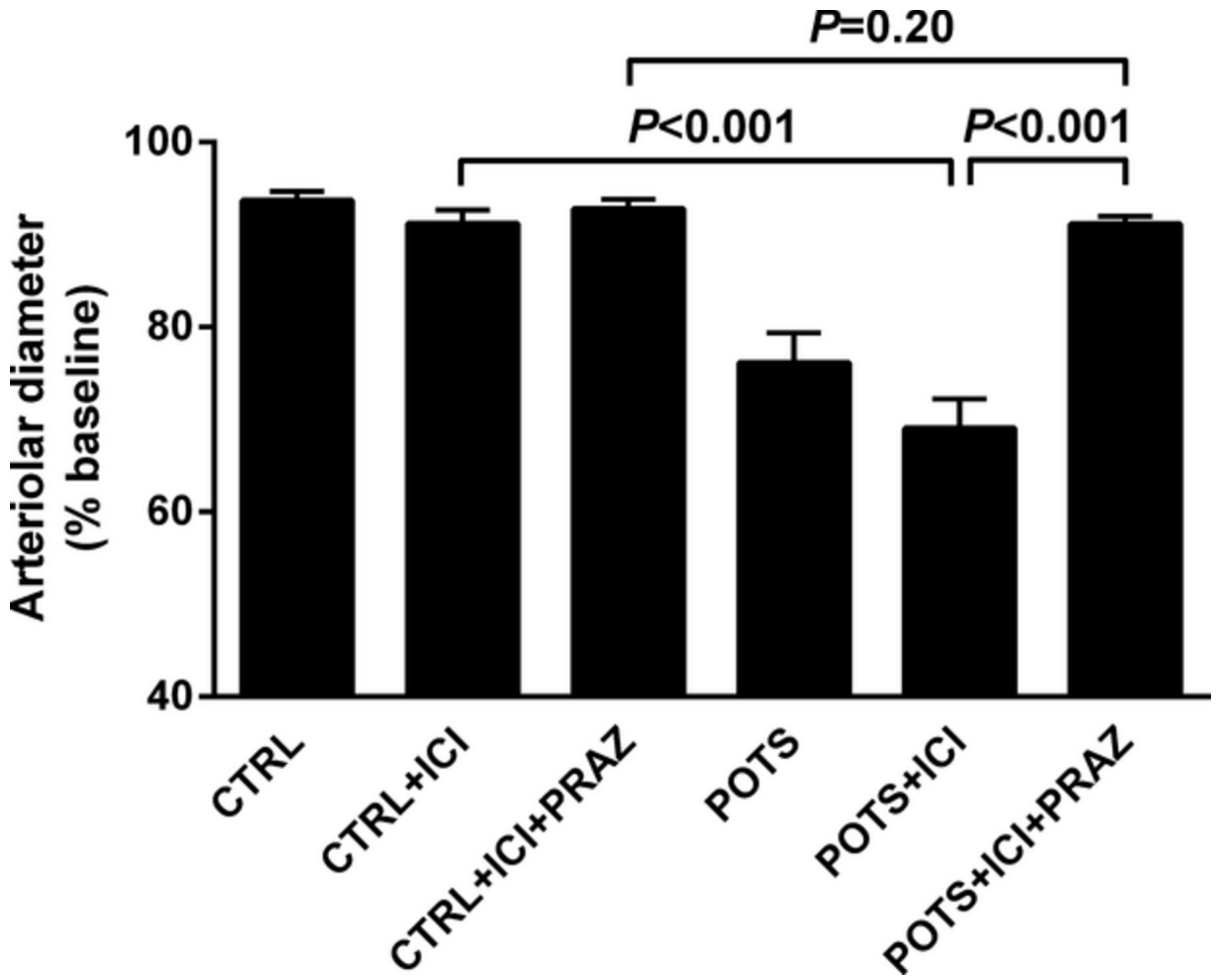
Ganglionic Acetylcholine Receptor Ab

- 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



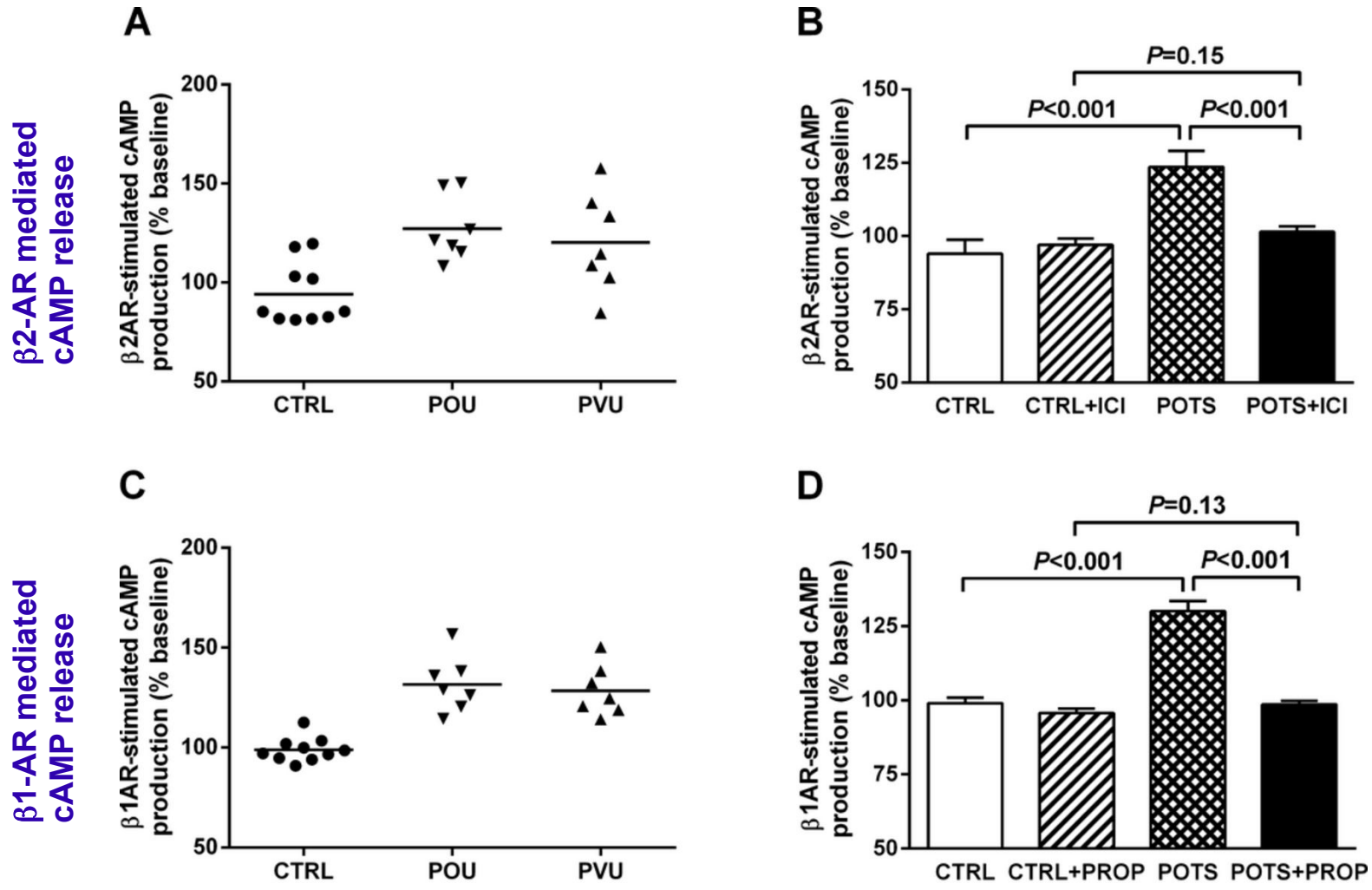
Schroeder C et al. NEJM 2005;353:1585-1590

POTS Patient serum stimulates adrenergic receptors



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

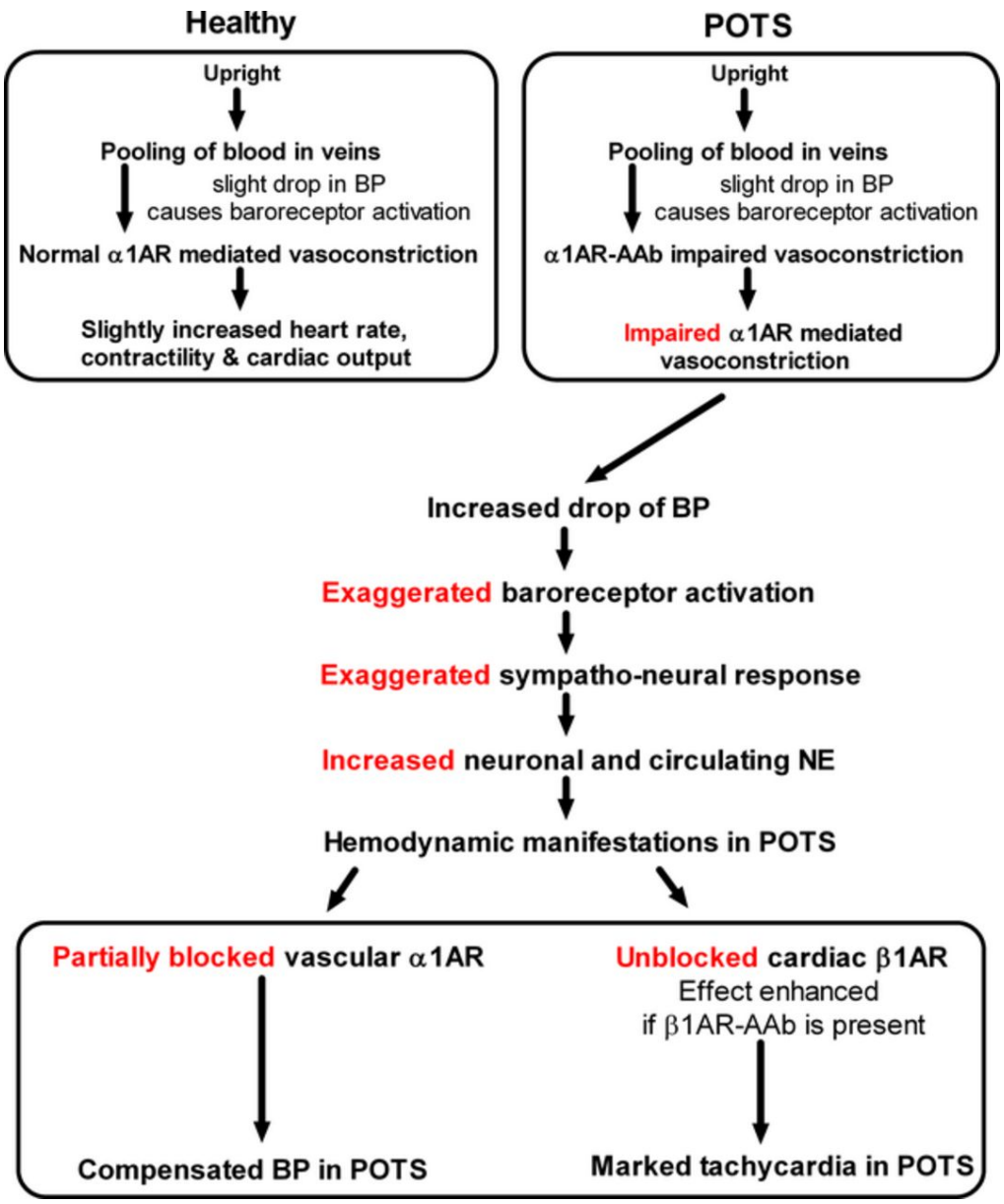
Beta-receptor activation from POTS sera



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

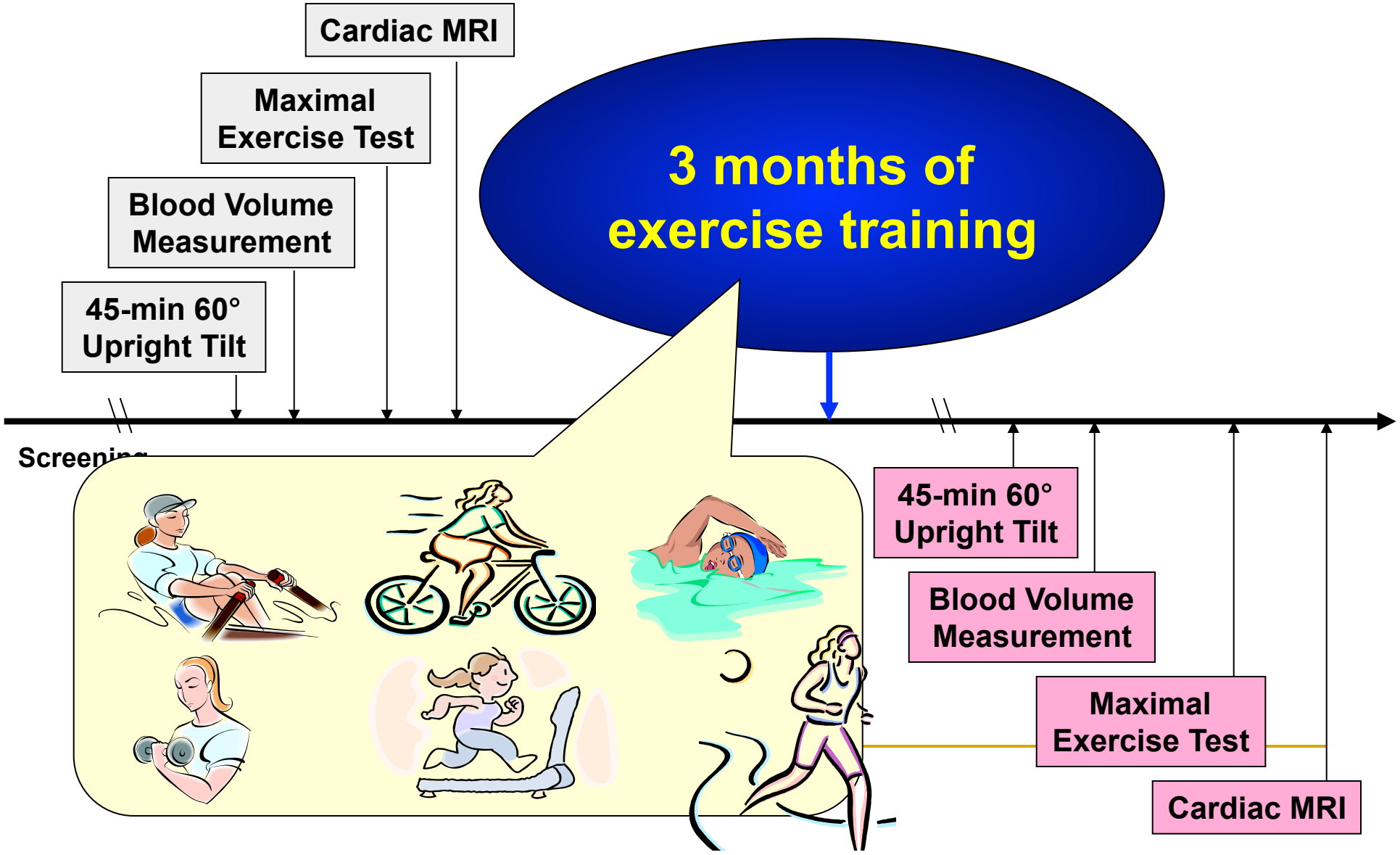
POTS: Treatment Approaches

- **Exercise**
- **Increase Blood Volume**
  - **Oral Water**
  - **Increase Salt (diet vs. tablets)**
  - **Fludrocortisone**
  - **Octreotide**
  - **IV Saline**
  - **Acute DDAVP-H_2O**
- **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



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?

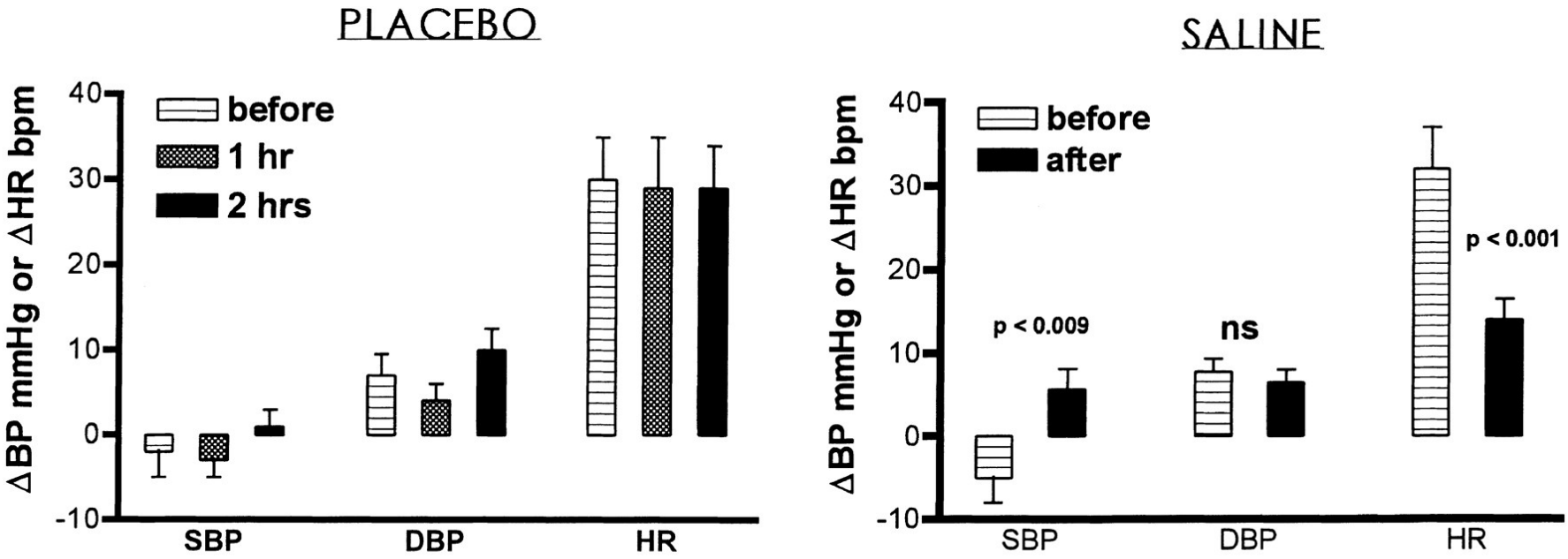
- **Focus on Aerobic Activity**
  - **Some resistance training focused on thighs**
- **Must be Regular**
  - **Every other day (4/week)**
- **30min/session -> 45-60min/session**
- **NO UPRIGHT EXERCISES**
  - **Rowing machines**
  - **Recumbent Cycles**
  - **Swimming**
- **Takes 4-5 weeks to start seeing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

Qi Fu et al., JACC 2010;55:2858-68

POTS: Treatment Approaches

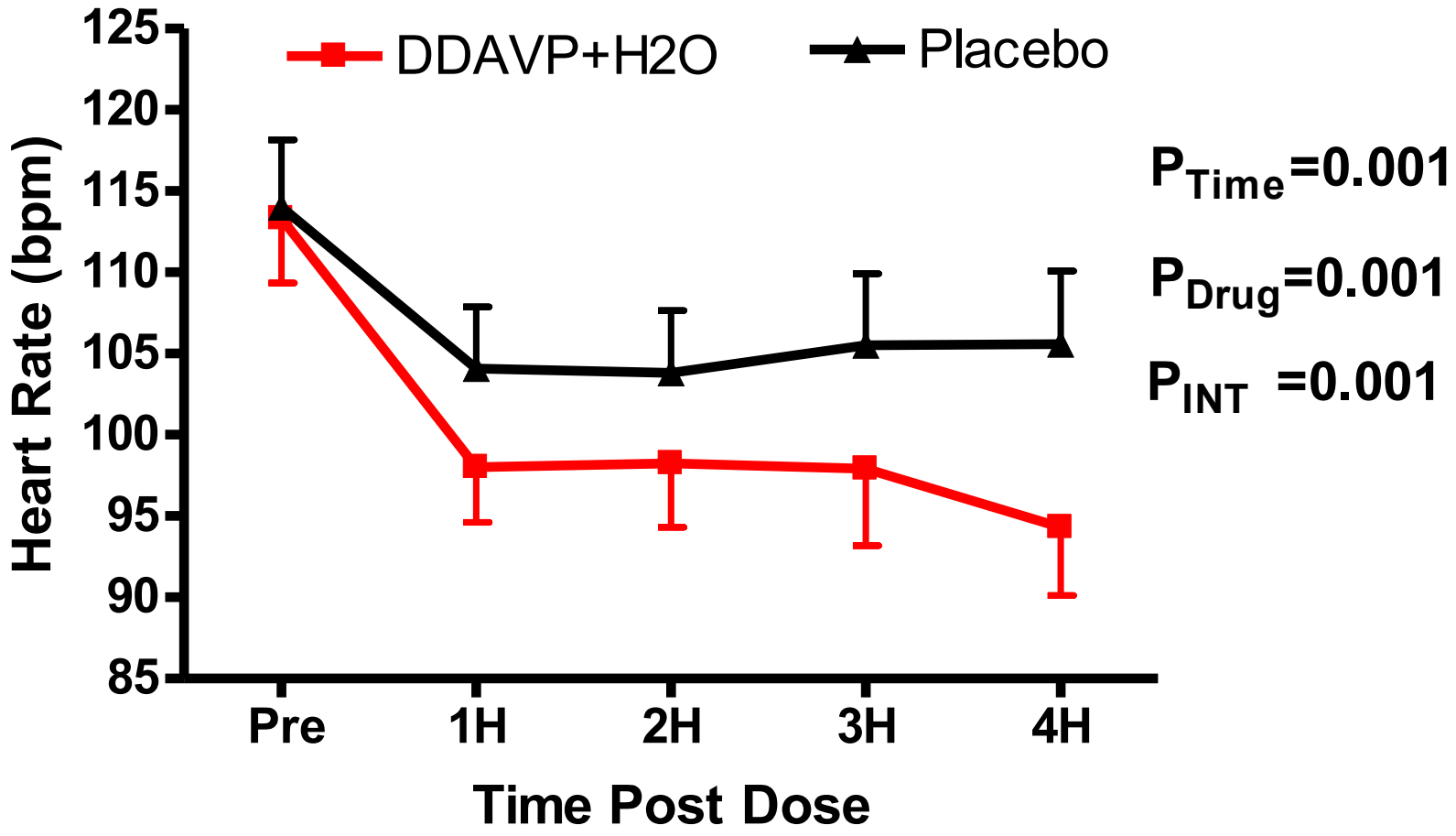
- Exercise
- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - Octreotide
  - IV Saline
  - Acute DDAVP-H_2O
- Hemodynamic Agents
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Ivabradine (emerging)
- Behavioral Therapies

IV Saline (1L) Acutely Decreases Orthostatic Tachycardia…a LOT!!



G Jacob et al. Circulation 1997;96:575-580

DDAVP+H_2O reduces standing HR

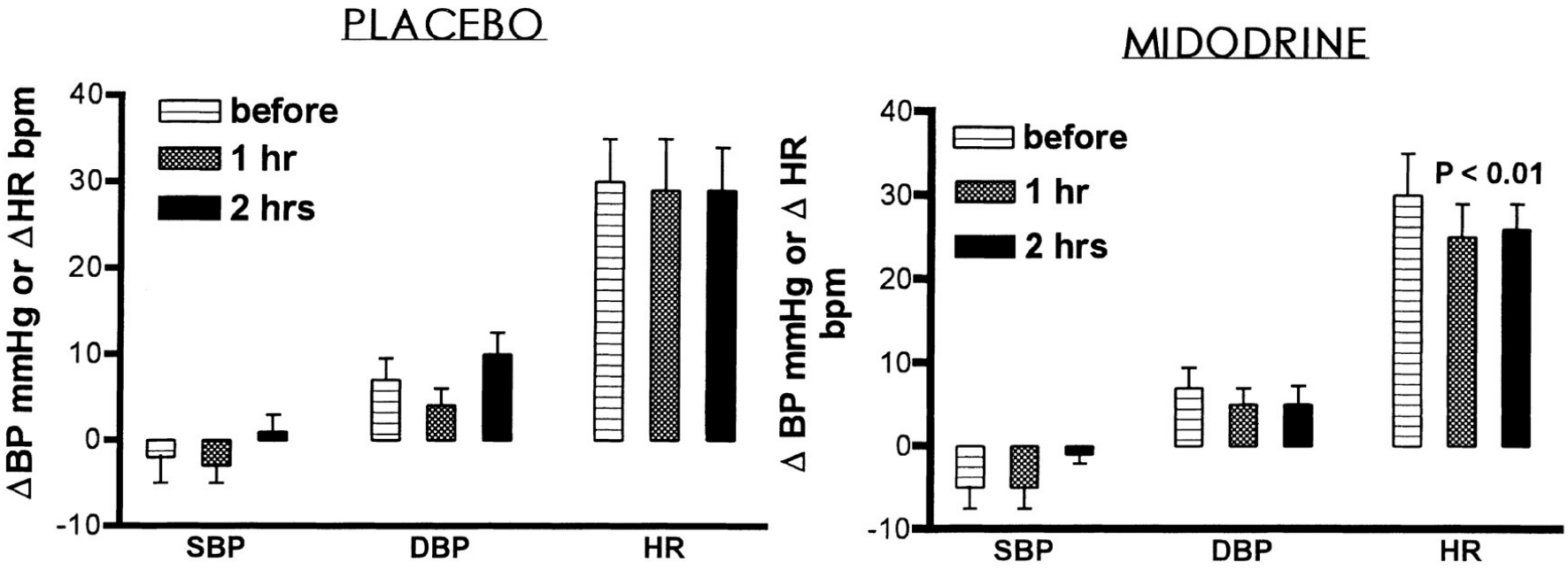


ST Coffin et al., Heart Rhythm. 2012;9:1484-90

POTS: Treatment Approaches

- Exercise
- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - Octreotide
  - IV Saline
  - Acute DDAVP-H_2O
- Hemodynamic Agents
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Ivabradine (emerging)
- Behavioral Therapies

Midodrine Decreases Orthostatic Tachycardia…a little bit.

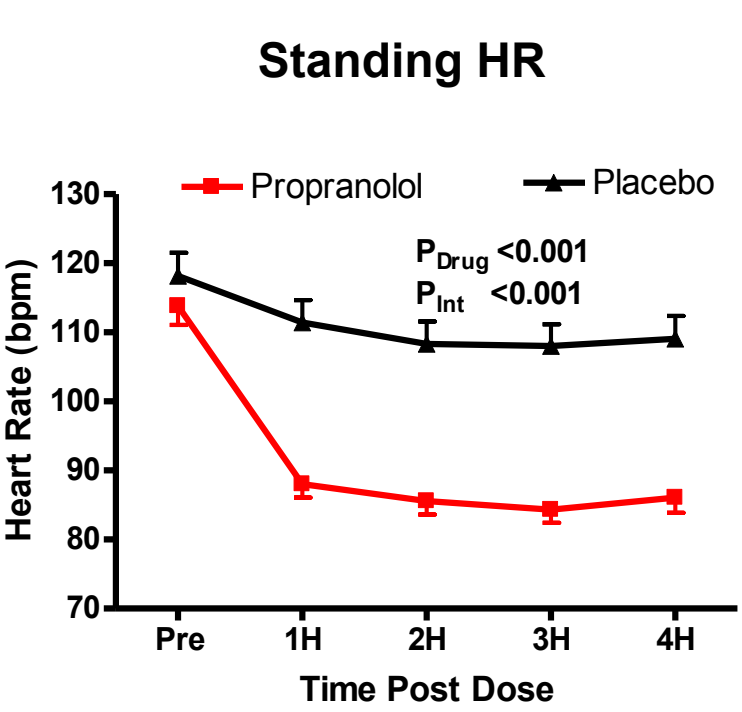


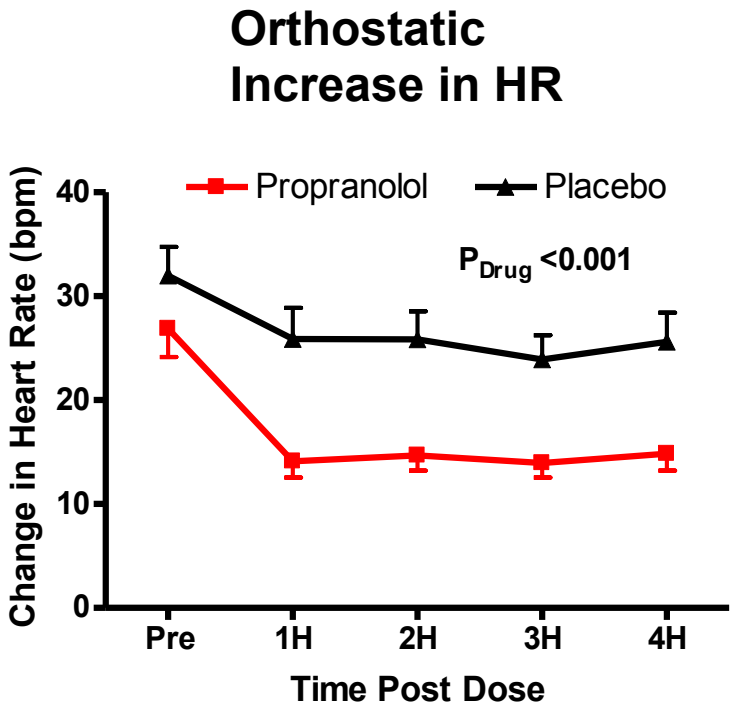
Jacob, G. et al. Circulation 1997;96:575-580

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"**

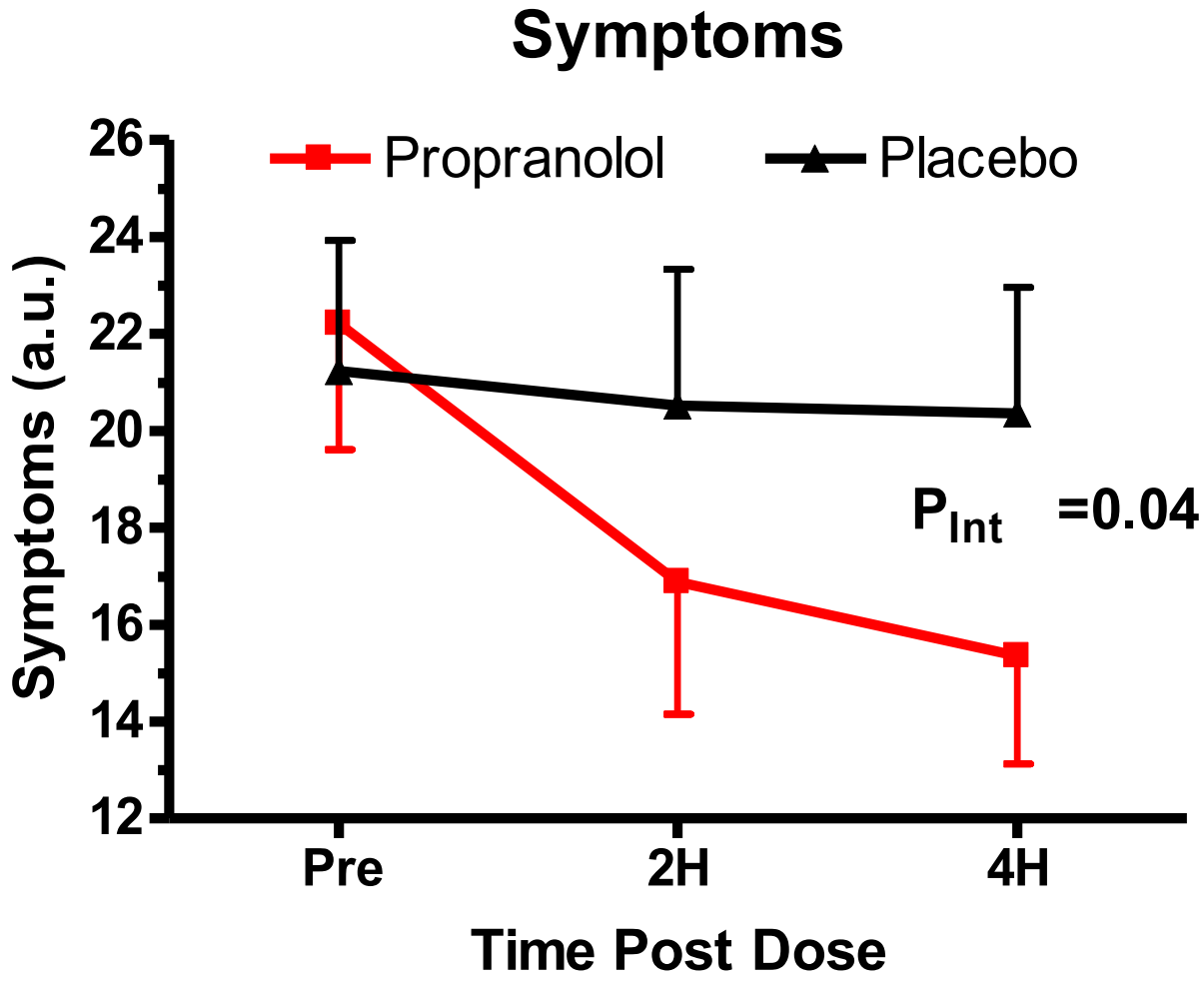
Propranolol 20mg lowers Orthostatic Tachycardia





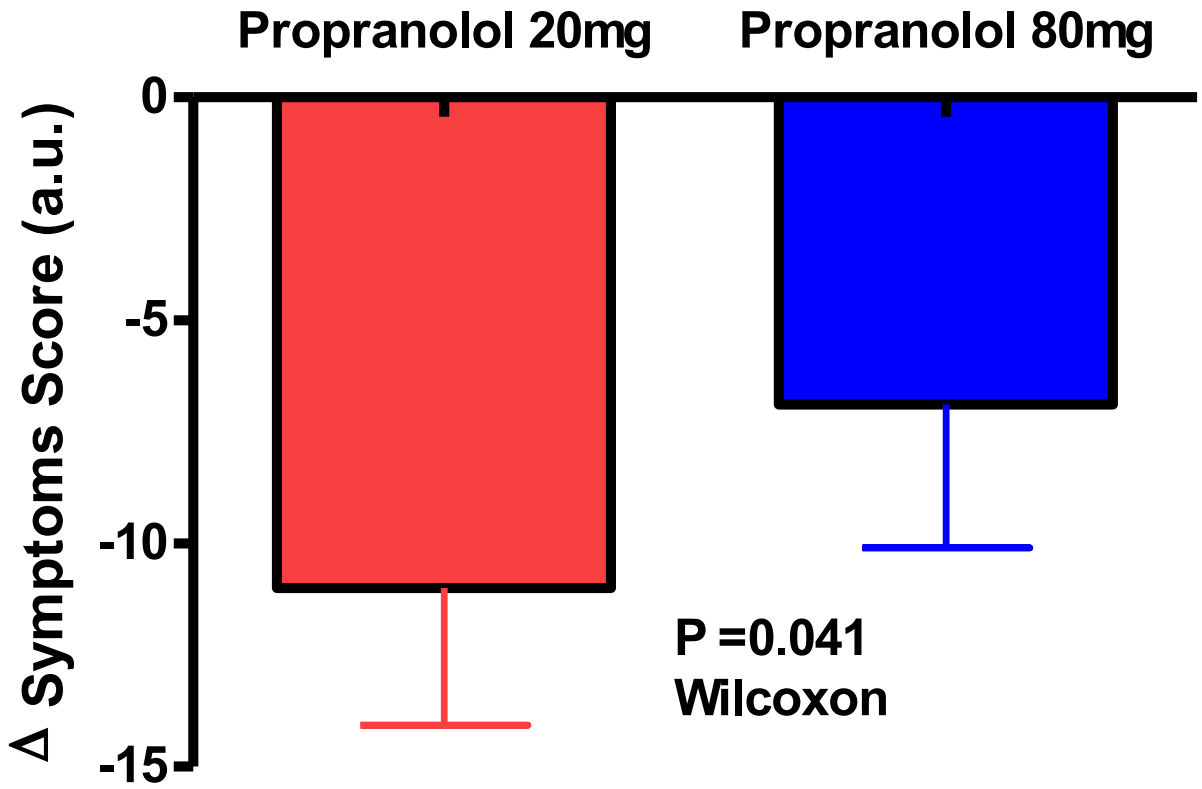
SR Raj et al. Circulation 2009;120:725-734

Propranolol Improves Symptoms…



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

…but Less is More



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

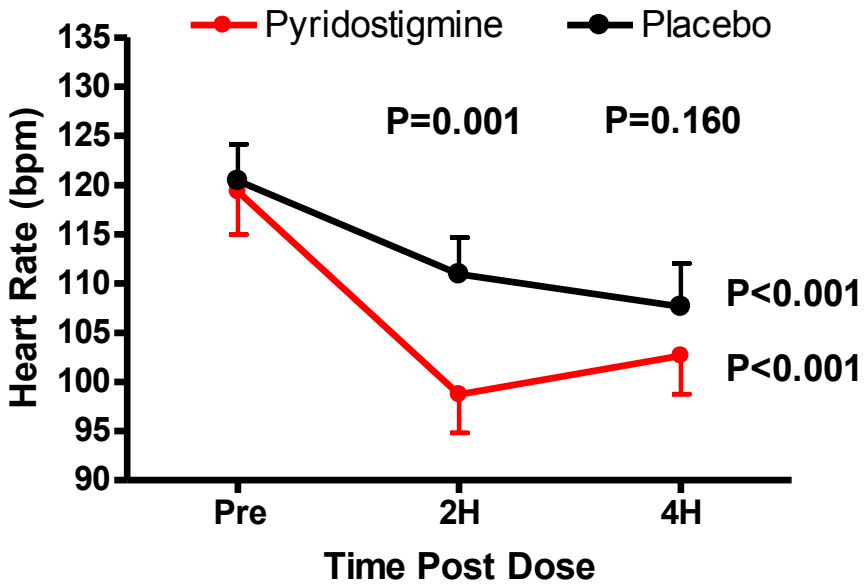
Acetylcholinesterase Inhibition

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

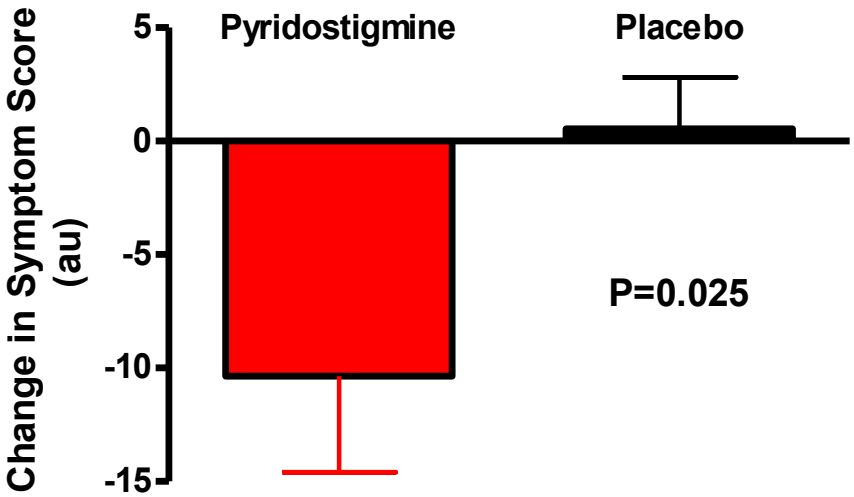
- **Might decrease tachycardia in POTS**

Acetylcholinesterase Inhibition

Standing Heart Rate

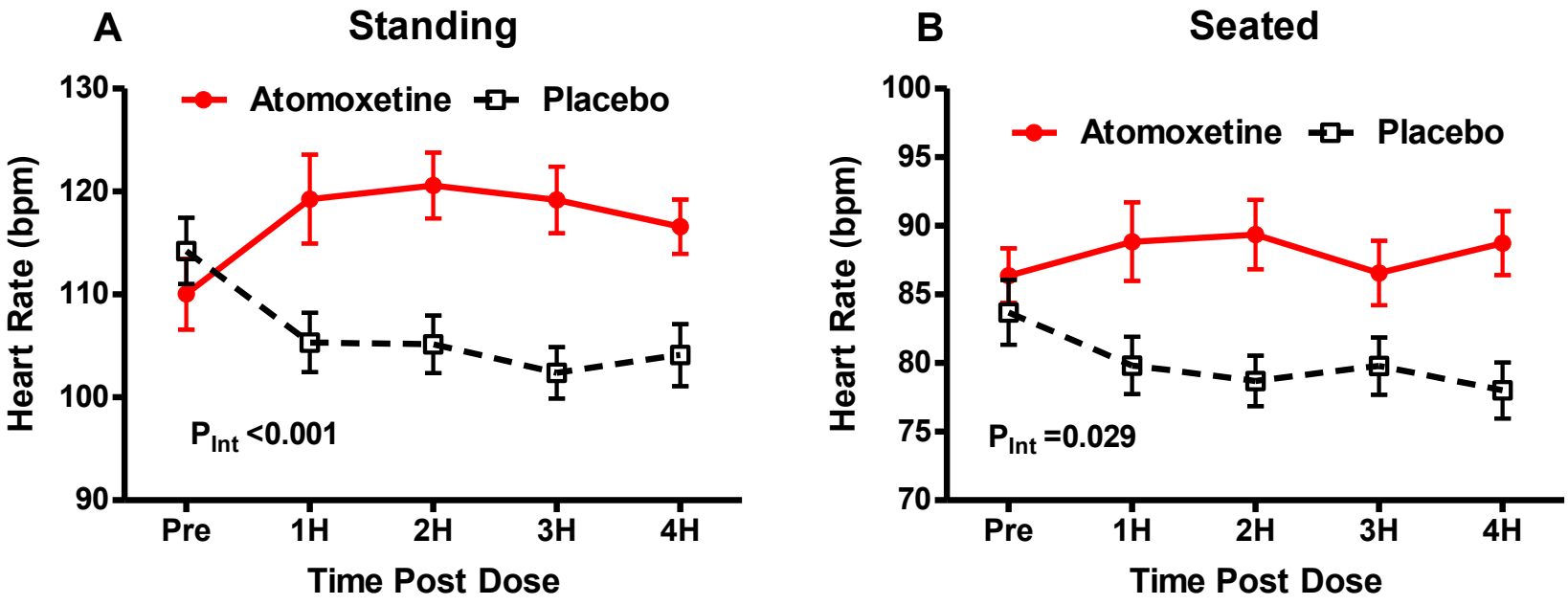


Symptoms



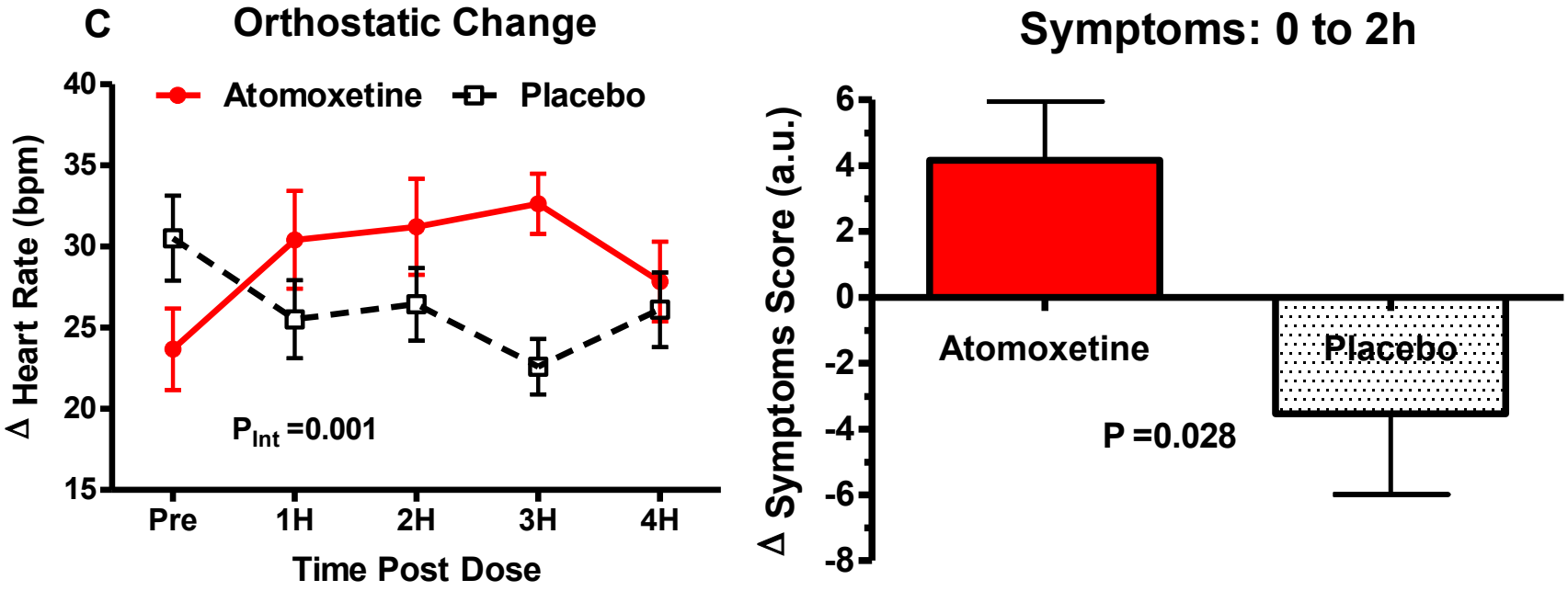
SR Raj et al., Circulation 2005;111:2734-2740

Norepinephrine Transporter Inhibition



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

Norepinephrine Transporter Inhibition



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

POTS: Treatment Approaches

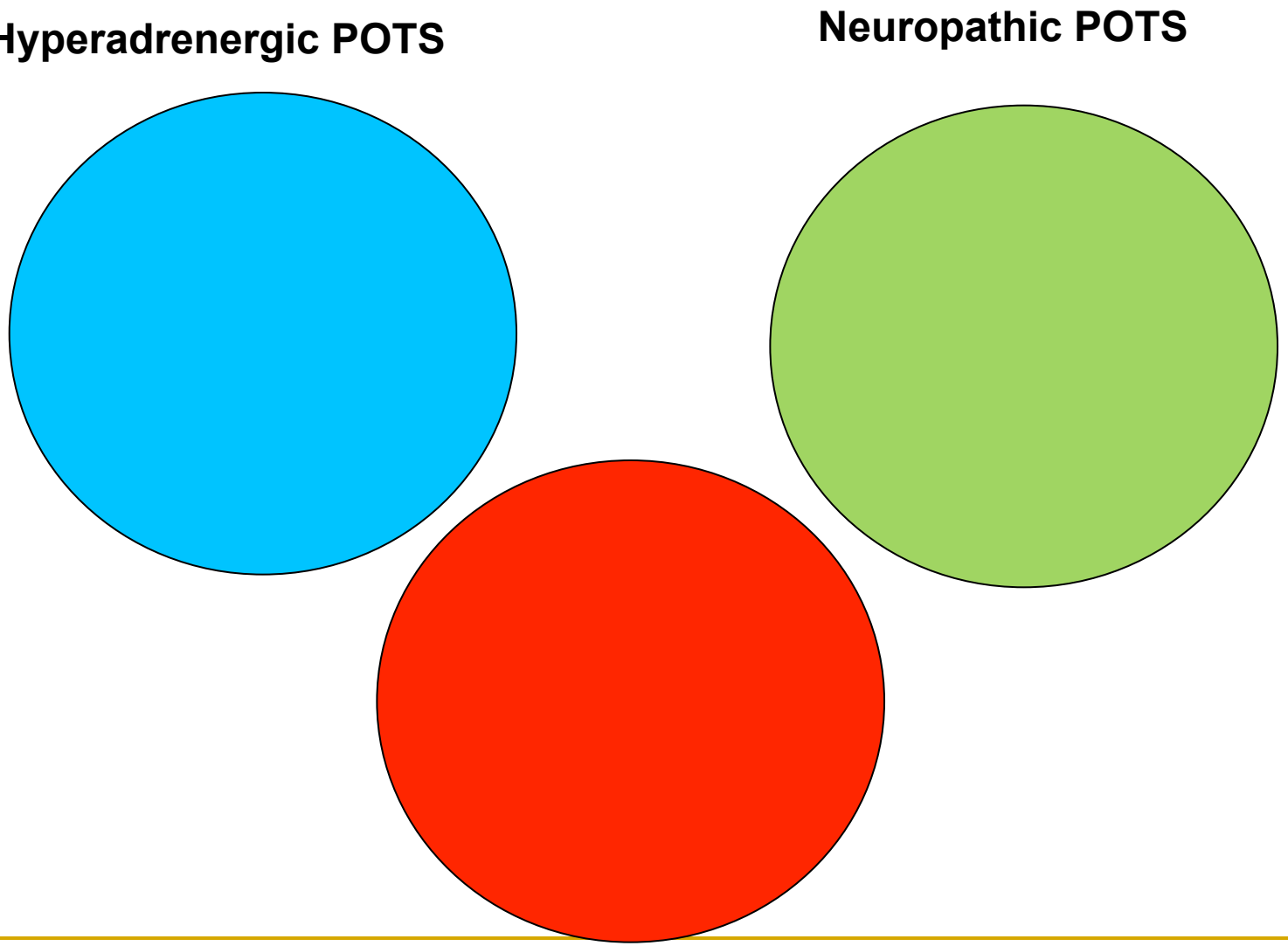
- Exercise
- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - Octreotide
  - IV Saline
  - Acute DDAVP-H_2O
- Hemodynamic Agents
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Ivabradine (emerging)
- Behavioral Therapies

What Type of POTS Do I Have?

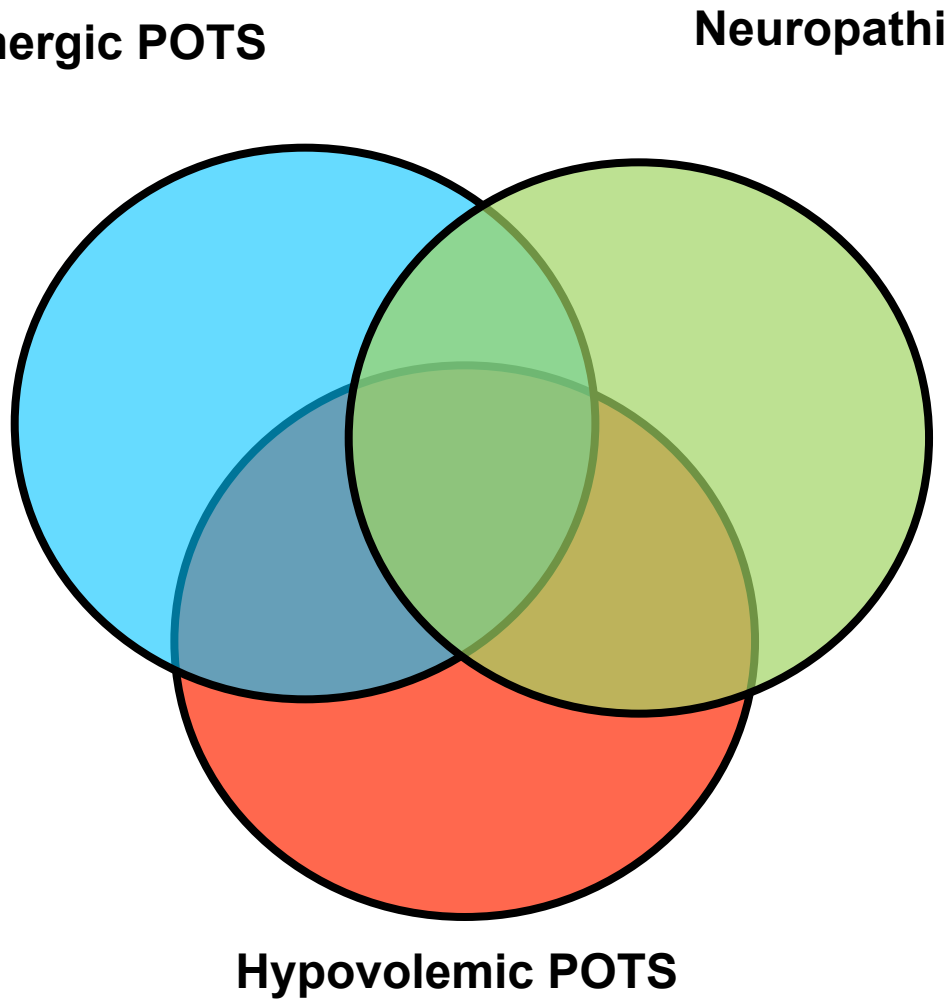
Challenges:

1. **Overlapping Subsets**
2. **Lost in Translation**

What Type of POTS Do I Have?



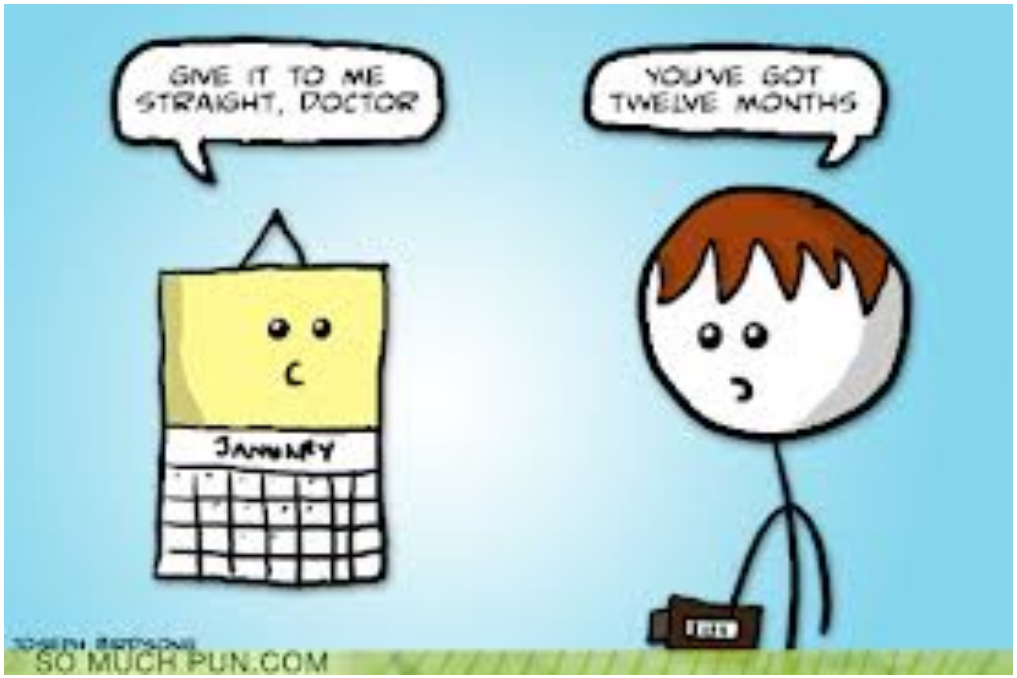
What Type of POTS Do I Have?



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 pathophysiologies**

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

Questions?

UNIVERSITY OF CALGARY