POTS and Dysautonomia 101

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Disclosures

- Consultant to Emisphere, Quest corporations
- Medicolegal Case Reviews
- Medical Consultant to Best Doctors, Inc.
- Stock ownership of Rural Healthcare Logistics, LLC

Autonomic Disorders assoc w/ Orthostatic Intolerance

- **Primary Disorders**
- Autoimmune Autonomic Neuropathy/Ganglionopathy (AAG)
- Postural Orthostatic Tachycardia Syndrome (POTS)
- Pure Autonomic Failure
- Multiple System Atrophy
- Reflex Syncope

- **Secondary Disorders**
- **Central origin**
  - Parkinson Disease
  - Multiple Sclerosis
  - Syringobulbia
  - Spinal cord lesions
- **Peripheral origin**
  - Guillain Barre
  - Diabetes
  - Sjogrens
  - Familial dysautonomia
  - Gastric bypass, celiac, others
  - Amyloidosis
  - B-hydroxylase deficiency

POTS (Postural orthostatic tachycardia syndrome)

- HR rise >30 bpm within 10 minutes of standing
- Or absolute rise over 120 bpm.
- No orthostatic hypotension
- HR rise >40 bpm in children
- Sx present > 6 months
- Sx worsen standing, improve supine
- No other cause found (anemia, medication, dehydration)

- POTS is not fatal
- Patients often misdiagnosed
  - Supraventricular tachycardia
  - Panic disorder/ anxiety
  - Chronic fatigue syndrome

Mayo Clin Proc. 2012;87:1214-25
Clin Auton Res 2011;21:69-72
Mayo Clin Proc 2007;82:308-313

Prevalence and Risk Factors

- Approx 500,000?
- 80-85% Female
- Childbearing age 13-50
- Triggers- pregnancy, Surgery, Trauma, Viral illness, other unknowns
- Joint hypermobility?
- Assoc with other disorders such as IBS, fibromyalgia, chronic fatigue syndrome

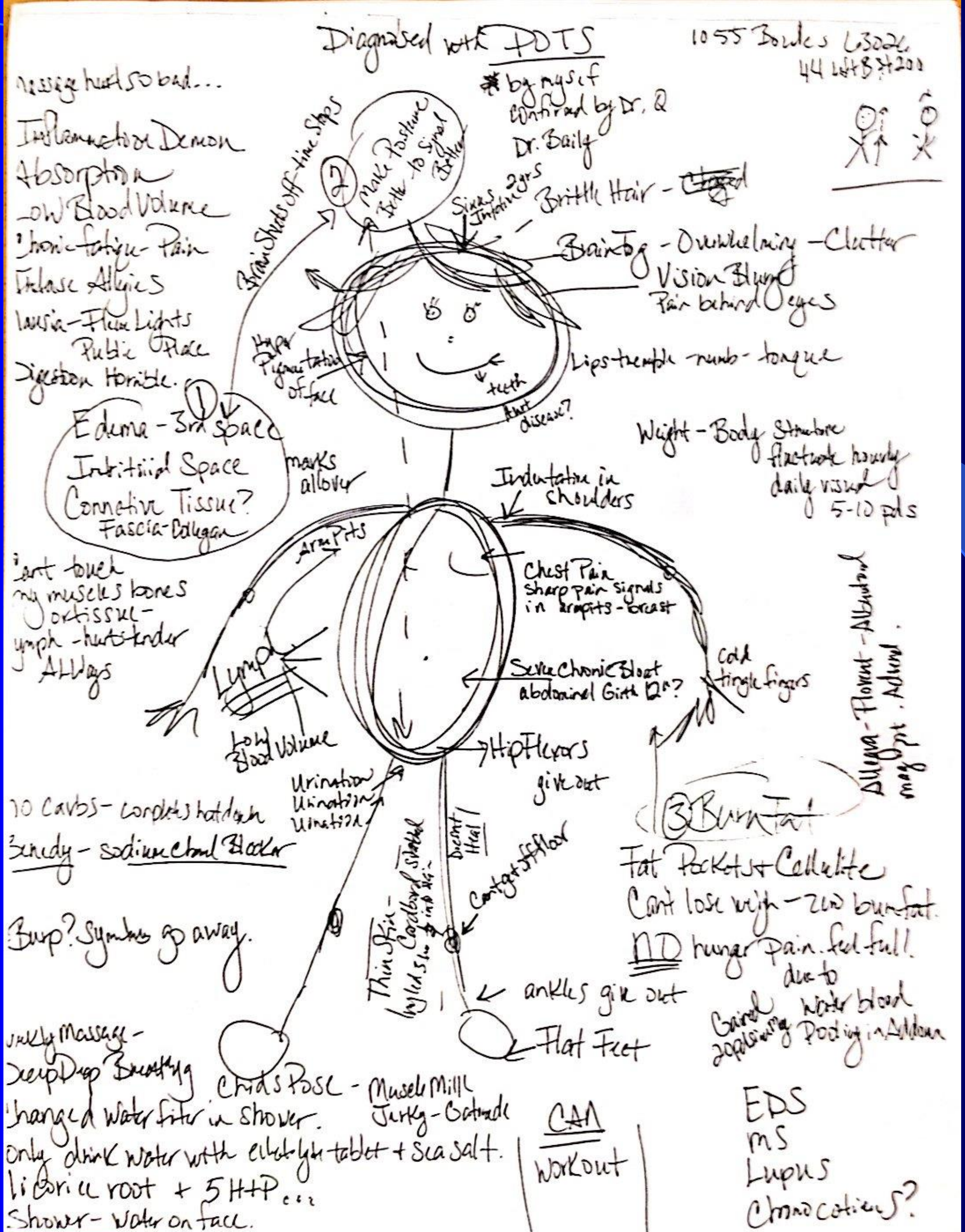
Circulation. 2013;127:2336-2342.

Mayo Clin Proc. 2012;87:1214-25

Proposed Mechanisms

- Sympathetic denervation, reduced sweating and excessive venous pooling in the legs (Neuropathic POTS)
- B adrenergic hypersensitivity, standing norepinephrine levels >600 (Hyperadrenergic POTS)
- Hypovolemia, low aldosterone levels
- Deconditioning
- All may be accompanied by somatic hypervigilance

Bennaroch EE. Mayo Clin Proc 2012; 87:1214-1225.


Diagnosed with POTS
by myself
confirmed by Dr. Q
Dr. Baily
Massage hurt so bad...
Inflammation Demon
Absorption
Low Blood Volume
Chronic fatigue - Pain
Allergies
Fluo Lights
Public Place
Digestion Horrible.
Make Posture Better to Signal Better
Brain Shuts off - time stops
Brittle Hair
Brain Fog - Overwhelming - Clutter
Vision Blurred
Pain behind eyes
Hyper Pigmentation of face
Lips - tremble - numb - tongue
teeth
Edema - 3rd space
Interstitial Space
Connective Tissue?
Fascia - Collagen
marks all over
Weight - Body Structure
fluctuate hourly
daily visual
5-10 pds
Indentation in shoulders
Arm Pits
Chest Pain
sharp pain signals in armpits - breast
Can't touch my muscles bones or tissue
lymph - hurt - tender
All days
Lymph
Severe Chronic Bloat
abdominal Girth 12"?
Cold tingle fingers
Low Blood Volume
Hip Flexors give out
Urination
Urination
Urination
Allegra - Flonase - Albuterol
No carbs
Burp? Symptoms go away.
Thin Skin
Doesn't Heal
3 Burn Fat
Fat Pockets + Cellulite
Can't lose weight - can't burn fat.
NO hunger pain. feel full.
due to
water blood
Pooling in Abdomen
ankles give out
Flat Feet
Massage -
Deep Breathing
Child's Pose - Muscle Milk
Jerky - Gatorade
Changed Water filter in Shower.
Only drink water with electrolyte tablet + Sea salt.
licorice root + 5 HTP...
Shower - Water on face.
CAM
Workout
EDS
MS
Lupus
Chronic ...?

Autonomic symptom review

- heat, cold intolerance
- blurred vision
- Orthostatic lightheadedness- 0 never, 1 mild, 2 frequent, 3 consistent, 4 with syncope
- palpitations
- Anxiety, tremulousness
- unsteadiness
- dry eyes, mouth
- vasomotor discoloration of hands and feet
- Headache, migraine
- reduced /excessive sweating
- Post prandial symptoms 0 never, 1 mild, 2 frequent, 3 consistent- anorexia, early satiety, weight loss of *** pounds
- Abdominal pain/cramping
- nocturnal diarrhea
- sexual problems, loss of libido

Low P, Bennaroch EE. Clinical Autonomic Disorders, 2008

Possible Investigations for POTS

- Cardiac- EKG, ECHO, Holter
- Head up tilt
- Autonomic tests of Cardiovagal and sudomotor function
- Supine and standing norepinephrine
- 24 hour BP/HR monitor
- Exercise testing
- Cortisol, thyroid function
- 4 hr urinary methylhistamine after flushing episode, 11 Beta-Prostaglandin F2
- Skin biopsy for small fiber neuropathy
- Gastric emptying study
- Behavioral Medicine

Raj SR. Circulation. 2013;127:2336-2342.
Bennaroch EE. Mayo Clin Proc 2012; 87:1214-1225.

Mast Cell Activation Syndrome (MCAS)

- A syndrome of flushing, itching, nausea, diarrhea, tachycardia with hypertension
- May be triggered by prolonged standing, exercise, premenstrual cycle, meals, and sexual intercourse.
- Allergy eval is normal
- No evidence of mast cell proliferation

Circulation. 2013;127:2336-2342.

MCAS:proposed criteria

- Skin: urticaria, angioedema, flushing
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping
- Cardiovascular: hypotensive syncope or near syncope, tachycardia
- Respiratory: wheezing
- Naso-ocular: conjunctival injection, pruritus, nasal stuffiness

J Allergy Clin Immunol. 2010 Dec; 126(6): 1099–104.e4

MCAS:proposed criteria

- Response to histamine blockade (benadryl, tagamet), leukotriene (zyrtec), cromolyn sodium, central adrenergic blockade (clonidine)
- Elevation of serum tryptase levels, or urinary methylhistamine, 11-beta-prostaglandin F2
- No treatments have been proven in clincal trials

Allergy. 2015 Jun 11. doi: 10.1111/all.12672.

Deconditioning and POTS

- Prevalence of deconditioning >90%
- Quality of Life scores often low
- Somatic Hypervigilance/hyperawareness disorder
- Graded exercise program
- Recumbent bicycle/swimming for 1 month, gradually introduce treadmill/spinning/jogging
- Weight training

Neurology 2012 ;79:1435-1439
Hypertension 2011;52:167–175.

Treatment of POTS

- 20-30# knee high stockings
- abdominal binder
- Spanks compression garments
- 2-3 liters water daily
- 3-5 teaspoons salt daily
- Or Thermotabs
- Propranolol 20 mg BID
- Other alternatives- pyridostigmine, pindolol, midodrine, florinef, SSRIs

Thieben M, Sandroni P. Mayo Clin Proc 2007;82:308-313.
Al-Shekhlee A, Lindenber JR, Hachwi RN, Chelimsky TC. The value of autonomic testing in postural tachycardia syndrome. Clin Auton Res. 2005 Jun;15(3):219-22

POTS: Treatment Approaches

- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - IV Saline
  - Acute DDAVP-H_2O
  - Exercise
- Hemodynamic Agents
  - Midodrine
  - Propranolol, pindolol
  - Pyridostigmine
  - Clonidine/α-Methyldopa
  - NET (norepinephrine transporter) Inhibitors-atomoxetine

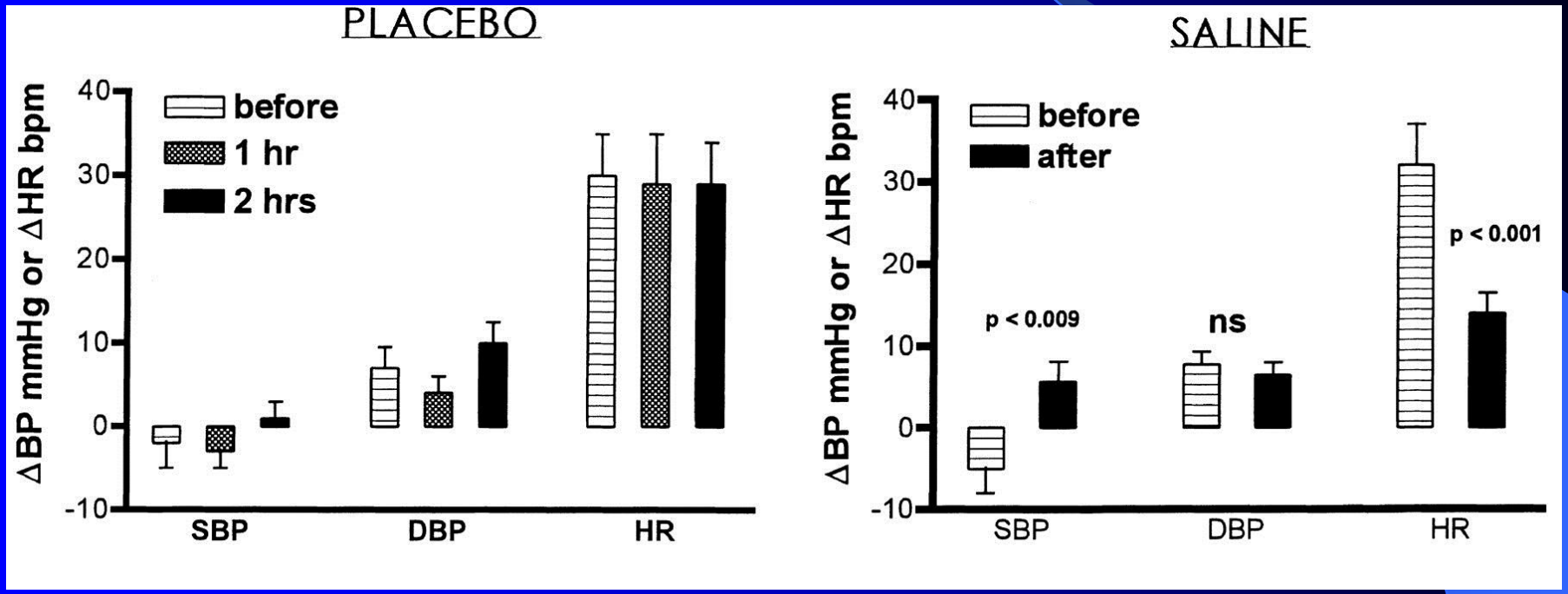
Courtesy of S Raj and Dysautonomia International

Volume Expansion- Salt and Water

- Recommendations vary
- 5-10 grams salt per day is reasonable start
- 1 tsp= 6 grams salt = 2300mg Na
- 1-3 teaspoons salt per day

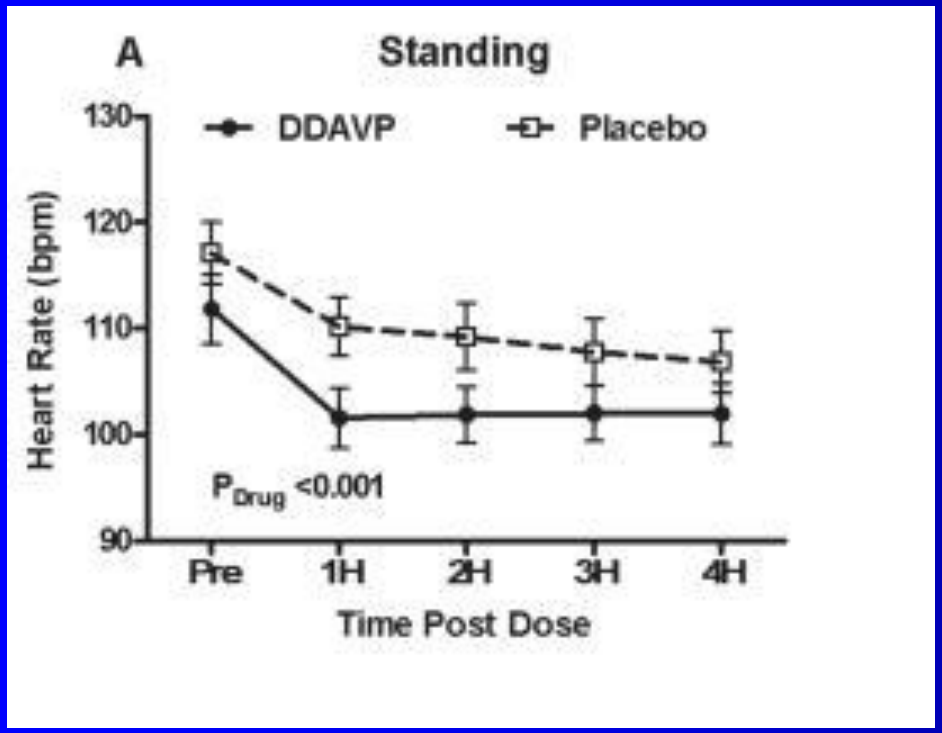
- 2-3 liters per day
- Non-caffeinated beverages
- Water, sports drinks, milk, juices, soups
- The goal is colorless urine

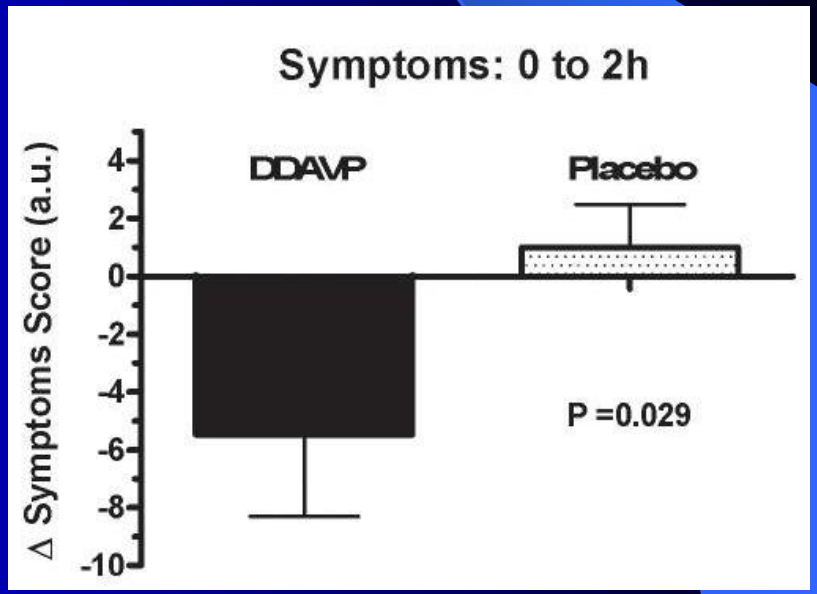
IV Saline (1L) Acutely Decreases Orthostatic Tachycardia



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

DDAVP 0.2 mg reduces tachycardia and symptoms

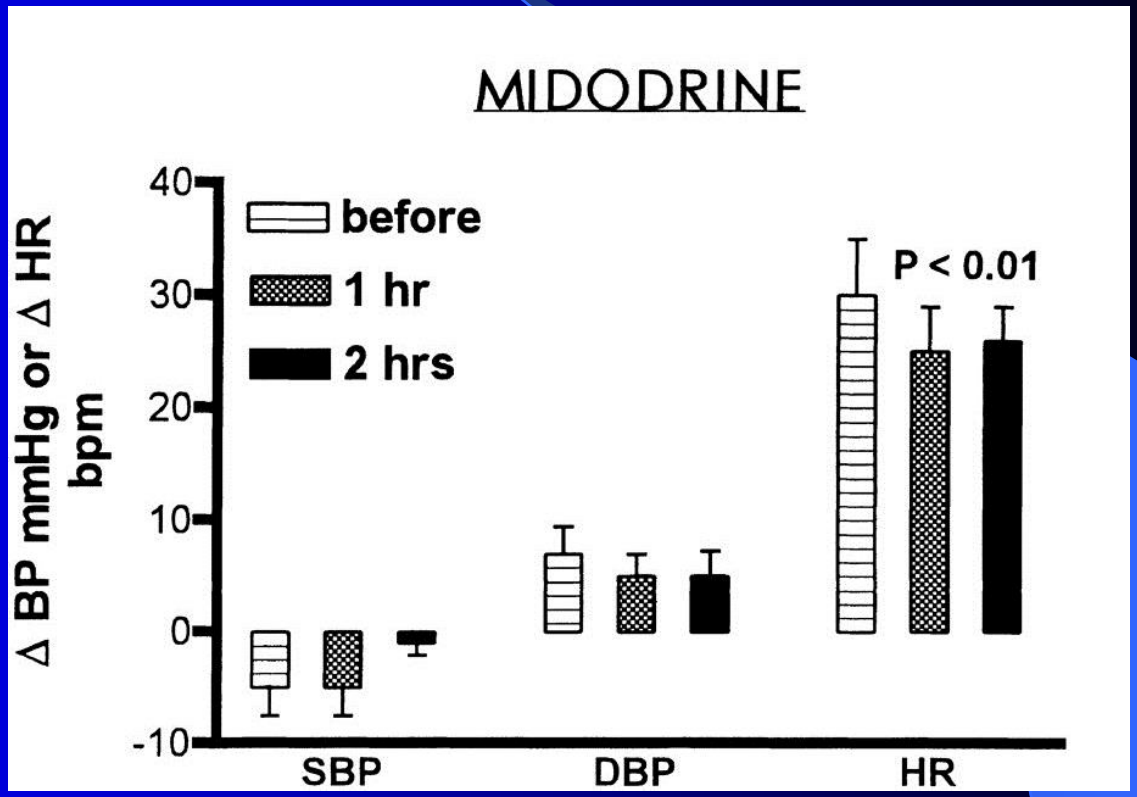




ST Coffin et al., Heart Rhythm. 2012;9:1484-90

Midodrine Decreases Orthostatic Tachycardia

More effective in Neuropathic POTS than hyperadrenergic POTS

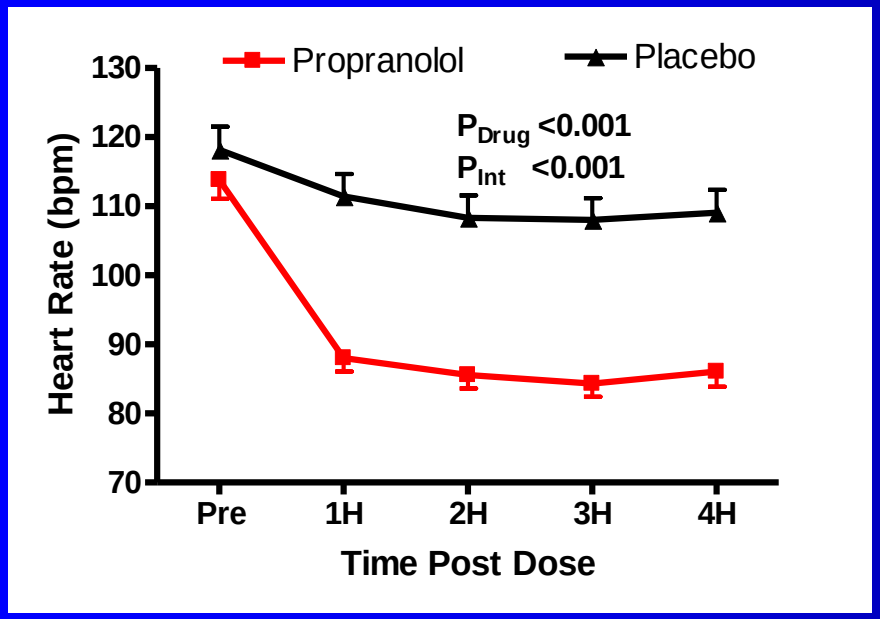


Clin Sci (Lond). 2013 Aug 27.

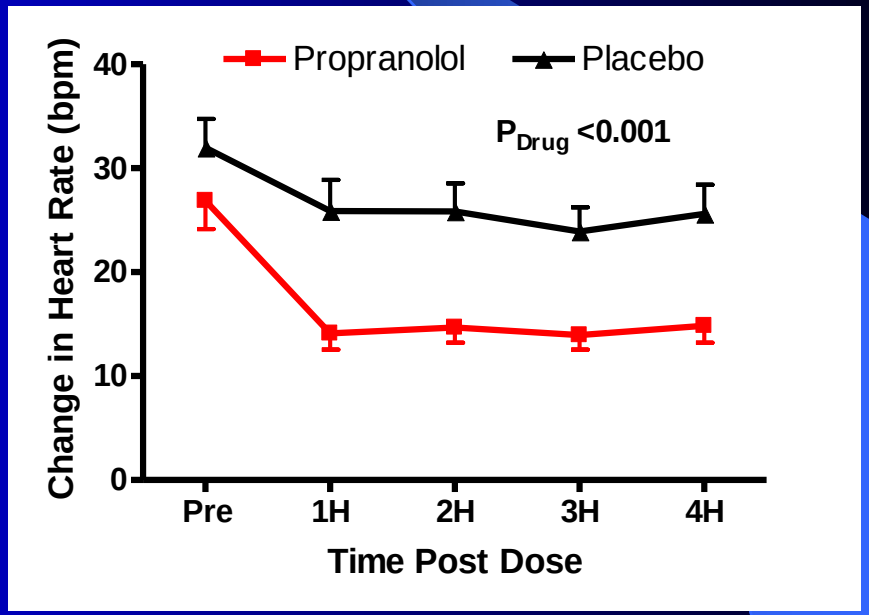
Jacob, G. et al. Circulation 1997;96:575-580

Propranolol 20mg lowers Orthostatic Tachycardia

Standing HR



Orthostatic Increase in HR



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

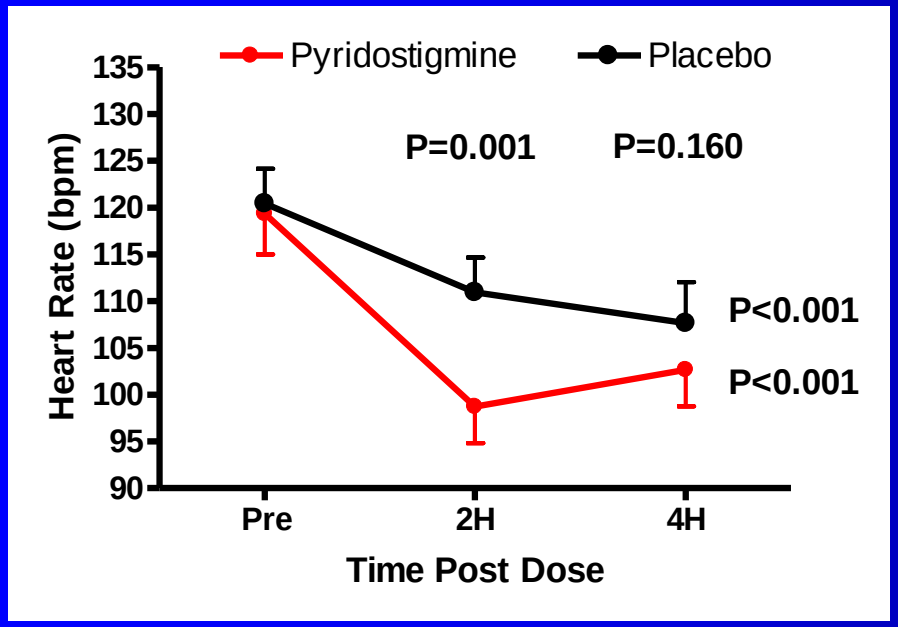
Acetylcholinesterase Inhibition

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

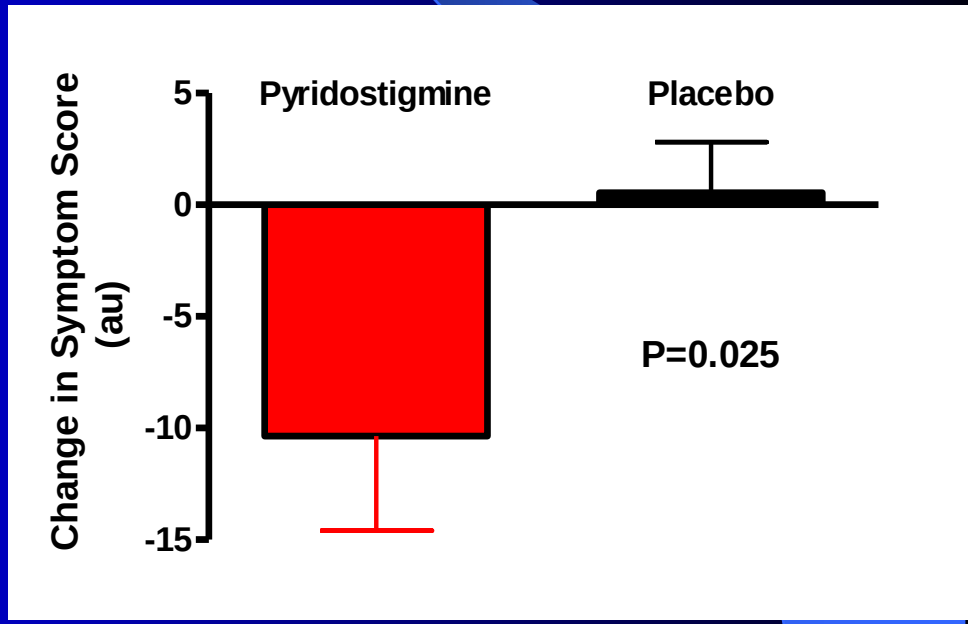
- Might decrease tachycardia in POTS

Acetylcholinesterase Inhibition

Standing Heart Rate



Symptoms

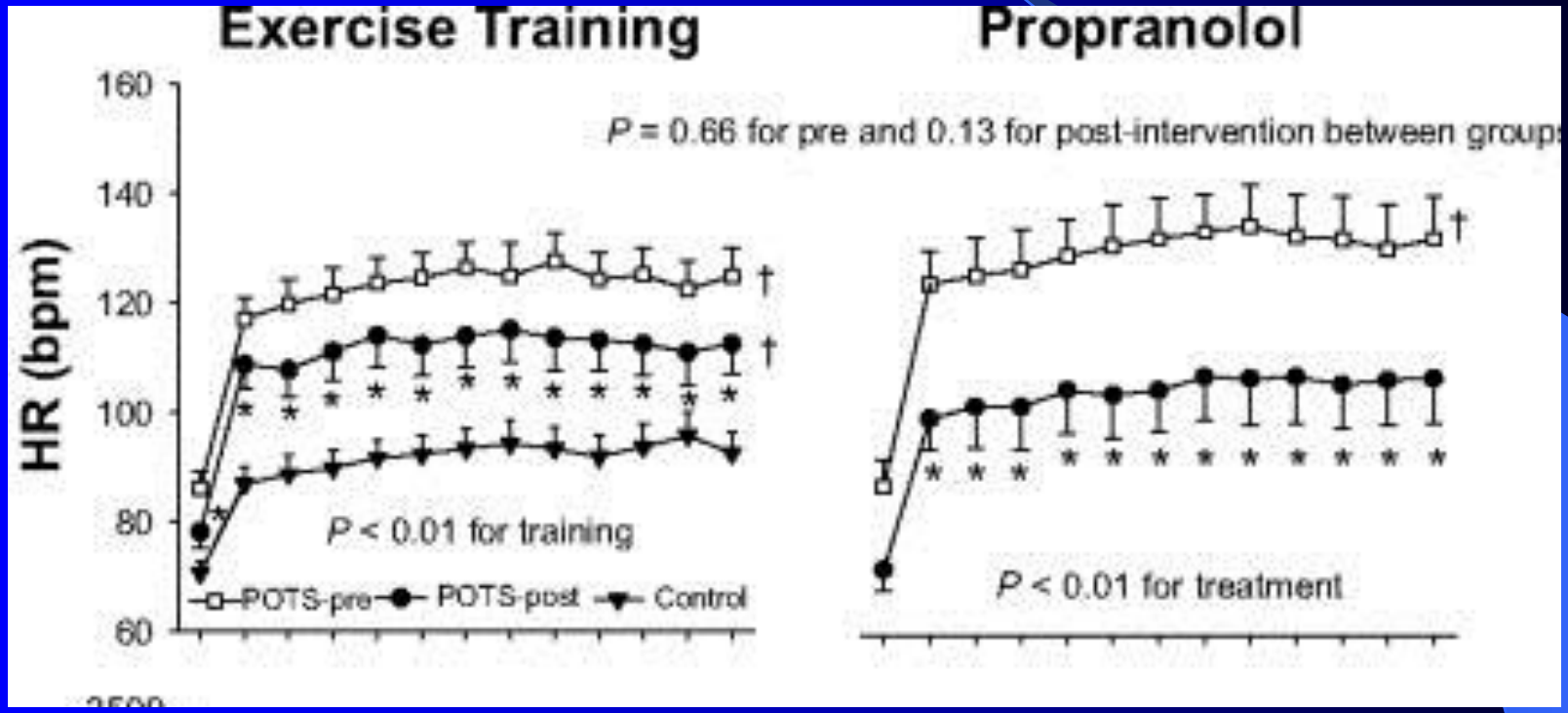


SR Raj et al., Circulation 2005;111:2734-2740

Exercise in POTS

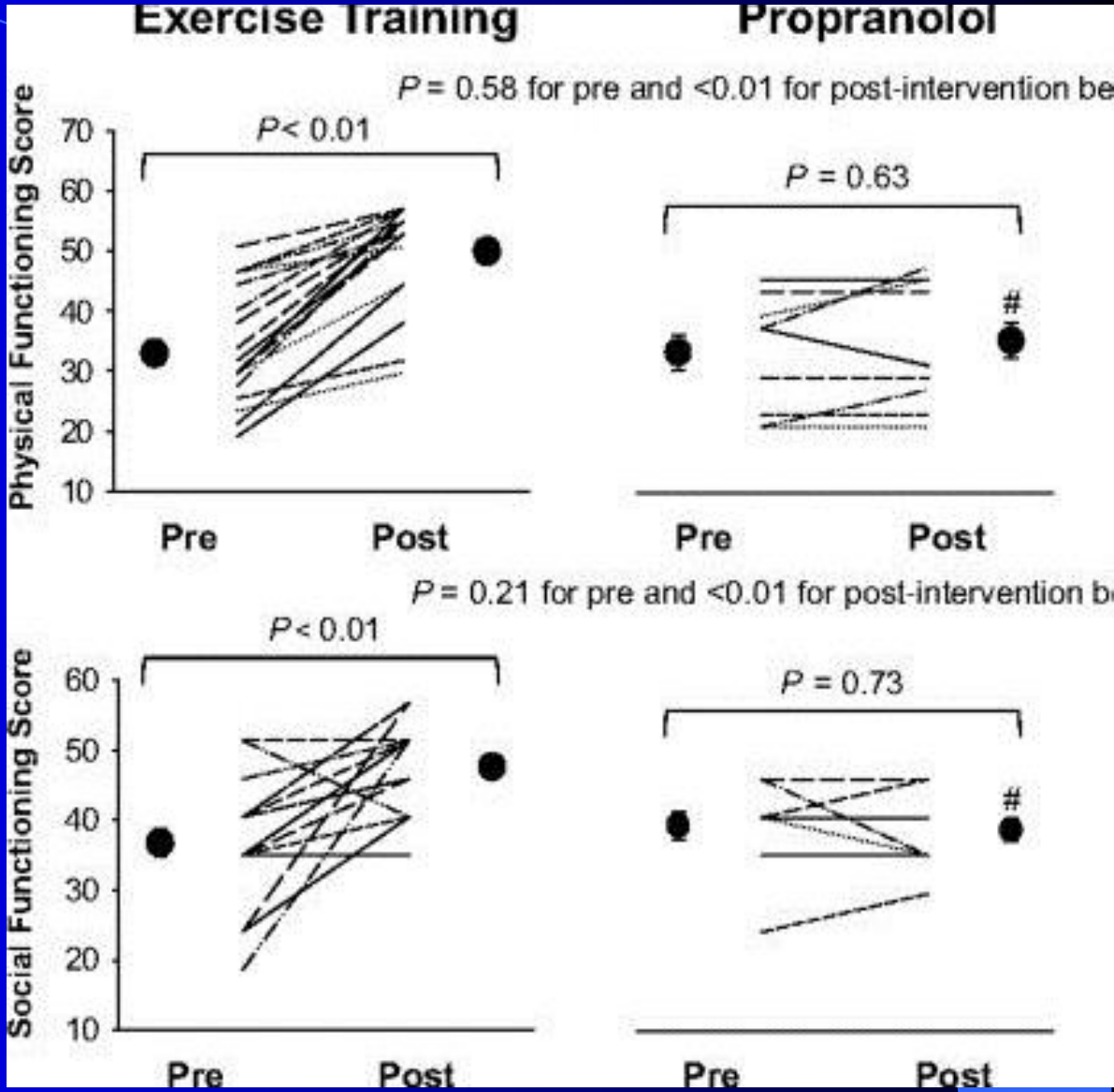
- Historically
  - “good thing to do”
  - Many patients could not/would not
    - excessive fatigue (~days) and intolerance
  - Anecdotally, those patients that did exercise did better over time
    - Cause/effect vs. selection bias
- Now
  - Data exists on effects of exercise training in POTS from Vienna, Dallas & Mayo…

Exercise vs Propranolol



Levine BD. Hypertension. 2011 August; 58(2): 167–175.

Exercise Improves physical and social functioning better than propranolol



Levine BD. Hypertension. 2011; 58(2): 167–175.

Exercise in POTS

- 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

Initial Steps in Evaluation of Orthostatic Intolerance

- 1) Review medications
- 2) review coexisting medical problems (diabetes, cancer, alcoholism)
- 3) relation of symptoms to meals, exercise, straining or Valsalva maneuvers, standing up from the bed
- Record supine and standing BP and Pulse p 3 minutes with arm horizontal.
- Perform a neurologic exam looking for evidence of parkinsonism, ataxia, neuropathy, or myelopathy.

Drugs that may worsen orthostatic intolerance

- ACE Inhibitors
- Alpha receptor blockers
- Ca channel blockers
- Beta blockers
- Phenothiazines, metoclopramide
- Tricyclic antidepressants
- MAO inhibitors
- Sildenafil
- Topiramate
- Pramipexole, ropinirole
- Carbidopa/levodopa
- Ethanol
- Opiates
- Diuretics
- Hydralazine
- Nitrates

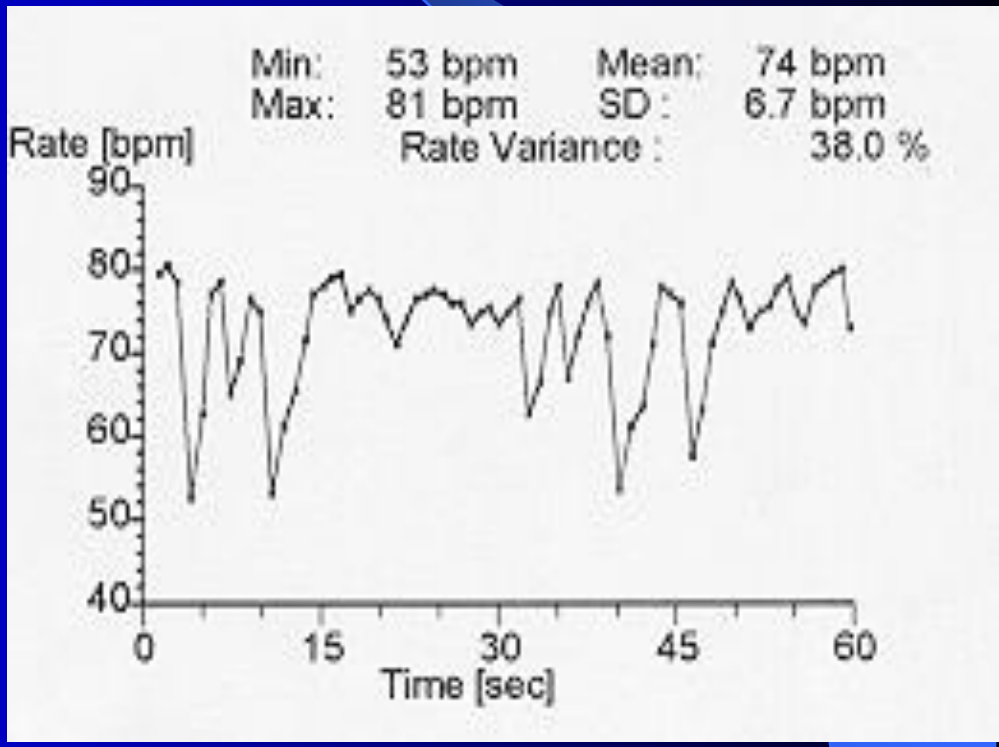
Autonomic Diagnostic tests

- Valsalva effect on HR and BP
- HR response to Deep breathing
- Tilt table testing
- Sympathetic Skin Response
- Thermoregulatory testing (sweat box)
- Quantitative Sudomotor Axon Reflex Testing (QSART)
- Supine and standing norepinephrine levels may help distinguish PAF from MSA

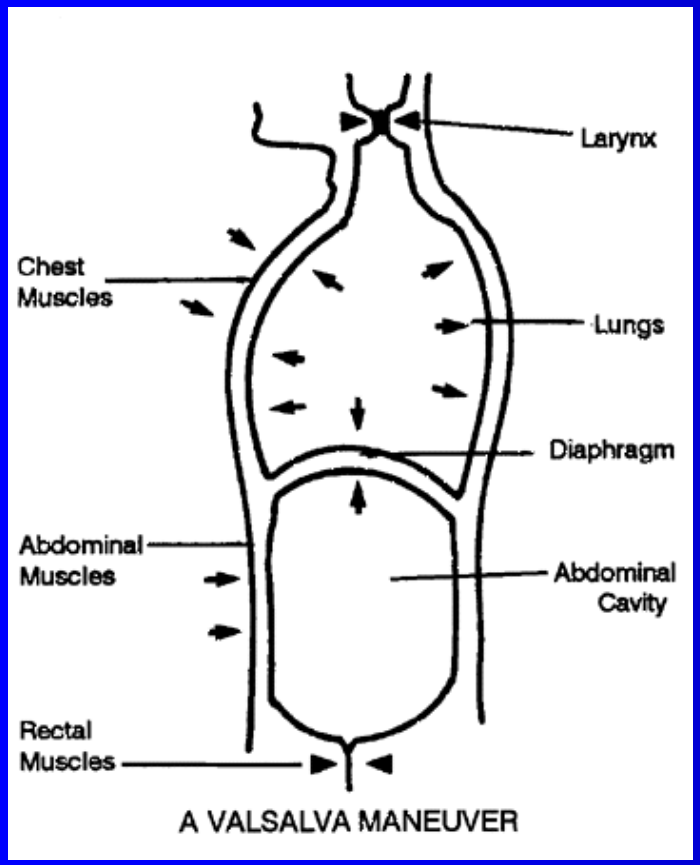
Cardiac Autonomic Testing- HR variability

- Breathe deeply 6 times/min
- Pure test of parsympathetic cardiac function
- Pulmonary J receptors-> vagus
- Insp-> incr pulm capacitance-> ^HR
- Exp-> blood returns from pulm bed -> decreased HR
- Normal difference of min-max HR 8-18 bpm

  Our patient- 28 bpm



Valsalva maneuver

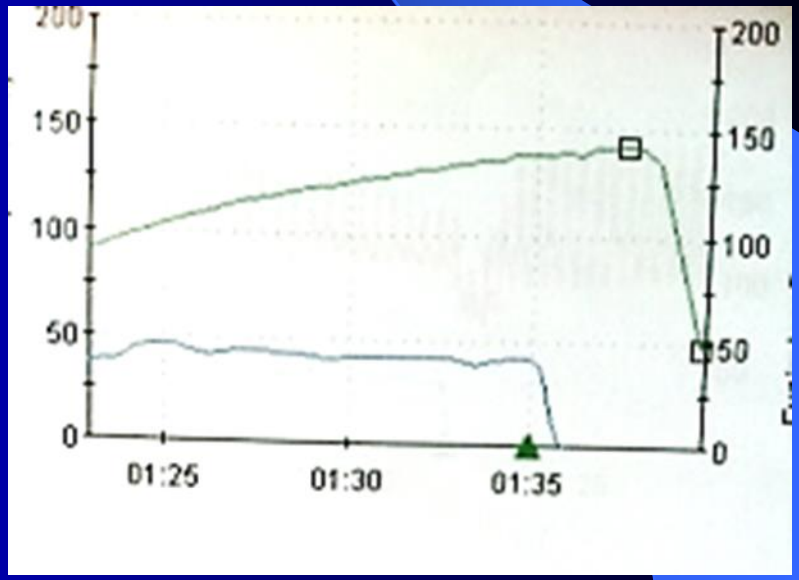


A VALSALVA MANEUVER

- **Stage 1**- aortic baroreceptor stimulation with sudden increased intrathoracic pressure causes bradycardia
- **Stage 2-**heart rate rises due to poor venous return during Valsalva
- **Stage 3**- brief overshoot of heart rate with release of pressure
- **Stage 4**- drop in thoracic pressure leads to increased venous return, and fall in heart rate.

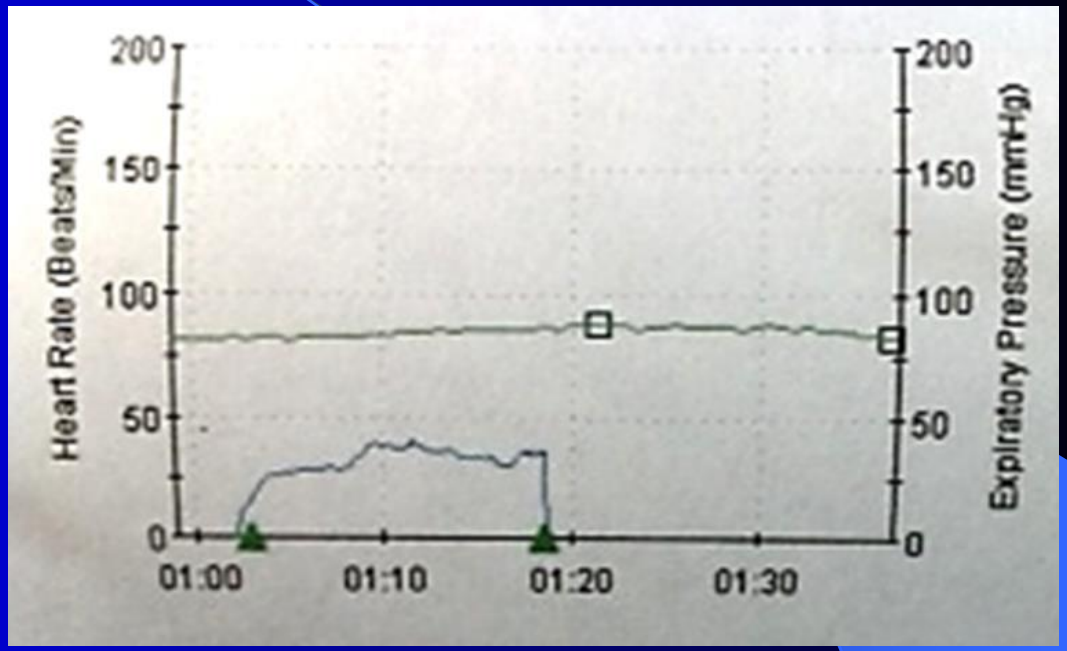
Cardiac Autonomic Testing- HR response to Valsalva

- Hold 40 mm Hg with open glottis for 15 sec (like bowel movement)
- Tests cardiac parasympathetic, sympathetic, and vasomotor functions
- **Hold pressure**- large venous load -> drop BP and increase HR
- **Release pressure**- sudden venous return-> increase BP, drop in HR
- Normal ratio of max-min HR= 1.3-1.5



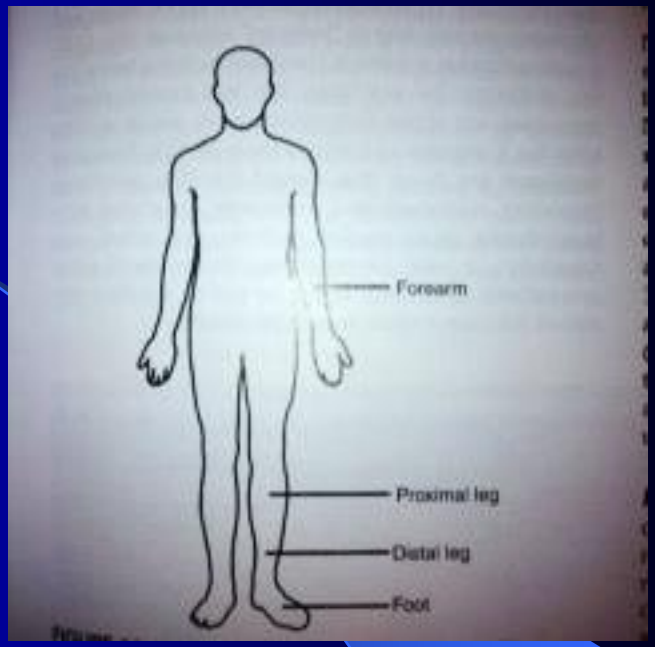
Valsalva-Abnormal

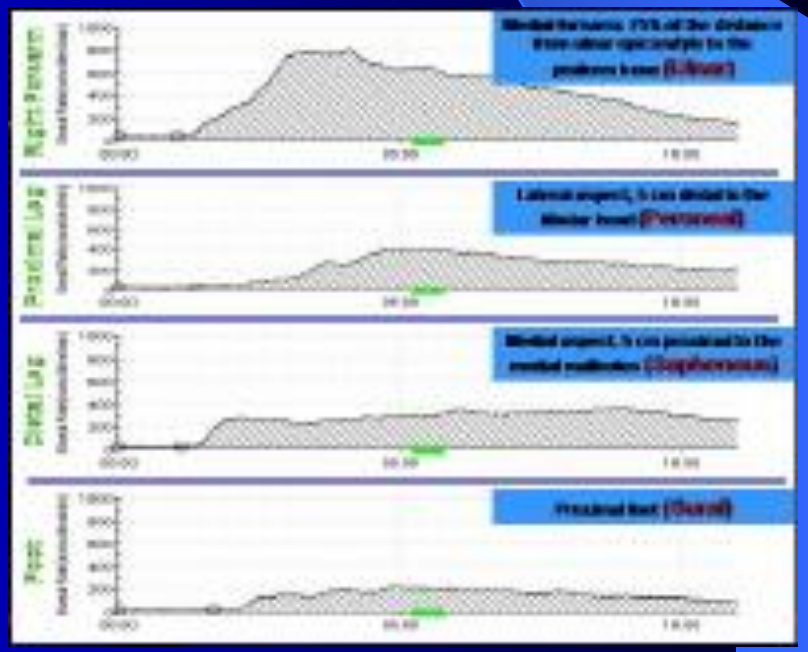
- 57 yo M with Multisystem atrophy
- Max/Min ratio 1.28
- (nl 1.3-2.0)
- Borderline abnormal



Quantitiative Sweat Testing (QSART)

- Records sweat production at 4 sites
- Assess distal to proximal sites
- sensitive for diabetic autonomic neuropathy, small fiber neuropathy





Tilt Table Testing

Tilt Table Testing in patients with unexplained syncope

- 2 protocols
  - Drug-free, 40-60 min
    - Sens 37-67%, Spec 90-94%

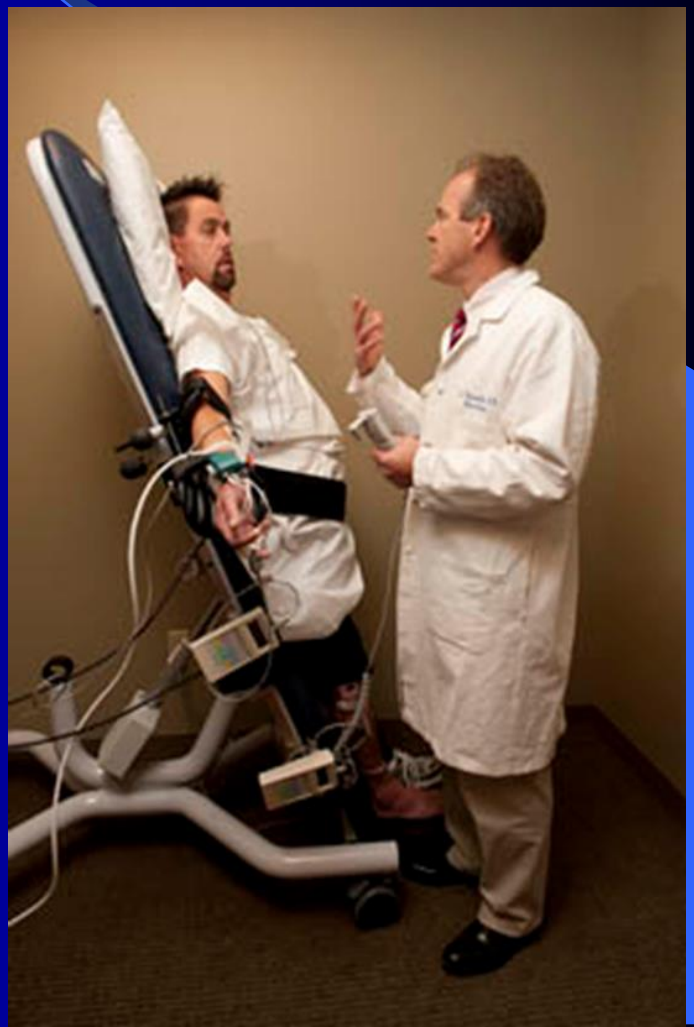
Oribe, Pacing Clin Electrophys 1997

Kenny, Lancet 1997.

  - Drugs (isoproteronol, nitrates), 10-30 min
    - Sens 53-61%, Spec 89-93%

Almquist , NEJM 1989

Morillo, Am Hear J, 1995



5 responses to TTT

- 1) **Normal, no symptoms**
- 2) **Cardio-inhibitory** –initial bradycardia, followed by hypotension
- 3) **Vasodepressor**- gradual hypotension, no change in pulse.
- 4) **Postural Tachycardia (POTS)-** BP unchanged, HR rise >30 bpm (or absolute rise >120 bpm) within 5 minutes of tilt
- 5) **Normal with Symptoms**- Cerebral syncope or conversion disorder

Non-pharmacologic Treatments

- Eliminate/ reduce medications known to worsen orthostasis
- Avoid prolonged standing
- Slow changes in position
- Avoid alcohol, hot environments/showers
- Multiple small meals

Non-pharmacologic Treatments 2

- Avoid rigorous exercise
- Sleeping with head up 20-30 degrees
- Schedule activities in afternoon
- Increase salt and fluid intake
- Countermaneuvers (leg crossing while standing, etc)

Therapy 1

Head up tilt of bed	30-45 degrees, requires footboard	Hypotension, sliding off bed, leg cramps
Elastic support hose	30-40 mmHg counterpressure, waist high	Uncomfortable, hot
Diet	Fluid intake of 2-3 liters, 1-2 tsps of salt per day	Supine hypertension
Exercise	Supine, then standing aerobic fitness program	Vigorous exercise may lower BP
Fludrocortisone	0.1-0.2 mg /day, not to exceed 1.0 mg/day	Hypokalemia, hypoMg++, edema, weight gain, CHF
Midodrine	2.5-10 mg q 2-4 hours	Nausea, supine hypertension

Therapy 2nd line

propranolol	10-60 mg 2- 4 times daily	Hypotension, CHF, bradycardia, exercise intolerance
Pyridostigmine (Mestinon)	30-120mg 3-4 x daily	Nausea, anorexia, diarrhea
Erythropoetin	4000 IU SQ twice weekly	Injections, burning, increased hematocrit
Desmopressin	Nasal spray	hyponatremia
Methylphenidate	5-10 mg tid w/ meals, last dose before 6 pm	Agitation, tremor, insomnia, supine hypertension
Caffeine	30-100 mg BID to TID	Same as above
Ephedrine sulfate	12.5-25 mg TID	Same as above

Syncope-Treatment

- **Neurocardiogenic (Vasovagal)**
  - Exercise, orthostatic standing 20-40 minutes BID
  - Light meal before prolonged standing
  - Countermaneuvers (West Point guards)
  - Sit or lie down if you feel faint
- **Orthostatic Hypotension**
  - Frequent small meals
  - Head of bed 15 degrees
  - Get up slowly and use countermaneuvers
  - Increase salt and fluid intake
  - Daily exercise/water aerobics

Beta Blockers

- Block peripheral sympathetic vasodilatation
- Prevent excessive tachycardia in POTS
- May prevent excessive cardiac contractility
- Conflicting evidence re. Efficacy
- Atenolol 25-100 mg daily
- First line therapy in patient with >2 episodes of syncope
- If recurs, tilt table testing

Fludrocortisone

- Useful in patients with vasodepressor syncope
- Boosts volume by mineralocorticoid effect
- 0.1-1 mg q day
- Side effects:
  - Supine hypertension
  - Edema and CHF
  - Hypokalemia and hypomagnesemia
  - Headache

Midodrine

- Useful in patients with dysautonomia, vasodepressor syncope, POTS, cardioinhibitory syncope
- Arteriolar and venous constriction
- Does not cross BBB
- Has no cardiac effects
- Peak plasma conc 20-40 min
- 30 min half life; metabolite 4 hours
- 2.5-10 mg TID (but not really TID)
- SE: piloerection and pruritus

Droxidopa

- Indicated for neurogenic orthostatic hypotension
- 100-600mg three times daily
- Increases BP by bypassing dopamine to produce norepinephrine
- Helpful in patients who do not respond /intolerant of midodrine, florinef

Take-home points

- Othostatic intolerance is a common presentation of POTS and autonomic disorders.
- medication effects, diabetic neuropathy, deconditioning may worsen symptoms.
- Volume expansion, healthy diet, exercise and medication are critical to recovery