Autonomic Neuropathies: From Amyloid to Zebras

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Disclosures

- Consultant for: Alnylam, Astrazeneca
- Speaker: Astrazeneca, Alnylam
- Research funding: CSL Behring, Inc, Healey Platform, NIH

Hardware Vs Software?

Autonomic Failure

- Orthostatic hypotension
- Heat intolerance with lack of sweating
- Dizziness/Lightheadedness while upright
- Syncope
- Urinary incontinence
- Constipation
- Nausea/bloating
- Difficulty concentrating while upright

Autonomic Dysregulation

- Tachycardia/palpitations with upright posture
- Heat intolerance
- Dizziness/Lightheadedness while upright
- Syncope
- Constipation or Diarrhea or both
- Nausea/bloating
- Difficulty concentrating while upright

Central Autonomic Disorders

- Multiple System Atrophy
- Chronic multiple sclerosis (affecting brainstem/spinal cord)
- Stroke (affecting basilar artery territory)
- Fatal familial insomnia
- Spinal cord lesions

Peripheral Autonomic Disorders

- Diabetic autonomic neuropathy
- Small fiber neuropathy associated with HIV
- Amyloidosis
- Chronic idiopathic anhidrosis
- Autoimmune autonomic neuropathy
- Acute Pandysautonomia
- Hereditary sensory autonomic neuropathy (Riley-Day Syndrome)
- Pure Autonomic Failure

Case 1

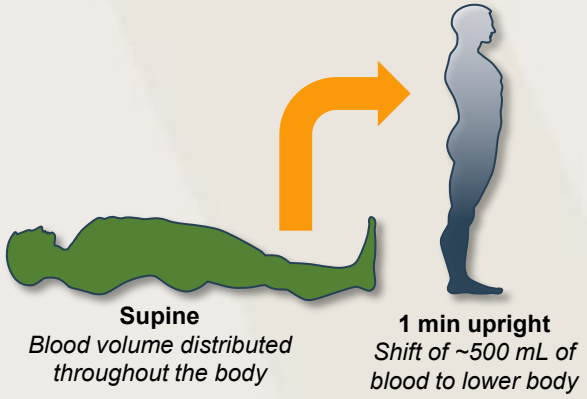
- 67-year-old with Parkinson's comes to the ED after syncopal event after getting up to go the bathroom.
- Exam is typical of Parkinson's, with right hand resting tremor.
- He notes dizziness when standing.
- What do you do next??

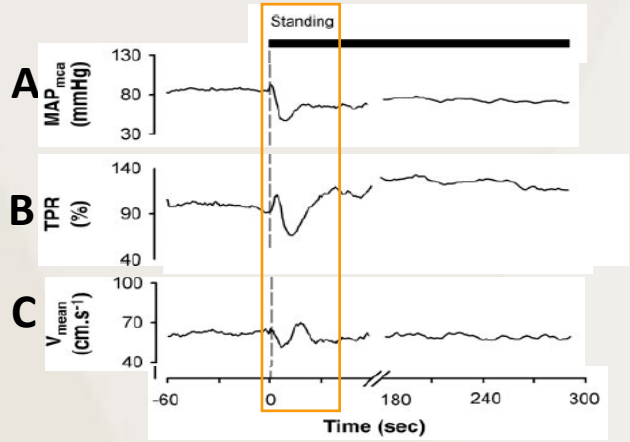
Orthostatic Vital Signs

- Most simple way to test sympathetic system
- Ideally have patient lay supine for at least five minutes before obtaining blood pressure, heart rate
- Have patient stand at least five minutes if tolerated
- Obtain blood pressures and heart rates at 1, 3, and 5 minutes. Some patients will not have an immediate drop in BP, but if symptomatic most likely will occur within 5 minutes of standing
- Normal heart rate should not increase greater than 30 beats per minute.
- Systolic should not fall greater than 20 mm Hg, diastolic 10 mm HG

Standing Involves Initial Reductions in BP

- Standing causes blood pooling in the lower part of the body[1,2]
- Physiologically, standing is followed by a rapid, transient reduction in mean arterial pressure (MAP) (A), total peripheral resistance (TPR) (B), and cerebral perfusion (C)[3]

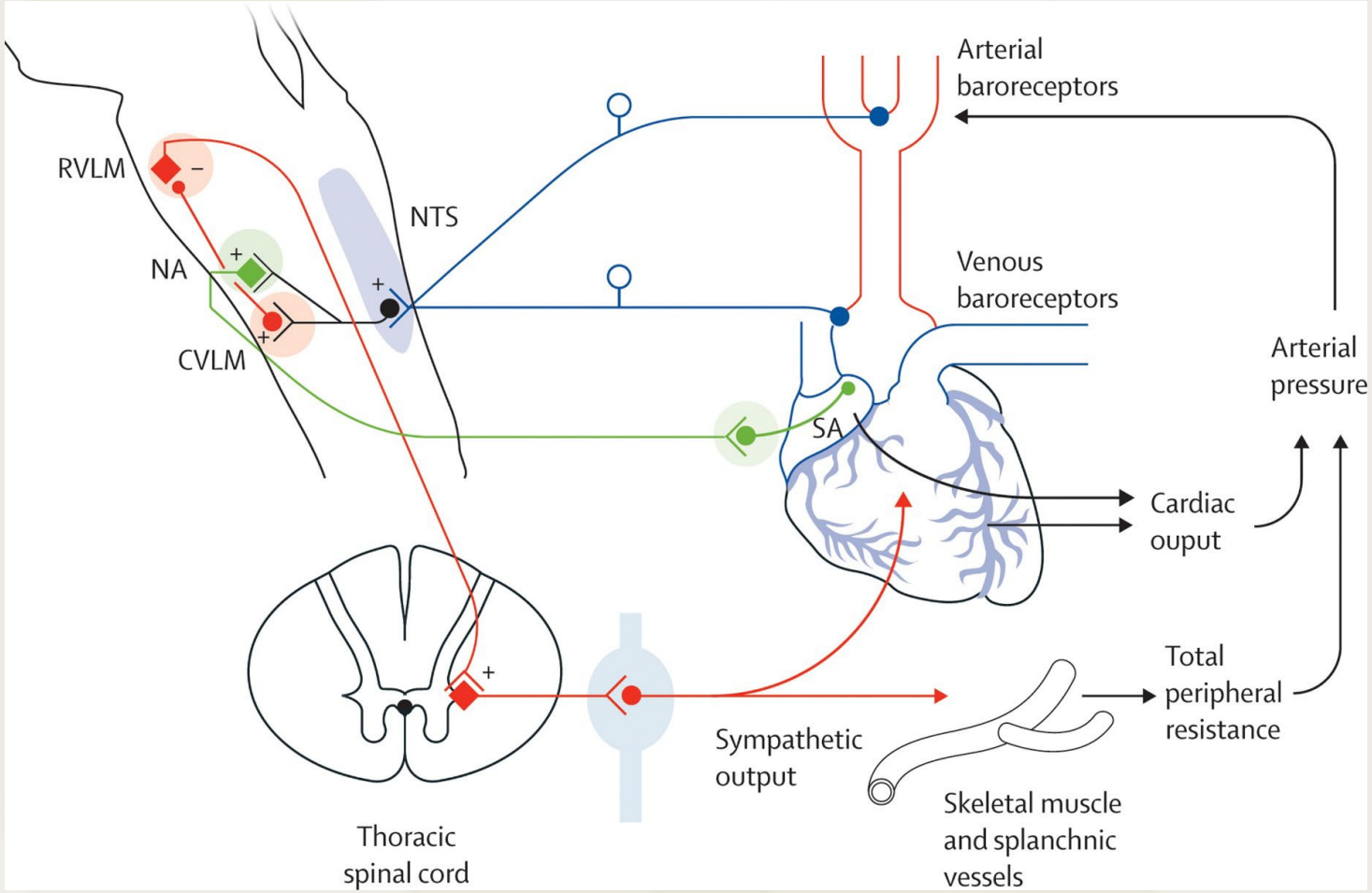




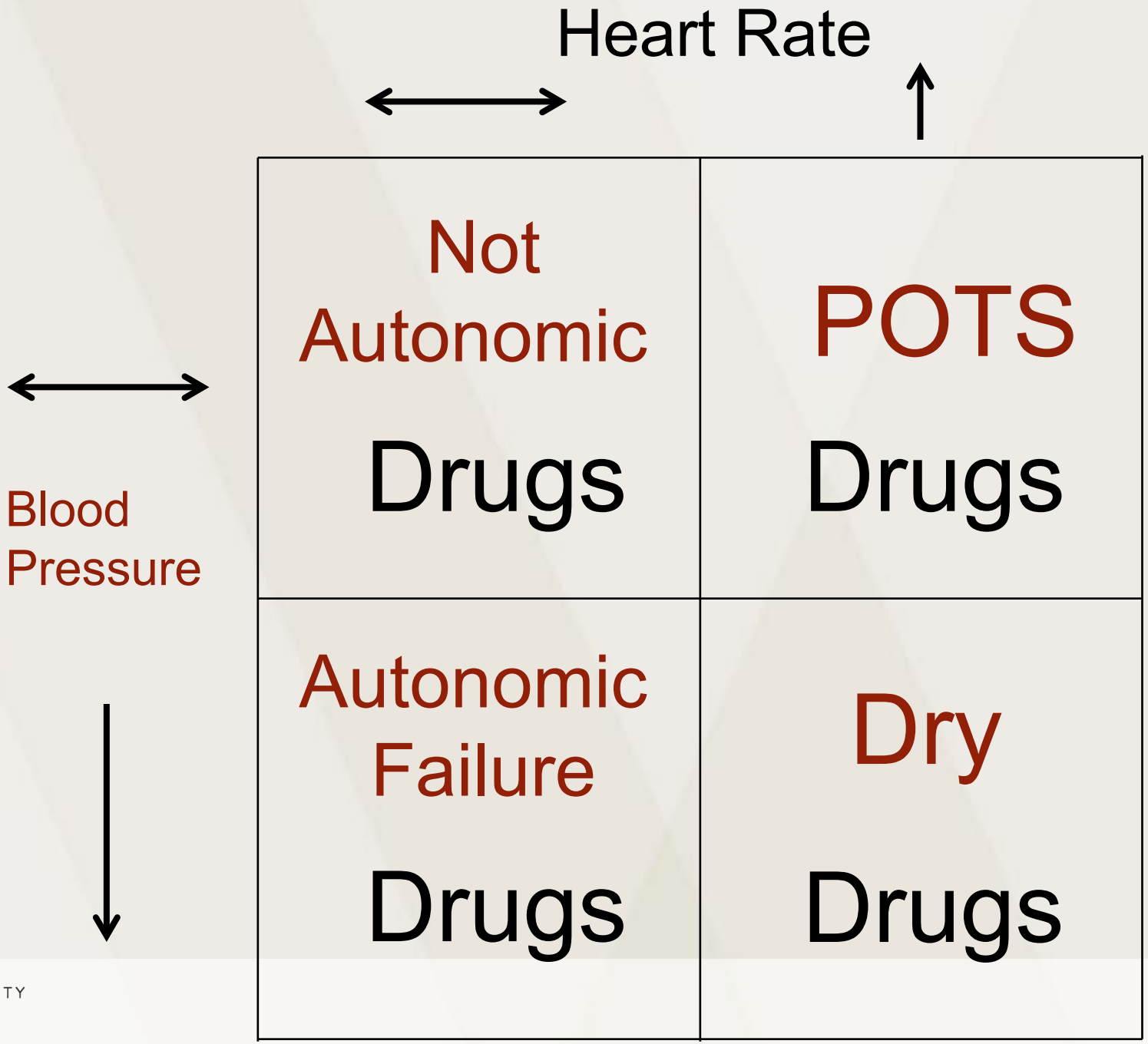
BP = blood pressure; V_{mean}= mean flow velocity in middle cerebral artery.

1. Robertson D. *Clin Auton Res.* 2008;18(Suppl 1):2–7; 2. Grubb B. *Circulation.* 2005;111:2997–3006; 3. Van Lieshout JJ, et al. *J Appl Physiol.* 2003;94:833–848.

Anatomy of Baroreflex



Low and Singer. Lancet 2008


Heart Rate
Blood Pressure
Not Autonomic
Drugs
POTS
Drugs
Autonomic Failure
Drugs
Dry
Drugs

Clinically Available Autonomic Tests

- Tilt table
- Heart rate response to deep breathing
- Valsalva maneuver with /without beat-to-beat blood pressure measurement
- Quantitative sudomotor axon reflex test
- Thermoregulatory sweat test
- Sudoscan

Types of Autonomic Failure

Parasympathetic Dysfunction	Parasympathetic And Sympathetic Dysfunction	Sympathetic Dysfunction
Diabetes Lambert Eaton Myasthenic Syndrome	Multiple System Atrophy Autoimmune Autonomic Ganglionopathy Amyloidosis	Pure Autonomic Failure Parkinson's Disease

Case 1: Autonomic Function Test

FORM AFT Worksheet 2014/05/07 11:16 Created by: **Peltier, Amanda C.** (Last modified by Maxwell, J

AFT Worksheet

(Autonomic Function Lab)

ORTHOSTATIC CHALLENGE

Standing Time (min):	10 bpm	
15 min Supine: HR:	60 bpm	BP:173 /97 mmHg
--Upright:1 min:	71 bpm	BP:161 /94 mmHg
--Upright:3 min:	77 bpm	BP:116 /71 mmHg
--Upright:5 min:	80 bpm	BP:108 /76 mmHg
--Upright:8 min:	82 bpm	BP:98 /72 mmHg
--Upright:10 min:	82 bpm	BP:102 /68 mmHg

SINUS ARRHYTHMIA

Heart Rate: Max:69 bpm **Min:**57 bpm
HR (max-min) = 12 bpm
SA Ratio (max/min) = 1.21

COLD PRESSOR TEST

Baseline: HR: bpm **BP:** / mmHg
1 minute: HR: bpm **BP:** / mmHg

VALSALVA MANEUVER

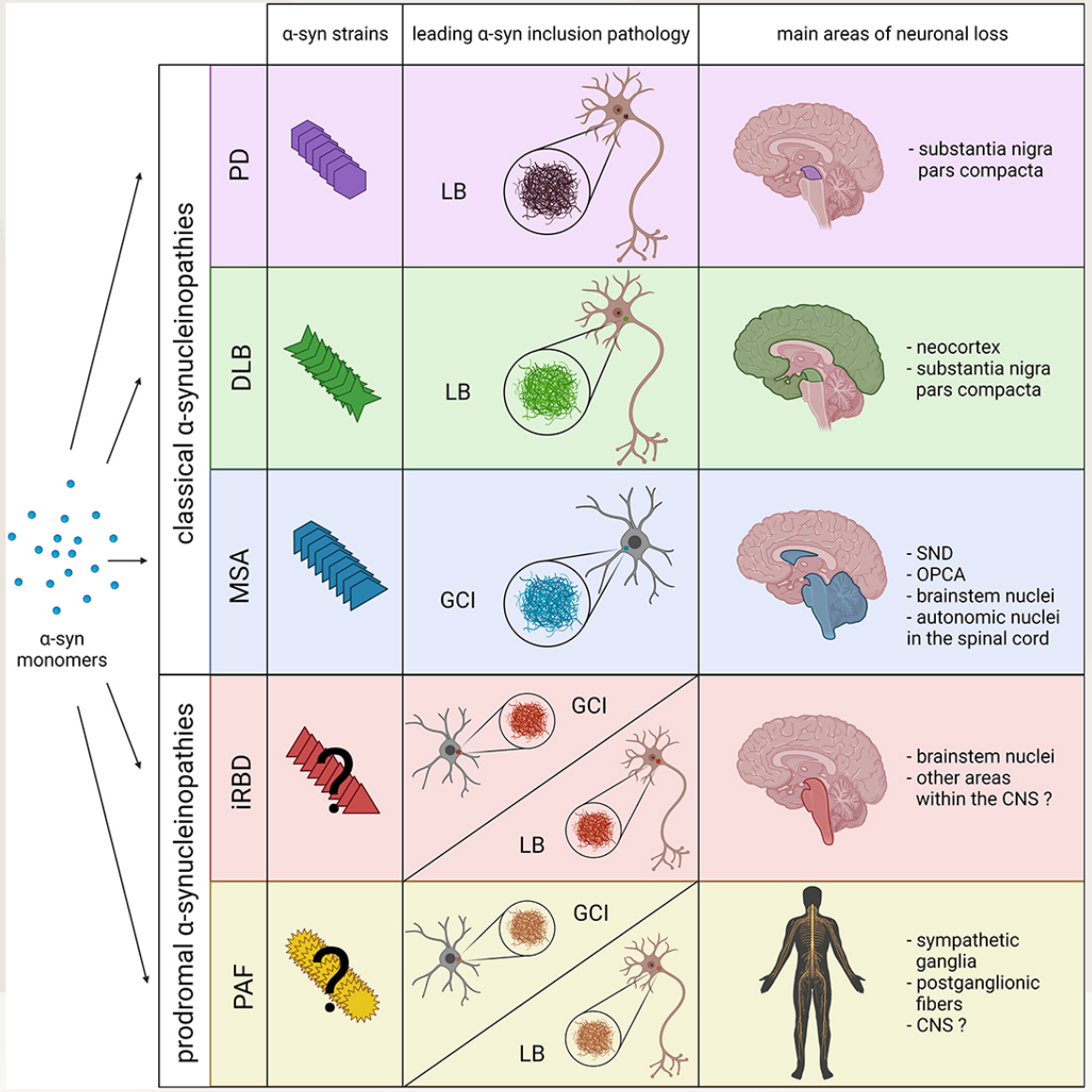
Valsalva Pressure Reached:	28 mmHg	
Baseline:	HR:65 bpm	BP:155 /72 mmHg
Phase 2E:	HR:70 bpm	BP:149 /74 mmHg
Phase 2L:	HR:70 bpm	BP:175 /79 mmHg
Phase 4:	HR:58 bpm	BP:173 /73 mmHg
Maximum HR (during or after Valsalva):	HR:70 bpm	
Minimum HR (after Valsalva):	HR:58 bpm	
Valsalva Ratio=	1.21	

Time Since Meal (hours):11

Height:-- cm. Weight:-- kg. Gender: M

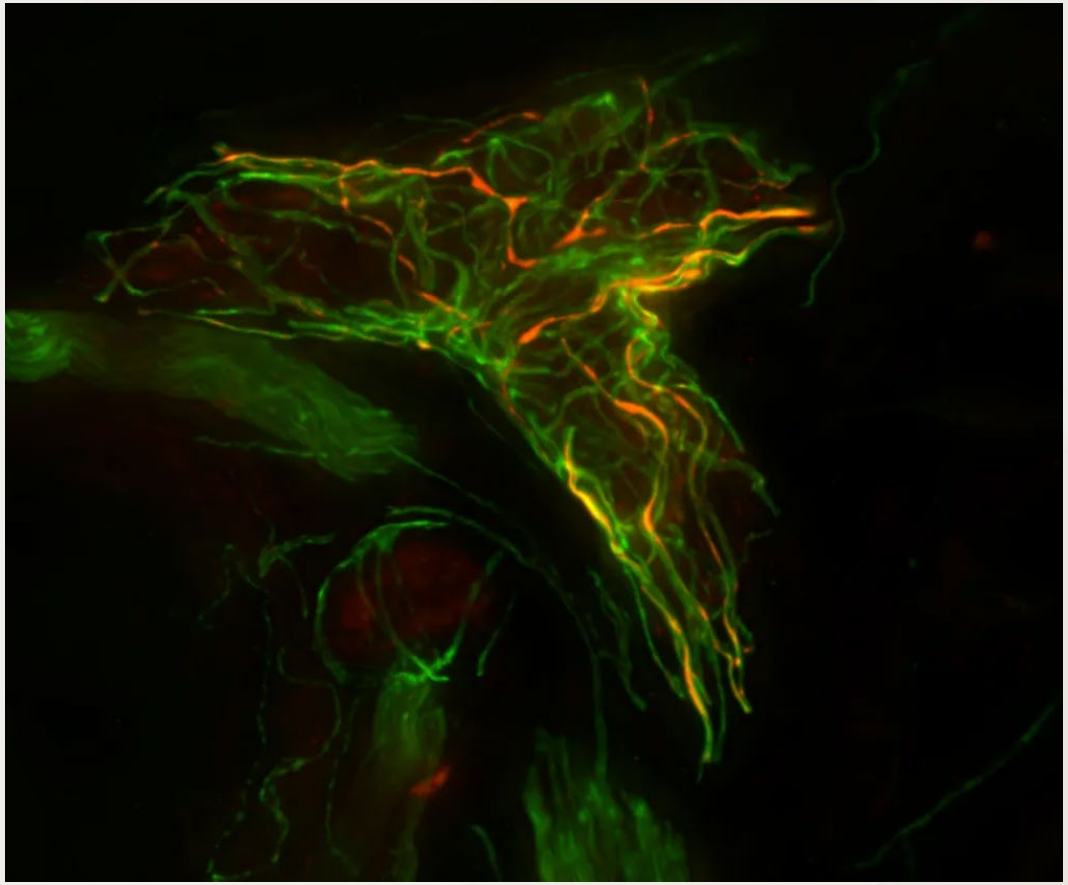
Alpha-Synucleinopathies

- Most have autonomic dysfunction (except RBD) which manifests as sympathetic >parasympathetic dysfunction, supine hypertension.



https://www.frontiersin.org/articles/10.3389/fneur.2021.737195/full

Alpha Synuclein in Cutaneous Sympathetic Nerves



- Phosphorylated alpha synuclein can be detected in cutaneous sympathetic nerves in Parkinson's disease (PD), pure autonomic failure (PAF), and multiple system atrophy (MSA).
- MSA typically has more widespread deposition in cutaneous nerves in arms and legs vs. PD which may only be seen in cervical skin.

https://www.the-scientist.com/diagnosing-synucleinopathies-with-skin-biopsies-73233

Most Common Peripheral Neuropathies Affecting the Autonomic System

- Diabetes mellitus and prediabetes
- Amyloidosis
- HIV neuropathy
- Toxic neuropathies
- ??? Mutation in the sodium channel Nav1.7 and other inherited neuropathies

Case 2: 64-year-old Woodworker

- 2017 had numbness and weakness in his legs, underwent lumbar decompression for spinal stenosis.
- Noted same year to have carpal tunnel syndrome.
- Severe carpal tunnel noted on right hand, moderate to severe on left.
- 2018: Referred to neuromuscular, further EMG on 5/2018 showed latency prolongation, significant weakness on exam raising concern for CIDP.
- Trial of IVIG revealed no benefit

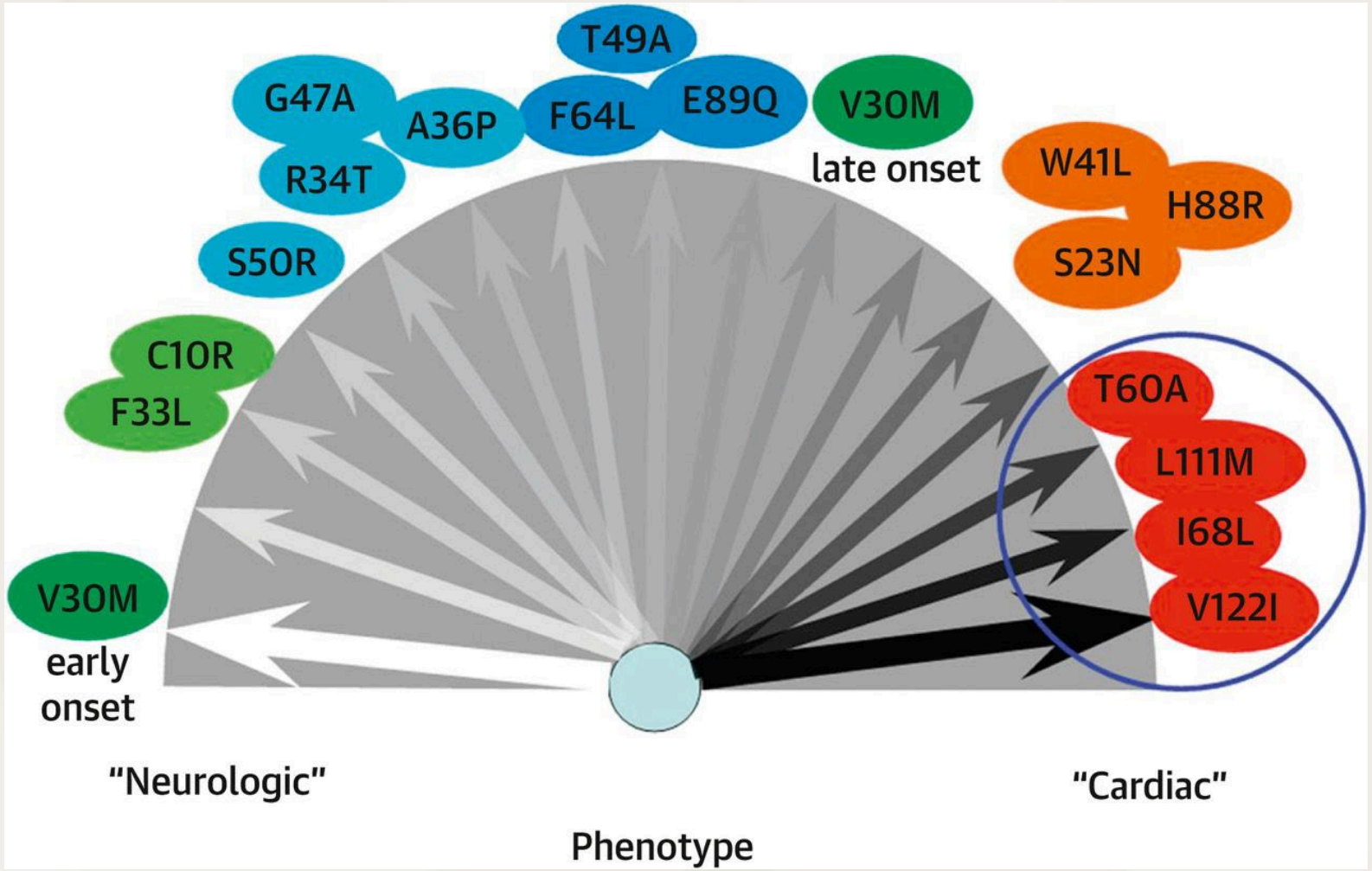
Case 2 Continued

- Lost 30 pounds, had CABG. Persistent edema on exam
- Referred to cardiology, had 40-50% EF, noted to have daily diarrhea on note. Patient had episode of bradycardia requiring pacemaker.
- Sural nerve biopsy demonstrated axonal neuropathy. Fat pad biopsy done and negative for amyloid.
- Bone marrow biopsy positive revealed amyloid.
- Typing on cardiac biopsy revealed ATTR amyloid.
- 2019 genetic testing performed which showed T60A TTR mutation

Neurology Evaluation

- In 2018 had 4/5 hip flexion weakness, normal reflexes
- 2/2019 had noted 4 finger abduction, thumb abduction weakness, 4 strength in hip flexors, 5 knee extensors and flexors, 4 ankle dorsiflexion, 5 plantar flexion
- Vibration reduced to fingertips and ankles, absent reflexes.
- Patient started on silencer treatment.

Hereditary Transthyretin Amyloidosis



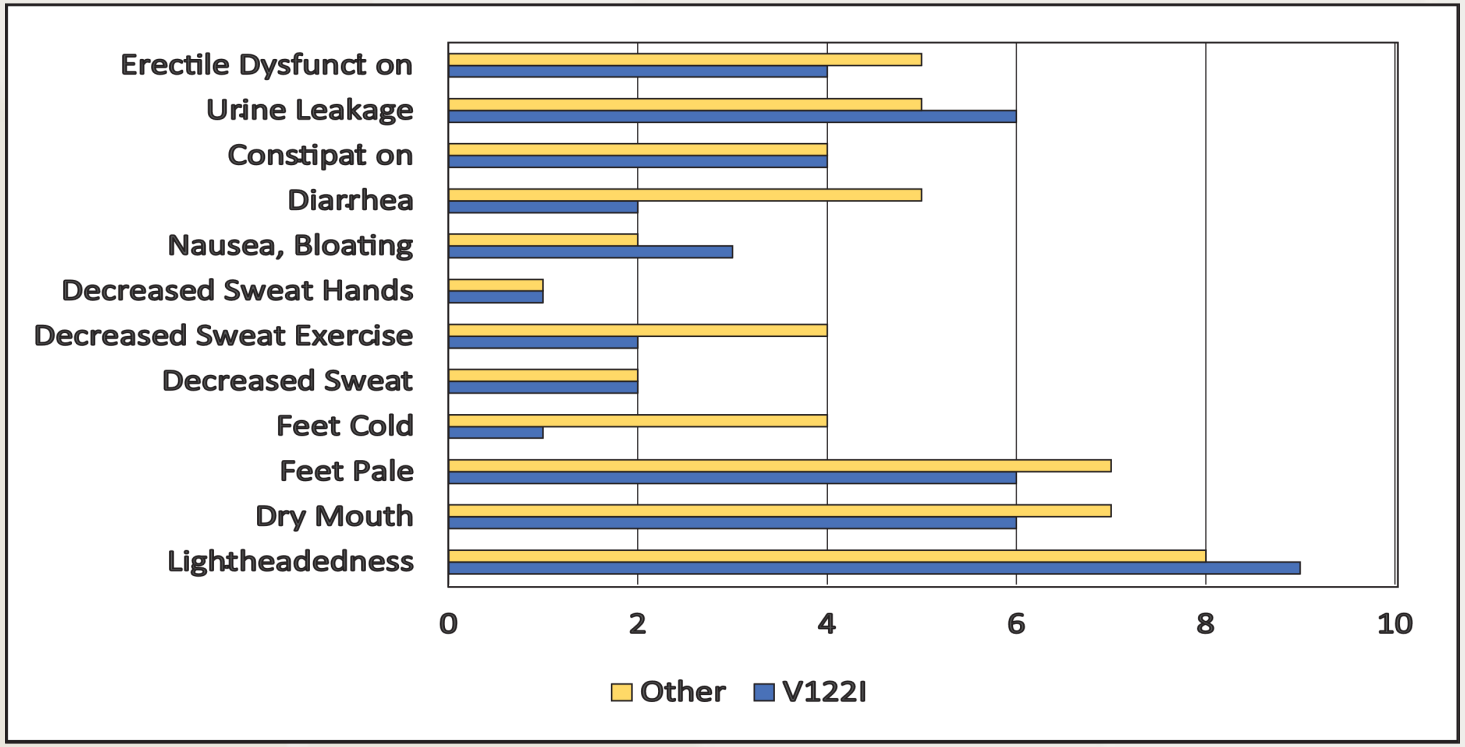
From: Semigran MJ. JACC 2016.

Autonomic Neuropathy

- Occurs more often in hATTR than in AL amyloidosis
- Affect survival rates and severity
- Orthostatic hypotension, erectile dysfunction, neurogenic bladder, syncope
- Most common: GI disturbances, typically causing diarrhea alternating with constipation caused by amyloid infiltration of mesenteric plexus
- Cause of ventricular arrhythmias and sudden death.
- Sudomotor and pupillary abnormalities can also be seen.

Autonomic Neuropathy in Amyloidosis

- Both parasympathetic, sympathetic systems involved.
- Sudomotor testing typically abnormal.
- NOH frequent in AL amyloidosis, certain TTR mutations
- GI symptoms highly prevalent with diarrhea most common, followed by bloating, early satiety, constipation



1. Gonzalez-Duarte A. *Clin Auton Res.* 2019;29(suppl 1):1-9,
Desai et al. Muscle and Nerve 2025.

Case 3: A young woman with SLE

- 21 year old woman presented to the Autonomic Clinic.
- Previously very active, in the club field hockey team, “several concussions”
- VU pred med/nursing student

- Initial AFT consistent with POTS and near syncope:

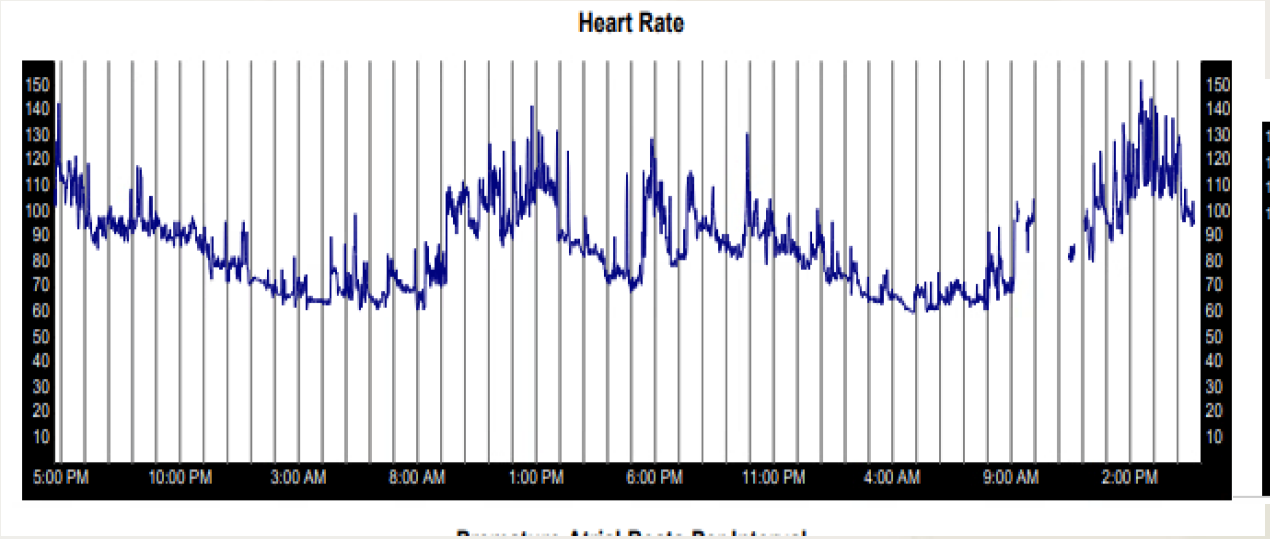
Other Medical History

- 3/22: Hyperparathyroidism (2ry to Vit D deficiency)
- 9/22: Mixed connective tissue disease vs lupus (ANA -) on plaquenil & azathioprine by VUMC rheumatologist
- 3/24: OSA (PSG), narcolepsy (clinical)
- 7/24: Thoracic outlet syndrome

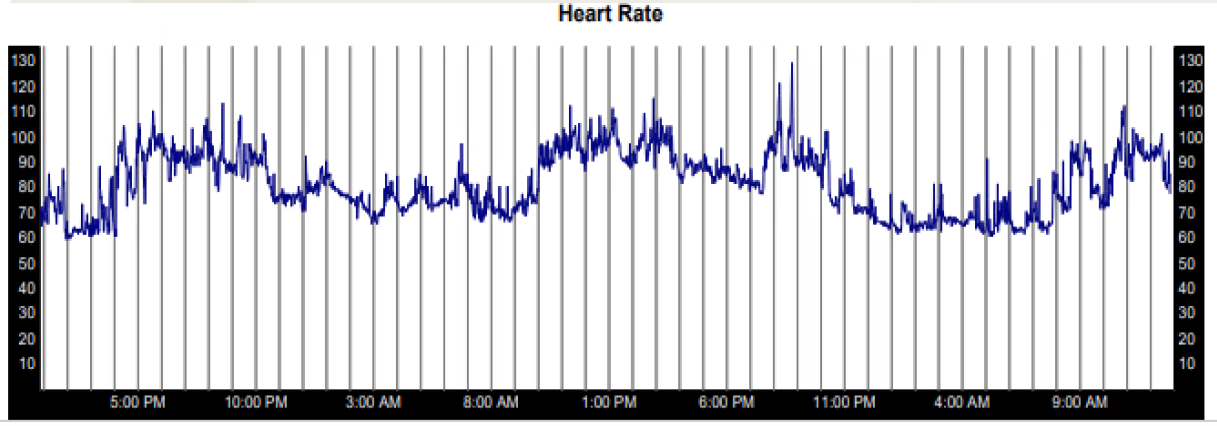
Other procedures

- 3/23: Dual chamber pacemaker for transient AV block and to allow for POTS control
- 7/23: R stellate ganglion block → R sympathectomy
- 7/24: sphincter palatoplasty for OSA
- 4/24: L stellate ganglion block → 10/24: L sympathectomy + thoracic outlet repair
  Pre surgery orthostatics 108 bpm→121 bpm

4/5/2024 59-158 bpm, x=86

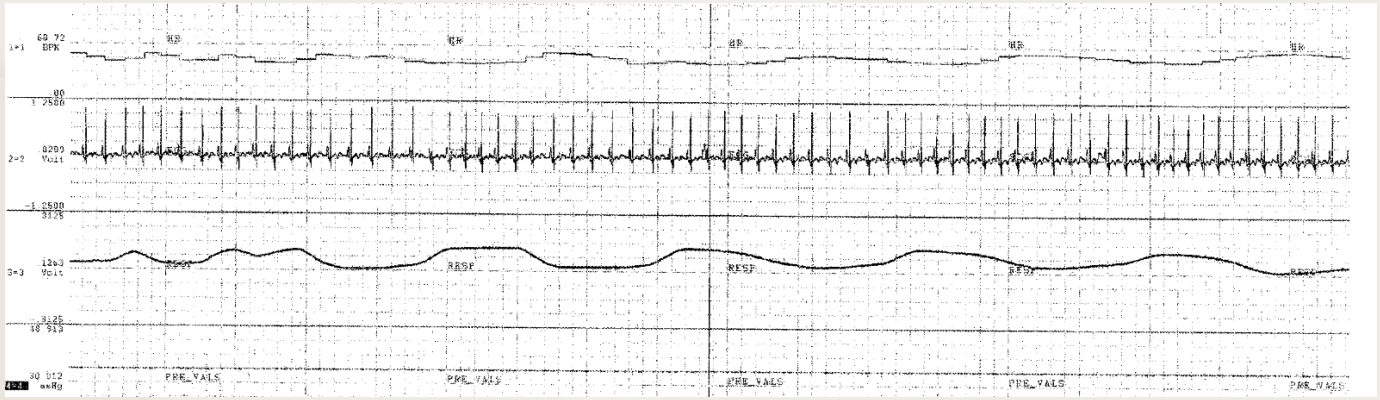


4/30/2024 59-130 bpm, x=82

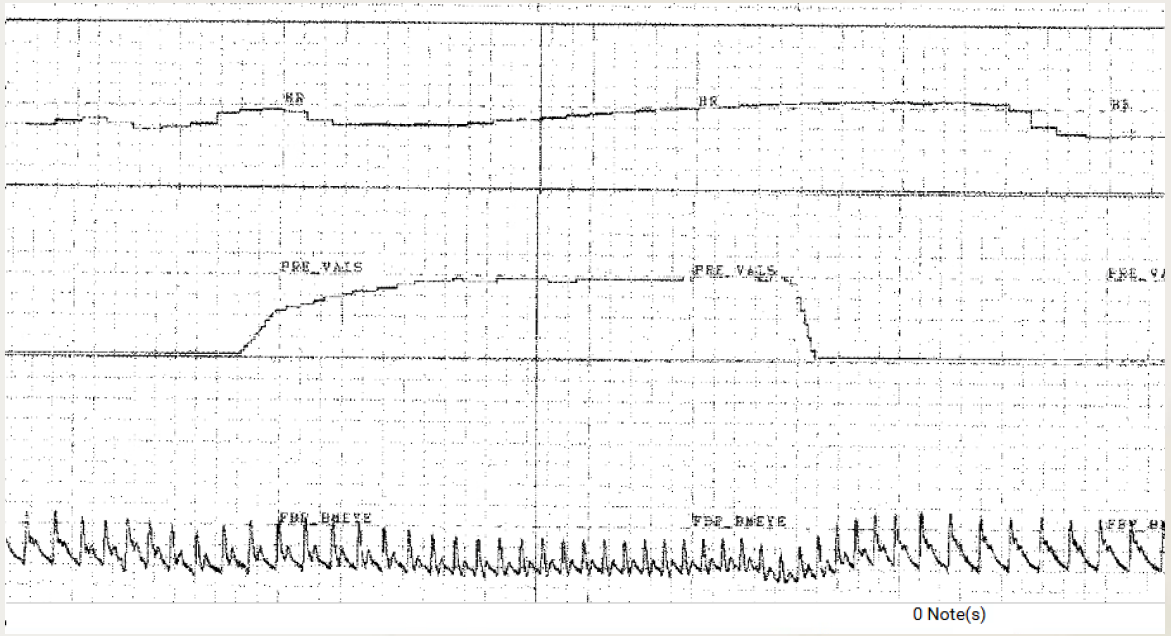


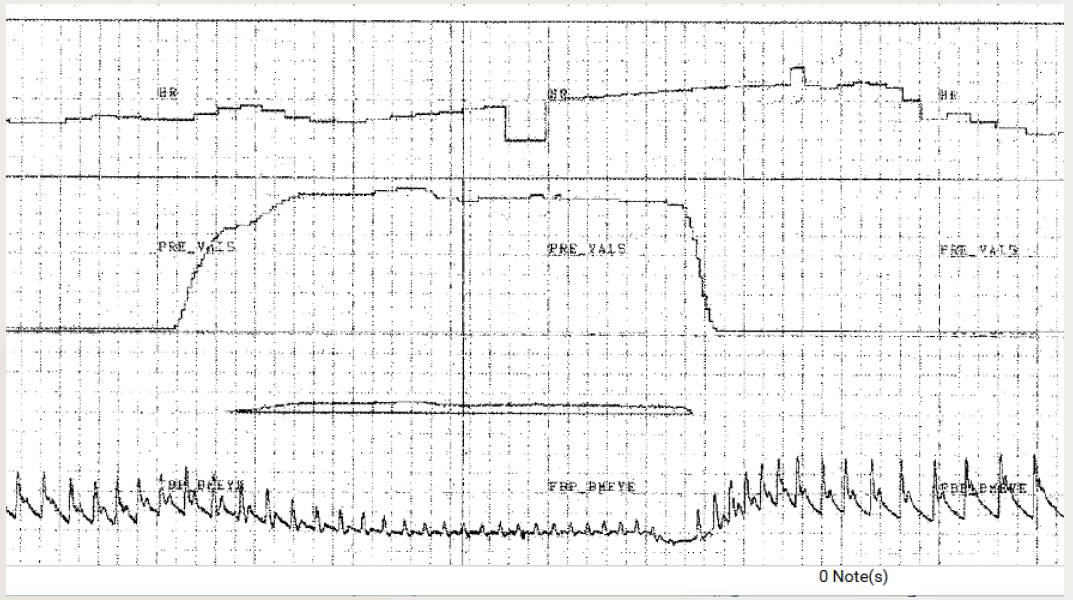
- L Horner, chylothorax (1.4 L) needed thoracocentesis and surgical repair

AFT 2/23



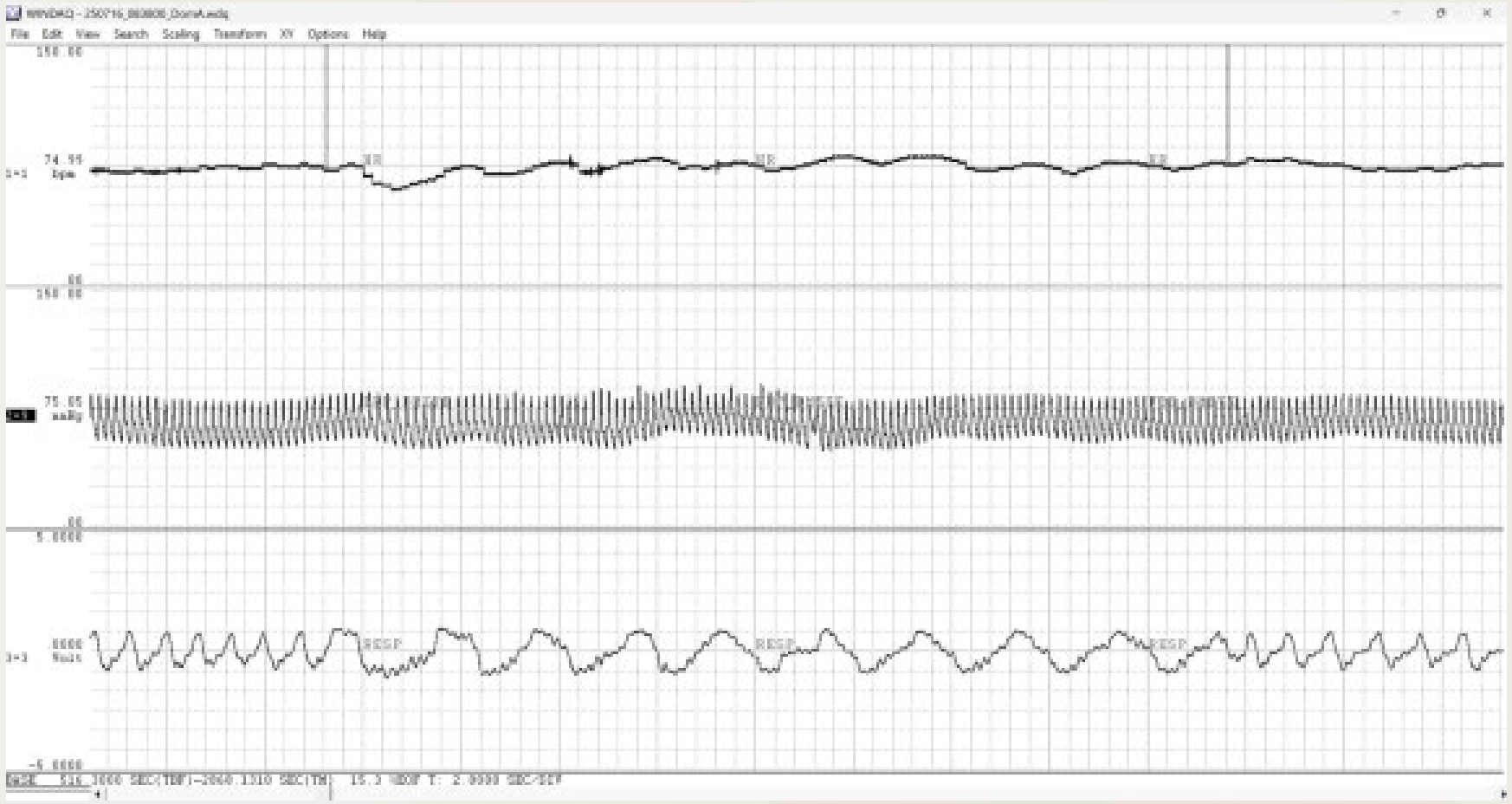
SA=1.26



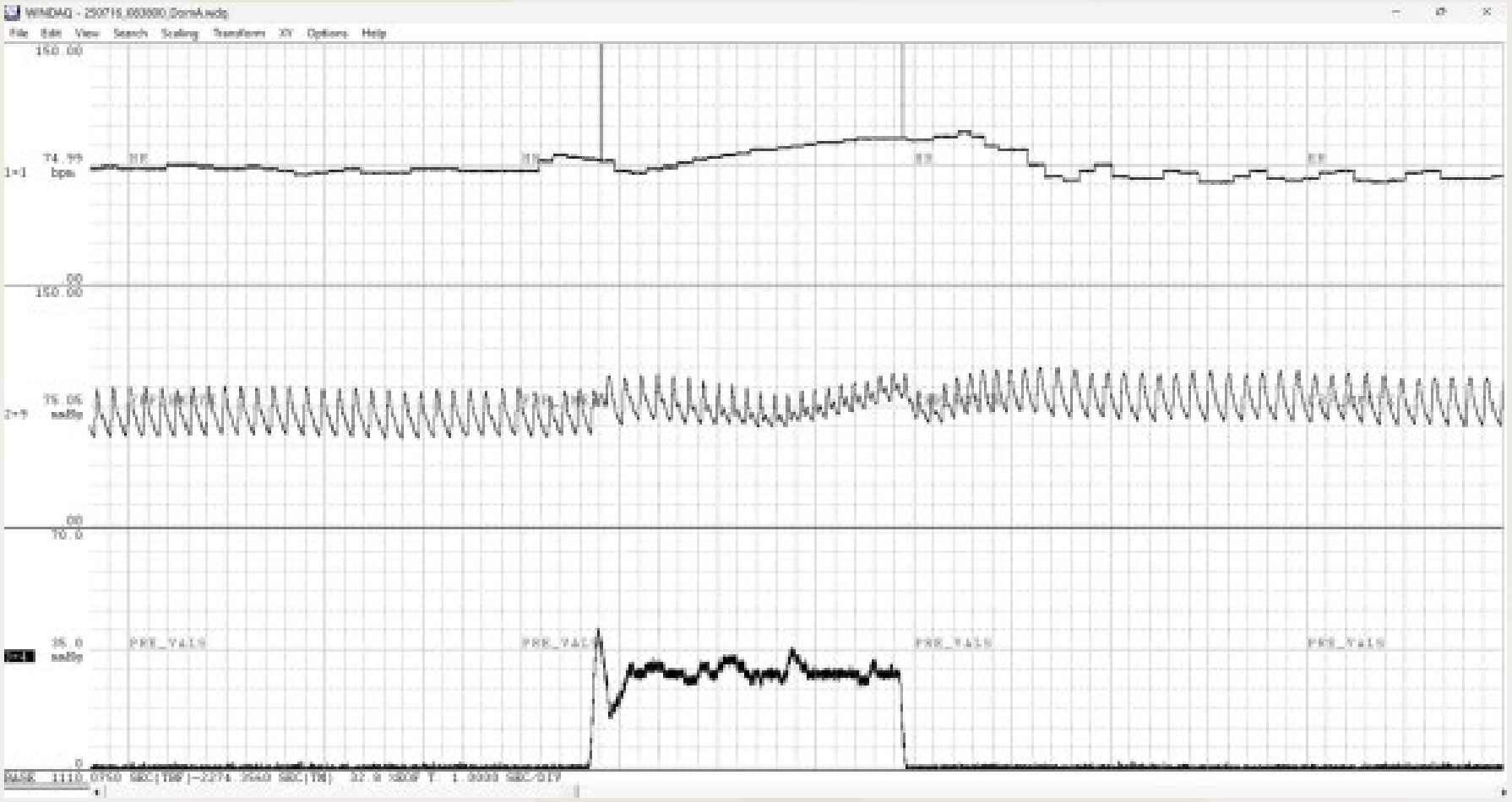


VR=2.16

After Plasma Exchange 7/25



Valsalva Maneuver After PE 7/25



Features of Autoimmune Autonomic Ganglionopathy (AAG) with AchRN Ab

- Severe parasympathetic and sympathetic failure,
- Absent sweat responses
- Abnormal pupillary reflexes
- Severe gastroparesis
- Associated with antibodies to the nicotinic acetylcholine receptor (ganglionic)
- Severity typically correlates with antibody titer
- Multiple malignancies including lymphoma, lung associated with AAN
- Reversible cognitive dysfunction has been described

Hereditary Sensory and Autonomic Neuropathies

- Only HSAN III and VI have significant cardiac autonomic symptoms. Most have predominantly anhidrosis as their “autonomic complaint.”
- HSAN III and VI have afferent loss of baroreceptor control which can lead to blood pressure lability, loss of tears, in addition to anhidrosis.
- HSAN I-IV with primary symptoms of pain insensitivity.
- HSAN VII exception: mutation in sodium channel 1.7 causing erythromelalgia. Some patients with coexistent orthostatic symptoms described by Faber et al.


AND NOW FOR SOMETHING
COMPLETELY DIFFERENT.

Postural Tachycardia Syndrome (POTS)

- Commonly affects young to middle aged women
- Multiple previous monikers including “soldier’s heart”, “mitral valve prolapse”, etc.
- No defined cause
- By definition require a significant heart rate elevation of at least 30 bpm on standing without hypotension
- Orthostatic symptoms of dizziness, palpitations, fatigue, “brain fog” and difficulty concentrating when standing present
- Often have mild GI symptoms and frequent diagnosis of irritable bowel syndrome, fibromyalgia, and other “software” diagnoses

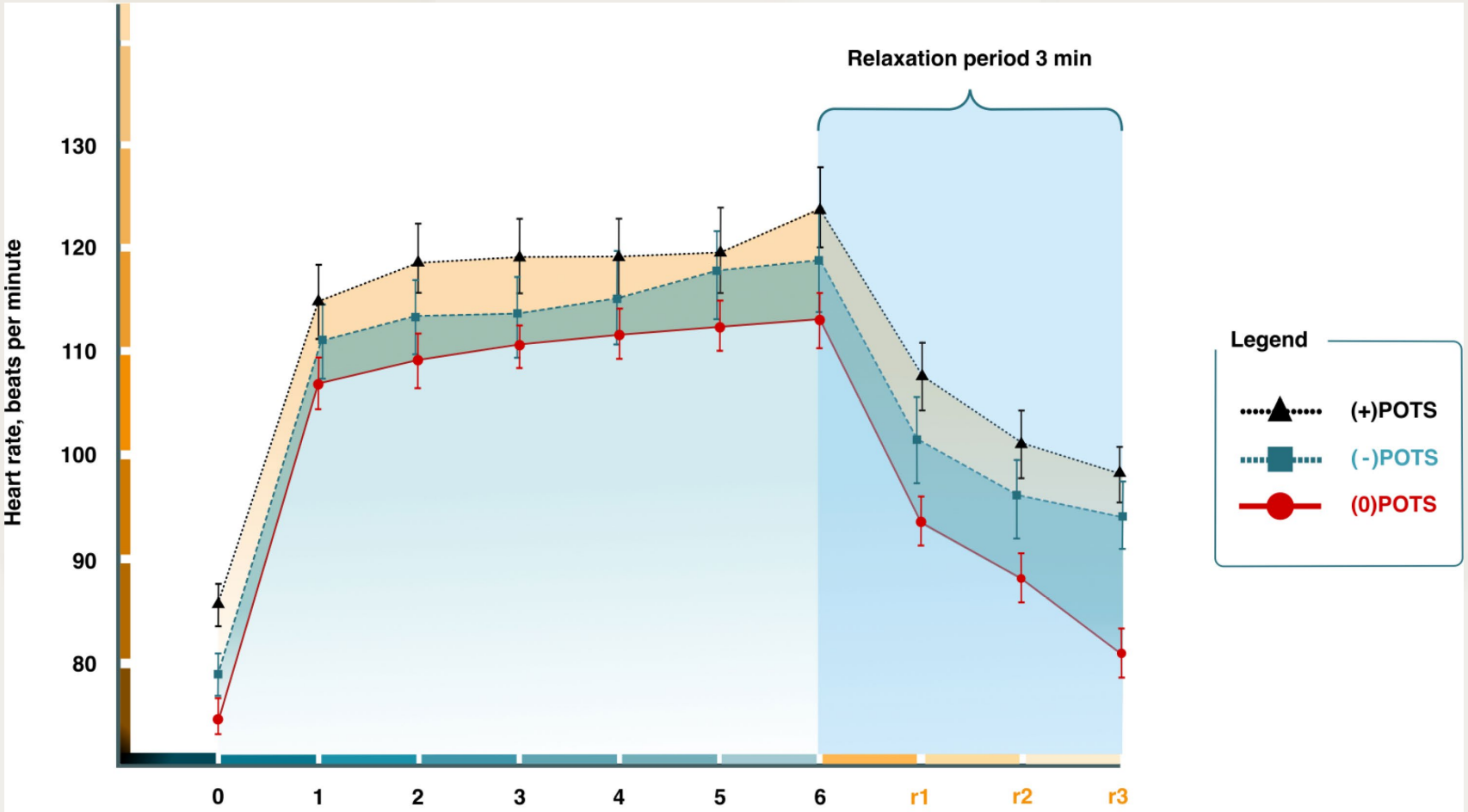
POTS

- A subgroup of POTS have very high catecholamines (over 600 pg/nl) others with normal levels
- Typically have high resting heart rate also, and can have heart rates of 130 or greater when standing
- Very high prevalence of headache
- Very high comorbidities of anxiety and depression
- Sweat tests mildly abnormal but not severe like PAF

POTS after COVID

- 134 cases reported associated with COVID infection (few with vaccine)
- Most reviews of COVID patients showed orthostatic intolerance without meeting hr criteria for POTS (Shouman et al. 2021).
- Raised again ? Re autoimmunity in POTS.
- Current study looking IVIg in POTS after COVID infection (RECOVER).

Prevalence of POTS in Long COVID



Björnson M et al. Prevalence and Clinical Impact of Postural Orthostatic Tachycardia Syndrome in Highly Symptomatic Long COVID. Circulation: Arrhythmia and Electrophysiology. https://doi.org/10.1161/CIRCEP.124.013629

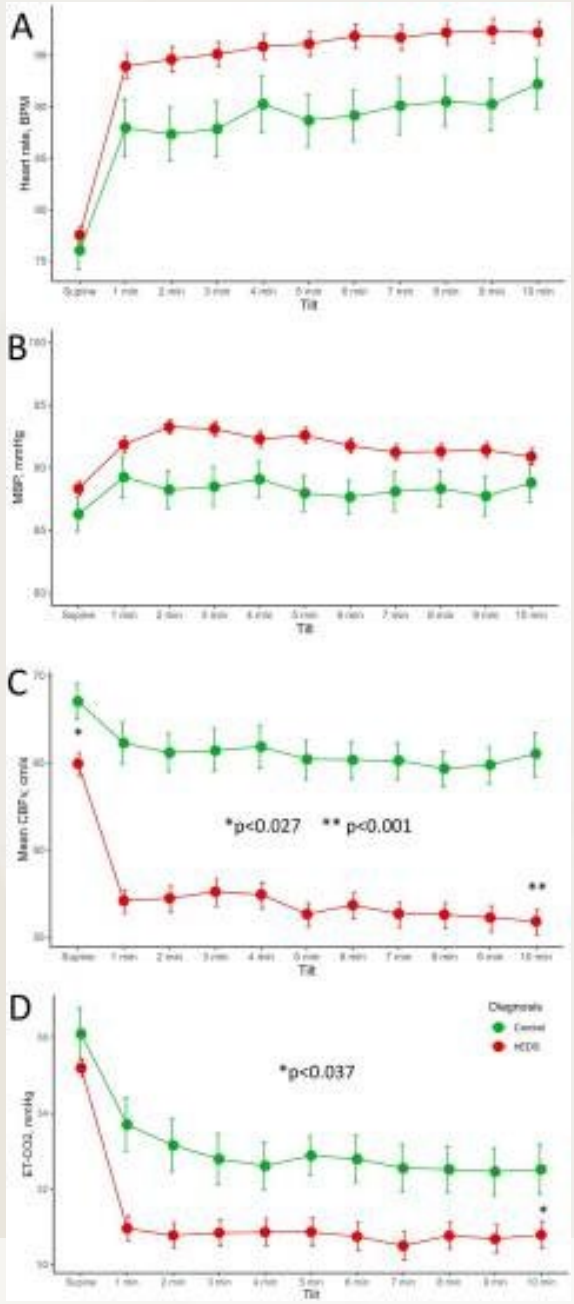
Autoimmunity in POTS and Dysautonomia?

- Frequency of young women, frequency after illness have prompted concerns for autoimmunity in POTS
- Nonspecific autoantibodies for beta receptors have been reported in POTS patients although not significantly different than controls.
- IVIg and other autoimmune treatments have been suggested as possible treatments in case series and case reports.
- Vernino and colleagues performed a randomized placebo-controlled study in POTS, showing no significant difference in either heart rate response or symptom burden (using COMPASS) in patients randomized to IVIg vs albumin (Vernino et al. 2024 CAR).

Ehler Danlos Syndrome and POTS

- Type 3 Ehler-Danlos, which is heritable but genetically undefined, has been cited as common in POTS.
- Patients typically have joint hypermobility, hyperextensible skin, and pain disorders. Increase heart rate on tilt compared to controls is common, as is lower epidermal nerve fiber density.

Novak et al. Hypermobile Ehlers-Danlos Syndrome: Cerebrovascular, Autonomic and Neuropathic Features. Am J Med Open. 2025 Jul 18;14:100111. doi: 10.1016/j.ajmo.2025.100111. PMID: 40843452; PMCID: PMC12365377.

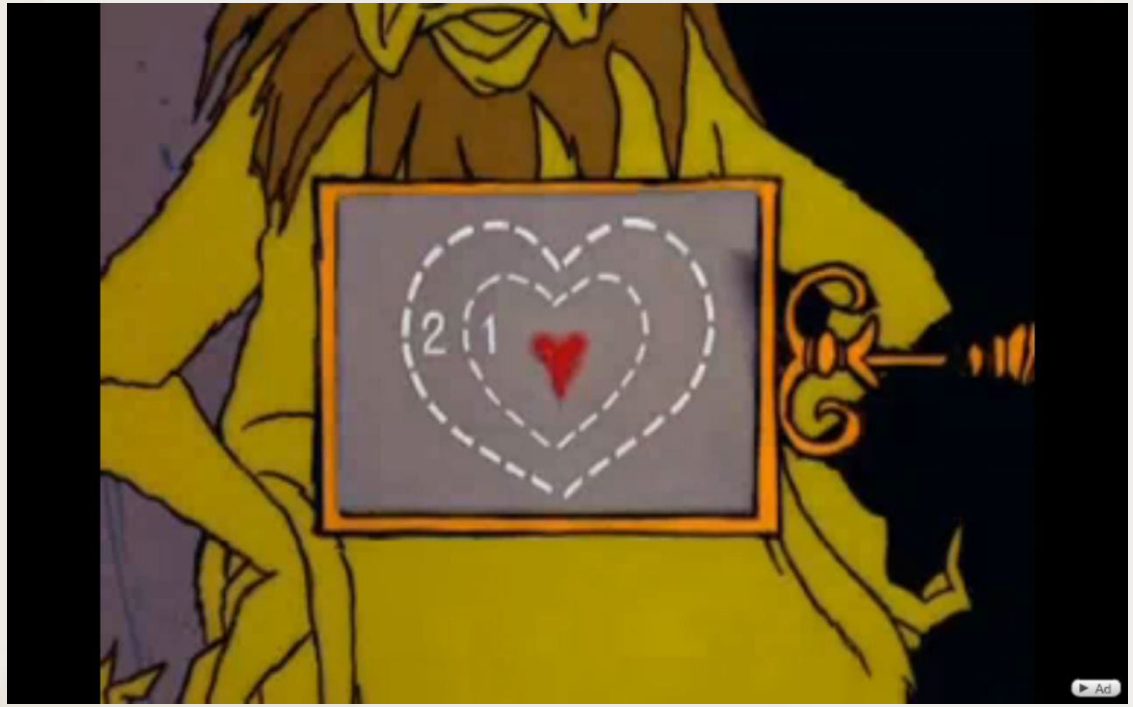


POTS: Treatment Approaches

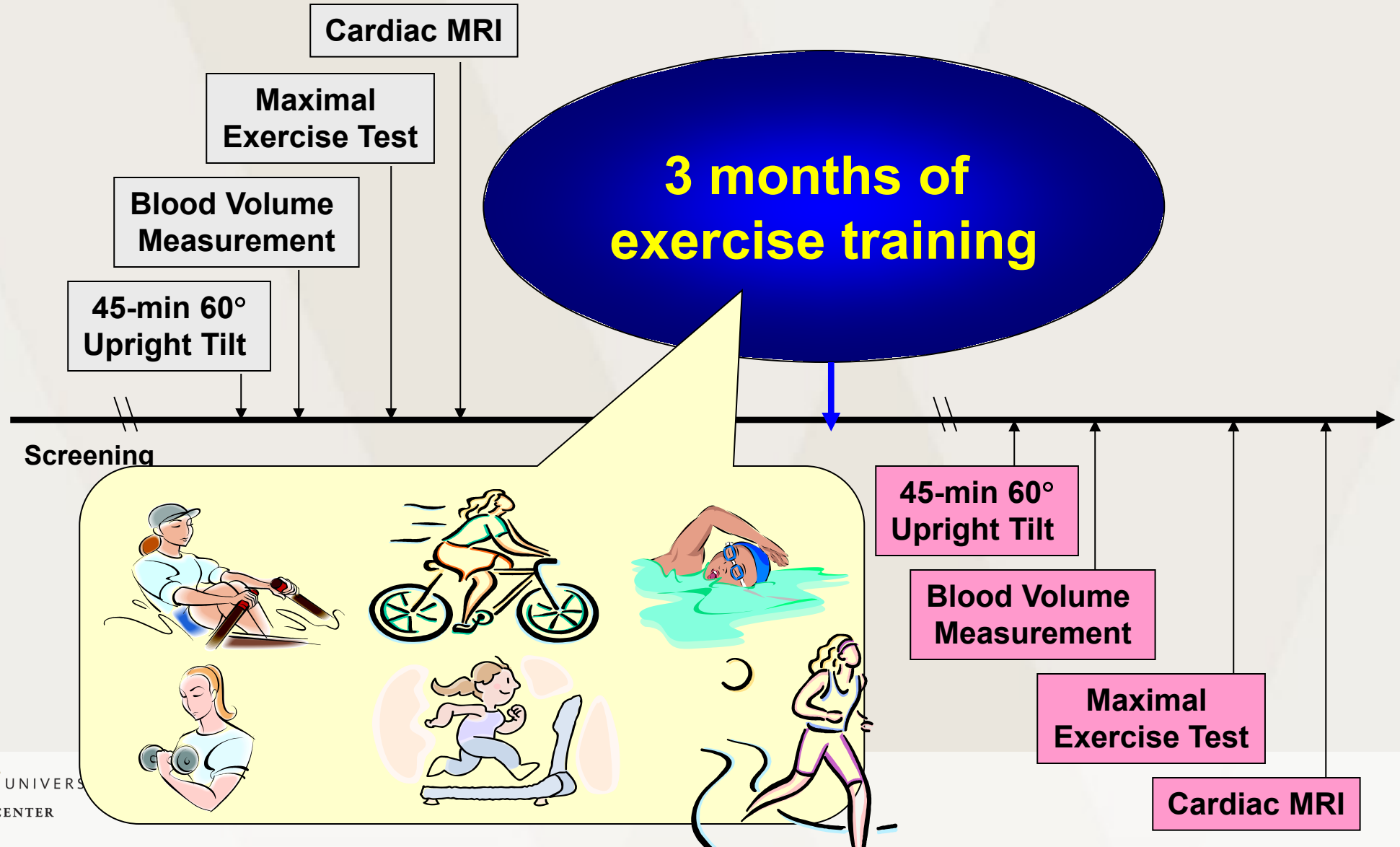
- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - IV Saline
  - Acute DDAVP-H_2O
- Hemodynamic Agents
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Clonidine/α-Methyldopa
  - NET Inhibitors…can be evil
- Exercise

Exercise Training

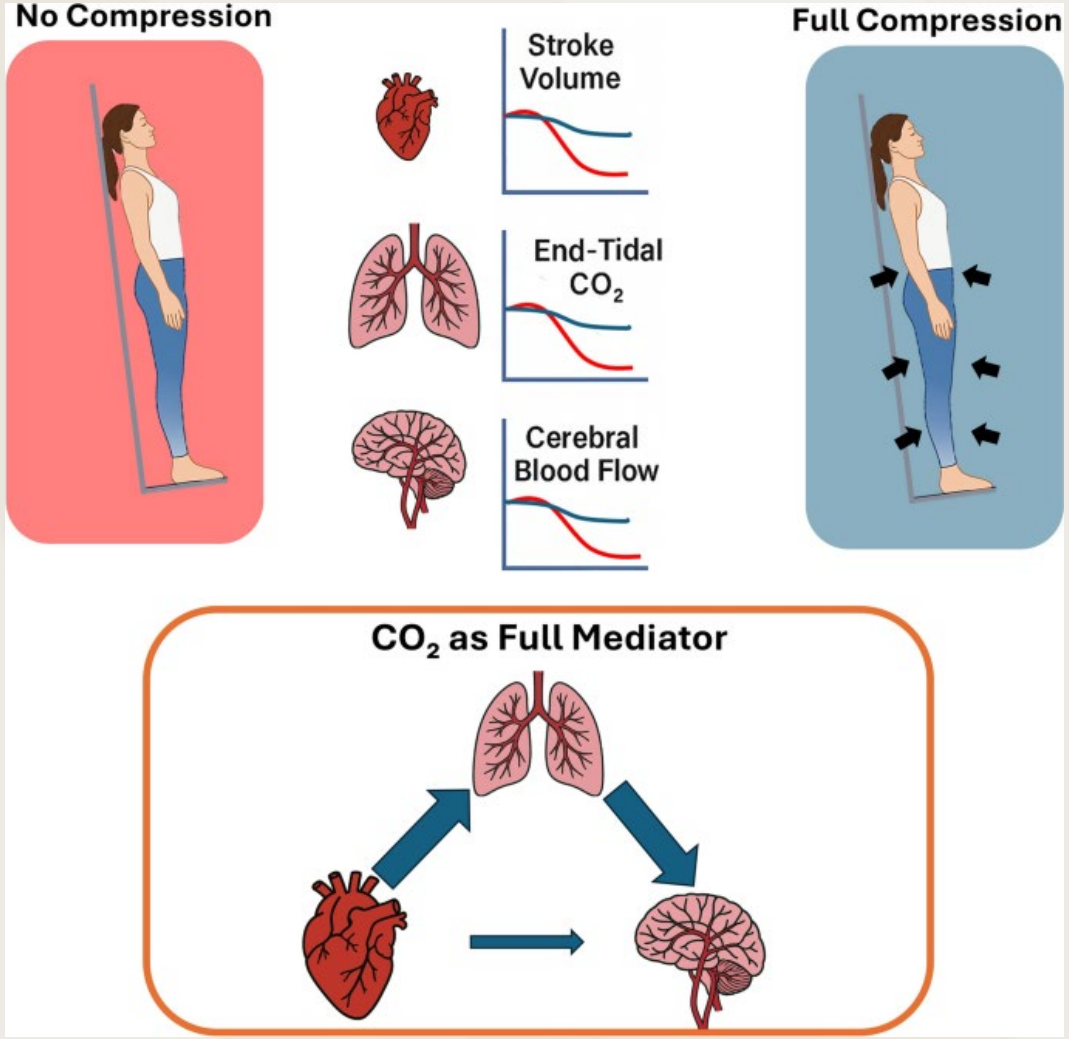
- Deconditioning leads to similar physiologic findings:
  - Increased orthostatic tachycardia
  - Impaired left ventricular filling and decreased stroke volume (Grinch heart)



Exercise Study in POTS - Design

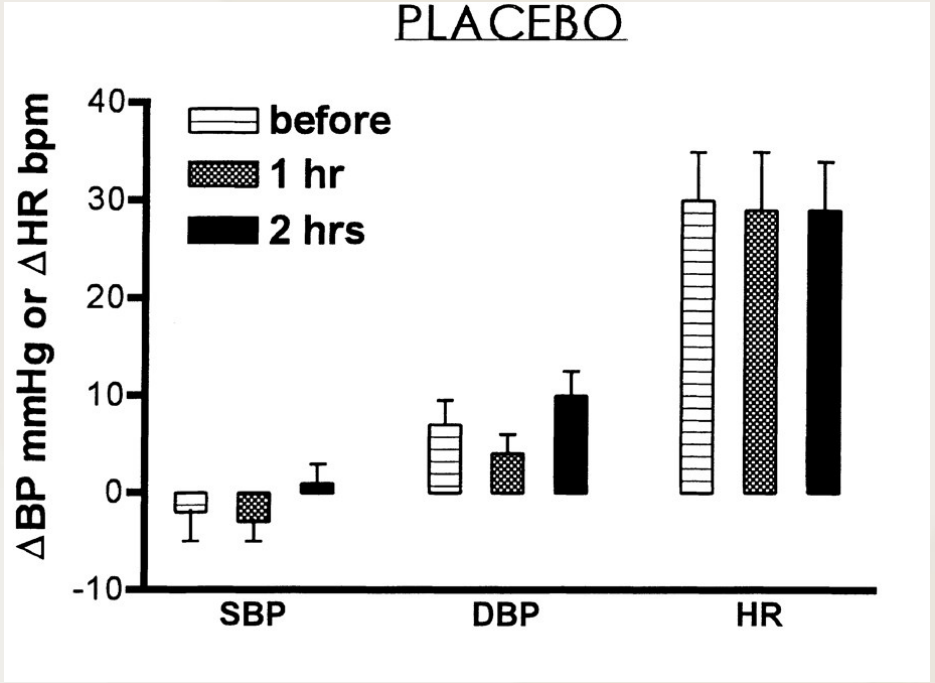


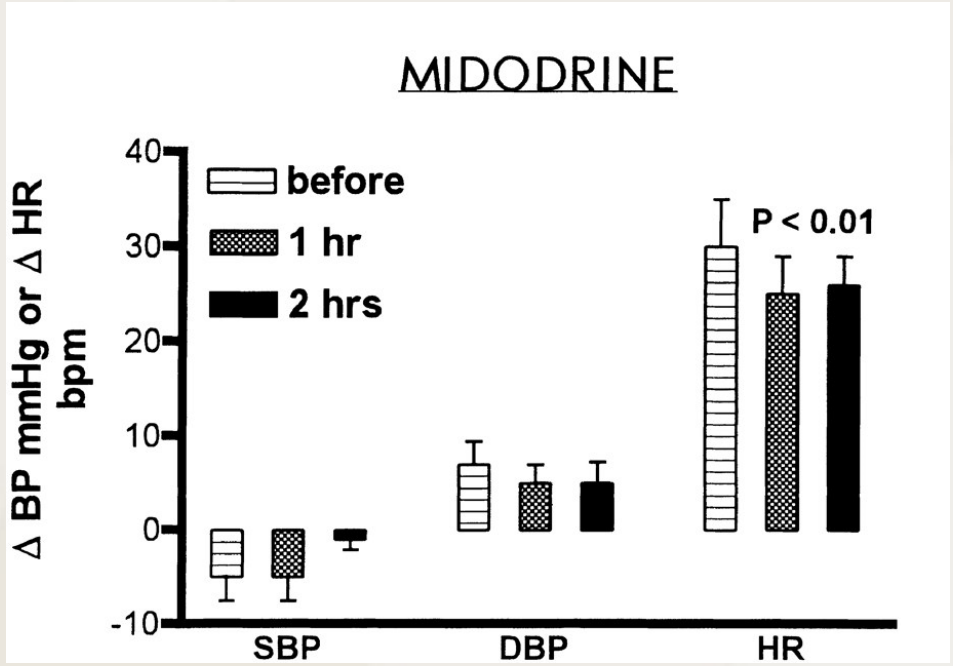
Brain Fog and Orthostatic Symptoms in POTS



Miranda-Hurtado, M., Hira, R., Bourne, K.M. *et al.* Stroke volume reduction impairs cerebrovascular regulation through $ETCO_2$ in postural orthostatic tachycardia syndrome. *Clin. Auton. Res.* **36**, 257–269 (2026). https://doi-org.proxy.library.vanderbilt.edu/10.1007/s10286-025-01181-1

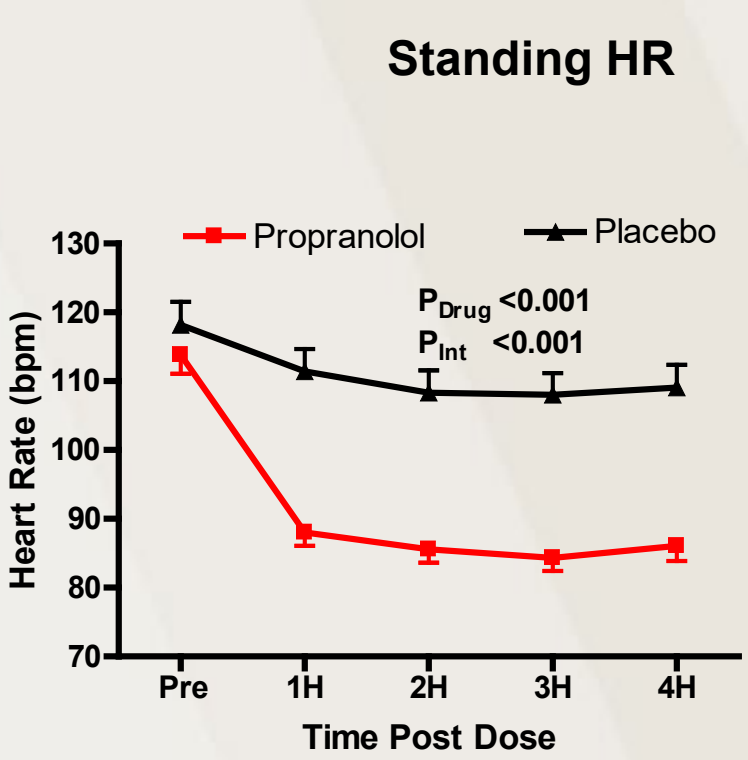
Midodrine Decreases Orthostatic Tachycardia

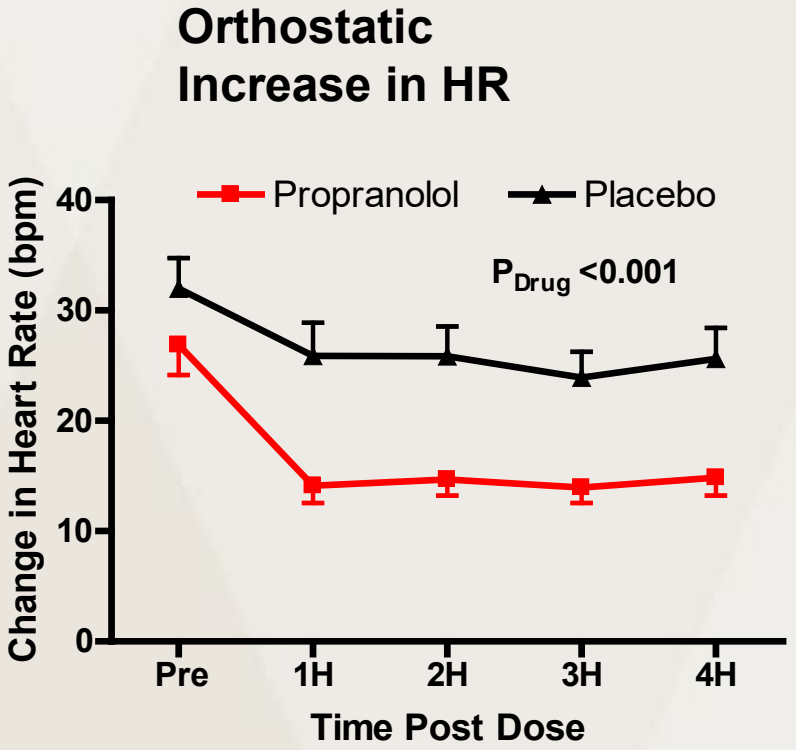




Jacob, G. et al. Circulation 1997;96:575-580

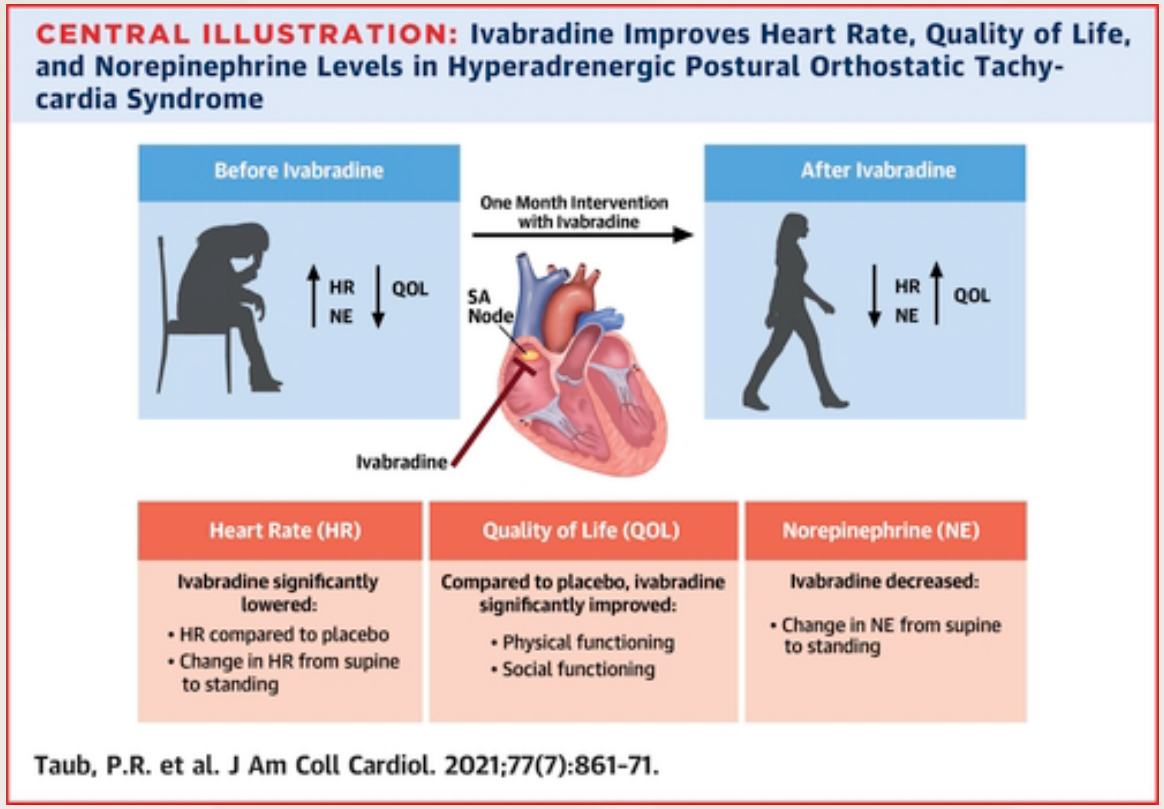
Propranolol 20mg lowers Orthostatic Tachycardia





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

Ivrabradine in POTS



Pam R. Taub et al. *JACC* 2021; 77:861-871.
22 Patients completed randomized crossover trial with significant reduction of supine (65 vs 78 placebo) and standing heart rate (80 vs 94 in placebo group) and improvement in QOL measures.

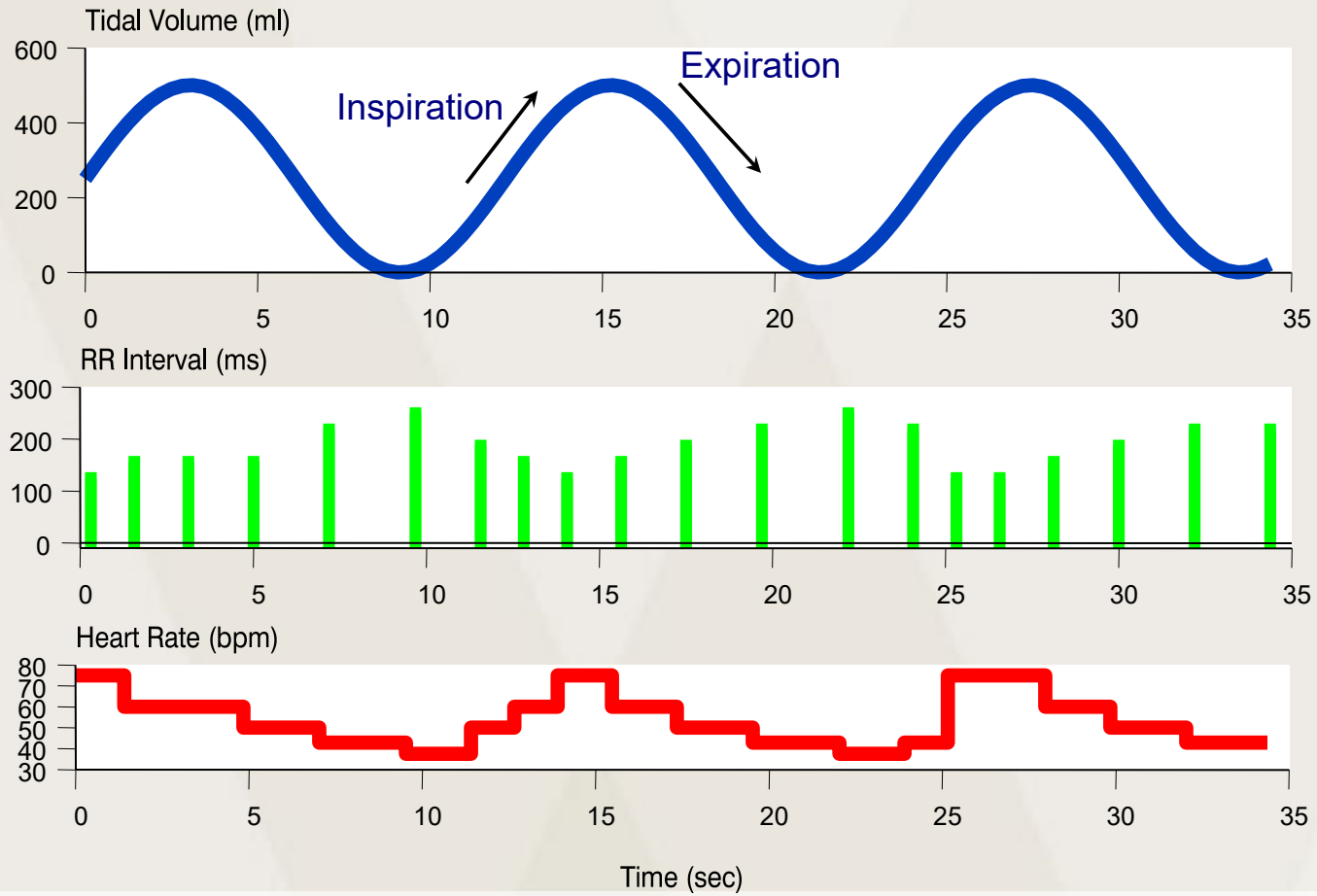
Take Home Points

- Autonomic causes of dizziness are postural.
- The simplest test is always the best.
- Careful editing of medication lists always important in evaluation of possible autonomic disorders.
- Any questions?

Acknowledgments

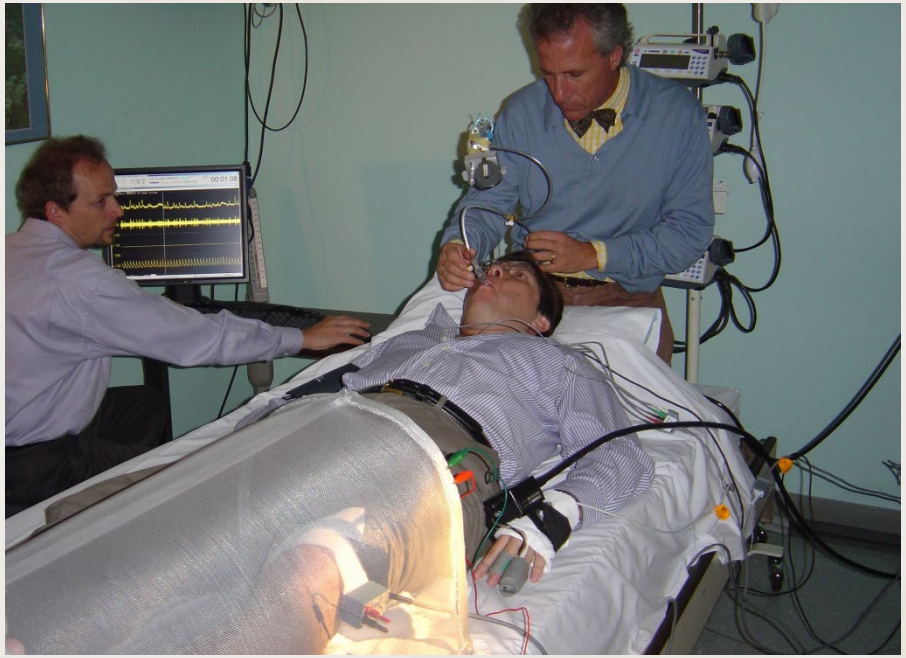
- Satish Raj
- Vidya Raj
- David Robertson
- Italo Biaggioni
- Cyndya Shibao
- Bonnie Black
- Emily Garland
- Sachin Paranjape
- Urvi Desai
- Hristelina Ilieva
- James Eyer
- Michelle Mauermann
- Pitcha Chompoopong
- Hasan Siddiqi

Respiratory Sinus Arhythmia



Valsalva Maneuver

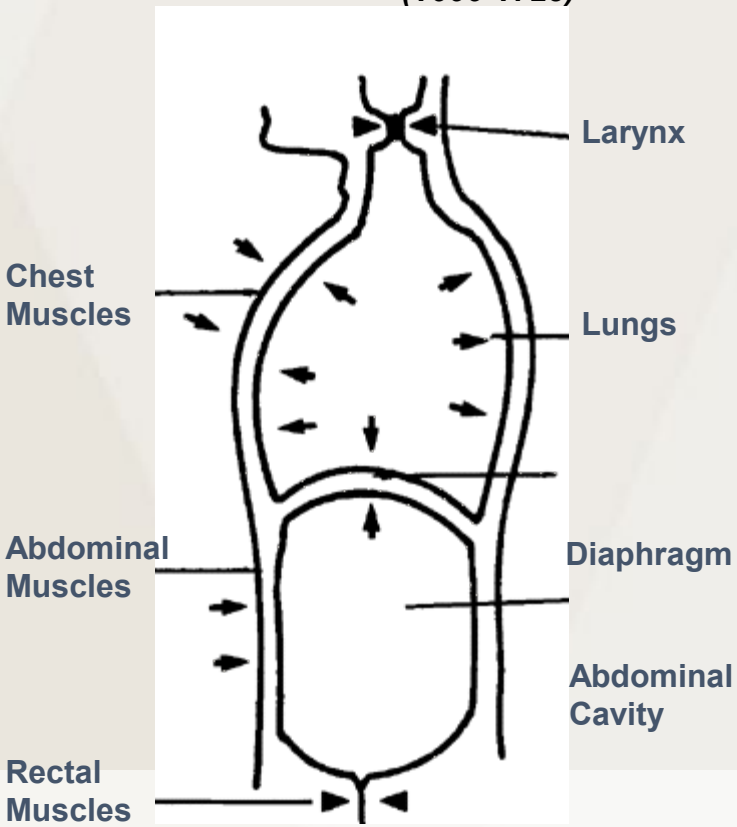
- Expelling all of the air from an individual's lungs, and straining against a closed airway.



S.P.Paranjape

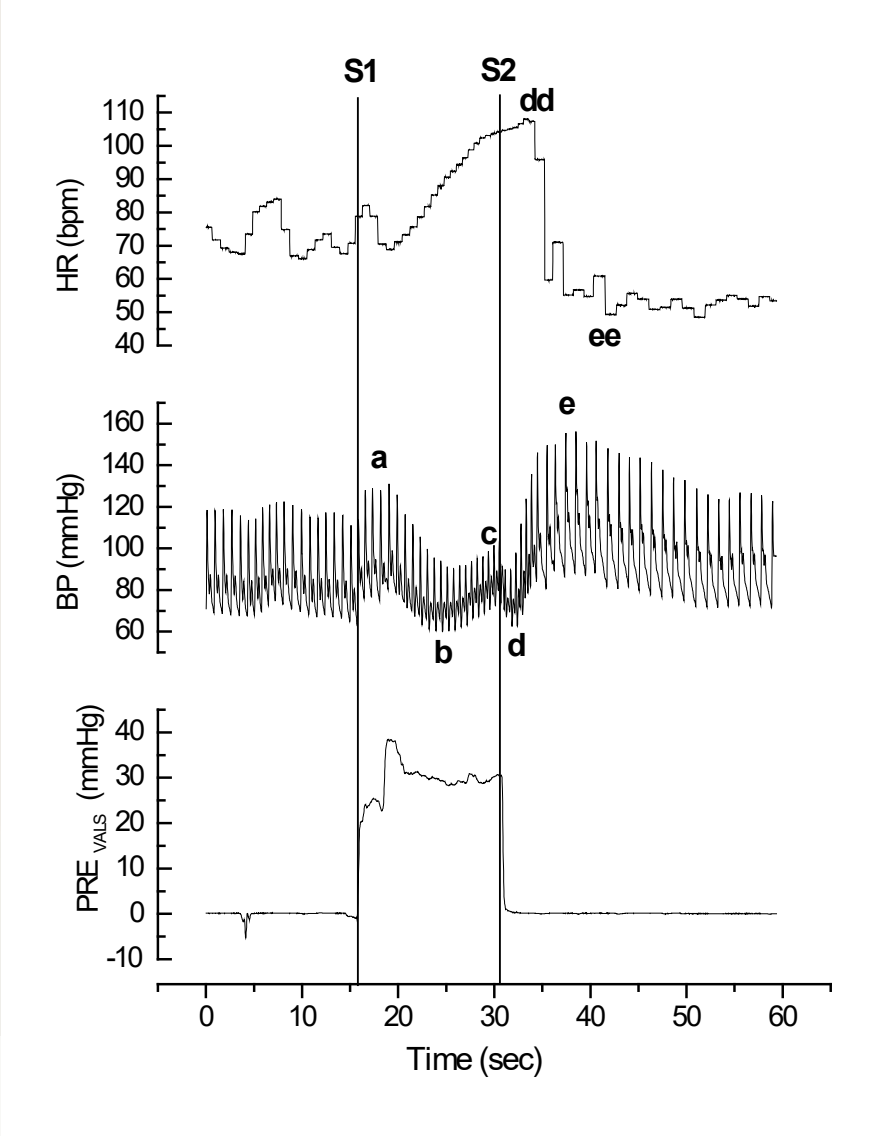
- Abrupt transient increase of intrathoracic & intraabdominal pressures, which will provoke changes in arterial blood pressure

Antonio María Valsalva
(1666-1723)



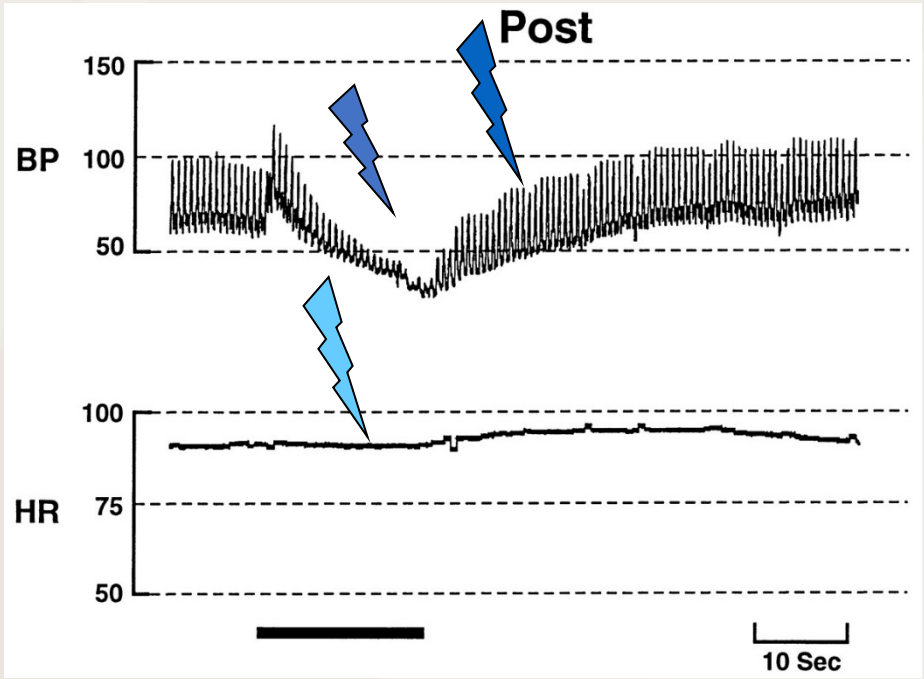
members.aol.com/wdparry/valsalva.htm

Valsava Response in Autonomic Dysfunction



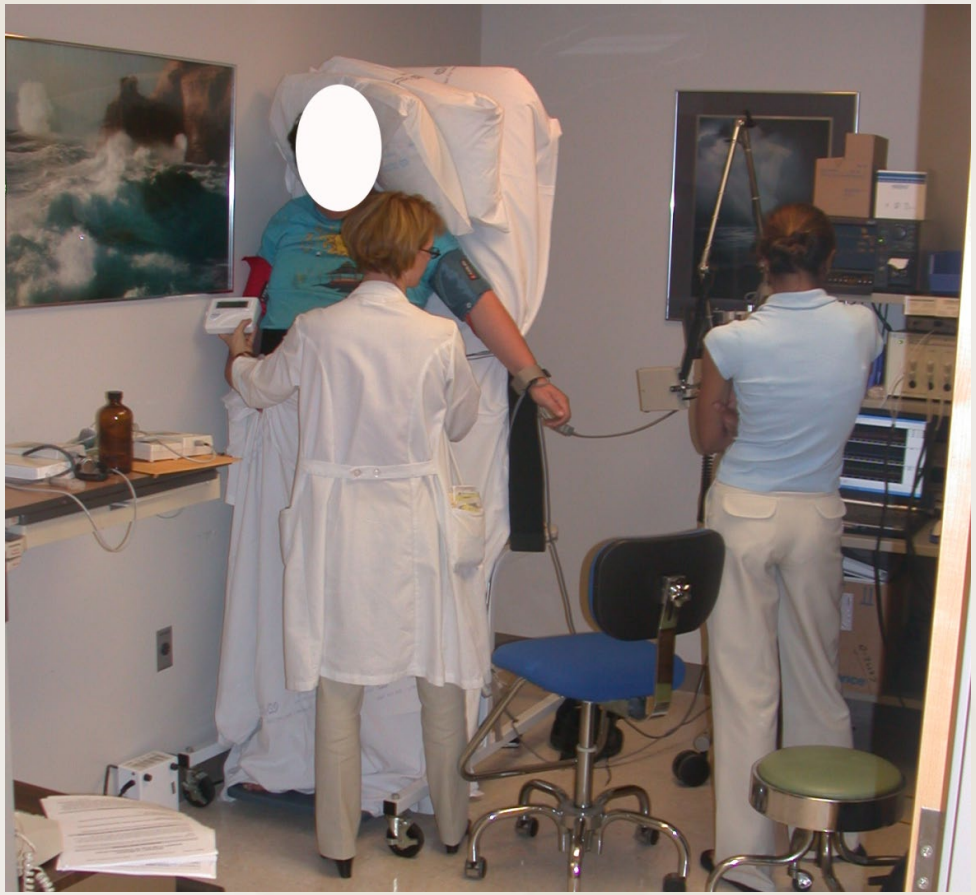
No BP recovery in late Phase II

No BP overshoot in Phase IV



No Heart Rate change

Tilt Table



Tilt Table Testing

- Most experts agree on an angle of 60-80º with a slow tilt over 10-20 seconds..
- Length of tilt testing hotly contested.
  - Some neurologists argue 10 minute tilt sufficient.
  - Cardiologists argue for 30-60 minutes of tilting
  - Depends on indication. To reproduce syncopal symptoms, a longer tilt may be necessary. For orthostatic hypotension/baroreflex evaluation, a shorter tilt is probably sufficient (or not needed).
- False positives: ~20-30% of normal volunteers will have syncope or feel pre-syncopal with prolonged tilting.

Vasovagal Syncope on Tilt