Autonomic Disorders and Management: It's All in the Numbers

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Disclosures

- **Consulting Fee (e.g., Advisory Board)**
  Alnylam, Astrazeneca, Argenx, CSL Behring, Alexion
- **Contracted Research (Principal Investigators must provide information, even if received by the institution)**
  CSL Behring
- **Speakers' Bureau**
  Astrazeneca, Alnylam

Learning Objectives

1. List common etiologies of autonomic disorders that are often encountered in neurology practice.

2. Identify typical tests used to classify autonomic disorders and patterns of common causes of autonomic dysfunction.

3. Recognize common treatments for autonomic disorders and common medications which can exacerbate orthostatic hypotension.

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 or Peripheral Localization

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

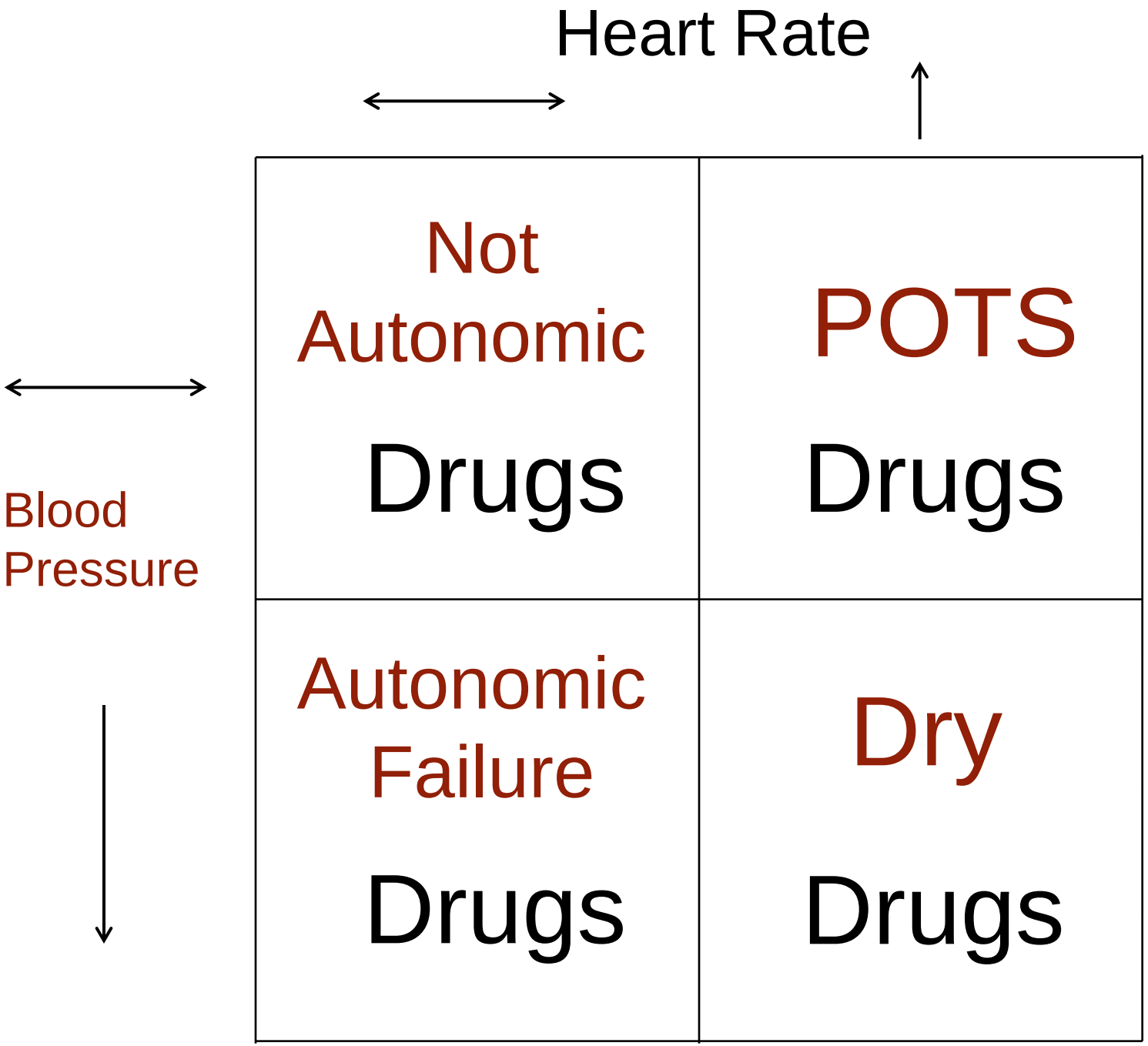
- Diabetic autonomic neuropathy
- Reflex sympathetic dystrophy
- Small fiber neuropathy associated with HIV
- Amyloidosis
- Chronic idiopathic anhidrosis
- Paraneoplastic autonomic neuropathy
- Acute Pandysautonomia
- Hereditary sensory autonomic neuropathy (Riley-Day Syndrome)
- Pure Autonomic Failure

Case

- 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??

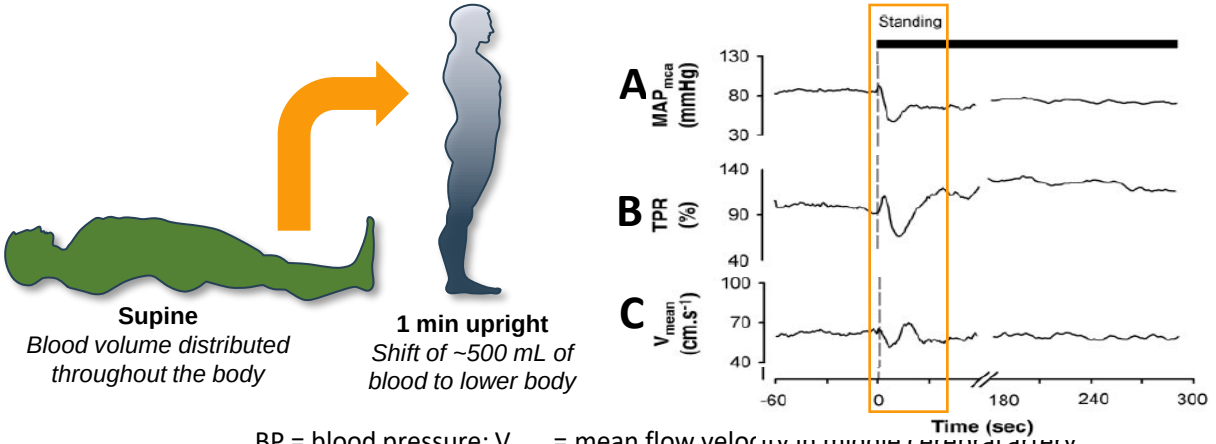
How to measure orthostatic vital signs

- Lie supine for at least 5 min, measure BP and HR
- Stand patient up (no sitting!!) and measure BP/HR (1 min)
- Keep patient standing minimum of 5 min and remeasure at 3 and 5 min)
- 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


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

Standing Involves Initial Reductions in BP

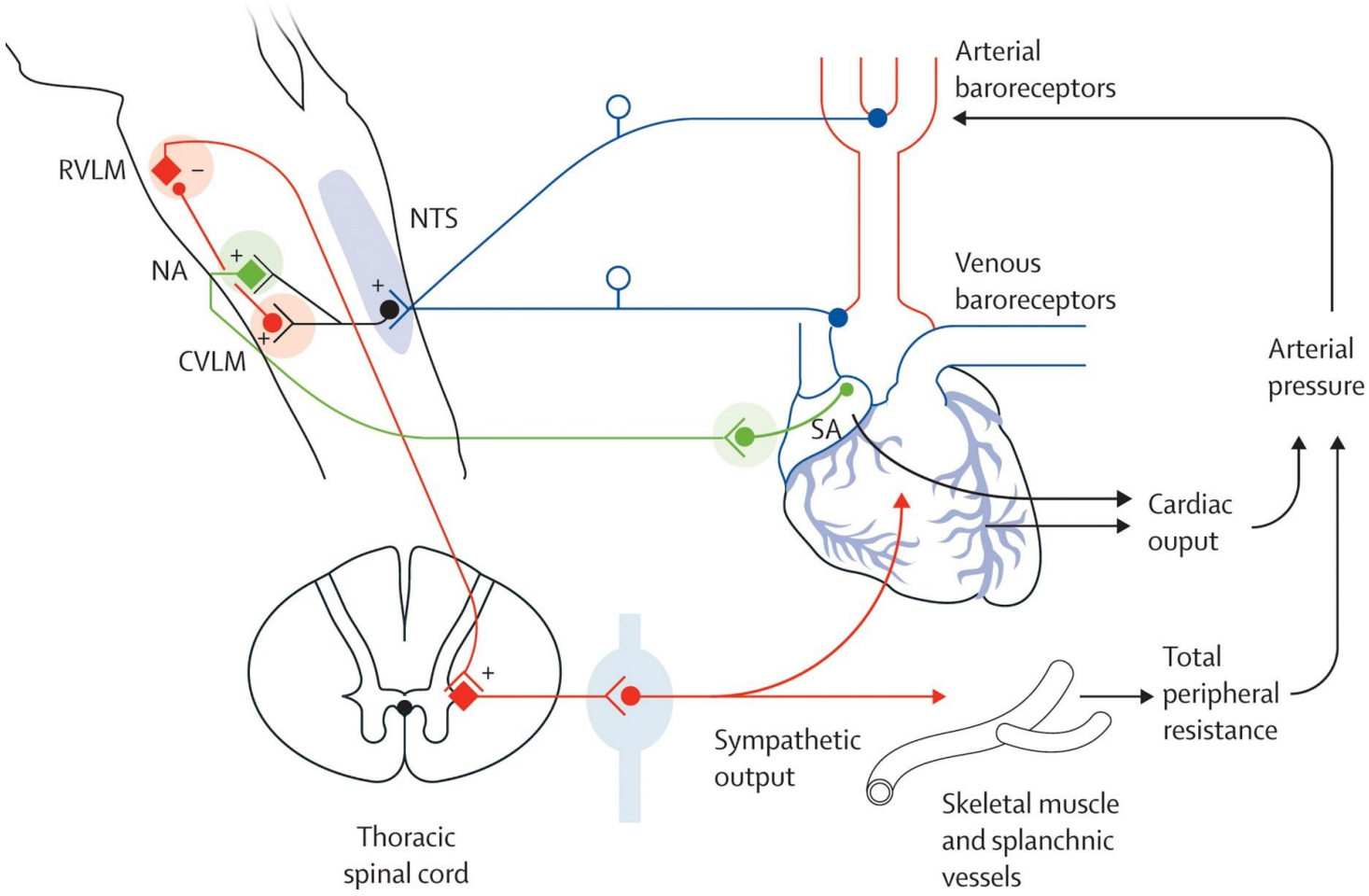
- Standing causes blood pooling in the lower part of the body[1,2]
- Physiologically, standing is followed by a rapid, transient reduction in mean arterial pressure (MAP) (A), total peripheral resistance (TPR) (B), and cerebral perfusion (C)[3]



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

Clinically Available Tests of Autonomic Function

- 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

- Diabetes
- Lambert Eaton Myasthenic Syndrome

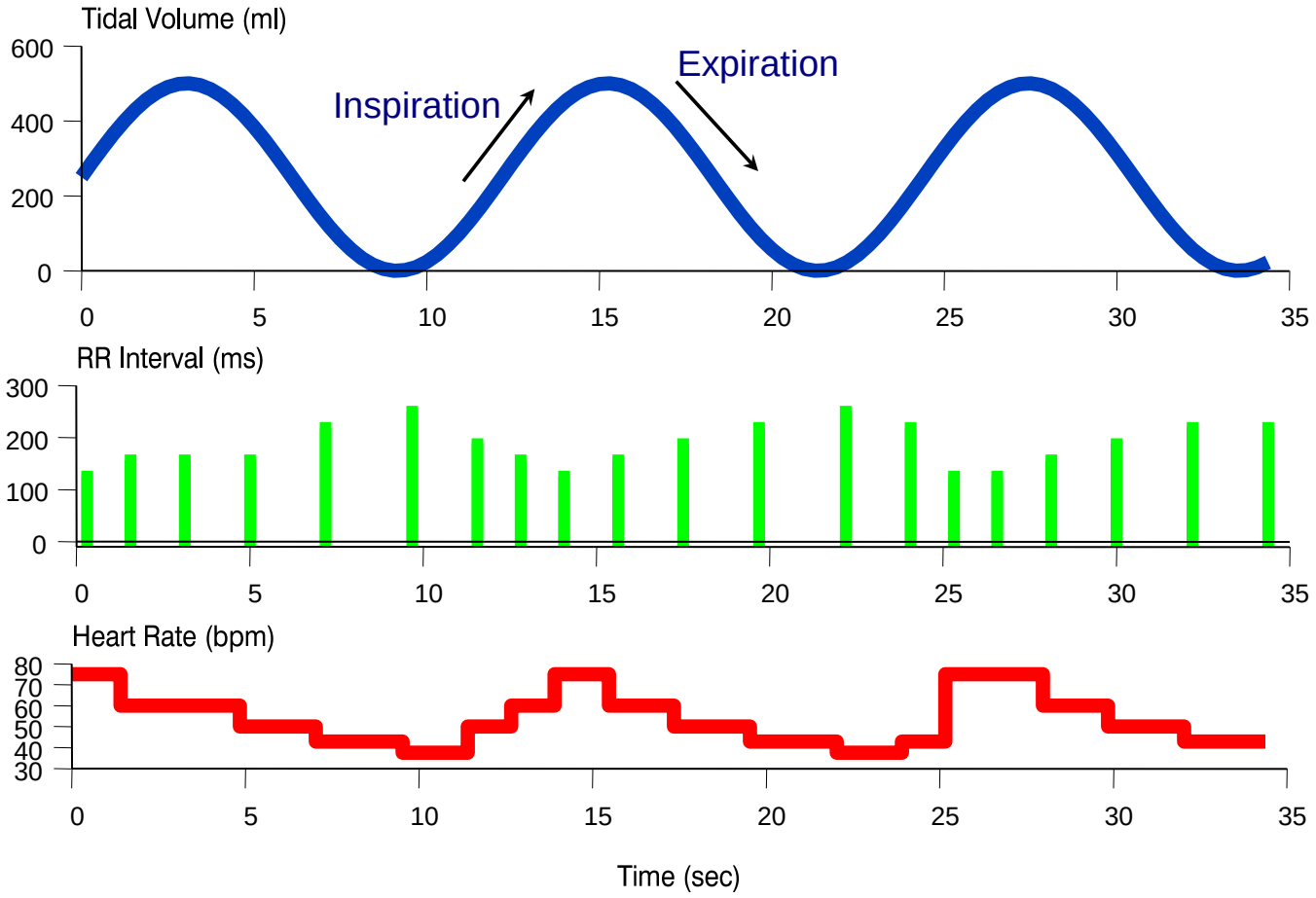
Parasympathetic And Sympathetic Dysfunction

- Multiple System Atrophy
- Autoimmune Autonomic Ganglionopathy
- Amyloidosis

Sympathetic Dysfunction

- Pure Autonomic Failure
- Parkinson's Disease

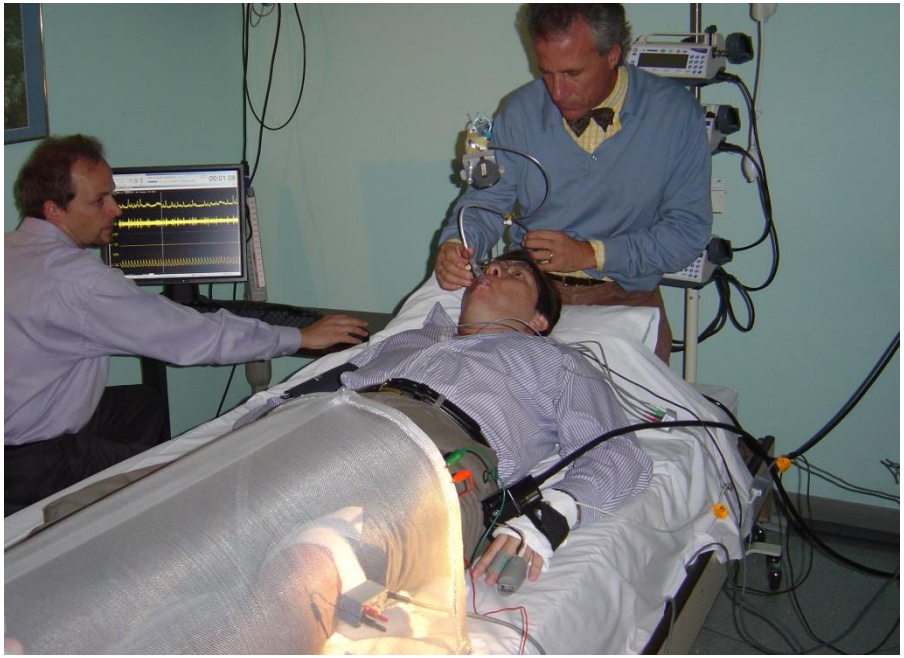
Respiratory Sinus Arhythmia



Diedrich

Valsalva Maneuver

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

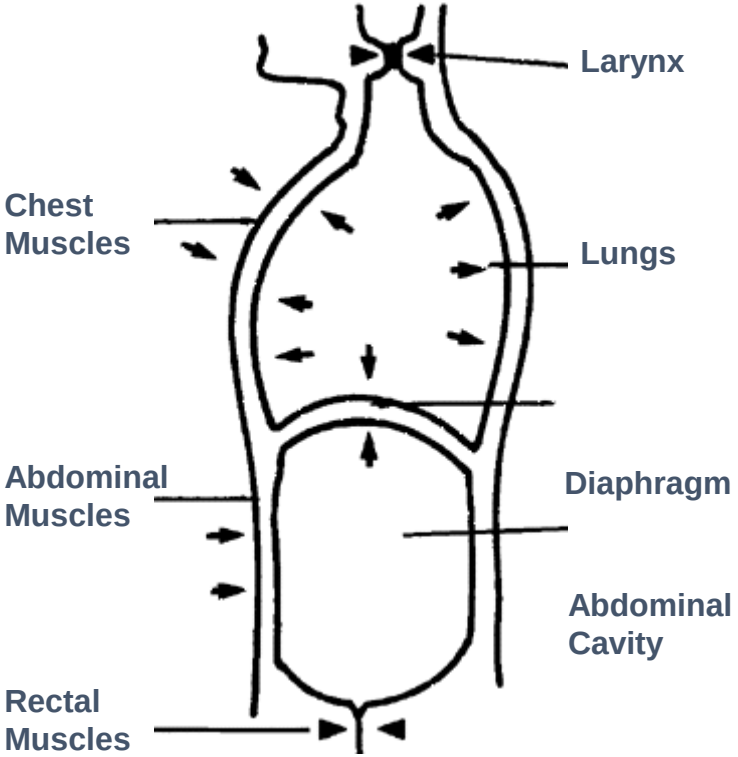


S.P.Paranjape

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

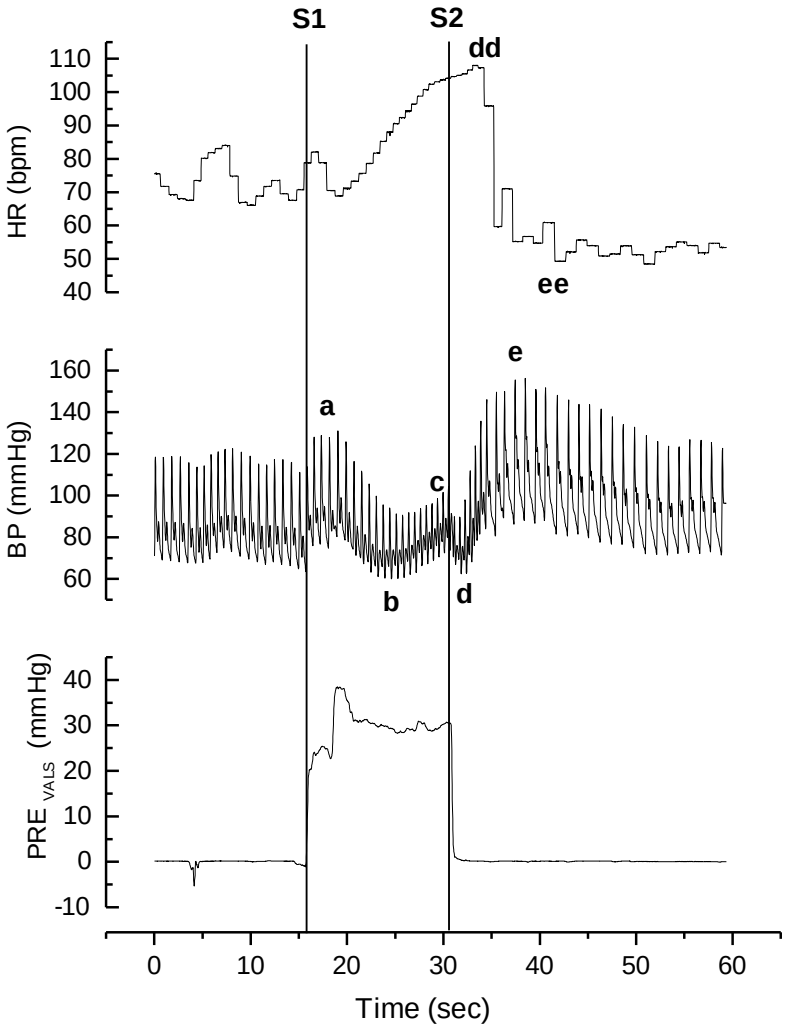
Antonio María Valsalva

(1666-1723)



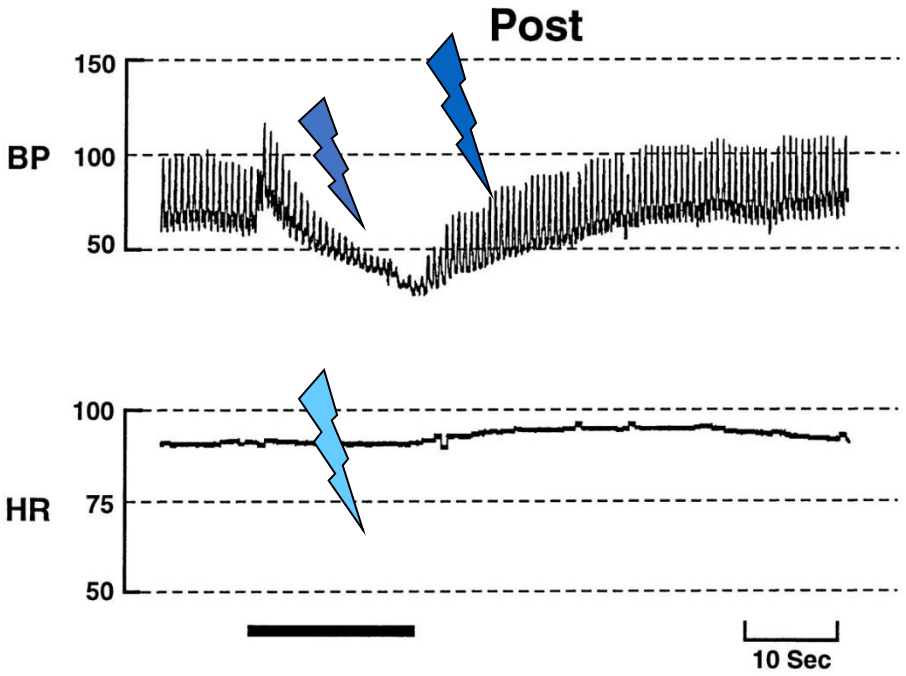
members.aol.com/wdparry/valsalva.htm

Valsava Response in Autonomic Dysfunction



No BP recovery in late Phase II

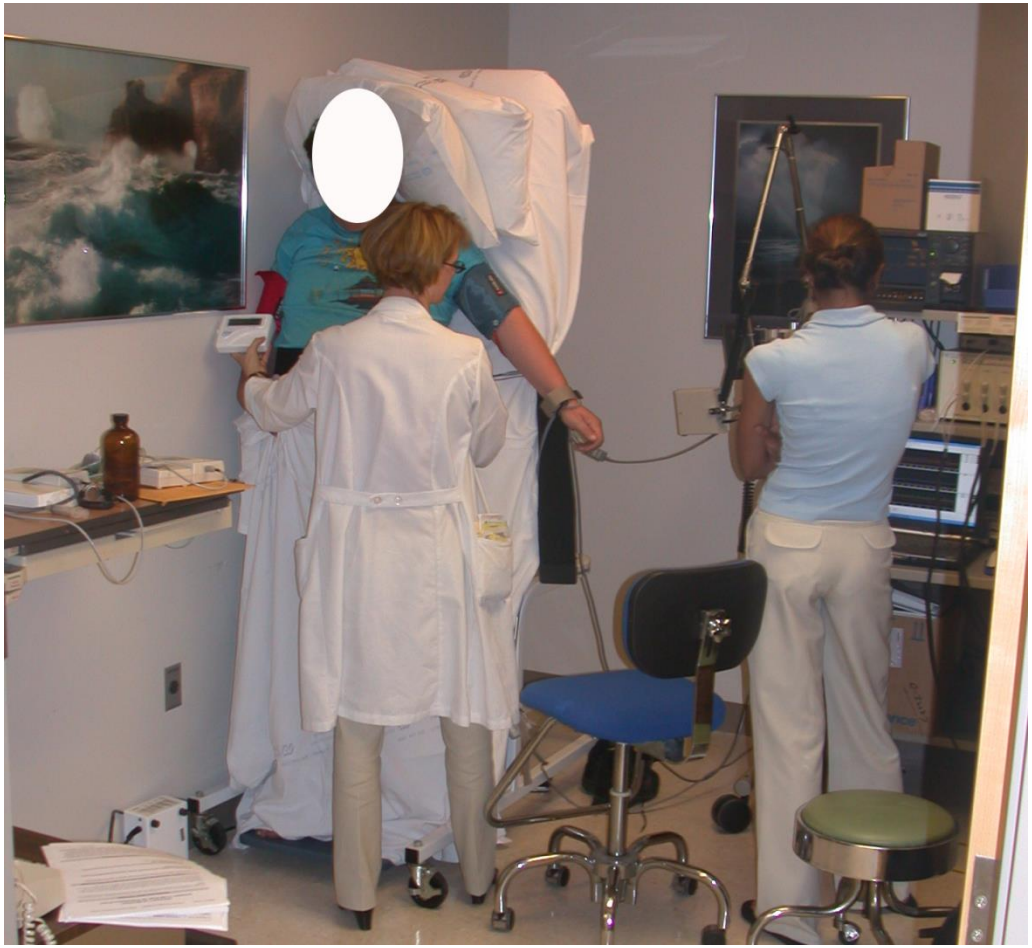
No BP overshoot in Phase IV



No Heart Rate change

Diedrich

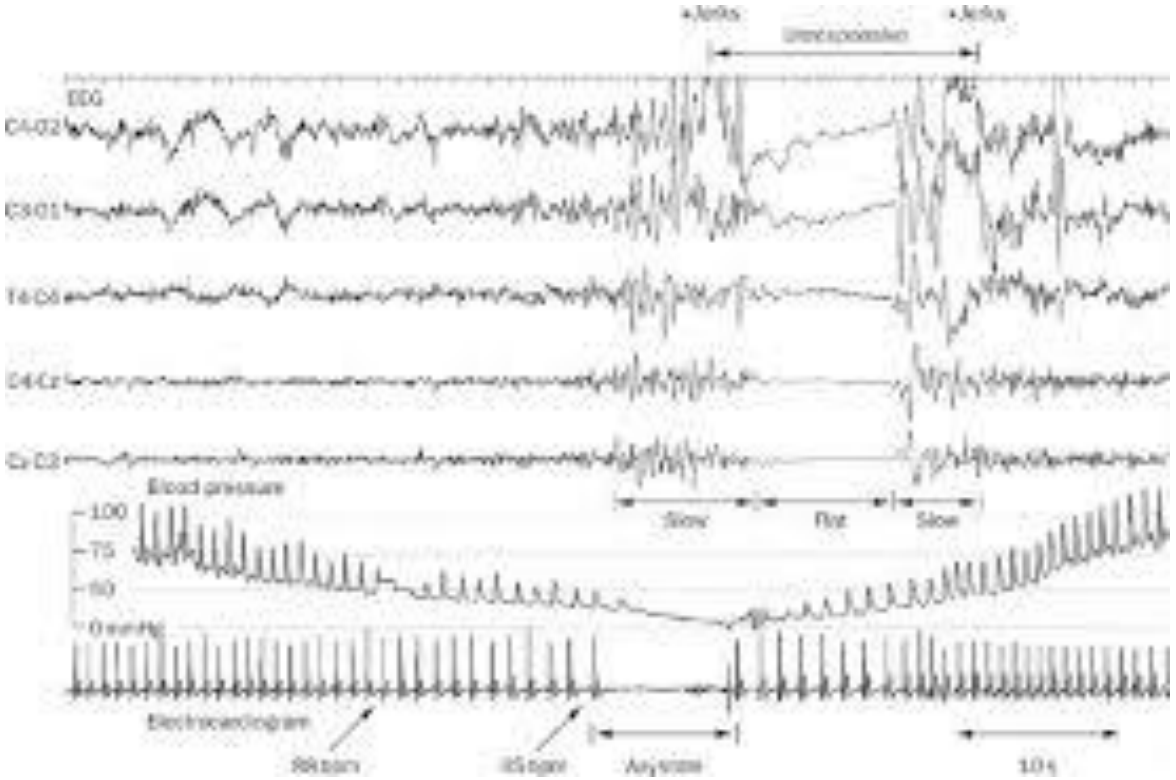
Tilt Table



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



Case: 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

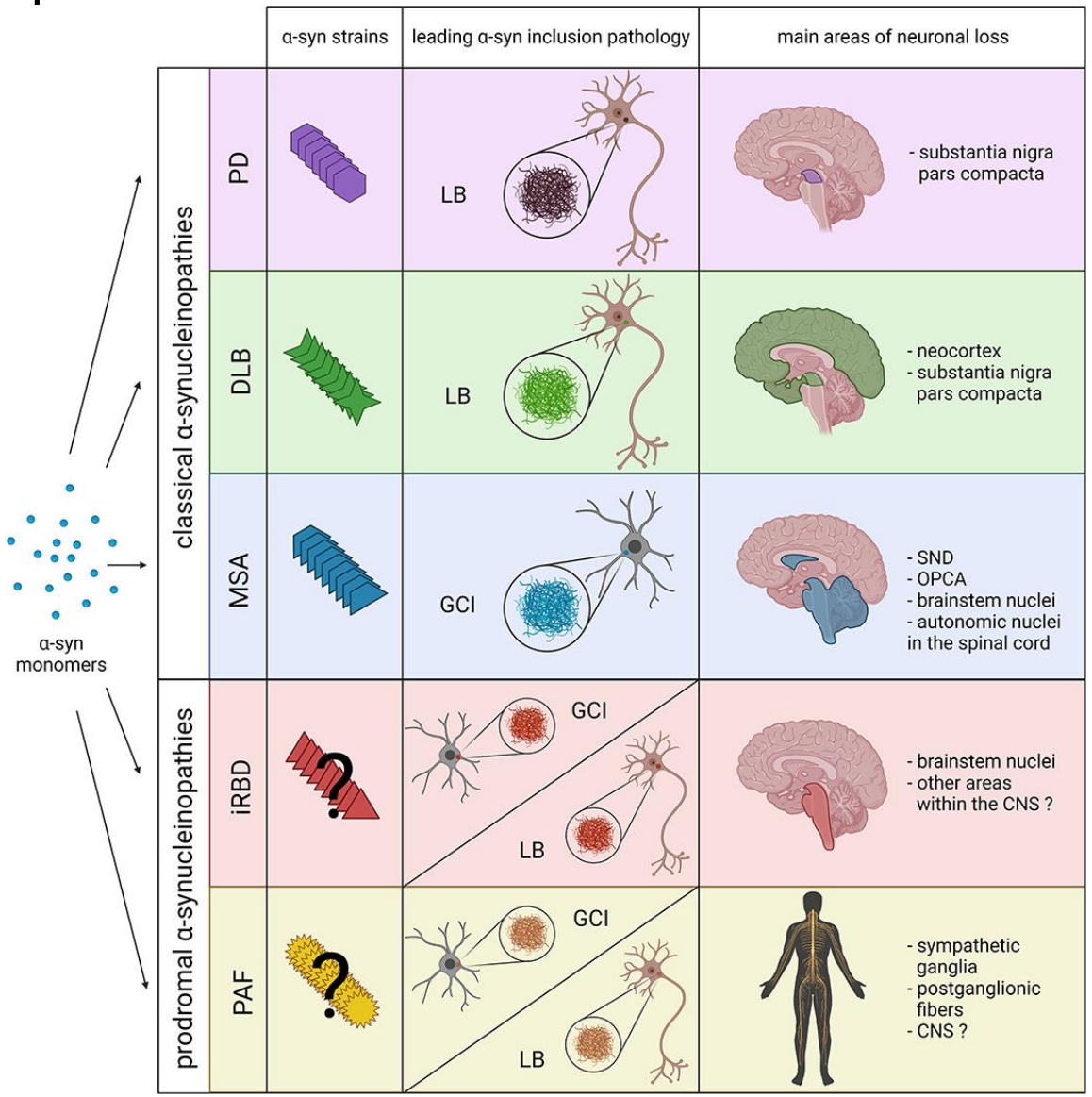
Valsalva Pressure Reached:	28 mmHg	
Baseline:	HR:65 bpm	BP:155 /72 mmHg
Phase 2E:	HR:70 bpm	BP:149 /74 mmHg
Phase 2L:	HR:70 bpm	BP:175 /79 mmHg
Phase 4:	HR:58 bpm	BP:173 /73 mmHg
Maximum HR (during or after Valsalva):	HR:70 bpm	
Minimum HR (after Valsalva):	HR:58 bpm	
Valsalva Ratio=	1.21	

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

Parkinson's Disease and Autonomic Dysfunction

- Between 30-50% of patients with PD have Orthostatic Hypotension (OH) but only 1/3 (16%) are symptomatic.
- Almost all patients with PD, DLB, and MSA develop gastrointestinal symptoms, usually constipation.
- Urinary dysfunction is mild to moderate in PD and DLB, affect up to 80% of patients.
- Sexual dysfunction is extremely common. For men, up to 79% of PD patients complain of erectile dysfunction.

(Palma and Kaufmann, 2018)

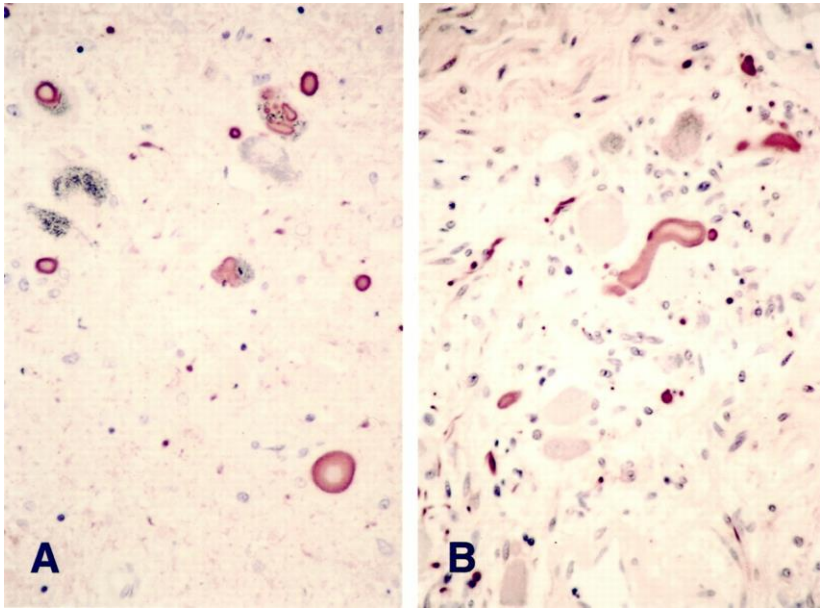
Multiple System Atrophy (MSA)

- Degenerative disorder by definition, affecting at least 3 systems (autonomic, basal ganglia (producing Parkinsonian symptoms), ataxia (cerebellum) in any order.
- Cerebral peduncles causing spasticity, brisk reflexes can occur
- Lower motor neuron (ALS) involvement can also occur.
- May present with ataxia (olivopontocerebellar atrophy)
- Prognosis is poor: Most patients die within seven years of diagnosis

MSA

- Catecholamines typically normal supine, but do not show rise with standing
- Typically significantly orthostatic
- Bladder involvement almost always
- Parasympathetic/Cholinergic symptoms common
- QSART typically normal
- Parkinsonism typically does not respond to levodopa

Pure Autonomic Failure



From Kaufmann et al.
Neurology 2001

- Alpha synuclein accumulates in autonomic nerves in the in the spinal cord and ganglia.
- Often begins as pure sympathetic failure.
- Diagnosis of exclusion
- Risk of developing Parkinson's or Lewy body dementia

Approach to Treat Orthostatic Hypotension

Step 1: Eliminate Iatrogenic Causes

Anti-hypertensives during the day

Diuretics

Alpha-blockers for BPH

Heavy Meals

Approach to Treat Orthostatic Hypotension

Step 2: Nonpharmacological Measures

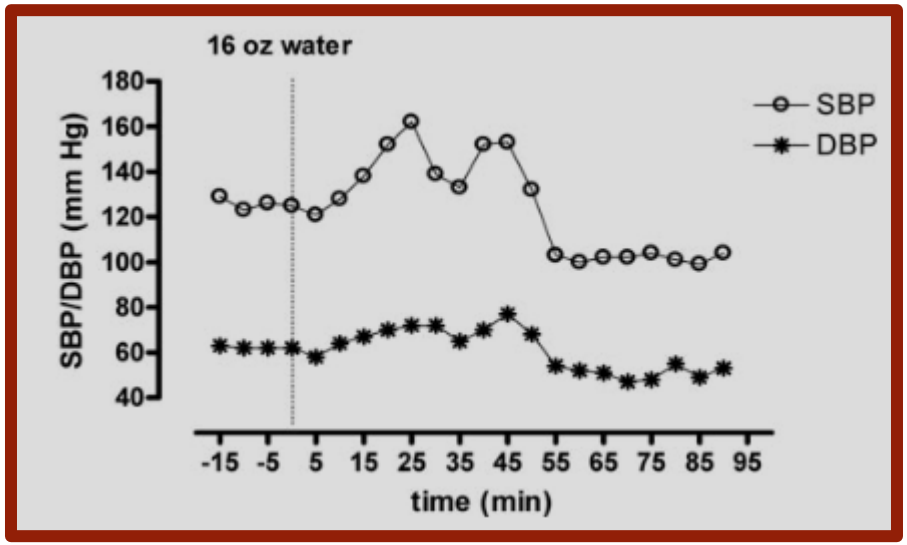
Increase Fluid Intake, 16 oz. tap water

Avoid standing quickly or standing motionless

Abdominal binder

Avoid supine position during the daytime

Hemodynamic Effects of 16oz of Water



Shibao HTN 2005

Approach to Treat Orthostatic Hypotension

Step 3: Improve Central Volume

Treat anemia even if mild

Fludrocortisone 0.1-0.3mg every day with increased salt intake

Add NaCl tablets 1 gram with meals if necessary

Approach to Treat Orthostatic Hypotension

Step 4: Short acting pressor agents PRN

Midodrine 2.5-10mg TID CC

Pyridostigmine 30-60mg TID CC

Droxidopa 100-600 TID CC

Other Atypical Pressors

- Atomoxetine :10-36 mg bid in am and noon
- Yohimbine 5.4 mg compounded
- Octreotide 12-50 mg SQ

Supine Hypertension

- Probably not as great of an issue in ER but common to most patients with synucleinopathies
- Need to use short acting antihypertensives at night to decrease blood pressure (failure to control will worsen OH during the day)
  - 10 mg nifedipine
  - 25-50 mg losartan

Most Common Peripheral Neuropathies affecting the Autonomic System

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

Autoimmune Autonomic Ganglionopathy

- First associated with Acetylcholine Receptor Antibodies to α3 subunit of the nicotinic ganglionic receptor in 2000 by Vernino and colleagues.
- Sensitivity of the antibody was about 50% in the patients felt to be autoimmune due to presence of malignancy or previous illness prior to onset of autonomic neuropathy
- Association of severity of symptoms with antibody titer is well-described with higher titers associated with pupillary dysfunction.

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

AAG Trial of IVIG

- Randomized placebo controlled study of 5 AAG patients with positive titer, enrolled by 3 centers.
- Did not meet study endpoint of changing CASS score
- The treated group had a mean systolic blood pressure improvement in orthostatic hypotension of 33+/-29 mmHg compared to the placebo treated group that had a 5.5+/-4.5 mmHg worsening in orthostatic hypotension.

Case 2

- 67 year old pastor with dizziness and constipation for 2 years. Dizziness improves on lying down.
- His voice has changed over time.
- He has worsened memory.
- He does not tolerate the heat.
- He has increased urinary frequency.
- He is noted to have decreased facial movement, increased muscle tone and ridgidity without tremor.

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, mod 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
- Lost 30 pounds, had CABG. Persistent edema on exam
- 2019 genetic testing performed which showed T60A TTR mutation
- Referred to cardiology, had 40-50% EF, noted to have daily diarrhea on note.
- Referred for treatment with patisiran.

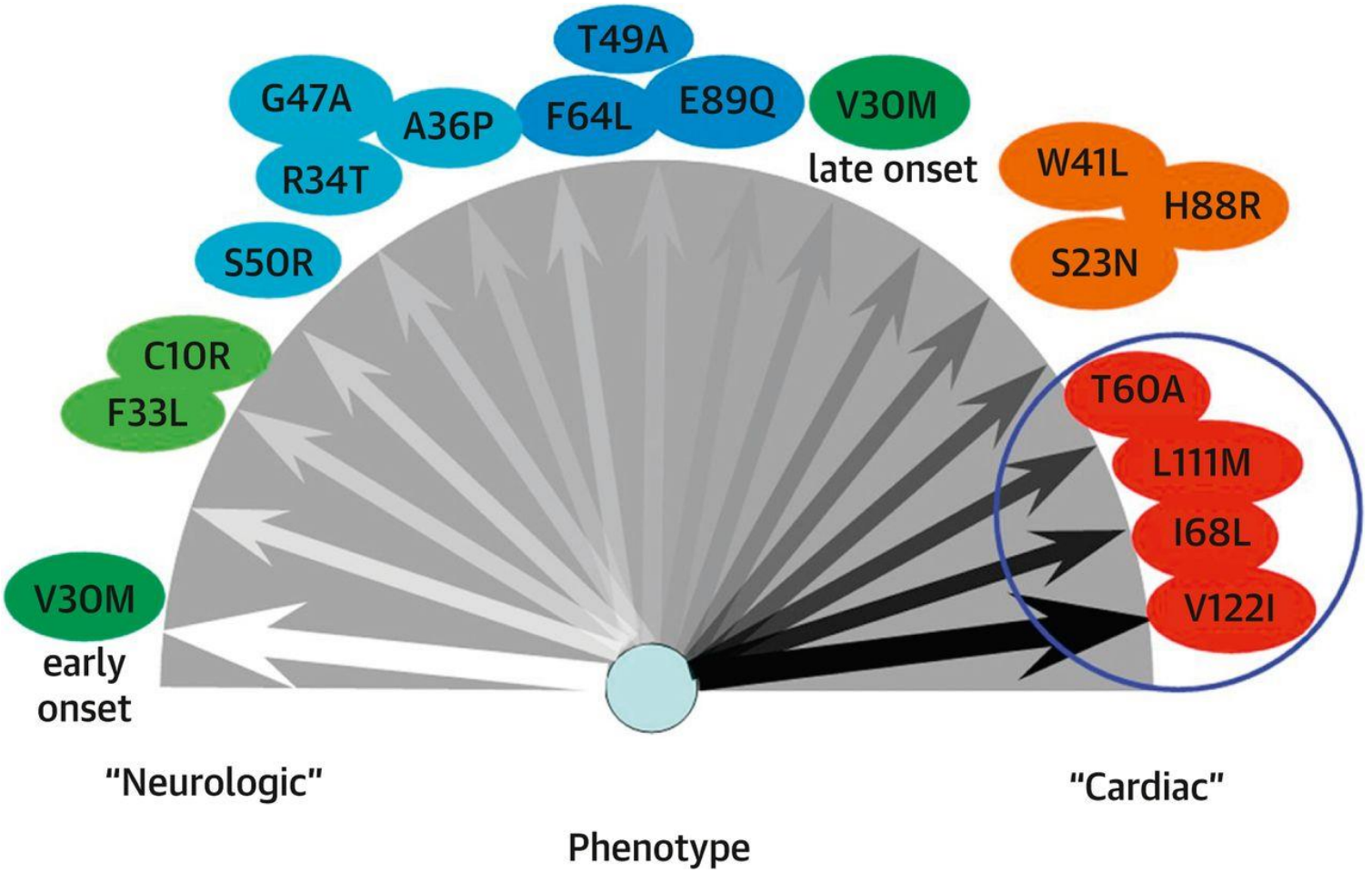
Neuro examination

- 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
- Reflexes absent.

Case 2 Continued

- 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. Genetic mutation was T60A.
- Patient sisters subsequently found to have mutation.
- Patient had episode of bradycardia requiring pacemaker.

Familial Amyloidosis



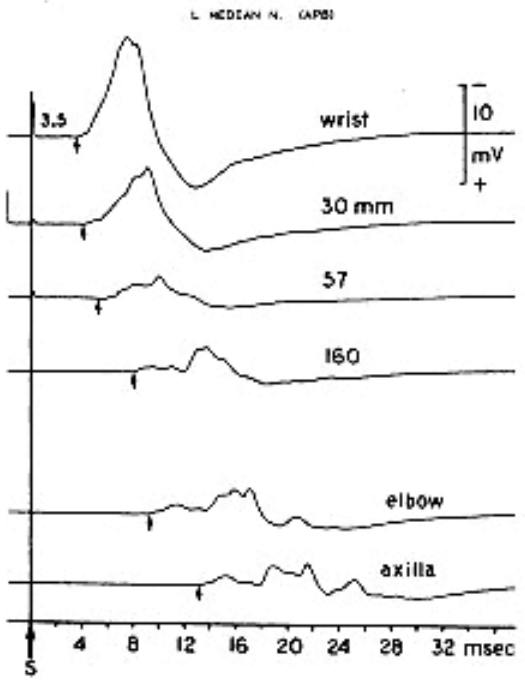
From: Semigran MJ. JACC 2016.

Neuropathy of Amyloidosis

- Autonomic failure common and often appears early. Secretory diarrhea common feature in amyloidosis compared to other AN.
- Neuropathy can be small fiber, large fiber, or appear like CIDP with CV slowing as in our case.
- Carpal tunnel syndrome in almost all patients predates neuropathy involvement by decades.

Role of NCS/EMG

- Typically abnormal in mutations other than early V30M
- May also show conduction block and temporal dispersion.
- Affect both sensory and motor fibers
- Useful as screening tool.



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.

AIDP and Autonomic Dysfunction

- Autonomic dysfunction is more common in AIDP compared to other subtypes such as AMAN, occurs in up to 10-50% of patients.
- Typically hypersympathetic activity:
  - Tachycardia
  - Elevated blood pressures which plunge with typical BP treatment/fluctuating BP
  - Occasionally pyrexia

Asahina M et al. Acta Neurologica Scandinavica. 2002

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

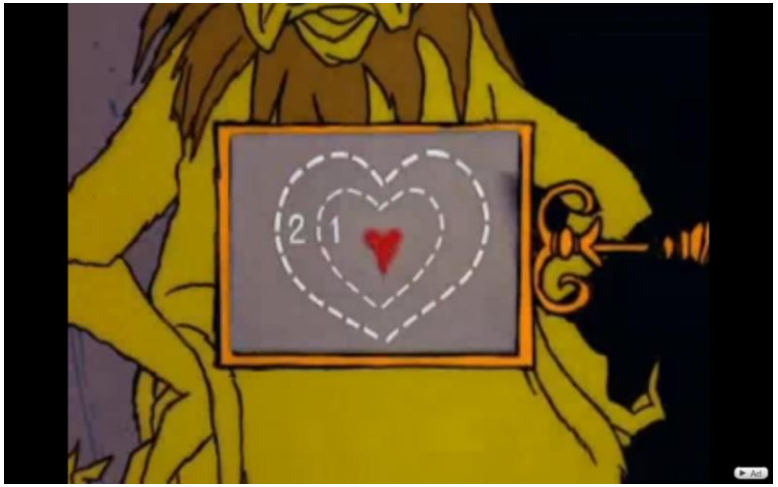
- 134 cases reported associated with COVID infection (few with vaccine)
- Most reviews of COVID patients showed orthostatic intolerance without meeting hr criteria for POTS (Shouman et al. 2021).
- Raised again ? Re autoimmunity in POTS.
- Current study looking at efgartigimod in POTS after COVID infection.

POTS: Treatment Approaches

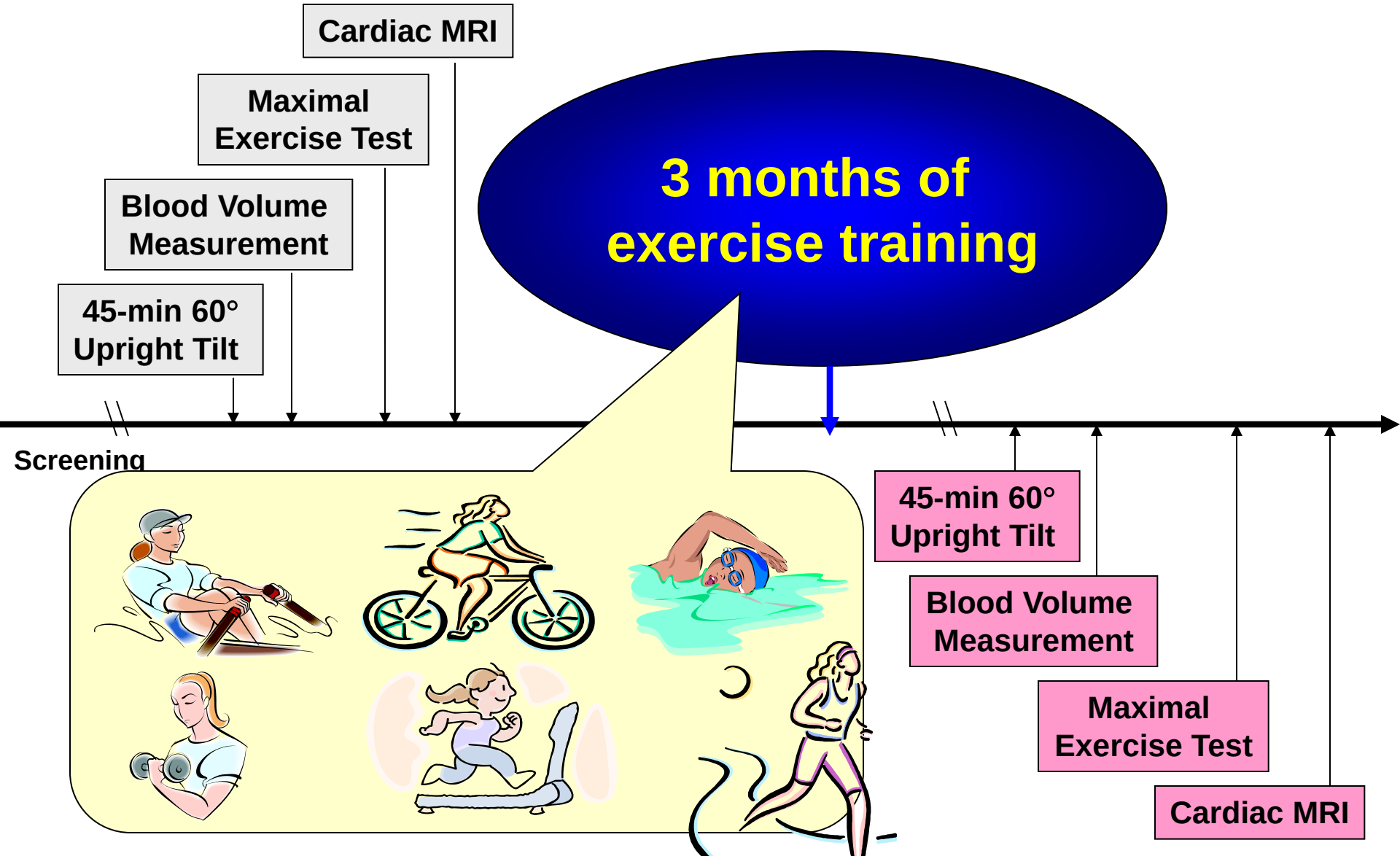
- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - IV Saline
  - Acute DDAVP-H_2O
- Hemodynamic Agents
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Clonidine/α-Methyldopa
  - NET Inhibitors…can be evil
- Exercise

Exercise Training

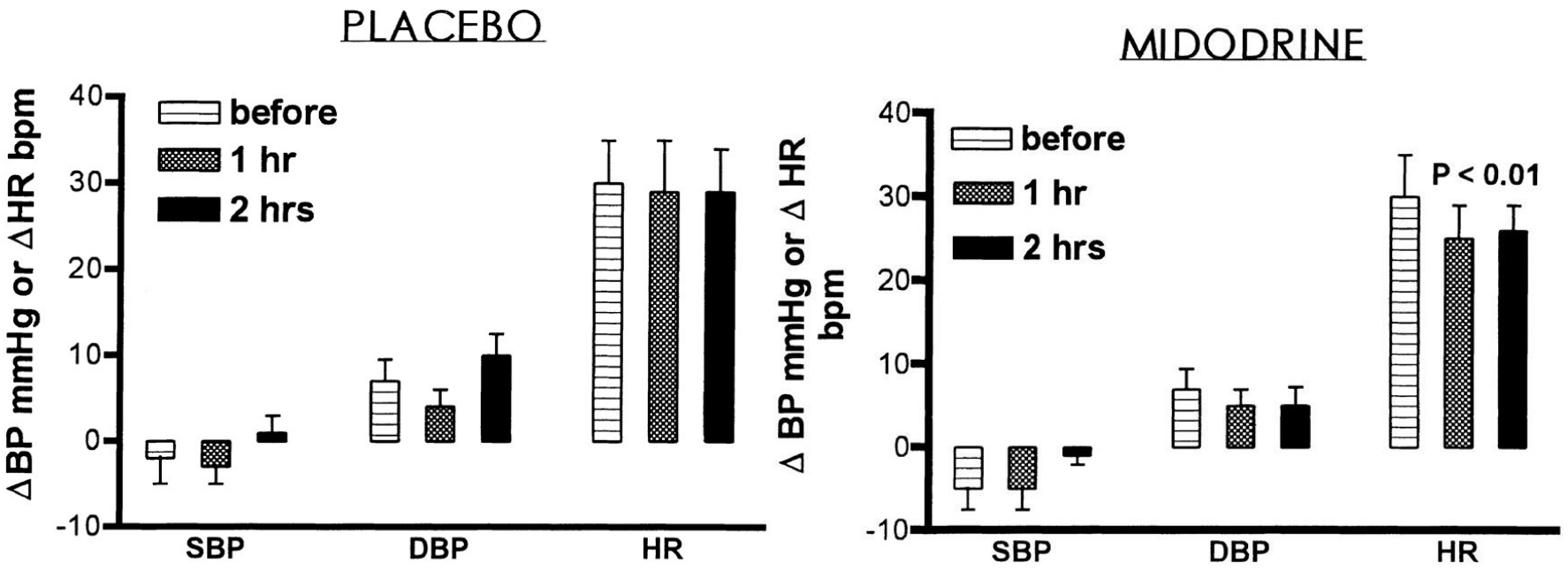
- Deconditioning leads to similar physiologic findings:
  - Increased orthostatic tachycardia
  - Impaired left ventricular filling and decreased stroke volume (Grinch heart)



Exercise Study in POTS - Design

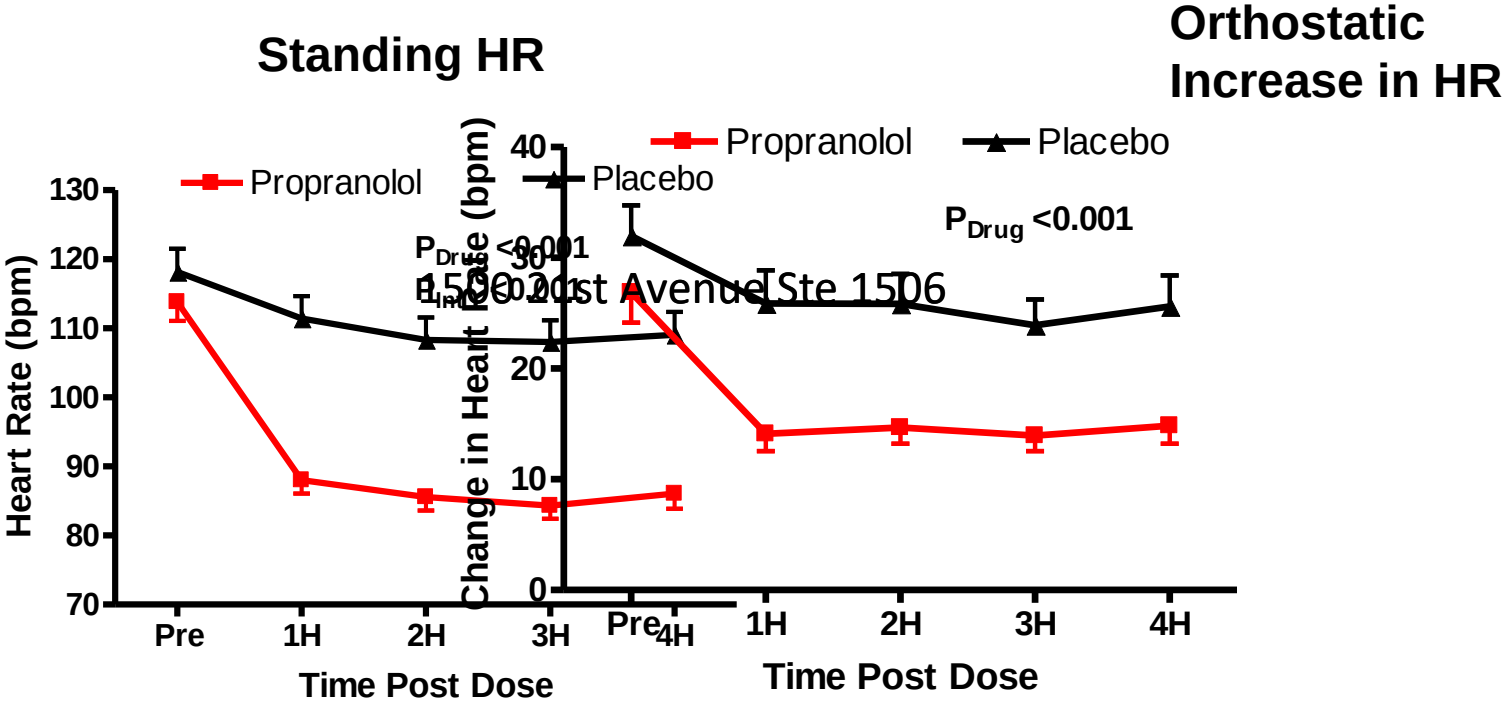


Midodrine Decreases Orthostatic Tachycardia

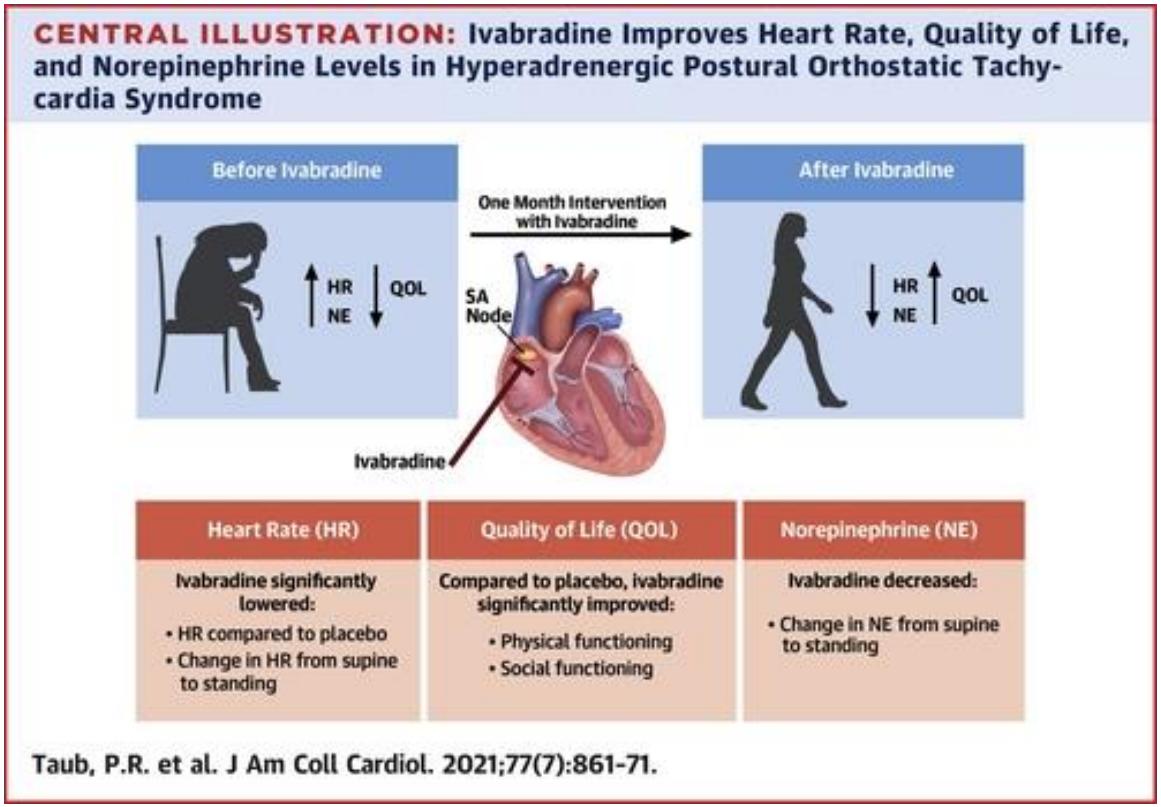


Jacob, G. et al. Circulation 1997;96:575-580

Propranolol 20mg lowers Orthostatic Tachycardia



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



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.

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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

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- Emily Garland
- Sachin Paranjape

Common Tests of Sympathetic Function

- Continuous blood pressure analysis of Valsalva maneuver
- Fall in blood pressure upon standing or head up tilt (60 to 75 degrees)
- Sustained hand grip
- Cold Pressor
- Plasma catecholamines
- QSART (cholinergic fibers only)

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

Vasovagal Syncope on Tilt