Remaining Upright: Approach to Orthostatic Intolerance

Bateman Horne Center
University of Utah
April 6, 2016

Melissa Cortez, DO
Assistant Professor
Director, Autonomic Physiology Laboratory
Department of Neurology
University of Utah

Disclosures

- None

Objectives

- Definitions and overview nomenclature, anatomy of autonomic function
- Introduction to clinical laboratory testing and role in diagnosis
- Case illustrations → diagnosis and management
  - Chronic Fatigue with orthostatic intolerance
  - POTS
  - POTS mimics
- Conclusions/Take Home points

Objectives

- Definitions and overview nomenclature, anatomy of autonomic function
- Introduction to clinical laboratory testing and role in diagnosis
- Case illustrations → diagnosis and management
  - Chronic Fatigue with orthostatic intolerance
  - POTS
  - POTS mimics
- Conclusions/Take Home points

“Milieu intérieur"

"The stability of the **internal environment** is the condition for the free and independent life.“

- Claude Bernard (1813 – 1878),

French physiologist

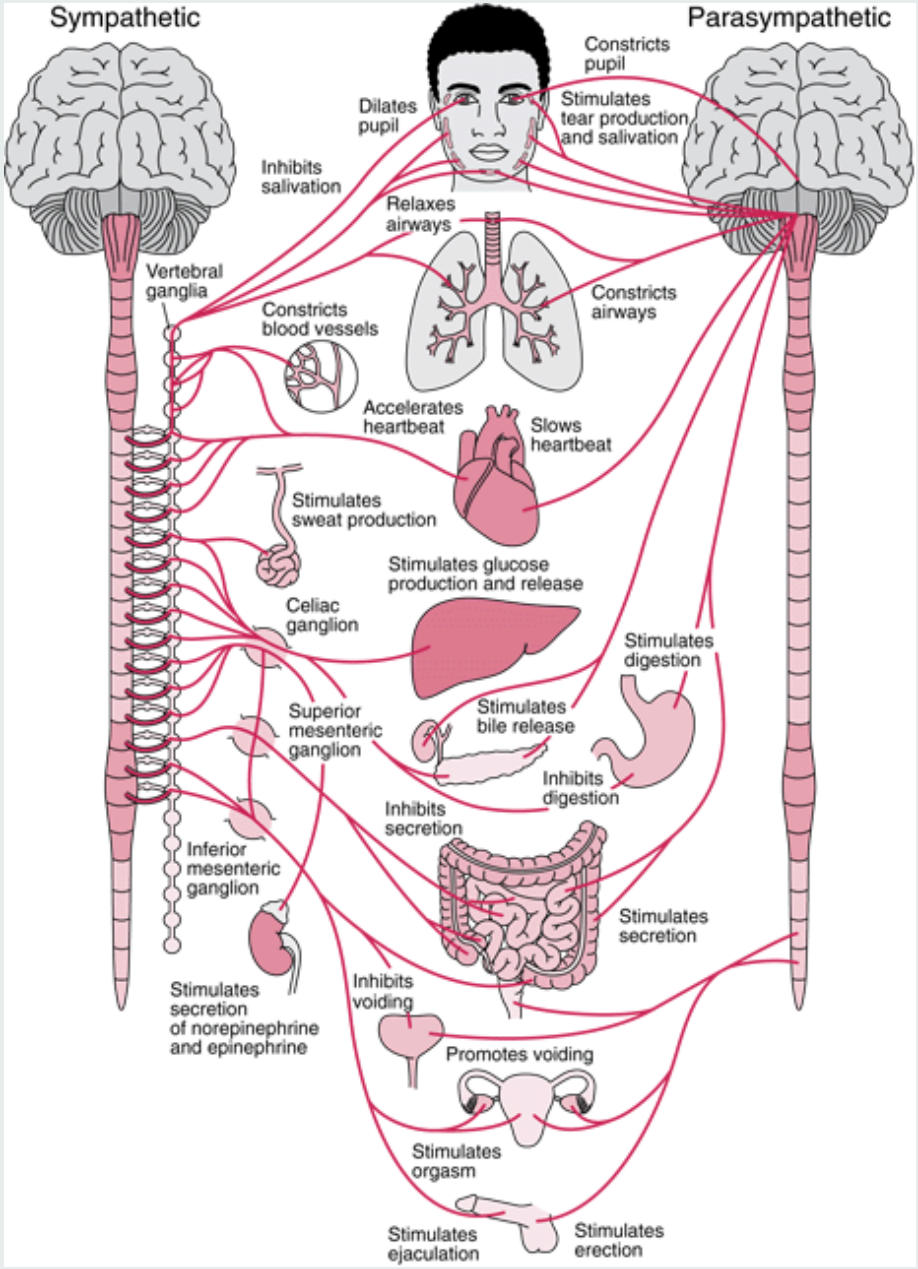
“Homeostasis”

- Walter Cannon, *The Wisdom of the Body* (1932),

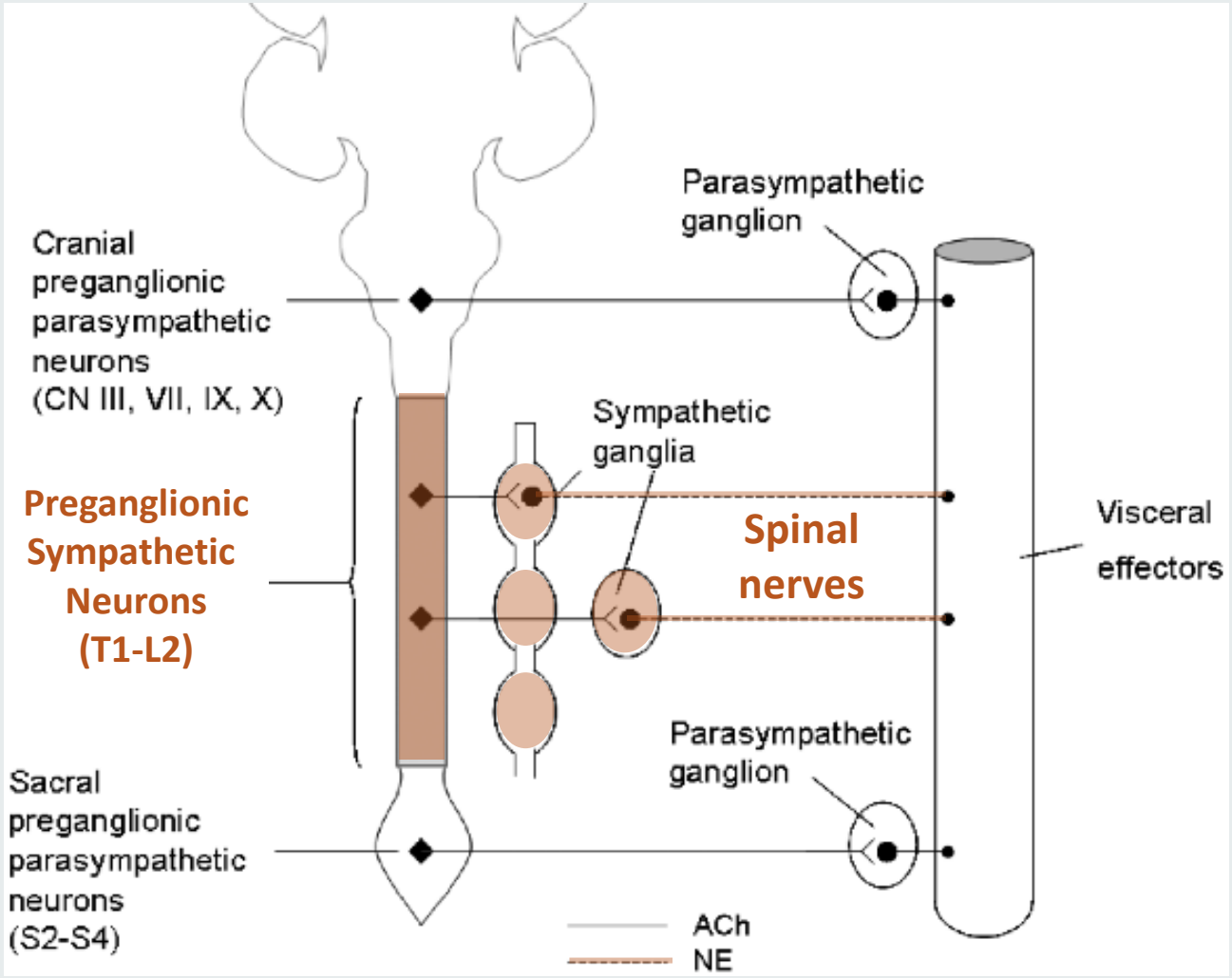
American physiologist

Autonomic nervous system (ANS)

- **Integrative network** for maintaining **homeostasis**
  - 2 structurally/pharmacologically different branches
- Coordinates **visceral** function:
  - Cardiorespiratory
  - Vascular
  - Visceral: urogenital, digestive
- Interacts with **metabolic** systems:
  - Renin-Angiotensin
  - Blood sugar
  - pH
  - Reproductive behavior
  - Motor behaviors
  - Endocrine



Peripheral Autonomic Division:
Sympathetic



"*Fight or Flight*"

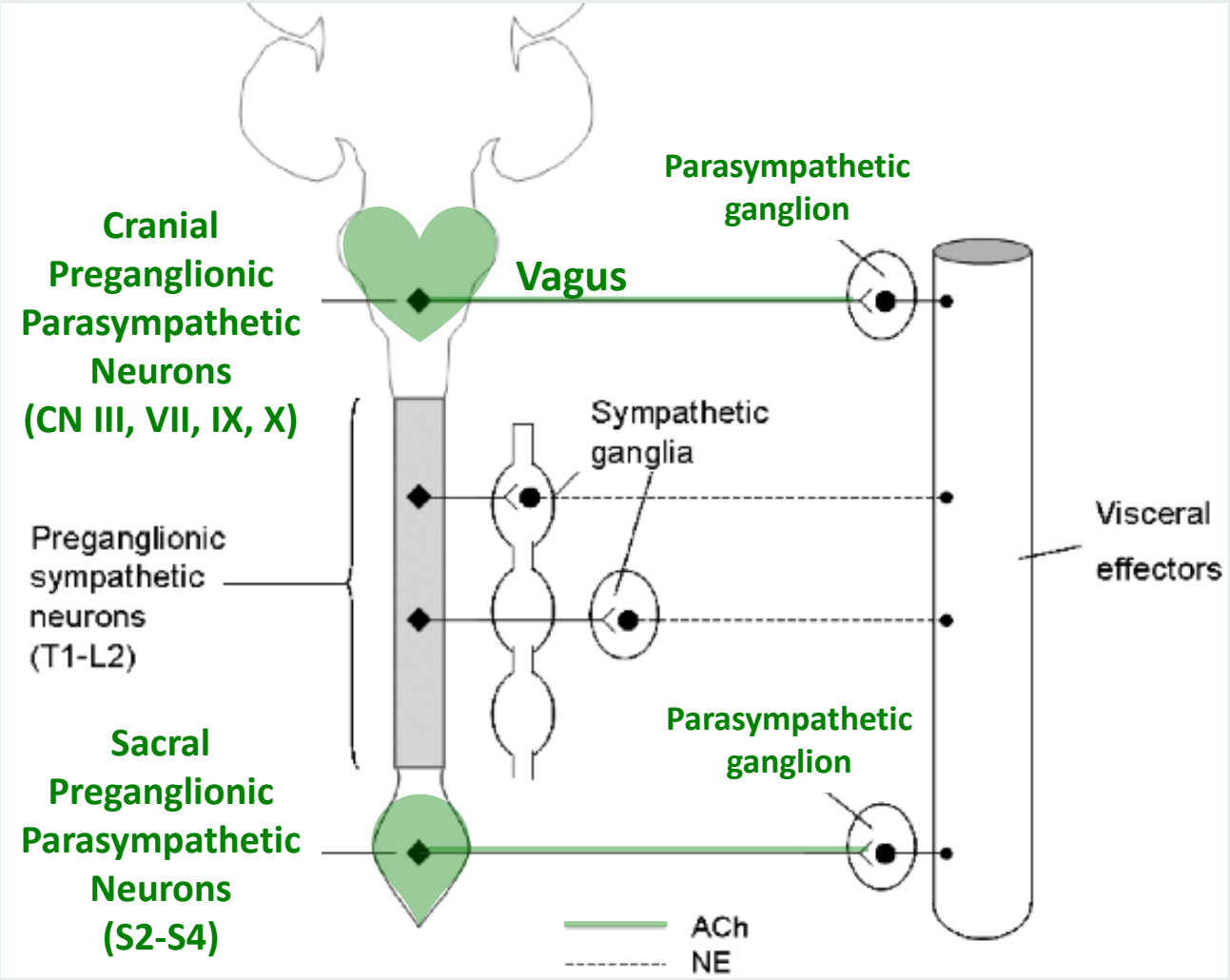
Thoracolumbar (T2-L2)

Functional Targets:

→ Vaso-motor
→ Cardio-motor
→ Viscero-motor
→ Sudo-motor
→ Pilo-motor function

Bennaroch. Continuum Lifelong Learning Neurol 2007;13(6):33–49.

Peripheral Autonomic Division:
Parasympathetic



"Rest and Digest"

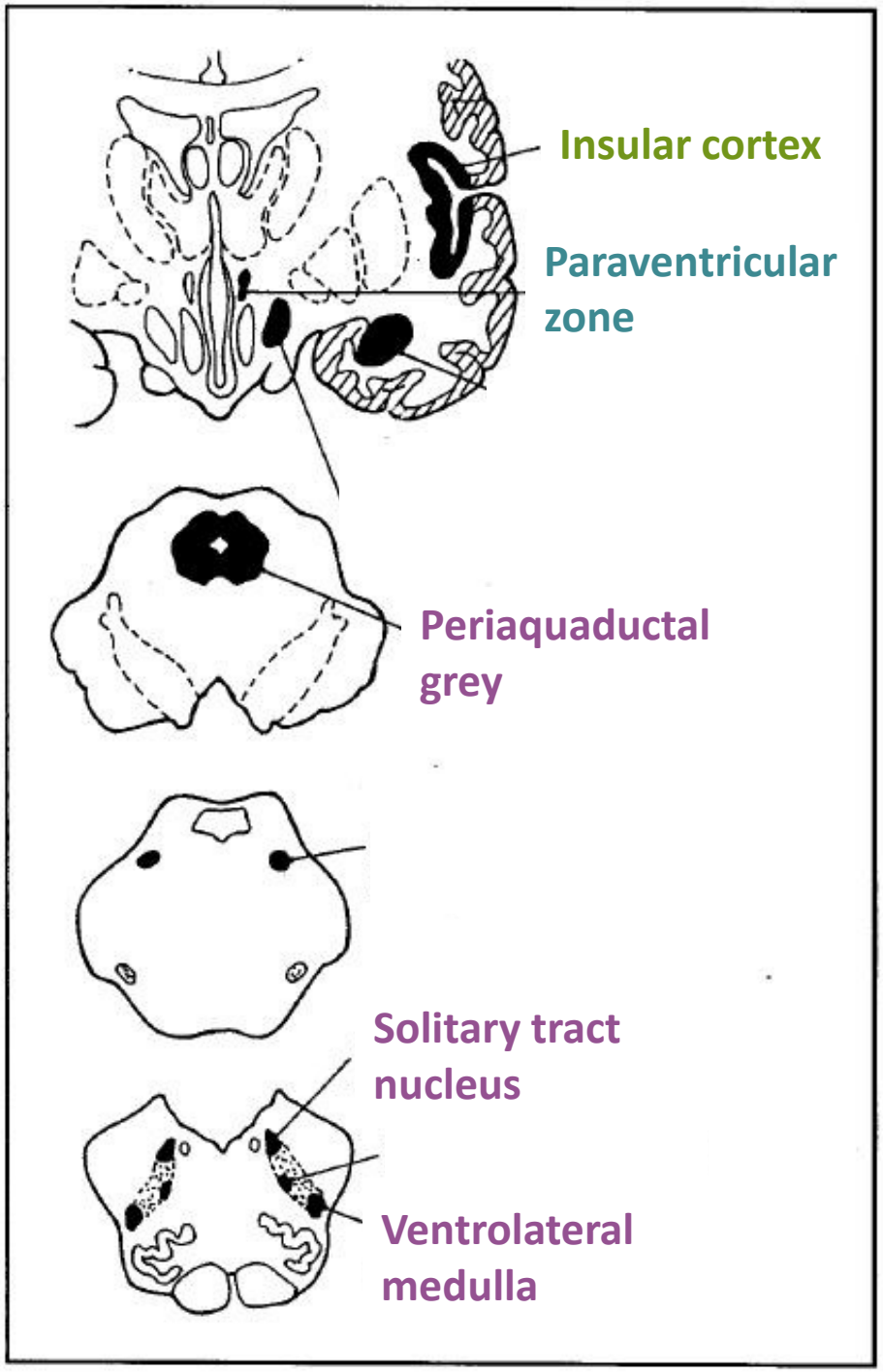
Craniosacral
(CN III, VII, IX, X + S2-4)

Functional Targets:

Vagus nerve (CN X)
→ Cardio-inhibitory
→ Pulmonary
→ GI

Sacral plexus
→ Genitourinary

Bennaroch. Continuum Lifelong Learning Neurol 2007;13(6):33–49.

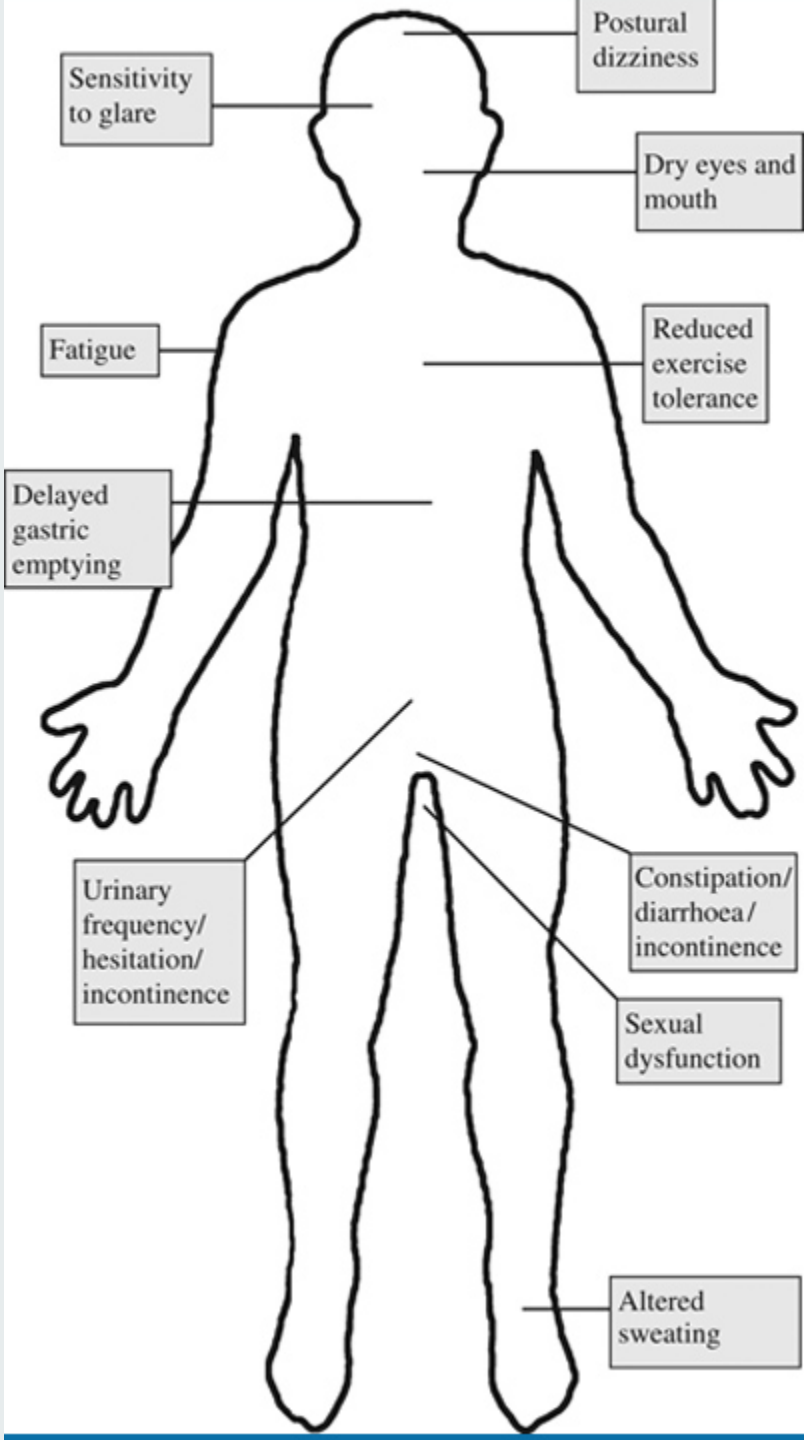


Central Autonomic Networks

- **Cerebrum**
  - Emotional significance to stimuli
- **Hypothalamus**
  - Periventricular zone - '**master controller**' – integrates:
    - Endocrine
    - Circadian rhythms
    - Thermoregulation
    - Immune modulation
- **Brainstem**
  - Baroreflex
  - Visceral control:
    - Heart, lungs
    - Urinary, erectile
    - Gastric motility

Autonomic symptoms

- Coordinated activation due to exercise/stress/emotion
  - e.g. BP maintenance, thermoregulation
- Sympathetic – diffuse
- Parasympathetic – organ specific



Objectives

- Definitions and overview nomenclature, anatomy of autonomic function
- Introduction to clinical laboratory testing and role in diagnosis
- Case illustrations → diagnosis and management
  - Chronic Fatigue with orthostatic intolerance
  - POTS
  - POTS mimics
- Conclusions/Take Home points

Autonomic Testing Laboratory

Opened Jan 2015

Imaging and Clinical Neuroscience (INC) Center

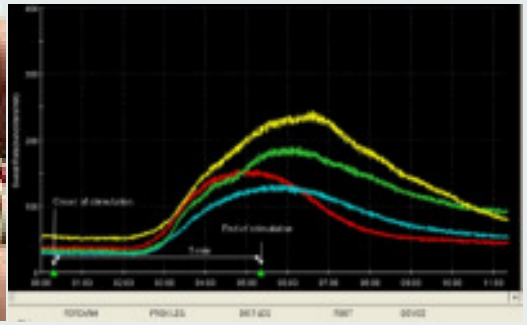
729 Arapeen

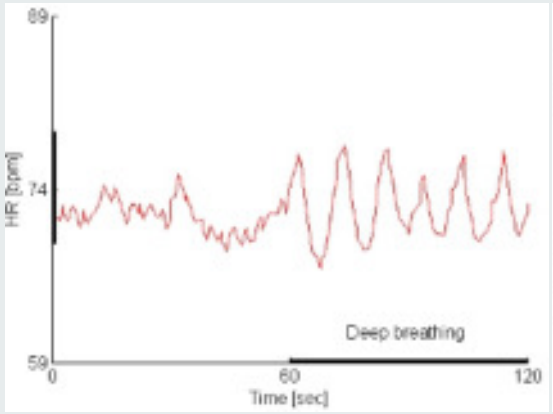
Standardized protocol/ laboratory setting

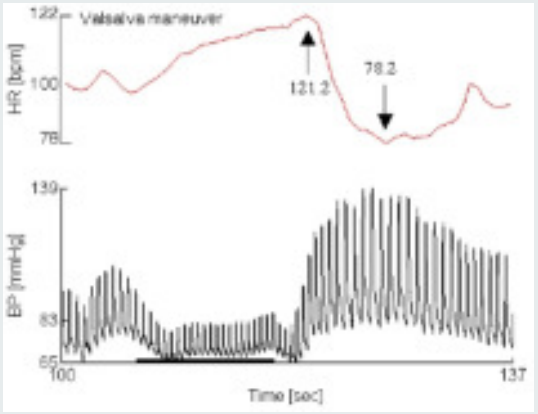
Autonomic Nervous System Testing

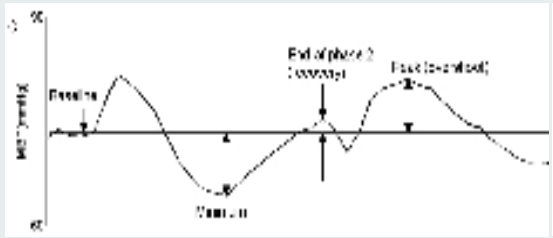
Standardized battery:

- Q-SWEAT
  - post-ganglionic sudomotor (**sweat**)
- Cardiovagal (**parasympathetic**)
  - **HR** changes with deep breathing
  - Valsalva ratio – **HR**
- Cardiovascular adrenergic (**sympathetic**)
  - Valsalva – **BP** changes
  - Tilt-table testing









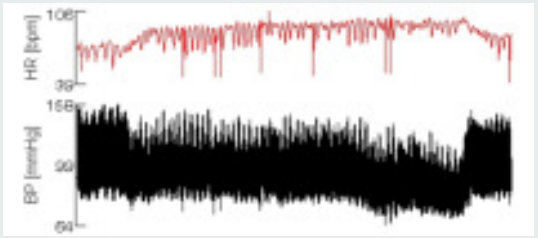


Image source: Novak, P. Quantitative Autonomic Testing. *J. Vis. Exp.* (53), e2502, doi:10.3791/2502 (2011).

Multi-Disciplinary Assessment

- Cardiac
  - Echocardiogram, 12-lead EKG, Holter monitor
  - “Cardiac tilt” protocol: typically 45 min + isoproterenol or nitroglycerine
- GI
  - Endoscopy, motility testing
  - Imaging (CT, ultrasound)
- Sleep study
  - Rule out/treat sleep apnea
- Endocrine
- Rheumatology
- Allergy/Immunology

Objectives

- Definitions and overview nomenclature, anatomy of autonomic function
- Introduction to clinical laboratory testing and role in diagnosis
- Case illustrations → symptoms, management, and diagnosis
  - Chronic Fatigue with orthostatic intolerance
  - POTS
  - POTS mimics
- Conclusions/Take Home points

Pietro Longhi, 1744 oil painting - *Fainting*

Orthostatic Intolerance (OI)

- **Clinical** definition:
  - symptoms worsen upon assuming/maintaining upright posture + ameliorated by recumbency
- **Physiological** definitions:
  - **Postural tachycardia** (= increase of HR with standing)
  - **Blood pressure instability** (e.g. oscillations, neurally mediated hypotension)
  - **Delayed** variants
- Associated with various forms of syncope ("**fainting**")

Symptoms of OI

- Common:
  - Lightheadedness, near-syncope/syncope
  - Impaired concentration
  - Headaches
  - Dim, tunnel or blurred vision
  - Palpitations
  - Tremulousness
  - Chest pain/short of breath
  - Fatigue, exercise intolerance
  - Weakness
  - Nausea, abdominal pain
- Specific:
  - **Cerebral under-perfusion**
  - **Sympathetic** (adrenergic) nervous system activation
- Non-specific:

Case #1

40 year old previously diagnosed with fibromyalgia, also reports 8 years of insidious onset **exercise intolerance** and **severe fatigue**

Marked "**payback fatigue**" after minimal exercise (10 minutes of treadmill or bike). Exacerbated by stress.

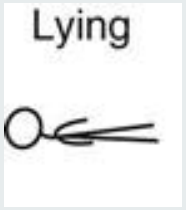
Now with more recently - color changes in skin suggesting vasomotor dysfunction. "*Doc, do I have a dysautonomia?*"

- ROS+: **insomnia, frequent headaches, cognitive dysfunction**
- PMHx:
  - migraines, depression/anxiety, history of significant psychosocial stressors
  - irritable bowel syndrome, degenerative disc disease

Case #1

Vital signs at bedside:

BP 120/60, HR 80



BP 112/70, HR 87

BP 110/65, HR 95

Orthostatic Hypotension (OH) =
sustained decrease SBP > 20 mm Hg or DBP > 10mm Hg
(May be accompanied by increase in HR)

Neurally Mediated Hypotension (NMH) =
decrease SBP > 25 mm Hg
+ preceded by symptoms
Without associated increase in HR (may decrease)

Tilt table testing…

Orthostatic Intolerance in ME/CFS

- Not initially included in Fukuda 1994 CFS case definition
  - Later (2003) recognized as part of spectrum of autonomic manifestations of ME/CFS

- **Prevalence varies** depending on definitions (30 - 97% in some samples)
  - **Symptomatic** >> physiological

References: Bou-Holaigah et al, 1995, JAMA. Miwa, 2015, Heart Vessels. Soetekouw et al 1999, Clin Auton Res. Timmers, et al, 2002, Clin Auton Res.

Orthostatic Intolerance in ME/CFS

- **Testing**
  - Higher resting/supine HR common
  - Orthostatic vital signs/tilt table
    - Orthostatic tachycardia (OI): current recommendations suggest **10 min testing**
    - Neurally mediated hypotension (NMH)/Syncope: **> 10 min** may be required
  - Otherwise normal sweat and cardiovascular autonomic function

- **Treatment** of OI/NMH → shown to improve CFS symptoms

References: Raj, 2013, Circulation. Benditt et al, 1991, PACE. Soetekouw et al 1999, Clin Auton Res. Timmers, et al, 2002, Clin Auton Res. Moya et al, 2009, European Heart Journal.

Management of Orthostatic Intolerance

DO's

- Review/Stop contributing medications
- Treat **anemia/iron deficiency**
- Increase **daily salt** (10+ grams) + **fluids** (2-4L)
  - Fluid boluses (8-16 oz cold H2O), transiently increase BP
- **Compression** garments
  - abdominal binders
  - thigh/waist high stockings

DONT's

- Dehydration
- Excessive exertion in heat (cooling vests useful)
- Large meals
- Excessive alcohol consumption
- Start management with medications alone
  - Midodrine – start 5mg tid, max 15mg tid
  - Fludrocortisone – start 0.1mg bid, max 0.2mg bid
  - **Combine** with fluids + salt

Royal Danish Guard at the Christiansborg Palace in Copenhagen (Keld Navntoft/European Pressphoto Agency)

Case #2

21 year old man describes a 1 year history of unexplained symptoms

- Episode of the “stomach flu” accompanied by abdominal pain and severe fatigue

- **Abdominal pain** never resolved after acute illness
  - negative GI work-up, except for a transit study that showed mild slowing
- **Fatigue** persistent

- Subsequently developed **lightheadedness**, **palpitations**, “**cognitive fog**”, **syncope x 2 –** all worse with standing

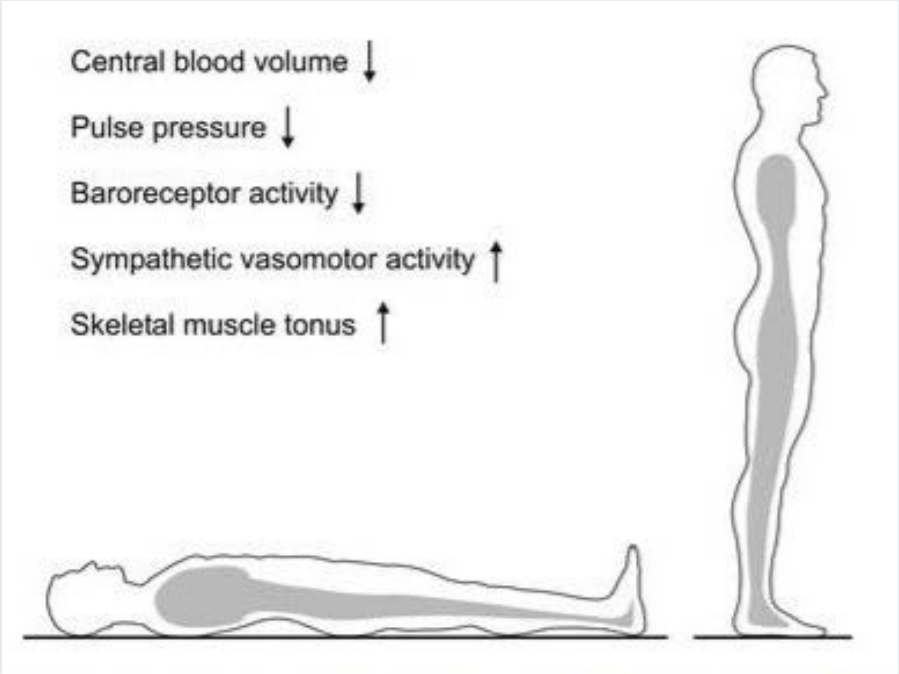
Syncope

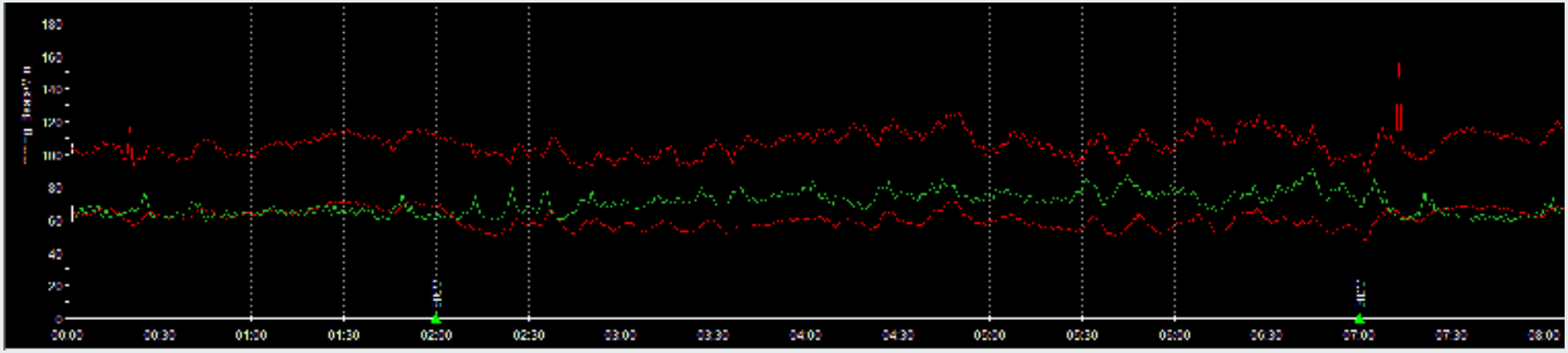
- Common (1-3% of hospital/ER visits)
  - Age 15 to 70+
  - Women 2x > Men
- Multi-factorial
  - Reflex-mediated (benign) – most common (21%)
  - Cardiac (highest mortality) – increases with age (10%)
  - Orthostatic hypotension (9%)
    - Medication
    - Volume depletion
    - Post-prandial (esp in HTN)
  - Other
    - Deconditioning/Venous pooling
    - Cardiac
      - Chronic heart disease/failure
      - Decreased baroreceptor sensitivity (occurs with aging)
      - Carotid sinus hypersensitivity
      - Arrhythmia
    - Endocrine
      - Diabetic (osmotic diuresis, dehydration)
      - Chronic adrenal insufficiency and hypopituitarism
    - Neurological
      - Neurodegenerative diseases or autonomic neuropathy

References: Soteriades et al. 2002. NEJM. Da Silva, 2014. Front Physiol. Kenny et al. 2013. Prog Cardiovasc Dis.

What happens when we stand…

- 500 - 1000 ml of Blood Pools
  - Lower Limbs
  - Splanchnic circulation
- To compensate –
  - NE is released → increase in vasomotor constriction

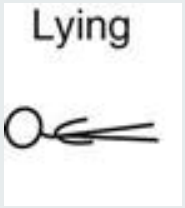




Case #2

- Neurological exam: normal
- VS:

BP 121/67, HR



BP 116/78, HR 68

Postural Tachycardia Syndrome (PoTS)=

Increase in HR > 30 bmp or HR > 120 bpm

+ typical symptoms

After 10 minutes for of upright posture

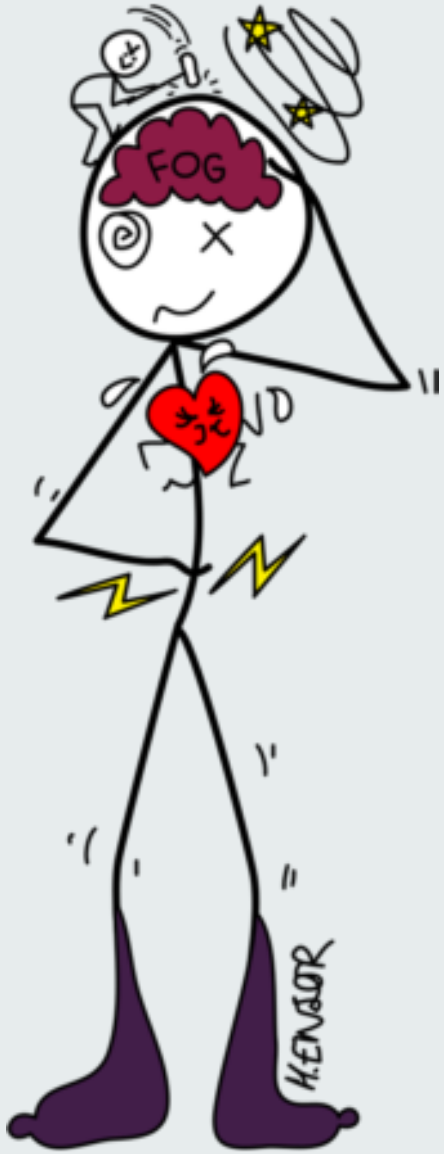
(absence of orthostatic hypotension)

Postural Tachycardia Syndrome (PoTS)

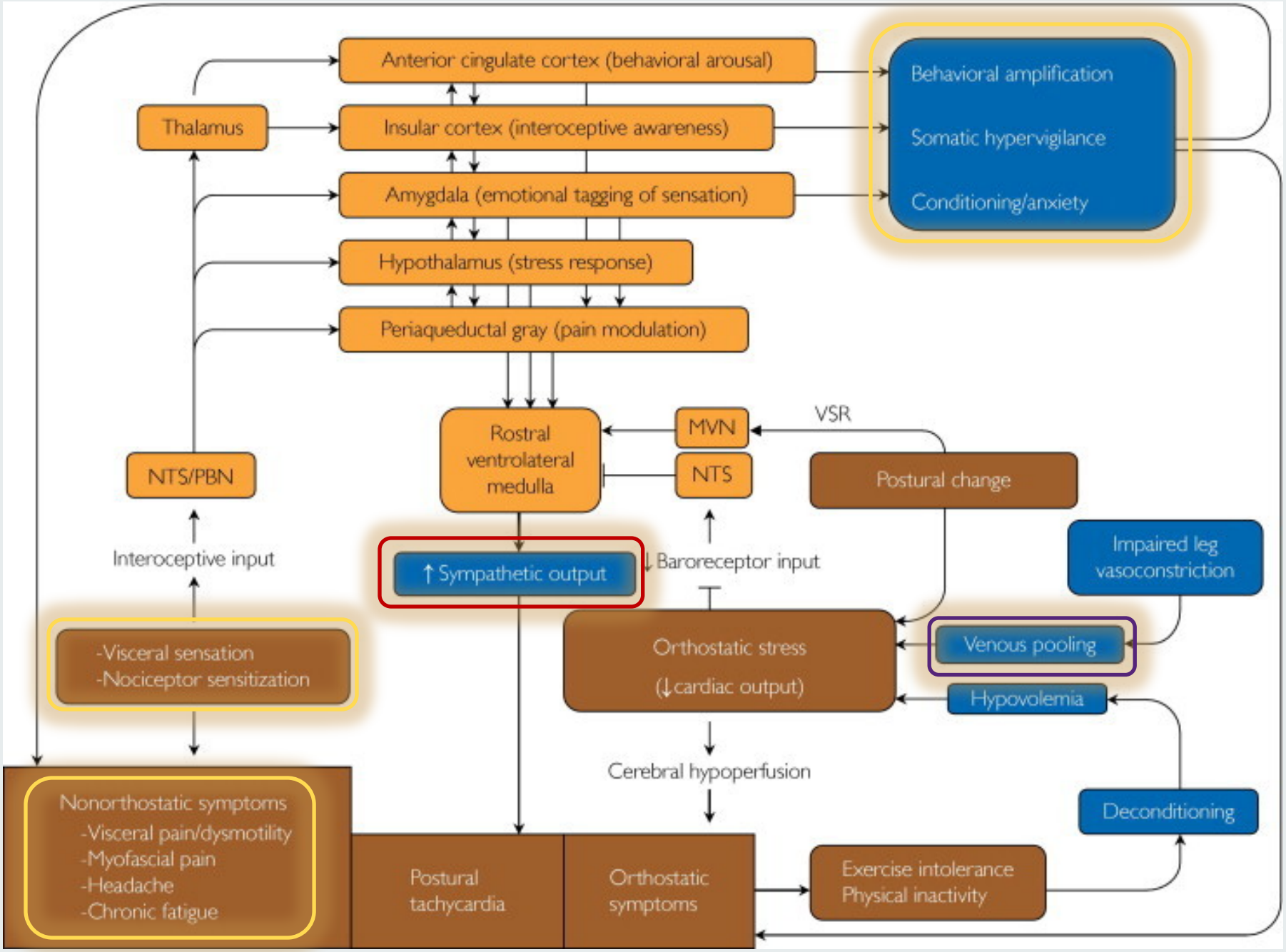
- **Idiopathic** (not explained by another disorder)
  - Chronic, recurrent, disabling symptoms with upright posture (often >6 months)

- Hypotheses: "final common pathway" for multiple overlapping pathophysiologies:

  - Limited **sympathetic neuropathy** affecting the lower body → impaired constriction → **venous pooling**
  - **Elevated sympathetic tone** → excessive **excitation**



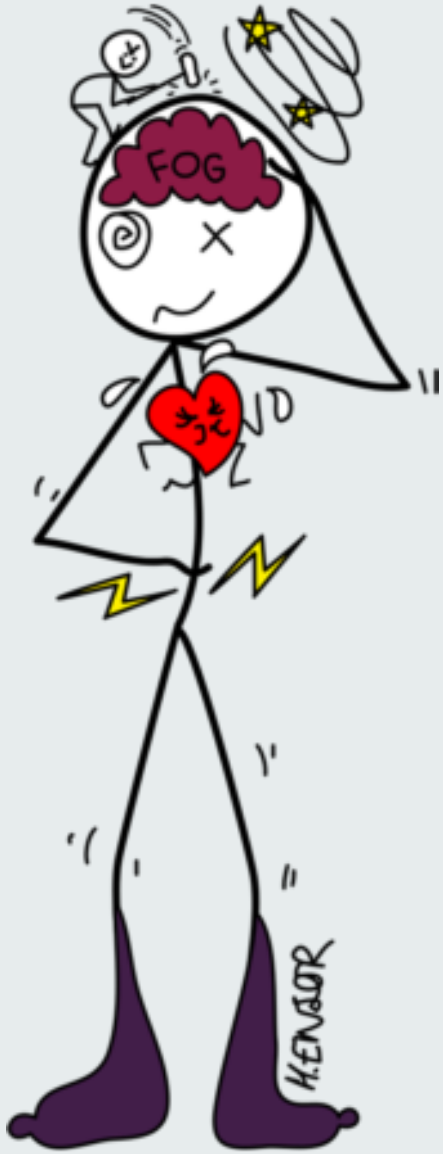
References: Benarroch, 2012. Mayo Clin Proc. Garland et al. 2015, Curr Neurol Neurosci Rep. Image: http://www.potsuk.org/



Reference: Benarroch, 2012. Mayo Clin Proc.

Postural Tachycardia Syndrome

- Young (usually under 40 yo), F>M (5:1)
- Onset:
  - Post-viral or other infection/illness
  - Post-surgical
  - Post-traumatic
  - Insidious
- Worsened by:
  - Heat
  - Eating
  - Prolonged standing
  - Deconditioning/dehydration



References: Benarroch, 2012. Mayo Clin Proc. Garland et al. 2015, Curr Neurol Neurosci Rep. Image: http://www.potsuk.org/

Management of Orthostatic Intolerance

DO's

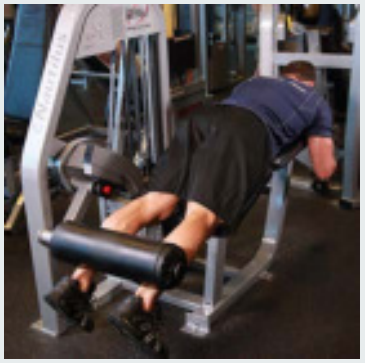
- Stop contributing medications
- Treat **anemia/iron deficiency**
- Increase **daily salt** (10+ grams) + **fluids** (2-4L)
  - Fluid boluses (8-16 oz cold H2O), transiently increase BP
- **Compression** garments
  - abdominal binders
  - thigh/waist high stockings

DONT's

- Excessive exertion in heat
- Deconditioned
- Dehydration
- Large meals
- Excessive alcohol consumption
- Start management with medications alone
  - Midodrine – start 5mg tid, max 15mg tid
  - Fludrocortisone – start 0.1mg bid, max 0.2mg bid
  - Combine with fluids + salt

Management of Orthostatic Intolerance

- **Graduated Exercise Program**
  - To increase muscle tone
  - Promote venous return
- **Aerobic**: **recumbent → → upright**
  - Beginning 5-10 min, goal 40 min
  - 5-6 days/week
  - Intervals
- **Weight Training**: **Core/Lower extremity**
  - Leg press, toe press, leg extension, leg curl
  - Low resistance, 2 sets of 8-15 reps
  - 2-3 times/week
- **Prevent syncope**
  - Avoid triggers
  - Physical counter maneuvers



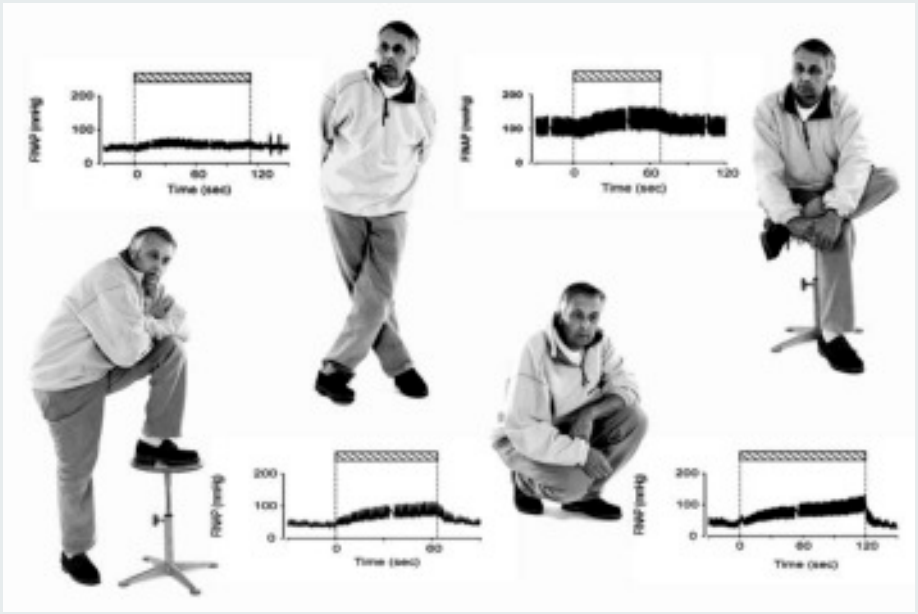


Figure: Wieling et al. Nonpharm treatment of reflex syncope. Clin Auton Res 2004; 14(suppl 1):62-70. Reprint in Continuum 2007.

John Singleton Copley, American
British Lord Injured in Crowd-Surfing Accident, 1779
Oil on canvas

Case #3

63 year old disabled physician presents with a 6 year history of evolving multi-systemic autonomic dysfunction:

FATIGUE with new **exercise intolerance**,
lightheadedness/near-syncope, increase in **headaches**,
GI motility with intractable nausea, **sleep** impairment,
flushing/**heat** intolerance, and **BP instability**

Exam: **reduced vibration** at ankle and signs of **joint hypermobility**, otherwise normal

Autonomic testing…

Approach to Orthostatic Intolerance (tachycardia) +

Fatigue:

- Iron deficiency
- Vitamin D deficiency
- Endocrine disorder
- Chronic fatigue syndrome with OI

Flushing:

- Mast cell activation
- Carcinoid

Neuropathy:

- Diabetes
- Amyloidosis
- Sjögren's
- Lupus
- B12/Copper defic
- Myeloproliferative disorders

Prominent GI Dysmotility:

- Diabetes
- Celiac
- Irritable bowel syndrome
- Autoimmune
  - Ganglionic acetylcholine receptor Ab's
  - Celiac disease/gluten intolerance
- PoTS

Headaches:

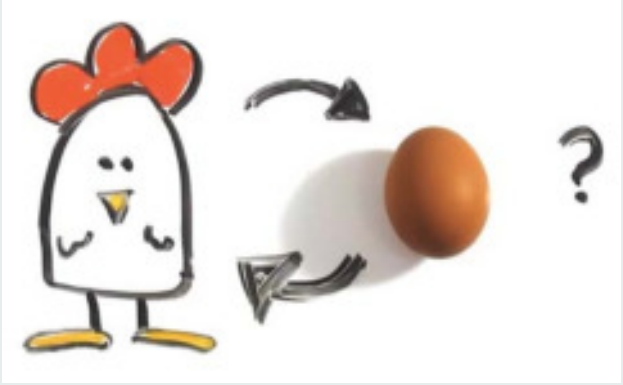
- Chronic migraine
- Chiari malformation
- PoTS

Joint Hypermobility

- Ehler's Danlos

Chronic Migraine and Chronic Daily Headache (CDH)

- Symptoms of **dizziness** common, variable (vertigo vs postural) in chronic HA
  - Estimated 33-50% of CDH has symptoms of OI
  - Orthostatic headache in 60% of POTS
- "Chicken or the egg?"
  - OI a Trigger for headache?
  - Headache pathology also causing autonomic dysfunction
- Responds to **directed headache management**
  - Hydration
  - Medications/headache prophylaxis
  - Exercise
  - Mind-Body therapies



References: Mack et al. 2010. Sem Ped Neurol. Heyer et al. 2013. Headache. Khurana and Eisenberg. 2011. Cephalgia.

Joint Hypermobility

- Strong association between **joint hypermobility** and both **CFS** (odds ratio of 3.5) and **POTS**

- Spectrum (likely genetically based):
  - **Benign** joint hypermobility syndrome (BJHS) → **Ehler's Danlos** (EDS) joint hypermobility type
  - Dysautonomia = "**extraarticular**" manifestation

- Hypothesis:
  - Abnormal **connective tissue** in dependent blood vessels → veins distend excessively with ordinary hydrostatic pressures → increased **venous pooling** + hemodynamic/symptomatic consequences

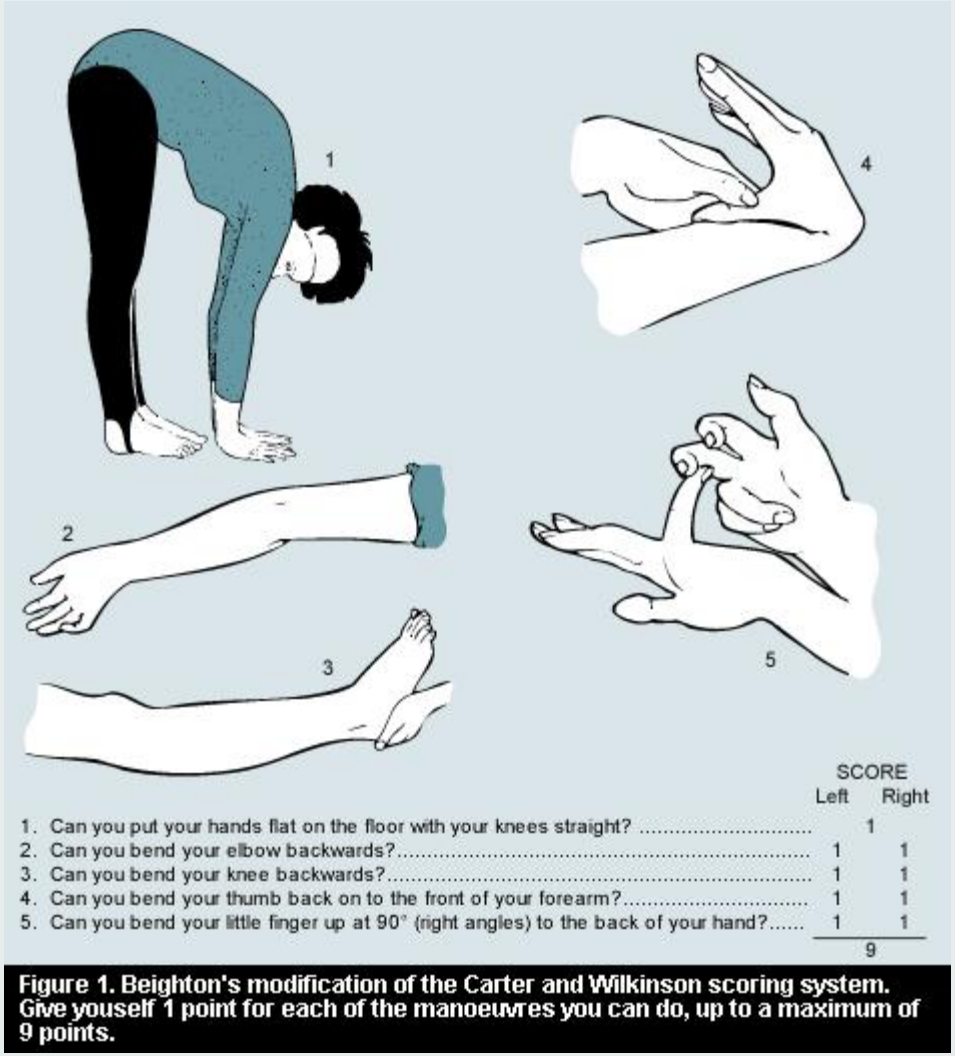
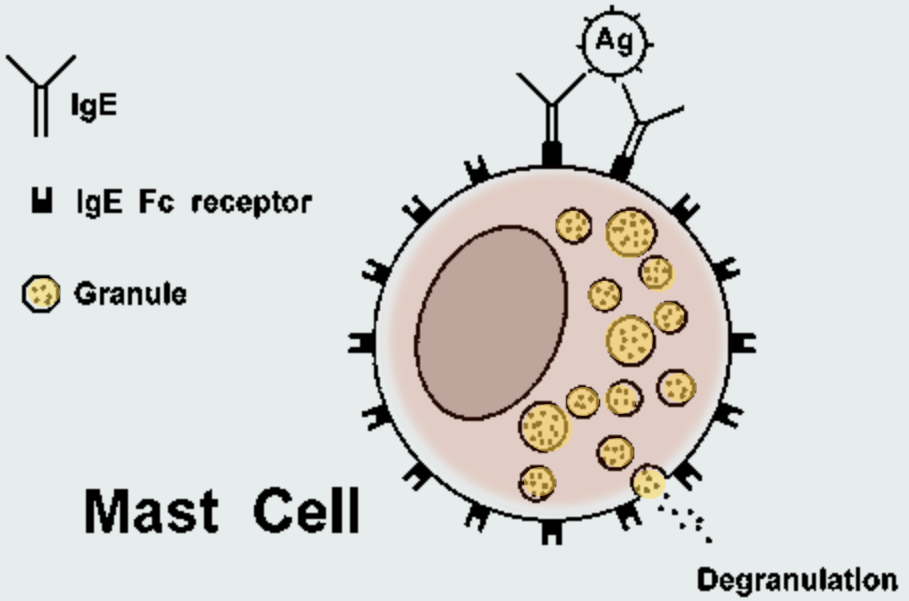


Figure 1. Beighton's modification of the Carter and Wilkinson scoring system. Give youself 1 point for each of the manoeuvres you can do, up to a maximum of 9 points.

References: Barron et al, 2002, J Pediatr. Nijs et al, 2006, J Manipulative Physiol Ther. Remvig et al. 2007, J Rheumatol. Rowe et al, 1999, J Pediatr. DeWandele et al, 2014, Semin Arthritis Rheum. Image: http://chkdsportsmed.com/2013/10/23/an-overview-of-hypermobility-and-ehlers-danlos-syndrome/

Mast Cell Activation Disorders



- (Relatively rare) Mimic of PoTS
  - Prominent GI symptoms/motility
  - **Flushing**
  - Asthma or other atopic conditions

- Spectrum: **Abnormal mast cell activation → Mastocytosis**
  - **GI, skin, respiratory symptoms**
  - Abnormal activation of mast cells → dilation of blood vessels → increased venous pooling + hemodynamic/ symptomatic consequences

- Diagnosis:
  - Serum tryptase
  - urine N-methylhistamine
- Treatment:
  - **mast cell degranulation inhibitor** (cromolyn)
  - anti-histamines

References: Shibao et al. 2005. Hypertension. Image: http://library.med.utah.edu/WebPath/IMMHTML/IMM101.html

Approach to Orthostatic Intolerance (tachycardia) +

Fatigue:

- Iron deficiency
- Vitamin D deficiency
- Endocrine disorder
- Chronic fatigue syndrome with OI

Flushing:

- Mast cell activation
- Carcinoid

Neuropathy:

- Diabetes
- Amyloidosis
- Sjögren's
- Lupus
- B12/Copper deficiency
- Polygammopathy

Prominent GI Dysmotility:

- Diabetes
- Irritable bowel syndrome
- Autoimmune
  - Ganglionic acetylcholine receptor Ab's
  - Celiac disease/gluten intolerance
- PoTS

Headaches:

- Chronic migraine
- Chiari malformation
- PoTS

Joint Hypermobility

- Ehler's Danlos

Case #3

- Treatment:
  - First line: **conservative measures** – failed, despite excellent adherence to recommendations
  - **Immune therapies** – resulted in full remission of symptoms
    - Anticipate requirement for conservative measures (exercise, hydration, etc) long-term

Thank you

Opened Jan 2015

Imaging and Clinical Neuroscience (INC) Center

729 Arapeen

- **Acknowledgements**:
- Stefan Pulst, MD – Dept of Neurology
- K.C. Brennan, MD – Headache Physiology Lab
- Chris Gibbons, MD – Harvard
- Ben Caler – lab technician

- **Support**:
- University of Utah, Department of Neurology
- School of Medicine, Office of Academic Development
- University of Utah Headache Physiology Laboratory