Orthostatic Intolerance (OI)

In the Young

(orthostasis = standing)

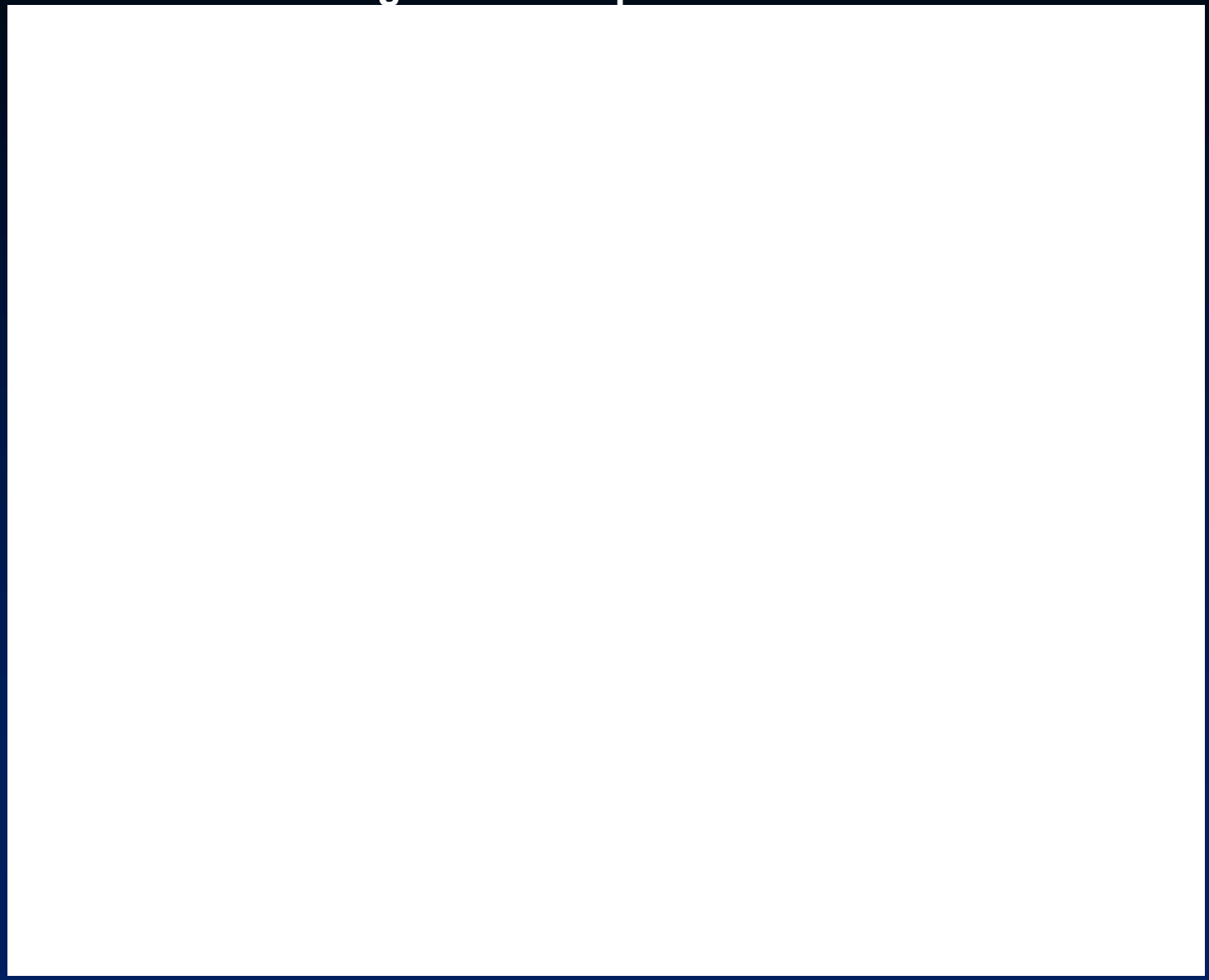
(OI= Can't remain standing)

maria Fareri children's Hospital

AT WESTCHESTER MEDICAL CENTER

Gravitational Blood Distribution in Man and Beast

Unconstrained Pooling Causes Rapid Loss of BP



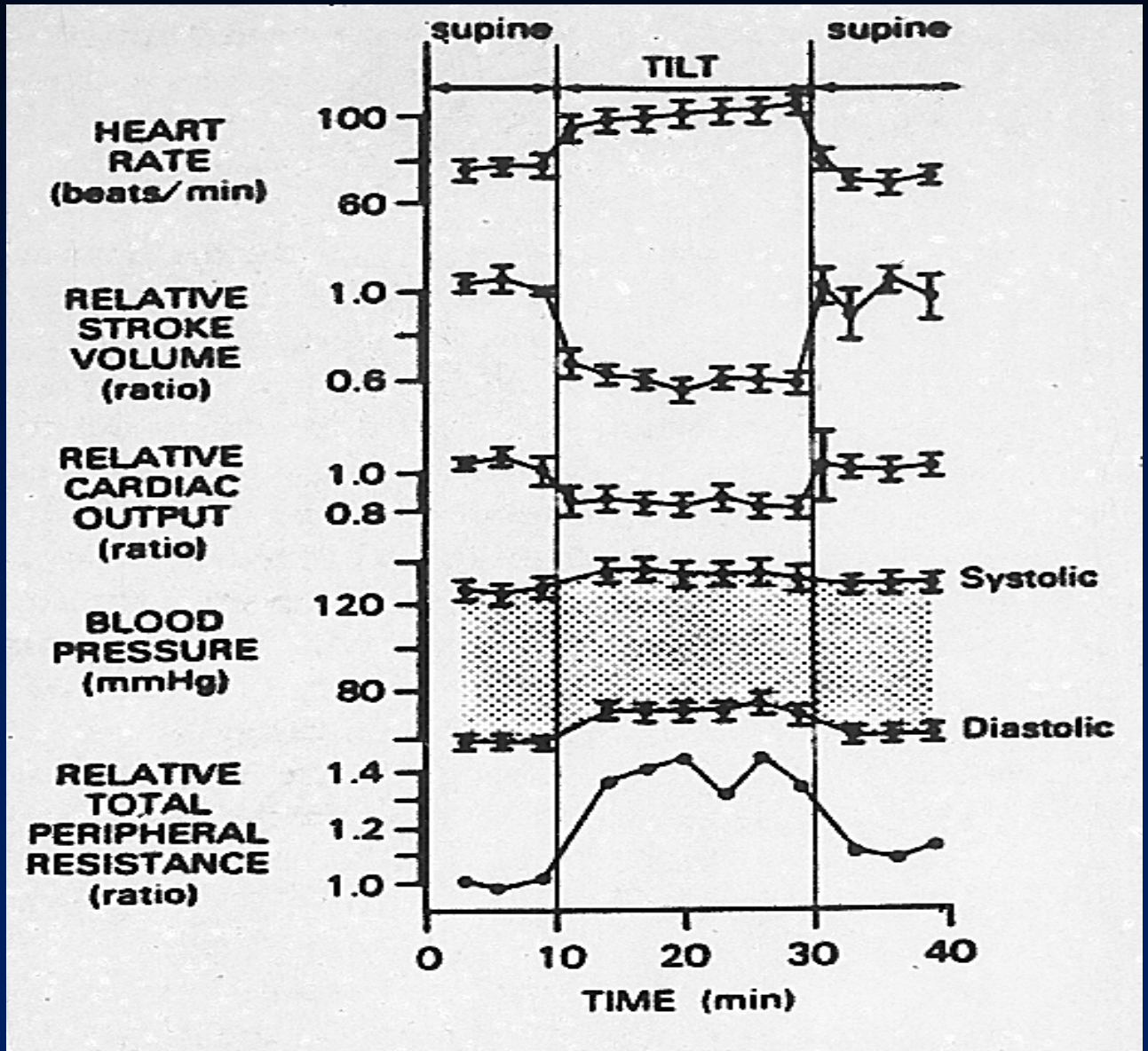
Circulatory Responses to Orthostasis

- Physical forces (muscle/abd –resp pump)
- Vascular structure and Blood volume
- Vascular regulation of O_2 Delivery
  - <u>Rapid</u>
    - ANS–Sympathetic/Parasymp
    - Myogenic
    - Flow Mediated
  - <u>Slower</u>
    - Setting the tonic milieu –NO/Ang
    - autocrine, paracrine, endocrine
    - Metabolic
    - Gene expression -> Epigenetics

Most of OI=

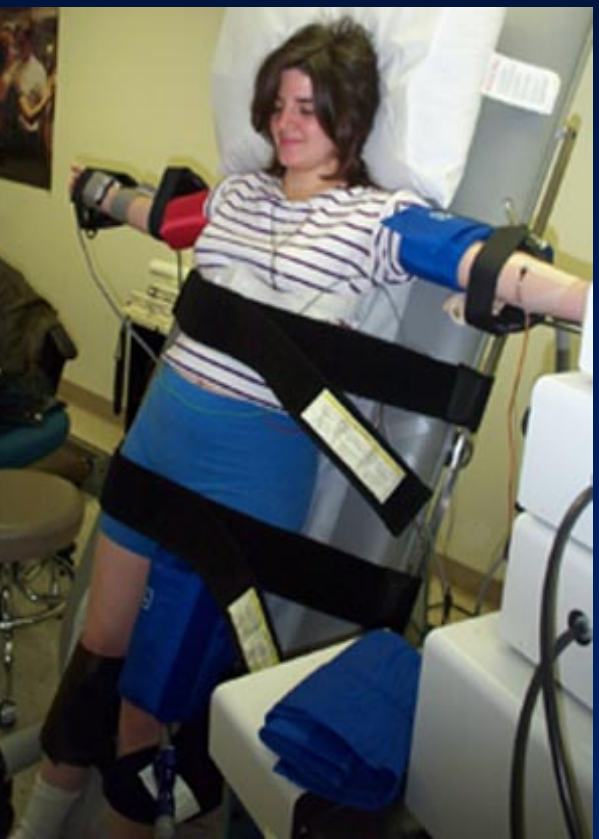
Abnormalities in adrenergic regulation and the modulation of adrenergic vasoconstriction in humans

Normal Circulatory Response to Orthostasis

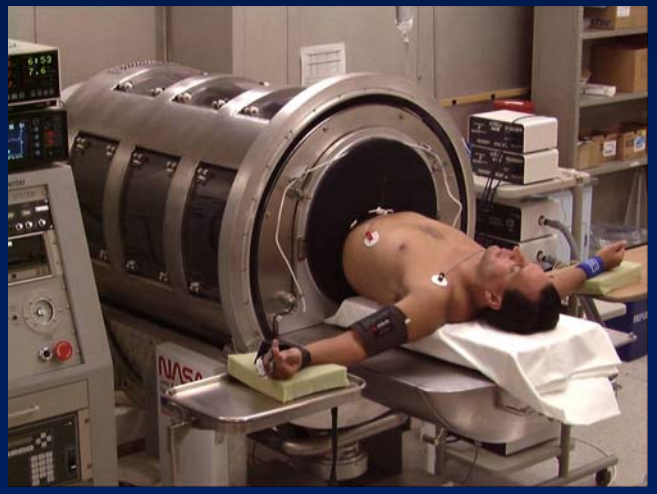


Impose Orthostatic Stress

~Model for Standing
↓Skeletal Muscle Pump ≠
100% Syncope in
Syncopizers



http://www.standingwave.ca/Support.html



LBNP=Surrogate Hemorrhage

Orthostatic Intolerance: defined by inability to tolerate the upright posture relieved by recumbence

- Loss of Consciousness
- Lightheadedness-Dizziness
- Neurocognitive Deficit
- Headache
- Fatigue – worst post-ictal

cerebral perfusion abnormalities despite cerebral autoregulation

- Orthostatic Hypotension/Hypertension
- Weakness – peripheral malperfusion?
- Nausea/abdominal pain
- Sweating, tremulousness
- Exercise Intolerance

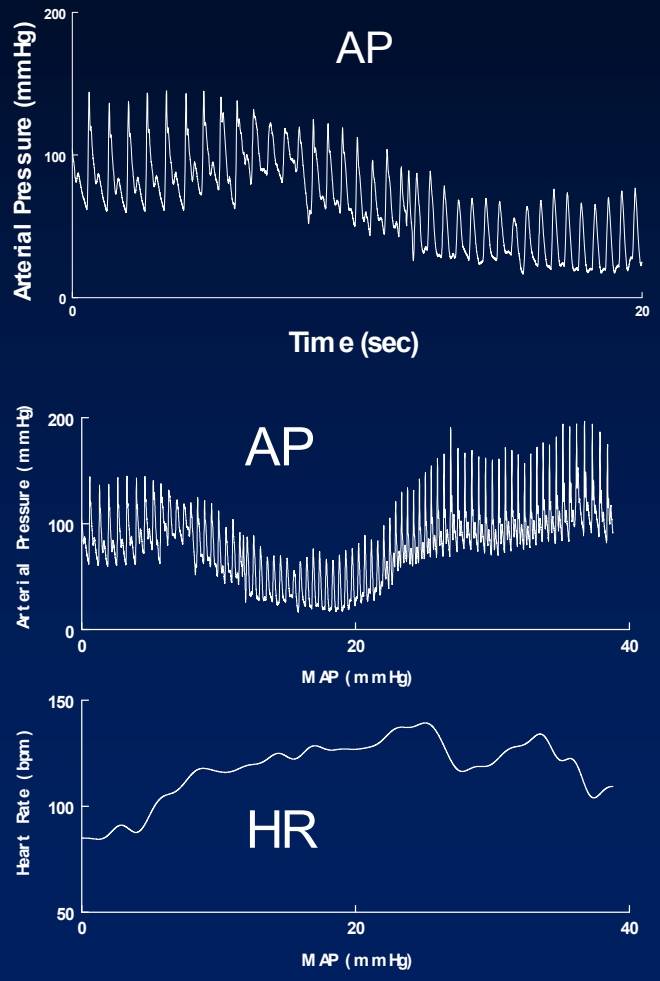
↓↑ Adrenergic vasoconstriction

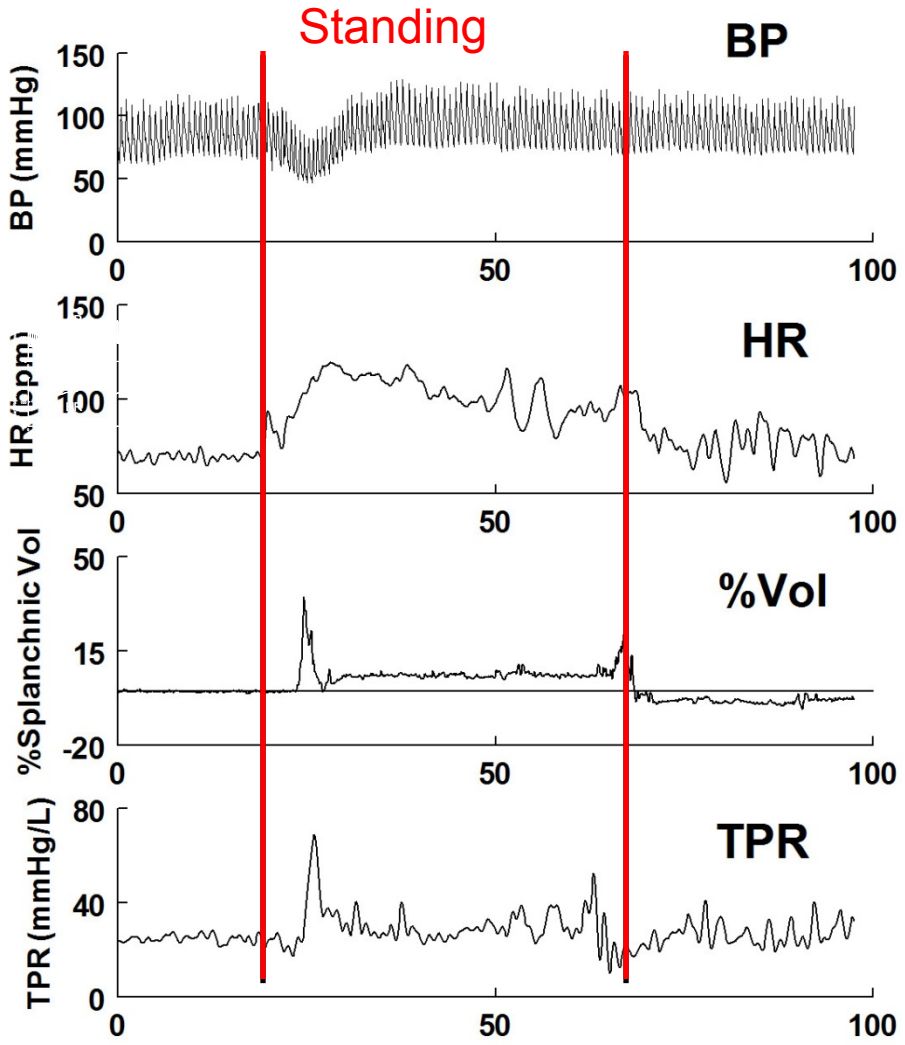
Parasympathetic ↓↑

Variants of Orthostatic Intolerance

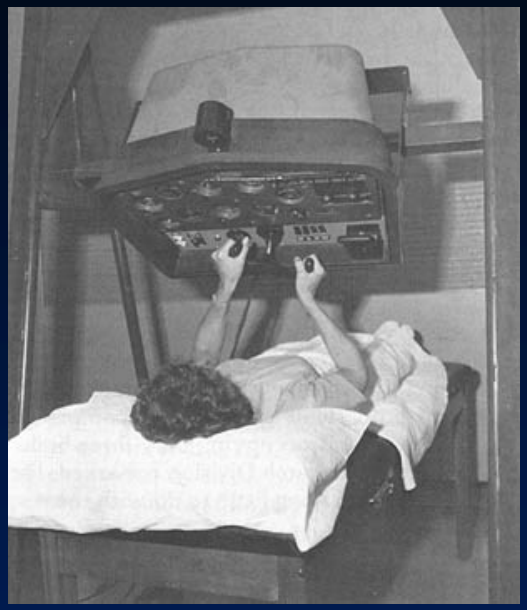
- Initial Orthostatic Hypotension
- Gravitational Deconditioning
- Orthostatic Hypotension
- Chronic Orthostatic Intolerance
  - Postural Tachycardia Syndrome (POTS)
  - Other
- Postural Vasovagal Syncope
- Newer variants –Hyperpnea, Cerebral Dysreg

Initial Orthostatic Hypotension





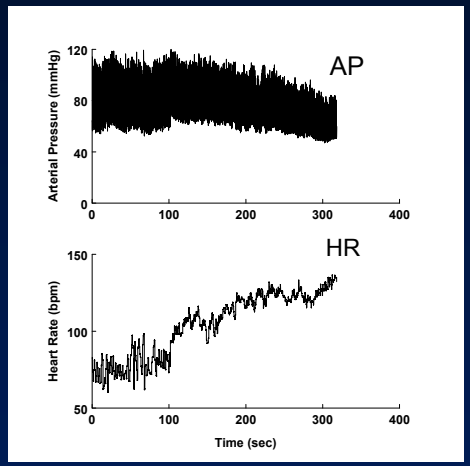
Gravitational Deconditioning



- Reduced blood volume
- Cardiovascular remodeling
- Different Regional blood volume redistribution
- Reduction in the response to norepinephrine/MSNA (and other pressors)

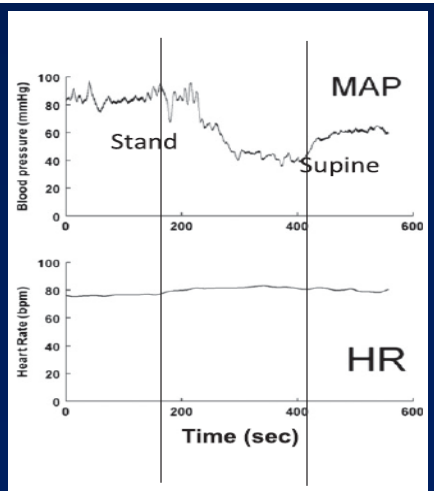
Orthostatic Hypotension (OH)

- OH is defined as a sustained reduction of systolic BP> 20 mmHg or diastolic BP>10 mmHg within 3 min of standing or head-up tilt to ≥60°



- Non-neurogenic OH Drugs,
- hypovolemia (pheochromocytoma,
- Addison Disease)

- Neurogenic OH is identified with Autonomic vasoconstrictor failure due to inadequate release of norepinephrine from sympathetic vasomotor neurons.



Chronic Orthostatic Intolerance: Postural Tachycardia Syndrome (POTS)

Day-to-Day Symptoms of OI

+

Excessive Tachycardia

(without Hypotension)

Adults Δ>30 or HR>120bpm within 10min

Adolescent – Δ>43

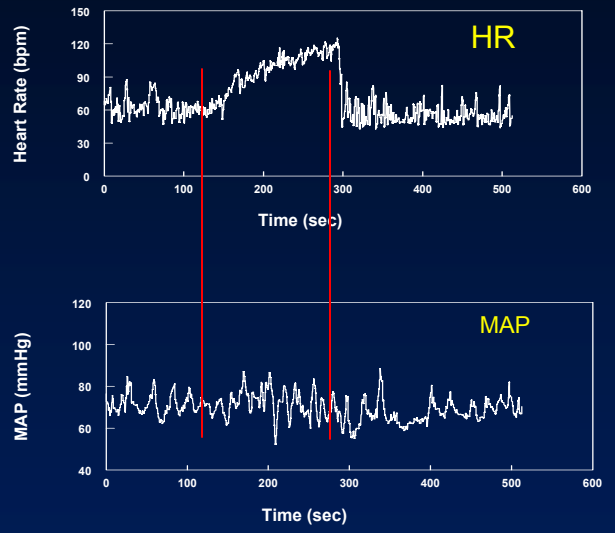
(IOH a confound)?

+

Concurrent Symptoms of OI

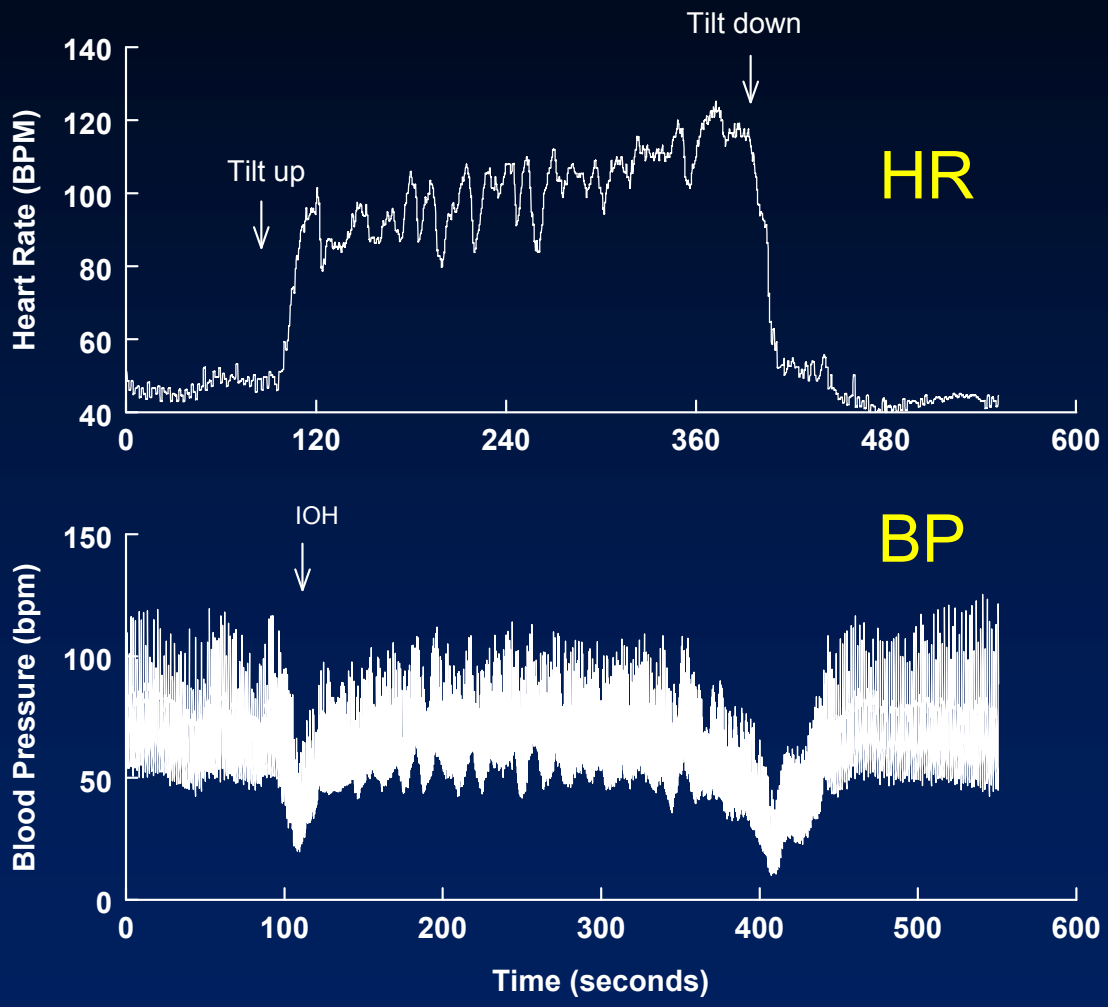
during testing

Improved by Recumbence



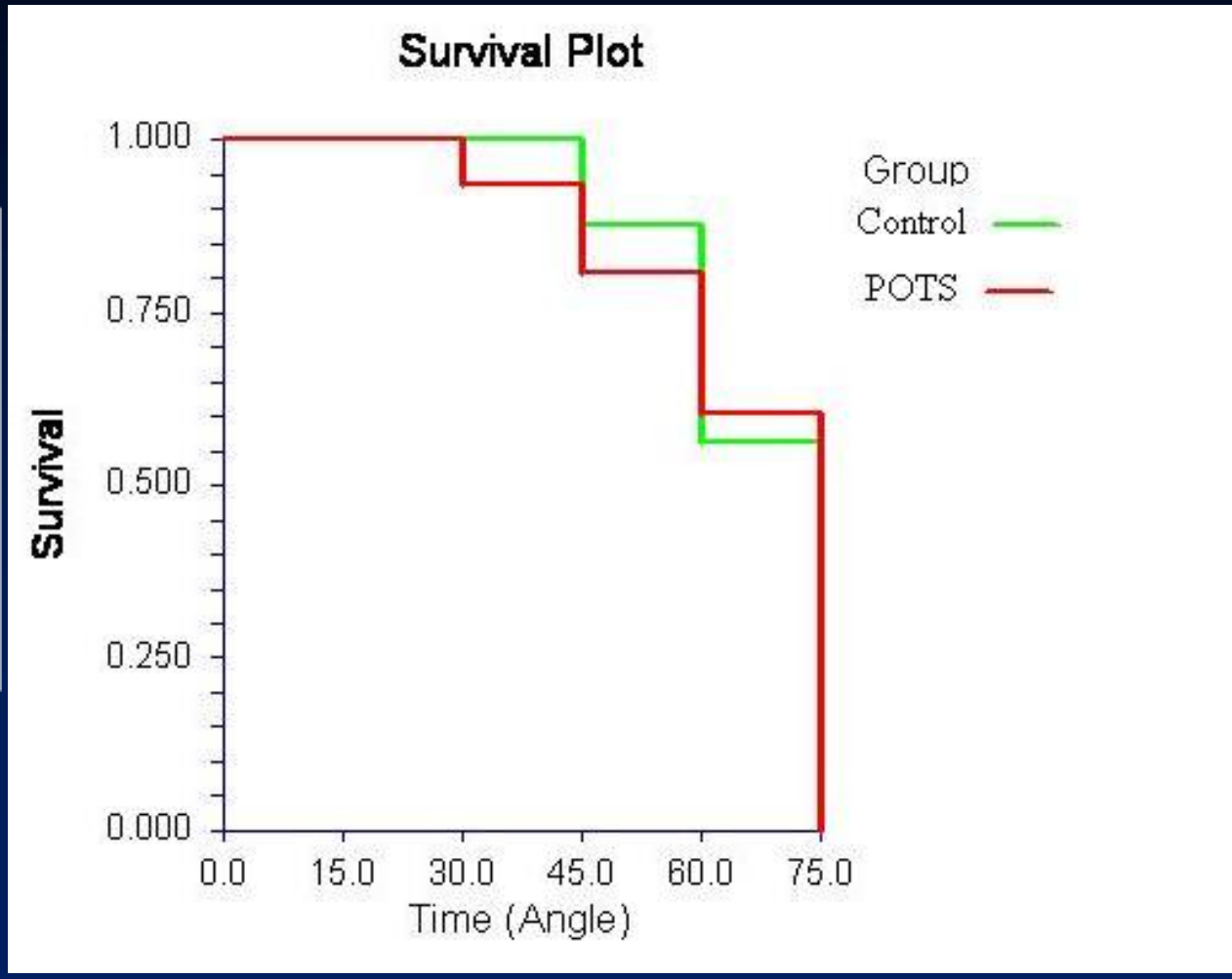
Schondorf and Low. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? Neurology 1995;43:132-137

What's This?


Tilt down
Tilt up
HR
Heart Rate (BPM)
140
120
100
80
60
40
0
120
240
360
480
600
IOH
BP
Blood Pressure (bpm)
150
100
50
0
0
100
200
300
400
500
600
Time (seconds)

Well, so what! Maybe POTS patients Faint?

Incremental tilt



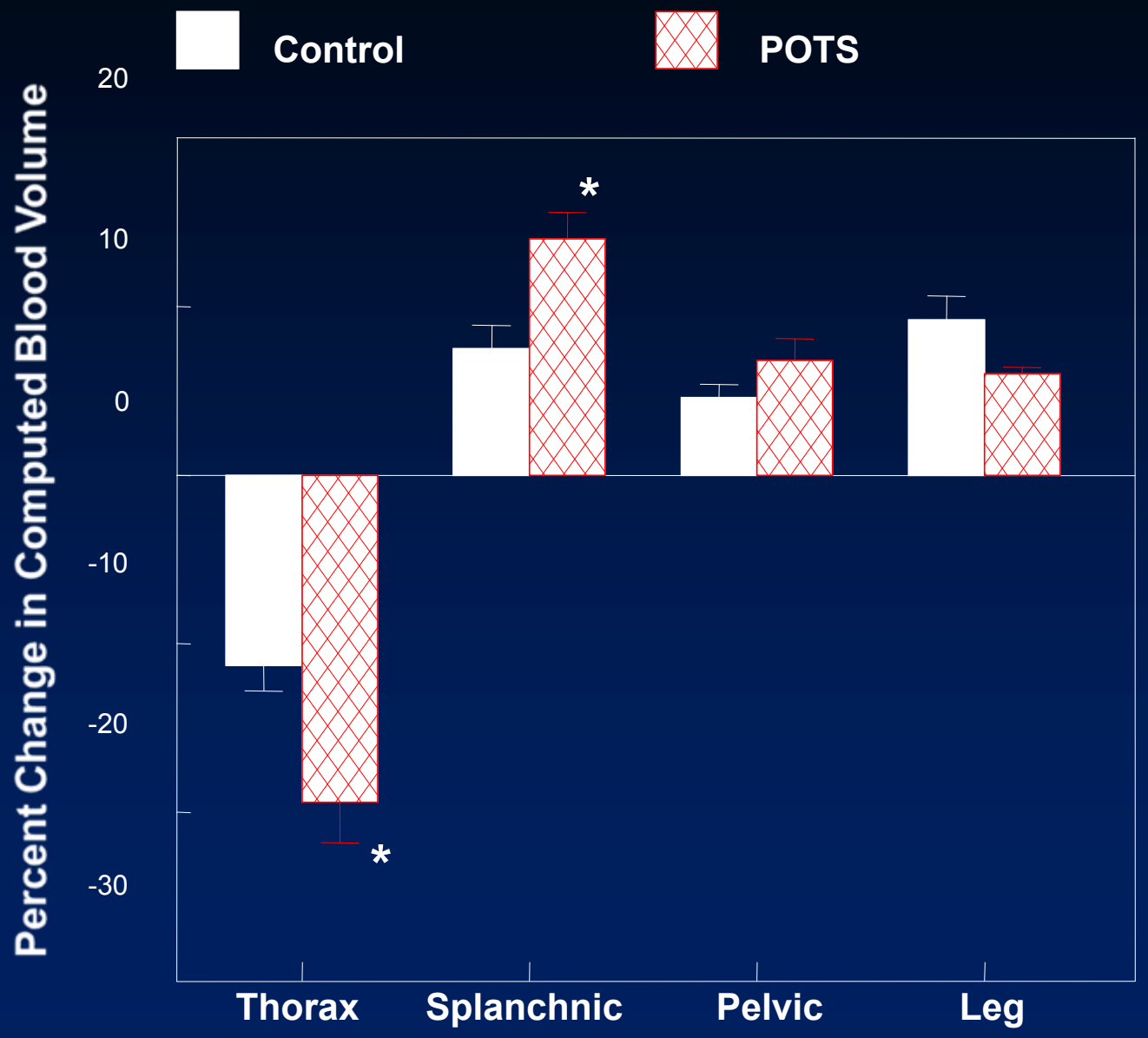
The Tachycardia of POTS

- **Sinoatrial Node Tachycardia**
  - Hypovagal POTS ***Parasympathetic*** due to cholinergic and nitrergic (NO) mechanisms. Channelopathy.
  - "Hyperadrenergic POTS" (↑adrenergic activity)
    - Increased sympathetic nerve activity
    - Increased peripheral transduction (NET, NPY, receptors, β-1 receptors, Ang, NO deficit)
    - Postural Hyperpnea – Hypocapnic sympathoexcitation

The Tachycardia of POTS

- **Reflex (Neuropathic)** **Central Hypovolemia with baroreflex mediated tachycardia (intact cardiac ANS)**
  - Absolute Hypovolemia
  - Regional Redistribution "Neuropathic POTS"
    - ↓ regional adrenergic vasoconstriction
    - Legs
    - Splanchnic

Neuropathic - Splanchnic Blood Pooling



POTS Factoids

- Female
- Prior Inflammation
- EDS
- Defects in Cerebral Autoregulation
- Cognitive Deficits/Exercise Intolerance
- Association with low BMI
- BP maintained
- Variable pale appearance
- Rx Beta Blocker? α_1 agonist
- Volume load, fludrocortisone
- Acetylcholinesterase Inhibitors
- AT1R antagonists
- Statin drugs
- Water Palliation
- Salt? – in very large amounts
- IV saline/oral rehydration – yes

Syncope

Transient loss of consciousness and postural tone due to global cerebral hypoperfusion and characterized by rapid onset, short duration, and spontaneous recovery.

Often the result of systemic hypotension

Very Common (~40%)

Syncope (nasty)

Syncope due to orthostatic hypotension

Primary autonomic failure:
- *pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia*

Secondary autonomic failure:
- *diabetes, amyloidosis, uraemia, spinal cord injuries*

Drug-induced orthostatic hypotension:
- *alcohol, vasodilators, diuretics, phenotiazines, antidepressants*

Volume depletion:
- *haemorrhage, diarrhoea, vomiting, etc*

Cardiac syncope (cardiovascular)

Arrhythmia as primary cause:

Bradycardia:
- *sinus node dysfunction (including bradycardia/tachycardia syndrome)*
- *atrioventricular conduction system disease*
- *implanted device malfunction,*

Tachycardia:
- *supraventricular*
- *ventricular (idiopathic, secondary to structural heart disease or to channelopathies)*

Drug induced bradycardia and tachyarrhythmias

Structural disease:

Cardiac: *cardiac valvular disease, acute myocardial infarction/ischaemia, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors, etc), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valves dysfunction*

Others: *pulmonary embolus, acute aortic dissection, pulmonary hypertension*

Syncope (not so nasty?)

Reflex (neurally-mediated) syncope

Vasovagal:
- *mediated by emotional distress: fear, pain, instrumentation, blood phobia*
- *mediated by orthostatic stress*

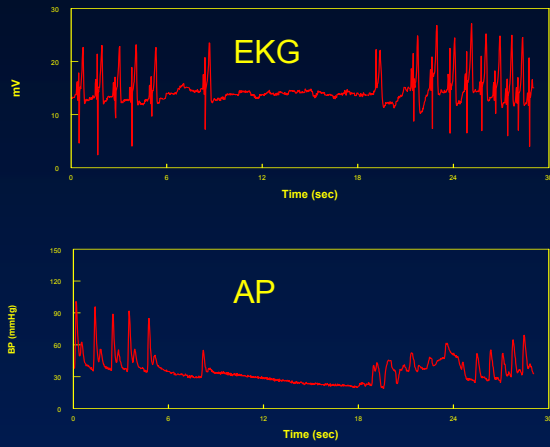
Situational:
- *cough, sneeze*
- *gastrointestinal stimulation (swallow, defaecation, visceral pain)*
- *micturition (post-micturition)*
- *post-exercise*
- *post-prandial*
- *others (e.g., laught, brass instrument playing, weightlifting)*

Peds – Hair-grooming, stretch

Carotid sinus syncope

Atypical forms (without apparent triggers and/or atypical presentation)

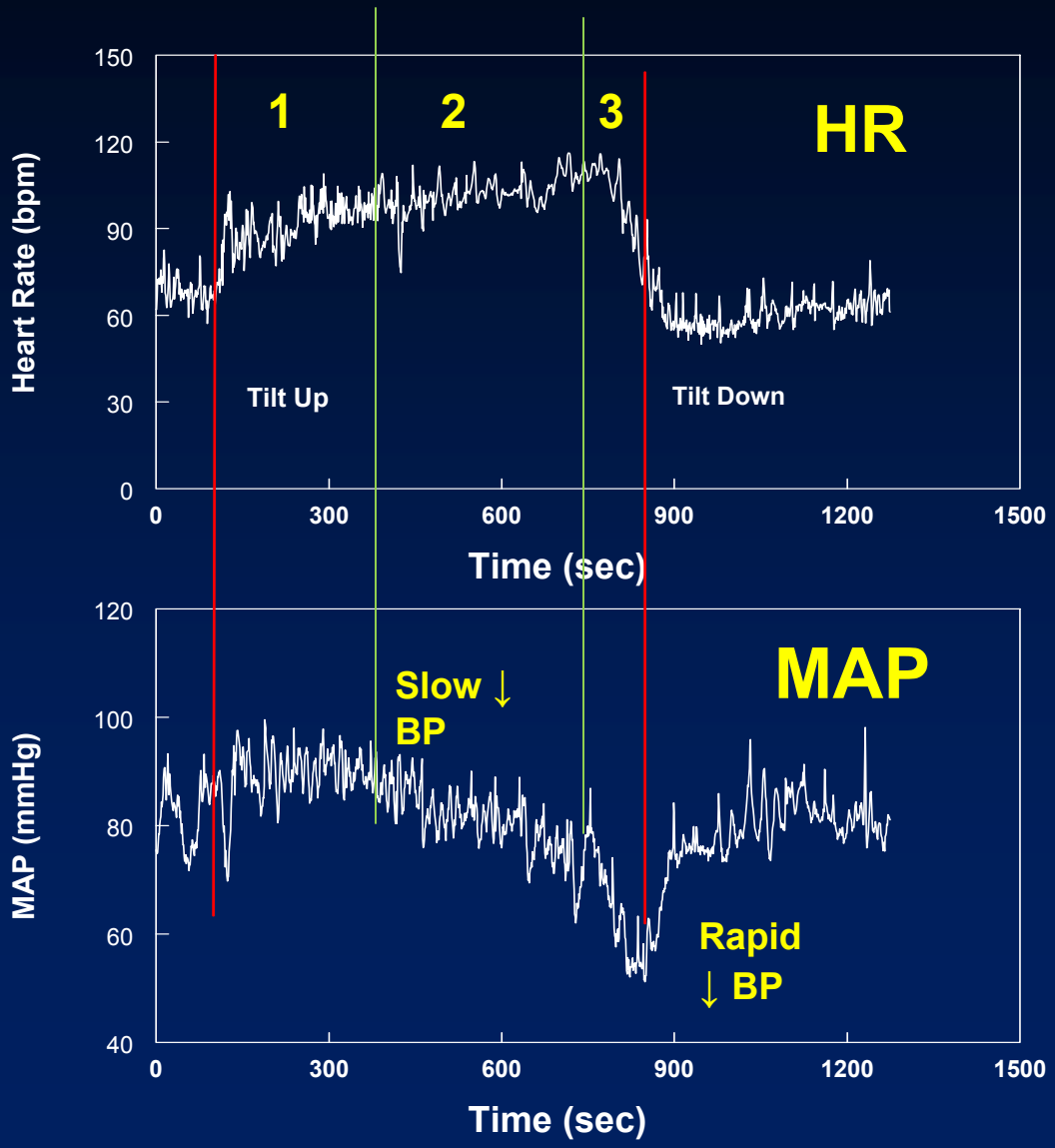
But then there is asystolic syncope.



And being in harm's way.

Postural Vasovagal Syncope in the Young

Mechanism Remains Elusive



Hemodynamics are Similar to Hemorrhage with impaired Adrenergic Vasoconstriction

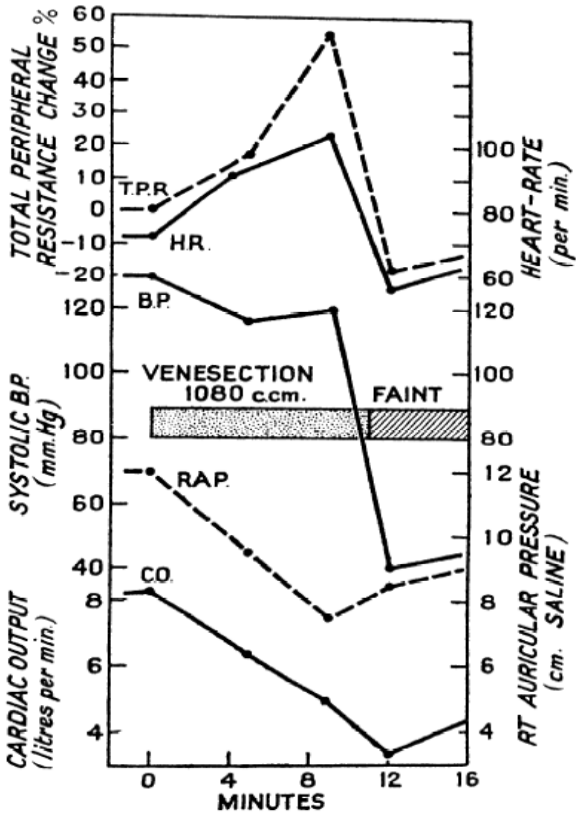
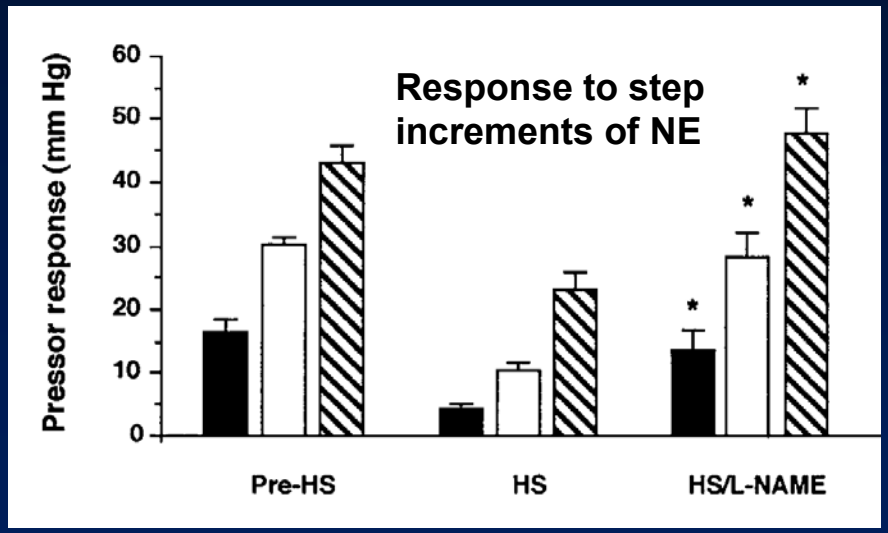


FIG. 1. Faint induced by venesection. Up to the end of the venesection, arterial pressure is maintained by peripheral vasoconstriction (increased total peripheral resistance) despite a falling cardiac output. During the faint, cardiac output increases slightly and the decrease in blood pressure is therefore due to a decrease in peripheral resistance. [From Barcroft et al. (5).]

- Barcroft, H., J. McMichael 0. G. Edholm, and E. P. Sharpey-Schafer. Posthaemorrhagic fainting. Study by cardiac output and forearm flow. Lancet 1: 489-491, 1944.

Reduced response to NE reversed with NOS inhibitors



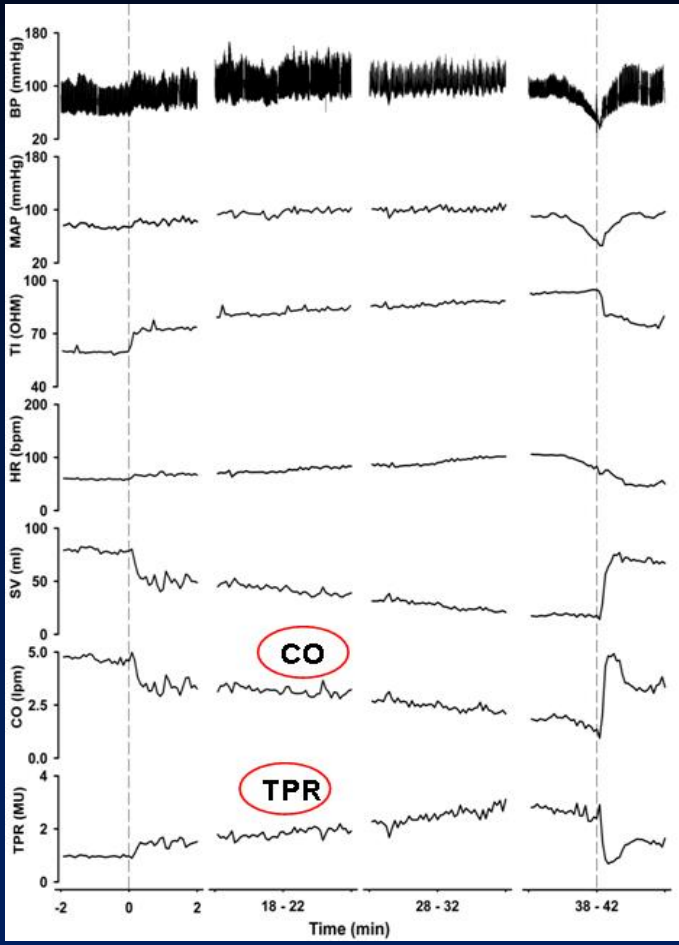
Szabo C, Thiemermann C. Role of Nitric Oxide in Hemorrhagic, Traumatic and anaphylactic shock and thermal injury. Shock 2(2):145, 1994

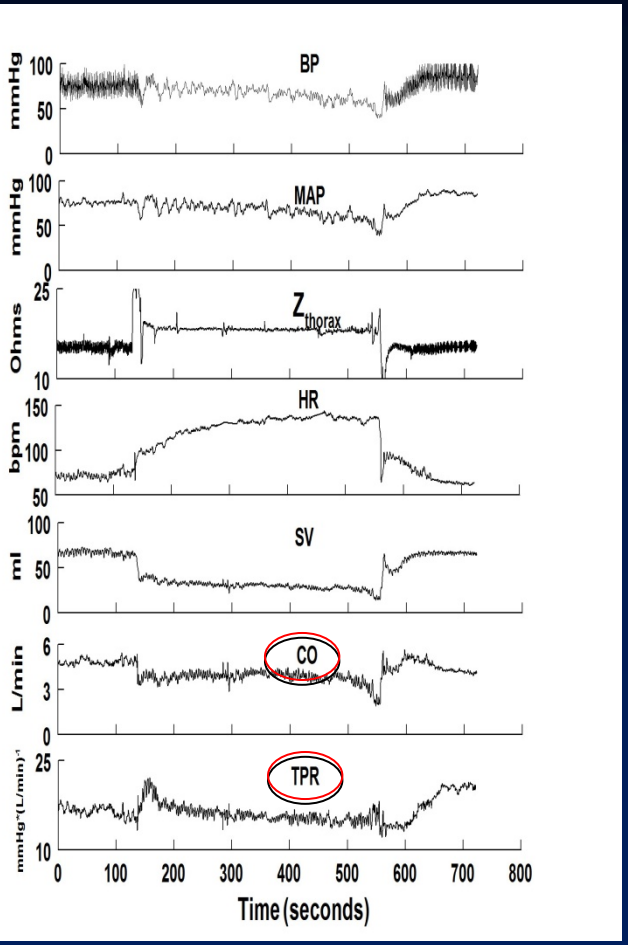
How do you explain Stage 2 gradual hypotension

MAP = CO x SVR

VVS in the Old vs Young: ↓CO vs ↓TPR

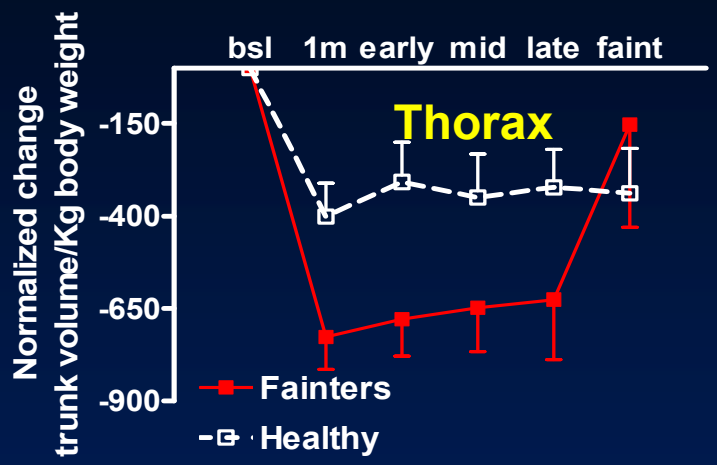
Older

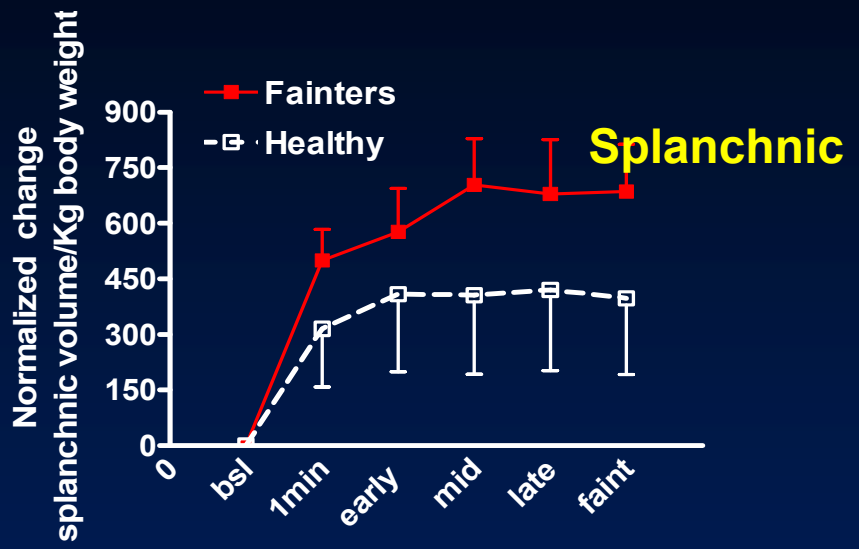


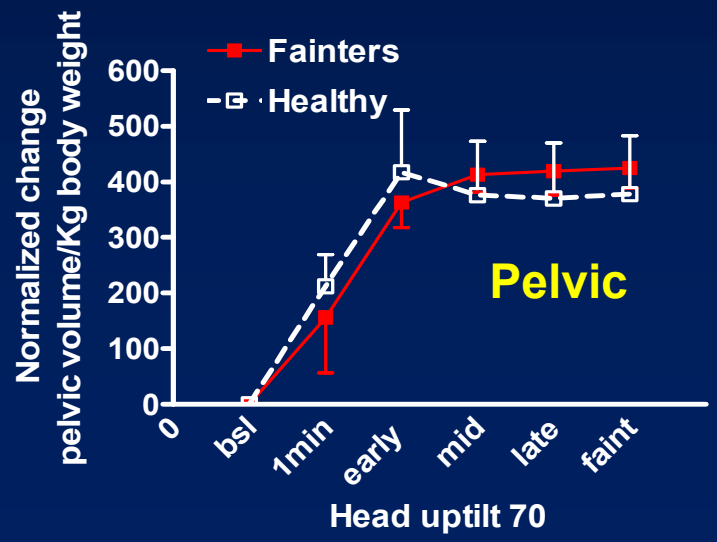


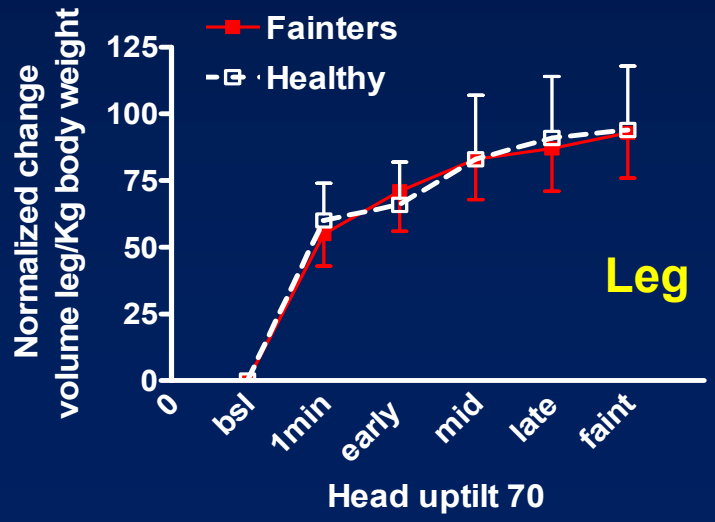
Younger

Excessive ↓Central Blood Volume ↑Splanchnic Blood Volume

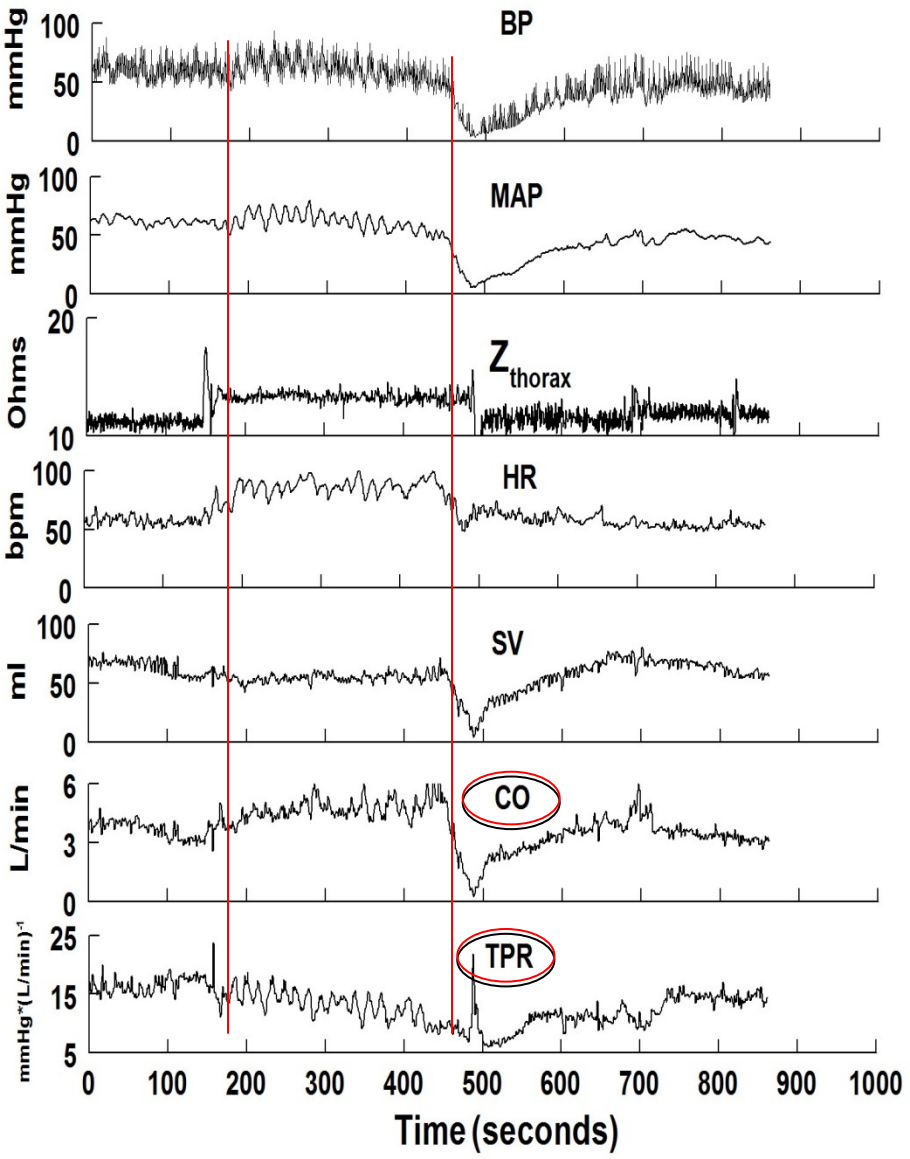








Or even


BP
MAP
Z_{thorax}
HR
SV
CO
TPR
mmHg
mmHg
Ohms
bpm
ml
L/min
mmHg*(L/min)-1
100
50
0
20
10
6
3
25
15
5
0
100
200
300
400
500
600
700
800
900
1000
Time (seconds)

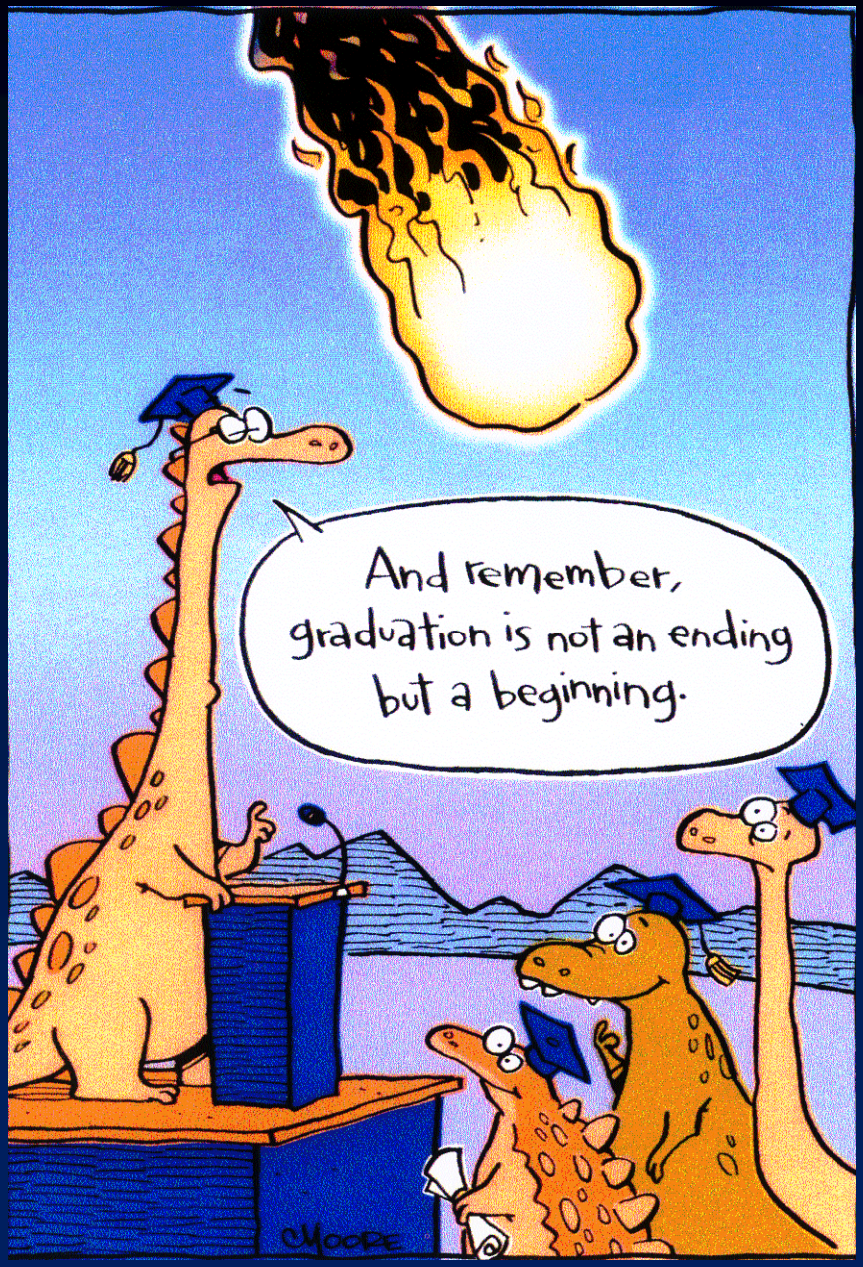
How do you explain Hypotension-Bradycardia?

Hyperpneic Hyperventilation
Loss of Cerebral Autoregulation
Baroreflex Failure

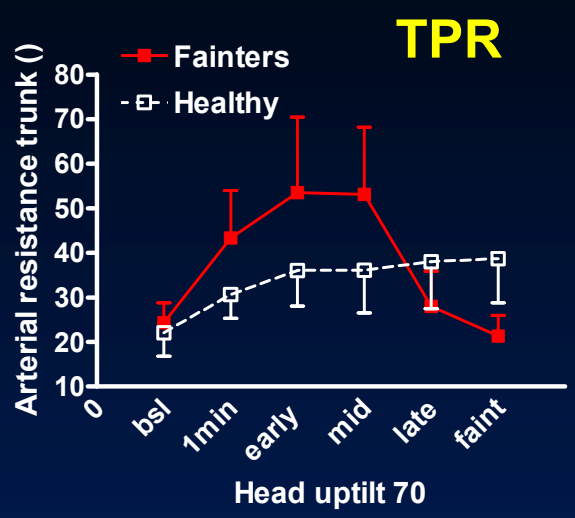
We do not know the mechanism

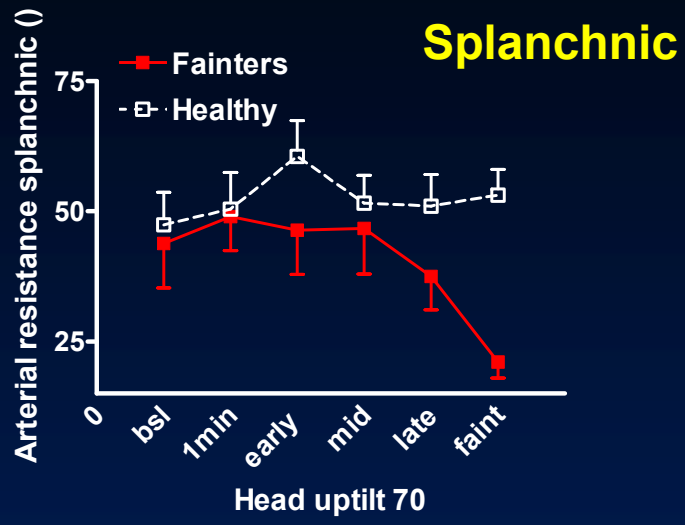
VVS Factoids

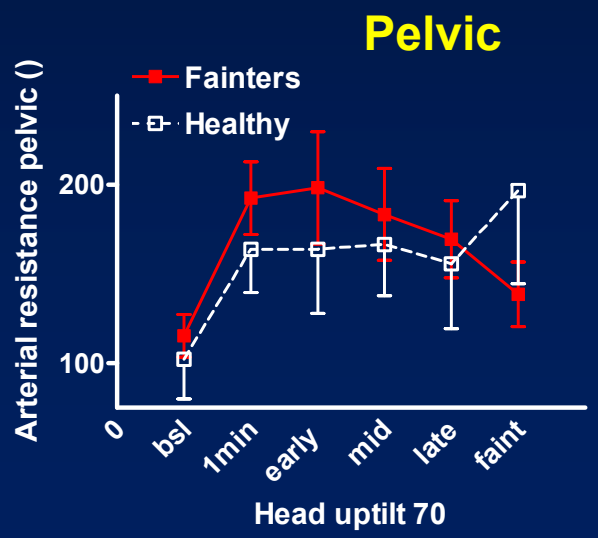
- Female 2:1
- Must R/O Cardiogenic (is not OI) but most exercise syncope is VVS. ?seizure
- VVS is not deadly unless in harm's way
- Iron/ferritin contribution
- Athlete>Sedentary
- Diagnosis by characteristic features: prodromal, ictal, post
- Tilt ?correlation with reallife?
- Variable pale appearance
- Adult studies of beta blocker, fludrocortisone not work
- Volume load needs to be huge
- If non-asystolic use physical countermeasures + water
- These require recognition of immanent faint.
- Don't stand!
- No prodrome/injury cardiogenic or asystolic VVS.
- Prolonged or very frequent

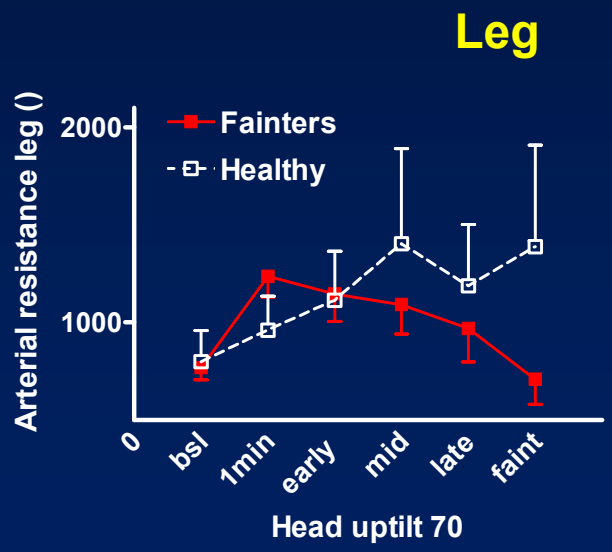

And remember, graduation is not an ending but a beginning.
MOORE

Arterial Resistance first↑, then↓ in VVS









Reflexes from Hypercontractile Underfilled Heart?

- **Bezold-Jarisch Reflex is an "an eponym for a triad of responses (apnea, bradycardia, and hypotension) following intravenous injection of veratrum alkaloids in experimental animals." The response to mechanical stimulation is much weaker.** Aviado DM, Guevara AD. The Bezold-Jarisch reflex. A historical perspective of cardiopulmonary reflexes. Ann N Y Acad Sci. 2001;940:48-58.

- **This mechanism was proposed despite the fact that any stimulus could only be short lived and baroreceptors would immediately be unloaded.** Hainsworth R. Syncope: what is the trigger? *Heart*. 2003;89:123-124.

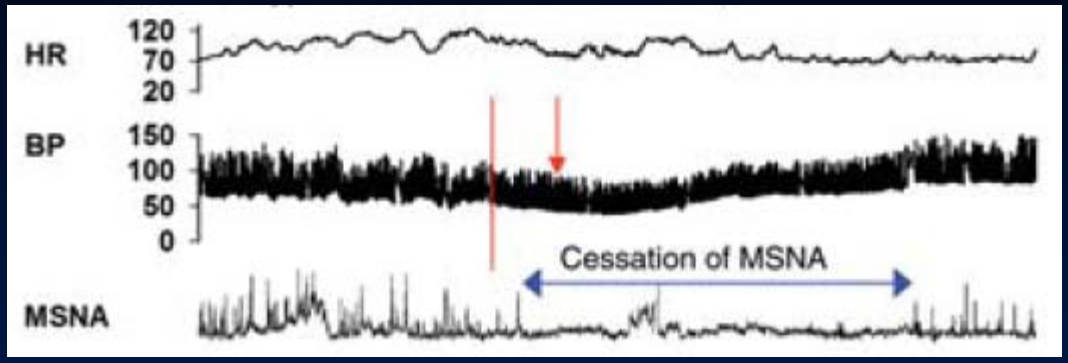
- **Relatively few afferent nerves were excited in the original Oberg and Thoren hemorrhaged cat model.** Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of the caval veins in the cat. A possible cause of the vasovagal reaction. Acta Physiol Scand 1972;85:164–73.

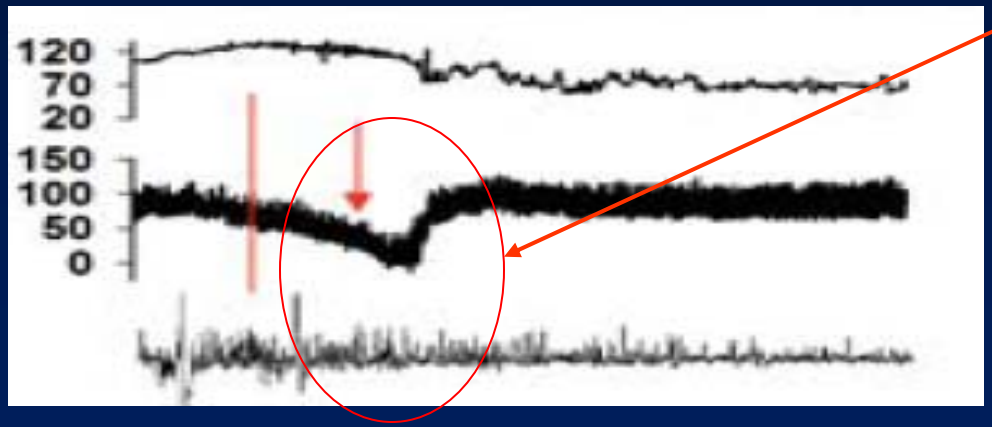
- **VVS can occur in a ventricular denervated transplant recipient given the SNP.** Scherrer U, Vissing S, Morgan BJ, Hanson P, Victor RG. Vasovagal syncope after infusion of a vasodilator in a heart-transplant recipient. *N Engl J Med*. 1990;322:602-604.

- **The heart before syncope need not be empty nor hypercontractile.** Novak V, Honos G, Schondorf R. Is the heart "empty' at syncope? J Auton Nerv Syst. 1996 Aug 27;60(1-2):83-92. Liu E et al Left ventricular geometry and function preceding neurally mediated syncope. Circulation. 2000 Feb 22;101(7):777-83.

Sympathetic Withdrawal:

↓MSNA at Faint Sufficient but not Necessary



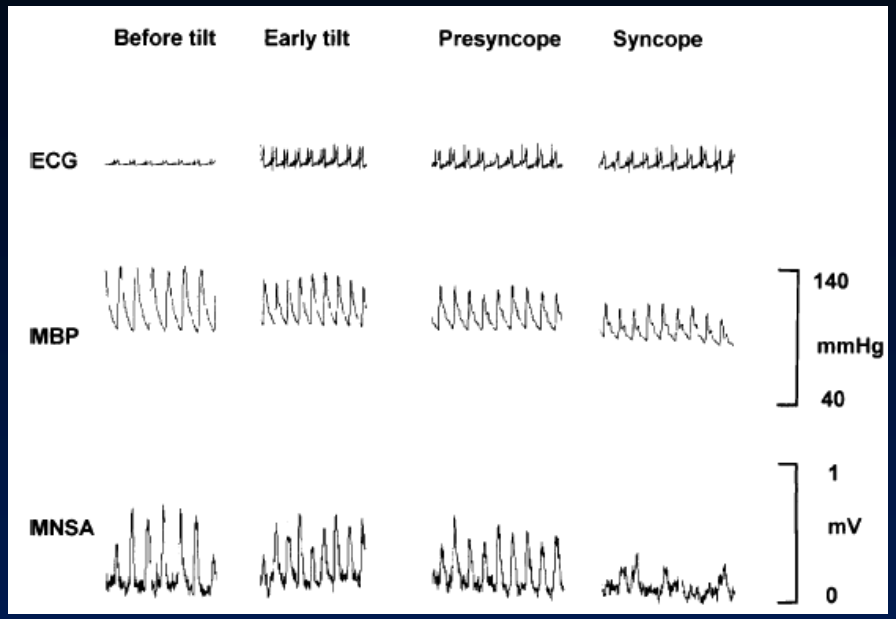


TPR decreases

MSNA does not

Eur Heart J. 2010 Aug;31(16):2027-33. **Persistence of muscle sympathetic nerve activity during vasovagal syncope.** Vavaddi G, Esler MG, Dawood T, Lambert E

Decreased MSNA in Syncope



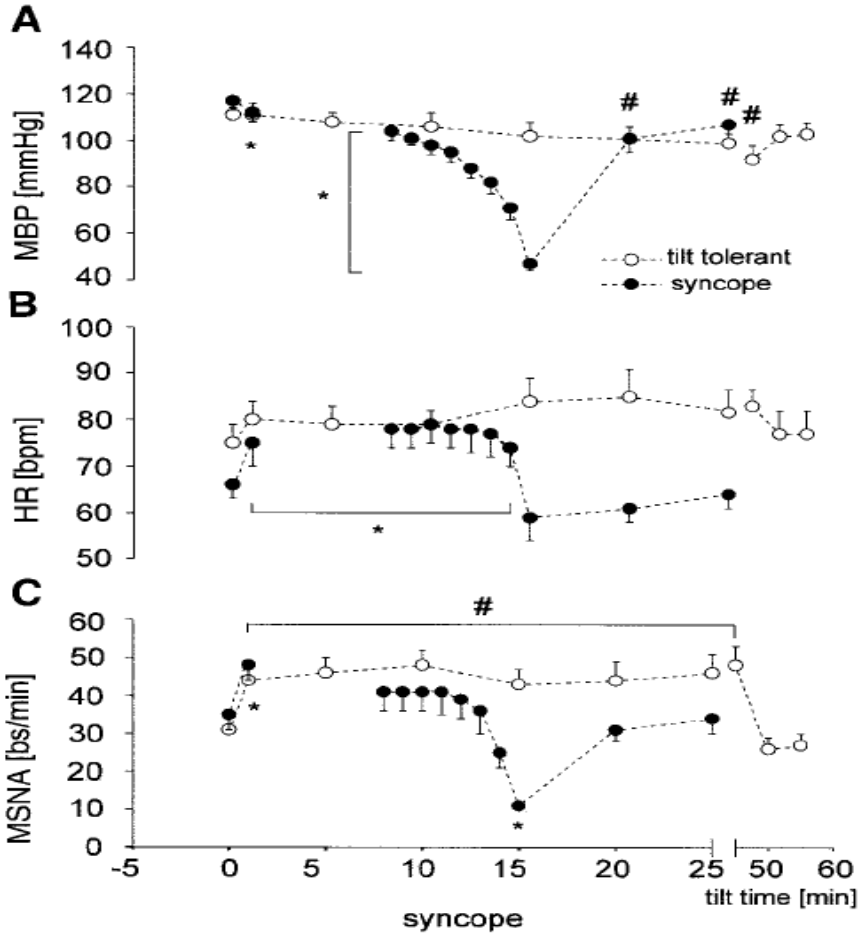


Fig. 1. Mean blood pressure (MBP) (*A*), heart rate (HR) (*B*), and muscle sympathetic nerve activity (MSNA) (*C*) during head-up tilt in tilt-tolerant (TT) and tilt-syncope (TS) patients. Mean time to syncope was 15.4 ± 2 min. In TT patients, MSNA increased for the duration of tilt and MBP did not fall below baseline levels until 20 min of tilt. In TS patients, MSNA initially increased during the first minute of tilt, but decreased to baseline levels at least 7 min before syncope. Values for MBP, HR, and MSNA from 7 min before syncope are plotted retrogradely from 15-min tilt time. bpm, Beats per minute; bs/min, bursts per minute. * Differences from baseline in TS group; # differences from baseline in TT group.

Jardine DL et al. Decrease in cardiac output and muscle sympathetic activity during vasovagal syncope. Am J Physiol Heart Circ Physio l282:H1804–H1809, 2002;