# POTS, IST, Abnormalities of Autonomic Function

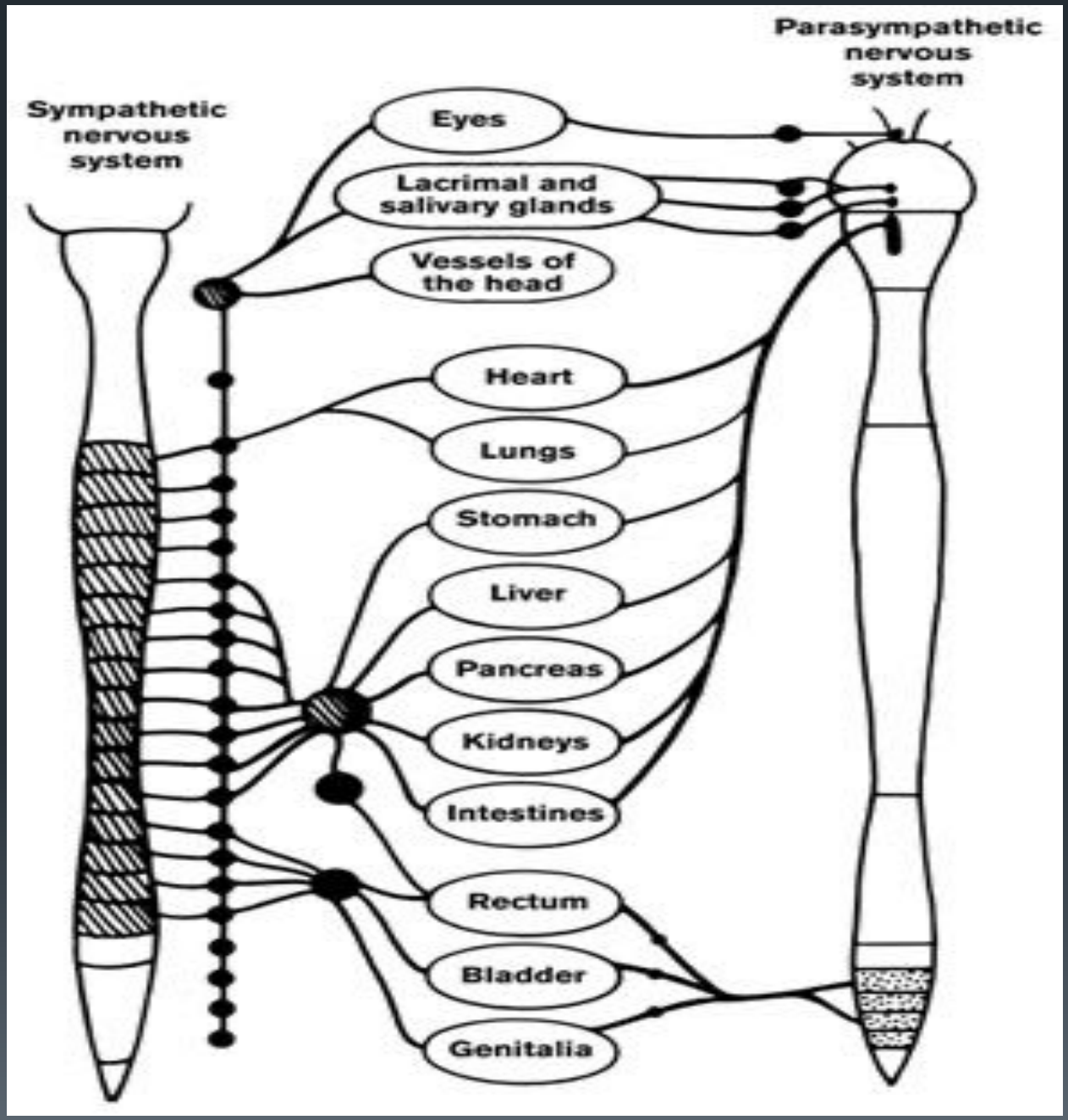
Pat Crawley

EP Conference

2012

# The Autonomic Nervous System

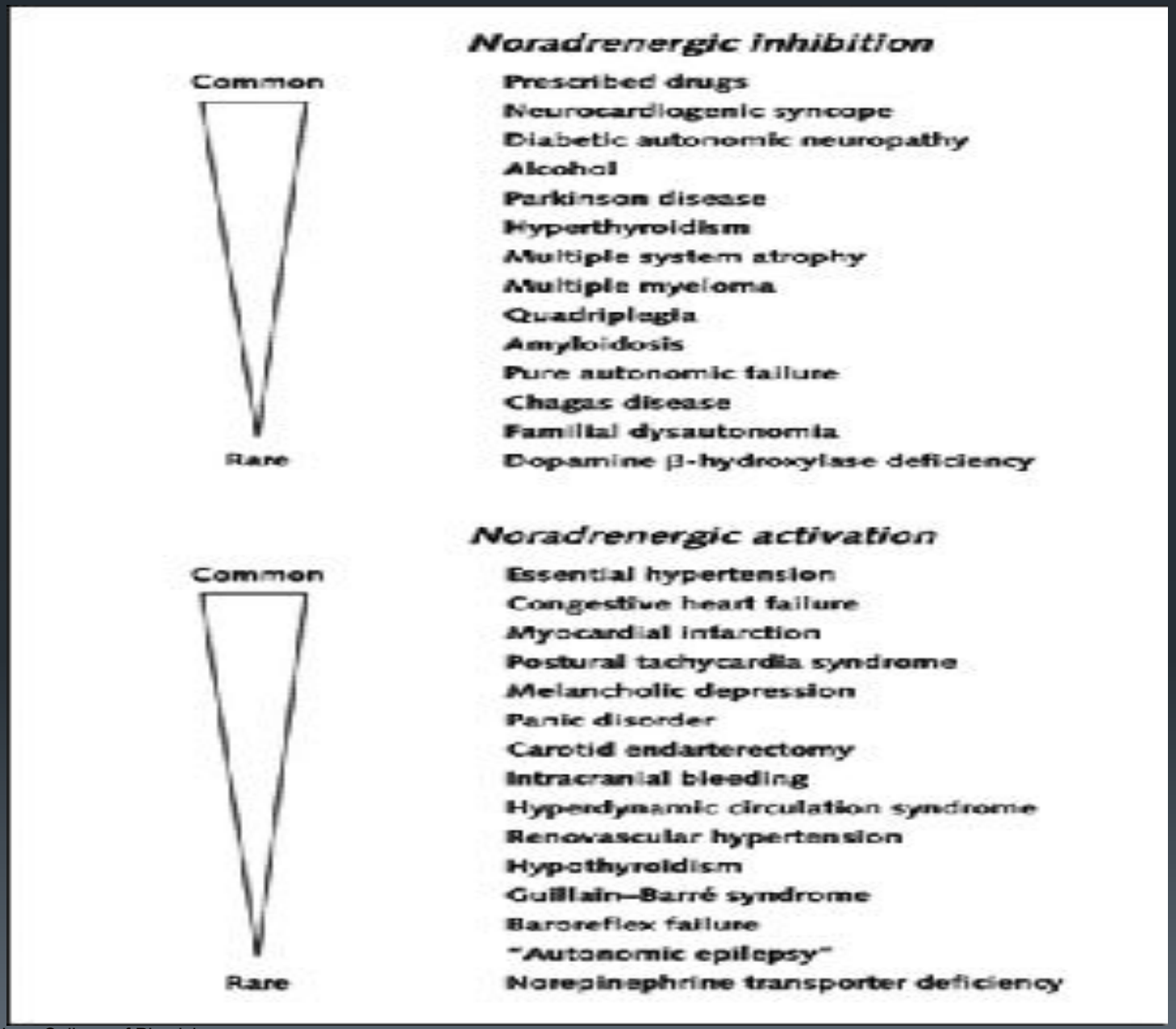
- Galen, second century
- 1552, Eustachius
- 1732, Winslow
- 1895, Oliver and Schäfer
- Abel and Takamine
- Langley
- 1920s, Walter Cannon
- Bradbury and Eggleston

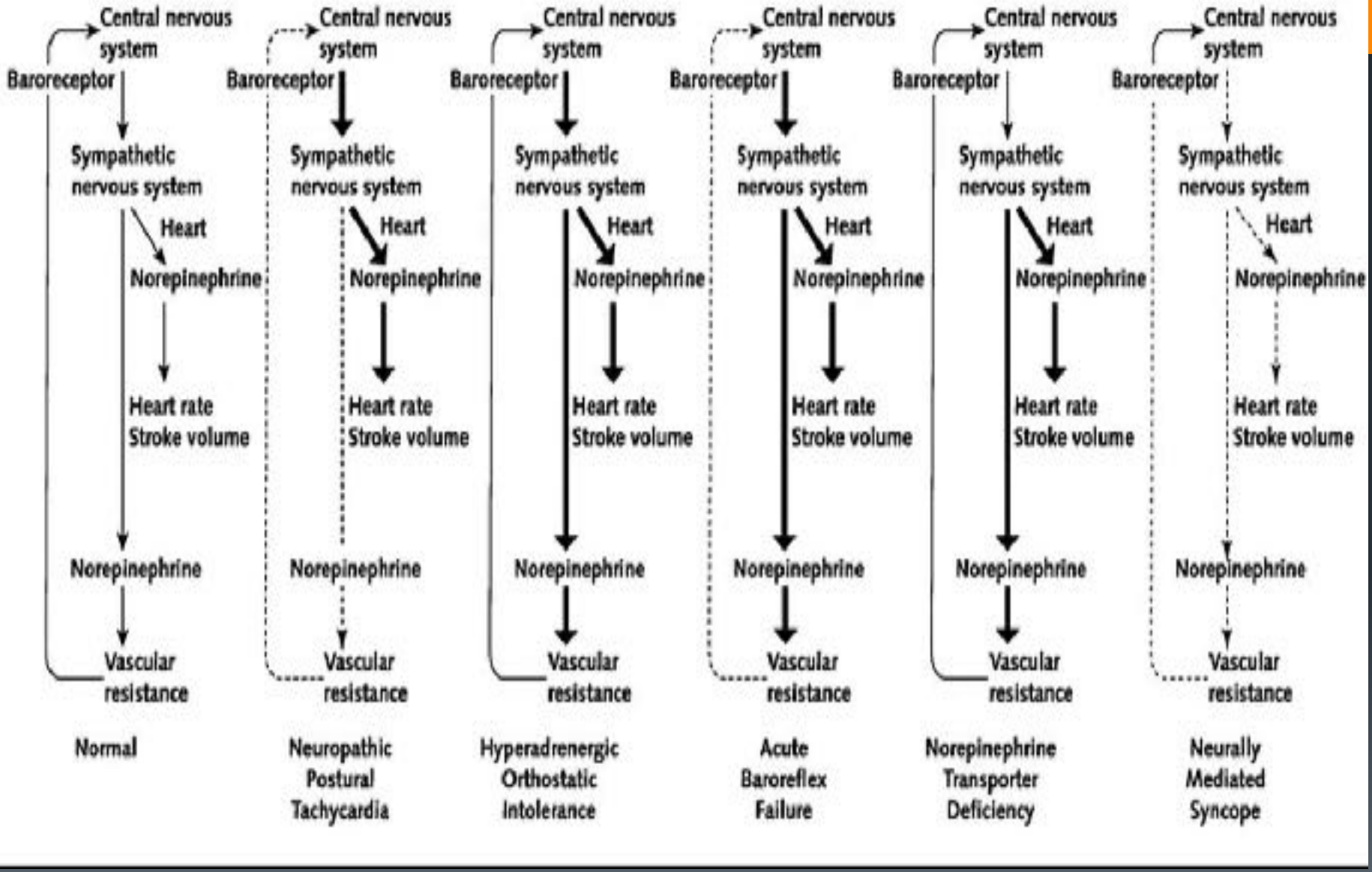

Parasympathetic nervous system
Sympathetic nervous system
Eyes
Lacrimal and salivary glands
Vessels of the head
Heart
Lungs
Stomach
Liver
Pancreas
Kidneys
Intestines
Rectum
Bladder
Genitalia

# Dysautonomia

- A condition in which altered autonomic function adversely affects health

# Dysautonomias featuring altered sympathetic noradrenergic function.




Central nervous system
Baroreceptor
Sympathetic nervous system
Heart
Norepinephrine
Heart rate
Stroke volume
Norepinephrine
Vascular resistance
Normal
Central nervous system
Baroreceptor
Sympathetic nervous system
Heart
Norepinephrine
Heart rate
Stroke volume
Norepinephrine
Vascular resistance
Neuropathic Postural Tachycardia
Central nervous system
Baroreceptor
Sympathetic nervous system
Heart
Norepinephrine
Heart rate
Stroke volume
Norepinephrine
Vascular resistance
Hyperadrenergic Orthostatic Intolerance
Central nervous system
Baroreceptor
Sympathetic nervous system
Heart
Norepinephrine
Heart rate
Stroke volume
Norepinephrine
Vascular resistance
Acute Baroreflex Failure
Central nervous system
Baroreceptor
Sympathetic nervous system
Heart
Norepinephrine
Heart rate
Stroke volume
Norepinephrine
Vascular resistance
Norepinephrine Transporter Deficiency
Central nervous system
Baroreceptor
Sympathetic nervous system
Heart
Norepinephrine
Heart rate
Stroke volume
Norepinephrine
Vascular resistance
Neurally Mediated Syncope

# Orthostatic Intolerance

- Defined by inability to remain upright without severe signs and symptoms such as hypotension, tachycardia, lightheadedness, pallor, fatigue, weakness and nausea
- Appears in many guises including overt dysautonomia, vasovagal syncope, and orthostatic tachycardia

# Physiology

- Assumption of the upright posture requires prompt physiological adaptation to gravity
- There is an instantaneous descent of approx. 500 ml of blood from the thorax to the lower abdomen, buttocks and legs
- In addition there is a 10-25% shift of plasma volume out of the vasculature and into the interstitial tissue
- This shift decreases venous return to the heart resulting in a transient decline in both arterial pressure and cardiac filling
- This has the effect of reducing the pressure on the baroreceptors, triggering a compensatory sympathetic activation that results in a increase in heart rate and systemic vasoconstriction

- So…the assumption of upright posture results in a 10-20bpm increase in heart rate, a negligible change in systolic blood pressure, and roughly a 5 mmHg increase in diastolic blood pressure

# Pathophysiology of Orthostatic Dysregulation

- Failure of the regulatory mechanism to respond properly may lead to either orthostatic hypotension as seen in autonomic failure, or orthostatic tachycardia, as seen in POTS
- Orthostatic hypotension is defined as a fall in pressure on standing of more than 20/10 mmHg.
- It is common in pts with autonomic failure for the decline to be much greater than this, which may result in loss of consciousness soon after standing
- In POTS, the blood pressure is typically maintained on standing or may even increase. Heart rate rises more than 30bpm and symptoms of impaired cerebral perfusion may develop

# POTS

# Other names

- Chronic orthostatic intolerance
- Mild orthostatic intolerance
- Orthostatic tachycardia
- Sympathotonic orthostatic hypotension
- Hyperdynamic beta adrenergic state
- Idiopathic hypovolemia
- Mitral valve prolapse syndrome
- Neurocirculatory asthenia
- Irritable heart
- Soldier's heart
- Effort syndrome

# Postural Orthostatic Tachycardia Syndrome (POTS)

- Has been described since 1940
- It is defined as the presence of symptoms of orthostatic intolerance for at least 6 months accompanied by a heart rate increase of least a 30bpm within 5-30 minutes of assuming an upright posture or  a HR≥120bpm, that occurs within the first 10 minutes of standing, without orthostatic hypotension.
- The syndrome must occur in the absence of prolonged bed rest, medications that impair autonomic regulation, or any other chronic debilitating disorders that might cause tachycardia.

# Criteria for the Postural Tachycardia Syndrome

- Heart rate increase ≥ 30 bpm from supine to standing (5-30min)
- Symptoms get worse with standing and better with recumbence
- Symptoms lasting ≥ 6 months
- Standing plasma norepinephrine ≥600 pg/ml
- Absence of other overt causes of orthostatic symptoms or tachycardia

# ETIOLOGY

- Heterogeneous
- Multiple different abnormalities have been reported
- Some proposed mechanisms:
  - Distal denervation
  - Hypovolemia
  - Changes in venous function
  - Baroreflex abnormalities
  - Increased sympathetic activity
  - Genetic abnormalities

# Symptoms

- Mental clouding (“brain fog”)
- Blurred or tunneled vision
- Shortness of breath
- Palpitations
- Tremulousness
- Chest discomfort
- Headache
- Lightheadedness
- Nausea

# Symptoms

- The symptoms may appear abruptly, often after a viral illness; or more insidious onset
- The severity of symptoms is also quite variable.
- Some patients experience only mild symptoms and often only in the setting of additional orthostatic stress (e.g., menstrual cycle, relative dehydration).
- Others are profoundly incapacitated.
- The course of the disorder may be self limited or may follow a relapsing remitting course over several years

# Symptoms

- Pre-syncope is common in these pts, only a minority actually pass out
- Chest pains are almost never due to coronary artery obstruction but are sometimes associated with electrocardiographic changes in the inferior leads, particularly when upright
- Many pts complain of significant exercise intolerance and extreme fatigue
- This may pose significant limitations on their functional capacity

# Epidemiology

- POTS is the most prevalent form of orthostatic intolerance.
- It is estimated that 500,000 Americans suffer from this disorder.
- It is the most common syndrome of young people seen in autonomic dysfunction clinics.
- Patients present at a relatively young age (14 to 45 years)
- Female:male ratio is 4:1
- Other disorders such as autoimmune diseases and irritable bowel syndrome are seen commonly seen

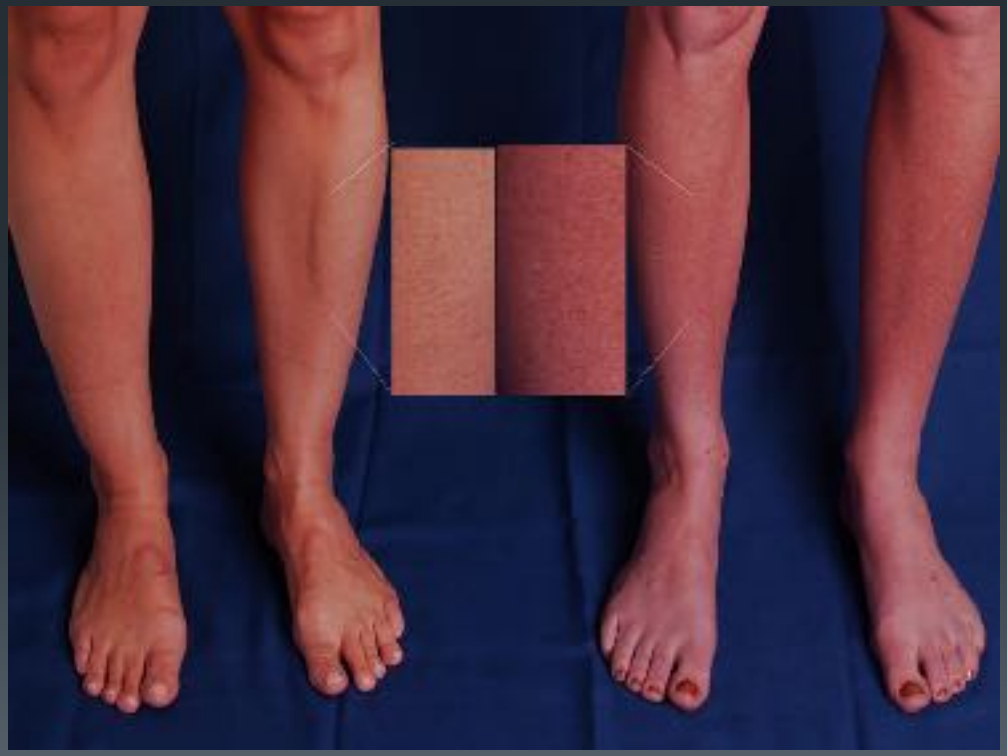
# Physical Findings

- Severe tachycardia that develops on standing from supine position
- Blood pressure and HR should be measured in both postures and should be taken immediately after standing, at 2,5, and 10 minutes.
- A sustained HR increase ≥ 30bpm is considered diagnostic
- The systolic blood pressure should not fall by more that 20mmHg.

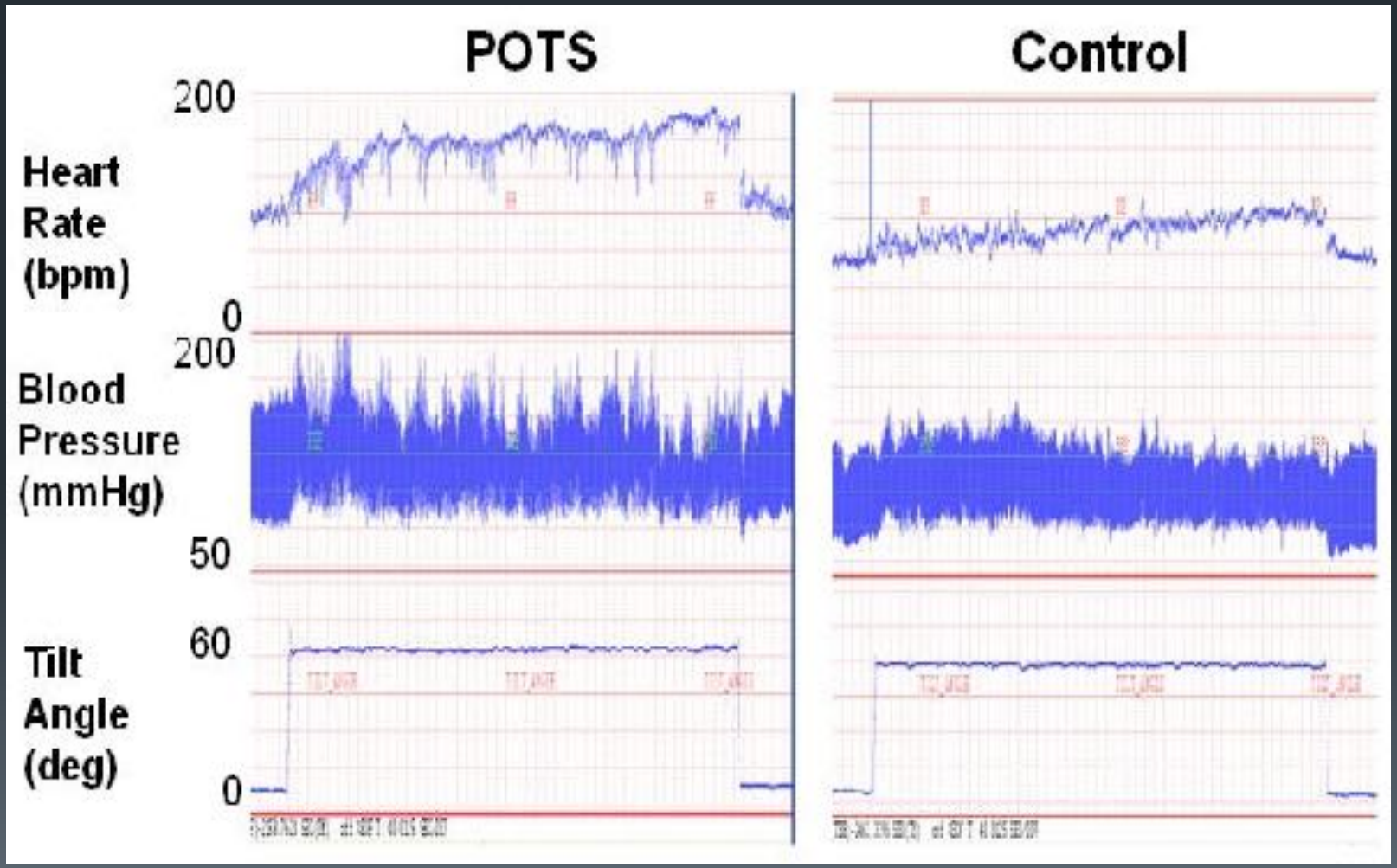
# Physical Findings

- One study noted that in pts with POTS, the orthostatic tachycardia was greater in the morning than in the evening, while there was no diurnal difference in the orthostatic change in blood pressure.
- Cardiac auscultation may reveal a murmur of MVP but significant MR is unusual
- Dependant acrocyanosis occurs in 40-50% of pts

# POTS Acrocyanosis



# Hemodynamics with Upright Posture in POTS



# Clinical Findings

- Tilt table
- POTS pts should only have ST
  - An ECG should be done routinely to rule out the presence of an accessory bypass tract or any abnormalities of cardiac conduction
  - A Holter monitor might prove useful to exclude a re-entrant dysrhythmia, esp. if the pts gives a history of paroxysmal tachycardia with sudden onset and sudden offset

# Clinical Findings

- Can measure supine and standing norepinephrine levels
  - Supine level is often normal in pts with POTS
  - Upright level is usually elevated
  - Standard plasma norepinephrine ≥ 600pg/ml in upright position is one criterion for defining POTS
- Tests of autonomic nervous system function typically show intact or exaggerated autonomic reflex responses
  - Pts often have a preserved vagal function
  - They often have a vigorous pressor response to the Valsalva maneuver, with an exaggerated blood pressure recovery and overshoot both before and after release

# Clinical Findings

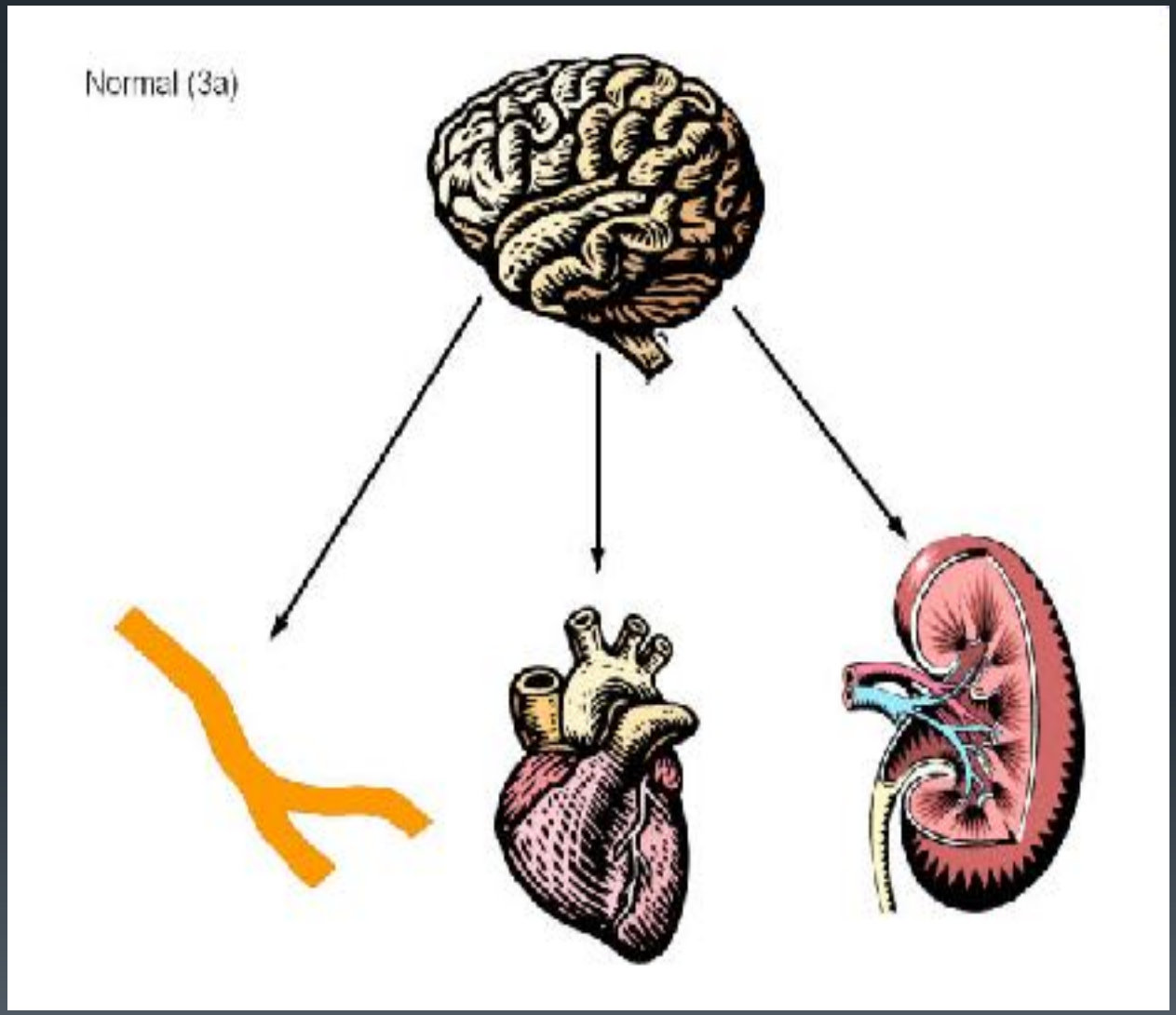
- The blood volume is low in many pts
- Pts can have co-existent complaints of episodic flushing
  - Some of these cases have an associated mast cell activation disorder

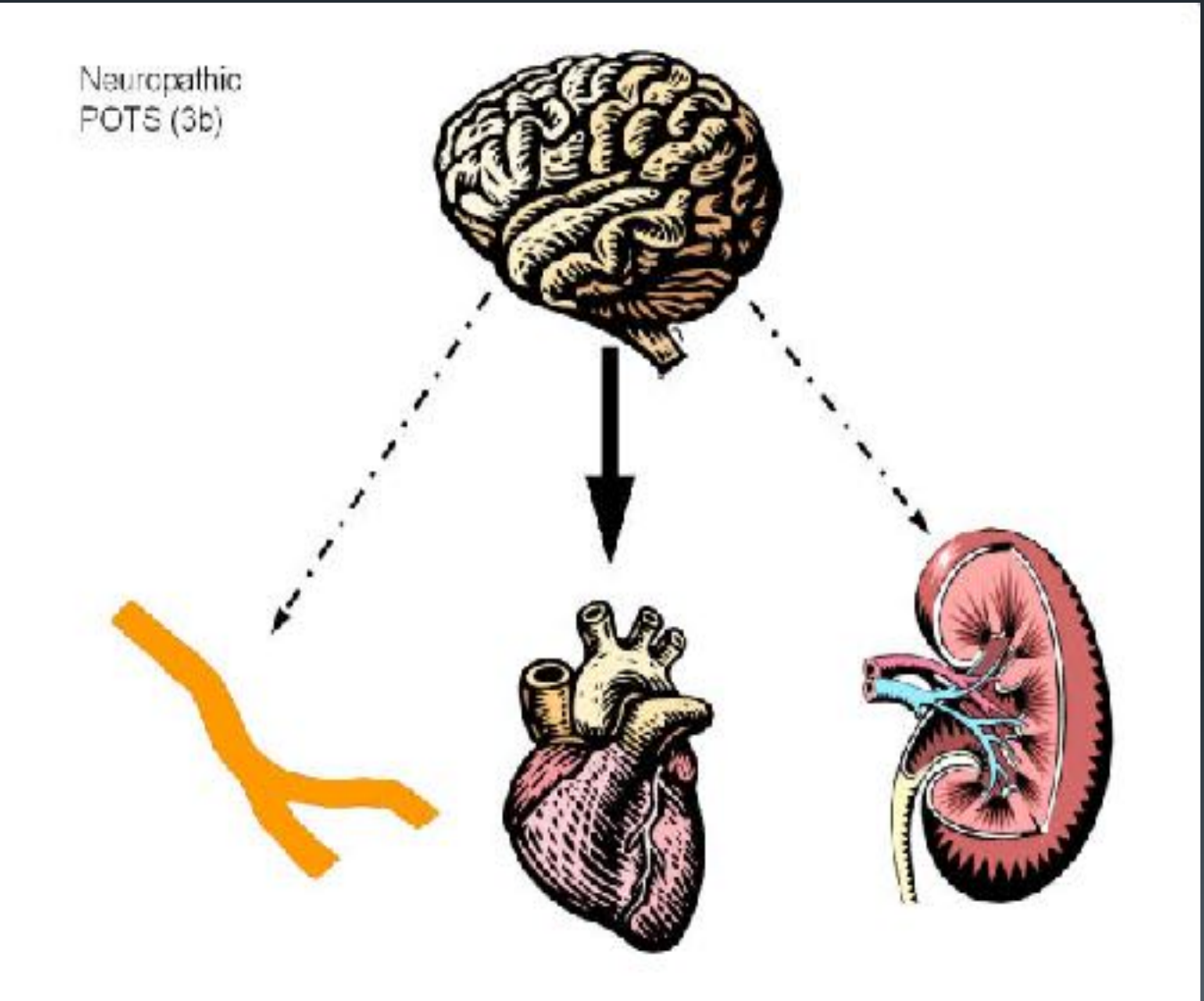
# Differential Diagnosis

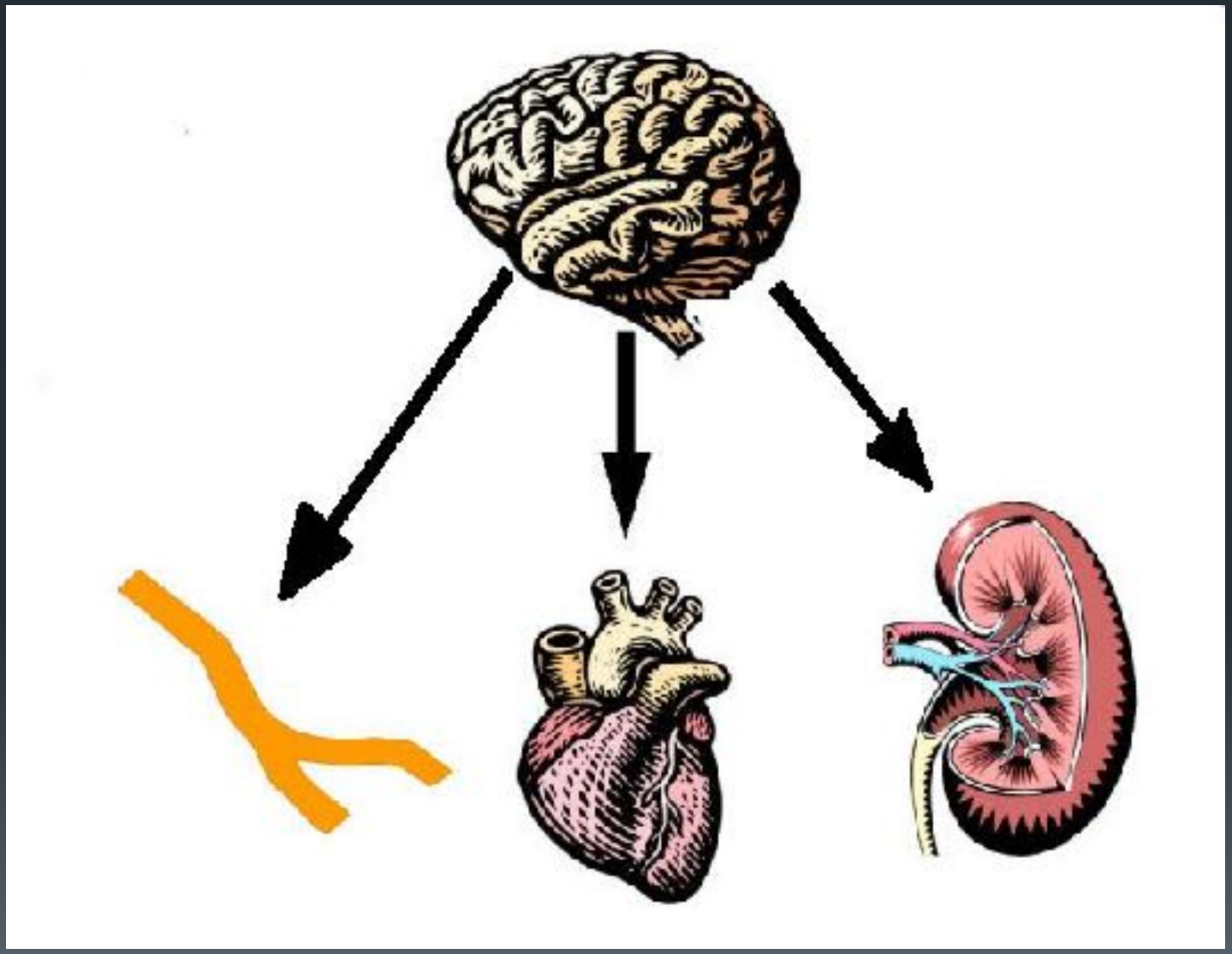
- Pheochromocytoma
- Neurally mediated syncope
- Chronic fatigue syndrome

# POTS

- Multiple distinct pathophysiological subtypes
- The most common phenotypes:
  - Neuropathy POTS
  - Central hyperadrenergic POTS


Normal (3a)


Neuropathic
POTS (3b)



# Neuropathic POTS

- Thought to be associated with partial dysautonomia with preferential denervation of sympathetic nerves innervating the lower limbs
  - Distal anhidrosis of the legs is commonly found on thermoregulatory sweat testing and quantitative sudomotor axon reflex testing
  - Ganglionic acetylcholine receptor antibody is positive in 10-15% of cases
  - There is a blunted increase in post-ganglionic sympathetic nerve discharge
  - It has been shown that leg arteriolar vasoconstriction is impaired
  - It has been shown that the increase in noradrenaline spillover in the legs is less during orthostasis compared to normal controls
  - There is excessive leg vein constriction with denervation hypersensitivity

# Neuropathic POTS

- There is patchy denervation of the sympathetic innervation of the blood vessels in the extremities (esp. the lower extremities) and the kidney with subsequent hypovolemia and increased orthostatic venous pooling.
- This feeds back to the brain to increase sympathetic nervous system outflow in a compensatory effort.
- The increased sympathetic flow is sensed mostly in the heart where no denervation is present
- Onset may occur after a viral infection, trauma, or surgery or may be associated with joint hypermobility

# Hypovolemia & Blood Volume Regulation

- Many pts with POTS have low plasma volumes
- The renin-angiotensin-aldosterone system plays a key role in the neurohormonal regulation

# Central Hyperadrenergic POTS

- Central hyperadrenergic POTS in its most florid form is much less common than neuropathic POTS comprising only ≈10% of pts.

# Central Hyperadrenergic POTS

- The underlying problem appears to be an excessive sympathetic nervous outflow from the brain that affects the blood vessels, kidneys and the heart; in addition to tachycardia, this form of POTS is often associated with orthostatic hypertension syndrome
- There is believed to be an inadequate feedback process that arises from above the level of the baroreflex
- In addition, these pts sometimes have large increases in BP on standing, indicating that baroreflex buffering is somehow impaired.
- It has been proposed that an increased noradrenergic tone at rest and a blunted post-ganglionic sympathetic response to standing with compensatory cardiac sympathetic overactivity
- This group of pts often have an upright norepinephrine level in excess of 1000pg/ml and is occasionally >2000pg/ml.

# Central Hyperadrenergic POTS

- Genetic studies have demonstrated that a defective gene causes a dysfunction in a norepinephrine transport protein, producing excessive serum norepinephrine levels
- Impairment of synaptic norepinephrine clearance may produce a state of excessive sympathetic activation in response to physiologic stimuli
- An attenuated post-viral panautonomic neuropathy could also represent another cause of dysautonomia

# Other POTS

- Norepinephrine Transporter Deficiency
  - A specific genetic abnormality.
  - A single point mutation in the norepinephrine transporter (NET)
  - Results in inability to adequately clear norepinephrine and produces a state of excessive sympathetic activation in response to a variety of sympathetic stimuli

# Other POTS

- Pharmacologic POTS
  - Many antidepressant and attention deficit medications work at least in part through inhibition of NET

# Other POTS

- Mast Cell Activation
  - Some pts with POTS have co-existent mast cell activation
  - Episodic flushing and abnormal increases in urine methylhistamine
  - Dyspnea, HA, lightheadedness, excessive diuresis and GI symptoms
  - Flushing can be triggered by long-term standing, exercise, premenstrual cycle, meals and sexual intercourse

# Diagnostic Evaluation

- H&P
- Look for overlap symptoms and alternative explanations
- Supine and upright BP
- 12-lead ECG
- Tilt testing
- If any cardiological abnormalities have been discovered at this point, the pts should undergo full cardiological assessment including echocardiography, stress testing, Holter monitoring, loop recording, and EPS as appropriate
- 24hr ambulatory monitoring is not helpful in the setting of POTS unless IST is suspected as the underlying diagnosis

# Diagnosis

- Cardinal diagnostic  criterion
  - Increased HR following orthostatic stress
  - A sustained increase in HR of ≥ 30 or to ≥ 120 bpm within 10 minutes of orthostasis is diagnostic of POTS

# POTS therapeutic management

- No therapy is considered as successful for all pts
- Identify and treat reversible causes
- Contributory medications, esp. vasodilators or diuretics, should be withdrawn and the treatment should be optimized for any chronic disease
- Educate pt and family to nature of the disorder
- Changing lifestyle, weight loss, mild aerobic exercises, avoidance of alcohol and dehydration.
- Increase fluid intake, sleeping with head of bed slightly elevated or resistance training to build up the lower extremities

# POTS Therapy

- There are no pharmacological agents that have been tested in a long-term properly powered randomized clinical trial
- Central sympatholytic agents such as clonidine or beta-adrenergic antagonists, like propranolol are often useful and well tolerated, esp. if used in low doses in pts with central hyperadrenergic POTS
- Methyldopa, a false neurotransmitter, is sometimes more successful in controlling symptoms in pts at doses of 125mg to 250 mg
- Midodrine and octreotide suppressed tachycardia in POTS and improved standing times in orthostatic intolerance. Both peripheral alpha-1 receptor antagonists showed potencies and combination therapy was not significantly better than monotherapy

# POTS Therapy

- Acute acetylcholinesterase inhibitors, like pyridostigmine, significantly attenuated tachycardia
  - It also provided an improvement in symptom burden
- Several studies have shown a disturbance of central serotonin production and regulation in pts with POTS and other symptoms of autonomic dysfunction
  - The selective serotonin reuptake inhibitors (SSRIs) have a role in the treatment of selected pts
    - Venlafaxine is probably more effective than other SSRIs
- There is some limited experience with phenobarbatal in POTS pts.

# POTS Therapy

- In the partial dysautonomic form, fludrocortisone may be used.
  - Expands volume
  - Appears to sensitize peripheral alfa 1-adrenergic receptors to the pts own catecholamine

| Therapy | Dosage | Mechanism | Drawbacks |
|---|---|---|---|
| Water | 8-10 cups/day (2-2.5 L/day) | Blood volume expansion | Hypernatremia |
| Increase Dietary Salt | 200-300 mEq $Na^+$/day | Blood volume expansion | Difficult to augment sufficiently w/o supplements |
| NaCl tablets | 1 gm tab PO TID | Blood Volume expansion | Poor taste; nausea & dyspepsia |
| Elastic support hose | 30-40 mmHg counter-pressure; waist high | Enhanced venous return | Hot, itchy & uncomfortable; edema above stocking if only knee high |
| Exercise | 30 min, 3 times a week, both aerobic and resistance | Blood volume expansion; reverse deconditioning | Vigorous exercise may worsen symptoms and result in prolonged fatigue |
| Acute IV saline | 1 L NS over 1-3 hr IV | Blood volume expansion | Effective at acute HR control; inconvenient; medical setting needed |
| Chronic IV saline | 1L NS IV q 2 days-q daily | Blood volume expansion | Anecdotal benefit only, requires central line; risks of access complications and infection. Logistically difficult |

# Medications to Augment Blood Volume

| Therapy | Dosage | Mechanism | Drawbacks |
|---|---|---|---|
| Fludrocortisone | 0.05-0.1 mg PO QD-BID | Blood volume expansion | Edema; fluid retention, hypokalemia; HA, HTN |
| Desmopressin (DDAVP) | 0.1-0.2 mg PO QD-BID | Blood volume expansion | Hyponatremia; HA; edema |
| Erythropoietin | 2000-3000 IU SQ 1-3 weeks | Blood volume expansion | Expensive; requires injection |

# Medications to Decrease Sympathetic Tone

| | | | |
|---|---|---|---|
| Clonidine | 0.05-0.2 mg PO BID | Agonist of pre-synaptic α-2 receptor; decreases SNS traffic | Mental clouding; fatigue; drowsiness; constipation; dry mouth |
| Methyldopa | 124-250 mg PO TID | False neurotransmitter; decreases SNS traffic | Hypotension; HA; constipation; drowsiness |

# Other medications

| Therapy | Dosage | Mechanism | Drawback |
|---|---|---|---|
| Propranolol | 10-20mg PO BID-QID | β-adrenergic receptor antagonist | Hypotension; drowsiness; fatigue; wheezing; nightmares |
| Midodrine | 2.5-10mg PO TID | α-1 adrenergic receptor agonist | Hypertension; goose bumps urinary retention; pins & needles sensation |
| Pyridostigmine | 30-60mg PO TID | Acetyl-cholinesterase inhibitor | Abdominal cramping; diarrhea; increased sweating; increased secretions/tearing |
| Midafinil | 100mg PO BID | Stimulant; mechanism of action unclear | May reduce mental cloudine; increase in HR |

# IST

- First described in 1979
- Also called chronic nonparoxysmal sinus tachycardia
- Ill defined clinical syndrome with varied clinical presentation
- Characterized by an increased resting HR or an increase in apparent sinus rate unrelated to or out of keeping with the level of physical or emotional stress
- May be associated with incapacitating symptoms requiring aggressive therapy

# Symptoms

- Palpitation
- Lightheadedness
- Easy fatigue
- Dyspnea
- Presyncope
- Syncope
- Chest pain

- Exercise intolerance
- Dyspnea
- Myalgia
- HA
- Abdominal discomfort
- Anxiety
- depression

# Epidemiology

- Primarily young women (15-50 yrs)
- Often health care workers
- Hypertensive

# Causes….Unknown

- May be related to
  - Ectopic atrial focus in the sinus node region
  - Normal sinus node with increased sympathetic tone or failure to respond to vagal stimulation
  - Intrinsic abnormality of the sinus node
- Autonomic imbalance?
  - Excess sympathetic and reduced parasympathetic tone
  - Antibodies against β adrenergic receptors

# Diagnosis

- Resting HR > 100 bpm
- P-wave morphology identical to sinus rhythm (paroxysmal) or positive in ECG leads I,II and AVF
- Exclusion of secondary causes
- Exclusion of SN reentry and right atrial tachycardia

# Diagnosis

- Diagnosis of exclusion
- Causes of appropriate ST must be ruled out:
  - Anemia
  - Pheochromocytoma
  - Hyperthyroidism
  - Volume depletion
  - Fever
  - Anxiety
  - Medications
  - cardiomyopathy

# Diagnosis

- ECG
- Holter monitor
  - the mean HR exceeds 95bpm, a daytime resting HR exceeds 95 bpm or an increase in SR from supine to upright position of more than 25-30 bpm
- Echocardiogram to exclude structural heart disease
- Blood or urine tests to exclude anemia, hyperthyroidism and pheo
- Medication review: hydralazine or other vasodilators, too much thyroid hormone replacement, sympathomimetics for asthma or COPD, anticholinergic meds for IBS, stimulants for ADD.

# Diagnosis

- Tilt table test to exclude autonomic disorders that can mimic IST
  - POTS, OH
- Eventually an EPS may be required to exclude tachycardias arising from near the SN

- Investigation of choice is a 24-h Holter recording
  - Demonstrates a persistent increase in sinus rate to >100bpm during waking hours

# Prognosis

- It does not shorten life or cause death, stroke or myocardial infarction
- Virtually never leads to tachycardiomyopathy

# Management

- There are no case series or clinical trial comparing management strategies
- Initial therapy should be low risk and moderate efficacy
- Pharmacologic therapy fits this description but is imperfect
- Aggressive invasive treatment strategies are accompanied by a small yet significant risk but offer the potential for a cure

# Pharmacologic Therapy

- β-adrenergic blocker or verapamil
- Agents that affect SN automaticity and/or autonomic tone such as amiodarone or propafenone, may warrant an empiric trial in selected pts

# Nonpharmacologic Therapy

- Surgical exclusion of the SN region or AV node radiofrequency catheter ablation
  - Usually accompanied by ppm
- Radiofrequency sinus node modification

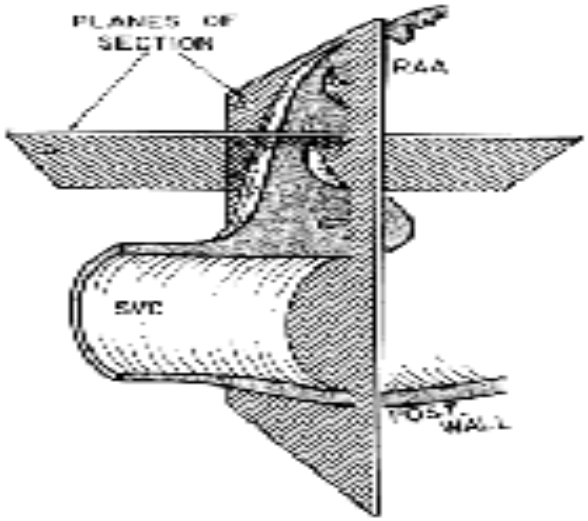



Fig. 1 *Diagram to illustrate the two methods of sectioning the tissue block for histological examination of the sinus node. (A) Frontal plane sectioning (8 hearts). (B) Transverse plane sectioning (17 hearts). SVC, superior vena cava; RAA, right atrial appendage; CT, crista terminalis.*

reconstruction was carried out with the aid of a calibrated measuring eye piece (Fig. 2).

## Results

The sinus node was easily identified in all the hearts studied. Though in several there was venous congestion of the node and adjacent atrial myocardium, no other pathology was recognised.

### LOCATION OF NODE

In 23 hearts the sinus node lay in the groove between the right atrial appendage and the lateral atrial wall (sulcus terminalis) (Fig. 3). The long axis of the node was parallel to the sulcus terminalis, with the anterosuperior 'head' situated between 2 and 4 mm below the crest of the right atrial appendage. The posteroinferior 'tail' was up to 10 mm below this level. The anterosuperior 'head' was subepicardial and the posteroinferior 'tail' predominantly intramyocardial with the tip of the 'tail' contacting subendocardial tissue. In 5 hearts the sinus node straddled the crest of the atrial appendage so that the anterosuperior 'head' was to

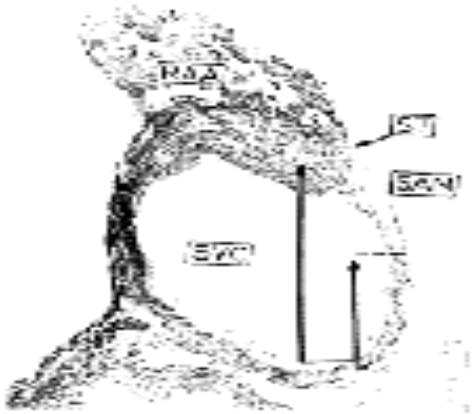



Fig. 2 *A transverse section of the sinoatrial junction showing the sinus node. Examples of some of the measuring lines used to reconstruct the anatomy of the region are superimposed. SVC, superior vena cava; RAA, right atrial appendage; SAN, sinoatrial node; CT, colour terminalis. (× 7.)*

the left of the crest and the 'body' and 'tail' were to the right of the crest (Fig. 4). In these hearts the posteroinferior 'tail' was situated at a higher level than in the other 23 hearts.

### DIMENSIONS OF NODE

The node measured between 4 and 6 mm in length, 2 and 3 mm in width, and less than 1 mm in thickness. These measurements did not include the transitional zone around the node (vide infra).

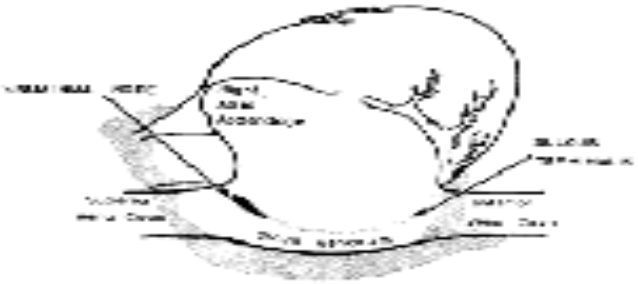
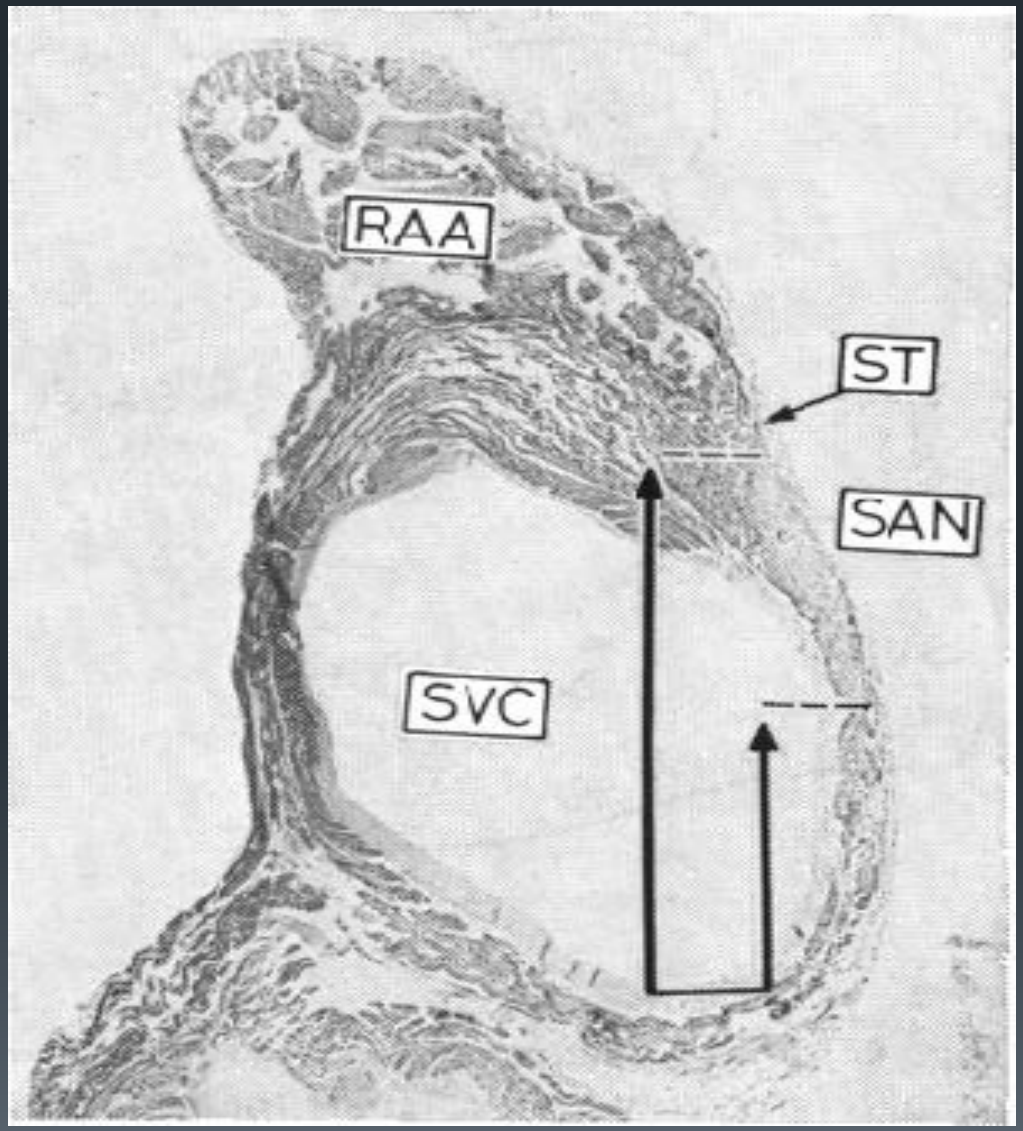


Fig. 3 *Diagram of a heart viewed from the right side of the chest showing the location of the sinus node in 22 of the 23 hearts studied.*


RAA
ST
SAN
SVC

# IAT and POTS: Definition, Clinical Presentation and Proposed Mechanisms

| | IST | POTS |
|---|---|---|
| Heart rate | Inappropriate for physiologic need, >90-100 bpm at rest or with minimal exertion, mean >95bpm on Holter | Persistent increase >30bpm or absolute rate >120bpm within 10 minutes when moving fro supine to upright position in the absence of orthostatic hypotension |
| Symptoms | Frequent multisystem | Frequent multisystem |
| Proposed mechanisms | Sinus node automaticity<br>Cardiac sympathetic tone<br>Cardiac sympathetic receptor sensitivity<br>Blunted cardiac para-sympathetic tone<br>Subtle or regional autonomic dysregulation overlapping with POTS | Length-dependent autonomic neuropathy<br>Venous pooling<br>α-hyposensitivity<br>β-hypersensitivity<br>Baroreceptor dysfunction<br>Hypovolemia<br>Brainstem dysregulation |