Laboratory Testing of Autonomic Function

Indications and Uses of Testing
- Conditions of generalized autonomic failure
- Help define the degree of autonomic dysfunction and distinguish more benign from life threatening disorders
- Localize the site and distribution of autonomic dysfunction
- Detection of small fiber neuropathy
- Evaluate for sympathetically mediated pain syndromes
- Conditions of orthostatic intolerance

Generalized Autonomic Failure
- Causes include
  - Diabetic autonomic neuropathy
  - Amyloid neuropathy
  - Sjogren’s syndrome
  - Panautonomic neuropathies: idopathic and paraneoplastic
  - Pure autonomic failure
  - Multisystem atrophy

Benign Disorders
- Vasovagal/neurocardiogenic and micturition syncope
- Chronic idiopathic anhidrosis
- Postural orthostatic tachycardia syndrome (POTS)
- Distal small fiber neuropathies
Commonly Used Techniques

- Quantitative sudomotor axon reflex test (QSART)
- Orthostatic BP and HR responses
- HR response to deep breathing and Valsalva
- Tilt table testing
- Thermoregulatory sweat testing

Patient Preparation

- No food, caffeine, nicotine for 3 hours prior to testing
- No anticholinergic medication, fludrocortisone, diuretics, sympathomimetics or parasympathomimetic agents for 48 hours
- No α- or β- antagonists for 48 hours
- Avoid analgesics the day of testing

QSART Testing

- Physiologic basis:
  - Neural pathway is an "axon reflex"
  - Postganglionic sympathetic pseudomotor axon is activated by acetylcholine
  - Impulse travels antidromically
  - Upon reaching a branch point it travels orthodromically to the nerve terminal
  - Results in release of ACh at the neuroglandular junction
  - ACh binds to M3 muscarinic receptors on sweat glands evoking the sweat response

Physiologic Setup

- Nitrogen gas is pumped into a microcompartment sweat capsule attached to the skin
- Acetylcholine is applied by iontophoresis into the skin using a constant current generator
- The sweat response is recorded from a second population of sweat glands
- Output is recorded by a sudorometer
- Stimulus is a constant current of 2mA applied for 5 minutes
- Response is recorded during stimulus and for a subsequent 5 minutes
Recording the QSART

- Recording sites:
  - Medial forearm: medial antebrachial cutaneous nerve
  - Proximal leg: peroneal nerve
  - Distal leg: saphenous nerve
  - Proximal foot: sural nerve
- Normal values are age and sex dependent
  - Sweat output of women about ½ that of men
  - Output normally decreases with age

Abnormal QSART Patterns

- Normal: indicates integrity of the postganglionic sympathetic sudomotor axon
- Reduced: postganglionic sympathetic failure
- Absent: suggests spontaneously active nerve activity
- Excessive: may be seen in patients with hyperalgesia such as diabetic neuropathies and RSD
- Latency may be reduced in the context of painful neuropathies

Sympathetic Skin Response

- Another method of measuring sudomotor activity
- Measures changes in voltage on the skin surface attributed to sudomotor activity and skin resistance
- Recorded via standard EMG electrodes applied to the palm and dorsal hand and sole and dorsal foot
- Response is generated via a noxious stimulus or deep inspiration
- Response is abnormal only when absent
- Studies have apparently shown good correlation with QSART
- Problems include rapid habituation of response and lack of quantitation

![QSART Graph](image.png)

Figure 5.2: The quantitative sudomotor axon reflex test (QSART) in Case Report 1 shows a height-dependent reduction of sweat output at distal sites. QSART output is normal in the forearm and proximal leg, reduced in the distal leg, and absent on the foot.
Thermoregulatory Sweat Test

- Evaluates the integrity of the entire efferent sympathetic cholinergic pathway instead of simply the unmyelinated postganglionic sudomotor axons
- The entire body is covered by alizarin red, cornstarch, and sodium carbonate
- The patient is then enclosed in a cabinet for 30-60 minutes at 44-50 degrees C with humidity of 40-50%
- The percentage of anterior body anhidrosis is measured

TST Result Patterns

- Normal: no areas of reduced sweating except pressure points, scars and other scattered skin lesions
- Distal: sweat is diminished in acral areas and lower abdominal wall seen with length dependent neuropathies
- Focal: sweat loss in isolated dermatomes or localized defects in the skin
- Segmental: large contiguous zone seen with injury to the sympathetic chain or white rami (pancoast tumor in apical lung)
- Regional: large anhidrotic areas less than 80% of the body
- Global: loss of >80% seen with damage to the CNS sympathetic pathways
- Mixed: more than one pattern in the same individual

Tests of Cardiovagal Function

- All are fairly sensitive
- Heart rate response to deep breathing is probably preferable because both afferent and efferent pathways are vagal mediated and most patients can comply with the procedure
- Other tests such as valsala ratio and cardiovascular response to standing have more complex physiology and also detects adrenergic failure
- Heart rate and beat to beat BP are measured using photoplethysmography which is a non-invasive technique providing arterial waveforms from a finger cuff
Physiology of Heart Rate and BP Control

- Control of heart rate is a balance between slowing effects of parasympathetic and accelerating effects of sympathetic input.
- In healthy individuals parasympathetic tone predominates.
  - Preganglionic neurons originate in nucleus ambiguous and travel to the heart via the vagus n.
  - Sinoatrial node innervated by the right vagus.
  - AV node innervated by left vagus.
- Sympathetic innervation is via β1 receptors and increases HR and contractility.
  - Preganglionic sympathetic fibers originate in intermediolateral cell column of C8-T6.
  - Synapse in the stellate ganglia.
  - Postganglionic fibers join with parasympathetic postganglionic fibers to form a complex of mixed efferent nerves to the heart.

Control of Blood Pressure

- Vasomotor center in the medulla assimilates information from multiple inputs.
  - Baroreceptors in the carotid sinus and aortic arch send input to the nucleus of the solitary tract via glossopharyngeal and vagus nerves.
  - Baroreceptors are also present in the cardiac chambers and large pulmonary vessels.
- Efferents from the vasomotor center descend in the bulbospinal tract and synapse with sympathetic preganglionic fibers in the intermediolateral column.
  - Preganglionic fibers join the paravertebral sympathetic chain.
  - Postganglionic fibers join segmental spinal nerves to provide vasomotor innervation throughout the body.

Heart Rate Response to Deep Breathing

- Based on the fact that the rate of breathing has a significant effect on the R-R interval, "respiratory sinus arrhythmia".
- These rhythmic changes are almost entirely due to vagal input.
- This is maximal at a rate of 5-6 breaths/minute.
- Typically about 8 cycles are recorded and repeated after a period of rest.
- The HR range is derived.
- Values may be affected by age, hypocapnia (hyperventilation), sympathetic activity, depth of breathing, salicylates, obesity.
Valsalva Ratio
- During this test, the subject is asked to maintain a column of mercury at 40mm Hg for 15 seconds via a mouth piece with a small air leak.
- VR is derived from maximum HR generated divided by the lowest HR occurring within 30 seconds of the max.
- The HR responses are mediated by the baroreflex.
- Increased HR occurs in response to a fall in BP.
- Beat to beat BP should also be recorded.

Normal Valsalva Maneuver Produces Four Phases
- Phase 1: Mechanical compression of the aorta propels blood into the peripheral circulation resulting in increased BP and fall in HR.
- Not dependant on autonomic activity
- Phase 2: divided into early and late
  - Early: BP falls as blood pools in splanchnic and low ext. HR increases mediated by baroreceptor response.
  - Late: Peripheral resistance increases in response to reduced BP via sympathetic outflow/increased plasma norepinephrine. BP returns to resting levels.

Valsalva Maneuver
- Phase 3: Forced expiration concludes, intrathoracic pressure decreases, BP falls and HR increases transiently
- Phase 4: BP overshoots baseline as venous return and cardiac output becomes normal but peripheral vascular resistance remains high. There is a baroreflex mediated bradycardia.
Patterns of Response

- Cardiovagal failure: BP response is normal, but the vagal influence over HR is lost and VR is reduced - diabetic neuropathy
- Conditions producing B1-adrenergic hypersensitivity causes an excessive phase 4 BP overshoot - POTS syndrome
- Adrenergic failure: there is an excessive fall of BP and pulse pressure during early phase 2, loss of BP recovery during late phase 2 and reduced overshoot in phase 4
- Global autonomic failure there is combination of cardiovagal and adrenergic results with late of HR increase during early phase 2 and lack of overshoot in phase 4

Response to Standing

- Divided into immediate phase (0-30 sec) and stable period (30sec-20 min)
- Immediate response is characterized by a sharp decrease in BP and total systemic resistance at 5-10 sec followed by rapid rebound and overshoot
- There is a corresponding HR increment at 3-5 sec
- There is an initial surge in cardiac output followed by a steady decrease
- Hemodynamics then become stable at 30sec- 20min
  - HR increases 15-30%
  - Diastolic BP increases 10-15%
  - Thoracic blood volume is decreased 25-30%
  - Cardiac output is decreased 15-30%

Tilt Table Testing

- Patients should not take any medications for at least 12 hours prior to testing
- NPO for at least 2 hours prior to testing
- Mechanisms involved in compensating for postural changes include
  - Withdrawal of vagal tone through activation of baroreceptors
  - Sympathetic activation producing tachycardia and peripheral vasoconstriction
  - Activation of the renin-angiotensin and vasopressin system
  - Muscle pumping in the legs
**Normal Response to Tilt**

- Transient reduction in systolic, diastolic and mean BP with recovery within 1 minute
- There is withdrawal of parasympathetic input followed by sympathetic activation
- Humoral response consisting of increased plasma norepinephrine and vasopressin
- Normal response is HR increment between 10 and 30 BPM
- BP remains stable

**Abnormal Response to Tilt**

- Grade 1/mild orthostatic intolerance
  - HR > 30 BPM but absolute HR < 120 BPM, pulse pressure reduced > 50%, BP stable
- Grade 2: seen with POTS syndrome
  - HR > 30 BPM and absolute HR > 120, pulse pressure reduced > 50%, BP normal or increased with prominent oscillations
- Grade 3: Asymptomatic orthostatic hypotension
  - Systolic BP reduced > 30 mm Hg, diastolic > 15 mm Hg, mean BP > 20 mm Hg
- Grade 4: same as grade 3 but is symptomatic

**Disease Specific Patterns on Autonomic Testing**
POTS Syndrome

- QSART: normal or reduced response in distal sites
- HR with deep breathing usually normal
- Valsalva maneuver: excess fall during early stage 2, reduced late stage 2 and prolonged stage 4
- Tilt table: HR increment > 30 BPM within 5 minutes of standing/tilt or absolute HR > 120 BPM, BP is normal or with prominent oscillations
- Othostatic symptoms develop

Autonomic Failure due to Amyloid Neuropathy

- QSART: sweat volume reduced in a length dependent or patchy pattern
- HR variability to deep breathing reduced
- Valsalva maneuver demonstrates excessive fall of BP during early phase 2 and absent phase 4 with reduced valsalva ratio
- Tilt table test produces a fall in systolic and diastolic BP without reflexive tachycardia