Autonomic Function Tests: Some Clinical Applications

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Modern autonomic function tests can non-invasively evaluate the severity and distribution of autonomic failure. They have sufficient sensitivity to detect even subclinical dysautonomia. Standard laboratory testing evaluates cardiovagal, sudomotor and adrenergic autonomic functions. Cardiovagal function is typically evaluated by testing heart rate response to deep breathing at a defined rate and to the Valsalva maneuver. Sudomotor function can be evaluated with the quantitative sudomotor axon reflex test and the thermoregulatory sweat test. Adrenergic function is evaluated by the blood pressure and heart rate responses to the Valsalva maneuver and to head-up tilt. Tests are useful in defining the presence of autonomic failure, their natural history, and response to treatment. They can also define patterns of dysautonomia that are useful in helping the clinician diagnose certain autonomic conditions. For example, the tests are useful in the diagnosis of the autonomic neuropathies and distal small fiber neuropathy. The autonomic neuropathies (such as those due to diabetes or amyloidosis) are characterized by severe generalized autonomic failure. Distal small fiber neuropathy is characterized by an absence of autonomic failure except for distal sudomotor failure. Selective autonomic failure (which only one system is affected) can be diagnosed by autonomic testing. An example is chronic idiopathic anhidrosis, where only sudomotor function is affected. Among the synucleinopathies, autonomic function tests can distinguish Parkinson’s disease (PD) from multiple system atrophy (MSA). There is a gradation of autonomic failure. PD is characterized by mild autonomic failure and a length-dependent pattern of sudomotor involvement. MSA and pure autonomic failure have severe generalized autonomic failure while DLB is intermediate.

**Key Words**
cardiovagal, sudomotor, adrenergic, dysautonomia.

Introduction

The autonomic nervous system regulates such important functions as blood pressure (BP), heart rate, thermoregulation, respiration, gastrointestinal, bladder, and sexual function. Autonomic dysfunction can occur as a result of many diseases that affect autonomic pathways. The clinician’s role is to seek out symptoms of dysautonomia, but it is then necessary to determine if these symptoms are really due to involvement of autonomic systems. In the past, methods to evaluate autonomic function has been unavailable or too invasive. Recent advances in technology and the development/selection of autonomic function tests have resulted in the availability of quantitative, non-invasive, and reproducible tests and have made autonomic function testing accessible to the clinician. The focus of this review is to briefly describe a number of tests that are available to the clinician and how they might help in clinical situations.

Autonomic Function Tests

The goals of autonomic function tests are summarized in Table 1. In clinical terms, they help the clinician diagnose the presence of dysautonomia, its distribution and severity, and since they are quantitative, whether it is getting better or worse. Goal #1 is to evaluate the severity and distribution of sudomotor, cardiovagal, and adrenergic function using non-invasive quantitative tests (described below). Goal #2 is to diagnose limited or restricted autonomic failure. When autonomic testing first
began, the goal was to diagnose generalized autonomic failure alone. With increasing sophistication, we can now diagnose dysautonomia confined to a single system or area. One example is distal small fiber neuropathy (DSFN), where unmyelinated fibers to the toes and feet are affected, causing loss of sweating and pain. Another example is chronic idiopathic anhidrosis, where widespread sudomotor failure occurs and adrenergic and cardiovagal functions remain intact. Goal #3 is to diagnose and evaluate orthostatic intolerance. Head-up tilt (HUT) will allow the laboratory to diagnose orthostatic hypotension (OH). It is now recognized that more subtle alterations, such as the postural tachycardia syndrome (POTS), can be diagnosed on HUT by an excessive heart rate response. Goal #4 is to monitor the course of dysautonomia. The laboratory permits the clinician to quantitatively determine if the condition is getting better or worse and the rate of change. For instance, the rate of change is quite slow in Parkinson’s disease and much more rapid in multiple system atrophy (MSA). Goal #5 is to monitor response to treatment either clinically or in research (Goal #6). Autonomic testing is very useful when incorporated into clinical trials. It is possible to provide a quantity of autonomic failure and determine whether treatment is making this number get better or worse. We have used this approach in evaluating if IVIG will work in treatment of autoimmune autonomic ganglionopathy.

Tests of sudomotor function
The tests are summarized in Table 2, the system evaluated, neural pathways involved, and clinical interpretation. We provide here a brief description of each test.

Quantitative sudomotor axon reflex test (QSART)
QSART evaluates the functional integrity of the postganglionic sympathetic sudomotor axon. Acetylcholine is iontophoretically applied into the skin, activating axon terminal. Impulses travel along the postganglionic sudomotor axon, initially antidromically, reaching a branch point, then orthodromically (hence an axon reflex) to release acetylcholine at nerve terminal, releasing acetylcholine, which activates muscarinic receptors on eccrine sweat gland. The resulting sweat response is recorded routinely from four sites (forearm, proximal leg, distal leg, and foot). The results are then interpreted by comparison with normative data derived from studies on 223 healthy subjects aged 10-83 years.

Thermoregulatory sweat test (TST)
The TST is a test where sweating is induced by thermoregulatory warming resulting in a rise of core temperature. Sweating occurs when core temperature exceeds thermoregulatory set point at the hypothalamus. This tests the intactness of thermoregulatory sympathetic pathways from the hypothalamus to eventually the eccrine sweat gland. Therefore, this is a test of lesions anywhere from the hypothalamus to the sweat gland. An unclad subject lies supine and his or her exposed body surface is covered with an indicator powder mixture. The body is warmed to a core temperature of 38°C; sweat is recog-
nized by a change in color in the indicator. The sweat distribution is documented by digital photography. The sweat pattern provides a pattern of intact sweating and of anhidrosis. Some patterns are highly characteristic, for instance of neuropathy, ganglionopathy, or of generalized autonomic failure. The digital images are processed by a pixel counter to derive an accumulative value for the area and percentage of anhidrosis. The percent anhidrosis has provided a useful number to follow quantitatively the course of an autonomic disorder.

**Tests of cardiovagal function**

Cardiovagal function can be evaluated by a number of methods. In the time domain, the commonly used and most reliable approach is to quantify heart rate response to deep breathing and to the Valsalva maneuver. The subject breathes at 6 breaths per minute and the magnitude of heart rate variation (maximal heart rate minus minimum heart rate) is averaged and provides an index of cardiovagal function. There are a number of alternative approaches, including mean circular resultant.

The Valsalva ratio is derived from the maximum heart rate generated by the Valsalva maneuver divided by the lowest heart rate occurring within 30 seconds of the peak heart rate.

Our studies suggest that 40 mm Hg for a duration of 15 seconds should be used as the standard since it has yielded the most reproducible results.

Cardiovagal function can also be quantified in the frequency domain. Spectral analysis of resting heart rate produces several peaks. The highest frequency peak (>0.15 Hz) reflects oscillations of heart rate due to respiratory sinus arrhythmia and is considered to be a measure of cardiovagal function.

**Tests of adrenergic function**

1. BP and heart rate responses to the Valsalva maneuver
2. Head-up tilt study
3. Plasma norepinephrine
4. MIBG, cardiac uptake

The evaluation of adrenergic function, specifically the vagal and adrenergic components of the baroreflex, can be made by studying dynamic alterations during the Valsalva maneuver. There are four main phases in the Valsalva maneuver (Fig. 1).

Phase I is a transient rise in BP due to the act of blowing. Early phase II is due to reduced preload (venous return). The baroreflex then results in efferent sympathetic discharge to muscle resulting in a rise in BP. This sustained rise in BP is interrupted by a transient fall in BP, phase III, which like phase I, is mechanical, lasting 1-2 seconds, during which BP falls (because the subject stops the maneuver). This rise in BP is described as phase II_L, BP recovery following phase III and phase IV, reflects the increase in total peripheral resistance (Fig. 1A). Evaluation of the baroreflex can be done non-invasively from the Valsalva maneuver. The vagal component of the baroreflex is evaluated by relating the beat-to-beat BP during phase II_E to the heart period (reciprocal of heart rate) providing baroreflex sensitivity in msec/mm Hg. The adrenergic component of the baroreflex can be evaluated by BP recovery time (PRT), which is the time (in seconds) that the BP takes to recover from phase III to baseline.

HUT complements the beat-to-beat BP responses to the Valsalva maneuver. HUT provides an evaluation of the BP and heart rate response to tilt. A normal response consists of a modest rise in heart rate (by 5-20 bpm) and BP remains relatively constant (modest fall in systolic BP by <10 mm Hg and modest diastolic rise). HUT is done to detect if OH is present. Fig. 2 are examples of HUT showing a normal response (Fig. 2A), neurogenic OH (Fig. 2B), POTS in Fig. 2C, and syncope (Fig. 2D). In Fig. 2B, there is a marked fall in BP with a blunted heart rate response, typical of neurogenic OH. This was re-
The Mayo Autonomic Laboratory was established in 1983. It now performs autonomic studies on over 4000 patients per year. A number of applications have been well-documented and have stood the test of time. We shall summarize examples of such applications.

Distal small fiber neuropathy

One of the most common and distressing neurologic complaints is DSFN. The patient complains of a burning sensation in their feet, especially toes and plantar aspect of their feet. There is typically troublesome alldynia, where a non-painful stimulus elicits pain. Sensory examination may demonstrate a loss of sharp/dull or temperature perception at the toes. Motor function is usually normal. Common causes are diabetic and inherited neuropathy, but the most common cause is idiopathic. Nerve conduction studies are often normal since this is a small fiber and not large fiber neuropathy. This condition causes a length-dependent involvement of unmyelinated fibers, both somatic and autonomic. Sympathetic sudomotor fibers are affected, so that QSART will show abnormalities at the feet and normal sweating more proximally (Table 3) in about 3 out of 4 patients tested. Similarly, the thermoregulatory sweat test shows anhidrosis that is confined to the distal feet. Skin biopsy and evaluation of intraepidermal fiber density on the same subjects and the same sites have been studied prospectively in patients with autonomic neuropathy. Both skin biopsy and QSART will accurately diagnose DSFN but their agreement is imperfect, since they measure different populations of unmyelinated fibers. QSART is also helpful in following the natural history of DSFN and to determine if the neuropathy re-
Table 3. Comparison of current study with earlier studies

| Number of patients | Stewart et al. | Tobin et al. | Novak et al. | Total | Abnormal | Normal | p value* |
|-------------------|---------------|-------------|-------------|-------|----------|--------|---------|
| 40                | 15            | 92          | 125         | 47    | 78       |        |         |
| QSART abnormalities | 32/40 (80%)  | 12/15 (80%) | 67/92 (73%) | 96/125 (77%) | 35/47 (74%) | 61/78 (78%) | 0.79    |
| TST distal patterns of anhidrosis | 18/25 (72%) | n/a         | 93/125 (74%) | 35/47 (74%) | 58/78 (74%) |        | 0.84    |
| TST any abnormality | 24/25 (94%)  | n/a         | 114/125 (91%) | 44/47 (94%) | 70/78 (90%) |        | 0.53    |
| Either TST or QSART abnormality | 36/40 (90%) | n/a         | 123/125 (98%) | 46/47 (98%) | 77/78 (99%) |        | >0.99   |
| Cardiovagal abnormality | 11/40 (28%) | 9/12 (75%)  | 43/125 (35%) | 15/46 (33%) | 28/76 (37%) |        | 0.78    |
| Adrenergic abnormality | 0/40* (0%)   | 2/12* (17%) | 0/92* (0%)  | 53/125 (43%) | 21/46 (46%) | 32/77 (42%) | 0.80    |

*Comparing current study with previous studies.

We used Pearson chi-squared test with Yates continuity correction except for “TST any abnormality” and “Either TST or QSART abnormality” which are based on Fisher exact test due to small numbers in some cells of the 2×2 table.

Generalized autonomic failure

Physicians have learnt to recognize symptoms of autonomic failure. These include orthostatic lightheadedness, syncope, erectile dysfunction, and symptoms suggestive of neurogenic bladder and bowel. However, it is not possible to quantitate the severity and distribution of such abnormalities to help the physician determine if the patient is getting better or getting worse or if they are responding to therapy. With the availability of autonomic testing, it is possible to determine if generalized autonomic failure is present. Generalized autonomic failure refers to autonomic failure that is diffuse (multiple regions) and involves more than one autonomic system. Examples of generalized autonomic failure are the autonomic neuropathies and multiple system atrophy. Examples of autonomic neuropathies are diabetic autonomic neuropathy, amyloid neuropathy, and autoimmune autonomic ganglionopathy. In severe diabetic autonomic neuropathy, there is widespread loss of sweating, cardiovagal failure is present, and OH with impaired baroreflexes is seen. In the synucleinopathies (Parkinson’s disease, multiple system atrophy, Lewy body dementia), generalized autonomic failure tends to be present in MSA, mild in PD, and intermediate in DLB.

Typically, for a comprehensive evaluation of autonomic function, we undertake an autonomic reflex screen and thermoregulatory sweat test as a routine. We often measure norepinephrine supine and standing to determine if supine values are reduced (indicating widespread postganglionic adrenergic denervation) and if an orthostatic increment (doubling) occurs. We will typically do additional studies to seek a cause. These include fat aspirate or nerve biopsy for amyloidosis or an antibody panel seeking especially for presence of ganglionic antibody. Detailed descriptions are available for a comprehensive coverage.

Selective autonomic failure

The astute clinician can suspect that autonomic failure may be restricted rather than generalized. This suspicion can be confirmed and quantified with autonomic testing. Autonomic tests can confirm that a specific autonomic function is affected and that other systems are intact. We provide 3 examples. A patient, aged 30 years, feels hot, weak, dizzy and uncomfortable when ambient temperature rises. BP supine and standing is normal. He looks hot and flushed but has dry skin. Orthostatic BP recording is normal without evidence of OH. The clinician may suspect this is restricted autonomic failure but testing is necessary. Autonomic testing demonstrates normal cardiovagal and adrenergic function. However, QSART and TST show global anhidrosis. This is a condition called chronic idiopathic anhidrosis. Another example is a patient with gastroparesis. This patient has postprandial bloating and weight loss. He vomits up food that is 3 days old. Autonomic testing shows normal sudomotor and adrenergic function. Gastric transit studies show marked delay in gastric transit. A third patient has Adies pupils. Tests can be done to confirm the entity, but autonomic testing is needed to demonstrate that the deficits are confined and not generalized.

The synucleinopathies

The term synucleinopathies is used to describe several neuro-
degenerative disorders characterized by fibrillary aggregates of alpha-synuclein protein in oligodendroglia (in MSA) and in selective population of neurons. These disorders include Parkinson’s disease (PD), dementia with Lewy bodies (DLB), PAF, and MSA. Although it is recognized that autonomic failure, manifest as erectile dysfunction, neurogenic bladder, constipation, and OH occur in the synucleinopathies, there has been little emphasis on the use of autonomic function tests in the differential diagnosis of these conditions. Based on our research on the involvement of autonomic structures in brain and spinal cord, we hypothesized that the severity and distribution of autonomic failure was different among synucleinopathies.

PD and MSA share clinical features of hypomimia, hypertonia, dysarthria, micrographia, and gait impairment. PD is more likely associated with rest tremor and is typically levodopa-responsive. However, MSA can also have rest tremor and levodopa responsiveness, albeit less robust. Recent studies indicate that MSA is distinguishable from PD using autonomic tests. PD is characterized by a length-dependent involvement of postganglionic sudomotor fibers, whereas MSA is characterized by widespread, early and preganglionic autonomic failure. MIBG or fluorodopa scan of the heart, which images postganglionic adrenergic innervation, is typically defective in PD and normal in MSA. However, denervation can occur in 25-30% of MSA patients. Another useful test is the TST. TST is either normal or shows very distal anhidrosis, typically affecting the toes. If both QSART and TST are performed, normal QSART volume in an anhidrotic region indicates that the lesion is preganglionic in site. When the autonomic reflex screen is performed and the aggregate score, the composite autonomic severity score (CASS) calculated, CASS separates MSA from PD with sensitivity and specificity. The autonomic and clinical characteristics of the synucleinopathies are distinctive (Table 4). PAF is characterized by severe OH, without clinical central involvement. Supine plasma norepinephrine is often markedly reduced and CASS is >6 and TST% >40%. PD is associated with normal NE, CASS <6, and TST% <40%. MSA is characterized by CASS >6 and TST% >40%. DLB has intermediate autonomic failure.

**Orthostatic intolerance**

Orthostatic intolerance refers to the development of symptoms after assuming the standing posture that clears on sitting or ly-

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**Table 4. Autonomic scores in the synucleinopathies**

| Variable | PD       | DLB      | MSA      | PAF      |
|----------|----------|----------|----------|----------|
| Age      | 71.5±8.5 | 74.4±7.2 | 73.0±5.5 | 59.9±16  |
| N        | 20       | 20       | 20       | 20       |
| CASS     | 2.2±1.2  | 5.2±2.0  | 8.1±1.3  | 9.4±1.2  |
| TST%     | 19.3±35.5| 26.4±30.0| 69.1±26.9| 73.1±36.3|

*All values expressed as SD and range in brackets. CASS: composite autonomic severity score, DLB: dementia with Lewy bodies, MSA: multiple system atrophy, PAF: pure autonomic failure, PD: Parkinson’s disease, TST: thermoregulatory sweat test.
Concluding Thoughts

Clinical management of the dysautonomias depends on good clinical acumen. The role of autonomic testing is to increase sensitivity and specificity in the detection of autonomic failure. The two work hand in glove and each enhances the other. There are limitations of clinical autonomic testing. The non-invasive approach is appropriate but imperfect. For instance, the beat-to-beat BP devices sometimes give erroneous signals, so that judgment is important in the interpretation of autonomic tests. Autonomic testing is a growing and evolving field so that guidelines will and should change over time.

Conflicts of Interest

The authors have no financial conflicts of interest.

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