ASSESSMENT:
CLINICAL AUTONOMIC TESTING

Report of the Therapeutics and Technology Assessment Subcommittee
of the American Academy of Neurology

Overview. The focus of this report is on noninvasive, quantitative tests of autonomic function that are currently used in autonomic laboratories. This has been a daunting task for a number of reasons. First, there are a large number of tests of autonomic function. Second, there is the concept that the evaluation is not only an extension of the clinical examination but also that the repertoire of tests is best interpreted together. It is somewhat simplistic to ascribe a single function to a single test. The particular clinical question may require the selection of a specific battery tailored to answer the question at hand. Third, although noninvasive tests are easy to perform, there are significant confounding variables,[1] including the patient's state of hydration and medication status. Fourth, the majority of tests of autonomic function evaluate end-organ responsiveness so that end-organ failure itself can affect test results.

There is also a specific background strength in autonomic tests. Contrary to many neurophysiologic tests, which typically were introduced straight from the basic to the clinical laboratory with little validation, autonomic tests have been used extensively in clinical trials, so that detailed information on sensitivity, specificity, reproducibility, and confounding variables is available.

This report is derived from a detailed analysis of the available literature on autonomic testing, including published reports and unpublished data from major autonomic laboratories, and the expertise of clinical autonomic physiologists who helped prepare this report. Copious data are available. For instance, in a literature search, cardiovascular combined with autonomic function for the last 5 years alone appeared in over 1000 publications. This report was derived from approximately 100 published articles and three major autonomic textbooks and a consensus report.[2] Medline was used, searching for only human subject data in English. For the purpose of this evaluation, we have focused on tests that meet the criteria of sensitivity, specificity, reproducibility (coefficient of variation, 20%), safety, and usefulness. The usefulness of the test was evaluated by considering its clinical and physiologic relevance, noninvasiveness, ease of use, and standardization. We also considered (1) availability, (2) noninvasiveness, and (3) a substantive published literature to render this evaluation.

There are several special clinical reasons for utilizing tests of autonomic function. There is increasing evidence that the function of unmyelinated and small myelinated peripheral nerve fibers may improve as neuropathy improves[3,4]; these fiber populations are at least as amenable to improvement as somatic fibers.[4] There is good clinical evidence that sympathetic fibers have a great propensity to regenerate.[5] Autonomic cardiovascular indices correlate with function, such as cardiovascular exercise performance. As the cardiovascular autonomic neuropathy worsens, the cardiovascular performance and systemic peripheral resistance responses become more abnormal,[6] so that autonomic neuropathy may contribute to exercise intolerance. Another reason for autonomic evaluation is that patients with autonomic failure show an increase in mortality.[7-9] For example, blood pressure instability (requiring pharmacologic treatment) predicts increased intraoperative mortality.[10,11]

The availability of clinical autonomic testing will likely remain the domain of the clinical neurophysiology laboratory, mostly in referral centers, in the foreseeable future. The role of the clinician in routine clinical practice is to undertake a thorough evaluation of clinical autonomic symptoms, perform a bedside autonomic examination, and determine if there are strong indications for further studies.[12]

The following tests or categories were selected for consideration.

1. Cardiovagal innervation (parasympathetic innervation): heart rate (HR) response or deep breathing, Valsalva ratio, and HR response to standing (30:15 ratio)
2. Adrenergic: beat-to-beat blood pressure (BP) responses to the Valsalva maneuver, sustained hand grip, and BP and HR responses to tilt-up or active standing
3. Sudomotor: quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test (TST), sympathetic skin response (SSR), and Silastic sweat imprint

Table *Evaluation summary of autonomic function tests*

Test	Application	Rating	Quality of Evidence Ratings (class)	Strength of Evidence Ratings
Cardiovagal heart rate	Diagnosing and monitoring the course of autonomic neuropathy	Established	I, II	B
Adrenergic	Diagnosing and monitoring the course of autonomic neuropathy	Established	I, II	B
Sudomotor	Diagnosing autonomic neuropathy	Established	III	D
Skin vasomotor		Investigational	III	D
Neurogenic flare		Investigational	III	D

Thermography has been the subject of a previous evaluation and was not further evaluated. It was the conclusion of the previous evaluation that there is inadequate evidence to justify its use in detecting radiculopathies, but that it is a reasonable test to use in patients with reflex sympathetic dystrophy.[13] Plasma catecholamine determinations will not be considered except to comment that this test, while relatively insensitive in detecting adrenergic failure, is essential in detecting the presence of dopamine-hydroxylase or related deficiencies.[14]

I. Individual tests of autonomic function
    A. Cardiovagal heart rate tests
        1. Heart rate response to deep breathing. This test approaches the optimal test for cardiovagal function. Both the afferent and efferent pathways are vagal.[15,16] The end point is the maximal HR variability obtained under laboratory conditions, where the confounding variables of age, rate, and depth of respiration were controlled.[7,8,15-23]
        2. Valsalva ratio. This ratio is derived from the maximal HR generated by the Valsalva maneuver divided by the lowest HR following the maneuver.[16,20-22,24-26]
        3. Heart rate response to standing. The initial HR responses to standing consist of a tachycardia at 3 then 12 seconds followed by a bradycardia at 20 seconds. The initial cardioacceleration is an exercise reflex, while the subsequent tachycardia and bradycardia are baroreflex mediated. The 30:15 ratio (R-R interval at beat 30)/(R-R interval at beat 15), has been recommended as an index of cardiovagal function.[7,16,20,23,24,27-29] The above three tests evaluate cardiovagal function. They have a high sensitivity and specificity and are safe, valuable, and cost-effective. The tests are well standardized. The confounding variables are well known for response to deep breathing and the Valsalva maneuver but less well known for the standing test. The tests are reproducible, with a coefficient of variation of 20%. They are also simple to perform and are *established* tests of autonomic function. These tests have been used in clinical neurophysiology laboratories for over a decade.

    B. Laboratory indices of adrenergic function
        1. Beat-to-beat BP recordings of the Valsalva maneuver. The availability of a well-validated photoplethysmographic volume clamp technique to measure beat-to-beat BP[30-35] has permitted the application of the well-known properties of the phases of the Valsalva maneuver to the clinical laboratory.[30,31] The test greatly enhances the sensitivity and specificity of the laboratory evaluation of adrenergic function.[30,31,34,35] The test should be classified as an *established* test.
        2. Sustained hand grip. Sustained muscle contraction causes a rise in systolic and diastolic BP and HR. The stimulus derives from exercising muscle and central command.[36,37] Efferent fibers travel to the muscle and heart, resulting in increased cardiac output, BP, and HR. This autonomic maneuver has been adapted as a clinical test of sympathetic autonomic function.[38] BP is measured using a sphygmomanometer cuff. The test is of limited sensitivity and specificity. Confounding variables are not well known. It should be regarded as an *investigational* test.
        3. Blood pressure and heart rate response to standing. Supine and tilted BP recordings, especially when supplemented with beat-to-beat BP and HR recordings, can be used as an established test of

adrenergic function and are an essential part of any laboratory evaluation of patients with suspected adrenergic failure. More recently, focus has shifted to lesser degrees of adrenergic failure and patients with vasodepressor syncope.[39] To evaluate these patients, the duration of tilt has been extended to 60 minutes and infusions of isoproterenol have been given.[16,40] Isoproterenol is given to induce vasodepressor presyncope and evaluate receptor supersensitivity and the presence of autonomic failure.[41-51] A tilt test for 40 minutes without isoproterenol infusion has been suggested to be adequate in separating patients with and without vasodepressor syncope; isoproterenol infusion should be avoided because it degrades the specificity of the test.[46,52,53] Extensive experience is now available in medical centers focused on syncope. The test is an *established* test.

C. Sudomotor tests

1. Quantitative sudomotor axon reflex test distribution. The QSART measures axon reflex-mediated sudomotor responses quantitatively and evaluates postganglionic sudomotor function.[54-56] Typically, recording from the forearm and three lower extremity skin sites are used to evaluate the distribution of postganglionic deficits. The test has a high sensitivity, specificity,[25] and reproducibility, with a coefficient of variation of 20%.[25,55] Confounding variables are well known. The test is straightforward in established laboratories and the equipment can be assembled from commercially available units.[57-60] The test has been in use in clinical laboratories for a decade. It is an *established* test.

2. Thermoregulatory sweat test. The TST is now well standardized.[21,24,61-63] It evaluates the distribution of sweating by a change in color of an indicator powder.[64,65] The test has recently been rendered semiquantitative and expressed as a percentage of anterior body anhidrosis.[62] The test has a high sensitivity. As a stand-alone test, it has a low specificity, and limited information is available on its reproducibility and confounding variables. Combined with QSART, its specificity for delineating the site of the lesion is greatly enhanced. The test has been in clinical use for at least four decades. It is an *established* test.

3. Sympathetic skin responses. The recorded skin potential is derived from activated eccrine sweat glands, and the amplitude and configuration are modulated by sweat gland epithelium and the overlying epidermis.[66] The test is of relatively low sensitivity and uncertain specificity and habituates. Its greatest advantage is its relative ease of performance in a standard EMG laboratory. The test is of some value as part of an autonomic battery. As an extension of an EMG laboratory it has significant value, and clinical neurophysiologic laboratories have now had considerable experience with the test for a decade.[32,66-74] It is a commonly used test that will likely be replaced by better tests such as the QSART or sweat imprint as these become more conveniently available. It is an *established* test.

4. Sweat imprint. This is formed by the secretion of active sweat glands into a plastic imprint.[75-78] This test can be used to determine sweat gland density; a histogram of sweat droplet size and sweat volume per area can be obtained. The test seems to be sensitive and quantitative. It is an *established* test.

II. Safety of autonomic tests. The noninvasive autonomic tests have an extremely high value to risk ratio. There are a small number of potential risks. The potential risk factors and safety of the tests will be evaluated by category.

The Valsalva maneuver increases intrathoracic pressure as well as intraocular and intracranial pressure. There is a small theoretic risk of intraocular hemorrhage and lens dislocation. Upright tilt may induce syncope, and prolonged tilt may induce cardiac arrhythmias in those so predisposed. In published reports of approximately 100 studies, totaling approximately 4000 cases, no complications with sequelae were reported. The larger studies are especially illustrative. The Diabetes Control and Complications Trial (DCCT) study evaluated cardiovascular tests of autonomic function in 1441 patients in 29 centers over a mean duration of 6.5 years without complications.[79] In the Rochester Diabetic study,[80] the 380 patients studied annually are now into their eighth year with no complications. Over this time 1400 tests (QSART, cardiovascular HR tests, adrenergic tests) were done. In one published series, approximately 20,000 cardiovascular HR tests were performed without complications.[16]

The QSART, like other tests that involve the administration of a current source, requires precautions for electrical safety. There is a small but controllable risk of local injury to the skin. In an experience of over 40,000 QSART tests,[13] local skin injuries were sustained with the QSART (Low, personal communication). These injuries were relatively minor. No injuries have been encountered in the last 3000

tests, since minor modifications to the test have been made. No symptomatic arrhythmias on tilt and no intraocular complications have been encountered.

The TST has been performed since at least 1940. In a series of 4661 sweat tests, complications were minimal, comprising chemical dermatitis in 0.13%, skin irritation in 0.6%, claustrophobia requiring premature cessation of the test in 2%, infrared burns (first degree) in 0.1%, and epistaxis in one technician on one occasion due to irritation by alizarin (Fealey, personal communication).

III.   Reported uses of tests of autonomic function. Consensus on the usefulness of tests of autonomic function exists for a number of disorders and conditions. These tests, in general, are definable in terms of their ability to diagnose a condition, to provide unique differential diagnostic information, or to quantify those aspects of autonomic function that have an impact on outcome or evaluate treatment efficacy.

1.   Progressive autonomic neuropathy. The role of autonomic testing in a patient suspected of having a progressive autonomic neuropathy is to diagnose the presence of autonomic neuropathy and determine its severity and distribution.[16] It is possible to delineate the severity, involvement by autonomic system (cardiovagal, adrenergic, sudomotor), distribution, and level (pre- versus postganglionic) of autonomic failure. This subset of patients needs to be studied for several reasons. Diagnosis might not be possible without autonomic studies.[16,81,82] These studies can differentiate among several related types of disorders, for instance, separating Parkinson's disease from multiple system atrophy and Shy-Drager syndrome, disorders whose autonomic burden differs in severity and distribution and is predictive of subsequent outcome.[83] The most common causes are diabetic autonomic neuropathy, amyloid neuropathy, Sjogren's syndrome, the immune-mediated, including panautonomic, neuropathies (idiopathic and paraneoplastic), pure autonomic failure, and multiple system atrophy.[84] Laboratory confirmation is important. The diagnosis of the disorder has a serious prognostic impact on disorders such as multiple system atrophy and pure autonomic failure.[83] In diabetes and amyloidosis, the development of generalized autonomic failure significantly worsens the prognosis.[7-9]

2.   Differentiation of benign from life-threatening autonomic disorders. Certain autonomic disorders[16,84] mimic the more malignant generalized autonomic disorders. For instance, chronic idiopathic anhidrosis, a restricted autonomic disorder with a good prognosis,[85-87] is diagnosable only by excluding adrenergic and cardiovagal failure. The differential diagnosis between certain complicated variants of syncopes from other causes of loss of consciousness may require autonomic tests. Similarly, when the response to β-receptor blockade might be inadequate in vasodepressor syncope, autonomic studies are needed, because the lack of response might be due to peripheral autonomic failure.[41,88,89]

3.   Distal small fiber neuropathy. This neuropathy is common, often distressing, and very difficult to diagnose.[84] Routine nerve conduction studies and EMG are usually normal, as the brunt of the disorder is on unmyelinated fibers. Peripheral autonomic surface potentials will detect a small minority of cases.[90] The QSART or the TST is abnormal in approximately 80% of cases.[91] For the patient with mild symptoms not requiring treatment or the patient who has a demonstrated neuropathy on EMG, autonomic studies are optional. For the patient who has distressing symptoms, autonomic studies are indicated, since this might be the only means of diagnosing the condition, and will often obviate the need for expensive investigations such as spinal MRI.

4.   Postural tachycardia syndrome. Patients with postural tachycardia syndrome [68,92-96] may have the disorder sui generis or as a result of an autonomic neuropathy.[89,93,94] The orthostatic tachycardia might be due to hypovolemia, peripheral adrenergic failure with preservation of cardiac autonomic innervation, β-receptor supersensitivity, or an abnormality in brain stem regulation[89,97] An autonomic screen is necessary to clarify this differential diagnosis.[68,93,94,98]

5.   Sympathetically maintained pain. Patients with unilateral limb pain in whom the suspicion of sympathetically maintained pain, as in reflex sympathetic dystrophy or causalgia, will have sympathetic overaction. Sympathetic overaction may also occur as a manifestation of augmented somatosympathetic reflexes. It is possible to use autonomic tests to demonstrate asymmetry of vasomotor and sudomotor activity as indices of such overaction and to establish the pattern of such dysfunction.[88,99]

6.   Monitoring the course of autonomic failure. The twin attributes of quantitation and noninvasiveness render autonomic laboratory evaluation ideally suited to monitor the alterations of autonomic

function over time. A numeric score is available with subscores for sudomotor, cardiovagal, and adrenergic deficits.[100] Such quantitation is not routinely needed. It is indicated for diagnosis, when the patient's autonomic deficits change in type, distribution, or severity.

7. Evaluation of the response to therapy. The autonomic deficits may lessen in response to treatment. When therapy is applied, quantitative methods are needed to evaluate if the response to therapy is adequate. Such therapy might include tight glucose control for diabetes, 3,4-diaminopyridine for Lambert-Eaton myasthenic syndrome, and immunotherapy for the immune-mediated neuropathies.

8. Peripheral neuropathies. For most patients with peripheral neuropathies, autonomic function tests are optional. The patient with a clear-cut somatic neuropathy, especially the demyelinating neuropathies, does not require autonomic evaluation, since autonomic function is usually spared.[16,54,84] The patient with an undiagnosed axonal neuropathy, or the patient with a suspected autonomic neuropathy, should have autonomic function tests. There is a typical pattern of autonomic involvement, with a length-dependent distribution of sympathetic deficits (maximal distally). However, some neuropathies purportedly affect cardiovagal before sympathetic function (e.g., diabetes, Chagas' neuropathy), and the distribution of the sudomotor deficit may be multifocal (e.g., leprosy).

9. Syncope. The patient with uncomplicated vasovagal syncope does not need autonomic studies. Studies are indicated in those patients in whom studies may aid in the differential diagnosis, patients whose recurrent syncope poses a management problem, or patients in whom a tilt study is needed to evaluate the response to treatment. The tilt study and autonomic screening, by demonstrating indices of orthostatic intolerance (such as changes in pulse pressure; low-frequency, high-amplitude oscillations; and trends in BP and HR), or those of autonomic failure, can aid in treatment and follow-up.[41,46,52,53,101]

   In the past two decades, tilt testing has become standardized, and tilt protocols have been developed with apparent sensitivity and specificity to effectively separate normal individuals from presyncope and syncope.[41-53]

IV. Training and experience of the autonomic clinical neurophysiologist. The training of the autonomic clinical neurophysiologist is still being defined, as is the training of the autonomic technician. The clinician will need a thorough grounding in basic neurophysiology, including sudomotor, cardiovascular neurophysiology, extended CPR training, and instrumentation. In addition, the autonomic clinical neurophysiologist should be experienced in autonomic testing.

V. Summary. Autonomic function tests are safe. They can be grouped into three general categories of autonomic activity: cardiovagal tests, adrenergic tests, and sudomotor tests (table). The selection of specific tests requires both a detailed knowledge of the testing paradigms and a match between the test of a suspected clinical/functional impairment and the autonomic activity. This may be achieved in consultation with a physician trained and experienced in autonomic disorders.

DEFINITIONS

Safety. A judgment of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effectiveness. Producing a desired effect under conditions of actual use.

Established. Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Promising. Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

Investigational. Evidence insufficient to determine appropriateness; warrants further study. Use of this technology for the given indication in a specified patient population should be confined largely to research protocols.

Doubtful. Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

Unacceptable. Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

Quality of evidence ratings

Class I. Evidence provided by one or more well-designed randomized, controlled clinical trials.

Class II. Evidence provided by one or more well-designed clinical studies such as case control and cohort studies.

Class III. Evidence provided by expert opinion, nonrandomized historical controls, or case reports of one or more.

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