Special Article

Neurology 1996;46:873–880

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is derived from a detailed analysis of the available literature on autonomic testing, including published reports and unpublished data from major autonomic laboratories, and the expertise of clinical autonomic physiologists who helped prepare this report.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

See also pages 619 and 881

Approved by the Therapeutics and Technology Assessment Subcommittee on March 7, 1995; the Practice Committee on March 7, 1995; and the Executive Board on July 8, 1995.

Address correspondence and reprint requests to American Academy of Neurology, 2221 University Avenue S.E., Suite 335, Minneapolis, MN 55414.

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	I, II	B
Skin vasomotor		Investigational	III	D
Neurogenic flare		Investigational	III	D

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

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, Sjögren'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.

Acknowledgments

The Therapeutics and Technology Assessment Subcommittee wishes to thank Phillip Low, MD, who prepared this assessment, and the panelists who reviewed and made comments: Michael Aminoff, MD; Thomas Chelimsky, MD; Robert Fealey, MD; Roy Freeman, MD; Jose Gutrecht, MD; Yadollah Harati, MD; Bradley Hiner, MD; Robert Hoeldtke, MD; Jack Hubbard, MD; Horacio Kaufmann, MD; William Kennedy, MD; Ramesh Khurana, MD; Michael Pfeifer, MD; Ronald Polinsky, MD; James Russell, MD; and John Stewart, MD.

Therapeutics and Technology Assessment Subcommittee: John H. Ferguson, MD, Chair; Paul H. Altrocchi, MD; Mitchell Brin, MD; Michael L. Goldstein, MD; Philip B. Gorelick, MD; Daniel F. Hanley, MD; Dale J. Lange, MD; Marc R. Nuwer, MD, PhD; and Stanley van den Noort, MD.

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.

References

1. Low PA. Pitfalls in autonomic testing. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown, 1993:355–365.
2. Report and recommendations of the San Antonio Conference on Diabetic Neuropathy. Consensus statement. Diabetes 1988;37:1000–1004.
3. McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome [see comments]. N Engl J Med 1989;321:1567–1571.
4. Hreidarsson AB. Pupil motility in long-term diabetes. Diabetologia 1979;17:145–150.
5. Warren J, Gutmann L, Figueroa AF Jr, Bloor BM. Electromyographic changes of brachial plexus root avulsions. J Neurosurg 1969;31:137–140.
6. Pfeifer MA, Peterson H, Snider H, et al. Relationship of diabetic autonomic neuropathy to cardiac performance. Clin Res 1985;33:851.
7. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med 1980;92:308–311.
8. Bellavere F, Ferri M, Cardone C, Guarini L, Bosello G, Fedele D. Analysis of QT versus RR ECG interval variations in diabetic patients shows a longer QT period in subjects with autonomic neuropathy [abstract]. Diabetologia 1984;27:255.
9. Chambers JB, Sampson MJ, Sprigings DC, Jackson G. QT prolongation on the electrocardiogram in diabetic autonomic neuropathy [see comments]. Diabetic Med 1990;7:105–110.
10. Burgos LG, Ebert TJ, Asiddao C, et al. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. Anesthesiology 1989;70:591–597.
11. Knuttgen D, Weidemann D, Doehn M. Diabetic autonomic neuropathy: abnormal cardiovascular reactions under general anesthesia. Klin Wochenschr 1990;68:1168–1172.
12. Low PA. Clinical evaluation of autonomic function. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown 1993:157–167.
13. American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee. Assessment: thermography in neurologic practice [see comments]. Neurology 1990;40:523–525.
14. Robertson D, Goldberg MR, Onrot J, et al. Isolated failure of autonomic noradrenergic neurotransmission. Evidence for impaired beta-hydroxylation of dopamine. N Engl J Med 1986;314:1494–1497.
15. Genovely H, Pfeifer MA. RR-variation: the autonomic test of choice in diabetes. Diabetes Metab Rev 1988;4:255–271.
16. Low PA. Laboratory evaluation of autonomic failure. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown 1993:169–195.
17. Sampson MJ, Wilson S, Karagiannis P, Edmonds M, Watkins PJ. Progression of diabetic autonomic neuropathy over a decade in insulin-dependent diabetics. Q J Med 1990;75:635–646.
18. Bellavere F, Ferri M, Guarini L, et al. Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? Br Heart J 1988;59:379–383.
19. Pfeifer MA, Weinberg CR, Cook DL, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 1984;7:447–453.
20. Low PA, Zimmerman BR, Dyck PJ. Comparison of distal sympathetic with vagal function in diabetic neuropathy. Muscle Nerve 1986;9:592–596.
21. Cohen J, Low P, Fealey R, Sheps S, Jiang N-S. Somatic and autonomic function in progressive autonomic failure and multiple system atrophy. Ann Neurol 1987;22:692–699.
22. Baldwa VS, Ewing DJ. Heart rate response to Valsalva manoeuvre. Reproducibility in normals, and relation to variation in resting heart rate in diabetics. Br Heart J 1977;39:641–644.
23. Ewing DJ, Campbell IW, Murray A, Neilson JM, Clarke BF. Immediate heart rate response to standing: simple test of autonomic neuropathy in diabetes. Br Med J 1978;1:145–147.
24. Low PA, Walsh JC, Huang CY, McLeod JG. The sympathetic nervous system in diabetic neuropathy. A clinical and pathological study. Brain 1975;98:341–356.
25. Low PA, Opfer-Gehrking TL, Proper CJ, Zimmerman I. The effect of aging on cardiac autonomic and postganglionic sudomotor function. Muscle Nerve 1990;13:152–157.
26. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years' experience in diabetes. Diabetes Care 1985;8:491–498.
27. Bellavere F, Cardone C, Ferri M, Guarini L, Piccoli A, Fedele D. Standing to lying heart rate variation. A new simple test in the diagnosis of diabetic autonomic neuropathy. Diabet Med 1987;4:41–43.
28. Kuroiwa Y, Wada T, Tohgi H. Measurement of blood pressure and heart-rate variation while resting supine and standing for the evaluation of autonomic dysfunction. J Neurol 1987;235:65–68.
29. Mitchell EA, Wealthall SR, Elliott RB. Diabetic autonomic neuropathy in children: immediate heart-rate response to standing. Aust Paediatr J 1983;19:175–177.
30. Imholz BP, van Montfrans GA, Settels JJ, van der Hoeven GM, Karemaker JM, Wieling W. Continuous non-invasive blood pressure monitoring: reliability of Finapres device during the Valsalva manoeuvre. Cardiovasc Res 1988;22:390–397.
31. Imholz BPM, Settels JJ, van der Meiracker AH, Wieling W. Orthostatic circulatory control in the elderly evaluated by noninvasive continuous blood pressure measurement. Clin Sci 1990;79:73–79.
32. Parati G, Casadei R, Gropelli A, Di Rienzo M, Mancia G. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. Hypertension 1989;13:647–655.
33. van Lieshout EJ, van Lieshout JJ, Wieling W, et al. Monitoring of finger blood pressure. J Neurol Neurosurg Psychiatry 1987;50:503–504.
34. Benarroch EE, Opfer-Gehrking TL, Low PA. Use of the photoplethysmographic technique to analyze the Valsalva maneuver in normal man. Muscle Nerve 1991;14:1165–1172.
35. Sandroni P, Benarroch EE, Low PA. Pharmacological dissection of components of the Valsalva maneuver in adrenergic failure. J Appl Physiol 1991;71:1563–1567.
36. Lind AR, Taylor SH, Humphreys PW, Kennelly BM, Donald KW. The circulatory effects of sustained voluntary muscle contraction. Clin Sci 1964;27:229–244.
37. Vissing SF, Victor RG. Central motor command activates sympathetic outflow to the skin during static exercise. Acta Physiol Scand 1989;136(suppl 584):44.
38. Ewing DJ, Irving JB, Kerr F, Wildsmith JAW, Clarke BF. Cardiovascular responses to sustained handgrip in normal subjects and in patients with diabetes mellitus: a test of autonomic function. Clin Sci Mol Med 1974;46:295.
39. Abi Samra F, Maloney JD, Fouad Tarazi FM, Castle LW. The usefulness of head-up tilt testing and hemodynamic investigations in the workup of syncope of unknown origin. Pacing Clin Electrophysiol 1988;11:1202–1214.
40. Almquist A, Goldenberg IF, Milstein S, et al. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope [see comments]. N Engl J Med 1989;320:346–351.
41. Atkins D, Hanusa B, Sefcik T, Kapoor W. Syncope and orthostatic hypotension. Am J Med 1991;91:179–185.
42. Benditt DG, Remole S, Bailin S, Dunnigan A, Asso A, Milstein S. Tilt table testing for evaluation of neurally mediated (cardioneurogenic) syncope: rationale and proposed protocols. Pacing Clin Electrophysiol 1991;14:1528–1537.
43. Eagle KA, Black HR. The impact of diagnostic tests in evaluating patients with syncope. Yale J Biol Med 1983;56:1–8.
44. Eagle KA, Black HR, Cook EF, Goldman L. Evaluation of prognostic classifications for patients with syncope. Am J Med 1985;79:455–460.
45. Gastaut H, Fischer-Williams M. Electroencephalographic

study of syncope. Its differentiation from epilepsy. Lancet 1957;2:1018–1025.
46. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. Lancet 1986;1:1352–1355.
47. Grubb BP, Temesy Armos P, Hahn H, Elliott L. Utility of upright tilt-table testing in the evaluation and management of syncope of unknown origin [see comments]. Am J Med 1991;90:6–10.
48. Grubb BP, Rubin AM, Wolfe D, Temesy Armos P, Hahn H, Elliott L. Head-upright tilt-table testing: a useful tool in the evaluation and management of recurrent vertigo of unknown origin associated with near-syncope or syncope. Otolaryngol Head Neck Surg 1992;107:570–576.
49. Hannon DW, Ross BA. Head-up tilt testing in children who faint [editorial]. J Pediatr 1991;118:731–732.
50. Kapoor WN. Evaluation and outcome of patients with syncope. Medicine 1990;69:160–175.
51. Kapoor WN. Evaluation and management of the patient with syncope. JAMA 1992;268:2553–2560.
52. Raviele A, Gasparini G, Di Pede F, Delise P, Bonso A, Piccolo E. Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study. Am J Cardiol 1990;65:1322–1327.
53. Fitzpatrick AP, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. J Am Coll Cardiol 1991;17:125–130.
54. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. Ann Neurol 1983;14:573–580.
55. Low PA, Opfer-Gehrking TL, Kihara M. In vivo studies on receptor pharmacology of the human eccrine sweat gland. Clin Auton Res 1992;2:29–34.
56. Maselli RA, Jaspan JB, Soliven BC, Green AJ, Spire J-P, Arnason BGW. Comparison of sympathetic skin response with quantitative sudomotor axon reflex test in diabetic neuropathy. Muscle Nerve 1989;12:420–423.
57. Low PA, Zimmerman IR. Development of an autonomic laboratory. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown 1993:345–354.
58. Lang E, Foerster A, Pfannmuller D, Handwerker HO. Quantitative assessment of sudomotor activity by capacitance hygrometry. Clin Auton Res 1993;3:107–115.
59. Levy DM, Reid G, Abraham RR, Rowley DA. Assessment of basal and stimulated sweating in diabetes using a direct-reading computerized sudorometer. Diabet Med 1991;8:S78–S81.
60. Sugenoya J, Iwase S, Mano T, Ogawa T. Identification of sudomotor activity in cutaneous sympathetic nerves using sweat expulsion as the effector response. Eur J Appl Physiol 1990;61:302–308.
61. Low PA, Fealey RD. Sudomotor neuropathy. In: Dyck PJ, Thomas PK, Winegrad A, Porte D, eds. Diabetic neuropathy. Philadelphia: WB Saunders, 1987:140–145.
62. Fealey RD, Low PA, Thomas JE. Thermoregulatory sweating abnormalities in diabetes mellitus. Mayo Clin Proc 1989;64:617–628.
63. Tuck RR, McLeod JG. Autonomic dysfunction in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1981;44:983–990.
64. Guttmann L. The management of the quinizarin sweat test (QST). Postgrad Med J 1947;23:353–366.
65. Guttmann L. Topographic studies of disturbances of sweat secretion after complete lesions of peripheral nerves. J Neurol Psychiatry 1940;3:197–210.
66. Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response—a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. J Neurol Neurosurg Psychiatry 1984;47:536–542.
67. Elie B, Guiheneuc P. Sympathetic skin response: normal results in different experimental conditions. Electroencephalogr Clin Neurophysiol 1990;76:258–267.
68. Hoeldtke RD, Davis KM, Hshieh PB, Gaspar SR, Dworkin GE. Autonomic surface potential analysis: assessment of reproducibility and sensitivity. Muscle Nerve 1992;15:926–931.
69. Macleod AF, Smith SA, Cowell T, Richardson PR, Sonksen PH. Non-cardiac autonomic tests in diabetes: use of the galvanic skin response. Diabet Med 1991;8:S67–S70.
70. Soliven B, Maselli R, Jaspan J, et al. Sympathetic skin response in diabetic neuropathy. Muscle Nerve 1987;10:711–716.
71. Niakan E, Harati Y. Sympathetic skin response in diabetic peripheral neuropathy. Muscle Nerve 1988;11:261–264.
72. Uncini A, Pullman SL, Lovelace RE, Gambi D. The sympathetic skin response: normal values, elucidation of afferent components and application limits. J Neurol Sci 1988;87:299–306.
73. Valls Sole J, Monforte R, Estruch R. Abnormal sympathetic skin response in alcoholic subjects. J Neurol Sci 1991;102:233–237.
74. Yokota T, Matsunaga T, Okiyama R, et al. Sympathetic skin response in patients with multiple sclerosis compared with patients with spinal cord transection and normal controls. Brain 1991;114:1381–1394.
75. Kennedy WR, Sakuta M, Sutherland D, Goetz FC. Quantitation of the sweating deficit in diabetes mellitus. Ann Neurol 1984;15:482–488.
76. Kennedy WR, Navarro X. Sympathetic sudomotor function in diabetic neuropathy. Arch Neurol 1989;46:1182–1186.
77. Navarro X, Kennedy WR, Fries TJ. Small nerve fiber dysfunction in diabetic neuropathy. Muscle Nerve 1989;12:498–507.
78. Kihara M, Opfer-Gehrking TL, Low PA. Comparison of directly stimulated with axon reflex–mediated sudomotor responses in human subjects and in patients with diabetes. Muscle Nerve 1993;16:655–660.
79. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus [see comments]. N Engl J Med 1993;329:977–986.
80. Dyck PJ, Karnes JL, O'Brien PC, Litchy WJ, Low PA, Melton LJ III. The Rochester Diabetic Neuropathy Study: reassessment of tests and criteria for diagnosis and staged severity. Neurology 1992;42:1164–1170.
81. Fealey RD, Robertson D. Management of orthostatic hypotension. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown, 1993:731–743.
82. Mathias CJ, Bannister R. Investigation of autonomic disorders. In: Autonomic failure, 3rd ed. Oxford: Oxford University Press, 1992:255–290.
83. Sandroni P, Ahlskog JE, Fealey RD, Low PA. Autonomic involvement in extrapyramidal and cerebellar disorders. Clin Auton Res 1991;1:147–155.
84. Low PA, McLeod JG. The autonomic neuropathies. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown 1993:395–421.
85. Ross AT. Progressive selective sudomotor denervation—a case with co-existing Adie's syndrome. Neurology 1958;8:809–817.
86. Faden AI, Chan P, Mendoza E. Progressive isolated segmental anhidrosis. Arch Neurol 1982;39:172–175.
87. Low PA, Fealey RD, Sheps SG, Su WP, Trautmann JC, Kuntz NL. Chronic idiopathic anhidrosis. Ann Neurol 1985;18:344–348.
88. Low PA, Amadio PC, Wilson PR, McManis PG, Willner CL. Laboratory findings in reflex sympathetic dystrophy: a preliminary report. Clin J Pain 1994;10:235–239.
89. Low PA, Opfer-Gehrking TL, Textor SC, et al. Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. J Auton Nerv Syst 1994;50:181–188.
90. Watson CPN, Evans RJ, Watt VR. Postherpetic pain and topical capsaicin. Pain 1988;33:333–340.
91. Stewart JD, Low PA, Fealey RD. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. Muscle Nerve 1992;15:661–665.
92. Jackson AC. Neurologic disorders associated with mitral valve prolapse. Can J Neurol Sci 1986;13:15–20.
93. Schondorf R, Low PA. Idiopathic postural tachycardia syndrome. In: Low PA, ed. Clinical autonomic disorders: evaluation and management. Boston: Little, Brown, 1993:641–652.
94. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? Neurology 1993;43:132–137.

95. Hoeldtke RD, Dworkin GE, Gaspar SR, Israel BC. Sympathotonic orthostatic hypotension: a report of four cases. Neurology 1989;39:34–40.
96. Hoeldtke RD, Davis KM. The orthostatic tachycardia syndrome: evaluation of autonomic function and treatment with octreotide and ergot alkaloids. J Clin Endocrinol Metab 1991; 73:132–139.
97. Low PA, Opfer-Gehrking TL, Textor SC, et al. Postural tachycardia syndrome (POTS). Neurology 1995;45(suppl 5): 519–525.
98. Gaffney FA, Karlsson ES, Campbell W, et al. Autonomic dysfunction in women with mitral valve prolapse syndrome. Circulation 1979;59:894–901.
99. Chelimsky TC, Low PA, Naessens JM, et al. Value of autonomic testing in reflex sympathetic dystrophy. Mayo Clin Proc 1995;70:1029–1040.
100. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993;68:748–752.
101. Kaufmann H. Neurally mediated syncope. Pathogenesis, diagnosis and treatment. Neurology 1995;45(suppl 5):512–518.