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Electrodiagnostic assessment of the autonomic nervous system: A consensus statement endorsed by the American Autonomic Society, American Academy of Neurology, and the International Federation of Clinical Neurophysiology

William P. Cheshire [a], Roy Freeman [c], Christopher H. Gibbons [c], Pietro Cortelli [d,e], Gregor K. Wenning [f], Max J. Hilz [g], Judith M. Spies [h], Axel Lipp [i], Paola Sandroni [b], Naoki Wada [j], Akiko Mano [k], Hyun Ah Kim [l], Kurt Kimpinski [m,n,o], Valeria Iodice [p], Juan Idiáquez [q], Pariwat Thaisetthawatkul [r], Elizabeth A. Coon [b], Phillip A. Low [b,*], Wolfgang Singer [b,*]

[a] Department of Neurology, Mayo Clinic, 4500 San Pablo Rd., Jacksonville, Florida 32224, USA
[b] Department of Neurology, Mayo Clinic, 200 First St. SW, Rochester, Minnesota 55905, USA
[c] Department of Neurology, Harvard Medical School, 330 Brookline Avenue, Boston, Massachusetts 02215-5400, USA
[d] DIBINEM – University of Bologna, Bologna, Italy
[e] IRCCS Istituto di Scienze Neurologiche, Bologna, Italy
[f] Section of Clinical Neurobiology, Department of Neurology, Medical University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria
[g] Department of Neurology, University of Erlangen-Nuremberg, Schwabachanlage 6, Erlangen 91054, Germany
[h] Department of Neurology, Level 8 East, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia
[i] Park-Klinik Weißensee, Schönstraße 80, Berlin 13086, Germany
[j] Department of Renal and Urologic Surgery, Asahikawa Medical University, 2-1-1-1 Midorigaoka Higashi, Asahikawa 078-8510, Japan
[k] Department of Cardiothoracic Surgery, Tokyo Metropolitan Geriatric Hospital, 35-2 Sakae-Cho Itabashi-ku, Tokyo 173-0015, Japan
[l] Department of Neurology, Keimyung University Dongsan Hospital, 2800 Dalgubeol Daero, Dalseo-gu, Daegu, South Korea
[m] School of Kinesiology, Western University, London, Ontario, Canada
[n] Department of Clinical Neurological Sciences, University Hospital, London Health Sciences Centre, London, Ontario, Canada
[o] Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada
[p] Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, Division of Clinical Neurology, Institute of Neurology, University College London, WC1N 3BG London, United Kingdom
[q] Department of Neurologia, Facultad de Medicina, University of Valparaíso, 7 Norte 1122, Valparaíso, 2531094, Chile
[r] Department of Neurological Sciences, 988435 University of Nebraska Medical Center, Omaha, Nebraska 68198-8435, USA

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HIGHLIGHTS

- Sensitive, validated, noninvasive electrodiagnostic tests of autonomic function have been developed.
- An international expert panel provides evidence-based recommendations to guide autonomic testing.
- Recommendations allow for standardized assessment of severity and distribution of autonomic failure.

ABSTRACT

Evaluation of disorders of the autonomic nervous system is both an art and a science, calling upon the physician's most astute clinical skills as well as knowledge of autonomic neurology and physiology. Over the last three decades, the development of noninvasive clinical tests that assess the function of autonomic nerves, the validation and standardization of these tests, and the growth of a large body of literature characterizing test results in patients with autonomic disorders have equipped clinical practice further with a valuable set of objective tools to assist diagnosis and prognosis. This review, based on

* Corresponding authors at: Department of Neurology, 200 First Street SW, Mayo Clinic, Rochester, MN 55905, USA.
E-mail addresses: low@mayo.edu (P.A. Low), singer.wolfgang@mayo.edu (W. Singer).

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current evidence, outlines an international expert consensus set of recommendations to guide clinical electrodiagnostic autonomic testing. Grading and localization of autonomic deficits incorporates scores from sympathetic cardiovascular adrenergic, parasympathetic cardiovagal, and sudomotor testing, as no single test alone is sufficient to diagnose the degree or distribution of autonomic failure. The composite autonomic severity score (CASS) is a useful score of autonomic failure that is normalized for age and gender. Valid indications for autonomic testing include generalized autonomic failure, regional or selective system syndromes of autonomic impairment, peripheral autonomic neuropathy and ganglionopathy, small fiber neuropathy, orthostatic hypotension, orthostatic intolerance, syncope, neurodegenerative disorders, autonomic hyperactivity, and anhidrosis.

Contents

1. Introduction

The discipline of autonomic medicine is concerned with the diagnosis and treatment of diseases and disorders of the autonomic nervous system. Invaluable to accurate diagnosis are autonomic function tests, which supply objective, quantifiable information about the integrity and behavior of autonomic nerves, ganglia, and central nervous system networks. As the autonomic nervous system is inaccessible to direct physiologic testing, clinical autonomic tests usually assess an end-organ response to a specific

physiologic provocation. In the same way that electrodiagnostic tests of motor and sensory nerve function are foundational to electrodiagnostic assessment of neurologic disease, tests of autonomic nerve function are essential to diagnosis of autonomic disorders. Unlike sensory and motor nerve conduction studies, the focus of electrodiagnostic autonomic testing is small-caliber myelinated and unmyelinated nerve fibers. Detection, quantification, and localization of autonomic dysfunction is relevant to diagnosis, prognosis, and clinical management of patients in an effort to improve their quality of life.

Diagnostic laboratory tests of sympathetic and parasympathetic responses have been established for more than three decades at leading centers, so that a large body of experience and publications has become available that define autonomic physiology in health and patterns of autonomic dysfunction in specific diseases. Much of this testing focuses on changes in heart rate (HR), blood pressure (BP), and sweating. Further, the equipment and methodology for autonomic testing has become standardized.

This review will focus on tests of autonomic function that expert consensus considers to be scientifically valid, reliable, and clinically useful. Tests of autonomic function involve measurement of a physiologic function in response to a specific manipulation of the body under standardized conditions. To be meaningful, the results must be interpreted in reference to normative values and with an understanding of the physiology of autonomic responses in health and in autonomic disorders.

2. Historical overview

Physicians since antiquity have recognized the importance of the strength and timing of the pulse, cutaneous flushing and pallor, and variations in bodily secretions in assessing health and disease. Following Langley's introduction of the term "autonomic nervous system" (Langley, 1898), in the early twentieth century a number of investigators reported on the use of tilting boards to investigate the effects of gravitational stress on circulation of the blood (Cheshire and Goldstein, 2019). Investigators in the mid-twentieth century described the BP responses to the Valsalva maneuver in the contexts of heart failure (Sharpey-Schafer, 1955) and autonomic disease (Appenzeller and Goss, 1971, Appenzeller and Kornfeld, 1973). At that time, assessment of dynamic, moment-by-moment changes in BP in response to tilting or straining required recording intra-arterial measurements. In obstetrics, the development of technology for continuous monitoring of fetal HR during labor enabled recognition of changes in HR as a marker of fetal distress (Hon and Lee, 1963), which led to its routine use to prevent hypoxic brain damage and decrease perinatal mortality (Kennedy, 1998). Concurrently with these hemodynamic developments, Guttmann pioneered the use of quinizarin as a color indicator to outline the anatomic distribution of sweating and its loss from impaired sudomotor neurons (Guttmann, 1947).

The technology that catalyzed the transition of autonomic testing from a research tool to clinical application was the development in the 1980 s of noninvasive means to detect BP for each pulse wave at the finger (Imholz et al., 1988). These devices utilize photoplethysmographic technology to measure BP indirectly as the change in infrared light transmitted through the finger as an index of the dynamic volume of blood flow. The calculated BP curve closely approximates an intra-arterial waveform, which allows assessment of moment-by-moment cardiovascular adrenergic responses (Goldstein and Cheshire, 2017b).

Following these seminal developments, methods for autonomic testing have advanced in parallel with increasing recognition of autonomic disorders as a major health problem and identification of a wide variety of specific autonomic disorders (Palma et al., 2015). The burgeoning field of autonomic medicine saw the introduction of the Journal of the Autonomic Nervous System in 1979 (subsequently renamed Autonomic Neuroscience: Basic and Clinical) and Clinical Autonomic Research in 1991. The American Autonomic Society was founded in 1990 and since then has held an annual international conference. Subspecialty certification in autonomic disorders has been offered since 2009 by the United Council for Neurologic Subspecialties, which also accredits autonomic fellowships. Supplementing these resources has been the availability of new pharmacologic and other effective therapies for patients with autonomic disorders. These collaborations have engendered a shared approach to the understanding and testing of autonomic disorders.

3. Common clinical questions

Patients with autonomic concerns are often clinically challenging. They may present with protean symptoms spanning multiple organ systems. When their symptoms involve some aspect of autonomic function, the label "dysautonomia" is often applied. It must be remembered that dysautonomia is not a specific diagnosis but rather a broad category, much as "weakness" is to the neuromuscular subspecialist. Further probing, including an intelligently gathered comprehensive autonomic history, physical examination, and appropriate autonomic testing, are needed to establish an accurate diagnosis (Cheshire and Goldstein, 2018, Goldstein and Cheshire, 2017a).

The aims of autonomic testing are to recognize the presence, distribution, and severity of autonomic dysfunction. Further, autonomic testing may detect characteristic patterns of autonomic failure or hyperfunction that can be related to specific disorders. The results of autonomic testing can enable the recognition of potentially treatable autonomic disorders as well as the distinction between potentially life-threatening and benign conditions. When abnormal, the results of autonomic testing can assist with earlier diagnosis, monitor clinical progression, and assess the response to treatment. When normal, the results of autonomic testing can provide objective evidence that a serious autonomic condition is not present.

4. Standardization of autonomic testing

The proliferation of autonomic tests and laboratories has led to diverse methods for assessing autonomic function. In order that research findings be generalizable to clinical practice, consensus has formed on the definitions of autonomic disorders and the appropriate methodology of autonomic testing. The American Autonomic Society, the International Society for Autonomic Neuroscience, the European Federation of Autonomic Societies, and the American Academy of Neurology, among others, have facilitated international collaboration making possible the development and endorsement of current consensus guidelines (Freeman et al., 2011, Gibbons et al., 2014, Gibbons et al., 2017).

4.1. Desirable attributes

Whereas autonomic centers differ in their research emphases, their approaches to autonomic testing have much in common. The preferred methodology for clinical autonomic testing is based on a number of desirable attributes (Low and Pfeifer, 1993). First, autonomic testing should be both sensitive and specific. Second, the testing should be reproducible. Third, the testing should be physiologically and clinically relevant, assessing the affected component of the autonomic nervous system. Fourth, the testing should be noninvasive, avoiding intraarterial or intravenous access,

needle microneurography, or infusion of vasoactive agents. Fifth, the testing should be relatively easy to perform and not excessively time-consuming. Sixth, the test stimulus should be standardized. Seventh, potentially confounding variables should be identified. Eighth, the necessary technology should be readily available for widespread use, and ninth, the equipment should be affordable.

4.2. Autonomic reflex screen and composite autonomic severity score (CASS)

Common approaches to autonomic testing typically assess cardiovascular sympathetic adrenergic, cardiac parasympathetic (cardiovagal), and sudomotor (sweating) function. A combination of autonomic tests in a screening battery provides a more accurate measure of autonomic function, as a single test alone cannot distinguish the severity or distribution of autonomic failure (Ewing et al., 1985).

The autonomic reflex screen (testing cardiovagal, sudomotor, adrenergic functions in a standardized fashion) can be scored as a 10-point Composite Autonomic Severity Score (CASS) by normalizing each component for the confounding effects of age and gender (Low, 1993b, Low and Sletten, 2008). The scheme allots 4 points for adrenergic failure and 3 points each for sudomotor and cardiovagal failure. Patients with a score of 3 or less on the composite autonomic scoring scale have only mild autonomic failure, those with scores of 4 to 6 have moderate failure, and those with scores between 7 and 10 have severe autonomic failure (Table 1). The validity of the method was assessed by evaluating the CASS in four groups of patients with known degrees of autonomic failure and was found to be highly sensitive (94%) and specific (100%) in separating diseases with different levels of autonomic failure, with coefficients of variation of 20% or less (Low, 1993b, Low and Sletten, 2008).

Table 1
Laboratory grading of autonomic failure by the Composite Autonomic Severity Score.

Sudomotor index		
	Quantitative sudomotor axon reflex test	*Thermoregulatory sweating test*
0	Normal	Normal
1	Single site abnormal, *or* length-dependent pattern (distal sweat volume < 1/3 of proximal values)	Anhidrosis present but < 25%
2	Single site < 50% of 5th percentile	Anhidrosis 25–50%
3	Two or more sites < 50% of 5th percentile	Anhidrosis > 50%
Adrenergic index		
	Beat-to-beat measurement of blood pressure in response to the Valsalva maneuver and head- up tilt to 70 degrees	
0	Normal	
1	Phase II_E decrease of mean blood pressure between 20 and 40 mmHg plus phase II_L or IV absent, *or* decrease in pulse pressure to $\leq$ 50% of baseline; PRT 6–10 seconds	
2	Phase II_E decrease of < 40 mmHg plus absent phase II_L or IV; PRT 11–20 seconds	
3	Phase II decrease of > 40 mmHg plus absent phase II_L and IV; PRT > 20 seconds	
4	Criteria met for 3 plus systolic blood pressure decrease of $\geq$ 30 mmHg (orthostatic hypotension)	
Cardiovagal index		
	Beat-to-beat measurement of heart rate in response to sinusoidal deep breathing at 5–6 breaths/min *and the Valsalva maneuver*	
0	Normal	
1	HR_{DB} or VR mildly decreased (>50% of 5th percentile)	
2	HR_{DB} or VR decreased to < 50% of 5th percentile	
3	Both HR_{DB} and VR decreased to < 50% of 5th percentile	

The table lists the components of autonomic testing results that contribute to the Composite Autonomic Severity Score (CASS). Test methodologies are listed in italics at the top for each category. Results from each category (sudomotor, adrenergic, cardiovagal) are assigned a numerical severity, 0 being normal, which add up to the CASS, which has a maximum score of 10. The sudomotor index can be based on either quantitative sudomotor axon reflex testing (QSART) or the thermoregulatory sweating test (TST). Percentiles are in reference to normative values. HR_{DB} = heart rate response to deep breathing, VR = Valsalva ratio. Phases refer to the components of the Valsalva maneuver: II_E and II_L the early and late portions, respectively, of phase II. PRT = BP recovery time.

5. Testing of cardiovascular adrenergic function

The Valsalva maneuver and the tilt table test represent the two cornerstones of cardiovascular adrenergic (baroflex-sympathoneural) assessment, which is key to the evaluation of orthostatic hypotension (OH), as discussed in detail in Section 10.1 below. They provide complementary information about autonomic responses, in the case of the Valsalva maneuver, to the transient reduction in cardiac preload induced by increased intrathoracic pressure during straining, and in the case of the tilt table test, to the gravitational redistribution of blood volume in the upright posture. Proper performance requires continuous monitoring of HR and beat-to-beat BP, which is accomplished noninvasively via ECG and photoplethysmography.

The baroreflex, which maintains a stable BP during changes in body position, ceases to function in many autonomic disorders. The function of baroreceptors in the carotid sinuses and aortic arch is to sense changes in BP and relay signals to the nucleus of the solitary tract. The efferent response has two components, which constitute a negative feedback loop. Elevated BP triggers a parasympathetic cardiovagal response (see section 6), which lowers HR, as well as a release of adrenergic outflow, which lowers total peripheral vascular resistance and thus BP. Lowered BP causes the opposite to occur. Both of these responses are blunted with advancing age. The baroreflex response is too rapid to be detected at the bedside using pulse detection devices or arm cuff sphygmomanometry.

5.1. Valsalva maneuver

The Valsalva maneuver is done in a standardized manner with the subject rested and recumbent (or seated, depending on the laboratory) and asked to maintain a column of mercury at 40 mmHg for 15 seconds. A maneuver < 10 seconds or < 20 mm Hg is inadequate (Benarroch et al., 1991). For subjects who have a "flat top" response (where induced BP change mimics expiratory pressure in configuration and early phase II does not develop), the study is repeated with the subject tilted to 20° or if necessary 40° until a significant fall in BP is obtained (Vogel et al., 2008). When BP recordings are done, the subject is asked to repeat the maneuvers until two reproducible beat-to-beat BP recordings are obtained.

There are four main phases in the VM (Fig. 1A). In phase I, there is a transient rise in BP due to increased intrathoracic and intra-abdominal pressure causing mechanical compression of the aorta. In early phase II (phase II_E), the reduced preload (venous return) and reduced stroke volume lead to a fall in cardiac output. Total peripheral resistance increases as a result of efferent sympathetic discharge to muscle and within 4 seconds after the increase in sympathetic discharge, the fall in BP is arrested. This is late phase

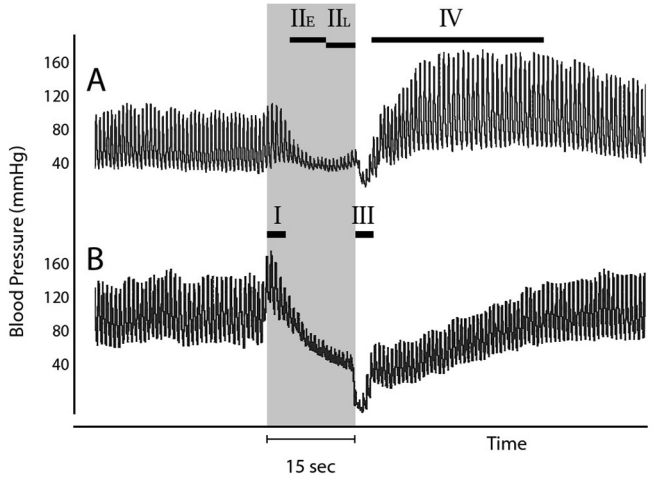

Fig. 1. Beat to beat blood pressure responses to the Valsalva maneuver from a normal subject (A) and a patient with generalized autonomic failure (B). In B, there is absence of phase II_L and IV and delayed recovery of BP.

II (II_L). Phase III, like phase I, is mechanical, lasting 1 to 2 seconds, during which BP falls. The major mechanism is the sudden fall in intrathoracic pressure. In phase IV, venous return and cardiac output have returned to normal while the arteriolar bed remains vasoconstricted; hence the overshoot of BP above baseline values. In a patient with adrenergic failure (Fig. 1B), there is loss of phases II_L and IV and delay in BP recovery.

In the clinical autonomic laboratory setting, the use of the phases of the VM to evaluate adrenergic function has been validated in two ways. First, pharmacologic dissection of the maneuver (Sandroni et al., 1991) showed that late phase II is primarily under peripheral α-adrenergic control, being selectively blocked by phentolamine, whereas phase IV is completely blocked by propranolol, indicating β-adrenoreceptor dependence. Assessment of the maneuver in a control and three age- and sex-matched patient groups with graded adrenergic failure demonstrated that the assessment of the phases of the VM were more sensitive and informative than measurements of orthostatic BP alone (Sandroni et al., 1991).

The VM can also be used to evaluate baroreflex sensitivity (Huang et al., 2007, Schrezenmaier et al., 2007, Vogel et al., 2005). Baroreceptors regulate BP by changing heart period (vagal component) and total peripheral resistance (adrenergic component). Vagal baroreflex sensitivity can be used to quantify the vagal component of the reflex, by regressing the beat-to-beat BP against heart period (Schrezenmaier et al., 2007). It is also possible to separately evaluate the adrenergic component of the baroreflex through indices based on the dynamics of BP recovery following the maneuver (Trimarco et al., 1983, Vogel et al., 2005). BP recovery time (PRT) is the simplest and most commonly used index of adrenergic baroreflex function and defined as the time, in seconds, for systolic BP to recover from phase III back to baseline. PRT significantly correlates with adrenergic indices including microneurographically recorded muscle sympathetic nerve discharges (Schrezenmaier et al., 2007), with highest correlations with phase II_L (reflex vasoconstriction after initial fall in BP) and phase IV (BP overshoot after the VM). Normative values have been generated (Huang et al., 2007).

The sensitivity of the test to detect adrenergic failure and to separate neurogenic from non-neurogenic OH is high with sensitivity of at least 80% and specificity of at least 80% (Huang et al., 2007, Low and Sletten, 2008, Schrezenmaier et al., 2007) (Table 2).

5.2. Tilt table test

Upon transitioning to the upright posture, the force of gravity causes the blood volume to redistribute away from the cerebral and thoracic vasculature toward the splanchnic and lower extremity vasculature. Within 3 minutes, 500–800 mL blood, or approximately 10% of the total blood volume and 25% of the thoracic blood volume, is displaced downward (Smith et al., 1994). The tilt table creates a controlled environment where the autonomic responses to orthostatic stress can be monitored closely.

In healthy persons, adaptation to the upright posture entails unloading of carotid and cardiopulmonary baroreceptors, which leads to a reflex increase in sympathetic adrenergic outflow, causing increased peripheral vasoconstrictor tone, HR, and inotropic state. In OH and disorders of orthostatic intolerance, the autonomic responses to orthostatic stress are insufficient.

Raising the patient on an inclining table is not the same as having the patient stand. Because leg contraction is not required to maintain the upright posture on the tilt table, passive tilting is a stronger orthostatic stimulus. As compared to passive tilt, active standing during the first 30 seconds causes a greater reduction in BP and total peripheral resistance and a larger increase in HR and cardiac output (Tanaka et al., 1996). The optimal conditions for performing tilt table testing have been reviewed in detail elsewhere and depend on the clinical question and context (Cheshire and Goldstein, 2019).

6. Testing of cardiovagal function

The influence of the vagus nerve on heart rate variability is an important aspect of autonomic regulation. This parasympathetic

Table 2
Summary evaluation of attributes of some autonomic function tests.

Parameters	HRV	VM	QSART	TST	CASS_Adr[3]
Sensitivity	≥80%	≥80%	80%	80%	80%
Specificity	≥80%	≥80%	≥80%	≥80%	≥80%
Reproducibility	High[1]	High	High	High?[2]	High
Physiologic Basis	+++	+++	+++	+++	+++
Clinical Relevance	+++	+++	+++	+++	+++
Non-invasive	+++	+++	+++	+++	++
Practical	+++	++	++	+	++
Availability	+++	+++	++	+	++
Affordability	+++	+++	+	++	++
Known Confounders	++	++	+++	++	+++

[1]Coefficient of variation < 20%; [2]Apparently high reproducibility but limited studies done; [3]Components are BP/HR to tilt and beat-to-beat BP responses of the Valsalva maneuver as indices of adrenergic failure; +++, easily fulfills criteria; ++, fulfills criteria; +, just fulfills criteria, with some difficulty in some situations. CASS_Adr = Composite Autonomic Severity Score, adrenergic subscale; HRV = heart rate variability; QSART = quantitative sudomotor axon reflex test; TST = thermoregulatory sweating test; VM = Valsalva maneuver.

regulation occurs more rapidly than changes in cardiovascular sympathetic adrenergic function.

6.1. Heart rate variability to breathing

Variation in HR in response to breathing has been quantified in a number of ways. In the time domain, those include SD of RR interval, mean circular resultant (MCR), mean successive difference, and mean squared successive difference (typically from using normal, spontaneous breathing), as well as expiratory-inspiratory (E:I) ratio and maximum – minimum HR response to deep breathing (HRDB; usually averaged over 5 cycles) (Weinberg and Pfeifer, 1984). Both the afferent and efferent limbs underlying respiratory sinus arrhythmia are vagal; although there is modulation, under normal conditions, by central and peripheral sympathetic activity (Levy et al., 1966), Bainbridge reflex (Bainbridge, 1920), Hering-Breuer reflex (Hering, 1871), and baroreflexes (Eckberg et al., 1980). There are, in addition, significant effects of medications and end organ (cardiac) disease (Low and Sletten, 2008). That these tests measure cardiovagal function derives from the finding that heart period has a linear relationship to vagal tone, varied under experimental conditions in the dog (Katona and Jih, 1975), and the findings were replicated in humans with pharmacologic blockade (Fouad et al., 1984).

The most widely used methods in clinical trials have been HRDB, E:I ratio, and MCR. These methods have not been subject to direct comparisons. HRDB is the most widely used method currently in clinical practice, is easy to perform and analyze, is highly reproducible, and sensitive in detecting pathology. It is not much affected by artifacts (which can be recognized and excluded), and is only modestly affected by mean HR; the stimulus is highly standardized and controlled. Shifting HR affects the response because of interference between the transient changes in HR induced by inspiration and expiration (Mehlsen et al., 1987).

MCR is a method based on vector analysis and plots the time of the R wave spike on a circular graph synchronized to the patient's respiratory cycle. The mean vector of all R waves is calculated as a function of timing and periodicity. The MCR bar is longer when R wave spikes cluster, depicting periodicity, and shorter when R wave spikes are uniformly distributed, depicting reduced heart rate variability (Weinberg and Pfeifer, 1984). It has the theoretical advantage of being little influenced by changes in HR and extrasystoles (Table 3). Derivative parameters that are dependent on the sequence of R-R intervals are the mean successive difference and mean square successive difference of R-R intervals, which are less dependent on trends on heart rate over time. The MCR and its derivatives have not found widespread use in clinical practice.

The E:I ratio also has not found widespread use in clinical practice and is greatly affected by baseline and shifting HR.

An alternative method of evaluating cardiovagal function is to evaluate HR fluctuations in the frequency domain. Power spectral analysis of resting HR derived from fast Fourier transformation of R-R interval changes on continuous ECG typically produces several prominent peaks. One peak at a frequency > 0.15 Hz reflects respiratory sinus arrhythmia. Quantification of these oscillations provides an index of parasympathetic modulation (Freeman, 2006). The ratio of low-frequency components, which reflect combined sympathetic and parasympathetic influences on HR, to high-frequency components, which reflect parasympathetic and respiratory activity, is occasionally reported as a measure of sympathovagal balance modulating the sinus node (Malliani and Montano, 2002, Novak et al., 1993). This method has not been used extensively in clinical trials nor in clinical practice and is limited by the lack of standardization of conditions and the uncertain relevance of resting measures of HR variability in the absence of specific excitatory stimuli.

Reproducibility, sensitivity and specificity of tests of cardiovagal function is high, with a coefficient of variation of 9–20% (Genovely and Pfeifer, 1988, Low and Sletten, 2008). Specificity is typically > 80% and sensitivity for detection of cardiac autonomic neuropathy is > 80%(Low et al., 1997, Low and Pfeifer, 1993, Low and Sletten, 2008, Nathan et al., 1993, Gelber, et al.,1997). Large normative databases of HR variability are available (Gelber et al., 1997, Low et al., 1997). There is good general agreement that HR variability declines with age, and that there is no effect of gender (Gelber et al., 1997, Low et al., 1997). The value of the tests are limited by the effects of concurrent medications (Low P.A. and Opfer-Gehrking T.L., 1992) and primary cardiac factors such as ischemic heart disease, alterations in HR and heart rhythm abnormalities, all of which could affect indices of cardiovagal function (Low and Sletten, 2008).

6.2. Valsalva ratio

The Valsalva ratio (VR) is the ratio of the maximum HR that develops in response to BP reduction induced by the Valsalva maneuver (described in Section 5.1), divided by the minimum HR that results from the maneuver-induced BP overshoot. The Valsalva ratio is the ratio of the maximal (following phases II/III) to minimal HR (occurring within 30 s of phase IV peak). Details and mechanisms of the maneuver are described above.

A large normative database is available. For instance, VR was studied in 425 subjects age 10 to 83 years and a significant gender difference was evident. As a result, data for male and female control subjects are considered separately. VR is typically coupled with HRDB on the basis that it is desirable to use more than one test of cardiovagal function, and more importantly, a test that evaluates a different aspect of cardiovagal reflexes. Whereas HRDB tests primarily vagal function related to ventilation, VR is primarily a test of the vagal component of arterial baroreflexes (Freeman, 2006, Low, 1993a).

The Valsalva ratio has a significant but avoidable limitation, which relates to the fact that the true stimulus (the fall in BP secondary to the maneuver) is not routinely recorded in some laboratories and remains unknown. It is common to have a partial or complete "flat top" or "square wave" response where the shape of the BP curve mimics the expiratory pressure, and early phase II does not develop, so that the stimulus is inadequate. VR has similar sensitivity and specificity as HRDB (Low et al., 1997, Low and Pfeifer, 1993, Low and Sletten, 2008, Nathan et al., 1993, Gelber, et al., 1997) (Table 3). However, in clinical trials, VR has consistently performed less well than HRDB, because a number of subjects cannot perform or are excluded from performing the maneuver. For instance, in the Rochester Diabetic Study (Dyck et al., 1992), HRDB showed a significant decline by 1 bpm per year whereas the decline in VR was not significant. Similarly in DCCT and EDIC (Anonymous, 1998, Pop-Busui et al., 2009), VR was less sensitive than HRDB in detecting progression of DAN (Anonymous, 1998).

Table 3
Some variables affecting cardiovagal function.

Variable	HRDB	Effect of Age
Age	+	Decrease with age
Respiratory rate	Yes	Maximal at 6 breaths per minute
Hypocapnia	Yes	Reduces response
Sympathetic tone	Yes	Suppresses HRV
Medications	Yes	Especially anticholinergic
Depth of respiration	Yes	Modest effect
Obesity	Yes	Modest effect

HR_{DB} = heart rate variability with deep breathing; HRV = heart rate variability.

Table 4
Comparison of studies of sudomotor testing in distal small fiber neuropathy.

Autonomic Test	Reference	Number of patients	Diagnostic Criteria	Sensitivity
TST	Stewart et al. 1992	25	Distal anhidrosis	72%
	Low et al. 2006	125	Distal anhidrosis	74%
QSART	Stewart et al. 1992	40	Distal abnormality	43%
			Any abnormality	80%
	Tobin et al. 1999	15	Any abnormality	80%
	Novak et al. 2001	92	Distal abnormality	71%
			Any abnormality	73%
	Singer et al. 2004	11	Any abnormality	64%
	Low et al. 2006	125	Distal abnormality	62%
			Any abnormality	77%
	Thaisetthawatkul et al. 2013	121	Any abnormality	52%
			Abnormal and at least 1 additional abnormality in pin sense, quantitative sensory testing, or skin biopsy	82%

QSART = quantitative sudomotor axon reflex test; TST = thermoregulatory sweating test.

6.3. 30:15 ratio

The 30:15 ratio is measured in the patient who lies quietly and then is asked to stand up unaided. The ratio is obtained by dividing the longest R-R interval at the 30th beat by the shortest R-R interval at the 15th beat. It is one component of Ewing's battery, which comprises also the Valsalva ratio, the HR response to deep breathing, and the BP response to standing and to sustained handgrip (Ewing et al., 1985). Ewing's battery is occasionally still used but has largely been supplanted by more precise methods of noninvasive autonomic testing.

7. Testing of sudomotor function

The goal of sudomotor testing is to evaluate the functional integrity of sudomotor neurons. Under controlled conditions a standardized stimulus is administered, and the response is measured.

7.1. Quantitative sudomotor axon reflex test (QSART)

The quantitative sudomotor axon reflex test (QSART) evaluates the functional integrity of the postganglionic sympathetic sudomotor axon. Acetylcholine is iontophoresed into the skin via the stimulus compartment of a multicompartmental sweat cell. The acetylcholine activates axon terminals in one compartment (outside stimulus compartment). Impulses travel along the postganglionic sudomotor axon, initially antidromically, reaching a branch point, then orthodromically (hence an axon reflex) to release endogenous acetylcholine at the nerve terminal, which activates muscarinic receptors on eccrine sweat glands (Low, 1993a, Low et al., 1983). The latency and volume of the resulting sweat response is measured from the recording (central) compartment during 5 minutes of stimulation followed by 5 minutes of additional recording. The responses are recorded simultaneously from four standard 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 (Low et al., 1997).

The QSART has the advantage of assessing the distribution of sudomotor impairment. The test is sensitive and reproducible in healthy controls (Low et al., 1983) and in patients with diabetic neuropathy (Low et al., 1986). Tests repeated on two different days show a decrease in sudomotor volume with a high coefficient of regression. The coefficient of variation was found to be 8% and 14% in two studies (Low et al., 1983, Low P.A. and Opfer-Gehrking T.L., 1992). In the diagnosis of distal small fiber neuropathy (DSFN), it has a sensitivity of 80% and a specificity of > 90% (Low et al., 2006, Stewart et al., 1992), using the criteria of absent response or response < 5th percentile at the foot, while sweating is normal in proximal sites (Table 4).

The main limitations of the test relate to medication effects and the efficiency of iontophoresis. Potentially confounding medications are those with anticholinergic effects or inhibitors of carbonic anhydrase, which, when not unsafe for the patient, should be held for 5 elimination half-lives prior to testing (Cheshire and Fealey, 2008, Low P. A. and Opfer-Gehrking T. L., 1992). Additionally, high skin resistance will reduce the efficiency of iontophoresis and reduce the sweat response. Normative values were generated from the original Mayo Clinic sudorometer (Low et al., 1983). A commercial unit of similar design results in a smaller response with a reasonably reproducible ratio to the Mayo Clinic device (Low and Sletten, 2008). A new set of normative values based on the commercial unit is currently in preparation.

7.2. Thermoregulatory sweat test

The thermoregulatory sweat test (TST) evaluates the integrity of central and peripheral sympathetic sudomotor pathways. The pathway is complex. From central nervous system thermoregulatory centers including the hypothalamus, bulbospinal tracts descend to the intermediolateral cell columns, which send forth preganglionic neurons that emerge from the spinal cord and travel through the sympathetic chain ganglia. Preganglionic neurons synapse onto postganglionic sudomotor axons, which innervate eccrine sweat glands (Fealey et al., 1989, Low and Sletten, 2008).

While variations exist, the most reliable technique utilizes a controlled environment in which temperature, humidity, and skin temperature are continuously monitored and kept within standardized parameters. Attaining an endpoint core temperature of 38.0 °C within 45–60 minutes ensures an adequate heat stimulus and recruitment of all skin areas capable of sweating. Environmental (cabinet air) temperature and relative humidity are maintained between 43–45 °C and 35–40%, respectively. Mean skin temperature is maintained close to 39.0 °C. An indicator powder applied beforehand to as much of the body surface as possible allows for a detailed examination at high sensitivity. Digital photographs and computerized drawings document the distribution of anhidrosis and allow for the calculation of percentage of anterior body surface anhidrosis (TST%).

Fealey (Fealey, 1997, Fealey et al., 1989) established the scientific basis for the TST by defining normal values, test conditions, and adequate endpoints. He also established the useful index of

TST% (Fealey et al., 2008). Advantages of the test are its ability to detect abnormalities anywhere along the sudomotor neuraxis, from brain to the periphery. By testing the whole anterior body surface, it also has greater sensitivity than tests such as QSART or skin biopsy, where testing is confined to sampled sites. Its sensitivity (80%) in the detection of DSFN and the distribution of autonomic failure is well-established (Fealey, 1997, Low and Sletten, 2008). When the results of TST and QSART are compared alongside one another, it may be possible to distinguish a postganglionic from a preganglionic sudomotor deficit.

Its main limitations are the discomfort of the heat stimulus of the test, so that some patients are reluctant to have repeat testing.

7.3. Sympathetic skin response

The sympathetic skin response (SSR) evaluates the momentary change in the electrical potential associated with induced sweating in the palms and soles. The response can be evoked by psychological or local nociceptive stimuli (Vetrugno et al., 2003). As the response is emotionally activated rather than thermoregulatory, it is highly variable and has limited sensitivity and specificity in the diagnosis of sudomotor nerve impairment (Arunodaya and Taly, 1995, Gutrecht, 1994, Maselli et al., 1989, Niakan and Harati, 1988).

8. Tests useful in research settings

A variety of additional autonomic tests have appropriate applications in select research settings but at this time are not practical for routine clinical use. Among them are pupillometry, microneurography, lower body negative pressure, the cold pressor test, and tests of male erectile function. Another is the modified Oxford test, which defines baroreflex sensitivity as the slope of the heart period to arterial BP during incremental manipulation by intravenous infusions of phenylephrine and nitroprusside (Ebert et al., 1992). As the modified Oxford test method is elaborate and invasive, its use is confined to research settings.

The cold pressor test measures the sympathetically mediated increase in BP in response to the stress of a controlled environmental temperature change. Following a baseline recording, BP is monitored as the patient immerses a hand or arm in ice water for one to several minutes. The cold pressor test has the advantage of being easily performed and the disadvantages of the stimulus being painful, the response being highly variable among subjects, and the occasional confounding phenomenon of a vasovagal reaction (Wirch et al., 2006). A variation is the cold face test, which activates trigeminal afferents and evokes reflex bradycardia and pressor responses as measures of vagal and cardiovascular adrenergic functions, respectively (Khurana and Wu, 2006).

The BP response to sustained handgrip has proven less useful than other tests of cardiovascular adrenergic function because of its dependence on hypertensive status and baseline diastolic BP (Korei et al., 2017). Tests of the venoarteriolar reflex, the neurogenic flare response, and skin vasomotor reflexes are insufficiently sensitive for autonomic diagnosis (Low and Pfeifer, 1993). Plasma catecholamine measurement, ^{123}I-MIBG SPECT, and PET imaging are not reviewed here, as the purpose of this review is electrodiagnostic testing. Similarly, skin biopsy for detecting epidermal nerve fiber density is not reviewed here, although skin biopsy is an accepted clinical test in the diagnosis of small fiber neuropathy (England et al., 2009).

Other useful clinical tests of autonomic function are specific to non-neurologic specialties. These include urodynamic studies of bladder emptying, radionuclide testing of gastrointestinal motility, Schirmer's test of lacrimation, and parotid gland scintigraphy to evaluate salivation.

9. Tests of unproven validity

A number of commercial tests have been introduced that record moisture or skin conductance due to spontaneous sweating. Although appealing in terms of simplicity, these tests are restricted to assessing sweat gland function in areas that have large sweating output, especially the palms and soles, which are highly responsive to emotional activation. As they do not evaluate the integrity of sudomotor axons, they are not truly tests of autonomic function (Rajan et al., 2019).

Automated devices have been marketed under the label of autonomic testing that collect HR or BP data in a simplified way without measuring beat-to-beat BP or controlling for respiration, expiratory pressure, or medications. So-called autonomic testing by automated devices without physician interpretation has not been validated, lacks a sound physiological basis, is potentially misleading, and should be interpreted with caution (Gibbons et al., 2014).

10. Autonomic testing in specific clinical situations

The range of clinical presentations of autonomic disorders is vast. Whereas a complete differential diagnosis of autonomic disorders is beyond the scope of this paper, a number of common indications may be identified in which autonomic testing has been shown to be useful in the clinical evaluation. In the following sections we review the evidence that supports the use of autonomic testing for each indication.

10.1. Orthostatic hypotension

Often the most disabling of autonomic symptoms, orthostatic hypotension (OH) is defined as a sustained reduction of systolic BP of $\geq$ 20 mmHg or diastolic BP of $\geq$ 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° (Freeman et al., 2011). The change in systolic BP correlates more closely than diastolic BP with orthostatic symptoms (Fedorowski et al., 2017). Tilt table testing for 3–5 minutes is usually adequate to detect OH (Cheshire and Goldstein, 2019), but in some cases the development of OH can be delayed (Gibbons and Freeman, 2015).

An important clinical distinction is that of neurogenic OH. Whereas OH from inadequate fluid intake, excessive fluid loss, deconditioning, venous pooling, or medications is quite common, a minority of patients with OH will have neurogenic OH, which is a cardinal manifestation of cardiovascular sympathetic adrenergic failure (Goldstein and Sharabi, 2009).

Direct demonstration of underlying adrenergic failure is achieved by assessing BP responses to the Valsalva maneuver. The most sensitive index defining neurogenic OH is the PRT (Huang et al., 2007). In a comparison of 162 patients with varying degrees of cardiovascular adrenergic failure, rho coefficients of BP recovery during late phase II and phase IV were 0.68 and 0.84, respectively, indicating that the PRT most closely parallels the severity of adrenergic failure (Vogel et al., 2005).

A decreased HR response to orthostatic hypotension has been shown to be a reasonable surrogate marker of neurogenic OH. In a prospective study of 423 patients, 378 of whom had α-synucleinopathies, neurogenic OH was reliably distinguished from other causes of OH when the ΔHR/ΔSBP ratio at 3 minutes of tilt was < 0.5 beats/min per mmHg (Norcliffe-Kaufmann et al., 2018). However, this criterion may not be adequate in patients with par-

tial or early autonomic failure, patients taking beta blockers, or those with a cardiac pacemaker (Cheshire and Goldstein, 2019).

10.2. Orthostatic intolerance

Many patients present with symptoms that occur when standing and are relieved by lying down and yet do not have OH. When disabling postural symptoms result from the physiologic response to the orthostatic stress in which gravity causes blood to pool upon standing, these patients are said to have orthostatic intolerance. The most recognized variety of chronic orthostatic intolerance is the postural tachycardia syndrome (POTS), which is a heterogeneous clinical condition defined as a sustained HR increment of $\geq$ 30 beats/min ($\geq$40 beats/min for patients < 20 years of age) within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension (Benarroch, 2012, Freeman et al., 2011, Singer et al., 2012). The diagnosis is based on averaged, rather than momentary peak, heart rates.

Tilt table testing with beat-to-beat assessment of BP and HR represents the standard of care in diagnosing POTS and is recommended by the Heart Rhythm Society for this purpose (Cheshire and Goldstein, 2019, Sheldon et al., 2015). Diagnostic evaluation should also include estimation of intravascular volume status. Additional autonomic testing may be warranted in selected patients to assess for peripheral denervation and hyperadrenergic state, as these patients have been found to have lower resting muscle sympathetic nerve activity, impaired cardiovagal responses, exaggerated BP drops in response to the Valsalva maneuver, and delayed cardiovascular adrenergic responses to hypotensive challenge (Arnold et al., 2018, Jacob et al., 2019, Low et al., 2009).

10.3. Syncope

Whereas isolated instances of neurally mediated syncope are quite common and often can be diagnosed by a careful history, recurrent or unexplained syncope are more serious matters that can be diagnostically challenging (Cheshire, 2017). Head-up tilt testing is well-established in the diagnosis of neurally mediated syncope (Saal et al., 2016) and is recommended by the Heart Rhythm Society for differentiating between convulsive syncope and epilepsy and for patients with suspected neurally mediated syncope who lack clear diagnostic features (Sheldon et al., 2015). Following supine rest of at least 10 minutes, the patient is tilted to an angle of 60°-70° for 30–45 minutes. Unlike the immediate fall in BP that occurs in OH, the vasodepressor response, when it occurs, develops more gradually and after the patient has been upright for some time.

Demonstration of a vasodepressor response by beat-to-beat BP testing during orthostatic challenge on a tilt table is useful in confirming a diagnosis of neurally mediated syncope. Tilt table testing in the evaluation of unexplained syncope has an estimated sensitivity of 25% to 75% and specificity of 90% to 100% (Cheshire and Goldstein, 2019). On the other hand, demonstration of normal BP and HR during apparent loss of consciousness is helpful in excluding neurally mediated syncope in the patient with psychogenic pseudosyncope (Raj et al., 2014). Beat-to-beat BP assessment is desirable, as routine sphygmomanometry cannot always capture BP changes quickly enough to correlate with behavioral changes.

A subset of patients with recurrent transient loss of consciousness have orthostatic syncope and may exhibit OH during tilt table testing. In the Framingham Heart Study, the incidence of orthostatic syncope was 9.4% among 822 study participants who reported syncope (Soteriades et al., 2002). In such cases additional autonomic testing is indicated to distinguish whether OH is neurogenic and whether there is evidence of widespread autonomic failure.

10.4. Peripheral polyneuropathy

Peripheral neuropathies are diverse in their clinical presentations and in which components of nerve fiber function are impaired. A substantial autonomic component frequently occurs in peripheral neuropathies in diabetes mellitus, human immunodeficiency virus infection, amyloidosis, Sögren syndrome and other rheumatologic disorders, Chagas disease, leprosy, Lyme disease and other rickettsial infections, Fabry disease, diphtheria, and botulism (Dineen and Freeman, 2015). The most common phenotype is a length-dependent sensory and autonomic neuropathy. Symptoms of dysautonomia may or may not be present or may be clinically subtle.

Autonomic peripheral neuropathies are subject to investigation and quantification by electrodiagnostic autonomic testing. Laboratory evidence of autonomic neuropathy may be found with or without corresponding symptoms. The most common laboratory changes comprise a concomitant involvement of distal postganglionic sudomotor and cardiovagal autonomic neuropathy without orthostatic hypotension (Low et al., 1986). These finding support the concept of a length-dependent process since the distal sudomotor and cardiovagal fibers involve the distal ends of very long nerves.

10.4.1. Distal small fiber neuropathy

The “burning feet” syndrome is perhaps the most common presentation of distal small-fiber neuropathy (DSFN) in clinical practice. These patients complain of distal burning, prickling, and some stabbing discomfort, with variable allodynia. They have completely normal motor function, intact tendon reflexes, and nerve conduction studies. About 10% of such cases are due to diabetes, and the cause remains unknown in as many as half of cases (Terkelsen et al., 2017). As both somatic and autonomic C fibers are involved, but large myelinated fibers are usually spared, this condition can be diagnosed by sudomotor testing when nerve conduction studies are normal (Illigens and Gibbons, 2009, Low et al., 2006, Thaisetthawatkul et al., 2013). Test results should be correlated with the patient’s symptoms and small fiber sensory findings on physical examination. Table 5 categorizes the degree of diagnostic confidence associated with specific QSART profiles.

Both TST and QSART show a distal pattern of anhidrosis in over 70% (Table 4). If both tests are combined, an abnormal study is seen in > 90%. In a prospective study combining both skin biopsy and QSART, diabetic neuropathy was associated with somatic and autonomic C-fiber impairment with good agreement. In other neuropathies, a variable correlation was found, presumably because these tests evaluate different fiber populations (Singer et al., 2004).

Table 5
Degrees of confidence in diagnosing small fiber neuropathy.

QSART Profile	Probability of SFN
Normal at all sites	No evidence
Abnormal but with potential medication effect	Indeterminate
Sudomotor volume < 5th percentile at 1 site without neuropathic symptoms or sensory exam abnormalities	Low probability
Sudomotor volume < 5th percentile at 1 or more sites with uncertain correlation anatomically with symptoms or exam findings	Intermediate probability
Sudomotor volume < 5th percentile at the foot and a length-dependent decrease, defined as a sudomotor volume at the foot less than one-third that at proximal sites, *or* Sudomotor volume < 5th percentile at the foot and either a history of distal dysesthesia or a distal deficit to small fiber sensory modalities on physical exam	High probability

QSART = quantitative sudomotor axon reflex test; SFN = small fiber neuropathy.

10.4.2. Regional neuropathy

The TST is particularly sensitive in detecting the neuroanatomical contours of regional anhidrosis, which are useful in identifying localizable deficits. The boundaries of segmental anhidrosis can define thoracic radiculopathies, cervical sympathetic deficits associated with Horner or Harlequin syndromes, or map the extent of surgical sympathectomy or subsequent reinnervation (Cheshire and Freeman, 2003, Fealey et al., 1989).

10.4.3. Inflammatory demyelinating neuropathy

Acute inflammatory demyelinating neuropathy, also known as Guillain-Barré syndrome, is an immune-mediated disorder of nerves and nerve roots that presents acutely. Autonomic involvement occurs in at least two-thirds of patients and can include tachycardia, bradycardia, hypertension, OH, urinary sphincter disturbances, and anhidrosis (Singh et al., 1987, Zochodne, 1994). In a series of 100 Guillain-Barré patients, low R-R interval variation on deep breathing was associated with increased incidence of serious cardiac rhythm disturbances (Winer and Hughes, 1988).

Chronic inflammatory demyelinating neuropathy (CIDP) is considered to be a chronic form of Guillain-Barré syndrome. Autonomic involvement has been described in 21% to 76% of cases of both the demyelinating and axonal subtypes (Stamboulis et al., 2006). Autonomic testing has detected subclinical signs of involvement in as many as 80% of patients without overt autonomic symptoms (Ingall et al., 1990, Lyu et al., 2002). Autonomic manifestations, though frequent, tend to be mild (Stamboulis et al., 2006). In a retrospective study of 47 CIDP patients, CASS scores were abnormal in 47%, but mild, with a mean ± SD of 0.8 ± 0.9, being ≤ 3 in all cases (Figueroa et al., 2012). This leads to the conclusion that, if autonomic testing in suspected CIDP were to show extensive or severe autonomic failure, then an alternative diagnosis should be sought.

10.4.4. Autoimmune autonomic ganglionopathy

Impaired cholinergic ganglionic synaptic transmission is one of the causes of severe autonomic failure. A subset of autonomic ganglionopathies is autoimmune and may be positive for ganglionic α_3-AChR antibody (Vernino et al., 2000). These patients have severe dysautonomia with postural hypotension, gastrointestinal dysmotility, anhidrosis, sicca symptoms, and pupillary and erectile dysfunction (Vernino et al., 2009).

Autonomic testing has proven useful in in characterizing the various autonomic presentations of autoimmune autonomic ganglionopathy (Sandroni and Low, 2009). In a retrospective study of 289 patients with positive ganglionic α_3-AChR antibodies who had undergone autonomic testing, CASS scores correlated closely with antibodies, with levels above 0.40 nmol/L predicting CASS scores of ≥ 7 (Cutsforth-Gregory et al., 2018).

10.4.5. Sensory neuronopathy

Autonomic dysfunction frequently accompanies sensory neuronopathies, which are characterized by non-length-dependent sensory deficits. Cardiovascular adrenergic, cardiovagal, and postganglionic sudomotor deficits have been described in nearly all patients. The autonomic involvement can be disabling, with orthostatic hypotension in 60% of patients adding to the risk of falling from sensory ataxia (Damasceno et al., 2011, Martinez et al., 2019).

10.4.6. Acute intermittent porphyria

Acute intermittent porphyria is an autosomal dominant inborn error of metabolism in which a block in the enzymatic biosynthesis of heme leads to excessive secretion of porphyrins and porphyrin precursors. Although quite rare, it is of importance for this discussion because symptomatic attacks are typically heralded by an autonomic neuropathy. The most common presenting symptom is abdominal pain caused by splanchnic autonomic dysfunction. Parasympathetic dysfunction may be an early feature. Other autonomic manifestations can include tachycardia, labile hypertension, orthostatic hypotension, hyperhidrosis, vomiting, bladder dysfunction, and constipation or diarrhea (Laiwah et al., 1985). Abnormalities on autonomic testing during symptomatic attacks have been shown to be reversible (Laiwah et al., 1985).

10.5. Diabetic neuropathies

Particular attention is given here to diabetic neuropathy, as diabetes mellitus is the most common cause of autonomic neuropathy in the developed world, and prevalence is increasing in the developing world (Freeman, 2005, 2014). Although major focus has been devoted to the common garden, length-dependent diabetic neuropathy, it is well-recognized that there are multiple phenotypes of diabetic neuropathy (Low, 1996, Low and Hilz, 2008). These are often classified into symmetric and asymmetric phenotypes (Sinnreich et al., 2005). The former include the most common type, comprising > 90% of cases, DSFN, and diabetic autonomic neuropathy. The latter include various mononeuropathies, mononeuropathy multiplex, radiculoplexus neuropathies and ganglionopathies (Low and Hilz, 2008). Autonomic involvement is known to occur in the majority of patients.

Diabetic autonomic neuropathy (DAN) impairs autonomic innervation at many levels, affecting thermoregulatory, male erectile, urogenital, gastrointestinal, pupillary, cerebral autoregulatory, and cardiac functions. Erectile dysfunction is common, occurring in about one-third of patients (McCulloch et al., 1980), and is due to a combination of autonomic failure and vascular disease (Low, 1996). Orthostatic hypotension develops in 8.4% and 7.4% of type 1 and 2 diabetic patients, respectively (Low et al., 2004). The manifestations of OH vary by age. Lightheadedness is common, but some elderly diabetic patients > 60 years of age complain instead of orthostatic cognitive difficulties (Low et al., 1995). Less common complaints involve gastrointestinal, bladder, and thermoregulatory functions. A detailed evaluation of symptoms of DAN and their correlation with abnormal autonomic function tests shows some imperfect correlations (Low, 1996, Low and Hilz, 2008).

In a review of 15 retrospective studies, estimates of the prevalence of DAN varied widely, from 1% to 90%, as the methodologies varied (Vinik et al., 2003). Information on the natural history of DAN is best derived from population-based studies using optimal study methodology, including autonomic testing. In one such study (Dyck et al., 1992), a cohort of 380 diabetic subjects from Rochester, Minnesota, was studied prospectively. The early changes over a 2-year period for autonomic tests deteriorated as follows: type I diabetes over 2 years deteriorated by 2.05 beats/min ($P = 0.005$) and type II diabetes by 1.56 beats/min ($P = 0.001$), averaging approximately 1 beats/min per year. VR did not have sufficient sensitivity to detect a change over 2 years.

Longterm follow-up in the Rochester Diabetic Study found a prevalence of 13.9% based on impaired HRDB (Dyck et al., 2006). Approximately 50% of diabetic patients are likely to have some clinical manifestations of neuropathy, and about 1 in 10 will have a clinical autonomic neuropathy (Dyck et al., 1993). DAN is usually not evident at the onset of diabetes or during the first 10 years. Clinical autonomic failure is less common, occurring in about 5%. The severity and distribution of autonomic failure increases with duration and severity of hyperglycemia, severity of somatic peripheral neuropathy, and with increasing age and likely with vascular disease (Low, 1996). Another population-based study (Neil et al., 1989) confirmed these findings, showing a prevalence of 20.9% for type 1 and 15.8% for type 2 (mean 16.7%).

Approximately 1% of diabetic patients will develop lumbosacral radiculoplexus neuropathy (DLRPN), also known as diabetic amy-

otrophy, or proximal diabetic neuropathy (Dyck et al., 1993). One-half of these patients experience some symptoms of autonomic disturbance (orthostatic hypotension, diarrhea or constipation, change in sweating, or change in sexual function). In a review of 44 such patients (Pascoe et al., 1997), generalized autonomic failure was usually present. This was quantitated using the CASS score. Patients had a mean value of 7.8, indicative of severe and generalized autonomic failure. Their scores ± SD were CASS, 7.8 ± 2.2; CASS-sudomotor, 2.3 ± 1.0; CASS-cardiovagal, 2.1 ± 1.0; CASS-adrenergic, 3.4 ± 1.0.

The Diabetes Control and Complications Trial (DCCT) followed 1441 type 1 diabetic patients. The primary prevention and secondary intervention cohorts were randomly assigned to either conventional or intensive therapy and followed for up to 9 years. Autonomic abnormalities increased during the trial; however, R-R variation was less abnormal in the intensively treated secondary intervention (7% with abnormal results at 4 ± 6 years) compared with the conventionally treated group (14% with abnormal results, $p = 0.004$) and in the combined cohorts (5% of intensive treatment subjects with abnormal results vs 9%of conventional treatment subjects, $p = 0.0017$). No significant difference in VR or postural tests occurred between the intensive and conventional treatment groups. Both the R-R variation and the VR had significantly greater slopes of decline over time in the patients randomized to conventional therapy (1.48 points per year and 0.015 per year, respectively) compared to those randomized to intensive therapy (0.912 points per year and 0.0025 per year). In summary, the DCCT documented that intensive therapy can slow the progression and the development of abnormal autonomic tests (Anonymous, 1998).

Following the DCCT findings, it was observed that the benefits of prior tight glycemic control persisted, even after both tight and conventional control was switched to tight control in an assessment done 8 years following DCCT completion (Martin et al., 2006). This observation, the notion of metabolic memory, led to The Epidemiology of Diabetes Interventions and Complications (EDIC) study, a prospective observational follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. In a study of the effects of prior intensive insulin therapy on the prevalence and incidence of autonomic neuropathy in former DCCT intensive and conventional therapy subjects 13 to 14 years after DCCT closeout (Pop-Busui et al., 2009), DCCT autonomic measures were repeated in 1226 EDIC subjects in EDIC year 13/14. In EDIC year 13/14, the prevalence of cardiovascular autonomic neuropathy (CAN), defined as either an R-R variation of < 15 or an R-R variation between 15–19.9 in combination with a VR $\leq$ 1.5 or a decrease of > 10 mmHg in diastolic BP, was significantly lower in the former intensive group versus the former conventional group (28.9% versus 35.2%; *P*_0.018). We conclude that, although CAN prevalence increased in both groups, the incidence was significantly lower in the former intensive group compared with the former conventional group. The benefits of former intensive therapy extend to measures of CAN up to 14 years after DCCT closeout.

Multiple reports have brought attention to the finding that the emergence of CAN in diabetes is associated with increased risk of morbidity and possibly also mortality on follow-up (Vinik et al., 2003, Vinik and Ziegler, 2007). CAN may be asymptomatic in its early stages and is frequently underdiagnosed (Bissinger, 2017). In a review of 16 studies (Low and Hilz, 2008), mortality rate varied from 13% to 69% in the duration of study (usually 5 years). In conclusion, there is little doubt that DAN is associated with increased mortality. There is some question as to whether it independently increases mortality.

Since the early observations that DAN is associated with silent myocardial infarction and increased mortality rate (Vinik et al., 2003), there has been considerable interest in the effect of DAN on cardiac function, separate from vascular disease. Some support is provided by preliminary studies showing increased left ventricular mass in normotensive diabetic patients with CAN (Gambardella et al., 1993). These patients commonly also have loss of the normal nocturnal reduction in BP. A recent EDIC study was more definitive (Pop-Busui et al., 2013). In this study on 371 subjects with CAN and 595 subject without CAN, participants with either abnormal R-R variation or a composite of abnormal R-R variation, abnormal VR and postural BP changes, had significantly higher LV mass, mass-to-volume-ratio, and cardiac output compared with those with normal tests ($p < 0.0001$ for all). After further adjustment for traditional cardiovascular risk factors, subjects with abnormal R-R variation had higher LV mass and cardiac output compared to those with a normal R-R variation ($p < 0.05$). Although the mechanisms by which impaired cardiovagal function could cause left ventricular hypertrophy are uncertain, there are a number of potential candidates. These patients have impaired baroreflex sensitivity and, therefore, impaired buffering of BP. They might lose the nocturnal increase in parasympathetic tone, resulting in increased sympathovagal balance and higher nocturnal BP. Support for this concept derives from the observation that these patients commonly also have loss of nocturnal reduction in BP (Gambardella et al., 1993).

In summary, there is strong evidence that autonomic function is impaired in diabetes and progresses over time. The presence of DAN worsens the prognosis by mechanisms that are likely a combination of dysautonomia and vascular disease (Agashe and Petak, 2018). As tight diabetic control is known significantly to prevent the development of diabetic autonomic neuropathy (Nathan et al., 1993), there has been considerable interest in the development and utilization of autonomic function tests in diabetes (Bernardi et al., 2011, Bissinger, 2017). The Toronto Consensus Panel on Diabetic Neuropathy recommends that all diabetic patients should be screened for autonomic neuropathy (Bernardi et al., 2011).

10.6. Pandysautonomia

The term pandysautonomia is often used when the patient has severe generalized autonomic failure, which can occur on the basis of central or peripheral autonomic nervous system disease. Typically the patient has orthostatic hypotension and involvement of at least two other systems such as neurogenic bladder or bowel or thermoregulatory failure.

Pandysautonomia occurs in a number of settings. One is end-stage diabetic neuropathy, where the patient has severe retinopathy, nephropathy, and neuropathy with progressive autonomic failure over a number of years (Low, 1996, Low and Hilz, 2008). Another is the autonomic neuropathy associated with primary and familial amyloidosis. Pandysautonomia frequently accompanies the parkinsonism or cerebellar ataxia that together are the clinical hallmarks of multiple system atrophy. Dysautonomia occurs in as many as two-thirds of patients with Guillain-Barré syndrome (Arcila-Londono and Lewis, 2012, Ropper, 1994, Zochodne, 1994), which occasionally presents as pandysautonomia (Ferraro-Herrera et al., 1997, Zochodne, 1994). Other settings in which a rapidly progressive autonomic neuropathy may present as pandysautonomia include paraneoplastic neuropathies (Golden and Vernino, 2019), botulism (Jenzer et al., 1975), and the spinal shock of acute tetraplegia (Mathias and Frankel, 1983).

When severe autonomic failure presents acutely, autonomic testing is useful to identify patients at risk of cardiovascular complications and to guide therapeutic interventions (Hilz et al., 2019). In follow-up, autonomic testing has been useful to monitor recovery and to correlate residual symptoms with persistent autonomic deficits (Kimpinski et al., 2012b, Topakian et al., 2009).

10.7. Familial dysautonomia

Autonomic testing is essential to diagnosing and characterizing familial dysautonomia, which is a rare autosomal recessive disorder caused by a splice mutation in the IKBKAP gene (Bickel et al., 2004, Norcliffe-Kaufmann et al., 2017). Autonomic risk factors for serious complications in these patients, such as sudden unexpected death during sleep, may have implications for other neurologic disorders, including epilepsy (Cheshire, 2014, Palma et al., 2017)

10.8. Afferent baroreflex failure

Obliteration, often by therapeutic irradiation for pharygeal cancer, of carotid sinus afferent baroreceptor input to the brainstem, or lesions of the nucleus tractus solitarius or vagus nerves can lead to baroreflex failure. These patients lack the ability to buffer their BP. Autonomic testing is required to differentiate their labile BP and episodic hypertensive crisis from other causes of labile hypertension, such as "white coat" syndrome (Ketch et al., 2002, Robertson et al., 1993).

10.9. Autonomic dysreflexia

Unstable BP, including OH and unstable hypertension, frequently occur following spinal cord injury when descending input from supraspinal centers to spinal sympathetic preganglionic neurons is disrupted (Krassioukov and Claydon, 2006). A potential longterm condition resulting from spinal cord injury at or above the level of T6 is autonomic dysreflexia, defined as episodic hypertension and concomitant baroreflex-mediated bradycardia initiated by unmodulated sympathetic outflow in the decentralized spinal cord (Eldahan and Rabchevsky, 2018). Autonomic tests supply the means to assess which pathways are impaired and to what extent, which has implications for prognosis and prevention of cardiovascular complications (Ravensbergen et al., 2012).

10.10. Paroxysmal autonomic instability with dystonia

Paroxysmal autonomic instability with dystonia is a syndrome of autonomic dysregulation that can mimic other life-threatening conditions and is seen in patients beginning the first week after severe traumatic or hypoxic brain injury, in intracranial hemorrhage, and occasionally in patients with brain tumors or hydrocephalus. Autonomic testing in a formal autonomic laboratory setting with the patient relaxed is usually not possible for the hemodynamically unstable patient who may be in an intensive care unit. Recognition of this syndrome is based on interpretation at the bedside of unstable autonomic signs, which consist of cyclic episodes of elevated temperature, tachycardia, tachypnea, hypertension, and diaphoresis, along with agitation and dystonia (Blackman et al., 2004). Early recognition is key to appropriate management as well as avoidance of pharmacologic overtreatment, prevention of end-organ injury, and alleviation of anxiety among the healthcare team and the patient's family when observing episodes of autonomic storm (Kapoor et al., 2014).

10.11. Anhidrosis

Extensive loss of the ability to generate a thermoregulatory sweating response, whether from lesions involving central, preganglionic, or postganglionic sudomotor neurons, can increase the risk of hyperthermia, including heat exhaustion and the potential for heat stroke (Cheshire, 2016). Global anhidrosis on sudomotor testing correlates well with heat intolerance and potential risk of heat illness (Cheshire, 2016, Mevorah et al., 1993). In the patient with a sudomotor deficit, collateral testing of cardiovascular adrenergic and cardiovagal function is useful in distinguishing the relatively benign condition of chronic idiopathic anhidrosis (Low et al., 1985) from more widespread forms of autonomic failure (Donadio et al., 2008).

10.12. Gastrointestinal dysmotility

Autonomic testing has proven useful in the assessment of autonomic involvement outside the gastrointestinal tract in selected patients presenting with gastroparesis, esophageal spasm, irritable bowel syndrome, and chronic intestinal pseudo-obstruction. In a retrospective study of 94 patients with suspected gastrointestinal dysmotility who underwent autonomic testing, there was a significant rank correlation between autonomic and motility scores ($r = 0.28$, $P < 0.05$) (Bharucha et al., 1993).

Autonomic testing is not needed in all patients who present with gastrointestinal complaints but should be considered if there is evidence of severe dysmotility or if there are additional signs to suggest neurologic disease, such as peripheral neuropathy, parkinsonism, or focal deficits. The strongest correlations have been found in patients with chronic intestinal pseudo-obstruction. In diabetic patients with chronic intestinal pseudo-obstruction, a majority were found to have an abdominal vagal neuropathy (Camilleri et al., 1993). An autonomic neuropathy involving adrenergic, cardiovagal, or postganglionic sudomotor responses was demonstrable in between 20% and 91% of patients with idiopathic intestinal pseudo-obstruction (Camilleri et al., 1993, Cuadrado and Lieberman, 1998, Mattsson et al., 2008).

10.13. Neurogenic bladder

Neural detrusor underactivity or atonia presents with incomplete urinary bladder emptying, elevated postvoid residual volumes, and slow urinary flow in the absence of urinary outlet obstruction. As for gastrointestinal dysmotility, some patients with neurogenic bladder will have evidence of more widespread autonomic neuropathy or myelopathy (Kadow et al., 2015, Osman et al., 2014). In a prospective cohort of 121 MSA patients, 18% had presented with urinary bladder dysfunction as the sole initial manifestation (Sakakibara et al., 2019). Autonomic testing is recommended for patients with unexplained bladder atonia to investigate for more widespread autonomic involvement.

10.14. Parkinsonism

Autonomic dysfunction has been recognized in Parkinson disease (PD), the second most prevalent human neurodegenerative disorder, since its earliest description. An estimated 30%-60% of patients with PD have orthostatic hypotension, and additional autonomic impairment may include constipation, urinary frequency or urgency, sialorrhea, and erectile failure (Cheshire, 2010).

Autonomic testing is useful in predicting the risk of falls in PD. In a prospective study of 50 patients with PD who underwent autonomic testing, CAN was present in 38% and was associated with a 15-fold higher probability of falls over one year of follow-up (Romagnolo et al., 2019). Another prospective study of 131 patients with PD reported worsening of OH prevalence during one year of follow-up from 31% to 47%, and OH was independently associated with impairment in daily living activities, health-related quality of life, and increased falls ($P \leq 0.009$) (Merola et al., 2018).

10.15. Multiple system atrophy

Early or severe autonomic failure is one of the clinical hallmarks of multiple system atrophy (MSA), which is a rare, sporadic, pro-

gressive, and ultimately fatal neurodegenerative disorder that manifests also with parkinsonism or cerebellar ataxia or both (Gilman et al., 2008, Low et al., 2015, McKay and Cheshire, 2018). Autonomic testing has found sudomotor involvement in nearly all patients, QSART being abnormal in 59% and TST abnormal in 95% of patients in a range of anhidrotic patterns, often with mixed preganglionic and postganglionic impairment (Coon et al., 2017). In a large retrospective study of 685 patients, OH was present in 59% of patients and was severe in 22% (Coon et al., 2015).

The clinical utility of autonomic testing relates to enhancement of diagnostic accuracy, particularly in the difficult task of distinguishing the parkinsonian subtype from PD and the cerebellar subtype from other causes of cerebellar ataxia (Koga et al., 2015, Pellecchia et al., 2020, Stankovic et al., 2019). A number of studies have utilized autonomic testing to differentiate MSA from PD. In a retrospective study of 35 MSA and 65 PD patients tested with Ewing's battery, OH was found in 63% of MSA and 5% of PD patients. In this study Ewing's battery discriminated MSA from PD with 91% sensitivity and 94% specificity (Baschieri et al., 2015).

In a prospective study of 52 MSA and 29 PD patients, autonomic impairment was greater in MSA than in PD as assessed by CASS (5.9 ± 1.9 vs 3.3 ± 2.3, $P < 0.001$) and TST% (57.4 ± 35.2 vs 9.9 ± 17.7, $P < 0.001$) (Lipp et al., 2009). Another prospective study of 9 MSA and 10 PD patients found CASS total and adrenergic scores to distinguish MSA from PD with 89% sensitivity and 70% specificity ($P < 0.001$), but overlap was seen (Kimpinski et al., 2012a). By contrast, minimal overlap was seen with TST ($P < 0.001$), leading also to the conclusion that autonomic dysfunction in MSA is primarily preganglionic, whereas in PD it is postganglionic (Kimpinski et al., 2012a). In another prospective study of 47 MSA and 34 PD patients, impaired HR variability during paced, but not spontaneous, breathing differentiated MSA from PD ($P < 0.01$) (Holmberg et al., 2001).

Quantitation of autonomic failure by autonomic testing is also relevant to prognosis. In a retrospective study of 685 patients clinically diagnosed with probable or possible MSA, whereas initial motor or autonomic symptoms did not influence length of survival, the degree of autonomic failure on laboratory testing was a predictor of survival. For every one-point increase in CASS scores, the hazard ratio was 1.07 ($P < 0.0023$); CASS scores of 2 and 10 were associated with mean survivals of 7.8 and 4.3 years, respectively (Coon et al., 2015). Further, in a review of 49 cases of autopsy-confirmed MSA, those with early laboratory evidence of severe autonomic failure, defined as CASS $\geq$ 6 within 3 years of disease onset, had shorter median survival time (5.7 vs 9.8 years, $P = 0.036$) (Figueroa et al., 2014).

In conclusion, autonomic failure in MSA in general occurs earlier and more severely than in PD, but there is considerable overlap, and no single autonomic test by itself is able to distinguish between them (Kimpinski et al., 2012a). Assessing autonomic dysfunction in MSA aids the targeting of therapeutic interventions, the estimation of prognosis, and the development of management strategies that benefit patients (Iodice et al., 2011).

10.16. Pure autonomic failure

Previously known as idiopathic orthostatic hypotension, pure autonomic failure is a postganglionic α-synucleinopathy affecting autonomic ganglia. As some patients will eventually phenoconvert to MSA (Kaufmann, 2000, Kaufmann et al., 2017, Singer et al., 2017), autonomic testing is useful to monitor the progression of autonomic deficits over time.

10.17. Dementia

Autonomic impairment has been increasingly recognized in some neurodegenerative dementias (Allan et al., 2007). Patients who are cognitively impaired may be unable to express symptoms of autonomic dysfunction, and assessment of autonomic involvement at the bedside may be confounded by such factors as deconditioning, decreased fluid intake, and medications. For these reasons noninvasive autonomic testing is finding an increasing role in the recognition of autonomic impairment in dementia as well as in differentiating among types of dementia (Idiaquez and Roman, 2011).

Objective measures of autonomic impairment are commonly associated with α-synuclein pathology, such as dementia with Lewy bodies (Akaogi et al., 2009, Thaisetthawatkul et al., 2004) and Parkinson disease with dementia (Allan et al., 2007, Norcliffe-Kaufmann et al., 2018), whereas it is less frequent and less prominent in dementias associated with tau pathology, such as Alzheimer disease (Idiaquez and Roman, 2011, Toru et al., 2018) or progressive supranuclear palsy (van Gerpen et al., 2019). Determination of neurogenic OH, rather than OH of all causes, has emerged as a key discriminator (Norcliffe-Kaufmann et al., 2018, van Gerpen et al., 2019). Further, in a prospective study of patients with dementia with Lewy bodies and Parkinson disease with dementia, OH and urinary incontinence were associated with a poorer prognosis for survival (Stubendorff et al., 2012).

10.18. Chronic kidney disease

Autonomic impairment in chronic kidney disease has long been recognized (Ewing and Winney, 1975). In a prospective study of 133 patients with end-stage renal disease followed over 5 years, cardiovascular autonomic neuropathy (CAN), which was present in 58% of patients, was found to be an independent risk factor for all-cause and cardiovascular mortality with cumulative survival being 33% vs 61% for patients with versus without CAN ($P = 0.001$) (Doulgerakis et al., 2017). In another prospective study of 50 patients with end-stage renal disease followed for one year, CAN was present in 88% at baseline and in 100% at repeat testing one year later. High autonomic scores were associated with all-cause mortality (56% vs 17%, $P = 0.02$), and all 7 with sudden cardiac death had high autonomic severity scores at baseline (Bokhari et al., 2018). The assessments of CAN were based on a composite score that drew from HR variability during deep breathing, the HR response to standing and the Valsalva maneuver, and orthostatic BP measurements.

11. Recommendations

Testing of the autonomic nervous system in the clinical autonomic laboratory should be performed by healthcare professionals with comprehensive knowledge of the neuroanatomy, physiology, and pathological profiles of autonomic disorders. Interpretation of autonomic test results should be based also on a medical history and physical examination, from which autonomic testing assists in confirming or eliminating potential conditions in a differential diagnosis.

A combination of autonomic tests in a screening battery provides a more accurate measure of autonomic function, as a single test alone cannot distinguish the type or severity of autonomic failure (Ewing et al., 1985, Low, 1993b). Ideally, assessment of autonomic function should include tests of cardiovascular adrenergic, cardiovagal, and sudomotor function (Table 6). In resource-limited settings the knowledge and expertise of the person interpreting autonomic tests is no less important. Before the results

Table 6
Recommended tests for the autonomic laboratory.

Sympathetic cardiovascular adrenergic	Continuous beat-to-beat heart rate and blood pressure responses to the Valsalva maneuver
	Continuous beat-to-beat heart rate and blood pressure responses to postural change on a tilt table
Parasympathetic cardiovagal	Continuous beat-to-beat heart rate responses to sinusoidal deep breathing The Valsalva ratio
Sympathetic sudomotor cholinergic	Quantitative sudomotor axon reflex test
	Thermoregulatory sweat test

Table 7
Valid indications for autonomic testing.

Diagnosis	Clinical Questions Addressed by Autonomic Testing
Autonomic failure	• Evaluate its presence, severity, distribution • Evaluate familial dysautonomia • Distinguish from benign symptoms or syndromes
Peripheral polyneuropathy	• Evaluate the presence, severity, and distribution of autonomic fiber involvement in peripheral neuropathy • Detect and quantitate distal small fiber neuropathy • Evaluate diabetic autonomic neuropathy • Evaluate amyloid autonomic neuropathy • Evaluate paraneoplastic autonomic neuropathy • Evaluate hereditary sensory and autonomic neuropathies • Evaluate Guillain-Barré syndrome • Evaluate chronic inflammatory demyelinating neuropathy • Evaluate Lambert Eaton myasthenic syndrome • Evaluate Chagas disease • Evaluate leprosy
Ganglionopathy	• Evaluate the presence, severity, and distribution of autonomic failure • Evaluate autoimmune autonomic ganglionopathy
Orthostatic hypotension	• Evaluate its presence, severity, and temporal profile • Distinguish neurogenic orthostatic hypotension from other causes of hypotension • Assess baroreflex function
Orthostatic intolerance	• Evaluate postural tachycardia syndrome • Evaluate delayed orthostatic hypotension
Syncope	• Evaluate recurrent or unexplained syncope • Distinguish neurally mediated syncope from psychogenic pseudosyncope
Neurodegenerative disorders	• Evaluate autonomic failure in multiple system atrophy • Evaluate autonomic failure in Parkinson disease • Evaluate autonomic failure in Lewy body dementia • Distinguish multiple system atrophy from Parkinson disease • Distinguish multiplesystem atrophy from other forms of cerebellar ataxia • Evaluate pure autonomic failure
Hyperadrenergic states	• Evaluate baroreflex function • Evaluate autonomic dysreflexia* • Evaluate autonomic storms* • Evaluate Morvan syndrome
Heat intolerance	• Evaluate the presence, severity, and distribution of anhidrosis • Evaluate Ross syndrome • Evaluate small fiber neuropathy in Sjögren syndrome
Regional autonomic failure**	• Evaluate for the presence, severity, and distribution of more widespread autonomic failure

*Bedside assessment of autonomic signs may be more useful than formal autonomic testing in these syndromes.
**For example, neurogenic bladder, intestinal pseudo-obstruction, gastroparesis, tonic pupils, Horner syndrome, afferent baroreflex failure, multiple sclerosis.

are interpreted as normal or abnormal, consideration should be given to potentially confounding factors, such as medications, equipment settings, room conditions, or patient factors that might have altered the findings.

12. Conclusion

A discussion of autonomic disorders could be organized by presenting clinical problem or by diagnosis. Either way, there is much overlap. The patient with orthostatic hypotension, for example, might have a central nervous system alpha synucleinopathy or a peripheral autonomic neuropathy. This review is structured according to the types of autonomic problems that present in clinical practice, in which the pathophysiology before autonomic testing is performed may or may not yet be apparent. A complementary structure focusing on pathophysiology is offered in Table 7.

The availability of standardized, validated, noninvasive electrodiagnostic tests that assess the functional integrity of the autonomic nervous system has enabled better recognition of disorders of the autonomic nervous system in clinical practice. Expert consensus on the proper performance of autonomic tests has allowed diagnostic and prognostic correlations to a variety of common and rare autonomic disorders and continues to enhance an understanding of their mechanisms. These developments together have laid the foundation for accelerated advances in autonomic neuroscience that hold promise in improving the lives of patients.

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