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This section, edited by Charles B. Berde, MD, PhD, and Michael C. Rowbotham, MD, presents timely topics in pain research and treatment.

Testing the Autonomic Nervous System

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The autonomic nervous system (ANS) is an extensive neural network whose main role is to regulate the *milieu intérieur* by controlling homeostasis and visceral functions. Although most functions regulated by the ANS are out of conscious control, emotions and somatosensory inputs profoundly influence the ANS. Observing the marked vasomotor and sudomotor changes after traumatic nerve injury, it became apparent long ago that the ANS plays an important role in pain modulation and perception. Despite the debate on whether the role of the sympathetic nervous system in generating and sustaining certain pain syndromes is significant, specialists in pain management have sought tools for investigating the ANS.

Anatomy

The ANS has components at every level of the nervous system. The central component, also known as the central autonomic network (CAN), includes the insula, medial prefrontal cortex, hypothalamus, amygdala, ventrolateral medulla, nucleus of the tractus solitarius (NTS), nucleus parabrachialis, periaqueductal gray, and the circumventricular organs.

The *insula*, through its connection with the hypothalamus, thalamus, parabrachial nucleus, and NTS, appears to be a crucial visceral sensorimotor area. Activation of the insular cortex induces hypertension, tachycardia, piloerection, pupillary dilatation, and salivation, and alters gastrointestinal function. Stimulation of the *medial prefrontal cortex*, which has connections with the amygdala, hippocampus, thalamus, hypothalamus, parabrachial nucleus, and NTS, induces bradycardia and hypotension and modulates gastric secretion.

The *hypothalamus* is the most important ANS organ, controlling every vital function and integrating neuroendocrine and autonomic systems. This is the site where the internal and external worlds interface. The *amygdala,* intercalated between the cerebral cortex, the hypothalamus, and the mesencephalic regions, plays a major role by coloring with emotions all stimuli and generating responses that include autonomic function modulation.

At the mesencephalic level, the *nucleus parabrachialis* and *periaqueductal gray* (PAG) are integrative relay areas. The PAG is also a crucial structure in pain modulation. Brainstem regions of the medulla oblongata that control most reflex and automatic cardiorespiratory functions include the *ventrolateral medulla* and the *NTS. Circumventricular organs,* by sensing humoral changes, participate in autonomic function modulation.

The peripheral components of the ANS are the *sympathetic* and *parasympathetic* nervous systems. The sympathetic system preganglionic neurons lie in the intermediolateral column ofthe spinal cord: their axons synapse in the prevertebral and para-vertebral ganglia from where postsynaptic fibers travel a relatively long distance to innervate each organ.

The sympathetic is a diffuse system, able to generate mass responses by epinephrine release from the adrenal medulla by virtue of its high postganglionic:preganglionic fiber ratio and long postganglionic fibers. Parasympathetic preganglionic neurons lie in cranial and sacral nuclear groups. The parasympathetic nervous system acts selectively because the preganglionic axons synapse in ganglia that lie in close proximity to the effector organs and because the parasympathetic postganglionic:preganglionic fiber ratio is much lower than in the sympathetic nervous system. The sympathetic and parasympathetic systems usually oppose each other, but in a few organs their effects are synergistic.

Neurotransmitters

Acetylcholine (Ach) is the "classic" neurotransmitter for preganglionic neurons in the sympathetic and parasympathetic nervous systems. Sympathetic postganglionic neurons release nor-epinephrine (NE), with the exception of sudomotor fiber release of acetylcholine. Parasympathetic postganglionic neurons all release Ach. A variety of neuropeptides and putative neurotransmitters coexist with Ach- and NE-containing neurons at various levels of the CAN, the spinal cord, and both pre- and postganglionic terminals. Neuropeptides and putative neurotransmitters play an important role in visceral function and also modulate a multitude of integrated functions, such as cognition, pain, and locomotion. The most common are: cholecystokinin (CCK), substance P (SP), somatostatin, enkephalins, neurokinins, nitric oxide (NO), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), serotonin (5-HT), and calcitonin gene-related peptide (CGRP). At the visceral level, purines, prostaglandins (PGs), and other peptides (such as dynorphins) are also present.

Clinical Investigations

Because of its many functions, a complete assessment of the ANS is extremely complex. Each specialty has developed its own test battery to assess those ANS functions most relevant to its field. ANS testing is used most often by cardiologists, gastroenterologists, urologists, and endocrinologists. Only recently have neurologists and pain specialists become directly involved in developing ways to evaluate patients with ANS dysfunction.

Because postganglionic fibers are unmyelinated, they cannot be tested directly by conventional neurophysiologic techniques, i.e., nerve conduction studies and electromyography. Therefore, the only way to assess their function is indirect, by evaluating the response elicited reflexly by appropriate stimuli. Until very recently, autonomic tests were available only in a few specialized centers. Now the equipment to measure noninvasively cardiorespiratory and circulatory parameters and to measure sweat production is commercially available. The cost of establishing a lab, however, is about $66,000, and reimbursement remains a major problem. The testing is time consuming, averaging 1 hour per patient. Furthermore, skilled technicians and physicians trained in correctly interpreting the studies are few. Adequate baseline acclimatization and proper positioning of subjects are crucial. Efforts should be made to keep the patients as comfortable as possible to limit pain-induced artifacts.

Drugs can have substantial effects on the results of ANS testing and are a common cause of abnormal results. Patients need to refrain from caffeine, nicotine, and alcohol *at least* 3 hours prior to testing. All medications with adrenergic and anticholinergic properties need to be discontinued at least 48 hours prior to the study (see Table 1). Among the drugs commonly used for treatment of pain, tricyclic antidepressants have the highest anticholinergic properties and can also impact adrenergic transmission. Selective serotonin reuptake inhibitor (SSRI) antidepressants can be continued, but mixed agents like venlafaxine and trazodone should be stopped. Medications used to control nausea (such as chlorpromazine) have weak anticholinergic effects and may have antiadrenergic effect. Some sedatives with antihistaminic properties (diphenydramine) may act as weak anticholinergics and should be stopped if possible. Agents altering adrenergic transmission are used in pain control regimens. Besides the obvious effect of beta-blockers and peripherally acting alpha-blockers, centrally acting agents such as clonidine may significantly alter the studies. Barbiturates, used in central pain syndromes, have beta-adrenergic antagonist properties that are often forgotten, but only in specific circumstances (such as in disorders of reduced orthostatic tolerance) are these clinically relevant. Calcium channel blockers can alter cardiac studies as well as studies of vaso-motor function. NSAIDs and steroids alter vessel wall reactivity and should be stopped if the reason for the study is orthostatic intolerance. Some muscle relaxants, such as cyclobenzaprine and orphenadrine, have mild nicotinic anticholinergic properties. Muscle relaxants usually have limited effects on autonomic testing, but ideally patients should refrain from taking them 48 hours prior to testing. Topical capsaicin, by inducing substance P release, causes neurogenic inflammation altering vasomotor tone, and to a lesser extent, sudomotor tone. Capsaicin should therefore be discontinued prior to testing.

Table 1. Medications and autonomic testing results

Medications that significantly affect autonomic testing results

Chlorpromazine, thioridazine	Anticholinergic, antiadrenergic
Tricyclic antidepressants	Anticholinergic, (amitriptyline > nortriptyline, imipramine > desipramine, doxepin)
Bupropion, mirtazepine, venlafaxine	NE reuptake inhibitors
Clonidine	Alpha-blocking agent
Alpha-blockers, beta-blockers, Ca'-channel blockers	Alter vasomotor tone and responses
Opiates	Intoxication: smooth muscle relaxation, histamine release. Withdrawal: hyperadrenergic state.
Topical capsaicin	Altered skin vasomotor responses

Pain medications that do not alter autonomic testing results

NSAIDs

Lithium

Mexiletine

Isomedieptene/dichloralphenazone/acetaminophen

SSRI antidepressants (fluoxetine, sertraline, fluvoxamine, citalopram); paroxetine has mild anticholinergic properties.

Carbamazepine, diphenylhydantoin, gabapentin

Benzodiazepines

Tramadol

Muscle relaxants have generally mild anticholinergic properties; usually they do not affect significantly the studies

Opioids are vasodilators and by histamine release can induce sweating. Opioids can be continued in patients who chronically use stable doses of long-acting agents. Short-acting preparations should be stopped, but withdrawal phenomena also affect autonomic testing. Medications that can be continued include anticonvulsants such as carbamazepine, valproic acid, and gabapentin, and membrane stabilizers such as mexiletine and lithium.

Specific Tests (Table 2)

Table 2. Tests to assess autonomic function

Test Panel	Function Assessed
Autonomic Reflex Screen (ARS)	
Tilt table test Deep breathing Valsalva maneuver QSART	Adrenergic vasomotor function Cardiovagal Cardiovagal and adrenergic vasomotor Postganglionic cholinergic sudomotor

CRPS Screen	
Temperature measurements RSO* QSART* TST	Index of sympathetic vasomotor tone Sudomotor and partially vasomotor Postganglionic sudomotor (stimulated) Thermoregulatory sudomotor pathways
*Performed simultaneously in bilateral, symmetrical sites.	

Quantitative Sudomotor Axon Reflex Test (QSART)

A variety of methods have been described to visualize sweat droplets, map sweat glands, and estimate sweat production by the resulting modification in skin potentials. Most of these techniques have become obsolete with the development of the QSART. QSART assesses the integrity both of the axon reflex arch and of sweat glands in the dermis. Postganglionic sympathetic sudo-motor fibers are activated by iontophoresis of Ach into the skin. The impulse travels antidromically to the first branching point and then travels orthodromically back to the skin to activate the corresponding sweat glands.

The equipment needed to perform this test consists of a 3-compartment capsule, a constant flow of N_2 to evaporate the sweat, a heat exchanger to detect the thermic change due to moisture of the returning N_2 flow, and a source of continuous current for the iontophoresis.

Ach is iontophorized into one compartment and sweat output is measured from a different compartment. A solution of 10% Ach is injected into the first compartment and a constant current of 2 mA is applied for 5 minutes. Sweat output is measured for 5 more minutes after stimulus discontinuation. After a stable baseline is obtained, 4 sites are tested simultaneously: medial distal forearm, proximal lateral leg, medial distal leg, and dorsum of the foot.

Abnormalities that can be found include: (1) reduced/absent output, frequently seen in small fiber neuropathies; and (2) persistent sweat activity: a sustained output after stimulus discontinuation indicates sweat gland overactivity. An excessive resting sweat output has similar meaning. A shortened latency of sweat production (<30 minutes) may be due to an exaggerated somatosympa-thetic reflex due to reduced threshold for fiber activation. When these abnormalities are seen in a painful neuropathy, the test is evidence of excessive sympathetic fiber activity.

Sympathetic skin response, widely used in the past, is still utilized where QSART is not available. By measuring change in skin resistance following a random electric stimulation, it provides an index of sweat production. However, this is non-thermoregulatory sweat that occurs on the palms and soles, is of different pharmacological and physiologic properties, and involves somatic afferents. Its sensitivity and specificity are inferior to QSART.

Resting Sweat Output (RSO)

No stimulus is applied for this test. Simultaneous recording is performed bilaterally in standard sites (upper extremity: the medial distal forearm and hypothenar eminence; lower limb: medial distal leg above the malleolus and dorsum of the foot). Sweat production is measured as in QSART, but larger capsules are used. RSO is recorded for 5 minutes, by which time a steady state is usually attained. Measurement is made of the last minute of sweat production.

Thermoregulatory Sweat Test (TST)

The thermoregulatory sweat test assesses the entire thermo-regulatory sudomotor pathway. It is a very useful complement to the QSART for differentiating pre- vs. postganglionic disorders. Neurologic disorders, drugs, and skin conditions are responsible for most abnormal results. This test is based on the proportional sweat production to a rise in core temperature. The temperature rise is sensed in the hypothalamus, activating the sympathetic sudomotor pathways. After appropriate acclimatization, the subject is disrobed and dusted with alizarin red powder. When moist, the powder changes color from orange to purple. A thermal probe is placed in the subject's mouth (to monitor core temperature) and another one on the skin (to monitor for excessive surface heating that could cause injuries as well as induce non-thermoregulatory sweat production mediated by pain). The subject enters a closed compartment heated by infrared heating units that control humidity and ambient temperature (respectively, 35–40% and 45–50°C). To generate the maximum sweat response, subjects are heated to a core temperature 1 degree above baseline or 38°C (whichever is greater). If profuse sweating occurs at a lower temperature, the test is stopped. Subjects are then photographed and by computer scanning the areas of anhidrosis/hypohidrosis are mapped and expressed as percentage of body surface.

Abnormal TST results can be classified as follows:

Hypo/anhidrosis can occur in different patterns:

• *Distal* (involving toes, legs below the knee, fingers, and in more advanced cases also the anterior lower abdomen and forehead): typically seen in peripheral neuropathies.

• *Focal*: follows dermatomal or peripheral nerve distribution. Also can be seen in isolated skin lesions.

• *Segmental*: usually larger areas than focal ones, following sympathetic distribution (such a pattern can be seen after sympathectomies).

• *Regional*: widespread anhidrosis but <80% body surface bordering with hypohidrosis that gradually evolves into normal areas.

• *Global*: diffuse, >80% anhidrosis (usually an advanced stage of the prior pattern) such as can be seen in multiple system atrophy (MSA) and progressive autonomic failure (PAF).

• *Mixed:* pattern not classifiable into any of the above.

Hyperhidrosis can occur as well; this can be classified as:

• *Essential* (idiopathic).

• *Compensatory* (perilesional), associated with autonomic hyperreflexia.

Vasomotor Function

Tests to assess cardiovagal, cardiosympathetic, and adrenergic vasomotor functions are based on reflex arches originating from stretch receptors located in the lungs (Bainbridge reflex) and low and high pressure receptors located in the atria and large vessels (aorta, carotid arteries). The afferent branches synapse in the ventrolateral medulla. The efferent branch of the reflex affects heart rate and blood pressure and can be monitored beat-to-beat noninvasively by photoplethysmographic technique utilizing a finger probe. An autonomic screen includes 3 studies (deep breathing, Valsalva maneuver, tilt test), the analysis of which allows for an adequate assessment of these functions.

Blood flow has been measured with techniques such as Doppler probes. These are very sensitive, but prone to artifact. Huge oscillations can be seen with even slight environmental stimuli. An extremely controlled setting, experienced technician, and cooperative subject are needed, making the technique impractical.

Indirect assessments of vasomotor function by temperature measurement are much more popular. Infrared thermometry and telethermography are widely used. Side-to-side comparison and pattern of asymmetry are used in study analysis. Sensitivity and specificity are not satisfactory, and in isolation these tests have limited clinical use.

The most common pain indication for studies of vasomotor function is complex regional pain syndrome type I (CRPS I), or reflex sympathetic dystrophy (RSD). Unfortunately, symptoms and signs evolve over time and can have diurnal fluctuations. Attempts have been made to stress patients to elicit asymmetries (such as ice water immersion). These maneuvers are time consuming and painful to the patients; somatosympathetic responses may be elicited that make interpretation problematic. Since diagnosis relies on detection of asymmetries, a bilateral syndrome is extremely difficult to diagnose, unless florid signs are present.

Applications in Pain Evaluation

Autonomic testing is safe and reliable. Two types of ANS screens are offered at the Mayo Clinic. In the screening battery, a tilt table study, deep breathing, and Valsalva maneuver plus the QSART are performed. In CRPS I patients, temperature measurements, RSO, and QSART are performed. TST is often added to complement the screens. Performing

the screening battery in pain syndromes is useful if peripheral neuropathy is suspected or to rule out associated conditions. No specific pattern is associated with chronic pain per se. Highly significant correlations have been found between the clinical and laboratory assessments in CRPS I patients using this battery of tests.

ANS testing is valuable in assessment of CRPS I and sympathetically maintained pain. In a prospective study, Willner and colleagues showed that different patterns of abnormality of the QSART could predict the response to sympathetic block in patients with CRPS I (Low et al. 1996). In patients with burning feet and erythromelalgia, autonomic tests have demonstrated subtle abnormalities suggesting selective involvement of small fibers even when clinical examination and nerve conduction studies are normal. When studying patients with postural tachycardia syndrome, a higher than expected incidence of migraineurs was found: further study revealed subtle adrenergic abnormalities suggesting vasomotor lability in migraineurs. Other pain conditions have been associated with reduced orthostatic tolerance, such as chronic fatigue syndrome. Anecdotal reports of abnormal autonomic testing in fibromyalgia have appeared; these data need confirmation.

Table 3. Indications for autonomic testing in some pain syndromes

Fibromyalgia	May detect other conditions such as small neuropathy or a disorder of reduced orthostatic tolerance.
Chronic fatigue syndrome	May detect a disorder of reduced orthostatic tolerance (such as postural tachycardia syndrome).
Painful neuropathies	Assess degree of impairment of small fibers functions and presence of a length dependent neuropathy.
CRPS	CRPS screen, to detect asymmetry or abnormality of sympathetic functions.

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