Neurocardiogenic Syncope and Related Disorders of Orthostatic Intolerance
Blair P. Grubb
Circulation 2005;111;2997-3006
DOI: 10.1161/CIRCULATIONAHA.104.482018
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Syncope, defined as transient loss of consciousness and postural tone with spontaneous recovery, has both challenged and perplexed physicians since the dawn of recorded time. The earliest written accounts come from Hippocrates, and the word syncope itself is derived from an old Greek term meaning “to cut short” or “interrupt.” Recurrent episodes of syncope may result from a large number of different disorders, all of which cause a transitory reduction in cerebral blood flow sufficient to disturb the normal functions of the brain. Over the last 2 decades, considerable attention has been given to types of syncope that occur due to a centrally mediated (or “reflex”) fall in systemic blood pressure, a condition that has been referred to as vasovagal (and later neurocardiogenic) syncope. However, research into the nature of this disorder revealed that it is but one aspect of a broad and varied group of disturbances in the normal functioning of the autonomic nervous system (ANS), each of which may result in orthostatic intolerance, hypotension, and ultimately syncope. Continued investigations into the nature of these similar yet different disorders has led to the development of a system of classification that attempts to more accurately reflect our understanding of these conditions and their interrelationships.1

The present system of classification has proven both functional and clinically relevant and includes a group of disorders that most investigators have thought to be principally autonomic in nature. Because both the cardiologist and the cardiac electrophysiologist frequently are expected to both diagnose and treat these conditions, the following review is designed to provide a basic framework for understanding their causes, clinical presentations, diagnosis, and management.

Autonomic Nervous System

To survive in the world, all animals must possess the ability to make moment by moment alterations that permit their internal environment to remain stable despite dramatic changes in their external environment. This includes not only changes in ambient temperature, humidity, and barometric pressure but also the ability to react quickly to the presence of perceived danger. The principal neural mechanisms by which this “homeostasis” is maintained and regulated are governed by the hypothalamus via its 2 effector systems, which include the ANS and the endocrine system.2

Although the adoption of upright posture represents one of the defining moments in human development, it nonetheless provided a unique challenge to a blood pressure control system that had principally evolved to meet the needs of animals who spent the majority of their time in a dorsal position.1–4 The ANS provides the principal means for both the short- and long-term responses to changes in position (the renin-angiotensin-aldosterone system also plays a role but over a longer time frame).5 In the normal person, approximately 25% to 30% of blood volume is located in the thorax when they are supine. On standing, there is a gravity-mediated downward displacement of roughly 300 to 800 mL of blood to the vasculature of the abdomen and lower extremities.6 This represents a volume drop of between 25% and 30%, half of which occurs within the first few minutes of standing. This sudden redistribution of blood results in a fall in venous return to the heart. Because the heart can only pump the blood that it receives, this causes a fall in stroke volume of about 40% and a decline in arterial pressure. The reference point around which these changes occur is called the venous hydrostatic indifference point (HIP) and is defined as the site in the vascular system where pressure is independent of posture (the venous HIP is around the diaphragm, the arterial HIP is near the level of the left ventricle).6 Compared with the arterial HIP, the venous HIP is dynamic in nature and is influenced by factors such as the degree of vascular compliance, intravascular volume, and muscular activity. While standing, contractions of the leg muscles (in conjunction with the venous valve system) actively pump blood back to the heart and move the venous HIP closer to the level of the right atrium.

In addition, standing produces a substantial increase in the transmural capillary pressure present in the dependent areas of the body, which causes a rise in fluid filtration into tissue spaces. This process reaches a steady state after approximately 30 minutes.
of upright posture and can produce a decline in plasma volume of up to 10%.

Successful maintenance of upright posture (and cerebral perfusion) requires the interplay of several cardiovascular regulatory systems. Orthostatic stabilization occurs within 1 minute. The exact response to postural change differs with standing (an active process) compared with responses seen during head-up tilt (a more passive process). Wieling and van Lieshout have described 3 phases of orthostatic response. These consist of (1) the initial response (during the first 30 seconds), (2) the early steady state alteration (at 1 to 2 minutes), and finally (3) the prolonged orthostatic period (after at least 5 minutes upright).

Immediately after head-up tilt, cardiac stroke volume remains normal despite the decline in venous return (believed to occur due to blood left in the pulmonary circulation). This is followed by a gradual fall in both arterial pressure and cardiac filling. This causes activation of 2 different groups of pressure receptors consisting of the high-pressure receptors of the carotid sinus and aortic arch and the low-pressure receptors of the heart and lungs. Within the heart, there are mechanoreceptors linked by unmyelinated vagal afferents in all 4 cardiac chambers. These mechanoreceptors produce a tonic inhibitory effect on the cardiovascular control centers of the medulla, in particular on the nucleus tractus solitarii. The baroreceptive neurons of the nucleus tractus solitarii directly activate cardiovagal neurons of the nucleus ambiguus and dorsal vagal nucleus while inhibiting the sympathoexcitatory neurons of the rostral ventrolateral medulla.

The reduced venous return and fall in filling pressure that occur during upright posture reduce the stretch on these receptors. As their firing rates decrease, there is a change in medullary input, which triggers an increase in sympathetic outflow. This causes a constriction not only of the systemic resistance vessels but of the splanchnic capacitance vessels as well. In addition, there is a focal axon reflex (the venoarteriolar axon reflex) that constricts flow to the skin, muscle, and adipose tissue. This may contribute up to 50% of the increase in limb vascular resistance seen during upright posture.

During head-up tilt, there is also activation of the high-pressure receptors in the carotid sinus. The carotid sinus contains a group of baroreceptors and nerve endings located in the enlarged area of the internal carotid artery, just after its origin from the common carotid artery. Here, the mechanoreceptors are located in the adventitia of the arterial wall. The afferent impulses generated by stretch on the arterial wall are then transmitted via the sensory fibers of the carotid sinus nerve that travels with the glossopharyngeal nerve. These afferent pathways terminate in the nucleus tractus solitarii in the medulla, near the dorsal and ambiguous nuclei. The initial increase in heart rate seen during tilt is thought to be modulated by a decline in carotid artery pressure. The slow rise in diastolic pressure seen during upright tilt is believed to be more closely related to a progressive increase in peripheral vascular resistance.

The circulatory changes seen during standing are somewhat different from those seen during tilt. Standing is a much more active process that is accompanied by contractions of muscles of both the leg and abdomen, which produces a compression of both capacitance and resistance vessels and results in an elevation in peripheral vascular resistance. This increase is sufficient to cause a transient increase in both right atrial pressure and cardiac output, which in turn causes an activation of the low-pressure receptors of the heart. This provokes an increase in neural traffic to the brain, with a subsequent decrease in peripheral vascular resistance, which can fall as much as 40%. This can allow a fall in mean arterial pressure of up to 20 mm Hg that can last for up to 6 to 8 seconds. The decline in pressure is then compensated for by the same mechanisms as during head-up tilt.

The early steady state adjustments to upright posture consist of an increase in heart rate of about 10 to 15 bpm, an increase of approximately 10 mm Hg, and little or no change in systolic blood pressure. The carotid sinus and aortic arch and the low-pressure receptors of the heart. This is followed by a gradual fall in both arterial pressure and cardiac filling. This causes activation of 2 different groups of pressure receptors consisting of the high-pressure receptors of the carotid sinus and aortic arch and the low-pressure receptors of the heart and lungs. Within the heart, there are mechanoreceptors linked by unmyelinated vagal afferents in all 4 cardiac chambers. These mechanoreceptors produce a tonic inhibitory effect on the cardiovascular control centers of the medulla, in particular on the nucleus tractus solitarii. The baroreceptive neurons of the nucleus tractus solitarii directly activate cardiovagal neurons of the nucleus ambiguus and dorsal vagal nucleus while inhibiting the sympathoexcitatory neurons of the rostral ventrolateral medulla.

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Conditions That Occur as a Result of Disturbances in Orthostatic Control

A growing number of autonomic disturbances of orthostatic regulation have been identified. Although in many ways similar, each has features that make it unique. In attempting to classify them into a useful system, one should remember that when we look at nature, in many ways we see what we wish to see that fits what we know about it at that moment. Conditions such as supraventricular tachycardia and long-QT syndrome were each first thought to be a single entity but with time were found to be composed of a variety of subgroups. To attempt to make sense of the apparent chaos of nature, we try to organize and classify it into a coherent framework and system that fits with both our knowledge and our expectations. Thus, any system of classification is in many ways arbitrary, subject to debate, and in a constant process of revision and refinement. The system presented in the Figure follows that developed by the American Autonomic Society and attempts to represent our current understanding of these disorders in a clinically useful framework. In some ways, all autonomic disturbances can be thought of...
as being either primary or secondary in origin. The primary forms tend to be idiopathic, unassociated with other diseases, and are either acute or chronic in nature. Conversely, the secondary forms are seen in conjunction with another disease process (such as diabetes and amyloidosis) or alternatively occur owing to a known biochemical or structural deficiency or after exposure to known toxic agents (such as alcohol and heavy metals). A brief description of each subtype follows, along with references for the reader who desires a more in-depth discussion.

**Reflex Syncope**

The reflex syncopes are a group of disorders that occur because of a sudden failure of the ANS to maintain adequate vascular tone during orthostatic stress, resulting in hypotension (frequently associated with bradycardia) that results in cerebral hypoperfusion and loss of consciousness. The 2 most frequent types of reflex syncope are neurocardiogenic (vasovagal) syncope and carotid sinus syndrome. The other types of reflex syncopes are often referred to as situational because they are often associated with specific activities or conditions. Neurocardiogenic syncope (NCS) can be quite varied in presentation.\(^{11}\) It tends to occur in younger patients and tends to exhibit 3 distinct phases that consist of a distinct prodrome (usually lightheadedness, nausea, diaphoresis, or visual changes) followed by a sudden loss of consciousness. Recovery is usually quite rapid, and postictal states are rare. However, nearly one third of patients (most commonly older adults) will experience few, if any, prodromal symptoms, and loss of consciousness occurs suddenly, with little warning. The cause of neurocardiogenic syncope is unclear. It can be brought on by pain, emotional distress, or by prolonged standing (especially in very warm environments), yet many episodes occur without any specific provocation. Although still the subject of considerable debate, it is presently believed that the pathophysiology of NCS often is related to prolonged orthostatic stress.\(^{12}\) This results in an increased amount of peripheral venous pooling to a point great enough that the venous return to the heart falls so precipitously that a significant increase in ventricular inotropy occurs. This hypercontractile state is believed to activate mechanoreceptors that would normally fire only during stretch.\(^{13}\) The sudden increase in neural traffic to the medulla is thought to mimic the conditions seen in hypertension, thus causing an apparent "paradoxical" decline in sympathetic activity that results in hypotension, bradycardia, and ultimately syncope.\(^{14}\) It should be remembered, however, that other stimuli (for example fear, strong emotion, or epileptic discharges) can elicit nearly identical responses, which raises the possibility that these patients may have an inherent susceptibility to these events.
During head-upright tilt-table testing, these individuals will demonstrate a relatively sudden fall in blood pressure that is often (but not always) followed by a decline in heart rate (sometimes to the point of asystole).

Sutton and Peterson\textsuperscript{15} have noted that there is a striking similarity between the hemodynamic collapse profile seen during NCS and carotid sinus syndrome, which suggests that they may be different aspects of the same underlying condition. Indeed, it has been postulated that all the reflex syncones occur in susceptible individuals when sudden activation of mechanoreceptors from any site (rectum, esophagus, bladder, or cough) produces a similar response. Recent studies on defecation syncope have supported this concept. What distinguishes the reflex syncones from the other conditions discussed herein is that between episodes of syncope, these patients complain of few (if any) autonomic symptoms. Thus, in this group, the autonomic system appears to function in a relatively normal manner, despite being somewhat “hypersensitive,” as opposed to other conditions in which the autonomic system appears to “fail,” functioning at a level inadequate for the body’s needs, which results in varying degrees of orthostatic intolerance.\textsuperscript{11}

**Primary Autonomic Failure: Chronic Forms**

The first of the autonomic failure syndromes described was by Bradbury and Eggleston in 1925.\textsuperscript{16} They used the phrase “idiopathic orthostatic hypotension” to describe the condition because of its apparent lack of other features; however, this term does not adequately describe the generalized state of autonomic failure that occurs in these patients, characterized by disturbed bowel, bladder, sudomotor, thermoregulatory, and sexual function (without somatic involvement). At present, the condition is referred to as pure autonomic failure (PAF).\textsuperscript{17} PAF usually begins between ages 50 and 70 years, and it displays a 2:1 male-to-female ratio.\textsuperscript{18} Symptoms are slow and insidious in onset, usually beginning with vague complaints of orthostatic weakness, dizziness, and lightheadedness that are often dismissed by physicians as insignificant.\textsuperscript{19} As their orthostatic hypotension worsens, patients experience near syncope or syncope, which often prompts the patient to seek initial medical attention. In men, the earliest symptoms are impotence and loss of libido, whereas in women, urinary retention and incontinence occur first. This condition is characterized by orthostatic hypotension, syncope or near syncope, constipation, urinary retention, inability to sweat, and impotence.\textsuperscript{20} Although PAF may lead to severe functional impairment, only rarely is it fatal.

A second, much more severe form of autonomic failure (associated with somatic defects) was subsequently described by Shy and Drager in 1960.\textsuperscript{21} As opposed to the situation in PAF, these patients not only have severe orthostatic hypotension but also have iris atrophy, urinary and rectal incontinence, loss of sweating, external ocular palsy, rigidity, tremor, and impotence. The condition is now referred to as multiple system atrophy (MSA) and usually begins in the fifth to sixth decade of life (although the disorder may occasionally begin in the late 30s or early 40s), with men affected twice as often as women.\textsuperscript{18} As in PAF, syncope and near syncope are the symptoms that most frequently prompt the patient to seek medical attention. Although MSA patients may start with symptoms that suggest PAF, they later begin to develop symptoms of somatic nervous system involvement, in addition to central nervous system involvement.\textsuperscript{22} Indeed, MSA is divided into 3 different subtypes depending on the somatic system involved.\textsuperscript{18,19} The first group displays a motor tremor similar to that seen in Parkinson’s disease (some authors refer to this group as having striatogniral degeneration on the basis of autopsy findings).\textsuperscript{23}

In contrast to true Parkinson’s disease, there tends to be more rigidity than tremor, yet the rigidity lacks the typical “cogwheel” or “lead pipe” rigidity seen in Parkinson’s disease.\textsuperscript{24,25} Patients with parkinsonian-type MSA frequently display a loss of facial expression and limb akinesia. The second subtype of MSA is characterized by prominent cerebellar and/or pyramidal features (also called olivopontocerebellar atrophy/degenerative form on the basis of autopsy findings).\textsuperscript{26} These patients have a significant gait disturbance and truncal ataxia that may impede the person from standing without support. Slurring of speech and loss of diction are common, as is a mild intention tremor of the extremities. The third group of MSA patients displays a combination of parkinsonian and cerebellar features and are referred to as having “mixed” MSA.\textsuperscript{22} A recent autopsy study reported that between 7% and 22% of patients diagnosed with Parkinson’s disease during life were found to have neuropathologic changes diagnostic for MSA after death.\textsuperscript{24} The natural history of MSA is one of relentless progression after onset, with most patients dying within 5 to 8 years after onset (although rarely, individuals have survived up to 20 years). Apnea, aspiration, and respiratory failure are the most frequent causes of death.\textsuperscript{19}

Over the last decade, considerable attention has been given to a relatively new subgroup of disorders currently referred to as the postural tachycardia syndrome (POTS). This appears to be a milder, less severe form of autonomic insufficiency that is characterized by excessive increases in heart rate while in the upright position.\textsuperscript{27} There are 2 primary forms of the disorder that have been identified. The more common variety is referred to as the peripheral (or partial) dysautonomic form.\textsuperscript{28} The hallmark of this group is a persistent tachycardia while upright, which can achieve rates of 160 bpm or higher, that typically is associated with complaints of severe fatigue, exercise intolerance, palpitations, near syncope, lightheadedness, and dizziness. Many patients also complain of cognitive impairment and visual disturbances and of intolerance to the heat while at the same time always feeling cold. During tilt-table testing, they will display a significant increase in heart rate of > 30 bpm in the first 10 minutes or will achieve a maximum heart rate of > 120 bpm over the same time frame, often associated with only a modest decline in blood pressure.\textsuperscript{29} The pathophysiology appears to be a failure of peripheral vascular resistance to increase adequately in the face of orthostatic stress. This results in excessive blood pooling in the dependent areas of the body, which is then compensated for by an increase in heart rate and inotropy. Investigators have reported that in some patients, POTS may be the earliest sign of autonomic dysfunction and that occasional patients (≤ 10%) may later progress to PAF. Onset
may occur after a viral infection, trauma, or surgery or may be associated with the joint hypermobility syndrome.30

The second type of POTS is referred to as the “β-hypersensitivity” or “central” form. In this form, there is believed to be an inadequate feedback process that arises from above the level of the baroreflex.30 Although the initial heart rate responses to upright posture are adequate, the brain does not know when to stop the response, and heart rate continues to elevate. Some patients who have this form of POTS will demonstrate orthostatic hypertension and postural tachycardia. Although the clinical presentations of both groups are similar, the hyperadrenergic form is often associated with migraines, excess sweating, and tremor. Serum catecholamine levels are usually quite high (serum norepinephrine is often >600 ng/dL), and patients exhibit an excessive response to isoproterenol infusion (>30 bpm increase in response to 1 μg/min).27

Recent investigations have suggested a genetic basis for this group of disorders. A landmark study by Shannon et al31 has identified the exact genes responsible for this subgroup in 1 family with a number of severely affected members. The defect was in the genetic code for a protein responsible for recycling norepinephrine in the intrasynaptic cleft, which allowed for excessively high levels of serum norepinephrine. There may be multiple genetic forms of this disorder, and studies are under way to determine this.

Acute Autonomic Dysfunction

Although uncommon, the acute autonomic neuropathies are dramatic in presentation.32 Onset is quite sudden and is heralded by severe diffuse failure of both the parasympathetic and sympathetic systems, whereas the somatic system remains unaffected.33 Orthostatic hypotension is often so severe that sitting up in bed results in syncope. Complete loss of sweating and severe bowel and bladder dysfunction are common, causing nausea, abdominal pain, bloating, and vomiting.34 Heart rates drop to 45 to 55 bpm, with complete chronotropic incompetence. Recent studies completed by Verino et al35 have demonstrated that many of these patients have high levels of antibodies to acetylcholine receptors in the autonomic ganglia, which suggests that the disorder is autoimmune in nature.

Secondary Causes of Autonomic Dysfunction

There are a number of different disorders that may disturb normal autonomic function, and the interested reader is directed elsewhere.9 It is important to keep in mind that any autonomic disturbance may be part of a larger disease process (for example, malignancy). A number of different drugs may either cause or contribute to orthostatic hypotension (Table 1). Systemic illness that affects multiple organs (eg, cancer, diabetes mellitus, amyloidosis, and renal failure) may disturb autonomic function to a degree that orthostatic hypotension and syncope occur. Recent studies have demonstrated a link between orthostatic hypotension and Alzheimer’s disease.36 Orthostatic hypotension may also occur owing to single enzyme abnormalities. Examples include isolated dopamine B-hydroxylase deficiency and nerve growth factor deficiency.37

**TABLE 1. Pharmacological Agents That May Cause or Worsen Orthostatic Intolerance**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example Drugs</th>
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</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Enalapril</td>
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<tr>
<td>α-Receptor blockers</td>
<td>Amlodipine</td>
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<tr>
<td>Calcium channel blockers</td>
<td>Propranolol</td>
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<tr>
<td>β-Blockers</td>
<td>Sodium nitroprusside</td>
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<tr>
<td>Phenothiazines</td>
<td>Hydroxyzine</td>
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<tr>
<td>Tricyclic antidepressants</td>
<td>Nortriptyline</td>
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<tr>
<td>Bromocriptine</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Opiates</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Bupropion</td>
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<tr>
<td>Hydralazine</td>
<td>Citalopram</td>
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<tr>
<td>Ganglionic blocking agents</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Sildenafil citrate</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Methylphenidate</td>
</tr>
</tbody>
</table>

Clinical Features

The main feature that is shared by each of these disorders is a disruption in cardiovascular regulation to such an extent that postural hypotension and/or tachycardia or bradycardia occurs. Historically, orthostatic hypotension has been described as a >20 mm Hg fall in systolic blood pressure or a >10 mm Hg fall in diastolic blood pressure over a 2-minute period after standing. Yet a less dramatic decline in blood pressure associated with symptoms may be equally important. Often, patients will display a gradual progressive decline in blood pressure over a more prolonged period of time (∼10 to 15 minutes) that will also result in symptoms. Whether symptoms occur will depend on the rate at which blood pressure falls and the total degree of change. The reflex syncopes tend to exhibit abrupt falls in blood pressure that are often associated with a definitive prodrome. In contrast, the loss of consciousness in the orthostatic (or “dysautonomic”) syncopes tends to be slow and gradual.37 This more gradual fall in blood pressure is often not perceived by a number of older patients, who often will report these episodes as “drop attacks” that occur with little warning. Those who do perceive the fall in blood pressure will relate feeling lightheaded, having blurred or tunnel vision, or having visual disturbances. One distinguishing factor between reflex and dysautonomic syncope is that the latter usually is not associated with diaphoresis and bradycardia.19 Dysautonomic syncopes tend to be more common in the morning after arising from sleep and are worsened by any condition that enhances peripheral venous pooling (eg, heat, alcohol, or fatigue). Patients with PAF and MSA may develop severe chronotropic incompetence with a relatively fixed heart rate (50 to 70 bpm).20 Some patients with significant autonomic dysfunction (particularly diabetes) may display a combination of upright hypotension and supine hypertension, which is believed to be due to an inability to adequately vasconstrict when upright or vasodilate when prone.19 At times, it is difficult to fully distinguish between the various disorders, because a considerable degree
of overlap may occur (not dissimilar to the situation seen in chronic obstructive pulmonary disease).

**Diagnosis**

The most important aspect of evaluation is a comprehensive history and physical examination. When did symptoms first appear? Is the main problem syncope, lightheadedness, or fatigue? When do symptoms tend to occur, and what factors make them worse or better? Are there other organ systems that appear to be involved? A detailed, careful history and physical examination will have a much greater yield than the indiscriminate ordering of multiple laboratory examinations. Indeed, testing should proceed in a prudent and directed fashion to evaluate the diagnosis suggested by the history and physical examination.

It is beyond the scope of this review to provide a detailed discussion of every autonomic disorder and the various laboratory tests used in their evaluation. The interested reader is referred to several excellent texts on the subject.1,2 Special attention should be given to identify any prescription or over-the-counter medications that could cause or exacerbate hypotension, as well as to recognize the possibility of illicit drug or alcohol abuse.

Because the autonomic centers of the brain are not readily accessible to direct measurement, autonomic function principally is evaluated by observing the responses of different functions or organ systems to a variety of pharmacological or physiological challenges.3,4 The simplest and most important of these is the recording of heart rate and blood pressure in the supine, sitting, and immediate upright positions, as well as at 3 and 5 minutes after being upright. Blood pressure measurements should be made with the arm extended horizontally (to minimize any hydrostatic effect produced by having the arm in a dependent position).5 Because the responses noted during standing differ from those seen during passive tilt, we often perform tilt-table testing on these patients. There is an extensive body of literature on tilt-table testing that is reviewed in detail elsewhere.6 There are other tests of autonomic function available that provide useful information in selected patients, the details of which are available elsewhere.1,3

Briefly, however, some aspects of tilt-table testing will be outlined. Tilt-table testing is based on the concept that an orthostatic stress, such as prolonged upright posture, could be used to cause venous pooling and thereby provoke the previously discussed responses in predisposed individuals.6 In contrast to standing, the patient is strapped to a table that is able to incline at an angle of 60° to 70° that serves to inhibit the skeletal muscle pump and thus force the autonomic system to function on its own. Deprived of a component of the compensatory mechanism that the person has come to depend on, abnormal hemodynamic and rate changes are more likely to be observed. At present, head-up tilt-table testing is the only diagnostic test for neurocardiogenic syncope to have been studied in detail. The specificity of tilt-table testing (without pharmacological challenge) is near 90% but is less with pharmacological provocation. The false-positive rate is 10%. Short-term (days to weeks) reproducibility of results is approximately 80% to 90%, whereas long-term reproducibility (>1 year) is ≈60%.7 Because there is no true “gold standard” against which to compare it, the exact sensitivity of tilt-table testing is unknown.8 The stress induced during tilt-table testing is different from that which the patient experiences clinically. The recent International Study of Syncope of Uncertain Etiology (ISSUE) that compared tilt-induced syncopal episodes with spontaneously recorded episodes (with an implantable loop recorder) showed that spontaneous events were more likely to be associated with significant bradycardia.9

Guidelines for tilt-table testing have been issued by the American College of Cardiology and the European Society of Cardiology.41,42 A list of indications for tilt-table testing is provided in Table 2. Although useful for diagnosis of NCS, tilt-table testing has not proved useful in determining the efficacy of therapy.41

Abnormal responses to tilt-table testing can be grouped into 5 basic types. The first of these is the classic neurocardiogenic (or vasovagal) response, which is characterized by a rapid drop in blood pressure (with or without associated bradycardia). The second pattern, which we have termed “dysautonomic,” demonstrates a gradual fall in blood pressure (with little change in heart rate) that ultimately results in loss of consciousness (usually seen in the autonomic failure syndromes). The third pattern, a postural tachycardia response, consists of a >30 bpm increase in heart rate (or a heart rate >120 bpm during the first 10 minutes of the baseline tilt). The fourth pattern we have called “cerebral syncope.”44 These individuals will experience syncope in the absence of systemic hypotension, associated with intense cerebral vasoconstriction (as measured by transcranial Doppler) and cerebral hypoxia (as measured by electroencephalogram). The last response is referred to as “psychogenic”; in this pattern, syncope occurs during tilt in the absence of hypotension or of any identifiable change in transcranial Doppler or electroencephalogram.44 These patients have been found to have psychiatric disorders ranging from conversion reactions to anxiety disorders and major depression.45

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**TABLE 2. Indications for Head-Up Tilt-Table Testing**

<table>
<thead>
<tr>
<th>Indications for head-up tilt-table testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unexplained recurrent syncope or single syncopal episode associated with injury (or significant risk of injury) in absence of organic heart disease</td>
</tr>
<tr>
<td>2. Unexplained recurrent syncopeps or single syncopal episode associated with injury (or significant risk of injury) in setting of organic heart disease after exclusion of potential cardiac causes of syncope</td>
</tr>
<tr>
<td>3. After identification of a cause of recurrent syncope in situations in which determination of an increased predisposition to NCS could alter treatment</td>
</tr>
</tbody>
</table>

Conditions in which tilt table testing may be useful:

1. Differentiating convulsive syncope from epilepsy
2. Evaluation of recurrent near syncope or dizziness
3. Evaluation of syncope in autonomic failure syndromes
4. Exercise of postexercise-induced syncope in absence of organic heart disease in whom exercise stress testing cannot reproduce an episode
5. Evaluation of recurrent unexplained falls

Adapted with permission from Sutton and Benditt.38
Any predisposing factors such as extreme heat and dehydration. Patients are encouraged to increase their fluid (and in some cases salt) intake and should be instructed to avoid any predisposing factors such as extreme heat and dehydration. Patients are encouraged to increase their fluid (and in some cases salt) intake and should be instructed to recognize potential warning signs of impending syncope and to take evasive actions (such as lying down).

Nonpharmacological treatments should be encouraged. Moderate aerobic and isometric exercise enhances peripheral muscle strength, thereby facilitating the ability of the skeletal muscle pump to augment venous return to the heart. Tilt training appears to be helpful in neurocardiogenic syncope; however, long-term compliance is poor. Sleeping with the head of the bed upright (≥6 inches) is useful in autonomic failure syndromes, as are elastic support hose that are at least waist high and provide a minimum of 30 mm Hg of ankle counterpressure. Isometric countermeasures, such as leg and arm muscle tensing, are useful in preventing neurocardiogenic syncope if used at the earliest sign of symptoms. Biofeedback therapy has also been helpful in preventing neurocardiogenic syncope induced by various psychological stimuli.

Despite all of the above measures, some patients will continue to be symptomatic. In the patient who has recurrent episodes of syncope (or near syncope) associated with injury or a high risk of injury (to themselves or others), prophylactic pharmacotherapy is indicated. In patients with very frequent or severe episodes of syncope (especially in those who have already sustained significant injury due to syncope-related falls), it is sometimes useful to initiate pharmacotherapy early in management to bring the episodes under control while waiting for more conservative measures to take effect. Any drug should be chosen carefully to fit the needs of each patient, not only with respect to the disorder being treated but also in relation to any concomitant conditions they may have.

**TABLE 3. Treatment Options**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Method or Dose</th>
<th>Common Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-up tilt of bed</td>
<td>45° Head-up tilt of bed (often will need footboard)</td>
<td>Hypotension, sliding off bed, leg cramps</td>
</tr>
<tr>
<td>Elastic support hose</td>
<td>Requires at least 30–40 mm Hg ankle counterpressure, works best if waist high</td>
<td>Uncomfortable, hot, difficult to get on</td>
</tr>
<tr>
<td>Diet*</td>
<td>Fluid intake of 2–2.5 L/d Na⁺ intake of 150–250 mEq/d</td>
<td>Supine hypertension; peripheral edema</td>
</tr>
<tr>
<td>Exercise</td>
<td>Aerobic exercise (mild) may aid venous return; water exercise particularly helpful</td>
<td>May lower blood pressure if done too vigorously</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Begin at 0.1–0.2 mg/d may work up to doses not exceeding 1.0 mg/d</td>
<td>Hypokalemia, hypomagnesemia, peripheral edema, weight gain, congestive heart failure</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>5–10 mg PO TID given with meals, give last dose before 6 pm</td>
<td>Agitation, tremor, insomnia, supine hypertension</td>
</tr>
<tr>
<td>Midodrine*</td>
<td>2.5–10 mg every 2–4 hours; may use up to 40 mg/d</td>
<td>Nausea, supine hypertension</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1–0.3 mg PO BID or patches placed 1/wk</td>
<td>Dry mouth, bradycardia, hypotension</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>8 mg PO BID-TID</td>
<td>Diarrhea, anxiety, nervousness</td>
</tr>
<tr>
<td>Ephedrine sulfate</td>
<td>12.5–25 mg PO TID</td>
<td>Tachycardia, tremor, supine hypertension</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10–20 mg PO QD (requires 4–6 weeks of therapy)</td>
<td>Nausea, anorexia, diarrhea, agitation</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 mg XR form PO QD or BID</td>
<td>Nausea, anorexia, hypertension</td>
</tr>
<tr>
<td>Paroxetine*</td>
<td>10 mg PO QD</td>
<td>Nausea, tremor, diarrhea, agitation</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>8000 IU SC once per week</td>
<td>Requires injections, burning at site, increased hematocrit, CVA</td>
</tr>
<tr>
<td>Metoprolol*</td>
<td>25–50 mg PO BID to TID</td>
<td>Hypotension, congestive heart failure, bradycardia (not effective in younger patients)</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>60 mg PO BID</td>
<td>Nausea, diarrhea, abdominal cramping</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>An analog of vasopressin used as a nasal spray or pill at 0.2 mg PO every night</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Octreotide</td>
<td>25 μg SC BID, may titrate to 100–200 μg TID</td>
<td>Nausea, abdominal pain, muscle cramps, hypertension</td>
</tr>
</tbody>
</table>

*BID indicates twice daily; PO, by mouth; TID, three times a day; and QD, every day.*

*Evaluated by randomized, controlled trials.

**Therapeutic Modalities**

A detailed discussion of all therapies used in the various types of autonomic dysfunction associated with orthostatic intolerance is beyond the scope of this review. The following review is brief, and more detailed discussions are available elsewhere.42

The first task of the clinician is to determine to the extent possible the type of autonomic disorder present. In addition, one must establish whether the disorder is primary or secondary in nature and identify any potentially reversible causes. It is equally important to educate the patient and family as to the nature of the disorder and counsel them to avoid any predisposing factors such as extreme heat and dehydration. Patients are encouraged to increase their fluid (and in some cases salt) intake and should be instructed to recognize potential warning signs of impending syncope and to take evasive actions (such as lying down).
or medications they may be taking. Any drug used to treat an autonomic disorder may, on occasion, worsen rather than lessen symptoms (a prosyncopal effect).

β-Blockers were among the first agents used to prevent neurocardiogenic syncope and are presumed to work due to their negative inotropic actions that lessen the degree of cardiac mechanoreceptor activation during periods of reduced venous return; however, randomized trials have yielded mixed results and are difficult to compare because of the wide range of methodologies used and the populations studied. The recently completed Prevention of Syncope Trial (POST) was a randomized, prospective, placebo-controlled trial of metoprolol versus placebo. In patients <42 years of age, metoprolol was no better than placebo; however, in those >42 years of age, the drug produced a significant decline in syncopal events. This would suggest that there may be important age-related differences in response to therapy.

Fludrocortisone is a mineral corticoid that expands fluid volume and increases peripheral α-receptor sensitivity, thus promoting vasoconstriction. Although very useful in treating orthostatic hypotension, its use in neurocardiogenic syncope is less well studied. A variety of vasoconstrictive agents have been used in the treatment of these disorders. The earliest of these were the ephedra alkaloids Dexedrine and methylphenidate, which cause vasoconstriction because of their α-receptor-stimulating actions. The related α-1 receptor stimulant midodrine offers a similar degree of vasoconstriction without causing central nervous system stimulation. It has been approved by the Food and Drug Administration for treatment of orthostatic hypotension and has proved effective for prevention of neurocardiogenic syncope in 2 randomized trials. Yohimbine, ephedrine, and theophylline have also been used; however, poor tolerance often limits their use.

The α-1 receptor agonist clonidine has been demonstrated to produce a paradoxical increase in blood pressure in autonomic failure patients who have profound postganglionic sympathetic disturbances. In this setting, the vascular postjunctional α-2 receptor density (distributed throughout the vascular system) increases significantly, which results in a hypertensive state. Thus, although clonidine causes the sympathetic system to lower its output and thereby reduce blood pressure in normal subjects, in patients with autonomic failure (who have little or no peripheral sympathetic stimulation), the vasoconstrictive effect of the drug becomes predominant. However, the drug must be used with caution, because it may worsen hypotension. Recently, investigators at the Mayo Clinic reported that the acetylcholinesterase inhibitor pyridostigmine was effective in preventing orthostatic hypotension without exacerbating supine hypotension. Further randomized trials of this promising agent are now under way.

There is a body of evidence that has demonstrated that serotonin plays an important role in the central nervous system’s regulation of both heart rate and blood pressure. In the reflex syncopes, there is thought to be a disturbance in both serotonin production and postsynaptic receptor density that leads to a “hypersensitive” state, characterized by excessive responses to fluctuations in sensory input. The serotonin reuptake inhibitors were explored as a potential therapy because of their ability to downregulate postsynaptic receptor density and thereby blunt the effects of serotonin in mediating sympathetic withdrawal. Several observational studies and one double-blind, randomized, placebo-controlled trial have demonstrated that the serotonin reuptake inhibitors can be remarkably effective in preventing neurocardiogenic syncope and orthostatic hypotension.

It had long been noted that many patients with autonomic failure may also be anemic. Hoeldtke and Streeter published a landmark study showing that erythropoietin given via subcutaneous injection could cause significant elevations in blood pressure and increasing blood counts. Subsequent studies have suggested that these effects are independent of each other and that erythropoietin possesses direct vasoconstrictive effects related to its effects on peripheral nitric oxide.

One of the more controversial therapies for neurocardiogenic syncope is permanent cardiac pacing. Some episodes of NCS, both spontaneous and tilt-induced, are associated with profound bradycardia or asystole. The results from early randomized trials suggested that permanent cardiac pacing resulted in a significant reduction in syncopal events. Concerns were raised about these studies because patients had been randomized to pacing or no pacing, with a possible placebo effect from pacing. To address this point, 2 trials, the Second Vasovagal Pacemaker Study (VPS 2) and the Vasovagal Syncope and Pacing Trial (SYNPACE), implanted permanent pacemakers in groups of patients with recurrent NCS, then randomized them to having the units programmed “on” or “off.” The VPS study reported there was not a significant difference between the 2 groups after 6 months of follow-up. Interestingly, although the SYNPACE trial showed that there was no significant difference between the 2 groups overall, those patients with asystolic responses during preimplant tilt-table testing had a significant increase in time to syncope recurrence compared with those who had bradycardia alone. At present, we do not recommend permanent pacing as first-line therapy in NCS because the majority of patients will respond to conservative measures and pharmacotherapy. Nonetheless, in those patients with recurrent syncope with little or no prodrome, in whom other forms of therapy are ineffective, permanent pacing may either reduce syncopal frequency or increase the time from onset of symptoms to loss of consciousness. This can give the patient a sufficiently long prodrome such that there is time to take evasive actions (ie, lying supine).

The physician should keep in mind that in the autonomic failure syndromes (unlike the reflex syncopes), hypotension is only one aspect of a much more diverse group of symptoms that occur as a consequence of autonomic dysfunction. Some symptoms are easier to treat than others, and one should avoid giving the patient unrealistic expectations. Both the patient and physician should remain cognizant of the fact that some of these disorders are chronic in nature and, in some individuals, may worsen over the course of time. Therefore, treatment plans will need to be reassessed periodically to determine whether they still meet the patient’s changing needs. It is also essential to realize that many patients with the severe
forms of autonomic disturbance may have a broad array of personal and social problems that include psychological, marital, occupational, legal, and, frequently, financial problems. Although many physicians feel uncomfortable assisting in these matters, these are the very issues that have the most important influence on patients’ lives. The treating physician should be prepared to assist in helping the patient obtain access to psychologists, social workers, rehabilitation services, and even legal counsel when necessary.72

The attitude of the physician treating the patient with a severe autonomic disorder of any form is of the utmost importance. A positive, yet at the same time realistic, approach by a knowledgeable and sympathetic caregiver can have a significant impact on the patient. Hope is a potent medicine that should be encouraged by all.73

Summary

The ANS is both complex and diverse and is involved in essentially every organ system and in the majority of disease processes. Disruptions in this system can be incredibly diverse in presentation, yet often culminate in a failure to maintain normotension, with resultant near syncope and syncope. A working knowledge of these disorders is required for both their recognition and their management. Further investigations will aid in our understanding of this wide range of disorders and at the same time identify better diagnostic and therapeutic modalities.

References


