

# Pathophysiology, Diagnosis, and Treatment of Orthostatic Hypotension and Vasovagal Syncope

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**Abstract:** Orthostatic hypotension (OH) occurs in 0.5% of individuals and as many as 7–17% of patients in acute care settings. Moreover, OH may be more prevalent in the elderly due to the increased use of vasoactive medications and the concomitant decrease in physiologic function, such as baroreceptor sensitivity. OH may result in the genesis of a presyncopal state or result in syncope. OH is defined as a reduction of systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing. A review of symptoms, and measurement of supine and standing BP with appropriate clinical tests should narrow the differential diagnosis and the cause of OH. The fall in BP seen in OH results from the inability of the autonomic nervous system (ANS) to achieve adequate venous return and appropriate vasoconstriction sufficient to maintain BP. An evaluation of patients with OH should consider hypovolemia, removal of offending medications, primary autonomic disorders, secondary autonomic disorders, and vasovagal syncope, the most common cause of syncope. Although further research is necessary to rectify the disease process responsible for OH, patients suffering from this disorder can effectively be treated with a combination of nonpharmacologic treatment, pharmacologic treatment, and patient education. Agents such as fludrocortisone, midodrine, and selective serotonin reuptake inhibitors have shown promising results. Treatment for recurrent vasovagal syncope includes increased salt and water intake and various drug treatments, most of which are still under investigation.

**Key Words:** orthostatic hypotension, autonomic dysfunction, syncope, vasovagal syncope

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Symptomatic orthostatic hypotension (OH) and vasovagal syncope are common conditions associated with major cardiovascular disability. In this article, the various etiologies

of these conditions are discussed, along with their clinical manifestations. In addition, diagnostic modalities are addressed, and nonpharmacologic and pharmacologic approaches to therapy are reviewed.

## DEFINITION AND PATHOPHYSIOLOGY

OH in humans has been used in a nonspecific way to describe a fall in systolic blood pressure (SBP) after assuming an upright position. However, recently a consensus group of the American Autonomic Society has defined OH as a reduction of SBP of at least 20 mm Hg or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing. OH is a physical sign and not a symptom of disease.<sup>1</sup>

A variety of symptoms can accompany OH, with some of the most significant referable to cerebral hypoperfusion.<sup>2</sup> The hypoperfusion is most likely related to the decreased venous return to the heart caused by standing which can result in a 40% reduction in stroke volume and a decrease in arterial pressure. These hemodynamic changes will then initiate activation of both high-pressure baroreceptors in the aortic arch and carotid sinus, and low-pressure receptors in the heart and lungs. The attendant hemodynamic changes initiate a cascade of events that result in compensatory alterations of both BP and heart rate that are effected through the activities of the autonomic nervous system (ANS). In addition, there are other physiologic compensations including the local axon reflex, the so-called venoarteriolar reflex, and the myogenic response, all of which serve to limit blood flow to skin, muscle, and adipose tissue that are activated during upright posture.

Standing is also accompanied by contraction of the abdominal and leg muscles that produce a compression of resistance and capacitance vessels with an increase in peripheral vascular resistance, resulting first in an increased venous return and then an increase in BP. The increased BP causes baroreceptor activation and a decreased heart rate. The drop in heart rate results in decreased venous return, baroreceptor inactivation, an increase in heart rate, increased peripheral resistance, decreased stroke volume, and an increased DBP. In addition, continued upright posture causes a host of neurohumoral responses which varies based upon the volume status of the individual. This involves activation of the renin-angiotensin-aldosterone system as well production of vasopressin, endothelin, and/or nitric oxide.<sup>3</sup>

The most important physiologic control mechanism that compensates for upright posture is the response of the

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arterial baroreceptors present in the carotid sinus, which can influence peripheral vascular resistance. The maintenance of adequate BP, cardiac return and cerebral vascular perfusion must be accomplished within the context of a dynamic system that may, at any one time, have about 5% of the body's blood in the capillaries, 8% in the heart, 12% in the pulmonary vasculature, 15% in the arterial system, and 60% in the venous vasculature.<sup>3</sup> It is interesting to consider that standing BP at the level of the brain is near the lower limit of cerebral autoregulation.

All of these mechanisms must function and respond in a coordinated fashion to postural changes during both the initial and prolonged phases of an orthostatic challenge. Failure to do so can result in transient hypotension, inadequate venous return, and a state of cerebral hypoperfusion that may result in loss of consciousness. Many of these compensatory changes are coordinated through the activities of the ANS. Thus, adequate function of the ANS is required to maintain adequate cerebral perfusion to support consciousness. The numerous interrelationships that exist, and that can result in a loss of orthostatic control because of autonomic dysfunction are illustrated in Figure 1. These autonomic disorders can be considered as being either primary or sec-

ondary to another disease entity. The primary forms are usually idiopathic and can occur as either acute or chronic conditions. Secondary disorders can result from other diseases, biochemical or structural deficiencies or from toxins.<sup>4</sup>

The consequences from the inability to maintain adequate cerebral perfusion are manifested clinically as symptoms ranging from lightheadedness to presyncope or syncope. Symptoms may also include dimming of vision and visual blurring, which occur early because intraocular pressure reduces the transvessel gradient or because the optic nerve is more sensitive than the rest of the brain. Neck pain (often the only symptom present), weakness or buckling of the legs, cognitive slowing, headache, seizure-like tonic movements, and postprandial angina pectoris are also frequently reported. Visual changes and neck pain are most likely due to ischemia of the retinal or occipital lobe and the neck muscles, respectively. Focal neurologic findings, if present, may be suggestive of concomitant cerebrovascular disease.<sup>5</sup>

In normal individuals, SBP drops no more than 5–10 mm Hg upon assuming an upright position, while DBP rises and pulse rate increases by 10–25 beats per minute. In some patients with OH and cardiovagal autonomic dysfunction, an increase in heart rate will not occur.<sup>6,7</sup> Although many inves-

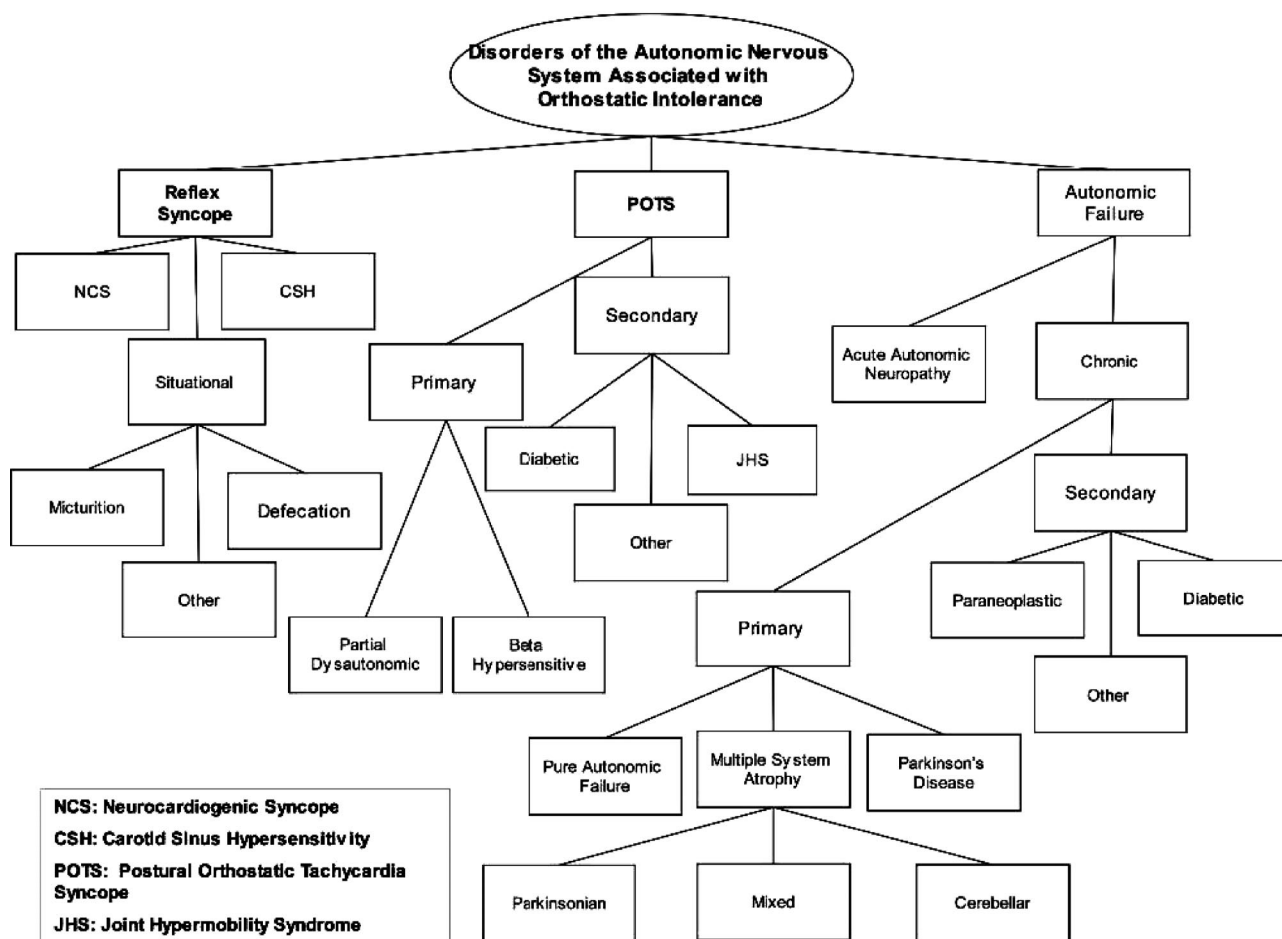


FIGURE 1. Disorders of the Autonomic Nervous System associated with Orthostatic Intolerance. Adapted with permission from Folino AF. Cerebral autoregulation and syncope. *Prog Cardiovasc Dis.* 2007;50:49–80.

tigators avoid absolute values to describe this condition and because an individual patient may tolerate a wide range of pressure changes, it is clear that standards are necessary. This need for a standard resulted in a consensus statement in which OH was defined as a reduction of SBP of at least 20 mm Hg or DBP of at least 10 mm Hg within 3 minutes of standing.<sup>1</sup> Thus, when OH is due to a primary condition such as autonomic failure, described in detail later, patients are often able to accommodate SBP drops of up to 50 mm Hg without significant symptoms. However, this is by no means normal and reflects highly abnormal cerebral autoregulation, or the capacity to maintain constant cerebral blood flow despite perfusion pressure changes. Thomas and Bannister showed that cerebral blood flow was preserved in normal subjects until mean arterial pressure fell to 60–70 mm Hg.<sup>8</sup> In patients with autonomic failure, however, autoregulatory ability remained intact with MAP values as low as 40 mm Hg.<sup>8</sup>

If syncope occurs, patients typically awaken almost immediately after a horizontal position is assumed, as hypoperfusion-related symptoms are typically relieved within 1–2 minutes when supine. The syncope of OH is generally characterized by the absence of postictal confusion or drowsiness. In contrast to neurally-mediated vasovagal syncope, the most common cause of syncope,<sup>9,10</sup> patients with autonomic failure or other causes of OH rarely report symptoms of associated pallor, nausea, vomiting, or diaphoresis. Other common findings with OH related to dysautonomia are mild anemia, hypohidrosis, a Parkinsonian-like syndrome, recurrent urinary tract infections and/or bladder dysfunction, sleep apnea, hoarseness, nasal stuffiness, impotence, and constipation or diarrhea. Symptoms of orthostasis and the occurrence of syncope are most commonly reported in the morning or soon after meals, as food provides a strong hypotensive stimulus.<sup>11</sup> Symptoms are also worse after sudden postural changes, prolonged exposure to heat (ie, a hot bath or shower or summer weather), fever, and alcohol consumption. Exercise and hyperventilation may also provoke symptoms, as will activities that involve strong muscular activities such as heavy lifting, coughing, or straining to defecate.<sup>12</sup> Patients are often more likely to tolerate their symptoms as the day progresses due to the gradual rise in BP. Although this is somewhat beneficial for a short time, it is temporary and by day's end can manifest as supine hypertension—a troubling problem for those in whom OH is secondary to autonomic failure. Supine hypertension may become most pronounced shortly after a patient retires at night and may also be accompanied by nocturnal polyuria as a result of a pressure natriuresis.

## EPIDEMIOLOGY

OH is a common problem in the general population, estimated to occur in 0.5% of individuals, but in an acute-care setting, the incidence may be as high as 7–17%.<sup>13</sup> When OH results in dizziness or syncope, it may account for up to 21% of patients presenting to an emergency room with these symptoms.<sup>14</sup> Moreover, when dealing with elderly patients, OH may be even more prevalent than these statistics might suggest.<sup>15–16a</sup> Baroreceptor sensitivity, a function that de-

clines with age, together with increased intake of vasoactive medications, among other causes, makes the elderly particularly susceptible to postural changes in BP. In fact, greater than 20% of the elderly experience a SBP drop of more than 20 mm Hg upon standing.<sup>17–19</sup>

In a study by Sloane et al, up to 18% of persons over the age of 60 were found to have symptoms of dizziness severe enough to interfere with activities of daily living; these complaints were associated with self-perceived depression, poor health, and other negative findings.<sup>20</sup> With an increasing number of elderly patients in our society, OH, with or without dizziness, is likely to be diagnosed more frequently than it was in the past.<sup>21</sup>

## DIFFERENTIAL DIAGNOSIS

As shown in Table 1, the following conditions are associated with OH and include primary and secondary autonomic neuropathies, vascular, hemodynamic, and volume disorders, and pregnancy.<sup>22</sup> OH can also result from certain medications. Classification of OH into specific etiologic categories has become more important as treatment is increasingly individualized, ie, hypoadrenergic patients are exquisitely sensitive to pressor agents, whereas hypovolemic patients may benefit greatly from a mineralocorticoid and an increased intake of sodium.<sup>23</sup> Furthermore, there are several conditions that, once recognized, can be easily treated, such as the removal of offending medications.<sup>24</sup> Patients with dopamine- $\beta$ -hydroxylase (D $\beta$ H) deficiency, a cause of primary autonomic failure, can be treated effectively with medication.<sup>25,26</sup> The following are conditions in which patients may exhibit OH.

### Primary Autonomic Disorders

Each of the following conditions represents a circumstance in which the integrative function of the central nervous system (CNS) to regulate BP through the peripheral ANS is adversely affected. Thus, they are considered to be neurogenic disorders.<sup>27</sup> Early on, many of these patients will accommodate to their fall in BP and thus may not have OH as an initial presenting finding, but eventually this becomes the most incapacitating symptom of all. Severely affected patients may experience syncope or presyncopal moments after leaving the supine position and many may be unable to live alone safely.

### Pure Autonomic Failure (PAF)

In a land report in 1925, Bradbury and Eggleston described a patient with a selective neuropathy involving the sympathetic and parasympathetic nervous systems caused by a progressive loss of the peripheral preganglionic and postganglionic autonomic nerves for reasons not yet understood.<sup>28</sup> This report described almost all the clinical features we now attribute to autonomic failure, and the syndrome became known as the Bradbury-Eggleston syndrome or idiopathic OH. This condition manifests in middle-to-late life and occurs 5 times more frequently in men. The onset of this illness is insidious, occurring over 2–5 years, and sparing the adrenal medulla until relatively late in the disease. Despite the fact that many patients are diagnosed when older, they

**TABLE 1.** Causes of Conditions Producing Orthostatic Hypotension

Autonomic Neuropathies
Primary
Bradbury-Eggleston syndrome
Shy-Drager syndrome
Riley-Day syndrome
Dopamine- $\beta$ -hydroxylase deficiency
Secondary
Diabetes mellitus
Uremia
Guillain-Barre syndrome
Amyloidosis
Porphyria
Idiopathic
Transient Neurogenic (Autonomic) Syncope
Micturition syncope
Carotid sinus syncope
Vasovagal syncope
Bezold-Jarisch reflex activation
Glossopharyngeal neuralgia
Endocrinologic Disorders
Pheochromocytoma
Hypoaldosteronism
Renal artery hypertension
Vascular Insufficiency/Vasodilatation
Varicose veins
Arteriovenous malformations
Absent venous valves
Carcinoid
Mastocytosis
Hyperbradykininism
Hypovolemic Disorders
Anemia
Decreased plasma volume
Hemorrhage
Anorexia nervosa
Diarrhea
Overdialysis
Overdiuresis
Miscellaneous Causes
Drugs (antihypertensives, diuretics, antidepressants, etc)
Pregnancy
Space flight

Adapted with permission from Robertson D. Treatment of cardiovascular disorders: orthostatic hypotension. In: Melmon KL, Morelli HF, Hoffman BB, et al, eds. *Clinical Pharmacology, Basics Principles of Therapeutics*. 3rd ed. New York, NY: Macmillan; 1992:84–103.

often have a good prognosis. Many live into their late 80s (surprisingly outliving the general population), often surviving 10–20 years after the initial diagnosis of their disease.<sup>29</sup> In these patients, death is most commonly due to pulmonary emboli.

There is no cognitive dysfunction or central deficit associated with the Bradbury-Eggleston syndrome. Although impotence occurs in males, and sphincter disturbances and postprandial problems are other early manifestations, light-

headedness is the symptom that drives most patients to seek medical attention. Nocturia that awakens the patient several times a night is often described. Patients complain of bowel and bladder dysfunction, past episodes of urinary tract obstruction and recurrent urinary tract infections, nasal stuffiness, reduced sweating, chest pain in which no significant atherosclerosis is found, and an intolerance to heat.<sup>13</sup> Patients commonly describe lifestyle changes to avoid situations where symptoms of syncope or presyncope may occur. It is important to remember that this symptom pattern differs from that of vasovagal syncope, wherein sweating, tachycardia and pallor are common prodromal symptoms.<sup>22,30,31</sup> Patients may also exhibit a mild anemia presumably due to the reduced  $\beta_2$ -adrenoceptor stimulation of erythropoietin release.<sup>32</sup>

OH in PAF is often quite severe, although in the early part of the illness or in individuals only mildly affected, BP may only drop within the hour of a large meal. It is therefore crucial to obtain both supine and upright BP readings postprandially in individuals suspected of having OH. BP is also reduced in these patients early in the day, especially after rising, after exercise, at high altitudes or high temperatures, after hyperventilation or with concurrent infection or fever. Urinary tract infections in patients with Bradbury-Eggleston syndrome can cause sudden declines in normal renal function.<sup>29</sup>

Because many of those most severely afflicted with Bradbury-Eggleston syndrome have BPs of 60/30 mm Hg or lower, absolute BP measurements alone may not predict functional abilities. Standing time (length of time a patient is able to stand motionless without symptoms) may be a better measure. If standing time is greater than 60 seconds, patients can usually continue to live alone; if less than 30 seconds, few can. Patients also exhibit an exquisite sensitivity to sympathomimetic amines and vasopressin as a result of denervation hypersensitivity with an increased sensitivity of autonomic receptors. Sympathomimetic amines and vasopressin are commonly used as pressor and depressor stimuli in patient testing.<sup>29</sup> Plasma levels of norepinephrine are dramatically reduced, as are urinary levels of all catecholamines. There is a reduced or absent catecholamine response to upright posture and there is a similar lack of response to insulin-induced hypoglycemia. As symptoms of autonomic instability may occur before the onset of CNS degeneration, as is also seen in multiple system atrophy (MSA, see below), the physician must maintain a close longitudinal surveillance of the patient's clinical course to establish the diagnosis.

### Multiple System Atrophy

MSA, formerly referred to as Shy-Drager syndrome, is defined as a failure of the ANS with associated neurologic deficits in the cerebellar and extrapyramidal systems, the corticobulbar and corticospinal systems, as well as the pons and medulla.<sup>33</sup> This dysfunction of the ANS is essentially a central defect that prohibits peripheral sympathetic and parasympathetic postganglionic neurons from being engaged. Because these neuron cell bodies are normal in this condition,



a functional disconnection of an intact peripheral nervous system can be envisioned. The pathology remains unknown, but patients have cerebrospinal fluid antibodies capable of specifically binding to the locus ceruleus in rats.<sup>34</sup> The disease first presents in mid to late life with a somewhat insidious onset that may initially seem to be PAF until defects in the other systems become apparent. Because of the more extensive involvement, prognosis for these patients is poor, as most patients survive no more than 7–10 years after diagnosis.

No cognitive or sensory deficits are present; OH is usually the only presenting physical examination finding. These patients typically exhibit nocturnal rises in BP, the reverse of normal circadian BP patterns.<sup>35</sup> Patients may also manifest extrapyramidal symptoms of tremor, rigidity, bradykinesia, and cerebellar abnormalities. Slow deterioration is typical, and sleep apnea, swallowing difficulties, and laryngeal stridor are common in later stages of the illness. This often portends respiratory arrest and pulmonary emboli, which are frequent causes of death. Posture-dependent hypoperfusion of the abdomen, so-called visceral OH, may also occur in these patients, which may present clinically as abdominal pain after standing.<sup>36</sup>

The clinician must attempt to differentiate Parkinson disease from certain manifestations of MSA.<sup>37,38</sup> A response to antiparkinsonian therapy alone may not distinguish MSA from Parkinson disease, because two-thirds of patients have an initial response to medication. Drug effects and a diminishing motor response over time reduce the responders to less than a third.<sup>39</sup> More recently, it has been shown that sympathetic cardiac innervation is selectively affected in Parkinson disease and PAF, but not in MSA.<sup>40</sup> Although plasma and urine catecholamine levels do not change with upright posture, their basal concentrations are normal in both disease states and increase with indirect acting sympathomimetic drugs, because postganglionic neurons remain functionally normal and are simply disengaged from the CNS.<sup>41</sup>

### Familial Dysautonomia

Familial dysautonomia, previously referred to as Riley-Day syndrome, is a failure of the afferent and efferent nerves of the peripheral nervous system due to a dysfunctional development of both the autonomic and sensory nerves during fetal development.<sup>42</sup> This disease is characterized by a decrease in unmyelinated and small myelinated neuronal fibers, as well as a paucity of neurons in the spinal cord and in sensory and autonomic ganglia. In addition, the metabolism of catecholamines is impaired. The gene responsible, *DYS*, has been mapped to chromosome 9q31-q33, and DNA markers now enable prenatal diagnosis and carrier identification.<sup>43</sup> The disease almost exclusively affects Ashkenazi Jews: approximately 1 in 30 have a single copy of the mutated gene; thus each child born to 2 parents of such ancestry has approximately a 1 in 3600 chance of having the disease for which there is currently no cure.

The disease is first identified at birth or soon thereafter. The diagnostic criteria include Ashkenazic Jewish heritage, diminished tear production, a lack of axon flare after intra-

dermal histamine, the absence of lingual fungiform papillae, and decreased deep-tendon reflexes. Clinical features include diminished pain sensation, unexplained fevers, hypertension, and OH caused by defective control mechanisms for temperature and BP. BP and heart rate are unable to be controlled and many patients die of cardiac standstill after exercise or when parasympathetic reflexes activated, for example by micturition, are unable to be opposed.<sup>13</sup> Patients have oropharyngeal incoordination and abnormal gastrointestinal motility, causing feeding difficulties, vomiting, and recurrent aspiration. Musculoskeletal problems are related to gait disorders, foot deformities, arthropathies, fractures, and spinal deformities.<sup>44</sup> The prognosis is poor, and death frequently occurs before age 30.

### Baroreflex Failure

Baroreflex failure occurs with a lesion along the baroreflex arc. The tract originates from the carotid sinus and great vessels of the thorax and neck, passing via the glossopharyngeal and vagal nerves, respectively, to the nucleus tractus solitarius in the brain stem. Patients have volatile and labile changes in BP and heart rate.<sup>9,11,13–15</sup> If a hypertensive crisis occurs, baroreflex failure can mimic pheochromocytoma. Lightheadedness is usually not a presenting symptom but may occur several years later, especially after treatment of hypertension with clonidine or phenoxybenzamine.<sup>45</sup>

### Dopamine $\beta$ -Hydroxylase Deficiency

D $\beta$ H deficiency is a condition in which the D $\beta$ H enzyme, required for conversion of dopamine to norepinephrine, is absent from peripheral noradrenergic and adrenergic tissue, that is, in the chromaffin granules of the adrenal medulla and the dense-core synaptic vesicles of noradrenergic neurons.<sup>46–48</sup> There is selective sympathetic impairment, and nerves release dopamine in response to stimuli that would normally elicit a release of norepinephrine. Parasympathetic function is normal in patients, as evidenced by the presence of sinus arrhythmia and increased heart rate after atropine administration. The disease frequently manifests itself at birth, and is frequently misdiagnosed as sudden infant death syndrome, hypoglycemia, hypothermia or a seizure disorder (Table 2). Symptoms include severe OH, ptosis of the eyelids, nasal stuffiness, and retrograde ejaculation in males. These symptoms tend to worsen in early adulthood. Although an effective treatment exists, it is difficult to determine life expectancy as it is postulated that many infants with D $\beta$ H deficiency die undiagnosed, which limits the opportunity to follow the natural course of this disease.

A pathognomonic feature of this disorder is the virtual absence of norepinephrine and epinephrine in plasma, urine and cerebrospinal fluid. There is also a 5- to 10-fold increase in levels of dopamine<sup>26,49,50</sup> without evidence of other neurologic deficits.<sup>29</sup> Upright SBP is typically below 80 mm Hg and heart rate rises only minimally in patients after leaving the supine position. OH is usually so severe that standing time is in the 30-second range. The availability of effective treatment measures for this disease makes it much more benign than the other primary autonomic neuropathies.

**TABLE 2.** Manifestations of Dopamine  $\beta$ -Hydroxylase Deficiency

Severe orthostatic hypotension
Ptosis of the eyelids
Nasal stuffiness
Retrograde ejaculation in males
Complicated prenatal course
Hypothermia
Hypoglycemia
Hypotension
Seizures
Hyperextensible joints
Nocturia
Normal cognition
Spontaneous abortions/stillbirths of affected mothers

Reproduced from Frishman WH, Shevell T. Drug therapy of orthostatic hypotension and vasovagal syncope. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York, NY: McGraw Hill; 1997:231–246 with permission from the BMJ Publishing Group.

**TABLE 3.** Causes of Peripheral Neuropathy Resulting in Orthostasis

Diabetes mellitus
Wernicke-Korsakoff syndrome
Uremia
Amyloidosis
Porphyria
Paraneoplastic syndromes
Nutritional deficiencies (vitamin B <sub>12</sub> , folate)
Guillain-Barre syndrome
Syringomyelia
Tabes dorsalis
Systemic collagen vascular diseases
Pernicious anemia
Spinal cord injury

Adapted from Hollister A. Orthostatic hypotension—causes, evaluation, and management. *Western J Med*. 1992;157:652–657 with permission from the BMJ Publishing Group.

## Secondary Autonomic Neuropathy

OH and autonomic impairment are common accompanying features of a number of disorders that are associated with peripheral neuropathy, albeit not as initial manifestations of these diseases (Table 3). OH and autonomic impairment are generally not as severe with these conditions as with primary autonomic disorders. The most common cause of secondary autonomic dysfunction is diabetes mellitus, the first manifestation of which is usually gastroparesis. However, insulin can act as a vasodepressor, and when given in combination with food, which also acts as a strong stimulus to decrease BP, patients with existing autonomic dysfunction may exhibit significant OH.<sup>51,52</sup> Acarbose, an  $\alpha$ -glucosidase inhibitor used to blunt postprandial rises in blood sugar, may be useful in such patients.<sup>53</sup> Furthermore, patients with diabetes often have decreased norepinephrine levels and a blunted renin response, which may also contribute to the

problem of OH as both norepinephrine and renin help to maintain BP upon rising from the supine position. Patients with diabetes may also receive angiotensin converting enzyme inhibitor therapy which also limits the defensive response to posturally induced reduction in BP.<sup>54</sup>

OH may also be associated with other diseases such as amyloidosis, porphyria and malignancy and/or is found in association with spinal cord lesions. OH has been observed in patients with encephalopathy and/or peripheral neuropathy secondary to human immunodeficiency virus infection, although interpretation of OH in the human immunodeficiency virus-infected patient can be complicated by the occasional finding of Addison's disease.<sup>55</sup> Patients with Parkinson disease have also been shown to manifest OH as a result of sympathetic neurocirculatory failure from generalized sympathetic denervation.<sup>56</sup>

## Postural Tachycardia Syndrome (POTS)

Over the last decade, considerable attention has been given to a new subgroup of disorders currently referred to as POTS. POTS is a chronic variant of autonomic dysfunction defined by an excessive increase in heart rate ( $>30$  beats per minute or to a heart rate  $>120$  beats per minute) in the first few minutes of assuming upright posture.<sup>3</sup> Patients with POTS often experience symptoms such as light-headedness, dizziness, fatigue, or near-syncope. In contrast to vasovagal syncope, in which patients experience an abrupt drop in both BP and heart rate after tolerating 5–30 minutes of asymptomatic upright tilt, POTS patients develop upright tachycardia within 10 minutes of orthostatic stress.<sup>57</sup> Some POTS patients display acrocyanosis in their lower extremities, suggesting abnormal peripheral vascular physiology for which many possible mechanisms have been postulated, such as  $\alpha_1$ -adrenergic denervation of the lower extremities and/or altered venoconstriction. In addition, a recent clinical trial by Stewart et al suggested that splanchnic hyperemia during tilt table testing might correlate with the rapid decrease in BP after a Valsalva maneuver in a subset of patients with POTS.<sup>58</sup> A second type of POTS referred to as the “ $\beta$ -hypersensitivity” form is believed to be due to an inadequate feedback process that arises from above the level of the baroreflex.<sup>59</sup> Thus far, treatment of POTS remains largely supportive and palliative, although recent studies have shown some success with acetylcholinesterase inhibition<sup>60</sup> and selective serotonin reuptake inhibitors.<sup>61</sup>

## Reflex Syncope (Including Vasovagal Syncope)

Reflex syncope is a group of disorders that result from a sudden failure of the ANS to maintain adequate vascular tone during orthostatic stress. These disorders are often associated with bradycardia and hypotension that can result in cerebral hypoperfusion and a loss of consciousness.<sup>3</sup> The 2 most frequent types are neurocardiogenic or vasovagal syncope, and carotid sinus syndrome. Because vasovagal syncope (neurocardiogenic syncope, a benign condition), is the most common cause of syncope, it deserves special mention.<sup>3,62–64</sup> Vasovagal syncope is frequently caused by an acute episode of hypotension, which results from a sudden disconnect between the ANS and cardiovascular system; the

event is quite acute and represents a paroxysmal malfunction of baroreflexes.<sup>65</sup> Vasovagal syncope can be quite varied in its presentation; it tends to occur in younger patients and generally exhibits 3 distinct phases that comprise its prodrome. These are usually lightheadedness, nausea, and diaphoresis, followed by a loss of consciousness.

In patients with OH, BP is consistently poorly regulated, and may be the result of an inability to effectively activate efferent sympathetic fibers. Vasovagal syncope often occurs while standing or walking. A lack of prodromal symptoms is especially common in older adults. Vasovagal syncope may also result from strong emotions, acute pain, or the triggering of parasympathetic reflexes, as occurs during micturition.<sup>66</sup> Although the exact mechanism of vasovagal syncope is still unclear, it is thought that provoking factors result from an increased amount of peripheral venous pooling that leads to increased sympathetic nervous system activity. A study by Stewart et al demonstrated that patients with a postural faint have a greater decrease in their thoracic blood volume and an increase in splanchnic blood volume during orthostatic stress compared with control subjects.<sup>67</sup> It is believed that this splanchnic pooling activates mechanoreceptors that would normally activate only during stretch. The brain interprets this "stretch" as one that occurs in conditions such as hypertension, and withdraws sympathetic outflow, and increases vagal activity, leading to bradycardia and a sudden decrease in systemic vascular resistance due, in part, to sympathetic inhibition and arterial vasodilatation.

It has also been shown that vasovagal responses can occur as a direct result of cardiac afferent nerves being acted upon in an excitatory fashion by adenosine and alkaloids. Adenosine may also act indirectly to elicit this response by its physiologic actions, which, in part, are to promote vasodilatation, inhibit renin release, and decrease efferent nerve activity.<sup>68</sup> A recent study by Saadjian et al<sup>69</sup> suggests that adenosine may indeed serve as a trigger mechanism for tilt testing-induced syncope. Baseline adenosine plasma levels were higher in patients with a positive tilt test than in patients having a negative tilt test. Furthermore, during syncope, adenosine plasma levels increased by an average of 52% from baseline levels. This study also showed that the higher the adenosine plasma level, the sooner the patients became symptomatic and a greater decrease in heart rate was evident. However, adenosine-sensitive syncope and tilt-induced vasovagal syncope seem to be 2 distinct clinical entities.<sup>70</sup>

The exact mechanisms that result in cerebral hypoperfusion and subsequent syncope are presently unclear. Dan et al<sup>71</sup> has shown that cerebral blood flow velocity decreases before any observed arterial pressure reduction associated with orthostatic presyncope, thus suggesting that primary changes in cerebrovascular autoregulation may contribute to the vasovagal syncope. This apparent paradoxical cerebral vasoconstriction is likely to be the result of hyperventilation-induced hypocapnia seen in habitual fainters.<sup>72</sup> However, sympathetic withdrawal alone does not adequately explain this form of syncope; norepinephrine does not disappear from the circulation; rather, it merely fails to increase. Vasoconstrictor peptides, such as vasopressin and endothelin-1, do

seem to increase appropriately. Vasopressin has been shown to increase up to 20-fold at the time of syncope when compared with baseline levels in tilt positive patients.<sup>73</sup> Recent studies suggest that the profound hypotension experienced before vasovagal syncope may be due to an increased synthesis of nitric oxide. The role of this powerful vasodilator in vasovagal syncope can be evaluated using urinary cyclic guanosine monophosphate as a biologic marker for nitric oxide activity.<sup>66</sup>

## EVALUATION AND DIAGNOSIS

When do patients with OH first seek medical attention? Many times a visit to a physician is prompted by patients having vague symptoms and/or with initial complaints such as lightheadedness or presyncope, which must be more clearly delineated. In 1985, a nationwide survey of primary care providers found that complaints of dizziness accounted for 1% of all chief complaints from patients over the age of 25.<sup>7</sup> Syncope, another common manifestation of OH, involves loss of consciousness and occurs in 3% of men, 3.5% of women, and accounts for up to 6% of hospital admissions.<sup>74–76</sup> In evaluating dizziness it is crucial to establish the patient's description of dizziness to best determine if the cause is due to anxiety, vertigo or OH. Presyncope and syncope are symptoms that, among other etiologies (ie, low output states and arrhythmias), are commonly caused by OH. Accordingly, the physician called upon to evaluate dizziness in a patient must be well skilled in identifying the characteristics of the varied diagnostic categories associated with this very common problem.

Syncope can arise from cardiogenic causes, including heart blocks, supraventricular and ventricular arrhythmias, mechanical problems such as outflow tract obstruction secondary to aortic stenosis or other valvular lesion, pulmonary embolism, myocardial ischemia, or as the result of neurally-mediated events.<sup>5,77</sup> In recurrent syncope and presyncope, when cardiac, neurologic, and metabolic causes have been excluded, evaluation of the ANS can aid in management by making, confirming, or excluding various factors or diagnoses.<sup>78</sup>

In the diagnosis of syncope, head-up tilt table testing had previously been considered as the reference standard. However, a recent Scientific Statement on syncope issued by the American Heart Association and the American Autonomic Society refer to tilt-table testing as only an aid in establishing the diagnosis of neurocardiogenic syncope.<sup>79</sup> Head-up tilt table testing simulates conditions known to trigger syncope. Most studies have favored tilts of 30- to 45-minute durations at an angle of 60–70 degrees. Other guidelines for tilt-table testing have been issued by the American College of Cardiology and the European Society of Cardiology.<sup>80</sup>

Although head-up tilt table testing is widely used in the diagnosis of vasovagal syncope, questions relating to its sensitivity, specificity, and reproducibility make its interpretation and clinical applicability difficult. Without pharmacologic provocation, specificity can approach 90%, although sensitivity is lower, falling in a range from 30% to



85%.<sup>67,80,81</sup> This wide range is partially caused by differences in tilt protocols, such as differing tilt angles and duration of tilt. In addition, differences in patient characteristics at study entry, eg, multiple versus single episodes of syncope, age, number and type of comorbid conditions, and/or exclusion of other types of syncope, are likely to have an effect on diagnostic sensitivity.<sup>82</sup> Recently, a study by Kinay et al<sup>83</sup> demonstrated that repeat tilt testing resulted in decreased episodes of syncope and increased orthostatic tolerance in patients with recurrent vasovagal syncope. It is possible that the sensitivity of tilt-table testing might be lower with repeated testing due to the repeated exposure and an increased orthostatic tolerance.<sup>83</sup> In OH, tilt table testing may not be as effective a diagnostic test, as the pathophysiology differs from vasovagal syncope; however, it is occasionally used to diagnose mild cases, when used at angles of less than 60 degrees. Regardless of that, observations about the different hemodynamic patterns of collapse seen during tilt table testing may provide clues for suggesting an initial line of therapy.

Pharmacologic agents are often used to provoke a positive test result if head-up tilt table testing alone does not induce vasovagal syncope. The agents are chosen for their effects on autonomic regulation during head-up tilt table testing. For example, because serum concentrations of catecholamines increase before spontaneous vasovagal syncope, isoproterenol is infused during head-up tilt table testing to augment the vasovagal response. Isoproterenol infusion, which stimulates  $\beta$ -adrenergic receptors, in essence provides exogenous catecholamines. Exogenous catecholamine administration may supercede patient variability in the amount of epinephrine/norepinephrine released under real life circumstances. The latter helps to explain the spontaneity of these neurally-mediated events.<sup>81</sup>

Similarly, adenosine (vasodilatory and probable direct activation of sympathetic afferents), edrophonium (cholinergic action), nitroglycerin (direct vasodilatory action) and other agents have been used to provoke syncope during head-up tilt table testing as well.<sup>84–89</sup> Nitroglycerin, initially studied as an infusion, was found to improve the sensitivity of testing when compared with isoproterenol.<sup>90</sup> Sublingual nitroglycerin has been shown to double the positive rate of tilting (51% vs. 25%) while it maintained a high specificity (94% vs. 100%).<sup>91</sup> Sublingual isosorbide dinitrate has also been evaluated.<sup>92</sup> Edrophonium, which inhibits acetylcholinesterase, significantly increases the identification of patients with vasovagal syncope, and may be particularly useful when provocation with isoproterenol is undesirable.<sup>93</sup> Acetylcholine, which is a potent stimulator of nitric oxide release, is increased during neurally-mediated syncope, which adds to vasodilatation.<sup>66</sup> The use of clomipramine, which blocks the reuptake of serotonin, can cause sympathetic withdrawal, and has been shown to improve the diagnostic value of the tilt table test.<sup>87</sup> Furthermore, it has been shown that isoproterenol-susceptible subjects have a higher level of baseline sympathetic activity as opposed to nitrate responders who seem to have a higher level of vagal activity, suggesting that there

may be more than 1 mechanism represented by these 2 patient groups responsible for the vasovagal reaction.<sup>94</sup>

Once vasovagal syncope is ruled out, the diagnosis of OH may best be made through a careful history and a physical examination that results in identification of the cause of syncope in 45% of patients.<sup>95</sup> More recent studies report the diagnostic yield of a standardized, sequential noninvasive clinical evaluation of syncope as high as 76%.<sup>96,97</sup> Laboratory evaluations should be obtained in a careful and directed manner, based on history and physical examination, and the mindless ordering of a multitude of tests is to be discouraged.<sup>98</sup> Working within a framework, such as the guidelines proposed by the European Society of Cardiology with the appropriate situational modification for varied patient presentations, would yield a more thorough and efficient investigation.<sup>99,100</sup> If symptoms are consistent with OH (lightheadedness, dizziness, neck ache), one must first seek reversible causes, such as medications or hypovolemia before proceeding further. Symptoms should not occur when a patient is supine. One must determine if symptoms occur at the time of first arising in the morning or postprandially. It must also be established that a patient does not exhibit a vasovagal prodrome. Physical examination can be extremely helpful; eye examination may reveal miosis, a check of the skin may reveal anhidrosis, sphincter tone may be decreased on rectal examination and/or parkinsonian signs may be present in patients with autonomic failure who respond to standing with a drop in BP without tachycardia or vasoconstriction. Hypovolemic patients respond to upright posture with tachycardia and vasoconstriction evidenced by cool hands and feet, whereas in those patients having excessive vasodilatation, extremities remain warm and pink.<sup>23</sup>

BP measurements are crucial in diagnosis, especially in subjects who may need repeated measurements taken in the morning hours for confirmation.<sup>101</sup> Responses measured after standing can be grouped into 3 categories according to the change in pulse rate: (1) a fall in BP with a simultaneous rise in pulse rate—normal physiologic response, (2) a fall in BP with either no rise in pulse rate or one which is always less than 10 beats per minute—defect in the ANS, and (3) a fall in BP with a drop in pulse rate, which implies a vasovagal response.<sup>6</sup> Once the ANS has been isolated as the cause of the dysfunction, many tests are available to help determine the exact site of the problem (Table 4).<sup>102</sup> Laboratory testing includes the measurement of supine and upright plasma and urine catecholamines and dopamine. Basal levels of plasma norepinephrine tend to be normal in patients with CNS disease, whereas those patients with peripheral autonomic disturbances tend to have lower levels. The severity of the OH can be assessed using sphygmomanometry if SBP is in a reliable range of measurement (>60–85 mm Hg) or by determining standing time, as this can also be used to assess an improvement or decline in functional status.<sup>12</sup>

If syncope remains unexplained, studies using implantable long-term monitoring devices have shown bradycardia to be the most common cause.<sup>103</sup> Recently, a few studies have been able to show that implantable loop recorders (ILRs) may be useful in the diagnosis and management of patients with



**TABLE 4.** Autonomic Testing: Appropriate Responses

Quantitative Valsalva maneuver—Baseline to shortest RR interval >1.4
Quantitation of sinus arrhythmic response to slow deep breathing—Longest to shortest RR interval >1.2
Response of blood pressure and heart rate to standing—systolic <10 mm fall. Diastolic rises or stays steady
Carotid sinus massage—heart rate slows >10 bpm
Diving reflex—blood pressure increase >10 mm
Cardiovascular sensitivity to phenylephrine—blood pressure up by 25 mm = 200 µg, heart rate decrease
Cardiovascular sensitivity to isoproterenol—heart rate increase by 25, blood pressure decrease by 25 = 5 µg
Cardiovascular sensitivity to tyramine—blood pressure increase by 25 = 2 mg, increased norepinephrine levels

Adapted from Hollister A. Orthostatic hypotension—causes, evaluation, and management. *Western J Med.* 1992;157:652–657 with permission from the BMJ Publishing Group.

unexplained syncope.<sup>104</sup> In addition to providing more specific diagnoses, the implantation of an ILR has led to more rapid introduction of therapy and to more varieties of treatment modalities.<sup>105,106</sup> Deharo et al reported that in many patients with highly symptomatic vasovagal syncope, the ILR helped recognize that the heart rhythms observed during spontaneous syncope did not always correlate with those found with tilt-table testing.<sup>104</sup> As such, ILRs might help to elucidate various mechanisms of syncope and to individualize treatment options.<sup>107</sup>

### NONPHARMACOLOGIC TREATMENTS

The goal of treating OH is to improve the quality of life. This can be accomplished by limiting the number and extent of episodes of cerebral hypoperfusion and/or by minimizing drug or alternative therapy-related side effects.<sup>108–110</sup> Pharmacologic therapy alone is often inadequate, and nonpharmacologic measures, including patient education, are a necessary foundation for an overall treatment plan. Once potentially reversible conditions have been identified, such as drug side effects and hypovolemia, patients can be educated about general nonpharmacologic treatment measures, many of which have been refined in recent years. Orthostatic demands are fairly constant throughout the day and by learning one's orthostatic BP pattern, many patients can plan activities accordingly. Improvement in quality of life can be seen in most patients if a nonpharmacologic treatment plan can be effectively implemented.

Careful dietary instruction is also important in the nonpharmacologic management of the patient with OH. Most periods of activity should be planned preprandially and meals should be larger at night when BP is usually higher. Meal regulation is centered on the physiologic principle that food evokes hypotensive responses secondary to postprandial shifts in blood flow to the splanchnic bed. Postprandial hypotension can also be minimized by decreasing alcohol intake, eating low cholesterol diets and by avoiding large meals.<sup>6</sup> A small meal high in carbohydrates for patients with supine hypertension may also be of benefit right before retiring and is even more valuable if patients are receiving

pressor agents during the day. Meals also trigger the release of vasoactive substances such as histamine and adenosine, which as previously mentioned, may increase vasodilatation.<sup>66</sup> Therefore, caffeine, which has a well-established pressor effect,<sup>111,112</sup> while also blocking adenosine receptors, should be considered as a treatment option. Patients can be advised to consume 2 cups of coffee (240 mg of caffeine) with breakfast and lunch.<sup>111,112</sup> It is suggested that patients avoid consuming caffeine with dinner, as this is when tolerance to its effects is most likely.<sup>23,113</sup> In a study by Dewey et al using caffeine, it was shown that a few patients with Parkinsonism and OH showed improvements in SBP and symptoms of syncope.<sup>114</sup> On the other hand, Berry et al suggested that the acute and chronic consumption of caffeine can lead to impaired cardiovascular function, possibly due to impaired baroreflex function during exposure to orthostatic stress.<sup>115</sup>

Patients can be taught to avoid situations that may exacerbate their condition such as straining, isometric exercise and hot showers (Table 5). They can also be advised to increase activity that may be safer and potentially beneficial. If patients wish to exercise, swimming should be recommended as the hydrostatic pressure of the water opposes the gravitational effect on blood pooling.<sup>116</sup> Exercise training also has a role in the management of patients with syncope and poor orthostatic tolerance. In patients who are incapacitated by their disease, a mild degree of exercise is highly desirable as it improves symptoms and increases orthostatic tolerance without increasing resting BP.<sup>117</sup> Mtinangi and Hainsworth assessed the effects of moderate exercise training (11–12 minutes/d) on the baroreceptor-heart rate reflex and plasma and blood volumes of untrained subjects. They reported that exercise training consistently increased plasma and blood volumes and decreased baroreceptor sensitivity.<sup>118</sup>

Other physical maneuvers, such as leg crossing and squatting, may allow patients with OH to increase their BP by as much as 13 and 44 mm Hg, respectively.<sup>116</sup> These maneu-

**TABLE 5.** Situations to be Avoided in Patients with Orthostatic Hypotension

Prolonged recumbency
Excessive laughter
Large meals
Isometric exercise
Hot weather
Hot showers
Rapid ascent to high altitude
Hyperventilation
Standing motionless
Consuming alcohol
Straining at stool or with voiding
Fever
Diet pills, nasal sprays, eye drops
Over-the-counter cold preparations
Vasodilators, diuretics, beta agonists, tricyclic antidepressants

Adapted from Hollister A. Orthostatic hypotension—causes, evaluation, and management. *Western J Med.* 1992;157:652–657 with permission from the BMJ Publishing Group.

vers, combined with tensing muscles at the onset of prodromal symptoms, have been shown to be effective in postponing or preventing vasovagal syncope as well.<sup>119–121</sup> Postural changes serve to maximize circulating blood volume as can Jobst stockings, which are waist high, custom-fitted elastic stockings that, when used with an abdominal binder, may provide great benefit by decreasing splanchnic pooling and increasing interstitial pressure on the legs.<sup>122</sup> For milder forms of OH, wearing knee-length elastic stockings may be sufficient to minimize orthostatic reductions in BP.

In addition to modifying postural blood volume redistribution, increasing blood volume can also be effective in eliminating OH-related symptoms. Patients with autonomic failure, because of decreased renal sympathetic function and decreased renin-angiotensin-aldosterone activity, may have inappropriate wasting of sodium in the urine.<sup>111</sup> Therefore, salt-containing foods should be recommended, except in patients with congestive heart failure; similarly, diuretics should be avoided. The head of the patient's bed should be raised to a 5- to 20-degree angle, which activates the renin-angiotensin-aldosterone system, and decreases both nocturnal diuresis and supine hypertension.<sup>123</sup> The head-up position can also help to increase preservation of interstitial fluid in the extremities, which may also decrease the drop in BP that many patients experience in the morning. Supine hypertension may also be lessened by consumption of a small amount of wine at night.<sup>111</sup> In achieving an erect posture from a supine position, patients should be advised to rise slowly, first dangling their legs over the side of the bed, which allows for an adjustment to the seated position, before rising completely to an elevated stance.

Drinking water significantly and rapidly increases sympathetic activity and this effect profoundly increases BP in patients with autonomic failure. Although the pressor effects of water remain unclear, a recent study by Lu et al<sup>124</sup> indicated that L-dopa levels were significantly greater in patients who had ingested water than in those who had not. Heart rate was also lower in the group that drank water suggesting that water might serve to modulate the baroreflex response. This effect can be exploited to improve the symptoms of OH.<sup>125</sup>

In addition, some recent studies suggest that tilt training, in addition to its diagnostic applications, can also be used as a therapeutic modality in the treatment of syncope. Tilt training generally helps patients to recognize one's own prodromal symptoms so that they are able to avoid syncope. At home, patients can lean against a wall with their feet approximately 15 cm away from the wall and increase the length of time to 30 minutes over days to weeks.<sup>126</sup> Patients should be observed by family members for safety reasons while attempting this maneuver. A recent study demonstrated that a regimen of once daily orthostatic self training for 30 minutes after an initial twice daily program was highly effective in preventing the recurrence of neurocardiogenic syncope in patients who were refractory to standard therapy.<sup>127</sup>

Finally, a bionic baroreflex system has been developed for the treatment of patients with central baroreflex failure.

This system consists of a computer-controlled negative feedback circuit that senses arterial pressure and can stimulate the sympathetic nerves in response to sudden hypotension.<sup>128</sup>

## PHARMACOLOGIC TREATMENT OF ORTHOSTATIC HYPOTENSION

In general, nonpharmacologic measures alone can benefit many patients with a mild form of OH; however, despite these measures, some patients will continue to be symptomatic. It is important to counsel patients regarding the use of nonpharmacologic measures because their effective implementation may decrease the requirement for pharmacological agents or augment drug efficacy.

Although some patients may derive great benefit from drugs that are currently available, the majority will only benefit slightly from pharmacotherapy alone. Most commonly, treatment is limited by the development of significant supine hypertension, with SBP values above 200 mm Hg, or by other drug-specific side effects. Currently, researchers have found promise in an approach that combines 2 highly beneficial agents, midodrine and selective serotonin reuptake inhibitors, which allows the OH of autonomic failure to be well controlled.<sup>12</sup> A listing of agents useful in the treatment of OH is shown in Table 6. Although many of these are used in patients with PAF, they are also used in patients with secondary causes. The most commonly used drugs are discussed in more detail.

**TABLE 6.** Pharmacotherapeutic Agents used in Orthostatic Hypotension

Fludrocortisone*
Erythropoietin (epoetin alfa)
Sympathomimetic amines
Midodrine
Ephedrine
Somatostatin analogues
Somatostatin
Octreotide
Nonsteroidal anti-inflammatory agents
Ibuprofen
Indomethacin†
Antihistamines
Selective serotonin reuptake inhibitors
Fluoxetine
Paroxetine
Other agents
Caffeine†
Vasopressin agonists
Yohimbine
Clonidine
Hydralazine
Ergotamine
Pindolol

\*Volume increasing agents.

†Nonspecific pressors to limit postprandial hypotension.

Adapted from Frishman WH, Shevell T. Drug therapy of orthostatic hypotension and vasovagal syncope. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York, NY: McGraw Hill; 1997:1231–1246.

## Fludrocortisone

Fludrocortisone (9- $\alpha$ -fluorohydrocortisone) is a potent mineralocorticoid with minimal glucocorticoid effect. It is the most important agent used for the therapy for chronic OH due to its ready availability, low cost, and demonstrated efficacy,<sup>129,130</sup> although issues have been raised about its value in children.<sup>131</sup> This drug increases blood volume by stimulating renal sodium retention. It also sensitizes the vasculature to circulating catecholamines. It requires 1–2 weeks for full action and patients will sometimes gain as much as 5–8 pounds when its effects are maximal.<sup>12</sup> Encouraging an increased dietary intake of sodium may not be sufficient to provide the “salt load” for achieving the maximal effect of fludrocortisone; consequently, 1–2 g of sodium chloride may need to be administered on a daily basis. With long-term therapy, plasma volume generally returns toward baseline, while the increase in BP is maintained.<sup>130</sup> Orally administered fludrocortisone has a half-life ranging from 1.5 to 2.5 hours; consequently, twice-daily administration may result in a more sustained effect at the mineralocorticoid receptor.<sup>132</sup> Therapy typically begins with 0.1 mg once a day and is increased at 1- to 2-week intervals that provides for an up-titration to a total dose of 1 mg/d. Most patients require 0.3–0.4 mg per day for optimal control of their symptoms.

Common side effects of fludrocortisone include hypokalemia within 2 weeks of therapy; often magnesium levels are reduced as well. Correction of hypokalemia with potassium supplementation often results in the secondary correction of hypomagnesemia. As fluid retention is crucial to the beneficial effects of the drug, supine hypertension may develop and limit its use, or preclude its use altogether in patients with congestive heart failure.<sup>130</sup> Headache is a commonly noted side effect and is more common in younger patients and in those having milder disease.<sup>12</sup> It has recently been shown that mineralocorticoid receptor stimulation can adversely affect cardiovascular structure and function,<sup>133</sup> and 1 case study has suggested that fludrocortisone might augment cardiac hypertrophy in patients with autonomic failure.<sup>134</sup> Drug interactions may also occur, and patients who use warfarin may require a substantial increase in their warfarin dose. Patients receiving fludrocortisone often note an improvement in their standing time and their overall quality of life. It is rare that the side effects from fludrocortisone are serious enough to require discontinuation of therapy.

Data supporting the value of fludrocortisone for the treatment of vasovagal syncope are extremely limited even though it is widely used and often considered one of the first line therapies. Recent studies have called into question the efficacy of fludrocortisone over placebo. Rowe et al examined the efficacy of fludrocortisone in patients with chronic fatigue syndrome and neurally-mediated hypotension and found that fludrocortisone alone was no more effective than placebo in ameliorating symptoms.<sup>135</sup> A double-blinded, randomized, placebo-controlled trial by Salim et al found that the combination of salt and fludrocortisone was ineffective in preventing recurrent syncope in children<sup>131</sup>; however, the

reliability of this study in children was limited by the relative low dose of both fludrocortisone and salt administered.

## Sympathomimetic Agents

### $\alpha_1$ -Agonists

Although increases in BP may provide a functional benefit in patients with OH, this only occurs sporadically in those treated with pressor agents such as ephedrine, pseudoephedrine and phenylpropanolamine, phenylephrine, and dextroamphetamine sulfate.<sup>6</sup> Phenylpropanolamine administration caused a significant increase in BP in patients with autonomic failure and OH.<sup>136</sup> In 2000, the Food and Drug Administration requested that phenylpropanolamine be removed from all drug products. This is based on a case-control study that showed an increased risk of hemorrhagic stroke associated with use of phenylpropanolamine.<sup>137</sup>

The  $\alpha_1$ -agonist midodrine is approved by the US Food and Drug Administration for the treatment of OH.<sup>138</sup> The drug elicits predictable increases in BP, seems to be well-tolerated, and has been shown to stimulate both arterial and venous systems without direct CNS or cardiac effects; it does not increase heart rate.<sup>139–141</sup> It has improved BP control both in patients with PAF and in patients with diabetic neuropathy. In a study of patients with neurogenic OH, midodrine increased systolic BP an average of 22 mm Hg.<sup>142</sup> In another study, patients reported improvement in presyncope/syncopal prodromal symptoms, energy level, feelings of depression, and standing time with only mild side effects reported.<sup>143</sup> The ability to stand was significantly improved with midodrine when compared with ephedrine,<sup>144</sup> and midodrine significantly reduced the rate of symptom reporting and attenuated the SBP decrease in patients with vasodepressor carotid sinus syndrome.<sup>145</sup>

Midodrine is a prodrug that is converted into the active agent desglymidodrine, and is best used to increase daytime BP. The dosage given is usually 2.5 mg at breakfast and lunch, and is increased by 2.5 mg or until a maximum dose of 30 mg; it is typically given 3 times daily. Side effects include piloerection, pruritis, and tingling of the scalp, all related to muscle contraction of integumentary hairs, and urinary hesitancy and retention in males.<sup>12</sup> Supine hypertension occurs in about 25% of patients treated with midodrine, which can be reduced by taking the final dose of midodrine at least 4 hours before bedtime.

In patients with refractory OH due to PAF, ambulatory norepinephrine infusion therapy has proven to be a promising therapeutic option.<sup>146</sup> In a recent study of patients with neurogenic OH, it was shown that a precursor of norepinephrine, L-threo-3,4-dihydroxyphenylserine (L-DOPS), could significantly increase both supine and standing BP and improve orthostatic tolerance in all study subjects. Furthermore, these BP increases were closely associated with plasma norepinephrine levels. The pressor effect resulted from the conversion of L-DOPS to norepinephrine outside the CNS.<sup>147</sup>

### $\alpha_2$ -Antagonists

Yohimbine is both a central and peripheral  $\alpha_2$ -adrenoceptor antagonist that increases BP by enhancing sympathetic



outflow centrally and augmenting norepinephrine release from postganglionic sympathetic neurons. It increases SBP and DBP, heart rate, and plasma norepinephrine in seated patients and is particularly useful in MSA syndrome or mild PAF.<sup>148</sup> The heterogeneity of its observed effects may be due to individual differences in the bioavailability of yohimbine or in its ability to block vascular  $\alpha_2$ -adrenoceptors.<sup>148,149</sup> Mosqueda-Garcia et al showed that yohimbine increased basal plasma levels of norepinephrine.<sup>150</sup> Therefore, its administration and/or use with other vasoactive medications provides a useful therapy in patients with OH.<sup>151</sup> The usual dose is 8 mg by mouth twice or thrice daily. Unwanted side effects with yohimbine include anxiety, nervousness, and diarrhea.<sup>108</sup> Other sympathomimetic agents, including clonidine and ergotamine, have been used to treat orthostasis<sup>152</sup>; ergot alkaloids produce vasoconstriction and arterial vasoconstriction which may be more beneficial for patients with OH than the “paradoxical” arterial vasoconstriction seen in patients with autonomic failure given clonidine.<sup>153</sup> The results of a trial by Shibao et al suggested that clonidine can effectively reduce BP and nighttime natriuresis in patients with supine hypertension and autonomic failure when administered before sleep; clonidine had no beneficial effect on morning symptoms of OH.<sup>154</sup> Because supine hypertension is a limiting factor for many treatments for OH, it is probable that clonidine would be useful as adjunctive therapy.

### Erythropoietin

Patients with OH in association with autonomic neuropathy frequently have a decreased red blood cell mass. This anemia is usually proportional to plasma norepinephrine levels. There is an inadequate response of erythropoietin, suggesting that its release, in part, is sympathetically driven. This decreases effective blood volume, aggravating the pre-existing hypotension.<sup>155,156</sup> It has been shown that this anemia responds dramatically to recombinant erythropoietin administered intravenously or subcutaneously.<sup>157</sup> BP also rises an average of 10 mm Hg, and although the mechanism of this increase is unclear, it is not believed to be due to an increase in either blood volume or viscosity.<sup>12</sup> Increased red blood cells are believed to be responsible for scavenging nitric oxide, thereby reducing the influence of this local vasodilator.<sup>158</sup> In a study performed in patients with various types of OH, including those with diabetes and PAF, erythropoietin was shown to increase both the hematocrit and BP and to improve the symptoms of orthostasis, especially dizziness.<sup>155</sup> Erythropoietin is administered subcutaneously in 25–75 U/kg doses 3 times per week. Although a “goal” hematocrit from this treatment has not been defined, it is suggested that it approach but not exceed gender-specific normal values.

Side effects of erythropoietin are minimal; iron deficiency that often develops from increasing the hematocrit is easily treated with oral iron supplementation. Doses of erythropoietin can usually be tapered to maintenance doses as low as 25 U/kg 2 or 3 times per week. Patients often report improvement in symptomatology, an increased appetite, and a tremendously improved sense of well-being. Although still a novel therapy tried on only a small number of patients, this

treatment strategy seems to be very effective and will no doubt undergo additional refinements as longer-acting forms of erythropoietin are introduced.

### Miscellaneous Agents

A variety of other agents have been used in the treatment of OH. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat OH, but their use is controversial and the mechanisms by which NSAIDs increase BP are not well understood. One suggested mechanism is through a decrease in vasodilatory prostanoids that may result in an increase in peripheral vascular resistance. NSAIDs also increase sensitivity to the pressor effects of angiotensin-II and norepinephrine in autonomic failure patients, and reduce sodium excretion, thereby causing volume expansion.<sup>23,159</sup>

Octreotide, a somatostatin analog, has been used to attenuate postprandial hypotension. Octreotide is a splanchnic vasoconstrictor that decreases the splanchnic pooling that follows eating.<sup>160</sup> Midodrine and octreotide, when administered together, have synergistic pressor effects that are therapeutically useful in patients with low BP as a result of autonomic neuropathy. The 2 drugs act by different mechanisms as they affect different vascular beds.<sup>161</sup> These agents might also be useful in managing vasovagal faint due to splanchnic hypervolemia during orthostatic stress.<sup>70</sup>

Antihistamines are used in mastocytosis and occasionally in diabetic dysautonomia.<sup>111</sup> Dihydroxyphenylserine is a unique, effective treatment to replace absent norepinephrine in DBH deficiency. The  $\beta$ -blocker pindolol, which has partial agonist activity, is reported to be useful in some patients, especially those with very low supine norepinephrine concentrations.<sup>162,163</sup>

## PHARMACOLOGIC TREATMENT OF VASOVAGAL SYNCOPE

Once a diagnosis of vasovagal syncope has been established (ie, via tilt table testing), patients must be counseled to avoid recognizable triggers. Patients should be sensitive to prodromal symptoms and take the necessary precautions when such symptoms occur. Salt intake should remain generous and situations avoided, where excessive volume losses are to be expected.<sup>67</sup> However, these steps are often inadequate and drug therapy is frequently required (Table 7).<sup>156</sup> Few double-blind, controlled studies exist comparing currently used medications to placebo or to one another, thus any treatment must be empiric and approached cautiously.<sup>164</sup> Low-dose  $\beta$ -blockers, such as metoprolol 50 mg twice daily, are considered to be effective because they could prevent both the excessive stimulation of ventricular mechanoreceptors and the excessive vasodilatation of arteries which are characteristic of vasovagal syncope.<sup>165</sup> However, recent studies have shown a lack of benefit with  $\beta$ -blockade for the treatment of patients with vasovagal syncope.<sup>166–168</sup>

A study by Flevari et al showed that propranolol, nadolol, and placebo were equally effective in treating vasovagal syncope as demonstrated by a decrease in the recurrence rate of vasovagal syncope and presyncope.<sup>168</sup> The recently completed Prevention of Syncope Trial (POST) was a randomized, pro-

**TABLE 7.** Drug Treatment of Recurrent Vasovagal Syncope

Current therapies
Low dose $\beta$ -blockers
Fludrocortisone
Disopyramide
Theophylline
Verapamil
Fluoxetine
Paroxetine
$\alpha$ -agonists
Midodrine
Future possibilities
Inhibitors of nitric oxide synthesis/blockade of action
Inhibitors of acetylcholine production
Theophylline regimens—in elderly
Dual chamber pacing for recurrent syncope

Adapted from Frishman WH, Shevell T. Drug therapy of orthostatic hypotension and vasovagal syncope. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York, NY: McGraw Hill; 1997:1231–1246.

spective, placebo-controlled trial of metoprolol versus placebo in vasovagal syncope prevention.<sup>169</sup> Although this study showed that metoprolol was no better than placebo in patients less than 42 years of age, the drug produced a significant decline in syncopal events in patients greater than 42 years of age. This finding suggests that there may be some age-related differences in response to therapy and other controlled studies will be necessary to elucidate the cause of these differences. If intravenous propranolol is effective in preventing neurocardiogenic syncope diagnosed during head-up tilt testing, it will predict a favorable response to oral  $\beta$ -blocker therapy.<sup>170</sup> In a study by Gielera et al, patients on continuous intravenous propranolol treatment and followed up in 1 year demonstrated a sustained improvement in tilt-induced syncope.<sup>171</sup> The recurrence rate of syncope is lowest when the efficacy of oral  $\beta$ -blocker therapy is confirmed by repeat head-up tilt testing.<sup>172</sup>

The utility of using disopyramide, because of its negative inotropic and anticholinergic properties, has not been established. A study by Morillo et al showed that disopyramide was not effective in a small, double-blind, placebo-controlled, randomized crossover trial.<sup>173</sup> Verapamil, fluoxetine,  $\alpha$ -agonists, and selective serotonin reuptake inhibitors have also been used in the treatment of vasovagal syncope with inconsistent results.<sup>67,174–178</sup> Results for selective serotonin reuptake inhibitors such as paroxetine and fluoxetine have been promising. Moffit et al, in a controlled experiment in rats were able to show that short-term fluoxetine resulted in enhancement of baroreflex control of sympathetic nervous system activity.<sup>179</sup> Furthermore, DiGirolamo et al, in a randomized controlled trial, showed that paroxetine was able to significantly improve symptoms in patients with vasovagal syncope who were unresponsive or intolerant to traditional medications.<sup>178</sup> In addition, midodrine, a selective  $\alpha$ -1 adrenergic agonist, has been shown to improve orthostatic tolerance during head-up tilt testing in patients with recurrent vasovagal syncope.<sup>180</sup>

As the possible role of adenosine and nitric oxide continues to expand as a cause of recurrent vasovagal events,

therapies may be directed toward these targets. The receptor-mediated actions of adenosine, both direct and indirect, can be antagonized by theophylline. However, many people do not tolerate this drug's adverse effects. Thus, theophylline, although not commonly used, may become more commonplace as the trigger to the vasovagal cascade focuses more on adenosine.<sup>79,181</sup> Adenosine may also be responsible for the diminished postural change in plasma renin activity in the elderly, which would be corrected after theophylline administration.<sup>182</sup> This may have important therapeutic implications for problems of orthostasis and vasovagal events in the elderly. It is further postulated that adenosine stimulates production of nitric oxide, which can cause vasodilatation and thus a fall in BP. In a study by Li et al, the addition of theophylline antagonized the production of adenosine by arterial, but not by venous endothelial cells.<sup>183</sup> In the future, the treatment of patients with vasovagal syncope may include targeting the decreased production of nitric oxide, either by inhibiting its synthesis or by blocking its action.

The utility of medical therapy to treat vasovagal syncope is unclear but many new strategies have recently become available. There are those who believe that when vasovagal syncope is associated with bradycardia or asystole, drug therapy is very effective.<sup>184</sup> Emphasis must, however, continue to be placed on the inclusion of nonpharmacologic measures into treatment plans as research on the newest pharmacologic therapy continues to unfold.

## PACEMAKER THERAPY FOR VASOVAGAL SYNCOPÉ

Expert consensus panels have recommended pacing for recurrent and refractory vasovagal syncope. Although implantation of a permanent pacemaker might seem excessively aggressive, patients who remain symptomatic despite multiple attempts at pharmacological therapy may benefit from such a procedure.<sup>185</sup> There are practical issues regarding the use of pacemakers in vasovagal syncope: (1) a pacemaker must be able to sense a syncopal event; and (2) the pacemaker must support the bradycardia and hypotension that accompany the syncope. Results of recent studies of pacemakers to prevent syncope have shown conflicting findings. Early randomized trials such as the Vasovagal Syncope International Study suggested that permanent pacing resulted in significant reduction in syncopal events.<sup>186</sup> However, more recent trials such as the Second Vasovagal Pacemaker Study (VPSII) and the Vasovagal Syncope and Pacing Trial were not able to reproduce those results, suggesting that pacemaker therapy should not be recommended as first-line treatment for patients with recurrent vasovagal syncope.<sup>187,188</sup> Alternatively, the Inotrope Controlled Pacing in Vasovagal Syncope trial by Occhetta et al, showed that dual-chamber, rate-adaptive closed loop stimulation was effective in preventing the recurrence of vasovagal syncope. They postulated that the success of their trial as opposed to VPSII may be due a different pacing algorithm as well as a difference in functional modality of the 2 types of pacemaker.<sup>189</sup> More studies in this area are required to elucidate the role of pacemakers in the treatment of recurrent vasovagal syncope.<sup>190</sup>

## CONCLUSIONS

Although there are numerous options available for the treatment of OH, only recently has the combination of agents such as fluoxetine, paroxetine, and midodrine been demonstrated to show beneficial results. Nonpharmacologic treatment, including tilt table training and moderate exercise, in addition to patient education, remains the mainstay for dealing with patients suffering from this often-incapacitating condition. Although current approaches have not yet defined the processes responsible for OH, it is hoped that research will continue to move forward and that physicians will better understand the nuances of this condition and thereby improve quality of life for patients with OH.

The utility of medical therapy to treat vasovagal syncope remains unclear.<sup>191</sup> Emphasis should continue to be placed on the inclusion of nonpharmacologic measures.

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