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# Management of Orthostatic Hypotension

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## Abstract

**PURPOSE OF REVIEW:** This article reviews the management of orthostatic hypotension with emphasis on neurogenic orthostatic hypotension.

**RECENT FINDINGS:** Establishing whether the cause of orthostatic hypotension is a pathologic lesion in sympathetic neurons (ie, neurogenic orthostatic hypotension) or secondary to other medical causes (ie, non-neurogenic orthostatic hypotension) can be achieved by measuring blood pressure and heart rate at the bedside. Whereas fludrocortisone has been extensively used as first-line treatment in the past, it is associated with adverse events including renal and cardiac failure and increased risk of all-cause hospitalization. Distinguishing whether neurogenic orthostatic hypotension is caused by central or peripheral dysfunction has therapeutic implications. Patients with peripheral sympathetic denervation respond better to norepinephrine agonists/precursors such as droxidopa, whereas patients with central autonomic dysfunction respond better to norepinephrine reuptake inhibitors.

**SUMMARY:** Management of orthostatic hypotension is aimed at improving quality of life and reducing symptoms rather than at normalizing blood pressure. Nonpharmacologic measures are the key to success. Pharmacologic options include volume expansion with fludrocortisone and sympathetic enhancement with midodrine, droxidopa, and norepinephrine reuptake inhibitors. Neurogenic supine hypertension complicates management of orthostatic hypotension and is primarily ameliorated by avoiding the supine position and sleeping with the head of the bed elevated.

## INTRODUCTION

Orthostatic hypotension is defined as a sustained reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg, usually within the first 3 minutes of standing or head-up tilt on a tilt table.[1] Thus, a diagnosis of orthostatic hypotension requires blood pressure measurements. Orthostatic hypotension is not a symptom but a sign that usually indicates volume depletion, impaired peripheral vasoconstriction, or both. When orthostatic hypotension impairs perfusion to organs above the level of the heart, most notably the brain, it causes disabling symptoms that reduce quality of life and increase morbidity and mortality.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Palma and Kaufmann discuss the unlabeled/investigational use of acarbose, ampreloxetine, atomoxetine, erythropoietin, fludrocortisone, octreotide, and pyridostigmine for the treatment of orthostatic hypotension.

Orthostatic hypotension is frequent in the elderly due to a variety of medical conditions, such as intravascular volume depletion, blood pooling (ie, varicose veins[2]), severe anemia, antihypertensive medications, and physical deconditioning; in these patients, orthostatic hypotension improves dramatically or resolves after the underlying cause is treated. In a minority of patients, orthostatic hypotension is due to reduced norepinephrine release from postganglionic sympathetic nerves, resulting in defective vasoconstriction when assuming the upright position.[1] This is referred to as *neurogenic orthostatic hypotension*[3] and is most frequently seen in patients with diabetes mellitus; neurodegenerative disorders caused by abnormal accumulation of α-synuclein (ie, synucleinopathies); and small fiber neuropathies caused by amyloid, autoimmune, or paraneoplastic diseases.[3,4] Patients with high spinal cord lesions can experience neurogenic orthostatic hypotension when sitting or when placed in an upright position for rehabilitation due to lack of baroreflex-mediated activation of spinal sympathetic neurons.[5] Complicating the management of neurogenic orthostatic hypotension is neurogenic supine hypertension, which occurs in approximately 50% of patients with neurogenic orthostatic hypotension.[6]

## EPIDEMIOLOGY AND PUBLIC HEALTH IMPACT

In the general population, the prevalence of orthostatic hypotension increases with age, and the numbers vary according to different clinical settings.[1,7,8] In large epidemiologic studies, such as the Cardiovascular Health Study, the prevalence of orthostatic hypotension in patients older than 65 years of age was approximately 20%, although only 2% had symptoms.[9] One factor influencing the high prevalence of orthostatic hypotension in the elderly is the frequency of use of antihypertensive medications.[10] Vasodilators (eg, α-adrenergic blockers, calcium channel blockers, nitrates), opioids, tricyclic antidepressants, and alcohol are frequently associated with orthostatic hypotension. In elderly patients, orthostatic hypotension frequently causes or contributes to hospitalization, and it is present in 25% of patients presenting with syncope in the emergency department.[11] The estimated orthostatic hypotension-related hospitalization rate is 36 per 100,000 adults and can be as high as 233 per 100,000 patients older than 75 years of age, with a median length of stay of 3 days and an overall in-hospital mortality rate of 0.9%.[7] In inpatient series, the prevalence of orthostatic hypotension in elderly patients is as high as 60%.[12,13] Orthostatic hypotension increases the risk of falls, cardiovascular disease, and all-cause mortality.[14-21]

Neurogenic orthostatic hypotension affects approximately 20% of unselected patients with type 1 or type 2 diabetes mellitus, but it can be as high as 65% (ie, 23 million people in the United States) with increasing age and duration of diabetes mellitus.[22-24] Neurogenic orthostatic hypotension is also common in patients with neurodegenerative synucleinopathies, disorders characterized by the abnormal accumulation of the misfolded protein α-synuclein in the central and peripheral nervous systems, such as Parkinson disease, dementia with Lewy bodies, pure autonomic failure, and multiple system atrophy. The prevalence of neurogenic orthostatic hypotension is 50% in Parkinson disease (ie, 500,000 people in the United States), 70% in multiple system atrophy, and 100% in pure autonomic failure. Other rare causes of neurogenic orthostatic hypotension include a number of genetic and autoimmune disorders. Neurogenic orthostatic hypotension is associated with

increased morbidity, including poorer prognosis[25]; development of cardiovascular,[26] renal, [26,27] and cerebrovascular disease[26,28,29]; and cognitive impairment.[28-30]

Neurogenic orthostatic hypotension occurs in up to 80% of patients with spinal cord injury resulting in quadriplegia and 50% of those with paraplegia immediately after the injury.[31] Position changes during physical therapy induce orthostatic hypotension in 74% of patients with high spinal cord injury, which is symptomatic in 59%.[31,32]

## CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

Orthostatic hypotension can be symptomatic or asymptomatic. Symptoms are a consequence of hypoperfusion of the brain (causing dizziness, lightheadedness, cognitive slowing,[33] [FIGURE 9-1] and syncope), the retina and visual pathways (causing blurry, dimmed vision), the upper body muscles (causing “coat hanger” pain), the lungs (causing fatigue and dyspnea due to hypoperfusion of the apices), and, rarely, the heart (causing angina even with patent coronary arteries). Symptoms appear exclusively upon standing up and abate when sitting and lying down. Severely afflicted patients are unable to leave the supine position without experiencing presyncopal symptoms or losing consciousness.

In patients with neurogenic orthostatic hypotension, symptoms worsen during exercise and after meals (postprandial hypotension). Marked worsening occurs after prolonged bed rest that results in striatal and myocardial muscle atrophy. These muscle changes of physical deconditioning impair both the skeletal “muscle pump” that helps venous return to the heart during active movements and left ventricular contraction reducing cardiac output.[34] Symptoms are worse in the morning because of overnight pressure natriuresis causing intravascular volume depletion in the morning.

In patients with neurogenic orthostatic hypotension, it is imperative to perform a careful neurologic examination with particular attention to subtle signs of parkinsonism or cerebellar ataxia as well as cognitive impairment or dream-enactment behavior indicative of probable rapid eye movement (REM) sleep behavior disorder. Any of these neurologic findings suggest that, in addition to autonomic failure, the patient has central nervous system (CNS) abnormalities and that autonomic failure is likely the presenting feature of a more widespread CNS synucleinopathy: Parkinson disease, dementia with Lewy bodies, or multiple system atrophy. Patients with chronic autonomic failure without motor, cognitive, or sensory symptoms receive a diagnosis of pure autonomic failure; this may remain as a restricted autonomic syndrome or patients may develop a CNS synucleinopathy years later.[4] In rare cases, patients with isolated autonomic failure have a chronic form of an autoimmune autonomic neuropathy.[35,36] If sensory symptoms accompany neurogenic orthostatic hypotension, a small fiber neuropathy should be suspected.[37] Most commonly, as in diabetes mellitus or amyloidosis, sensory symptoms are length dependent (affecting the distal areas of extremities) and can include burning pain or absent/reduced pain and temperature sensation. Less commonly, as in paraneoplastic and immune-mediated neuropathies or ganglionopathies, sensory symptoms can be patchy and diffuse, sometimes severe and widespread, resulting in devastating sensory proprioceptive ataxia.[38] A family history of

neurogenic orthostatic hypotension and sensory symptoms suggests hereditary transthyretin amyloidosis.

In patients presenting with "orthostatic intolerance" (ie, difficulty maintaining the upright position), it is necessary to determine whether symptoms are due to orthostatic hypotension or to other causes. In patients reporting typical symptoms but without a fall in blood pressure within 3 minutes of standing, a more prolonged orthostatic stress with a tilt-table test may be necessary to define the condition. Patients with milder or earlier forms of autonomic failure may experience orthostatic hypotension after a longer time of standing (ie, delayed orthostatic hypotension). In patients with vasovagal syncope, prolonged tilt may reproduce an episode.[39,40] Not infrequently, patients may present with symptoms mimicking those of orthostatic hypotension but without an identified fall in blood pressure, including patients with vestibular disorders, gait abnormalities, CNS depression from alcohol and drug use, and "the inebriationlike syndrome" (in which patients with parkinsonism report feeling imbalanced and unsteady, as if they were slightly inebriated, but unrelated to alcohol intake).[41] Conversely, patients with cognitive impairment may not accurately identify symptoms of organ hypoperfusion, despite low blood pressure when standing.[42]

If sustained orthostatic hypotension is confirmed, it is key to establish whether the cause is a pathologic lesion in sympathetic neurons (ie, neurogenic orthostatic hypotension) or if it is secondary to other medical causes (ie, non-neurogenic orthostatic hypotension), such as anemia- or dehydration-related volume depletion, excessive venous pooling sometimes aggravated by varicose veins, or medication side effects (eg, from alpha-blockers for benign prostate hyperplasia, antihypertensive agents, diuretics, tricyclic antidepressants, opioids, benzodiazepines, and antiparkinsonian agents).

TABLE 9-1 lists features that are useful to distinguish neurogenic versus non-neurogenic orthostatic hypotension. A heart rate increase of at least 0.5 beats/min for each mm Hg fall in systolic blood pressure (ie, change in heart rate [ΔHR]/change in systolic blood pressure [ΔSBP] ratio of ≥0.5 beats per minute/mm Hg) has very high sensitivity and specificity to diagnose non-neurogenic orthostatic hypotension (CASE 9-1). Conversely, a ΔHR/ΔSBP ratio of <0.5 beats per minute/mm Hg strongly suggests neurogenic orthostatic hypotension.[43]

## GENERAL PRINCIPLES OF MANAGEMENT

Because normalizing blood pressure is not possible, the goal of treatment in patients with orthostatic hypotension is to attenuate symptom burden and reduce target organ damage and mortality. Expert consensus guidelines for the treatment of neurogenic orthostatic hypotension are available.[44] Approximately 50% of patients with neurogenic orthostatic hypotension also have neurogenic supine hypertension (a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg after at least 5 minutes in the supine resting position), which poses a therapeutic challenge as treating one exacerbates the other.[6] The steps of management include correcting aggravating factors and initiating nonpharmacologic measures before using pharmacologic therapies (FIGURE 9-3).[44]

Patients with asymptomatic neurogenic orthostatic hypotension usually require education and nonpharmacologic measures only. An exception to this might be patients with cognitive impairment who might not recognize symptoms of neurogenic orthostatic hypotension.[42] Patients with hypotension-related symptoms of brain hypoperfusion do require treatment to increase standing blood pressure above the lower limit of cerebral autoregulation, ideally without aggravating neurogenic supine hypertension.[45,46] The degree of tolerable hypertension when supine is unknown.

## Correction of Aggravating Factors

Correction of aggravating factors can increase blood pressure sufficiently to improve orthostatic tolerance in some patients and should be the first step in the management of neurogenic orthostatic hypotension.

**DRUGS.—**Medications that reduce intravascular volume or trigger vasodilatation can cause or worsen orthostatic hypotension. These drugs include nitrates, tricyclic antidepressants, diuretics, calcium channel blockers, alpha-blockers (usually prescribed for benign prostatic hypertrophy), phosphodiesterase-5 inhibitors (eg, sildenafil for erectile dysfunction), centrally acting $\alpha_2$-agonists (eg, clonidine or tizanidine), and beta-blockers, as illustrated in CASE 9-1. Levodopa and dopamine agonists may also lower blood pressure, and a dose adjustment may be considered based on an individual risk-benefit assessment.[10,16,18,47]

**ANEMIA.—**Anemia of chronic disease is common in patients with neurogenic orthostatic hypotension.[48] Anemia reduces blood viscosity and oxygen-carrying capacity and, consequently, worsens orthostatic hypotension. Hemoglobin scavenges nitric oxide, which is a potent vasodilator[49]; it is therefore possible that nitric oxide-mediated mechanisms enhance vasodilation in patients with orthostatic hypotension and anemia.[50] Therefore, anemia must be investigated and treated appropriately. Increasing the red cell mass with recombinant erythropoietin improves orthostatic hypotension.[51]

## Nonpharmacologic Management

Patient education on nonpharmacologic measures is the cornerstone of successful management of orthostatic hypotension. Nonpharmacologic treatments for orthostatic hypotension are listed in TABLE 9-2.[52-54]

**LIFESTYLE, PHYSICAL ACTIVITY, AND MEALS.—**Hot, humid weather and environments cause vasodilatation and exacerbate orthostatic intolerance. Consequently, hot showers and saunas should be avoided. Short periods of bed rest worsen neurogenic orthostatic hypotension by causing cardiovascular deconditioning. The symptomatic burden can result in reluctance to stand up and avoidance of physical activity; physical immobility and skeletal muscle loss, in turn, worsen the severity of orthostatic hypotension. This results in a vicious cycle of deconditioning.[55] It is therefore important for patients not to stop exercising, but to exercise in a recumbent or seated position (eg, using a stationary bicycle or a rowing machine) as those positions are better tolerated than the standing position. Exercise in a swimming pool is recommended, as the hydrostatic pressure of water counteracts the gravity-induced fall in blood pressure and improves orthostatic tolerance. Of note, patients

must be very careful when getting out of the swimming pool, as the sudden decrease of hydrostatic pressure when exiting the pool can trigger venous pooling and worsen symptoms of orthostatic hypotension.

Food digestion is associated with blood pooling within the gastrointestinal (splanchnic) circulation.[56] Normally, this is compensated for by increases in sympathetic nerve traffic causing splanchnic vasoconstriction. In patients with neurogenic orthostatic hypotension, however, vasoconstriction is deficient, and some patients become hypotensive within 2 hours of eating.[1,57] This is referred to as postprandial hypotension, and it is particularly pronounced after high glycemic index carbohydrate-rich meals. Low glycemic index carbohydrates are preferable, and frequent smaller meals should be implemented. Alcohol should be avoided during the daytime as it is a vasodilator. Alternatively, a high-carbohydrate treat or a glass of alcohol can be reserved for before bedtime, as these could contribute to managing supine hypertension.

**VOLUME EXPANSION.—**Less intravascular volume causes reduced circulating blood volume and aggravates the blood pressure drop when standing. This is particularly relevant in elderly patients who are chronically volume depleted.[58] It is important that patients and families understand the diuretic effects of caffeine and alcohol, a potent vasodilator. Patients should avoid sugary beverages (eg, sodas, bottled juices) as high glycemic index carbohydrates can induce or worsen hypotension.[59] Water and salt liberalization are necessary to expand intravascular volume. Ideally, daily fluid intake should be 2 L to 2.5 L of water. In patients with neurogenic orthostatic hypotension, bolus water drinking (500 mL [16 oz]) produces a marked increase in blood pressure.[60,61] Bolus water drinking has a fast pressor effect (the blood pressure increases within 5 to 10 minutes), which can be useful as a rescue measure, although the effect is relatively short (30 to 45 minutes). Patients should increase salt intake by adding 1 teaspoon of salt to a healthy diet. Some patients prefer using salt tablets (0.5 g to 1.0 g), although they may cause abdominal discomfort.

**PHYSICAL COUNTERMANEUVERS.—**A number of physical countermaneuvers can help maintain blood pressure and reduce orthostatic symptoms during daily activities, including leg crossing, standing on tiptoes, stooping, squatting, and buttock clenching.[52] Making sure that patients understand the effect of gravitational fluid shifts on blood pressure and orthostatic symptoms is key. Patients should be instructed to change positions gradually and briefly sit before standing. Straining with a closed glottis and other Valsalva-like maneuvers cause a sudden and severe fall in blood pressure and should be avoided.

**COMPRESSION GARMENTS.—**Elastic compression stockings apply counterpressure to the lower limbs and abdomen, reducing venous pooling.54 High-waist stockings producing at least 15 mm Hg to 20 mm Hg compression are effective to increase venous return and increase blood pressure. However, a major problem with the use of compression stockings is noncompliance. Elderly patients, patients with movement disorders, and those with sensory neuropathy may struggle to put the stockings on, which limits their applicability in everyday life.61 Elastic abdominal binders can be a good alternative.[53,62] A recently developed abdominal binder that inflates automatically only on standing and provides sustained

splanchnic venous compression (40 mm Hg) showed promising results in patients with neurogenic orthostatic hypotension.63

**SLEEPING WITH THE HEAD OF THE BED RAISED.—**Neurogenic supine hypertension is frequent in patients with neurogenic orthostatic hypotension.6 It is a side effect of antihypotensive treatment, but it also occurs in untreated patients. Managing neurogenic supine hypertension in patients with neurogenic orthostatic hypotension can be challenging, as treating one usually exacerbates the other. During the daytime, the best treatment is to avoid the supine position. Patients can sit in a reclining chair with their feet on the floor if they need to nap or rest. At night, elevating the head of the bed at least 30 to 45 degrees (accomplished with an electric bed or mattress) is effective to lower the blood pressure.64 Avoiding nocturnal supine hypertension with postural changes reduces the exaggerated nocturnal diuresis and natriuresis characteristic of these patients, therefore reducing the overnight fluid loss and ameliorating orthostatic hypotension in the morning. The use of pressor agents should be avoided within at least 4 hours before bedtime. Eating high glycemic index carbohydrate snacks or drinking a glass of wine right before going to bed contributes to hypotension and can therefore be harnessed to decrease nocturnal supine hypertension.

## Pharmacologic Management

Despite removal of aggravating factors and implementing nonpharmacologic methods, many patients remain symptomatic and require pharmacologic treatment.44 Current pharmacologic approaches are based on two complementary strategies: (1) expanding intravascular volume with fludrocortisone and (2) increasing peripheral vascular resistance with midodrine, droxidopa, or norepinephrine reuptake inhibitors. Selection of one strategy or the other or both strategies depends on the specific features and needs of each patient as well as the degree of peripheral sympathetic denervation. Pharmacologic strategies can be combined (TABLE 9-3). When medications for neurogenic orthostatic hypotension are implemented, patients should be taught to avoid the horizontal position, sleep with the head of the bed raised 30 to 45 degrees, and measure their own blood pressure. They should provide a series of blood pressure recordings taken over several days to their clinician, including blood pressure taken when supine, sitting, and standing upon awakening; before and 1 hour after lunch; and before retiring to bed. Alternatively, ambulatory blood pressure monitors can be employed. Ambulatory monitors also measure blood pressure during sleep and can define the circadian blood pressure patterns before and after pharmacologic treatment.

**LOCALIZING THE LESION.—**When planning therapeutic strategies in patients with neurogenic orthostatic hypotension, localization of the autonomic lesion is important and has therapeutic implications (TABLE 9-4). Peripheral sympathetic neurons are affected in Lewy body disorders (Parkinson disease, dementia with Lewy bodies, pure autonomic failure) as well as in amyloidosis and autoimmune autonomic neuropathies but typically are spared in multiple system atrophy. More accurate than the clinical diagnosis is to determine the degree of sympathetic denervation by measuring plasma norepinephrine levels. Because norepinephrine is released by postganglionic sympathetic neurons, low levels of plasma

norepinephrine in a patient with neurogenic orthostatic hypotension indicates sympathetic denervation (ie, a peripheral lesion), whereas normal or elevated norepinephrine levels indicate decentralization (ie, a central lesion),65 although considerable overlap exists. Determination of norepinephrine levels should be made in patients who are not taking norepinephrine precursor or reuptake inhibitors.

**VOLUME EXPANSION.—**Two strategies can be used to expand intravascular volume in patients with orthostatic hypotension: fludrocortisone and erythropoietin.

**FLUDROCORTISONE.:** Fludrocortisone is a synthetic mineralocorticoid that increases renal sodium and water reabsorption, therefore expanding intravascular volume and increasing blood pressure in all positions. It also enhances the pressor effect of adrenergic agonists. Fludrocortisone is perhaps the most frequently prescribed agent for the treatment of orthostatic hypotension despite the fact that it is not approved by the US Food and Drug Administration (FDA) for this indication. Because activation of renal mineralocorticoid receptors results in inflammation and fibrosis and may have a direct nephrotoxic effect leading to a faster decline in renal function and hypertension,[66] fludrocortisone should be used with extreme caution in the treatment of orthostatic hypotension, preferably for short-term periods, and the dosage should never be higher than 0.2 mg/d. Higher dosages do not improve therapeutic effects but intensify side effects. Fludrocortisone usually requires at least 7 days of treatment to exert significant clinical effect. Short-term side effects are frequent and include supine hypertension, hypokalemia, and ankle edema.[67] Patients receiving fludrocortisone must eat potassium-rich foods or take potassium supplements (potassium chloride 20 mEq/d) to reduce the risk of hypokalemia. Long-term use exacerbates hypertension and organ damage,[66] including left ventricular hypertrophy[68] and renal failure,[66] and is associated with a higher risk of all-cause hospitalization in patients with orthostatic hypotension.[69]

**ERYTHROPOIETIN.:** It is important to test for and treat anemia as it is common in patients with cardiovascular autonomic failure and frequently contributes to hypotension.[48,51] If anemia is deemed to be idiopathic (ie, anemia of chronic disease), treatment with erythropoietin should be considered. Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with orthostatic hypotension. Recombinant human erythropoietin is administered subcutaneously at doses between 25 U/kg and 75 U/kg 3 times a week until the patient's hematocrit returns to normal levels. Lower maintenance doses (25 U/kg 3 times a week) may then be used. Concurrent iron supplementation is typically required during the period when the hematocrit is increasing.

**SYMPATHETIC ENHANCEMENT.—**Commonly used pharmacologic strategies to induce vasoconstriction and increase peripheral vascular resistance include the $\alpha_1$-adrenoceptor agonist midodrine, the norepinephrine precursor droxidopa, and norepinephrine reuptake inhibitors.

**MIDODRINE.:** Midodrine is an oral prodrug converted peripherally into the active metabolite desglymidodrine, a selective $\alpha_1$-adrenoceptor agonist that constricts arteriolar and venous vasculature, thus increasing blood pressure. The FDA approved midodrine in

1996 for the treatment of symptomatic orthostatic hypotension after clinical trials showed efficacy to increase standing blood pressure and improve orthostatic tolerance.[70] As with other drugs for orthostatic hypotension, administration of midodrine increases blood pressure in all positions. In contrast to fludrocortisone, midodrine is a short-acting agent. Standing systolic blood pressure increases by 10 mm Hg to 30 mm Hg approximately 1 hour after a 10-mg dose, with some effect persisting up to 3 hours. Treatment should begin with 2.5 mg or 5 mg, which can then be increased up to 10 mg 3 times a day. As with other pressor agents, supine hypertension is common with midodrine; hence, patients should not take it within 3 to 4 hours before bedtime. Other common side effects are piloerection (goose bumps), scalp itching, and urinary retention. Midodrine has no effect on heart rate as it does not stimulate cardiac β-adrenergic receptors and, owing to its poor diffusion across the blood-brain barrier, has no CNS side effects.

**DROXIDOPA.:** Droxidopa is an oral synthetic amino acid that converts to norepinephrine.[71] Droxidopa is decarboxylated to norepinephrine by the enzyme aromatic L-amino acid decarboxylase, the same enzyme that converts levodopa to dopamine. Conversion of droxidopa to norepinephrine occurs in the remaining sympathetic postganglionic terminals as well as in non-neuronal tissues, particularly the kidney.[72] Droxidopa was approved in Japan in 1989 for the treatment of neurogenic orthostatic hypotension in hereditary amyloidosis, Parkinson disease, and multiple system atrophy.[71] The FDA approved droxidopa in 2014 after clinical trials showed its efficacy to improve symptoms of orthostatic dizziness, lightheadedness, or “feeling about to faint” in adult patients with symptomatic neurogenic orthostatic hypotension caused by Parkinson disease, multiple system atrophy, pure autonomic failure, and other rare disorders affecting norepinephrine production, such as dopamine β-hydroxylase deficiency characterized by defective norepinephrine release from sympathetic nerves upon standing.[73-76]

Similar to midodrine, droxidopa is a short-acting agent (FIGURE 9-4[77,78]). The peak pressor response occurs within approximately 3.5 hours after oral administration. The recommended dosage varies from 100 mg to 600 mg up to 3 times a day. To identify the best dose for each patient, supervised titration by a clinician is recommended.[79,80] Although in clinical trials droxidopa was administered 3 times a day, clinical experience shows that the dose of droxidopa should be individualized to each patient’s needs, taking into account when the patient is standing and active. For example, in a patient with a movement disorder and orthostatic hypotension who is active for only a few hours in the morning (eg, showering, preparing breakfast), it is reasonable to use a single morning droxidopa dose and skip the afternoon and evening doses. Other patients with different needs may receive droxidopa only 2 times a day or take a higher dose in the morning with lower doses in the afternoon and evening. The most robust pressor response occurs in patients with low plasma norepinephrine levels, indicating loss of peripheral sympathetic neurons.[65] A supine plasma norepinephrine level lower than 220 pg/mL in patients with neurogenic orthostatic hypotension has high sensitivity and specificity to predict a pressor response to droxidopa.[65]

Droxidopa may be less effective in patients with neurogenic orthostatic hypotension and parkinsonism receiving high dosages of carbidopa (higher than 200 mg/d) as carbidopa blocks the conversion of droxidopa to norepinephrine.[75,76,78,79] The most common side

effects of droxidopa are hypertension, headache, and nausea. Although no specific studies have been done, concomitant use of droxidopa with norepinephrine reuptake inhibitors (eg, atomoxetine, venlafaxine) or adrenergic agonists (eg, midodrine) may enhance the pressor effect; caution is advised.

**NOREPINEPHRINE REUPTAKE INHIBITORS.:** An emerging approach in the treatment of neurogenic orthostatic hypotension is the use of inhibitors of the norepinephrine membrane transporter, which inhibit norepinephrine reuptake and increase its availability in the neurovascular junction.

In healthy subjects, norepinephrine reuptake inhibition has little effect on blood pressure. Although norepinephrine reuptake inhibitors enhance noradrenergic vasoconstriction at the level of the sympathetic postganglionic fibers, this is counteracted by norepinephrine-mediated stimulation of central $\alpha_2$-receptors in the CNS, which has a vasodilator effect. However, in patients with central autonomic dysfunction, norepinephrine reuptake inhibitors result in only peripheral vasoconstriction, making them particularly suitable for patients with multiple system atrophy.

Short-term controlled clinical trials have shown that atomoxetine (10 mg to 18 mg, 2 times a day), a short-acting norepinephrine reuptake inhibitor, increases standing blood pressure and reduces the burden of symptoms compared to placebo in patients with neurogenic orthostatic hypotension.[81-83] The higher the norepinephrine level, the greater the pressor effect and symptomatic improvement with atomoxetine, which makes it a particularly attractive option for patients with neurogenic orthostatic hypotension caused by autonomic decentralization (eg, multiple system atrophy).[84] A multicenter controlled trial to confirm the efficacy of atomoxetine in patients with neurogenic orthostatic hypotension is under way.[85] A phase 2 trial with ampreloxetine (TD-9855), a long-acting investigational norepinephrine reuptake inhibitor, showed that this compound was safe and increased blood pressure and orthostatic tolerance in patients with neurogenic orthostatic hypotension; a large multicenter phase 3 study to confirm its efficacy is ongoing.[86]

Conversely, lower supine plasma norepinephrine levels appear to predict a greater symptomatic and pressor response to droxidopa, a synthetic oral norepinephrine precursor.[65] These responses can be explained by denervation supersensitivity of adrenergic receptors.[87] Consequently, patients with low plasma norepinephrine levels (usually seen in Lewy body disorders [CASE 9-2] or peripheral autonomic neuropathies) may respond better to droxidopa and midodrine,[65] whereas patients with normal or high norepinephrine levels (usually multiple system atrophy) may respond better to norepinephrine reuptake inhibitors.

In patients with refractory neurogenic orthostatic hypotension, norepinephrine reuptake inhibition could theoretically be combined with droxidopa or midodrine, with or without fludrocortisone or pyridostigmine. However, no safety data are available on the combined use of most of these agents, and extreme caution is advised.

**OTHER MEDICATIONS.—**Pyridostigmine, a cholinesterase inhibitor, enhances cholinergic neurotransmission in sympathetic and parasympathetic ganglia. A double-blind

study showed that pyridostigmine increases systolic blood pressure, on average, by only 4 mm Hg.[88] The combination of 5 mg midodrine with 60 mg pyridostigmine was slightly more effective than pyridostigmine alone. Similarly, the combination of pyridostigmine with atomoxetine appears to have a synergistic effect to increase blood pressure and improve orthostatic tolerance.[89]

## POSTPRANDIAL HYPOTENSION

Hypotension after meals regularly occurs in patients with sympathetic failure and can be its only manifestation, even in patients without overt orthostatic hypotension.[90] Postprandial hypotension is defined as a fall of at least 10 mm Hg in systolic blood pressure within 2 hours of eating.[1,56,57,90,91] Management starts by eating smaller and more frequent meals with low carbohydrate content and avoiding alcohol. Drugs that delay or block the release of insulin, a known vasodilator, such as the α-glucosidase inhibitor acarbose (50 mg to 100 mg before meals), decrease gastrointestinal absorption of glucose and are useful to treat postprandial hypotension (CASE 9-3).[59] Midodrine taken right before or during meals may also help. The somatostatin analogue octreotide induces vasoconstriction of splanchnic vessels; it is administered subcutaneously (0.2 mcg/kg to 0.4 mcg/kg) and is very effective to attenuate postprandial hypotension, although it can induce nausea and abdominal pain.[92]

## NEUROGENIC SUPINE HYPERTENSION

The prevalence of neurogenic supine hypertension is 30% to 50% in Parkinson disease, 40% in multiple system atrophy, and 50% to 70% in pure autonomic failure. The frequency of neurogenic supine hypertension in diabetes mellitus and amyloid neuropathy is unknown.[6]

Treatment of supine hypertension focuses on reducing blood pressure to lower the risk of target organ damage without worsening hypotension. Achieving this goal is challenging. Patients should avoid the supine position. For daytime naps, patients should sit in a reclining chair with their feet on the floor. At night, tilting the head of the bed to a 30- or 45-degree angle lowers blood pressure.[64] This is best accomplished with an electric bed or mattress. A carbohydrate-rich snack or an alcoholic drink before bedtime lowers blood pressure. The application of an abdominal heating pad to lower blood pressure by inducing splanchnic vasodilation is being currently studied in a clinical trial.[93]

In patients with severe prolonged supine hypertension at night despite elevation of the head of the bed (systolic blood pressure of at least 180 mm Hg or diastolic blood pressure of at least 110 mm Hg), short-acting antihypertensives (eg, captopril 25 mg, losartan 50 mg, or nitroglycerin patch 0.1 mg/h) at bedtime could be considered, particularly in patients who already have target organ damage, although none of these approaches has been studied in large controlled trials.[94-96] Patients should be advised about the augmented risk of hypotension and falls if they stand up at nighttime (eg, to urinate). To avoid this, the use of a urinal or bedside commode should be encouraged.

## CONCLUSION

Orthostatic hypotension is a disabling disorder that occurs frequently in the elderly as a consequence of drug effects, volume depletion, or cardiovascular deconditioning. Neurogenic orthostatic hypotension is common in patients with diseases affecting central or peripheral sympathetic neurons. Patients with orthostatic hypotension with no or minor symptoms can be treated with nonpharmacologic measures only. Patients with a moderate burden of symptoms typically require a combination of nonpharmacologic and pharmacologic therapies (eg, the synthetic mineralocorticoid fludrocortisone and the pressor agents midodrine, droxidopa, or atomoxetine).

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RELATIONSHIP DISCLOSURE:

Dr Palma serves as managing editor for *Clinical Autonomic Research* and as a consultant for Biogen, Dr Reddy's Laboratories Ltd, Lundbeck, and PTC Therapeutics. Dr Palma receives research/grant support from the Familial Dysautonomia Foundation, Inc; the Michael J. Fox Foundation for Parkinson's Research; the Multiple System Atrophy Coalition; and the National Institute of Neurological Disorders and Stroke (R01NS107596, U54NS065736). Dr Kaufmann serves as editor-in-chief of *Clinical Autonomic Research* and as a consultant for and on the scientific advisory boards of Biogen, Biohaven Pharmaceuticals, Lundbeck, and Pfizer Inc. Dr Kaufmann receives research/grant support from the Familial Dysautonomia Foundation, Inc; the Michael J. Fox Foundation for Parkinson's Research; the Multiple System Atrophy Coalition; the National Institutes of Health (R01HL103988, U54NS065736); Theravance Biopharma; and the US Food and Drug Administration (FDR3731-01) and publishing royalties from UpToDate, Inc. Dr Kaufmann has served as an expert witness for the Department of Justice regarding the alleged relationship between human papilloma virus vaccination and autonomic disorders.

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## KEY POINTS

- Diagnosing orthostatic hypotension requires blood pressure measurements. The presence of orthostatic intolerance is not sufficient or necessary to diagnose orthostatic hypotension.
- Orthostatic hypotension is very common in the elderly, usually due to drug effects, volume depletion, or cardiovascular deconditioning.
- Neurogenic orthostatic hypotension is a feature of neurologic disorders affecting sympathetic pathways, including diabetes mellitus, neurodegenerative synucleinopathies, and amyloid neuropathies.
- Exercise, meals (postprandial hypotension), prolonged bed rest (physical deconditioning), and hot and humid environments typically worsen symptoms of neurogenic orthostatic hypotension.
- Patients with cognitive impairment may not accurately identify symptoms of orthostatic hypotension, despite low blood pressure when standing.
- A heart rate increase of at least 0.5 beats/min for each 1 mm Hg fall in systolic blood pressure (ΔHR/ΔSBP ratio ≥0.5 beats per minute/mm Hg) is sensitive and specific to diagnose non-neurogenic orthostatic hypotension.
- Treatment of orthostatic hypotension should be geared to the patients' symptoms and their impact on daily function rather than a target blood pressure.
- The initial treatment of orthostatic hypotension focuses on nonpharmacologic measures first: removing offending medications, increasing salt and fluid intake, using compression garments, and instituting physical maneuvers and exercise.
- Drugs that reduce intravascular volume (eg, diuretics) or induce vasodilatation (eg, α-adrenergic blockers, nitrates, phosphodiesterase-5 inhibitors, tricyclic antidepressants, centrally acting α-adrenergic agonists) exacerbate orthostatic hypotension and worsen symptoms; thus, they should be reduced or discontinued.
- In patients with orthostatic hypotension, anemia should be investigated and treated.
- Because carbohydrate-rich meals trigger insulin, a potent vasodilator, patients with neurogenic orthostatic hypotension should reduce carbohydrate content, eat smaller and more frequent meals, and choose low glycemic index carbohydrates.
- Bolus water drinking produces a marked, albeit short-lived, increase in blood pressure in patients with neurogenic orthostatic hypotension.

- Waist-high compression stockings are effective to increase blood pressure in patients with neurogenic orthostatic hypotension, although compliance is very low. Elastic abdominal binders are a good alternative.
- Sleeping with the head of the bed raised 30 to 45 degrees reduces nocturnal hypertension, thus decreasing natriuresis, which, in turn, prevents volume depletion overnight and improves orthostatic tolerance the next morning.
- When medications for neurogenic orthostatic hypotension are used, patients should be taught to avoid the flat position, sleep with the head of the bed raised 30 to 45 degrees, and measure their own blood pressure.
- Determining the site of the autonomic lesion (central versus peripheral) in patients with neurogenic orthostatic hypotension has important therapeutic implications. Patients with central autonomic dysfunction (ie, decentralization) have a more pronounced pressor response to norepinephrine reuptake inhibitors, whereas patients with peripheral autonomic dysfunction (ie, denervation) have a more pronounced pressor response to norepinephrine enhancers and agonists.
- For patients who still remain symptomatic despite nonpharmacologic measures, stepwise pharmacologic treatment begins with low-dose fludrocortisone (0.1 mg/d), particularly in patients with volume depletion.
- Frequently used fludrocortisone dosages range from 0.05 mg/d to 0.2 mg/d. There is little benefit in increasing fludrocortisone to dosages higher than 0.2 mg/d. Common short-term side effects include hypokalemia; long-term side effects include left ventricular hypertrophy and renal failure.
- In patients with anemia of chronic disease and orthostatic hypotension, subcutaneous recombinant human erythropoietin increases blood pressure and improves orthostatic tolerance.
- When starting droxidopa, a careful titration is required to identify the best dose for each patient and prevent excessive supine hypertension.
- Treatment with norepinephrine reuptake inhibition is emerging as a potentially effective option for patients with neurogenic orthostatic hypotension, particularly those with autonomic dysfunction from damage to the central nervous system (eg, decentralization).
- Pyridostigmine alone has little effect to increase blood pressure. It appears to have synergistic effects when combined with midodrine or atomoxetine.
- Neurogenic supine hypertension is best treated with postural measures, ie, avoiding the flat position and sleeping with the head of the bed raised 30 to 45 degrees with the help of an electric bed or mattress. In patients with refractory supine hypertension and high risk of organ damage, short-acting antihypertensives at bedtime might be considered.

**CASE 9-1**

A 72-year-old man presented with a 6-month history of orthostatic lightheadedness, which he first noticed after mild exercise. Lightheadedness was often accompanied by blurry vision and a dull pain in both shoulders and the back of his neck, shortness of breath, and, rarely, chest discomfort. He was taking furosemide 40 mg/d for "swollen legs," amitriptyline 200 mg/d for depression, diazepam 5 mg 3 times a day for anxiety, and tamsulosin 0.8 mg in the morning for benign prostatic hyperplasia.

His neurologic examination was normal. His blood pressure in the supine position was 139/91 mm Hg with a heart rate of 89 beats/min. After 3 minutes standing, his blood pressure fell to 79/48 mm Hg with a heart rate of 123 beats/min, and he was severely lightheaded (change in heart rate [ΔHR]/change in systolic blood pressure [ΔSBP] ratio of 0.56 beats per minute/mm Hg) (FIGURE 9-2).

His ECG, complete blood cell count, and metabolic panel were normal. His plasma norepinephrine level when supine was normal at 198 pg/mL and increased to 491 pg/mL after 3 minutes of standing. The patient was instructed to discontinue furosemide and tamsulosin and switch amitriptyline to fluoxetine 20 mg/d.

At 4-week follow-up, his blood pressure in the supine position was 142/87 mm Hg with a heart rate of 81 beats/min. After 3 minutes of standing, his blood pressure was 131/79 mm Hg with a heart rate of 92 beats/min. He was asymptomatic.

**COMMENT**

This is a case of non-neurogenic orthostatic hypotension, a problem frequently caused by drugs with well-known hypotensive side effects, including the diuretic furosemide, the α-adrenergic blocker tamsulosin, and the tricyclic antidepressant amitriptyline. General physical and neurologic examination are normal, with the exception of severe orthostatic hypotension with a significant increase in heart rate, a ΔHR/ΔSBP ratio above 0.5 beats per minute/mm Hg, and plasma norepinephrine levels that more than doubled upon standing up.

**CASE 9-2**

A 68-year-old woman with Parkinson disease presented with a 9-month history of dizziness, lightheadedness, and shortness of breath after walking for 100 yards and climbing stairs. She had been diagnosed with Parkinson disease 2 years earlier and was taking carbidopa/levodopa 25 mg/100 mg 3 times a day with excellent response and remaining very active.

Her blood pressure in the supine position was 148/92 mm Hg with a heart rate of 69 beats/min. After 3 minutes in the standing position, her blood pressure was 84/59 mm Hg with a heart rate of 71 beats/min (change in heart rate [ΔHR]/change in systolic blood pressure [ΔSBP] ratio of 0.03 beats per minute/mm Hg), and she reported feeling severely dizzy and lightheaded (FIGURE 9-5). ECG, complete blood cell count, and metabolic panel were normal. Autonomic testing confirmed neurogenic orthostatic hypotension with plasma norepinephrine levels of 102 pg/mL when supine and 138 pg/mL when standing.

She was educated on nonpharmacologic measures, including liberalization of salt and water intake, wearing compression garments (waist-high stockings), and sleeping with the head of the bed raised 30 to 45 degrees with the help of an electric bed or mattress.

She returned 2 months later reporting symptomatic improvement, although she still reported dizziness when standing for a few minutes. Her blood pressure in the supine position was 147/82 mm Hg with a heart rate of 69 beats/min. After 3 minutes in the standing position, her blood pressure was 91/79 mm Hg with a heart rate of 72 beats/min, and she reported feeling moderately dizzy and lightheaded.

Based on her low plasma norepinephrine levels indicating postganglionic sympathetic denervation, an in-office titration with droxidopa was performed, after which the patient was started on 300 mg 3 times a day and reminded to avoid the supine position and sleep with the head of the bed raised 30 to 45 degrees. She returned 1 month later reporting a significant abatement in her symptoms. Her blood pressure in the supine position was 151/92 mm Hg with a heart rate of 68 beats/min. After 3 minutes in the standing position, her blood pressure was 101/81 mm Hg with a heart rate of 72 beats/min and she remained asymptomatic.

**COMMENT**

Symptomatic neurogenic orthostatic hypotension afflicts approximately 20% of patients with Parkinson disease. The neurogenic origin of orthostatic hypotension was confirmed in this patient by a ΔHR/ΔSBP ratio below 0.5 beats per minute/mm Hg and a blunted norepinephrine release when standing up. The stepwise approach for patients with neurogenic orthostatic hypotension begins with nonpharmacologic measures and, when these are not sufficient, implementing pharmacologic therapy. Droxidopa, a synthetic norepinephrine precursor, was expected to produce a pressor response in this patient given her low plasma norepinephrine levels indicative of peripheral sympathetic denervation, and as anticipated, it resulted in significant symptomatic improvement.

**CASE 9-3**

A 63-year-old man presented for evaluation 10 days after an episode of brief unresponsiveness and collapse. After a large and typical Thanksgiving dinner, he stood up, walked a few steps, and suddenly collapsed to the floor. He was unresponsive but came to in a few seconds, startled but not confused. His wife was with him and reported that he had no involuntary movements, loss of urine, or tongue biting. He was taken by ambulance to a local hospital, where his blood pressure was 160/95 mm Hg. ECG, echocardiogram, complete blood cell count, metabolic panel, urinalysis, and a 24-hour Holter monitor were normal. He was diagnosed at that hospital with arterial hypertension, and antihypertensive treatment was recommended, which he did not take.

On questioning during the current visit, he recalled having brief episodes of mild lightheadedness and blurry vision when standing up after meals, mostly after breakfast, for about 2 years. His wife measured his blood pressure on one of these occasions, and it was approximately 80/60 mm Hg. His symptoms abated after sitting or lying down, and he had never lost consciousness until the episode that took him to the hospital. He reported moderate constipation, erectile dysfunction, and nocturia.

On physical examination, he appeared healthy. He had preserved cognition, intact cranial nerves, normal deep tendon reflexes, flexor plantar responses, and no sensory deficits. His supine blood pressure was 157/102 mm Hg with a heart rate of 72 beats/min and after standing for 3 minutes was 119/75 mm Hg with a heart rate of 79 beats/min (change in heart rate [ΔHR]/change in systolic blood pressure [ΔSBP] ratio of 0.18 beats per minute/mm Hg). He had no orthostatic symptoms in the office.

He was given an ambulatory 24-hour blood pressure monitor, which showed symptomatic drops in blood pressure associated with breakfast, lunch, and dinner, consistent with postprandial hypotension (FIGURE 9-6). After these findings were reviewed, the patient was contacted over the phone and instructed to eat smaller and more frequent meals, to decrease carbohydrate-rich meals during daytime, and to start taking acarbose 100 mg before breakfast, lunch, and dinner for the off-label indication of lessening his postprandial hypotension. He was instructed to recognize symptoms of orthostatic hypotension, to quickly sit down to prevent syncope, and to follow nonpharmacologic measures to increase his orthostatic tolerance. One month later, the patient came for a follow-up visit reporting marked improvement in his postprandial symptoms.

**COMMENT**

This patient had asymptomatic neurogenic orthostatic hypotension in the office (his blood pressure fell 38/27 mm Hg and his ΔHR/ΔSBP ratio was below 0.5 beats per minute/mm Hg) with supine hypertension. He became symptomatic only after meals, consistent with postprandial hypotension. His autonomic failure (orthostatic hypotension, constipation, erectile dysfunction, bladder dysfunction) in the absence of motor or sensory deficits is suggestive of pure autonomic failure. Treatment of postprandial hypotension includes reducing high glycemic index carbohydrates, eating smaller and more frequent meals, and using the α-glucosidase inhibitor acarbose. These patients require close follow-up as

they may develop worsening symptoms of orthostatic hypotension at times other than after meals.

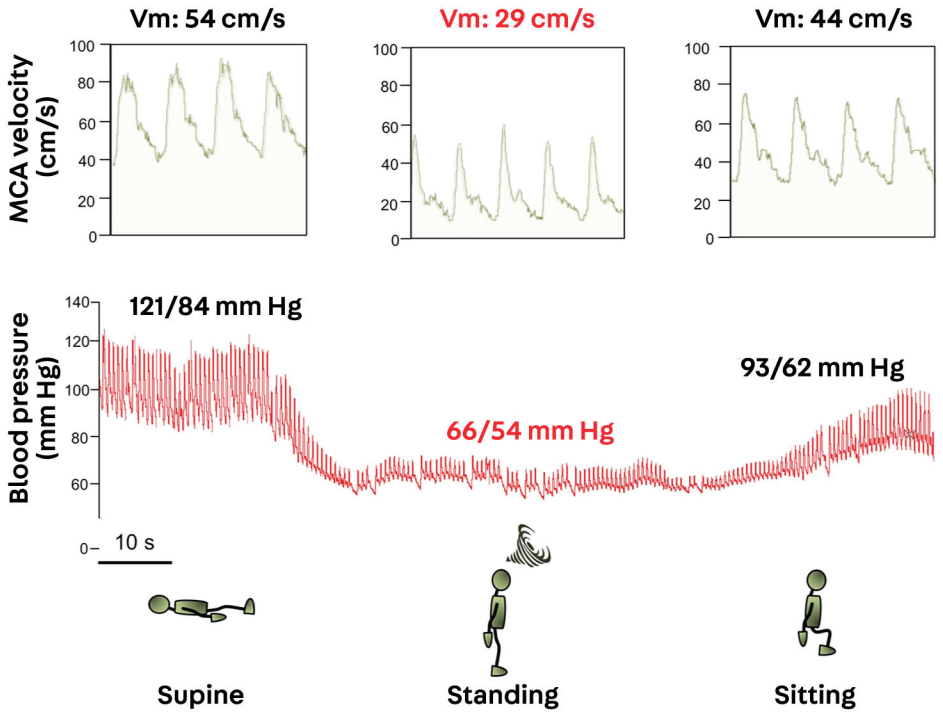


**FIGURE 9-1.**

Blood pressure and cerebral blood flow in a patient with neurogenic orthostatic hypotension. The upper tracing shows blood flow velocity as measured by middle cerebral artery (MCA) transcranial Doppler ultrasound, which indicates cerebral blood flow. The lower tracing shows continuous blood pressure acquired with plethysmography. When the patient is in the supine position, both blood pressure (121/84 mm Hg) and mean velocity (Vm) of MCA blood flow (54 cm/s) are normal. When the patient stands up, blood pressure plummets rapidly to 66/54 mm Hg and cerebral blood flow falls by nearly 50% (Vm, 29 cm/s). The patient becomes symptomatic, feels lightheaded and about to faint, and is unable to remain standing. Patient sits down and his blood pressure increases to 93/62 mm Hg. Although this blood pressure is still low, the patient is not symptomatic anymore because the Vm increased to 44 cm/s, indicating almost normal cerebral blood flow. The blood pressure of a patient with symptomatic orthostatic hypotension does not have to return to normal values for the patient to become asymptomatic but only to increase above the lower limit of cerebral autoregulation.

Vm = mean velocity.

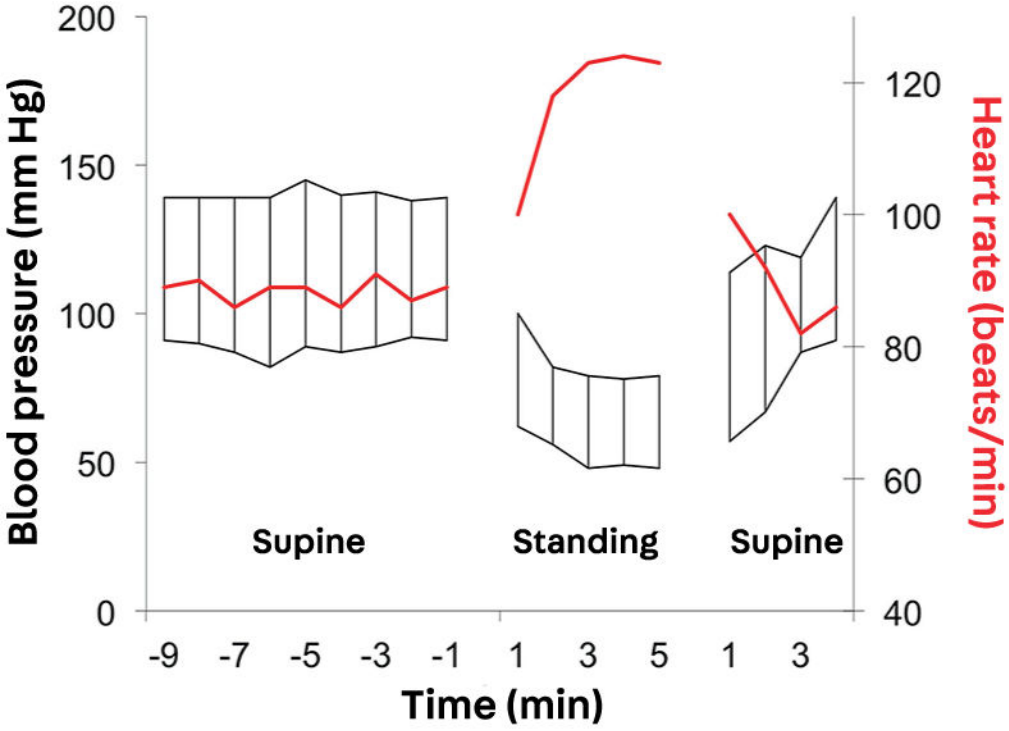


**FIGURE 9-2.**

Blood pressure and heart rate of the patient in CASE 9-1 supine and standing. The tracing shows severe orthostatic hypotension with a significant compensatory increase in heart rate, with a change in heart rate (ΔHR)/change in systolic blood pressure (ΔSBP) ratio above 0.5 beats per minute/mm Hg, indicative of non-neurogenic orthostatic hypotension.

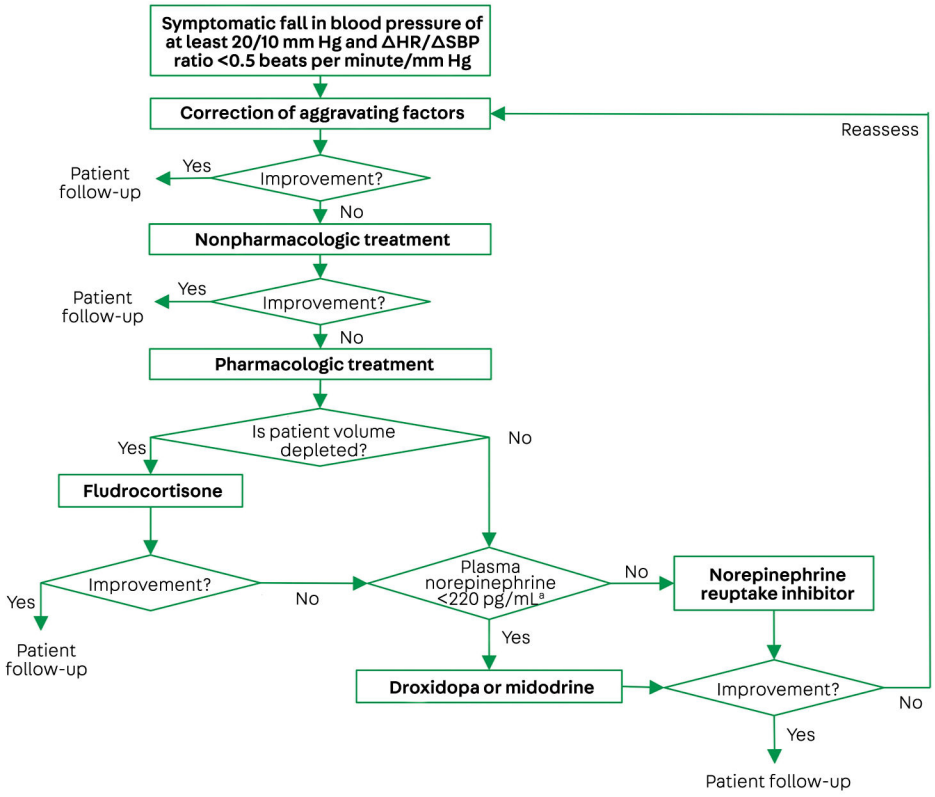


**FIGURE 9-3.**

Flowchart of the management of neurogenic orthostatic hypotension. Removal of aggravating factors and initiation of nonpharmacologic measures must always precede the use of pharmacologic agents.

ΔHR = change in heart rate; ΔSBP = change in systolic blood pressure.

[a] Supine.

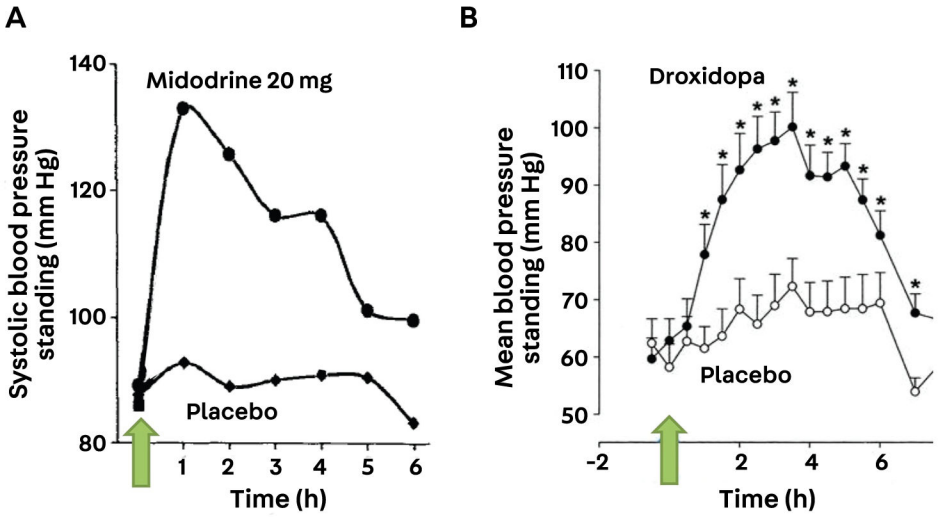


**FIGURE 9-4.**

Pressor effect of midodrine and droxidopa versus placebo. Midodrine (*A*) and droxidopa (*B*) have a similar short-acting pressor effect profile. Both medications have a fast pressor effect beginning approximately 1 hour after oral administration (*green arrows*). The pressor effect of midodrine remains for 4 to 5 hours, whereas the pressor effect of droxidopa is slightly longer at 5 to 6 hours. The peak standing systolic blood pressure occurs 1 hour after midodrine administration, whereas the peak standing mean blood pressure occurs 3.5 hours after droxidopa administration.

Panel A modified with permission from Wright RA, et al, Neurology.[77] © 1998 American Academy of Neurology. Panel B modified with permission from Kaufmann H, et al, Circulation.[78] © 2003 American Heart Association, Inc.

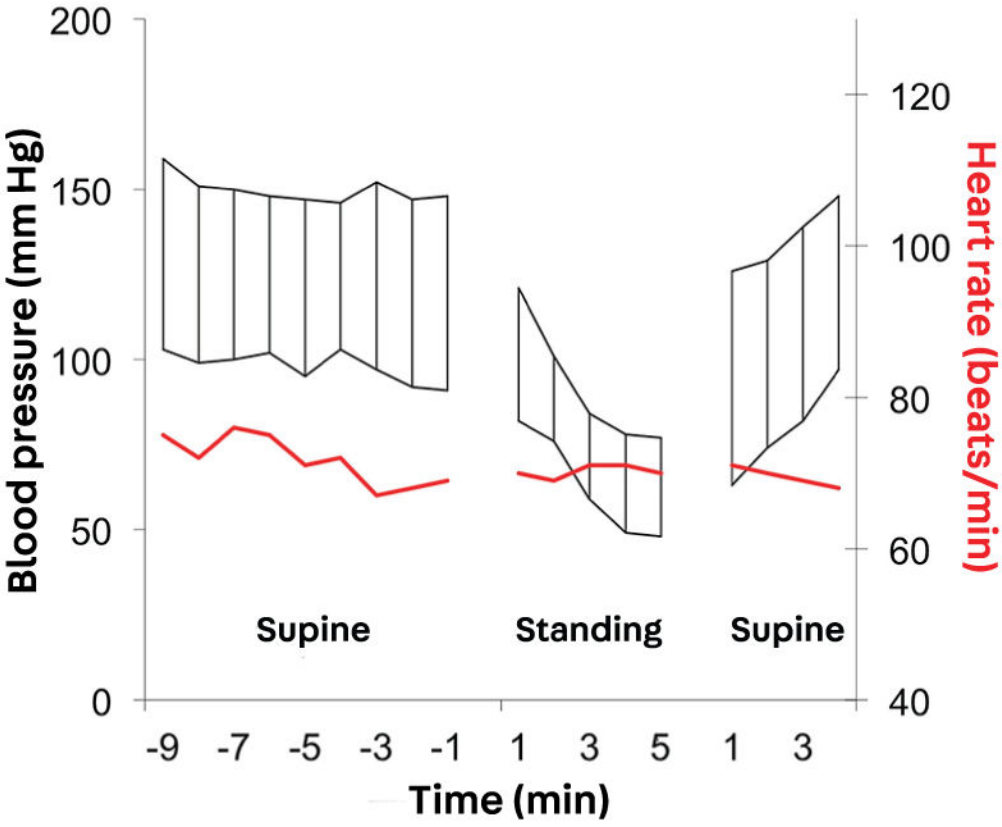


**FIGURE 9-5.**
Blood pressure and heart rate of the patient in CASE 9-2 supine and standing. The tracing shows severe orthostatic hypotension with no compensatory increase in heart rate, with a change in heart rate (ΔHR)/change in systolic blood pressure (ΔSBP) ratio below 0.5 beats per minute/mm Hg, indicative of neurogenic orthostatic hypotension.

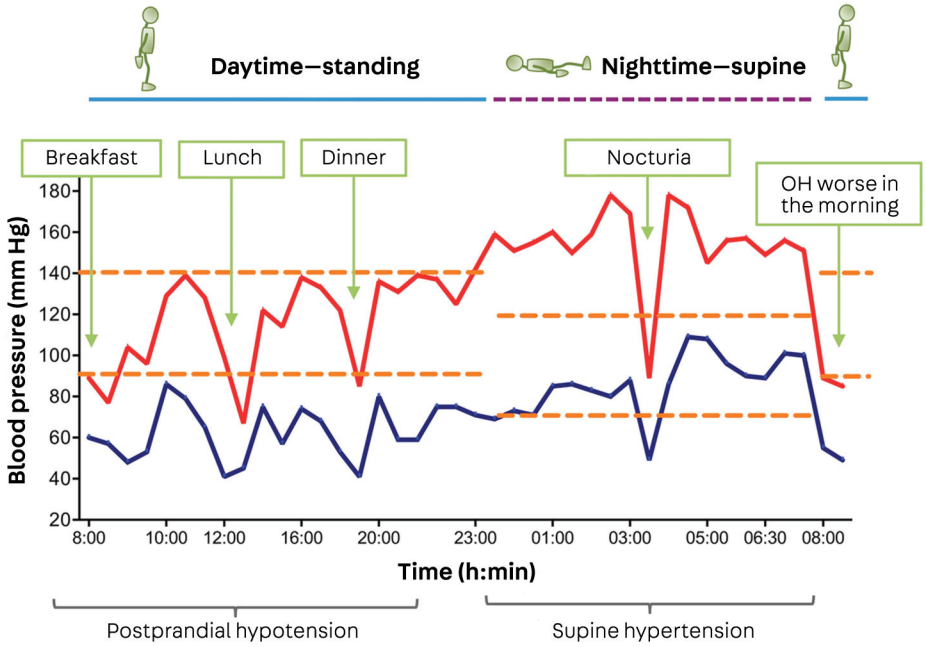


**FIGURE 9-6.**

Ambulatory 24-hour blood pressure monitor results of the patient in CASE 9-3. The *orange horizontal dashed lines* denote arbitrary limits for normal blood pressure (140/90 mm Hg during daytime, 120/70 mm Hg during nighttime). The *red tracing* denotes systolic and the *blue tracing* denotes diastolic blood pressure readings throughout one day. A significant drop in blood pressure is seen right after breakfast, lunch, and dinner (*arrows*), consistent with postprandial hypotension. The tracing also shows nocturnal hypertension while the patient was sleeping, except for an episode of hypotension when standing as the patient got up to urinate (nocturia).

OH = orthostatic hypotension.

**TABLE 9-1**

Distinguishing Features of Neurogenic and Non-neurogenic Orthostatic Hypotension

| | Non-neurogenic Orthostatic Hypotension | Neurogenic Orthostatic Hypotension |
|---|---|---|
| **Age at presentation** | Typically 65 years and older | Typically 40-60 years |
| **Onset** | Variable | Usually chronic; acute or subacute with immune-mediated etiology |
| **Causes** | Physical deconditioning, antihypertensive medications, intravascular volume loss (eg, dehydration, anemia), blood pooling (eg, large varicose veins, skeletal muscle atrophy), advanced heart failure, adrenal insufficiency | Reduced norepinephrine release from sympathetic postganglionic nerves when standing up |
| **Prognosis** | Resolves when underlying cause is corrected | Chronic disorder |
| **Sympathetic activation upon standing** | Increased | Low or absent |
| **Increase in heart rate upon standing** | Pronounced | Mild or absent |
| **Change in heart rate (ΔHR)/change in systolic blood pressure (ΔSBP) ratio** | >0.5 beats per minute/mm Hg | <0.5 beats per minute/mm Hg |
| **Blood pressure overshoot (phase IV) in Valsalva maneuver** | Present | Absent |
| **Increase in plasma norepinephrine levels upon standing** | Normal or enhanced (at least ×2) | Reduced or absent (less than ×2) |
| **Other symptoms of autonomic failure** | None | Gastrointestinal dysfunction, urinary dysfunction, sudomotor abnormalities, erectile dysfunction (men) |
| **Concomitant neurologic deficits** | None (or, if present, they are unrelated to orthostatic hypotension) | May have none, or may have parkinsonism, cerebellar signs, cognitive impairment, sensory neuropathy |

**TABLE 9-2**

Nonpharmacologic Treatments for Orthostatic Hypotension

| |
|---|
| ♦ Liberalization of salt consumption |
| ♦ Liberalization of water intake (up to 2.5 L/d) |
| ♦ Acute water bolus (drinking 500 mL water) |
| ♦ Sleeping with the head of the bed raised 30 to 45 degrees with the help of an electric bed or mattress |
| ♦ Physical activity with recumbent exercises (eg, stationary bicycle, rowing machine) or in a swimming pool |
| ♦ Physical countermaneuvers (eg, standing up slowly, leg crossing, buttock clenching)[52] |
| ♦ Abdominal binder[53] |
| ♦ Waist-high compression stockings producing at least 15 mm Hg to 20 mm Hg pressure[54] (knee-high or thigh-high stockings are typically not useful) |

**TABLE 9-3**

Mainstream Pharmacologic Treatments for Neurogenic Orthostatic Hypotension

| Treatment | Recommended Dosage | Mechanism of Action | Side Effects |
|---|---|---|---|
| **Specifically approved for orthostatic hypotension** | | | |
| Midodrine | 2.5-15 mg 2 or 3 times a day (dosed morning, midday, and 3-4 hours before bedtime) or tailored to the patient's needs | Direct $\alpha_1$-adrenergic receptor agonist | Supine hypertension, piloerection ("goose bumps"), scalp itching, urinary retention; caution in congestive heart failure and chronic renal failure |
| Droxidopa | 100–600 mg 3 times a day (dosed morning, midday, and 3–4 hours before bedtime) or tailored to the patient's needs | Synthetic norepinephrine precursor | Supine hypertension, headache, nausea, fatigue; caution in congestive heart failure and chronic renal failure |
| **Not specifically approved for orthostatic hypotension** | | | |
| Atomoxetine | 10–18 mg 2 times a day | Norepinephrine reuptake inhibitor | Supine hypertension, insomnia, irritability, decreased appetite |
| Fludrocortisone | 0.05–0.2 mg once a day; no benefit with dosages higher than 0.2 mg/d | Synthetic mineralocorticoid, volume expander that increases sodium and water reabsorption | Supine hypertension, hypokalemia, renal failure, edema, target organ damage; caution in congestive heart failure |
| Pyridostigmine | 30–60 mg 2 or 3 times a day | Acetylcholinesterase inhibitor | Abdominal cramps, diarrhea, sialorrhea, excessive sweating, urinary incontinence |

**TABLE 9-4**

Distinguishing Features of Peripheral and Central Autonomic Lesions Causing Neurogenic Orthostatic Hypotension

| | Peripheral Autonomic Lesion[a] | Central Autonomic Lesion | |
|---|---|---|---|
| | | Multiple System Atrophy | Spinal Cord Injury |
| **Plasma norepinephrine levels** | Usually low (<200 pg/mL) | Usually normal or high (>200 pg/mL) | Depends on the level of the lesion |
| **Cardiac MIBG or fluorodopamine positron emission tomography (PET) scan** | Reduced sympathetic innervation | Preserved sympathetic innervation in most patients | Preserved sympathetic innervation |
| **Hypotension-induced vasopressin release** | Present | Absent | Present |
| **Hypotensive response to trimethaphan** | Minor | Pronounced | Unknown |
| **Pressor response to yohimbine** | Less pronounced | Pronounced | Unknown |
| **Pressor response to droxidopa** | Pronounced | Less pronounced | Present |
| **Pressor response to atomoxetine** | Less pronounced | Pronounced | Unknown |

MIBG = metaiodobenzylguanidine.

[a]Diabetes mellitus, Parkinson disease, pure autonomic failure, dementia with Lewy bodies, amyloidosis, autoimmune and other causes of autonomic neuropathy.