

CLINICAL PRACTICE

Neurogenic Orthostatic Hypotension

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 65-year-old man reports a 6-month history of dizziness, light-headedness, weakness, and fatigue while upright. He takes no medication and has no personal or family history of neurologic disease. On physical examination, his supine blood pressure is 160/100 mm Hg, with a heart rate of 72 beats per minute; on standing, his blood pressure falls to 70/40 mm Hg, with no change in heart rate. The results of the remainder of the examination, including neurologic examination, are normal. How should he be evaluated and treated?

THE CLINICAL PROBLEM

Orthostatic hypotension, defined as a reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg during the first 3 minutes of standing or a head-up tilt on a tilt table,¹ is a classic manifestation of sympathetic vasoconstrictor (autonomic) failure. In many (but not all) cases, there is no compensatory increase in the heart rate, despite hypotension; with milder autonomic failure, the heart rate may increase, but not to a rate sufficient to maintain blood pressure. A variant of orthostatic hypotension is delayed orthostatic hypotension, which occurs after 3 minutes of standing; this condition may represent a mild or early form of sympathetic adrenergic dysfunction.² In some cases, orthostatic hypotension occurs within 15 seconds of standing (so-called initial orthostatic hypotension); this may represent a transient mismatch between cardiac output and peripheral vascular resistance rather than autonomic failure.³

Orthostatic hypotension increases in prevalence with age; aging is associated with reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex. Orthostatic hypotension is more common in elderly people living in care facilities (54 to 68%) than in those living in the community (6%),⁴ an observation most likely explained by the greater prevalence of predisposing neurologic disorders, physiological impairment, and medication use among people living in care facilities.

PHYSIOLOGICAL AND CLINICAL FEATURES

Standing results in pooling of 500 to 1000 ml of blood in the lower extremities and splanchnic circulation. There is a decrease in venous return to the heart and reduced ventricular filling, resulting in diminished cardiac output and blood pressure. These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, that results in increased sympathetic outflow and decreased vagal-nerve activity (Fig. 1). This reflex increases peripheral resistance, venous return to the heart, and cardiac output, thereby limiting the fall in blood pressure. If this response fails, orthostatic hypotension and cerebral hypoperfusion occur.⁵

Characteristic symptoms of orthostatic hypotension include light-headedness, dizziness, presyncope, and syncope in response to sudden postural change. However, symp-

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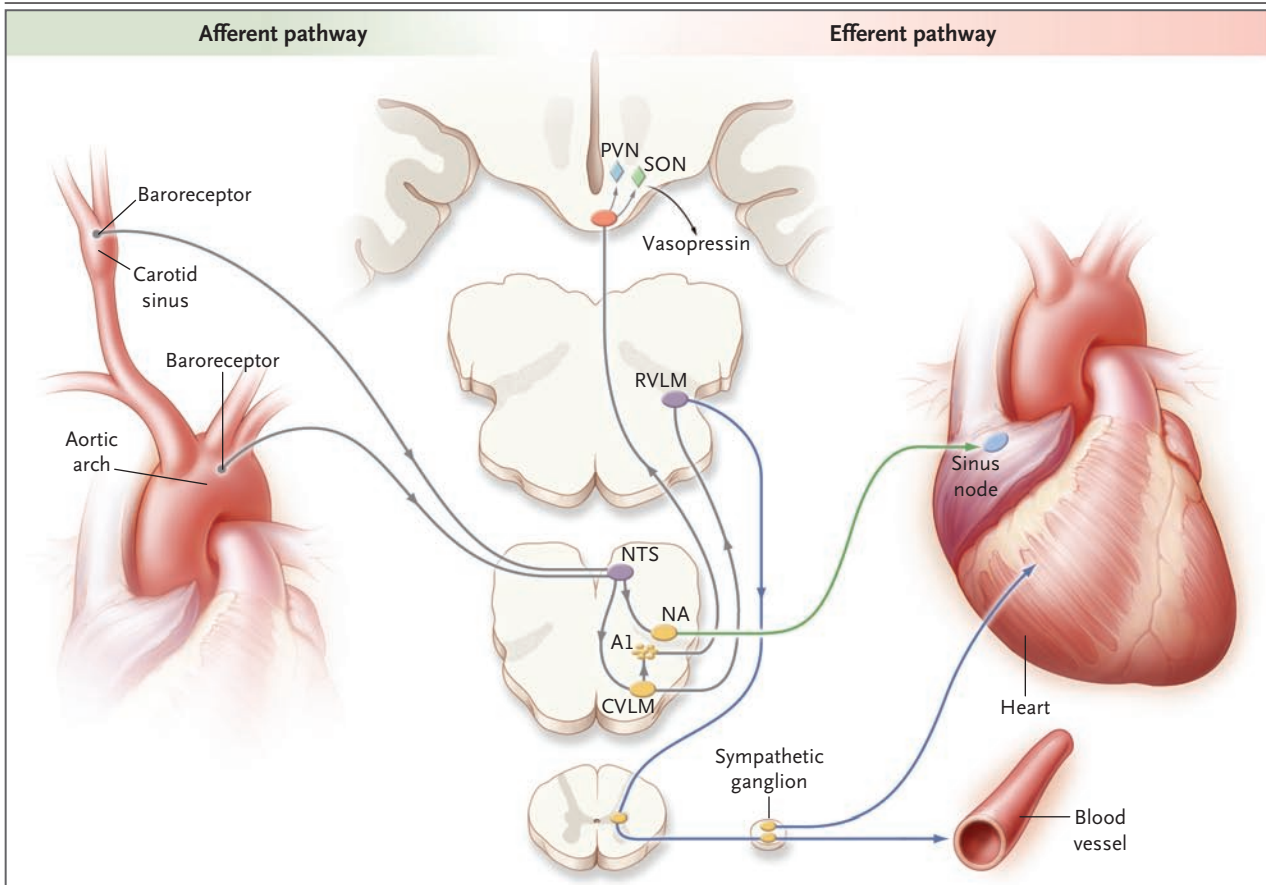


Figure 1. The Baroreflex.

A decrease in arterial pressure unloads the baroreceptors — the terminals of afferent fibers of the glossopharyngeal and vagus nerves — that are situated in the carotid sinus and aortic arch. This leads to a reduction in the afferent impulses that are relayed from these mechanoreceptors through the glossopharyngeal and vagus nerves to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla. The reduced baroreceptor afferent activity produces a decrease in vagal nerve input to the sinus node that is mediated by the neuroanatomical connections of the NTS to the nucleus ambiguus (NA). There is an increase in sympathetic efferent activity that is mediated by the NTS projections to the caudal ventrolateral medulla (CVLM) (an excitatory pathway) and from there to the rostral ventrolateral medulla (RVLM) (an inhibitory pathway). The activation of RVLM presympathetic neurons in response to hypotension is thus predominantly due to disinhibition. In response to a sustained fall in blood pressure, vasopressin release is mediated by projections from the A1 noradrenergic cell group in the ventrolateral medulla. This projection activates vasopressin-synthesizing neurons in the magnocellular portion of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. Blue denotes sympathetic neurons and green parasympathetic neurons.

toms may be absent or nonspecific, such as generalized weakness, fatigue, nausea, cognitive slowing, leg buckling, or headache. Visual blurring may occur, probably because of retinal or occipital-lobe ischemia. Neck pain may occur, typically in the suboccipital, posterior cervical, and shoulder region (called the coat-hanger headache), which is most likely due to ischemia in the trapezius and neck muscles.⁶ Patients may report orthostatic dyspnea (thought to reflect ventilation–perfusion mismatch due to inadequate perfusion of ventilated lung apices)⁷ or angina (attributed to impaired myocardial perfusion even in patients with normal

coronary arteries). One or more of these nonspecific symptoms may be the presenting or only symptom of orthostatic hypotension. Symptoms may be exacerbated by exertion, prolonged standing, increased ambient temperature, or eating. Syncope is usually preceded by warning symptoms but may occur suddenly, suggesting the possibility of a seizure or cardiac cause.

Supine hypertension is common in patients with orthostatic hypotension, affecting more than 50% of patients in some series. Orthostatic hypotension may occur after therapy for hypertension, and supine hypertension may follow treatment of

Table 1. Primary Autonomic Degenerative Disorders Causing Orthostatic Hypotension (the Synucleinopathies).*

Disorder	Autonomic Dysfunction	Motor Manifestations	Other Prominent Clinical Features	Pathological Hallmark	Diagnostic Tests
Multiple-system atrophy with autonomic failure (Shy-Drager syndrome)	Severe autonomic dysfunction develops early in clinical course and may be only or most prominent clinical feature ^{1,11} ; median survival, 7 to 9 yr ^{1,2}	Parkinsonism† (predominant in 80% of patients), cerebellar dysfunction (predominant in 20% of patients), corticospinal tract abnormalities	Dysarthria, stridor, contractions and dystonias (particularly antecollis), REM sleep behavior disorder, dementia	α-Synuclein precipitation in glia (glial cytoplasmic inclusions) and some CNS neurons	MRI of brain may show abnormalities, including putaminal atrophy, putaminal hypointensity relative to pallidum on T ₂ -weighted images, slight signal change at posterolateral putaminal margin, atrophy and signal change in pons, middle cerebellar peduncle, and cerebellum ^{1,3}
Parkinson's disease	Autonomic dysfunction occurs later in clinical course, ^{1,4} often associated with or exacerbated by antiparkinsonism medications; rarely as severe as in multiple-system atrophy ¹⁵	Parkinsonism†	REM sleep behavior disorder; dementia later in clinical course	α-Synuclein precipitation in Lewy bodies in cytoplasm of CNS neurons	Cardiac SPECT scanning with sympathomimetic amine ¹²³ I-MIBG shows MIBG uptake is impaired, particularly with autonomic failure ¹⁶ ; PET scanning with ¹⁸ F-dopa shows similar results ¹⁷
Lewy-body dementia	Autonomic dysfunction occurs early in clinical course ¹⁸	Parkinsonism†	Progressive dementia precedes or accompanies parkinsonism, fluctuating alertness and cognitive impairment, visual hallucinations. REM sleep behavior disorder	α-Synuclein precipitation in Lewy bodies in cytoplasm of CNS neurons, prominent in neocortical and limbic system neurons	Cardiac SPECT scanning with sympathomimetic amine ¹²³ I-MIBG shows MIBG uptake is impaired, particularly with autonomic failure ¹⁶
Pure autonomic failure	Gradually progressive autonomic dysfunction that responds well to therapy; quality of life and prognosis substantially better than for patients with other primary autonomic degenerative disorders ¹⁹	No motor manifestations, rare progression to Parkinson's disease or dementia with Lewy bodies ²⁰	None	α-Synuclein precipitation predominantly in Lewy bodies in pre- and postganglionic peripheral autonomic neurons of sympathetic and parasympathetic nervous system	Cardiac SPECT scanning with sympathomimetic amine ¹²³ I-MIBG shows MIBG uptake is impaired, particularly with autonomic failure ¹⁶

* CNS denotes central nervous system, ¹⁸F-dopa [¹⁸F]fluoro-L-dopa, ¹²³I-MIBG ¹²³I-metaiodobenzylguanidine, MRI magnetic resonance imaging, PET positron-emission tomography, REM rapid-eye movement, and SPECT single-photon-emission computed tomography.

† Symptoms of parkinsonism include resting tremor, bradykinesia, rigidity, and postural instability.

orthostatic hypotension. In other cases, however, the association of the two conditions is unrelated to therapy and may be explained in part by baroreflex dysfunction in the presence of residual sympathetic outflow, particularly in patients with central autonomic degeneration.⁸

CAUSES OF NEUROGENIC ORTHOSTATIC HYPOTENSION

Causes of neurogenic orthostatic hypotension include central and peripheral autonomic nervous system diseases or disorders. Autonomic dysfunction of varying severity in other organ systems (including the bladder, bowels, sexual organs, and sudomotor system) frequently accompanies orthostatic hypotension in these disorders.

The primary autonomic degenerative disorders are multiple-system atrophy (the Shy-Drager syndrome), Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure. These disorders are often referred to collectively as synucleinopathies because of the presence of α -synuclein, a small protein that precipitates predominantly in the cytoplasm of neurons in the Lewy-body disorders (Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure) and in the glia in multiple-system atrophy.^{1,9,10} Characteristic features of these disorders are summarized in Table 1.

Peripheral autonomic dysfunction may also accompany small-fiber peripheral neuropathies, such as those seen in diabetes, amyloidosis, immune-mediated neuropathies, hereditary sensory and autonomic neuropathies (particularly hereditary sensory and autonomic neuropathy type III, also called familial dysautonomia), and inflammatory neuropathies (Table 2). Less frequently, orthostatic hypotension is associated with the peripheral neuropathies that accompany vitamin B₁₂ deficiency, exposure to neurotoxins, neuropathies due to infections, including human immunodeficiency virus, and porphyria.^{29,30}

STRATEGIES AND EVIDENCE

EVALUATION

Dehydration and acute blood loss should be ruled out in patients presenting with orthostatic hypotension, and other non-neurogenic causes should also be considered. These include drugs (e.g., antihypertensive agents and antidepressants), reduced cardiac output (e.g., constrictive pericarditis, cardiomyopathy, and aortic stenosis), endocrine disorders (e.g., adrenal insufficiency and pheochro-

mocytoma), and excessive vasodilatation (e.g., systemic mastocytosis and the carcinoid syndrome). The history taking should address other features suggestive of central or peripheral autonomic dysfunction, such as gastrointestinal, urinary, sexual, and sudomotor dysfunction; motor system dysfunction, such as parkinsonism, pyramidal tract dysfunction, and cerebellar ataxia; and peripheral neuropathy (Tables 1 and 2).

Blood pressure should be measured while the patient is in the supine position and at least 3 minutes after the patient stands up. In the absence of an apparent cause of symptoms, screening blood tests typically include a complete blood count, electrolyte assessment, blood glucose level, serum immunoelectrophoresis, vitamin B₁₂ level, and a morning cortisol level.

Autonomic testing is often performed in specialized centers to uncover any asymptomatic abnormalities.³¹ Testing includes functional assessments of the parasympathetic nervous system (e.g., heart rate variability with deep respiration and during a Valsalva maneuver), the sympathetic cholinergic system (e.g., thermoregulatory sweat response and quantitative sudomotor axon reflex test), and the sympathetic adrenergic system (e.g., blood-pressure response to a Valsalva maneuver and a tilt-table test with beat-to-beat measurement of blood pressure). Autonomic testing may be useful in distinguishing orthostatic hypotension due to autonomic failure from neurally mediated syncope.

The primary autonomic degenerative disorders (Tables 1 and 2) can be differentiated according to clinical criteria, although imaging studies may be helpful when the diagnosis remains unclear. Characteristic findings on magnetic resonance imaging¹³ and single-photon-emission computed tomographic scanning (with the radiolabeled sympathomimetic amine ¹²³I-metaiodobenzylguanidine)¹⁶ in the various disorders are noted in Table 1.

TREATMENT

Neurogenic orthostatic hypotension is usually the most incapacitating symptom of autonomic failure, but the quality of life of affected patients can be improved substantially with nonpharmacologic or, when necessary, pharmacologic interventions.

Nonpharmacologic Interventions

Patients with orthostatic hypotension should be educated about simple measures they can use in situations that typically precipitate symptoms (Ta-

Table 2. Peripheral Autonomic Disorders Commonly Associated with Orthostatic Hypotension.

Disorder	Associated Features	Comments	Diagnostic Tests
Diabetes	Usually but not always associated with generalized polyneuropathy; orthostatic hypotension may occur early in clinical course; other autonomic manifestations may include gastroparesis, diarrhea, constipation, urinary retention, and erectile dysfunction ²¹	Most common cause of autonomic dysfunction in developed countries	Fasting blood glucose and glucose-tolerance test
Hereditary amyloidosis (familial amyloid polyneuropathy)	Usually associated with generalized polyneuropathy, with prominent small-fiber (pain and temperature) abnormalities; other associated conditions include carpal tunnel syndrome (often an early manifestation), cardiomyopathy and conduction abnormalities, vitreous opacities, and increased intraocular pressures; scalloped pupils may be present; diarrhea and weight loss are common; macroglossia is not present ^{22,23}	Develops in the 3rd to 5th decade of life, characterized by deposition of insoluble beta-fibrillar proteins in epineurium, perineurium, and endoneurium; perineuronal tissues, and neural vasculature; most common amyloid precursor is mutant transthyretin; sporadic cases may be common; mutations in genes encoding for apolipoprotein A1, fibrinogen A α , lysozyme, and gelsolin also give rise to amyloidosis	Assessment of fat aspirate or rectal- or gingival-biopsy specimen for amyloid deposits; genetic testing
Primary amyloidosis (AL amyloidosis; immunoglobulin light-chain-associated)	Usually associated with generalized polyneuropathy, with prominent small-fiber (pain and temperature) abnormalities; other associated conditions include carpal tunnel syndrome (often an early manifestation), cardiac involvement, macroglossia (with tooth indentation in about 20% of patients), periorbital purpura, easy bruising, organomegaly, weight loss, nephrotic syndrome, and edema ^{23,24}	Presents in the 6th to 7th decade of life; caused by production of amyloidogenic monoclonal immunoglobulin protein (M protein, light chains or light-chain fragments) by monoclonal population of bone marrow cells; deposition of insoluble beta-fibrillar proteins in epineurium, perineurium, and endoneurium; perineuronal tissues, and neural vasculature	Assessment of fat aspirate or rectal- or gingival-biopsy specimen for amyloid deposits, immunoelectrophoresis of blood and urine
HSAN type III (also called familial dysautonomia)*	Insensitivity to pain and temperature stimuli but sparing visceral pain, absence of tears (alacrima), hypoactive corneal and tendon reflexes, and absence of lingual fungiform papillae ²⁵	An autosomal recessive disorder seen primarily in Ashkenazi Jewish children	Test for a splicing mutation in the <i>IKBKAP</i> kinase-associated protein gene (<i>IKBKAP</i>), which is present in 99.5% of patients
Idiopathic immune-mediated autonomic neuropathy	Gastrointestinal hypomotility, urinary retention, xerostomia, and xerophthalmia ²⁶	May respond to immunomodulating therapy	Test for nicotinic ganglionic acetylcholine receptor antibodies, which are present in some patients
Sjögren's syndrome	Sicca syndrome, features of dysautonomia other than orthostatic hypotension may occur ²⁷	Autonomic manifestations may be present with normal serologic tests	Tests for anti-Ro (SSA) and anti-La (SSB) antibodies
Paraneoplastic autonomic neuropathy	Autonomic features of underlying cancers may be first manifestation of a cancer ²⁸	Occurs most often in patients with small-cell lung cancer; also seen in non-small-cell lung cancer, cancers of gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testicle, and ovary	Tests for anti-Hu antibodies (type 1 anti-neuronal nuclear antibodies [ANNA-1]), which are most prevalent; type 2 Purkinje-cell antibodies (PCA-2); and colapsin response mediator protein 5 (CRMP-5), which may also be present

* HSAN denotes hereditary sensory and autonomic neuropathy.

Table 3. Nonpharmacologic Interventions Used in the Treatment of Orthostatic Hypotension.

Intervention	Comments
Perform gradual staged movements with postural change.	Time should be allowed for autonomic adaptation.
Avoid straining, coughing, and other maneuvers that increase intrathoracic pressure.	These maneuvers decrease venous return to the heart and thereby reduce cardiac output.
Avoid prolonged recumbency.	Deconditioning exacerbates orthostatic hypotension.
Perform isotonic exercise.	The straining associated with isometric exercise decreases venous return to the heart.
Perform physical counter-maneuvers, such as crossing legs, stooping, squatting, and tensing muscles.	These maneuvers reduce peripheral pooling and increase venous return to the heart.
Raise the head of the bed by 10–20 degrees.	This positioning decreases supine hypertension and minimizes pressure diuresis.
Discontinue or reduce hypotensive and antihypertensive medications.	It may be necessary to accept some supine hypertension in order to maintain orthostatic tolerance.
Wear custom-fitted elastic stockings and abdominal binder.	Wearing these reduces peripheral pooling in the lower limbs and splanchnic circulation.
Minimize postprandial hypotension.	Small meals, low in carbohydrates, are recommended. Alcohol should be avoided.
Increase intake of fluid and salt.	A daily dietary intake of up to 10 g of sodium per day and a fluid intake of 2.0 to 2.5 liters per day is recommended.
Drink water rapidly.	Rapid ingestion of approximately 0.5 liter of tap water raises blood pressure within 5–15 minutes.

ble 3). Patients should be advised to move from a supine to a standing position in gradual stages, particularly in the morning, when orthostatic tolerance is lowest, owing to the nocturnal diuresis induced by supine hypertension and fluid redistribution.³² It is also advisable to raise the head of the bed. In addition, several physical counter-maneuvers — including crossing the legs, stooping, squatting, and tensing the muscles of the leg, abdomen, or buttock or of the whole body — can help maintain blood pressure during daily activities. These maneuvers reduce venous pooling and thus increase central blood volume and cardiac filling, with resultant increases in cardiac output, blood pressure, and cerebral perfusion.³³

Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance. Because the intramuscular vasodilatation that accompanies exercise may exacerbate orthostatic hypotension, recumbent or seated exercise may be preferable. During exercise, patients should avoid straining, which can result in reduced venous return to the heart.

The use of custom-fitted elastic stockings, which apply graded pressure to the lower extremities and abdomen, may also be beneficial. These stockings minimize peripheral-blood pooling in the lower extremities and in the splanchnic circulation. It is preferable for compression to extend to the waist, since most peripheral pooling

occurs in the splanchnic circulation. Abdominal binders that compress the splanchnic circulation with an application pressure of about 20 mm Hg may provide an additional benefit.³⁴ The long-term benefit of these interventions is uncertain.

Patients with autonomic failure and even healthy elderly persons are susceptible to substantial drops in blood pressure after eating.³⁵ Postprandial hypotension can be minimized by avoiding large meals, eating foods that are low in carbohydrates, and minimizing alcohol intake. Patients should be advised against sudden standing or physical activity immediately after eating.

The recognition and removal (when possible) of reversible causes of orthostatic hypotension are also important. Diuretics, antihypertensive agents, antianginal agents, α -adrenoreceptor antagonists for the treatment of benign prostatic hyperplasia, antiparkinsonism agents, and antidepressants are the most common offending agents.

Adequate plasma volume is essential for orthostatic tolerance. In patients with supine hypertension, elevated nocturnal blood pressure causes a pressure diuresis, resulting in volume depletion. Raising the head of the bed 10 to 20 degrees (6 to 10 in.) reduces supine hypertension and decreases nocturnal diuresis.³⁶

Central blood volume can be augmented by increasing the intake of sodium (with high-sodium foods or salt tablets) and fluid.⁵ Patients' daily dietary intake should include up to 10 g of

sodium and 2.0 to 2.5 liters of fluid. Urinary sodium excretion that exceeds 170 mmol and urinary volume greater than 1500 ml over a 24-hour period are considered to indicate adequate salt and fluid intake.³⁷

Rapid ingestion (e.g., over a period of 3 to 4 minutes) of approximately 0.5 liter of tap water elicits a marked pressor response and improvement in symptoms in many, but not all, patients with autonomic failure. The pressor response, a systolic blood pressure increase of more than 30 mm Hg in some patients, is evident within 5 minutes of water ingestion, peaks at 20 to 30 minutes, and lasts for up to 1 hour. The mechanisms underlying the pressor effect are not established. The observation that venous plasma norepinephrine increases after water ingestion suggests that activation of the sympathetic nervous system may be implicated.³⁸

Pharmacologic Interventions

Table 4 lists doses and side effects of medications used for orthostatic hypotension. The aim of therapy is to control symptoms, not to restore normotension.

Administration of 9- α -fluorohydrocortisone (fludrocortisone acetate), a synthetic mineralocorticoid, may be helpful for patients in whom plasma volume cannot be adequately increased with fluid and salt.³⁶ Sodium retention and plasma volume return to normal with long-term use, although the pressor effect persists because of increased peripheral vascular resistance.³⁹

Since neurogenic orthostatic hypotension is in large part a consequence of the failure to release the norepinephrine from sympathetic neurons, the administration of sympathomimetic medications is central to the care of patients whose symptoms are not controlled with other measures. Midodrine, a peripheral, selective, direct α_1 -adrenoreceptor agonist, is the only medication approved by the Food and Drug Administration for the treatment of orthostatic hypotension.⁴⁰ Double-blind, multicenter, placebo-controlled trials have shown that midodrine is associated with significantly increased standing blood pressures and reduced symptoms of orthostatic intolerance.^{40,41}

The mixed α -adrenoreceptor agonists — which act directly on the α -adrenoreceptor and release norepinephrine from the postganglionic sympathetic neurons — include ephedrine and pseudoephedrine (a stereoisomer of ephedrine).⁴² Both agents stimulate α , β_1 , and β_2 receptors; their β_2

vasodilatory effects may attenuate their pressor effects.⁴² There have been few studies comparing the effects of different α -adrenoreceptor agonists. In a small trial, midodrine (mean dose, 8.4 mg three times a day) improved standing blood pressure and orthostatic tolerance significantly more than ephedrine (mean dose, 22.3 mg three times a day).⁴³

Other agents may be considered for cases in which symptoms do not respond to the above interventions. Data supporting the use of many of these agents are from small, single-center trials.

The postural release of arginine-vasopressin is reduced in some patients with autonomic failure⁴⁹ (particularly when autonomic failure is due to a central neurodegenerative process in which there may be loss of vasopressin neurons in the suprachiasmatic nucleus of the hypothalamus). The vasopressin analogue desmopressin acetate can be used to supplement volume expansion and reduce nocturnal diuresis.⁴⁴

Erythropoietin increases standing blood pressure, and controlled trials have shown that it improves orthostatic tolerance in patients with orthostatic hypotension and anemia⁴⁵; normochromic normocytic anemia is frequently associated with autonomic failure. The mechanism for the pressor effect has not been determined but may involve increases in red-cell mass and central blood volume, alterations in blood viscosity, and neurohumoral effects on the vascular wall.⁴⁵

Pyridostigmine, the acetylcholinesterase inhibitor, has been shown in controlled trials to cause a modest increase in blood pressure in patients with neurogenic orthostatic hypotension. The associated increase in supine blood pressure may not be as great as that seen with other pressors. The therapeutic rationale is that inhibition of acetylcholinesterase enhances sympathetic ganglionic neurotransmission and that the effect is maximal when the patient is upright, since sympathetic-nerve traffic is greatest in this position.⁴⁸

Other agents that have been used to treat orthostatic hypotension include cyclooxygenase inhibitors, β -adrenoreceptor antagonists, clonidine, yohimbine, somatostatin, dihydroergotamine, and dopamine antagonists. Clinical experience and small controlled trials of these agents have yielded inconsistent results.⁵⁰

AREAS OF UNCERTAINTY

Among the agents used to treat orthostatic hypotension, only midodrine has been subjected to a

Table 4. Drugs Used in the Treatment of Neurogenic Orthostatic Hypotension.*

Drug	Mechanism of Action	Dosage	Adverse Effects	Comments
Volume-expanding agent				
9- α -fluorohydrocortisone ^{3,6,39}	Promotes sodium absorption in distal tubule of kidney and may enhance sensitivity of blood vessels to circulating catecholamines	0.05–0.3 mg daily	Supine hypertension, ankle edema, hypokalemia, headache, and rarely, congestive heart failure	Prolonged duration of effect; potassium supplementation may be required
Vasoconstricting agents				
Midodrine ^{40,41}	Direct α 1-adrenoreceptor agonist	2.5–10 mg 2–4 times a day	Piloomotor reactions, pruritus, supine hypertension, bradycardia, and gastrointestinal symptoms, and urinary retention	Only FDA-approved agent for treatment of orthostatic hypotension; desglymidodrine is active metabolite; should not be taken in the 4-hr period before recumbency
Pseudoephedrine ⁴²	Direct and indirect (releases norepinephrine from presynaptic neuron) α 1-adrenoreceptor agonist	30–60 mg 3 times a day	Supine hypertension, tachycardia, central sympathomimetic side effects (e.g., anxiety, tremulousness); in rare cases, intracerebral hemorrhage, vasculitis, arrhythmias, and cardiovascular events; potential for abuse	Should not be taken in the 4-hr period before recumbency
Ephedrine ⁴³	Direct and indirect (releases norepinephrine from presynaptic neuron) α 1-adrenoreceptor agonist	25–50 mg 3 times a day	Supine hypertension, tachycardia, central sympathomimetic side effects (e.g., anxiety, tremulousness); in rare cases, intracerebral hemorrhage, vasculitis, arrhythmias, and cardiovascular disease; potential for abuse	Should not be taken in the 4-hr period before recumbency
Supplementary agents				
Desmopressin acetate (DDAVP) ⁴⁴	Vasopressin analogue that acts on V2 receptors in collecting ducts of renal tubules; supplements volume expansion and reduces nocturnal diuresis	Nasal spray, 5–40 μ g daily; oral formulation, 100–800 μ g daily	Water intoxication and hyponatremia	Fluid and electrolyte status should be monitored carefully
Erythropoietin ⁴⁵⁻⁴⁷	Erythropoietic agent that corrects the normochromic normocytic anemia of autonomic failure, increasing red-cell mass and central blood volume; may have direct or indirect effects on vascular wall	25–75 U per kilogram of body weight, given subcutaneously 3 times a week, until hematocrit approaches normal range; lower maintenance doses may then be used	Supine hypertension, polycythemia; long-term risks (including cardiovascular risk) in this patient population are not known	Iron supplementation is usually required
Pyridostigmine ⁴⁸	Acetylcholinesterase inhibitor that enhances sympathetic ganglionic neurotransmission	30–60 mg 3 times a day	Excessive salivation, increased peristalsis, nausea, vomiting, and stomach cramps	Effect is maximal in an upright position, when sympathetic nerve traffic is greatest

* This list of treatments is not exhaustive. FDA denotes Food and Drug Administration.

large, multicenter, placebo-controlled trial. There have been few head-to-head comparisons of agents and no long-term assessments of efficacy and safety. Multicenter, controlled trials assessing dihydroxyphenylserine, a synthetic precursor of norepinephrine, are currently in progress.^{51,52}

Although severe supine hypertension may limit therapeutic intervention, many patients appear to tolerate elevations in supine blood pressures without untoward effects, perhaps because supine hypertension is accompanied by orthostatic hypotension. Myocardial hypertrophy is observed in some patients⁵³; the incidence of hypertensive end-organ damage, such as cerebrovascular disease, nephropathy, and cardiomyopathy, has not been prospectively studied. The use of short-acting oral antihypertensive agents at bedtime should be considered in patients with severe, sustained supine hypertension. Because patients with autonomic failure cannot generate the appropriate compensatory reflexes, treatment of supine hypertension, even with short-acting agents, may increase the likelihood of syncope and falls. These risks must be balanced against the potential benefits of treatment.

GUIDELINES FROM PROFESSIONAL SOCIETIES

The European Federation of Neurological Societies has published guidelines for the treatment of orthostatic hypotension.⁵⁴ The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

A fall in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg within 3 minutes after standing, as in the case in the vignette, is diagnostic of orthostatic hypotension. The history and physical examination, as well as laboratory testing, should

be focused on ruling out non-neurologic causes (e.g., blood loss, dehydration, and cardiovascular or endocrine disorders) and determining whether other features of primary autonomic degenerative disorders or autonomic peripheral neuropathies are present. If the diagnosis remains unclear, additional testing, including autonomic testing and imaging studies, may be useful.

In the case presented in the vignette, the absence of another apparent cause of symptoms and of neurologic findings on examination suggests a diagnosis of pure autonomic failure. Nonetheless, because orthostatic hypotension may be the first manifestation of multiple-system atrophy or autonomic neuropathy, follow-up is essential.

Reversible causes of orthostatic hypotension (in particular, the use of hypotensive medications) should be addressed as soon as possible. Patients should be counseled regarding nonpharmacologic strategies that can reduce symptoms, such as performing physical counter-maneuvers (e.g., crossing the legs, stooping, and tensing muscles), raising the head of the bed, and ingesting adequate salt and fluid. If symptoms persist, a low dose of fludrocortisone (0.05 or 0.1 mg daily) should be considered. If these approaches do not control symptoms, an α -adrenoreceptor agonist can be added (e.g., midodrine, at an initial dose of 2.5 mg two or three times a day, with a gradual increase to 10 mg three times a day), with use avoided in the 4-hour period before recumbency. Supplementary agents are sometimes needed. Patients should maintain a blood-pressure diary, measuring blood pressure and noting any accompanying symptoms while supine or standing or after meals, and they should understand that the aim of therapy is to minimize symptoms, not to restore normotension.

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An audio version of this article is available at www.nejm.org.

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