Neurogenic Orthostatic Hypotension: Pathophysiology and Diagnosis

Phillip A. Low, MD

Abstract

Although orthostatic hypotension in elderly patients is common, neurogenic orthostatic hypotension (NOH) is a condition with substantial morbidity and a variable prognosis. Patients with severe NOH have difficulty standing for any period of time and must scrupulously avoid orthostatic stressors that exacerbate their condition. In about half of patients, supine hypertension complicates management. The diagnosis is based on measurements of supine and standing blood pressures or head-up tilt testing and is confirmed by autonomic testing. Two self-report questionnaires, the Orthostatic Hypotension Questionnaire and the Orthostatic Grading Scale, can help evaluate a patient's level of impairment, document progression, and assess the response to pharmacotherapy in clinical practice. There are many gaps in our knowledge of this rare disorder; this review summarizes what is currently known about the pathophysiology, epidemiology, prognosis, signs and symptoms, and the diagnosis of NOH.

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For author information and disclosures, see end of text.

When an individual stands up, the autonomic nervous system ensures that adequate blood flow keeps the heart pumping and the brain perfused, in addition to preventing almost a liter of blood from pooling in the abdomen and lower extremities. The cardiac output that is caused by standing and the drop in blood pressure stimulates a reflex response by baroreceptors that increases sympathetic outflow and decreases vagal nerve activity.[1] Baroreflex pathways send coordinated signals to the heart to increase heart rate and cardiac output. The coordinated signals are also sent to arterioles and venules to increase systemic vascular resistance. Vasoconstriction of the splanchnic-mesenteric bed in the abdomen, mediated by alpha-adrenergic receptors, plays an important role because this vascular bed accounts for up to 30% of total blood volume.[2]

In the normal body, these complex actions maintain a similar level of blood pressure whether supine, sitting, or standing.[2,3] Orthostatic hypotension (OH) occurs when the body is unable to maintain the same blood pressure when standing. A consensus statement, developed and endorsed by international experts, defines OH as a sustained reduction of systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing. However, with the head-up tilt (HUT) test, a decrement of 30 mm Hg is more appropriate.[1,4]

Pathophysiology of Orthostatic Hypotension

OH has both non-neurogenic and neurogenic causes that can be acute or chronic.[5] It can be multifactorial, with non-neurogenic causes more common than neurogenic causes. For example, dehydration and drug therapy can contribute to the development of OH in an elderly patient.[6] Non-neurogenic causes of OH fall into 3 categories: hypovolemia, cardiac pump failure, and venous pooling. Hypovolemia has myriad causes, ranging from acute

dehydration due to nausea and vomiting to chronic blood loss from colon cancer or gastric ulcers. Cardiac pump failure can be caused by bradycardia, tachyarrhythmia, aortic stenosis, myocardial infarction (MI), or pericarditis. Venous pooling can be caused by prolonged standing, such as when a soldier faints while standing in formation; however, it can also be caused by fever, severe varicose veins, postprandial dilation of splanchnic blood vessels, and heat exposure.[5]

Drugs cause or exacerbate OH through a variety of mechanisms that mimic the primary non-neurogenic causes of OH: hypovolemia, cardiac pump failure, and venous pooling. Classes of drugs that commonly cause OH include diuretics (ie, hypovolemia) and alpha$_1$-adrenergic antagonists (reduced systemic vascular resistance).[7,8] OH with the nondihydropyridine calcium channel blockers diltiazem and verapamil is attributed to their negative inotropic and chronotropic effects.[9] Nitrates induce OH by causing vasodilation.[9]

In neurogenic orthostatic hypotension (NOH), impaired vasoconstriction is caused by inadequate release of norepinephrine from sympathetic vasomotor neurons.[1] In addition to having inadequate vasoconstriction, patients with NOH may have an inadequate increase in heart rate when they stand up.[1] This stands in contrast to the exaggerated increase in heart rate that occurs with OH due to hypovolemia.[10] NOH occurs primarily in autonomic degenerative disorders that are characterized by abnormal accumulation of alpha-synuclein. The synucleinopathies include Parkinson's disease (PD), multiple system atrophy (MSA), Lewy body dementia, and pure autonomic failure (PAF). In addition to experiencing NOH, patients with these conditions experience other forms of autonomic dysfunction, including erectile dysfunction, neurogenic bladder, and constipation.[11]

NOH can also be caused by peripheral neuropathies, such as diabetic neuropathy, amyloidosis, and Guillain-Barré syndrome; it also occurs with spinal cord injury.[5] Just as drugs can mimic non-neurogenic causes of OH, they can exacerbate the defect in sympathetic nerve activity that is characteristic of NOH. For example, alpha-adrenergic agonists (ie, clonidine, guanfacine) reduce sympathetic outflow from the central nervous system. Monoamine oxidase inhibitors may cause OH by depleting norepinephrine.[12]

Epidemiology

OH is common in elderly patients and increases with age. In the longitudinal Cardiovascular Health Study, the prevalence of symptomatic OH increased from 14.8% in patients aged 65 to 69 years to 26% in patients 85 years or older.[13] The incidence of OH is also greater in frail populations, with a prevalence as high as 50% in nursing homes compared with 6.4% in community-living elderly.[14,15] Common causes of OH in elderly patients include drugs, dehydration or volume depletion, and heart failure (HF).[5]

In contrast to OH in elderly patients, NOH is rare enough to be classified as an orphan disease in the United States.[16] Symptomatic NOH is estimated to affect approximately 80,000 patients with PD, MSA, or PAF.[17] NOH is present in approximately 80% of patients with MSA, occurring within the context of rapidly progressing autonomic failure, Parkinsonism, and cerebellar ataxia.[18] It is present in about half of patients with Lewy body dementia.[19] The reported prevalence of NOH in PD varies widely, with estimates ranging from 18% to 58%.[20,21] The point prevalence of OH in PD was 30.1% (95% CI, 22.9%-38.4%) in a meta-analysis that pooled data from 25 studies.[22] In the population-based Rochester Diabetic Neuropathy Study, the incidence of OH was 8.4% among patients with type 1 diabetes and 7.4% among patients with type 2 diabetes.[23] In 65 patients with biopsy-proven amyloidosis, 74% had orthostatic intolerance.[24]

Prognosis and Associated Comorbidities

Epidemiologic studies suggest that OH in elderly patients increases the risk of frequent falling, syncope, chronic kidney disease, stroke, HF, coronary events, and all-cause mortality.[13,25-32] In 2004, the rate of hospitalization associated with OH was 36 per 100,000 adults in the United States.[33] In addition, among the approximately 80,000 admissions of patients with OH that year, 4% were associated with PD, 4% with autonomic neuropathy, and 0.9% with abnormal degeneration of basal ganglia. In contrast to extensive data about the prognosis of OH in elderly patients, few studies describe the prognosis in NOH.

Maule and colleagues described the course of NOH in 104 patients (45 with MSA, 43 with PD, 9 with PAF, and 7 with other autonomic neuropathies) treated at an Italian center over 14 years. More than half of the patients either had comorbid cardiovascular disorders (primarily hypertension) or developed cardiac complications (primarily HF) during the course of their disease. Forty-four (42.3%) had died by the end of follow-up, with the highest mortality in patients with MSA. The death rate was higher in patients with comorbid cardiovascular disease (53% vs 31%, $P = .04$). Infection, respiratory diseases, and cachexia were the most common causes of death. Patients with NOH had a 3-fold higher risk of death than the general population in that geographic area.[34]

Table 1. Symptom Grade of Orthostatic Intolerance[2]

	Orthostatic Symptoms	Standing Time (minutes)	Activities of Daily Living	Blood Pressure
Grade I	Infrequent, inconsistent, or only if orthostatic stress	~15	Unrestricted	May or may not be abnormal
Grade II	Frequent (≥once weekly), commonly with orthostatic stress	~5	Some limits	Some changes (OH; 50% reduction in pulse pressure, excessive blood pressure oscillations)
Grade III	On most occasions; regularly unmasked by orthostatic stressors	~1	Marked limitations	OH present 50% of the time
Grade IV	Symptoms consistently present	<1	Seriously incapacitated; bed-ridden or wheelchair-bound; syncope/pre-syncope with attempts to stand	OH consistently present

OH indicates orthostatic hypotension.
Adapted from Low PA, Singer W. *Lancet Neurol.* 2008;7(5):451-458.

A French treatment center followed 31 NOH patients with autonomic failure (7 with MSA, 10 with PD, and 7 with PAF) over successive 19-day periods in August 2003 and 2004.[35] There was a dramatic heat wave in Europe during the observation period in August 2003, followed by a normal summer in 2004. The primary goal of the study was to document the effects of heat exposure, a factor known to exacerbate NOH. Clinical events were compared with a control group of PD patients who did not have NOH.

In 2003, 45.1% of NOH patients experienced at least 1 clinical adverse event compared with 11.5% of control patients. Ten events were severe in patients with NOH (6 fractures due to falls, 2 cases of head trauma due to syncope, 1 case of dehydration, and 1 hip fracture after discontinuation of midodrine) compared with none in control patients ($P = .0025$). During the year, 5 patients with NOH died (2 sudden deaths, 1 brain hemorrhage, 1 MI, and 1 respiratory event). During the second study period, in 2004, 42.3% of NOH patients experienced at least 1 clinical adverse event compared with 12% of control patients. These rates were similar to the summer before, but there were fewer severe events in NOH patients in the second year (2 cases of severe dehydration and 1 fall with head trauma). This study demonstrates the harmful effect of heat on patients with NOH. However, with 7 fractures due to falls, 3 cases of head trauma, and 5 deaths over 1 year in a cohort of 31 patients, it also documents substantial morbidity and mortality in patients with severe NOH.[35]

Signs and Symptoms of NOH

Patients with NOH tend to have more severe symptoms than patients with OH due to other causes.[2,3] They can experience dramatic drops in blood pressure during the day, especially after meals. Debilitating symptoms can make it difficult to complete simple activities of daily living[36] because patients live in fear of falling, with attendant risks of fractures and trauma.[34] This can lead them to limit physical activities and become debilitated, which further aggravates orthostatic intolerance. As a result, patients may suffer from depression, social isolation, and poor quality of life (QOL).[36] The Symptom Grade of Orthostatic Intolerance (SGOI) is used to describe the severity of NOH based on symptoms, standing time, ability to complete activities of daily living, and blood pressure measurements (see Table 1[2]). Most of the patients seen by a physician are highly symptomatic and are in grades III and IV.[37] In the managed care environment, this scale has utility in assessing the need for pharmacotherapy, in that patients with grades III or IV are likely to need aggressive therapy.

Worsening morning symptoms are related to hypovolemia, which are secondary to supine hypertension and nocturnal pressure diuresis.[1] Throughout the day, symptoms are triggered by exposure to orthostatic stressors. Postprandial worsening, due to venous pooling in the splanchnic mesenteric bed, occurs within 30 minutes of a meal and typically lasts about 1 hour[2]; this effect has been reported to be worse with breakfast and high-carbohydrate meals compared with other meals.[38,39] Drinking alcohol, especially with a meal, also exacerbates NOH through vasodilation.[2] Exacerbation of NOH by high ambient temperatures is due to vasodilation of skin vessels, while vigorous exercise can cause muscle vasodilation, especially at the end of exercise.[39] Prolonged bed rest because of deconditioning can also exacerbate NOH.[2]

Acute causes of non-neurogenic OH, such as drugs and dehydration, can worsen NOH. For example, NOH may be exacerbated by the treatment of PD with levodopa-carbidopa and other drugs.[8,40]

During evaluation at the Mayo Autonomic Reflex Laboratory, symptoms and aggravating factors were characterized in 90 patients with severe NOH. Three diseases were responsible for 90% of cases in this group: PAF, MSA, and autonomic neuropathy, including diabetic neuropathy. Based on a mean Composite Autonomic Symptom Score (CASS) of 6.9, patients had moderate to severe autonomic failure and the severity of NOH symptoms correlated with the severity of autonomic failure.[38] These patients tended to be in grades III and IV on the SGOI.[37]

The most commonly reported symptoms of orthostatic intolerance included lightheadedness (88%), weakness (72%), impaired cognition (47%), blurred vision (47%), tremulousness (38%), and vertigo (37%).[38] Half of patients developed symptoms within less than 1 minute of standing and 75% of patients developed symptoms within 5 minutes of standing. Orthostatic stressors that exacerbated OH included prolonged standing (58%), exercise (53%), warm temperatures (32%), and eating (24%). Symptoms of autonomic hyperactivity (palpitations, tremulousness, anxiety, and nausea) occurred in patients who were younger or had autonomic neuropathies, likely because they suffered from partial autonomic failure. Syncope was not a predominant symptom, with 58% of patients reporting that they had never lost consciousness completely, 28% reporting syncope less than once a month, and 14% reporting it more frequently. Although about half of patients reported that their symptoms were not worse at a particular time of day, 34% had exacerbation early in the morning.[38] Other nonspecific symptoms of NOH include fatigue, leg buckling, orthostatic dyspnea, and chest pain.[1]

In the Mayo Autonomic Reflex Laboratory study, about half of patients with NOH reported difficulty concentrating.[38] This symptom was most common in patients older than 70 years, and it was the only symptom of orthostatic intolerance in some patients.[41] Identifying NOH as the cause of atypical symptoms such as this is especially important, both to avoid an incorrect diagnosis of possible dementia and to offer access to drug therapy that can dramatically improve cognition.[38]

In NOH, a characteristic form of pain affects the back of the head and muscles in the neck in a coat-hanger distribution and may be due to ischemia of large neck muscles.[42] In a study in 22 patients with severe adrenergic impairment, almost 60% reported experiencing a coat-hanger ache during daily activities.[43] Pain would typically occur with 3 to 5 minutes of standing, had a slower onset during sitting, and was relieved within 5 to 20 minutes of lying down.

Patients with NOH become symptomatic when standing SBP falls below the range of cerebrovascular autoregulation.[44] In the autoregulated range of SBP, which is typically between 80 and 150 mm Hg, cerebral blood flow remains constant in spite of changes in blood pressure. Some patients with NOH have expansion of this range with lower pressures down to about 60 mm Hg and may be asymptomatic in spite of large falls in blood pressure.[45,46]

Quality of Life With NOH

Considering that NOH is an orphan disease, it is not surprising that studies have not formally assessed QOL in patients who have NOH. Nonetheless, the majority of reports allude to impairment of QOL.[2,6,47] One can safely estimate that QOL is poor for many patients because they may be wheelchair-bound, disabled by their symptoms, and have difficulty completing activities of daily living without assistance.

QOL has been found to be substantially impaired in patients with postural tachycardia syndrome, another disorder that is characterized by orthostatic intolerance and autonomic dysfunction.[48] Patients reported impairment across multiple domains of the short form (SF)-36, including physical functioning, role functioning, bodily pain, general health, vitality, and social functioning. Another study reported low QOL in patients with MSA, with patients reporting life satisfaction as low (mean score of 39 on a 100-point visual analog scale).[49] The average Physical Component Score on the SF-36 was 26.0 ± 8.7, 1.5 standard deviations below the mean for a cohort of healthy people of an equivalent age.

Supine Hypertension in NOH

Approximately half of patients with NOH also have supine hypertension (SH).[10,50] Consensus has not been reached about the level of blood pressure that defines SH, but studies on NOH and SH have defined SH as 150 to 180/≥90 mm Hg.[6,50] The baseline blood pressure determines the size of the fall in orthostatic blood pressure; therefore, a reduction in SBP of at least 30 mm Hg may be a more appropriate criterion for OH than at least 20 mm Hg in patients with SH.[1]

Patients with SH experience a pressure diuresis if they lie flat at night. The resulting volume depletion worsens

Table 2. Some Tests of Autonomic Nervous System Function[11]

Test	ANS Evaluated	Pathways	Interpretation
Quantitative sudomotor axon reflex test	Postganglionic sudomotor axon	Axon reflex	Integrity of postganglionic axon or sweat gland
Thermoregulatory sweat test	Thermoregulatory pathway from hypothalamus to sweat gland	Central, preganglionic, postganglionic pathways and eccrine sweat gland	Provides accurate patterns of anhidrosis; pattern can suggest site of lesion
Heart rate variability	Cardiovagal function	Vagal afferent and efferent pathways	Normal or impaired cardiovagal function
Valsalva ratio	Cardiovagal function	Vagal pathway mediating baroreflex function	Normal or impaired cardiovagal function
Blood pressure and heart rate responses to Valsalva Maneuver	Adrenergic function and baroreflex sensitivity	Baroreflex afferents and efferents	Baroreflex function, both vagal and adrenergic
Head-up tilt	Baroreflex function	Baroreflex afferents and efferents	Detection of OH
Plasma norepinephrine supine/standing	Adrenergic terminals and baroreflexes	Baroreflexes and adrenergic terminals	Norepinephrine supine provides index of postganglionic adrenergic fibers; response to standing evaluates baroreflex unloading

ANS indicates autonomic nervous system; OH, orthostatic hypotension.
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orthostatic symptoms in the morning.[51] The clinical significance of SH has not been established in longitudinal studies, but in cross-sectional studies of patients with autonomic faxilure, it has been linked to renal impairment and left ventricular hypertrophy.[52-54] Avoiding a supine blood pressure ≥180/110 mm Hg is a practical management goal for patients with SH.[2] First-line management of SH includes raising the head of the bed by inches, if necessary by 6 to 9 inches (10° to 20°), and avoiding the supine position during the day.[10]

Diagnosis of NOH

The initial diagnosis of NOH is based on blood pressure and heart rate measurements taken after the patient has been supine for at least 5 minutes, and then after 1 and 3 minutes of active standing.[10] In addition to the substantial reductions in blood pressure when standing, as specified in the definition of OH, the diagnosis of NOH is likely when the associated increase in heart rate is less than 15 beats per minute.[55] The initial diagnosis can be based on auscultatory or oscillometric measurements during active standing in the clinic or in an autonomic laboratory, where patients are placed on a tilt table in the head-up position at an angle of at least 60°.[39] HUT, which evaluates the blood pressure and heart rate response to tilt, can help distinguish between NOH and postural tachycardia syndrome.[11] European guidelines recommend HUT if the active standing test is negative, especially if the patient's history suggests OH.[56]

It should be noted that patients with milder NOH may have a normal or exaggerated heart rate increment.[57] The latter is due to a preserved and increased sympathetic response, which can manifest as orthostatic tachycardia and increased orthostatic plasma norepinephrine. These patients typically also have symptom of sympathetic activation, such as palpitations, tremulousness, sweatiness, and nausea.[58]

Patients may be asked to maintain a diary documenting supine and standing blood pressures throughout the day, as well as their symptoms and blood pressure response to orthostatic stressors (eating, exercise, etc). Sensitivity may be increased by obtaining blood pressure measurements in the morning, when NOH may be worst.[10] Diaries like these help physicians to determine a patient's level of impairment and orthostatic stressors that patients need to avoid or minimize. These diaries also provide a good opportunity to educate patients about strategies to help manage their exposure to orthostatic stressors.

Autonomic testing confirms the clinical diagnosis (see Table 2[11]). During continuous blood pressure monitoring of the Valsalva maneuver, a diagnosis of NOH is indicated by an exaggerated and sustained decrease in blood pressure without a compensatory increase in heart rate during straining (phase 2), a lack of reflex vasoconstriction shown through a loss of late phase 2 and blood pressure over-

shoot, and delayed blood pressure recovery.[59,60] By determining the distribution, severity, and progression of autonomic dysfunction with autonomic testing, a physician can distinguish between the synuceinopathies.[11] Such tests include the autonomic reflex screen, thermoregulatory sweat test, measurement of supine and standing norepinephrine, and 24-hour urinary sodium.

The autonomic reflex screen includes the quantitative sudomotor axon reflex tests of cardiovagal function (heart rate variability and Valsalva ratio), and tests of adrenergic reflex function (beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver and HUT). The 24-hour urinary sodium helps determine if the patient is drinking enough fluids and ingesting enough salt. Urine volume of 1500 to 2500 mL in 24 hours indicates adequate fluid intake, while urinary sodium excretion of more than 170 mmol/24 hours indicates adequate salt intake.[61]

The diagnosis of NOH should consider 2 variants: initial and delayed OH.[1] In initial OH, a transient drop in blood pressure (≥40 mm Hg SBP or ≥20 mm Hg DBP) occurs within about 15 seconds of standing. Initial OH can cause syncope and may be caused by a transient mismatch between cardiac output and peripheral vascular resistance. Patients may report that, when standing up quickly, they experience transient orthostatic symptoms and feel normal immediately afterward. Continuous beat-to-beat blood pressure monitoring is used to detect initial OH because blood pressure changes are too fleeting to be detected with auscultatory or oscillometric measurements.[62]

Delayed OH is defined as a drop in blood pressure that does not occur until after at least 3 minutes of standing.[1] One study found that patients with delayed NOH were younger and had smaller drops in blood pressure during the Valsalva maneuver, suggesting that delayed OH may represent earlier or less severe autonomic failure[63]; however, longitudinal studies have not been performed to confirm this. A study in more than 600 patients undergoing prolonged tilt testing used logistic regression to determine the minimum duration of testing needed to detect delayed OH.[64] The study results showed that 30 minutes was long enough to detect delayed OH

Table 3. Orthostatic Grading Scale[37]

1. Frequency of orthostatic symptoms:
- 0 I *never or rarely* experience orthostatic symptoms when I stand up.
- 1 I *sometimes* experience orthostatic symptoms when I stand up.
- 2 I *often* experience orthostatic symptoms when I stand up.
- 3 I *usually* experience orthostatic symptoms when I stand up.
- 4 I *always* experience orthostatic symptoms when I stand up.

2. Severity of orthostatic symptoms:
- 0 I *do not* experience orthostatic symptoms when I stand up.
- 1 I experience *mild* orthostatic symptoms when I stand up.
- 2 I experience *moderate* orthostatic symptoms when I stand up and *sometimes* have to sit back down for relief.
- 3 I experience *severe* orthostatic symptoms when I stand up and *frequently* have to sit back down for relief.
- 4 I experience *severe* orthostatic symptoms when I stand up and *regularly* faint if I do not sit back down.

3. Conditions when orthostatic symptoms occur:
- 0 I *never* or rarely experience orthostatic symptoms under any circumstances.
- 1 I *sometimes* experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower).
- 2 I *often* experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower).
- 3 I *usually* experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower).
- 4 I *always* experience orthostatic symptoms when I stand up; the specific conditions do not matter.

4. Activities of daily living:
- 0 My orthostatic symptoms *do not interfere* with activities of daily living (eg, work, chores, dressing, bathing).
- 1 My orthostatic symptoms *mildly interfere* with activities of daily living (eg, work, chores, dressing, bathing).
- 2 My orthostatic symptoms *moderately interfere* with activities of daily living (eg, work, chores, dressing, bathing).
- 3 My orthostatic symptoms *severely interfere* with activities of daily living (eg, work, chores, dressing, bathing).
- 4 My orthostatic symptoms *severely interfere* with activities of daily living (eg, work, chores, dressing, bathing). *I am bed-ridden or wheelchair-bound because of my symptoms.*

5. Standing time:
- 0 On most occasions, I can stand as long as necessary without experiencing orthostatic symptoms.
- 1 On most occasions, I can stand *more than 15 minutes* before experiencing orthostatic symptoms.
- 2 On most occasions, I can stand *5 to 14 minutes* before experiencing orthostatic symptoms.
- 3 On most occasions, I can stand *1 to 4 minutes* before experiencing orthostatic symptoms.
- 4 On most occasions, I can stand *less than 1 minute* before experiencing orthostatic symptoms.

Reprinted from *Mayo Clin Proc.* 80(3), Schrezenmaier C, Gehrking JA, Hines SM, Low PA, Benrud-Larson LM, Sandroni P. Evaluation of orthostatic hypotension: relationship of a new self-report instrument to laboratory-based measures, 330-334, Copyright (2005), with permission from Elsevier.

Figure 1a. Orthostatic Hypotension Questionnaire[69]

AUTONOMIC DYFUNCTION SCORES
ORTHOSTATIC HYPOTENSION QUESTIONNAIRE (OHQ)

Patient Instructions:

We are interested in measuring the symptoms that occur because of your problem with low blood pressure (orthostatic hypotension) and the degree that those symptoms may interfere with your daily activity. It is important that we measure the symptoms that are due ONLY to your low blood pressure, and not something else (like diabetes or Parkinson's disease). Many people know which of their symptoms are due to low blood pressure. Some people who have recently developed problems with low blood pressure may not easily distinguish symptoms of low blood pressure from symptoms caused by other conditions. In general, symptoms of your low blood pressure problem will appear either upon standing or after you have been standing for some time, and will usually improve if you sit down or lie down. Some patients even have symptoms when they are sitting which might improve after lying down. Some people have symptoms that improve only after sitting or lying down for quite some time.

Please answer the questions on the following pages, keeping in mind that we want to know only about those symptoms that are from your problem with low blood pressure.

Figure 1b. Orthostatic Hypotension Questionnaire[69]

OH SYMPTOM ASSESSMENT (OHSA)

Please tick the number on the scale that best rates how severe your symptoms from low blood pressure have been on the average over the past week. You should respond to every symptom. If you do not experience the symptom, circle zero (0).

YOU SHOULD RATE ONLY THE SYMPTOMS THAT ARE DUE TO YOUR LOW BLOOD PRESSURE PROBLEM.

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6 ☐ 7☐ 8☐ 9☐ 10☐ **Worst possible**

2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)
None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6 ☐ 7☐ 8☐ 9☐ 10☐ **Worst possible**

3. Weakness
None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6 ☐ 7☐ 8☐ 9☐ 10☐ **Worst possible**

4. Fatigue
None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6 ☐ 7☐ 8☐ 9☐ 10☐ **Worst possible**

5. Trouble concentrating
None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6 ☐ 7☐ 8☐ 9☐ 10☐ **Worst possible**

6. Head/neck discomfort
None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6 ☐ 7☐ 8☐ 9☐ 10☐ **Worst possible**

in patients aged at least 65 years, while 40 minutes was necessary in younger patients.

Ambulatory blood pressure monitoring (ABPM) can capture the wide fluctuations in blood pressure experienced by patients with NOH. It can help confirm the diagnosis in patients who report OH symptoms but have equivocal blood pressure measurements in the office or on the tilt test.[65] ABPM records only blood pressure and not posture, so its utility can be enhanced by documenting the patient's posture during monitoring.[10] It also has a role in the diagnosis and monitoring of SH.[66] A study that compared ABPM with office tilt test measurements found that supine office blood pressure values were predictive of nocturnal SH.[65] A study that enrolled 74 patients with MSA or PD with and without autonomic failure compared 24-hour ABPM with HUT to diagnose OH.[67] Using the standing test during 24-hour ABPM, a reduction in SBP of at least 20 mm Hg had sensitivity and specificity of 82% and 100% (area under the curve 0.91; 95% CI, 0.84-0.98), respectively, in differentiating between patients with and without OH.

Several factors may contribute to the diagnosis of NOH being missed. One reason is that symptoms of lightheadedness may be absent. Additionally, patients may instead have subtle symptoms, such as cognitive slowing.[38] Another reason is that a patient may truly be asymptomatic, due to expansion of the autoregulated range.[46] Awareness of this rare disease also presents a problem because it is understandably low among both clinicians and patients. In addition, patients may attribute NOH symptoms to their primary disorder. An online survey collected data from 178 patients with disorders that may be affected by NOH (PD, MSA, PAF, dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy) and their caregivers (n = 180).[68] Although most patients reported experiencing at least 1 symptom of NOH, 24% of patients and 22% of caregivers had never heard of NOH.

Tools for Assessing NOH Symptoms

Two self-report questionnaires have been developed specifically to assess symptoms in patients with NOH: the Orthostatic Grading Scale (OGS; Table 3[37]) and the Orthostatic

Hypotension Questionnaire (OHQ; Figure 1a-c[69]).[37,69] These instruments may be used in diagnosis to assess progression of NOH and to assess the response to pharmacotherapy in clinical practice.[41] The OHQ has been used to evaluate the clinical efficacy of droxidopa and midodrine for NOH in clinical trials.[70,71]

The OGS, which was adapted from the autonomic symptom profile, has 5 items that address the frequency and severity of orthostatic symptoms, relationship of symptoms to orthostatic stressors, and impact of symptoms on activities of daily living and standing time.[2,37] Scores for each item are summed to provide a total score for the instrument, ranging from 0 for no impairment to 20 for maximal impairment. The OGS robustly correlated with autonomic deficits on the CASS in patients undergoing full autonomic laboratory evaluation. Using a CASS adrenergic subscore of at least 3, an OGS score of at least 9 had sensitivity of 65.6% and specificity of 69.2%.[37]

Figure 1c. Orthostatic Hypotension Questionnaire[69]

OH DAILY ACTIVITY SCALE (OHDAS)

We are interested in how the low blood pressure symptoms that you experiences affect daily life. Please rate each item by ticking the number that best represents how much on the average the activity has been interfered with over the past week by the low blood pressure symptoms you have experienced.

If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

													Cannot do for other reasons
1. Activities that require standing for a short time													
No Interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	**Complete Interference**	☐
2. Activities that require standing for a long time													
No Interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	**Complete Interference**	☐
3. Activities that require walking for a short time													
No Interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	**Complete Interference**	☐
4. Activities that require walking for a long time													
No Interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	**Complete Interference**	☐

The OHQ has 2 domains: OH symptoms and their impact on walking.[69] The 6-item Orthostatic Hypotension Symptom Assessment (OHSA) asks about dizziness/lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, and head or neck discomfort. The 4-item Orthostatic Hypotension Daily Activity Scale (OHDAS) assesses the interference of NOH with daily activities: standing a short time, standing a long time, walking a short time, and walking a long time. Patients score items on a scale of 0 to 10 for the average severity of symptoms over the past week. Two factors raise questions about content validity of the OHQ: the questionnaire asks patients to rate only symptoms related to their low blood pressure problem and to average the severity of their symptoms over the past week.[72] An improvement of 0.8 to 1.0 units is considered a minimal important change on the OHSA, OHDAS, and OHQ composite score.[69]

A study in 201 patients with PD evaluated the relationship between the orthostatic drop, standing blood pressure, and symptoms of OH as characterized by the OHQ. Using the criteria of a 20/10 mm Hg drop in blood pressure for the diagnosis of NOH, 50% of patients in the cohort met the diagnosis and 33% of them were symptomatic. Using the criteria of a 30/15 mm Hg drop in blood pressure, 30% of patients met the diagnosis and 44% were symptomatic. A mean standing blood pressure lower than 75 mm Hg had 97% sensitivity and 98% specificity for detecting symptomatic OH. The authors propose a mean standing blood pressure lower than 75 mm Hg as a marker for determining if OH symptoms are substantial enough for pharmacotherapy.[73]

SUMMARY

Although NOH is rare disorder, it is important for managed care clinicians to recognize signs and symptoms of the disease and orthostatic stressors that aggravate it.

Clinicians are better able to care for patients with NOH if they understand the prognosis, the significance of SH, and the diagnostic process. Assessment tools such as the SGOI, the OGS, and the OHQ have a role in clinical practice. The SGOI can help to assess whether a patient's condition is severe enough to benefit from pharmacotherapy. The OGS and OHQ questionnaires have a role in diagnosis, as well as assessing progression and evaluating the response to pharmacotherapy.

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Address correspondence to: low@mayo.edu.

REFERENCES

1. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res.* 2011;21(2):69-72.

2. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. *Lancet Neurol.* 2008;7(5):451-458.

3. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med.* 2008;358(6):615-624.

4. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. *Muscle Nerve.* 1997;20(12):1561-1568.

5. Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. *Circulation.* 2009;119(1):139-146.

6. Arnold AC, Shibao C. Current concepts in orthostatic hypotension management. *Curr Hypertens Rep.* 2013;15(4):304-312.

7. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. *J Clin Pharm Ther.* 2005;30(2):173-178.

8. Perez-Lloret S, Rey MV, Fabre N, et al. Factors related to orthostatic hypotension in Parkinson's disease. *Parkinsonism Relat Disord.* 2012;18(5):501-505.

9. Milazzo V, Stefano CD, Servo S, et al. Drugs and orthostatic hypotension: evidence from literature. *J Hypertens.* 2012;1(2):1-8.

10. Shibao C, Lipsitz LA, Biaggioni I. Evaluation and treatment of orthostatic hypotension. *J Am Soc Hypertens.* 2013;7(4):317-324.

11. Low PA, Tomalia VA, Park KJ. Autonomic function tests: some clinical applications. *J Clin Neurol.* 2013;9(1):1-8.

12. Gugger JJ. Antipsychotic pharmacotherapy and orthostatic hypotension: identification and management. *CNS Drugs.* 2011;25(8):659-671.

13. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension.* 1992;19(6 pt 1):508-519.

14. Mader SL, Josephson KR, Rubenstein LZ. Low prevalence of postural hypotension among community-dwelling elderly. *JAMA.* 1987;258(11):1511-1514.

15. Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. *Am J Med.* 2000;108(2):106-111.

16. National Organization for Rare Diseases. Orthostatic hypotension. NORD website. http://rarediseases.org/rare-diseases/orthostatic-hypotension/. Accessed June 19, 2015.

17. Chelsea Therapeutics. Northera (droxidopa) for the treatment of neurogenic orthostatic hypotension. FDA website. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm294077.pdf. Accessed July 3, 2015.

18. Low PA, Reich SG, Jankovic J, et al. Natural history of multiple system atrophy in the USA: a prospective cohort study. *Lancet Neurol.* 2015;14(7):710-719.

19. Thaisetthawatkul P, Boeve BF, Benarroch EE, et al. Autonomic dysfunction in dementia with Lewy bodies. *Neurology.* 2004;62(10):1804-1809.

20. Low PA. Prevalence of orthostatic hypotension. *Clin Auton Res.* 2008;18(suppl 1):8-13.

21. Ha AD, Brown CH, York MK, Jankovic J. The prevalence of symptomatic orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. *Parkinsonism Relat Disord.* 2011;17(8):625-628.

22. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM. Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord.* 2011;17(10):724-729.

23. Low PA, Benrud-Larson LM, Sletten DM, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. *Diabetes Care.* 2004;27(12):2942-2947.

24. Wang AK, Fealey RD, Gehrking TL, Low PA. Patterns of neuropathy and autonomic failure in patients with amyloidosis. *Mayo Clin Proc.* 2008;83(11):1226-1230.

25. Mussi C, Ungar A, Salvioli G, et al; Evaluation of Guidelines in Syncope Study 2 Group. Orthostatic hypotension as cause of syncope in patients older than 65 years admitted to emergency departments for transient loss of consciousness. *J Gerontol A Biol Sci Med Sci.* 2009;64(7):801-806.

26. Franceschini N, Rose KM, Astor BC, Couper D, Vupputuri S. Orthostatic hypotension and incident chronic kidney disease: the atherosclerosis risk in communities study. *Hypertension.* 2010;56(6):1054-1059.

27. Jones CD, Loehr L, Franceschini N, et al. Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities study. *Hypertension.* 2012;59(5):913-918.

28. Chou RH, Liu CJ, Chao TF, et al. Association between orthostatic hypotension, mortality, and cardiovascular disease in Asians. *Int J Cardiol.* 2015;195:40-44.

29. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J.* 2010;31(1):85-91.

30. Ricci F, Fedorowski A, Radico F, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J.* 2015;36(25):1609-1617.

31. Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation.* 1998;98(21):2290-2295.

32. Angelousi A, Girerd N, Benetos A, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. *J Hypertens.* 2014;32(8):1562-1571; discussion 1571.

33. Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. *Am J Med.* 2007;120(11):975-980.

34. Maule S, Milazzo V, Maule MM, Di Stefano C, Milan A, Veglio F. Mortality and prognosis in patients with neurogenic orthostatic hypotension. *Funct Neurol.* 2012;27(2):101-106.

35. Pathak A, Lapeyre-Mestre M, Montastruc JL, Senard JM. Heat-related morbidity in patients with orthostatic hypotension and primary autonomic failure. *Mov Disord.* 2005;20(9):1213-1219.

36. FDA Cardiovascular and Renal Drugs Advisory Committee. Transcript for the January 14, 2014 meeting. FDA website. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM396030.pdf. Accessed July 4, 2014.

37. Schrezenmaier C, Gehrking JA, Hines SM, Low PA, Benrud-Larson LM, Sandroni P. Evaluation of orthostatic hypotension: relationship of a new self-report instrument to laboratory-based measures. *Mayo Clin Proc.* 2005;80(3):330-334.

38. Low PA, Opfer-Gehrking TL, McPhee BR, et al. Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clin Proc.* 1995;70(7):617-622.

39. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. *Cleve Clin J Med.* 2010;77(5):298-306.

40. Rascol O, Perez-Lloret S, Damier P, et al. Falls in ambulatory non-demented patients with Parkinson's disease. *J Neural Transm.* Published online: April 7, 2015.

41. Low PA, Fealey RD. Management of neurogenic orthostatic hypotension. In: Low PA, Benarroch EE, eds. *Clinical Autonomic Disorders*. Baltimore, MD: Lippincott Williams & Wilkins; 2008:547-559.

42. Humm AM, Bostock H, Troller R, Z'Graggen WJ. Muscle ischaemia in patients with orthostatic hypotension assessed by velocity recovery cycles. *J Neurol Neurosurg Psychiatry.* 2011;82(12):1394-1398.

43. Khurana RK. Coat-hanger ache in orthostatic hypotension. *Cephalalgia.* 2012;32(10):731-737.

44. Isaacson SH, Skettini J. Neurogenic orthostatic hypotension in Parkinson's disease: evaluation, management, and emerging role of droxidopa. *Vasc Health Risk Manag.* 2014;10:169-176.

45. Arbogast SD, Alshekhlee A, Hussain Z, McNeeley K, Chelimsky TC. Hypotension unawareness in profound orthostatic hypotension. *Am J Med.* 2009;122(6):574-580.

46. Novak V, Novak P, Spies JM, Low PA. Autoregulation of cerebral blood flow in orthostatic hypotension. *Stroke.* 1998;29(1):104-111.

47. Mathias CJ. L-dihydroxyphenylserine (Droxidopa) in the treatment of orthostatic hypotension: the European experience. *Clin Auton Res.* 2008;18(suppl 1):25-29.

48. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin Proc.* 2002;77(6):531-537.

49. Benrud-Larson LM, Sandroni P, Schrag A, Low PA. Depressive symptoms and life satisfaction in patients with multiple system atrophy. *Mov Disord.* 2005;20(8):951-957.

50. Biaggioni I, Robertson RM. Hypertension in orthostatic hypotension and autonomic dysfunction. *Cardiol Clin.* 2002;20(2):291-301, vii.

51. Ten Harkel AD, Van Lieshout JJ, Wieling W. Treatment of orthostatic hypotension with sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *J Intern Med.* 1992;232(2):139-145.

52. Garland EM, Gamboa A, Okamoto L, et al. Renal impairment of pure autonomic failure. *Hypertension.* 2009;54(5):1057-1061.

53. Vagaonescu TD, Saadia D, Tuhrim S, Phillips RA, Kaufmann H. Hypertensive cardiovascular damage in patients with primary autonomic failure. *Lancet.* 2000;355(9205):725-726.

54. Maule S, Milan A, Grosso T, Veglio F. Left ventricular hypertrophy in patients with autonomic failure. *Am J Hypertens.* 2006;19(10):1049-1054.

55. Biaggioni I. Treatment: special conditions: orthostatic hypotension. *J Am Soc Hypertens.* 2015;9(1):67-69; quiz 70.

56. Lahrmann H, Cortelli P, Hilz M, et al. Orthostatic hypotension. In: *European Handbook of Neurological Management*. Wiley-Blackwell; 2010:469-475.

57. Mar PL, Shibao CA, Garland EM, et al. Neurogenic hyperadrenergic orthostatic hypotension: a newly recognized variant of orthostatic hypotension in older adults with elevated norepinephrine (noradrenaline). *Clin Sci (Lond).* 2015;129(2):107-116.

58. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. *Neurology.* 1999;52(3):523-528.

59. Vogel ER, Sandroni P, Low PA. Blood pressure recovery from Valsalva maneuver in patients with autonomic failure. *Neurology.* 2005;65(10):1533-1537.

60. Schrezenmaier C, Singer W, Swift NM, Sletten D, Tanabe J, Low PA. Adrenergic and vagal baroreflex sensitivity in autonomic failure. *Arch Neurol.* 2007;64(3):381-386.

61. Low PA, Tomalia VA. Orthostatic hypotension: mechanisms, causes, management. *J Clin Neurol.* 2015;11(3):220-226.

62. Stewart JM, Clarke D. "He's dizzy when he stands up": an introduction to initial orthostatic hypotension. *J Pediatr.* 2011;158(3):499-504.

63. Gibbons CH, Freeman R. Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. *Neurology.* 2006;67(1):28-32.

64. Gurevich T, Machmid H, Klepikov D, Ezra A, Giladi N, Peretz C. Head-up tilt testing for detecting orthostatic hypotension: how long do we need to wait? *Neuroepidemiology.* 2014;43(3-4):239-243.

65. Norcliffe-Kaufmann L, Kaufmann H. Is ambulatory blood pressure monitoring useful in patients with chronic autonomic failure? *Clin Auton Res.* 2014;24(4):189-192.

66. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med.* 2006;354(22):2368-2374.

67. Vichayanrat E, Low DA, Stuebner E, Iodice V, Mathias CJ. 24-hour ambulatory blood pressure monitoring in Parkinson's disease and multipe system atrophy [abstract 1556]. *Mov Disord.* 2014;29(suppl 1):S571.

68. Chelsea Therapeutics. Neurogenic orthostatic hypotension (also known as neurogenic OH or NOH). http://www.msa-ams.be/MSA-AMS/NEWS-NIEUWSFLASH/Artikelen/2012/2/9_Neurogenic_orthostatic_hypotension_(also_known_as_Neurogenic_OH_or_NOH)..html. Accessed July 2, 2015.

69. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. *Clin Auton Res.* 2012;22(2):79-90.

70. Biaggioni I, Freeman R, Mathias CJ, Low P, Hewitt LA, Kaufmann H. Randomized withdrawal study of patients with symptomatic neurogenic orthostatic hypotension responsive to droxidopa. *Hypertension.* 2015;65(1):101-107.

71. Shire Pharmaceuticals. Clinical efficacy of midodrine in symptomatic orthostatic hypotension. Clinicaltrials.gov website. https://www.clinicaltrials.gov/ct2/show/results/NCT01515865?sect=X70156&term=midodrine&rank=12#outcome1. Accessed June 17, 2015.

72. NDA 203202 Study Endpoint Review: Orthostatic Hypotension Questionnaire. FDA website. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm294076.pdf. Accessed July 8, 2015.

73. Palma JA, Gomez-Esteban JC, Norcliffe-Kaufmann L, et al. Orthostatic hypotension in Parkinson disease: how much you fall or how low you go? *Mov Disord.* 2015;30(5):639-645.