Orthostatic hypotension (OH) is defined as a persistent, consistent, orthostatic fall in systolic blood pressure of ≥20 mm Hg or diastolic pressure of ≥10 mm Hg by 3 minutes of standing up. Acute, unexpected, episodic falls in blood pressure while standing, as in neurocardiogenic syncope, do not satisfy criteria for OH.

Medical records for ≈0.4% of all hospitalizations in the United States include OH as a diagnosis, and of these ≈17% have OH as the primary diagnosis. OH is associated with increased mortality in middle-aged adults and occurs especially commonly in the elderly, with a prevalence in the United States of ≈12%. The rate of hospitalization for nonacute OH increases exponentially with age. Therefore, as the US population ages, the prevalence of OH and the incidence of OH-related morbidity are likely to increase.

OH can be an asymptomatic sign or manifest as symptoms that range from lightheadedness to loss of consciousness. In our experience, patients with OH do not typically present with recurrent syncope because they come to recognize and respond to premonitory symptoms such as generalized weakness, dizziness, fading vision, or lightheadedness that are relieved by lying down. Instead, OH patients often present with orthostatic intolerance and recurrent falls, an important risk factor for hip fracture and head trauma.

Moreover, OH often occurs concurrently with supine hypertension, which can be severe. The combination of OH and supine hypertension poses a challenging clinical dilemma because the clinician must balance the risk of chronic high blood pressure versus the immediate risk of falls and consequent morbid events.

Causes of OH

Many causes of OH have been identified. The listing in Table 1 stratifies these in terms of drugs, secondary nonneurogenic causes, secondary neurogenic causes, and primary neurogenic causes. Accordingly, the clinical approach to a patient with OH (Figure 1) is, first, to determine that the patient has a persistent, consistent orthostatic fall in blood pressure. Common reversible causes of orthostatic decreases in pressure, such as gastrointestinal hemorrhage and nitroglycerin treatment, should be excluded. Second, one should look for identifiable causes of OH. Probably the most common are medications, hypovolemia, dehydration, cardiac pump failure, and diseases—mostly irreversible—that are associated with autonomic neuropathies (eg, diabetes mellitus, chronic renal failure, and amyloidosis).

Even after extensive evaluation, approximately one third of patients with persistent, consistent OH have no identified cause. For these, the term idiopathic OH has been used. In virtually all such cases, OH is associated with an abnormality of reflexive regulation of the circulation by the sympathetic noradrenergic system—that is, idiopathic OH is neurogenic. Failure of the sympathetic nervous system always results in a failure to tolerate upright posture because of OH. Conversely, OH is a cardinal manifestation of sympathetic failure. Indeed, absence of OH excludes generalized sympathetic failure. Therefore, the third step is to confirm that OH is neurogenic—neurogenic OH (NOH).

Clinical Laboratory Tests to Identify NOH

A variety of means are available to identify failure of reflexive sympathetically mediated cardiovascular responses (sympathetic neurocirculatory failure) as the cause of OH in individual patients. Different medical centers have different tests available.

Such failure produces characteristic abnormalities of beat-to-beat blood pressure associated with the Valsalva maneuver (Figure 2). In patients with NOH, systolic blood pressure decreases progressively during the maneuver; after release of the maneuver, systolic pressure increases slowly toward the baseline value, and no pressure overshoot occurs. Beat-to-beat blood pressure can now be measured noninvasively with any of a variety of commercially available devices.

Measurements of forearm or total peripheral resistance responses provide other indirect physiological measures. In sympathetic neurocirculatory failure, these resistances fail to increase during orthostasis or other stimuli that decrease venous return to the heart.

A neurochemical index to detect NOH is the plasma norepinephrine response to orthostasis. Normally, plasma norepinephrine levels approximately double within 5 minutes
of standing. In NOH, plasma norepinephrine usually increases by \( <60\% \) or by \(< 1\ \text{nmol/L} \ (\approx 150\ \text{pg/mL}) \).10

Patients with NOH typically also have baroreflex-cardiovagal failure. This explains why heart rate responses to the Valsalva maneuver or deep breathing usually are subnormal in NOH (Figure 2). It should be noted, however, that these responses are mediated mainly by the parasympathetic cholinergic system, not the sympathetic noradrenergic system.

NOH is a major manifestation of several diseases that are associated with chronic autonomic failure. Approximately 40% of patients with Parkinson disease (PD) have OH11 and according to our experience, in all such patients the OH is neurogenic. Multiple system atrophy (MSA), pure autonomic failure (PAF), autoimmune autonomic ganglionopathy (AAG12), familial dysautonomia, and dopamine-\( \beta \)-hydroxylase deficiency also cause NOH.

Studying diseases in which the sympathetic nervous system fails can shed light on the pathophysiology of NOH and allow better understanding of this clinically challenging condition. Appraisal of published data by our group and others has induced us to view primary NOH syndromes with a somewhat new perspective that puts more emphasis on the pathophysiological findings than on the specific diagnosis, which can require postmortem pathologic confirmation and therefore may not ever be established with surety in individual patients. The following section focuses on these data and the insights that can be drawn from them about NOH in general.

Stratification of NOH in Terms of Sympathetic Noradrenergic Denervation

Analysis of our data, summarized below, indicates that NOH patients can be classified pathophysiologically in terms of the presence or absence of sympathetic noradrenergic denervation. Moreover, this categorization applies to NOH with or without central neurodegeneration and regardless of whether the neurological clinical diagnosis is definite or equivocal.

### Table 1. Some Causes of Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Class</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Vasoconstrictors (eg, norepinephrine)</td>
</tr>
<tr>
<td></td>
<td>Dopamine receptor agonists</td>
</tr>
<tr>
<td></td>
<td>Sympatholytics</td>
</tr>
<tr>
<td></td>
<td>Drugs for erectile dysfunction (eg, sildenafil)</td>
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<tr>
<td></td>
<td>Phenothiazines</td>
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<tr>
<td></td>
<td>Diuretics</td>
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<td></td>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td></td>
<td>Narcotics/tranquilizers/sedatives</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Primary neurogenic causes</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>PAF</td>
</tr>
<tr>
<td></td>
<td>Lewy body dementia</td>
</tr>
<tr>
<td></td>
<td>Familial dysautonomia (incomplete development of sympathetic noradrenergic innervation)</td>
</tr>
<tr>
<td>Intact sympathetic noradrenergic innervation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSA, in most cases</td>
</tr>
<tr>
<td></td>
<td>Dopamine ( \beta )-hydroxylase deficiency (intact innervation but norepinephrine deficiency)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune ganglionopathy (rare; probably intact sympathetic noradrenergic innervation)</td>
</tr>
</tbody>
</table>

(Continued)
Neurochemical Tests to Identify Sympathetic Noradrenergic Denervation

In PAF, MSA, and PD, NOH is associated with attenuated orthostatic increments in plasma norepinephrine levels. The conditions differ, however, in terms of plasma norepinephrine levels during supine rest. In MSA and PD, plasma norepinephrine is generally normal, whereas in PAF, plasma norepinephrine is generally low. The finding of normal plasma norepinephrine levels in PD does not necessarily indicate normal overall sympathetic noradrenergic innervation. Plasma levels of dihydroxyphenylglycol (DHPG) provide a better measure of noradrenergic innervation, and plasma DHPG is subnormal in both PD and PAF.

One can assess the density of noradrenergic innervation of skeletal muscle by measuring concentrations of catechols in

Figure 1. Algorithm for clinical evaluation of OH. The algorithm asks if OH is persistent and consistent; if it is neurogenic; and if it is associated with postganglionic, sympathetic, noradrenergic denervation. BP indicates blood pressure; CNS, central nervous system; LBD, Lewy body dementia; and NE, norepinephrine.

Figure 2. Heart rate and blood pressure responses in the 4 phases of the Valsalva maneuver in (left) a control subject and (right) a patient with NOH. NOH is characterized by a progressive decline in blood pressure in phase II (arrow), slow recovery of blood pressure in phases III and IV (gray polygon), and absence of overshoot in pressure above baseline in phase IV (thick black line).
Microdialysate. Microdialysate DHPG concentrations are similarly low in PD+NOH and PAF compared with MSA and control subjects. These results point to generalized peripheral noradrenergic denervation in PD+NOH and PAF.

Sympathetic noradrenergic denervation is associated not only with decreased norepinephrine turnover, as indicated by low plasma DHPG levels, but also with decreased neuronal uptake of norepinephrine from the extracellular fluid, via the uptake-1 process mediated by the cell membrane norepinephrine transporter. Patients with PAF have decreased uptake-1 activity in the body as a whole, whereas MSA patients have normal uptake-1 activity. Collectively, the neurochemical profile identifies 2 groups of patients: those with postganglionic noradrenergic denervation, as in PD+NOH and PAF, and those with intact postganglionic innervation, as in MSA.

**Neuroimaging Tests to Identify Sympathetic Noradrenergic Denervation**

The aforementioned suggestion of grouping by pathophysiology is supported by many reports in which neuroimaging methods have been used. The introduction of cardiac sympathetic neuroimaging in the mid-1990s added a new dimension to assessment of the sympathetic nervous system in NOH. 6-[18F]Fluorodopamine positron emission tomographic scanning and [123I]MIBG scintigraphy (superseded by single photon emission tomographic scanning) revealed cardiac noradrenergic denervation in vivo for the first time in patients with NOH. Over the past decade, >50 studies in which these and analogous radioactive drugs were used have reported results of cardiac sympathetic neuroimaging in PAF, PD, and MSA that in general have confirmed cardiac noradrenergic denervation in PAF and PD+NOH and normal innervation in most patients with MSA (Figures 3 and 4).

Important confirmation of the validity of cardiac sympathetic neuroimaging to identify cardiac noradrenergic denervation in NOH syndromes has come from neurochemical studies demonstrating decreased cardiac spillovers of norepinephrine and DHPG and from several postmortem studies showing profound loss of tyrosine hydroxylase immunoreactivity in all patients who during life had neuroimaging evidence of cardiac sympathetic denervation. Patients with PD from parkin gene mutation, which is not associated with NOH and is thought not to be a Lewy body disease, have been found to have normal cardiac [123I]MIBG-derived radioactivity.

Although patients with PAF have neuroimaging evidence of cardiac sympathetic denervation, a few have approximately normal innervation. This subgroup includes at least some who have a circulating antibody to the nicotinic cholinergic receptor, resulting in a diagnosis of AAG. All 3 patients we have tested with AAG and high titers of antibodies to the neuronal nicotinic receptor have had normal cardiac 6-[18F]fluorodopamine–derived radioactivity (D.S.G., unpublished data, 2008), and another patient evaluated by [123I]MIBG scanning also had normal results.28 Moreover, animal models of AAG have intact postganglionic neurons.29

Even in patients with NOH and evidence of central neurodegeneration in whom the neurological diagnosis is equivocal, cardiac sympathetic neuroimaging clearly separates a group with cardiac noradrenergic denervation from a group with normal innervation, in a manner closely resembling the distributions among patients with a definite diagnosis (Figure 5).

**Neuropharmacological Tests to Identify Sympathetic Noradrenergic Denervation**

Several neuropharmacological tests have been used to identify sympathetic noradrenergic denervation in primary NOH syndromes. In general, patients with sympathetic noradrenergic denervation would be expected to have attenuated neurochemical or hemodynamic responses to drugs that work by releasing norepinephrine from sympathetic nerves and normal or augmented responses to drugs that stimulate adrenoceptors directly.

**Yohimbine**

Yohimbine is an α2-adrenoceptor blocker. This drug increases release of norepinephrine from sympathetic nerves via in-
increasing sympathetic neuronal outflows and inhibiting $\alpha_2$ adrenoceptors on sympathetic nerves.\textsuperscript{30} Yohimbine infusion evokes large increases in both blood pressure and plasma norepinephrine levels in patients with intact noradrenergic innervation, in contrast to attenuated increases in patients with noradrenergic denervation.\textsuperscript{31,33}

**Trimethaphan**

Trimethaphan decreases sympathetic neuronal outflows by blocking nicotinic receptors mediating ganglionic neurotransmission. Blood pressure and plasma norepinephrine levels therefore decrease. The decrements are relatively large in patients with intact noradrenergic innervation.\textsuperscript{31,33}

**Tyramine**

Sympathetic nerves take up tyramine via the cell membrane norepinephrine transporter, and the vesicles in sympathetic nerves take up tyramine via the vesicular monoamine transporter, displacing norepinephrine. The norepinephrine displaced into the cytoplasm undergoes deamination catalyzed by monoamine oxidase to form DHPG, which readily crosses the cell membrane and enters the plasma. Plasma DHPG responses to tyramine therefore provide a measure of uptake-1 activity and of norepinephrine turnover in sympathetic nerves.\textsuperscript{34} Plasma DHPG responses to tyramine are attenuated in patients with noradrenergic denervation.\textsuperscript{35}

Some of the norepinephrine displaced by tyramine enters the extracellular fluid by a nonexocytotic process and binds to $\alpha$-adrenoceptors, thereby increasing blood pressure.\textsuperscript{36,37} The absence of vasoconstriction responses to tyramine has been associated with absence of catecholamine-specific fluorescence in skeletal muscle,\textsuperscript{38} supporting the validity of the tyramine infusion test as a means to detect sympathetic denervation. Pressor responses to tyramine, however, can be normal in patients with partial noradrenergic denervation, possibly due to effects of concurrent, counterbalancing baroreflex failure and denervation supersensitivity. PAF patients have a shift to the left of the curve relating pressor responses to increments in plasma norepinephrine.\textsuperscript{39} Therefore, in detecting noradrenergic denervation by the intravenous tyramine infusion test, neurochemical responses are more sensitive than systemic physiological responses.

**Isoproterenol**

Infusion of isoproterenol, a nonselective $\beta$-adrenoceptor agonist, evokes release of norepinephrine from sympathetic nerves via reflexive increases in sympathetic nerve traffic in response to systemic vasodilation and stimulation of $\beta_2$ adrenoceptors on sympathetic nerves.\textsuperscript{40,41} The plasma norepinephrine response to isoproterenol therefore provides a measure of the ability to release norepinephrine by exocytosis from sympathetic nerves. Patients with noradrenergic denervation have attenuated plasma norepinephrine responses for given isoproterenol plasma levels.\textsuperscript{16}

Isoproterenol infusion increases heart rate via direct stimulation of $\beta$-adrenoceptors on myocardial cells. For a given plasma isoproterenol level, patients with cardiac noradrenergic denervation detected by sympathetic neuroimaging have an augmented tachycardia response, consistent with upregulation of cardiac $\beta$-adrenoceptors.\textsuperscript{35}

### Agreement Among Modalities to Identify Sympathetic Noradrenergic Denervation

Individual values for concentrations of 6-[$^{18}$F]fluorodopamine–derived radioactivity in the interventricular septal myocardium are correlated positively with a variety of neurochemical and neuropharmacological indices of noradrenergic innervation, whether data from all subjects or from patients with NOH (Table 2) specifically are considered. Positive correlations between DHPG levels in plasma or skeletal muscle microdialysate and cardiac 6-[$^{18}$F]fluorodopamine–derived radioactivity indicate that loss of cardiac noradrenergic nerves is associated with more generalized noradrenergic denervation. Smaller norepinephrine or DHPG responses to tyramine, yohimbine, and isoproterenol in subjects with low cardiac 6-[$^{18}$F]fluorodopamine–derived radioactivity indicate decreased turnover of stored norepinephrine in sympathetic nerves in patients with cardiac noradrenergic denervation.\textsuperscript{18}

### Table 2. Correlation Coefficients for Relationships Between Cardiac 6-[$^{18}$F]Fluorodopamine–Derived Radioactivity and Neurochemical and Neuropharmacological Indices of Overall Noradrenergic Innervation: Supine Plasma DHPG, DHPG in Microdialysate of Skeletal Muscle, Change in Plasma Norepinephrine Level in Response to Yohimbine and Isoproterenol, and Change in Systolic Blood Pressure in Response to Yohimbine

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects</th>
<th>Patients With NOH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$n$</td>
</tr>
<tr>
<td>DHPG plasma</td>
<td>0.22</td>
<td>158</td>
</tr>
<tr>
<td>DHPG microdialysate</td>
<td>0.48</td>
<td>33</td>
</tr>
<tr>
<td>$\Delta$norepinephrine/ yohimbine</td>
<td>0.27</td>
<td>60</td>
</tr>
<tr>
<td>$\Delta$norepinephrine/ isoproterenol</td>
<td>0.40</td>
<td>27</td>
</tr>
<tr>
<td>$\Delta$BP/yohimbine</td>
<td>0.37</td>
<td>43</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.
Isoproterenol levels for 25-bpm increments in heart rate correlated positively with cardiac 6-[18F]fluorodopamine–derived radioactivity (Table 2). Analogously, a positive relationship was found between the increment in cardiac contractility (reflected by the acceleration index, an impedance cardiographic measure of cardiac contractility) and cardiac 6-[18F]fluorodopamine–derived radioactivity. These findings are consistent with upregulation of cardiac β-adrenoceptors. The positive relationship between the ratio of Δsystolic pressure to Δplasma norepinephrine and cardiac 6-[18F]fluorodopamine–derived radioactivity is consistent with upregulation of α-adrenoceptors on vascular smooth muscle cells.

In general, neurochemical responses to the test drugs correlate more closely with cardiac 6-[18F]fluorodopamine–derived radioactivity than with hemodynamic responses. An explanation for these differences is that the physiologically dependent measures are more indirect, influenced by adrenoceptor upregulation and individual differences in baroreflex function.

The ratio of cerebrospinal fluid to plasma norepinephrine, a neurochemical index of central norepinephrine deficiency, is approximately normal in PD+NOH, whereas MSA patients have low ratios of cerebrospinal fluid to plasma compared with control subjects. Individual values for cardiac 6-[18F]fluorodopamine–derived radioactivity are correlated negatively with this index of central norepinephrine deficiency (r = -0.37, P = 0.0003). Therefore, the central noradrenergic abnormalities in primary NOH seem to be a mirror image of those in the periphery. PD+NOH seems to be associated with more severe peripheral noradrenergic deficiency, whereas MSA seems to be associated with more severe central noradrenergic deficiency.

Pathophysiological Classification of NOH

The clinical importance of NOH warrants special and separate consideration by medical practitioners. This analysis has identified 2 distinct groups of patients with primary NOH, regardless of clinical diagnosis. Patients with neuroimaging evidence of cardiac noradrenergic denervation also have evidence of loss of noradrenergic innervation in the body as a whole, corresponding abnormalities in neurochemical responses to test drugs, and evidence of compensatory upregulation of adrenoceptors. Patients with central neurodegeneration and neuroimaging evidence of intact cardiac noradrenergic innervation have neurochemical abnormalities suggesting central norepinephrine deficiency. Collectively, the neurochemical, neuroimaging, and neuropharmacological results complement each other.

Considering the many positive intercorrelations across a variety of assessment modalities, we propose a classification for patients with NOH based on evidence of peripheral noradrenergic denervation. An algorithm for clinical evaluation of OH therefore emphasizes identifying NOH and then peripheral noradrenergic deficiency (Figure 1).

Diagnostic and Therapeutic Implications

This classification schema has implications for the clinical management of patients with NOH in terms of both diagnosis and predicted responses to treatment. Table 3 lists some causes of NOH and diagnostic challenges.

In patients with NOH who have no clinical evidence of central neurodegeneration, the finding of normal peripheral noradrenergic innervation casts doubt on the diagnosis of PAF. Testing for a circulating antibody to the neuronal nicotinic receptor (nAChR) is appropriate in this situation because of the potential for improvement of AAG by total plasma exchange or immunosuppressive therapy. In patients with NOH and central neurodegeneration, the finding of normal cardiac noradrenergic innervation seems to exclude PD+NOH and favors a diagnosis of MSA.

Once the patient has been placed into 1 of the 2 categories, therapy may be tailored according to the pathophysiological classification. Patients with NOH and intact peripheral noradrenergic innervation might benefit from oral yohimbine. One must exercise caution because of the likelihood of oral yohimbine worsening supine hypertension. An indirectly acting sympathomimetic amine such as tyramine given with a monoamine oxidase inhibitor might also be tried, but with the same precaution.
Patients with NOH have baroreflex failure and therefore have exaggerated responses to vasoactive drugs. For the same severity of baroreflex failure, patients with peripheral noradrenergic denervation have larger responses to drugs that increase occupation of adrenoceptors and smaller responses to drugs that work by releasing norepinephrine. In NOH with peripheral noradrenergic denervation, when evidence for adrenoceptor upregulation is obtained, a directly acting adrenoceptor agonist would seem appropriate. Midrodrine is the only orally acting α-adrenoceptor agonist approved for marketing in the United States. Norepinephrine precursor treatment with L-threo-3,4-dihydroxyphenylserine might play a role here in the future because conversion of L-threo-3,4-dihydroxyphenylserine to norepinephrine does not require intact noradrenergic nerves. Patients with noradrenergic denervation would be less likely to respond well to yohimbine or to an indirectly acting sympathomimetic amine.

Patients with symptomatic OH despite treatment with these drugs may also be treated with the salt-retaining steroid fludrocortisone (on a high-salt diet), octreotide, or desmopressin because these drugs have separate mechanisms of action from those acting directly or indirectly on adrenoceptors.

Because of supine hypertension in NOH patients, drugs that increase blood pressure should be given only during active hours. At night, patients should be instructed to sleep with the head of the bed elevated. Bedtime medications in patients with supine hypertension might include nitrates or fludrocortisone (on a high-salt diet), octreotide, or desmopressin because these drugs have separate mechanisms of action from those acting directly or indirectly on adrenoceptors. Because of supine hypertension in NOH patients, drugs that increase blood pressure should be given only during active hours. At night, patients should be instructed to sleep with the head of the bed elevated. Bedtime medications in patients with supine hypertension might include nitrates or fludrocortisone (on a high-salt diet), octreotide, or desmopressin because these drugs have separate mechanisms of action from those acting directly or indirectly on adrenoceptors.

Conclusions

NOH adversely affects well-being and is associated with increased morbidity, especially in the elderly. Advances in the understanding of the pathophysiology of NOH have led us to propose a classification of NOH based on the occurrence of peripheral noradrenergic denervation. Categorizing patients in terms of the presence or absence of peripheral noradrenergic denervation can aid diagnosis and rationalize treatment.

Acknowledgments

The authors thank the many individuals who have contributed to the research summarized in this review, including (in alphabetical order) Graeme Eisenhofer, PhD; Basil Eldadah, MD, PhD; Courtney Holmes, CMT; Richard Ingrisch, MD, PhD; Terezia Jenkins; Irwin J. Kopin, MD; Shengting Li, MD, PhD; Jeffrey Moak, MD; Sandra Pechnik, RN; and Ahmed Saleem, MD.

Sources of Funding

The research was supported by the intramural research program of the National Institutes of Health.

Disclosures

None.


Neurogenic Orthostatic Hypotension: A Pathophysiological Approach
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Circulation. 2009;119:139-146
doi: 10.1161/CIRCULATIONAHA.108.805887
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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