Neurogenic Orthostatic Hypotension. Lessons From Synucleinopathies

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Maintenance of upright blood pressure critically depends on the autonomic nervous system and its failure leads to neurogenic orthostatic hypotension (NOH). The most severe cases are seen in neurodegenerative disorders caused by abnormal α-synuclein deposits: multiple system atrophy (MSA), Parkinson's disease, Lewy body dementia, and pure autonomic failure (PAF). The development of novel treatments for NOH derives from research in these disorders. We provide a brief review of their underlying pathophysiology relevant to understand the rationale behind treatment options for NOH. The goal of treatment is not to normalize blood pressure but rather to improve quality of life and prevent syncope and falls by reducing symptoms of cerebral hypoperfusion. Patients not able to recognize NOH symptoms are at a higher risk for falls. The first step in the management of NOH is to educate patients on how to avoid high-risk situations and providers to identify medications that trigger or worsen NOH. Conservative countermeasures, including diet and compression garments, should always precede pharmacologic therapies. Volume expanders (fludrocortisone and desmopressin) should be used with caution. Drugs that enhance residual sympathetic tone (pyridostigmine and atomoxetine) are more effective in patients with mild disease and in MSA patients with spared postganglionic fibers. Norepinephrine replacement therapy (midodrine and droxidopa) is more effective in patients with neurodegeneration of peripheral noradrenergic fibers like PAF. NOH is often associated with other cardiovascular diseases, most notably supine hypertension, and treatment should be adapted to their presence.

Keywords: autonomic nervous system; blood pressure; hemodynamics; hypertension; orthostatic hypotension; synucleinopathies; treatment.

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Neurogenic orthostatic hypotension (NOH) is the consequence of impaired sympathetic vasoconstriction due to defective norepinephrine release from postganglionic neurons.[1] Orthostatic symptoms occur when the patient changes position from lying/sitting to standing; symptoms disappear when the patient reassumes the lying position because the blood flow is restored in the brain and other tissues.[2]

Classic symptoms are lightheadedness, dizziness, blurry vision, faintness, and syncope due to a reduction of cerebral blood flow. However, NOH may present with a range of severity and variety of symptomatology. NOH may be asymptomatic, particularly in patients with chronic disease, due to adaptive changes in cerebral blood flow regulation so that patients can tolerate lower blood pressures (BP) on standing. Other symptoms are occipital headache, neck, and shoulder ("coat hanger") pain, dyspnea, angina pain, transient cognitive dysfunction, generalized weakness, and fatigue. It is important to recognize OH because it is a risk factor for falls and it is a predictor of mortality.[3]

Our aim is to provide a practical approach to the evaluation and treatment of patients with NOH. Most of our knowledge in this area, and novel therapies highlighted herein, are derived from research in NOH associated with synucleinopathies, a group of neurodegenerative disorders, including Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF). In the absence of evidence in which to base recommendations for the treatment of more common causes of NOH, we rely on the understanding of the pathophysiology of these conditions.

DEFINITIONS

Orthostatic hypotension (OH) is defined as a sustained reduction of systolic BP ≥20 mm Hg or diastolic BP ≥10 mm Hg within 3 minutes of active standing or passive 60° head-up tilt using a tilt table.[4] Patients with NOH meet the definition for OH, but, in addition, show sympathetic nervous system dysfunction, characterized by an abnormal response to postural baroreflex activation with impairment of both systemic vasoconstriction and the compensatory heart rate (HR)

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increase that maintains normal BP on standing. In NOH, the increase seen in HR at standing up is usually less than 20 bpm.[5] Related conditions include delayed OH, which occurs when BP falls after 3 minutes of standing or head-up tilt-table testing,[6] and postprandial hypotension, which is defined as a systolic BP drop of ≥20 mm Hg within 2 hours after a meal.[7]

Mechanisms regulating cardiovascular responses to orthostatic stress

Upon standing, gravitational forces produce a blood volume shift of about 500–800 ml, with venous blood pooling in the lower part of the body; thus, venous return and stroke volume decrease, and BP consequently falls. In response to this stress, the arterial baroreflex buffering mechanisms send afferent information (via IX and X cranial nerves) to the brainstem in order to activate the sympathetic vasoconstrictor response to raise BP and to inhibit cardiovagal outflow to increase HR.[8] Cardiopulmonary volume receptors also activate in response to the fall in central blood volume and send information (via X cranial nerve) to the brainstem for BP modulation through the sympathetic efferent pathways and by the release of antidiuretic peptide vasopressin (AVP) and renin. Short- and long-term control of the BP on standing depends on baroreflex modulation of sympathetic vasomotor efferent pathways and activation of both AVP release and the renin–angiotensin system.[9]

Pathophysiology and symptoms of NOH

In the context of synucleinopathies, NOH is the result of sympathetic denervation at different levels of the nervous system, depending on each specific disease. The baroreflex activation of the sympathetic vasoconstrictor efferent limb is defective, so, on standing, total peripheral resistance fails to increase and cardiac output decreases due to impaired venous return. Normally plasma noradrenaline levels are double the supine value on standing, but this increase is blunted in NOH. There is a reduced HR response to orthostatic BP fall. In PD and PAF, this HR reduction is more pronounced than in MSA.[10]

The resulting sustained orthostatic fall in BP leads to a reduction of perfusion pressure in organs above the heart level. The main and most frequent symptoms are due to a reduction in cerebral blood flow, but hypoperfusion to other territories like the retina, neck, heart, and lung may also be responsible for other symptoms listed.[1] The spectrum of NOH symptoms is summarized in Table 2. NOH is frequently associated with supine hypertension, a phenomenon not completely understood, but possible mechanisms causing this condition are denervation hypersensitivity, residual sympathetic activity, and baroreflex dysfunction.[11]

NOH symptoms associated with brain hypoperfusion

Frequent symptoms when a NOH patient stands up quickly are dizziness, lightheadedness, and tunnel, blurred, or diminished vision. Arm movements while standing may worsen these symptoms due to a subclavian steal phenomenon, reducing brainstem blood flow. Presyncope and syncope are often seen in MSA and PAF patients during the initial stages of the disease. As patients learn to recognize presyncope symptoms, they become able to prevent fainting by adopting a seating or recumbent position. The beginning of syncope may be more insidious in older patients with PD and DLB and the presence of NOH can be initially ignored, leading to unnecessary investigations.[12] A less frequent symptom associated with brain hypoperfusion is a transient cognitive deficit on standing.[13,14]

NOH symptoms associated with hypoperfusion of other territories

Suboccipital, neck and shoulder (coat hanger distribution) pain while standing are characteristic symptoms of NOH. The discomfort may be severe and is possibly due to a reduction of muscle blood flow in the neck muscles, which are active on standing. Unexplained chest pain occurring only on standing or walking may occur in patients without coronary artery disease.[15,16] In patients with NOH, orthostatic dyspnea also may occur in the absence of any cardiac or pulmonary disease, and it is due to ventilation–perfusion mismatch in the lung apices.[17]

Nonspecific symptoms of NOH

Generalized weakness, fatigue, headache, or nausea may be the predominant complaints in some patients; in others, they may appear concomitantly to classic orthostatic symptoms. When these nonspecific manifestations occur in isolation, it is hard to suspect the presence of NOH. It is important to ask the patient if the symptoms occur only while standing and whether they are relieved by lying down.[12,18,19]

NOH without orthostatic symptoms

The association between the degree of orthostatic BP fall and symptom appearance is complex: in the presence of a significant BP fall, some patients may show symptoms, while other patients may remain unaware.[18] In some patients, in whom NOH symptoms are minimal or absent, this is probably due to chronic adaptive changes in cerebral blood flow autoregulation that allow patients to tolerate low mean BP on standing. In other cases, patients may be unable to recognize NOH symptoms because of neurodegeneration of those cerebral areas responsible for interoceptive integration.[20] These patients are at a greater risk of falls, and it is, thus, important to periodically check orthostatic BP changes in synucleinopathy patients to reduce falls risk.

Clinical approach to patients with suspected OH

Orthostatic vitals are arguably the most important "autonomic test" available to the clinician but, unfortunately, one that is rarely done. Ideally, BP and HR are

measured after the patient is in supine position for 5 or more minutes, and after 1 and 3 minutes of standing up. Passive head-up tilt table (>60°) is useful in patients with physical disability. Although less informative, seated-to-standing BP and HR measurements are more practical in a busy practice and, if used, a lower threshold must be considered for OH diagnosis (systolic BP drop ≥15 mm Hg or diastolic BP drop ≥7 mm Hg).[19] The 24-hour ambulatory BP monitoring is useful to correlate BP changes during the daytime if the patient is careful in keeping an event diary (their relationship to symptoms and the effect of drug schedule, posture and activity, meals, etc.), and during the night. Supine hypertension and abnormal circadian BP changes (nondipping pattern) can be detected with this method.[21]

Workup

When OH is confirmed, a thorough workup should be done to study possible causes (Table 1). A medical history and examination are useful in identifying nonneurogenic causes of OH (low intravascular volume, drugs with vasodilatory effect, diuretic agents, cardiac disorders like atrial myxoma, myocarditis, constrictive pericarditis, aortic stenosis, etc.). It is also useful to characterize aggravating factors of OH: rapid postural change, warm ambient temperature, postprandial hypotension (after heavy, carbohydrate-rich meals), exercise, prolonged standing, straining during micturition or defecation, and being bedridden; and it is crucial to identify medications that can precipitate or aggravate NOH (see Management section).

Autonomic testing with beat to beat BP monitoring during the Valsalva maneuver is useful in documenting the neural basis for OH but is available mostly in specialized centers. Plasma norepinephrine response to orthostasis, which is blunted in NOH, is a useful test in assessing sympathetic efferent noradrenergic function.

It is important to identify the rare patient in whom the onset and initial progression of NOH are acute or subacute because these are frequently related to autoimmune autonomic ganglionopathy and paraneoplastic syndromes. On

Table 1. Clinical characteristics of NOH symptoms

1. NOH symptoms occur only during standing position and alleviate when the patient seats or lies down.
2. The recognition and description of NOH symptoms varies from patient to patient. OH can be asymptomatic in some patients.
3. Factors that may worsen NOH symptoms include getting up quickly in the morning, prolonged standing position, walking, activation of arm muscles during standing, eating carbohydrate-rich meals, a hot environment, immobility, Valsalva maneuver, and drugs with hypotensive effects.
4. In patients with NOH, it is important to ask about symptoms related to other autonomic domains like gastrointestinal, genitourinary, sudomotor, and pupillary function.

Abbreviations: NOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension.

Table 2. Characteristics of OH in nonneurogenic and in neurogenic orthostatic hypotension

		Neurogenic orthostatic hypotension		
	Nonneurogenic orthostatic hypotension	Multiple system atrophy	Parkinson's disease, Lewy body dementia	Pure autonomic failure
Causes	Intravascular volume loss (dehydration and anemia) Large varicose veins Cardiopathy Physical deconditioning Drugs (vasodilatation)	Central sympathetic denervation Intact postganglionic noradrenergic fibers	Predominantly peripheral sympathetic denervation	Peripheral sympathetic denervation
Neurological deficits	None	Parkinsonism Cerebellar ataxia	Parkinsonism Dementia	None
Other symptoms of autonomic failure	None	Constipation, erectile dysfunction (men), urinary abnormalities, and sweating abnormalities		
Autonomic tests				
Increase in HR on standing	Pronounced	Mild or absent		
BP overshoot phase 4 Valsalva	Present	Absent		
Orthostatic rise in norepinephrine	Normal or enhanced	Reduced or absent		
Cardiac imaging sympathetic PET	Normal	Normal	Reduced	Reduced

Abbreviations: HR, heart rate; PET, positron emission tomography.

Table 3. Characteristics of NOH in synucleinopathies

1. In PD, DLB, and PAF, the NOH is predominantly due to sympathetic denervation of peripheral neurons. In MSA, there is a loss of the central sympathetic neurons.
1. NOH is a prominent and disabling feature in all synucleinopathies and it is a sign of bad prognosis.
2. In synucleinopathies, there is a generalized autonomic dysfunction. MSA shows severe dysautonomia. In PD, DLB, and PAF, the dysautonomia is less severe.
3. MSA, PD, DLB, and PAF patients may show supine hypertension associated with NOH.
4. NOH may precede for several years the motor manifestations of PD and MSA and the cognitive decline of DLB.
5. Ambulatory BP monitoring is useful to detect daytime BP fluctuations, postprandial hypotension, and nocturnal nondipping or reverse dipping pattern.

Abbreviations: BP, blood pressure; DLB, dementia with Lewy bodies; NOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease; MSA, multiple system atrophy.

the other hand, chronic NOH is most commonly caused by synucleinopathies, diabetes mellitus, and amyloidosis.[15,22]

NOH in synucleinopathies

The synucleinopathies are neurodegenerative disorders characterized by abnormal intracellular deposition and aggregation of a misfolded form of the protein α-synuclein in specific regions of the central and/or peripheral nervous system[2] (Table 3). In the spectrum of Lewy body diseases, which include PD, DLB, and PAF, α-synuclein is deposited in neurons, forming cytoplasmic Lewy bodies. In all of these disorders, the autonomic failure is due to the degeneration of peripheral postganglionic noradrenergic nerve fibers. In MSA, α-synuclein deposits form glial cytoplasmic inclusions and cause neuronal degeneration in central cardiovascular autonomic pathways resulting in NOH and either in striatonigral centers resulting in atypical parkinsonism (MSA-P) or in the cerebellum resulting in truncal ataxia (MSA-C).

Parkinson's disease

Lewy bodies are intraneuronal α-synuclein deposits located in the cortex, brainstem, intermediolateral columns of the spinal cord, and peripheral visceral (autonomic and enteric) nervous system. In PD, the postganglionic sympathetic fibers are severely affected, and the autonomic involvement includes cardiovascular, gastrointestinal, genitourinary, and sudomotor dysfunction. The prevalence of NOH in PD is about 30%,[23] being more frequent in patients with long-term disease.[24] Symptomatic NOH, however, may precede parkinsonism for several years as a premotor feature of the disease.[25] In many cases, initial consultations for unexplained NOH can lead to a diagnosis of early PD in patients with mild bradykinesia or rigidity that remain unnoticed. Indicators of possible progression to PD are the presence of anosmia and rapid eye movement (REM) sleep behavior disorders and the following laboratory variables: a $^{<}$10 bpm increase of HR on standing and a $^{>}$65 pg/ml orthostatic increase of plasma noradrenaline levels.[26,27] In a significant group of PD patients, OH may be asymptomatic[28] and some patients may underreport their orthostatic symptoms to health care providers.[29] Delayed OH in PD patients may be a precursor of NOH, possibly a sign of a partial sympathetic vasomotor denervation.[30] In contrast to centrally originated motor symptoms, autonomic failure in PD is due to the degeneration of peripheral noradrenergic fibers as evidenced by cardiac imaging showing sympathetic denervation and low plasma noradrenaline levels.[31] The occurrence of supine hypertension in PD patients is associated with cardiovascular diseases, history of hypertension, and diabetes mellitus.[32] Ambulatory BP monitoring in PD patients may show a nocturnal nondipping or a reverse dipping pattern.[33]

Multiple system atrophy

MSA is a sporadic rapidly progressive neurodegenerative disease that affects several structures in the central nervous system, presenting with 2 subtypes, MSA-P and MSA-C. The main autonomic features of both subtypes are NOH, neurogenic bladder, erectile dysfunction, and progressive anhidrosis.[2] In MSA, central autonomic pathways are compromised, whereas postganglionic sympathetic innervation is spared, an important consideration when choosing drug treatments. The prevalence of NOH is high (80% or more) and orthostatic symptoms become disabling in most of the patients.[34] NOH may precede motor manifestations[27] and autonomic failure is more severe than in PD. MSA patients' median survival is 9.8 years, but severe NOH and urinary incontinence at diagnosis indicate a worse prognosis.[35] It may be difficult to differentiate PD from MSA-P in the initial stages of the disease, but patients with MSA-P tend to show a poor response to levodopa treatment and a rapid progression of motor and autonomic symptoms. In MSA, supine hypertension is associated with the severity of NOH.[32]

Dementia with Lewy bodies

In DLB, α-synuclein intracellular deposits are found in the neocortex, brainstem, and peripheral autonomic nervous system. DLB is the second most frequent cause of neurodegenerative dementias. It is characterized by progressive and fluctuating cognitive decline, with visual hallucinations, parkinsonism, and autonomic dysfunction. NOH is present in about 30–50% of the patients, and it is less severe than in MSA.[2] The presence of syncope in a patient with dementia

raises the suspicion of DLB and PD.[36] NOH, gastrointestinal, and urinary symptoms are progressive and disabling. As cognitive impairment can hinder patient recognition of orthostatic symptoms, the information provided by relatives or caregivers becomes crucial to prevent syncope and falls. NOH is a bad prognostic sign in DLB patients.[37] Indeed, it may precede dementia for several years: 18% of patients initially evaluated for NOH and considered as "possible PAF" progress to DLB after 4 years.[27]

Pure autonomic failure

PAF is a synucleinopathy affecting the peripheral autonomic nervous system without parkinsonism or cerebellar signs. Orthostatic symptoms are due to a slowly progressive sympathetic denervation. Most patients show OH and syncope is frequent. Supine hypertension occurs in about 50% of the patients. In addition to NOH, patients show signs of cardiovagal, enteric, genitourinary, and sudomotor denervation.[38] As mentioned, a group of patients with an initial phenotype of PAF may phenoconvert to MSA, PD, and DLB over time.[27]

NOH management

NOH causes considerable limitations and quality of life impairment and is a risk factor for falls and other morbidities. The main goal of therapy is to reduce symptom burden and not necessarily to restore normotension. In patients that can reliably recognize and report their symptoms, the Orthostatic Hypotension Questionnaire can be used to assess the severity of symptom burden and response to treatment.[39] The first question of this instrument alone has been used to assess treatment efficacy; it asks the patient to rate, on a scale from 0 (none) to 10 (worst possible), the severity of "dizziness, lightheadedness, feeling faint, or feeling like you might black out" over the past week.

A consensus panel from the American Autonomic Society and the National Parkinson Foundation[40] recently recommended a treatment algorithm for NOH based on a 4-step stratified sequential approach (ideally, with a 2-week period to assess the benefit of each step): first, assess and adjust preexisting medications; then, attempt symptom control with nonpharmacological measures, and, if needed, implement single-drug treatments. Combined pharmacologic approaches must be tried lastly and with great caution. Nonpharmacologic measures may provide significant symptom control and must be always stressed. Important considerations for treatment are, as mentioned, the identification and removal of factors that aggravate OH, the assessment of the presence of residual sympathetic tone we can harness for treatment, and the assessment of the presence of supine hypertension.

We will review common nonpharmacologic and pharmacologic measures with consideration on particularities of the management of NOH patients with cardiovascular comorbidities. We will also review precautions when patients undergo surgical procedures.

Nonpharmacologic approach

Education is of paramount importance in the management of patients with NOH.[40] A thorough review of their medications should be the first step. Antihypertensive drugs, antidepressants (especially tricyclics), and anticholinergic drugs may exacerbate OH. Dopaminergic agents too, but they may be necessary for the treatment of motor symptoms, particularly in PD, so they must be adjusted cautiously. Indication, dose, and time schedule of possible aggravating drugs must be reviewed and adjusted, eliminating them if possible. The patient should learn to recognize: (i) environmental or behavioral stimuli exacerbating the symptoms (warm temperature, large and carbohydrate-rich meals, Valsalva, rapid change to the upright position when supine, and prolonged standing), (ii) the need of adequate hydration and salt intake, (iii) the benefits of regular physical exercise (such as those that are water based or in a seated position to prevent falls), and (iv) physical maneuvers to raise BP (leg crossing or muscle tensing, compressive garments, and acute water ingestion). Nonpharmacologic measures are summarized in Table 4. In patients with supine hypertension, raising the head of their beds 20–30 cm reduces nighttime BP and diuresis, improving morning orthostatic tolerance.[41]

Pharmacological treatments

Treatments for NOH can be classified according to their mechanism of action[2,40,42] as follows (summarized in Table 5).

Volume expansion. Fludrocortisone is a synthetic steroid with a selective mineralocorticoid effect: it increases renal sodium reabsorption and, consequently, circulating plasma volume. This effect is transient, peaking in the first 2 weeks of treatment, and the persistent pressor effect may be related to the sensitization of the vascular bed to circulating catecholamines. Hypokalemia can occur due to its mineralocorticoid effect. Potassium plasma levels should be monitored and should be supplemented if necessary.

Small doses of desmopressin, a synthetic analog of the posterior pituitary antidiuretic hormone AVP, may be useful in NOH patients by reducing nocturnal polyuria and improving morning OH, but it may worsen supine hypertension. It may be used as intranasal spray or orally, and plasma sodium must be monitored closely to avoid hyponatremia.

Noradrenergic stimulation replacement. As a central feature of NOH is the impairment of the sympathetic efferent arm of the baroreflex, the use of agonists of the sympathetic target-organ postsynaptic receptors is considered the first line of pharmacologic treatment. Midodrine is a pro-drug that is enzymatically hydrolyzed to desglymidodrine, its active compound. It is a selective alpha-1 adrenoreceptor agonist that increases vascular peripheral resistance and elevates BP, attenuating

Table 4. Nonpharmacologic management of NOH

Nonpharmacologic measure	Mechanism
Medication adjustment	Avoiding diuretics and drugs with anticholinergic effects (including tricyclics). Caution with dopaminergic agents if indicated, and careful selection of antihypertensive drugs and their dose schedule, if necessary.
Adequate hydration and liberal salt intake	>2–3 l of daily fluid intake and up to 10 g of salt to expand circulating blood volume.
Avoidance of increased body core temperature (environmental, high-intensity exercise, and hot baths)	Increased core body temperature decreases vascular peripheral resistance reducing BP.
Avoidance of large meals (especially if carbohydrate rich)	Large meals may cause postprandial hypotension worsening OH. Nocturnal large meals may help patients with supine hypertension.
Avoidance of Valsalva maneuver (coughing and breath holding)	Increased thoracic pressure further decreases venous return, already low in NOH patients in upright position.
Postural interventions	Slowly staged movements to reach the upright position from supine or seated allows for compensatory mechanisms to start acting. Avoiding the supine position during the day prevents physical deconditioning. Prolonged standing may exacerbate OH. Head rising at night helps controlling supine hypertension and may decrease morning OH.
Physical conditioning	Nonstrenuous, moderate physical exercise, and lower extremities strength training promote compensatory mechanisms. Upright exercises should be avoided to prevent falls.
Physical counter-maneuvers against peripheral blood pooling	Leg crossing, squatting, muscle tensing, and use of compressive garments may increase venous return (or prevent its reduction).
Acute oral water ingestion	Ingestion of 0.5 l of water in 3–4 minutes has a rapid transient vasopressor effect in NOH patients that may provide acute symptom control.

Abbreviations: NOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension.

Table 5. Pharmacologic management of NOH

Volume expansion			
Fludrocortisone	Volume expansor (mineralocorticoid action)	0.1–0.3 mg/day q.d.	Supine hypertension, edema, and hypokalemia
Desmopressin	Vasopressin V2 receptor agonist	10–40 ug (1–4 puffs intranasal spray) nightly or 100–800 ug p.o. q.d. (usually 100–200 ug)	Water intoxication and hyponatremia
Noradrenergic stimulation replacement			
Midodrine	Alpha-1 adrenoceptor agonist (pro-drug)	2.5–10 mg p.o, b.i.d. to q.i.d.	Scalp itching/piloerection, supine hypertension, coldness sensation, and urinary retention
Droxidopa	Norepinephrine precursor	100–600 mg p.o, t.i.d.	Supine hypertension, dizziness, headaches, and nausea
Harness residual sympathetic tone			
Pyridostigmine	Increases ACh in autonomic ganglion synapses	30–60 mg p.o, t.i.d.	Salivation, lacrimation, bradycardia, diarrhea, urinary urgency, and sweating (some may improve other autonomic symptoms)
Atomoxetine	Norepinephrine transporter inhibitor	18 mg p.o, b.i.d	Dry mouth, headache, and anorexia

Abbreviations: NOH, neurogenic orthostatic hypotension.

orthostatic symptoms. Besides the potential worsening of supine hypertension, side effects are related to its sympathomimetic activity, including piloerection (itchy scalp) and urinary retention.[43]

Droxidopa is a modified amino acid that is converted to norepinephrine by the actions of neuronal and nonneuronal forms of the enzyme DOPA decarboxylase. It raises BP and improves NOH symptoms and is FDA approved for the treatment of NOH (recently reviewed[2,42]). Low plasma norepinephrine levels (<220 pg/ml) are a good predictor of response to droxidopa.[25] In PD patients using high doses of levodopa combined with

DOPA decarboxylase peripheral inhibitors, a blunted response may be observed. Both midodrine and droxidopa are short-lasting agents and dosing schedules can be tailored to patients' needs and circumstances.

Drugs that harness residual sympathetic tone. In patients with residual sympathetic tone (particularly patients with MSA, but also, to different degrees, patients with milder forms of the other synucleinopathies), an alternative approach to treatment is the use of agents that promote the release of norepinephrine by the residual sympathetic postganglionic neurons. Pyridostigmine, a reversible acetylcholinesterase inhibitor increasing the postsynaptic availability of neurotransmitter at the sympathetic ganglia, and atomoxetine, a selective inhibitor of norepinephrine reuptake (blocking its transporter on the postganglionic neuron presynaptic membrane), have this effect. By harnessing a physiological phenomenon, these agents have a preferential vasopressor effect in the upright position (when the sympathetic tone normally increases), so they could be a good alternative for patients with supine hypertension.[40]

Special considerations

NOH in patients with cardiovascular comorbidities. It is not infrequent for patients with synucleinopathies to present NOH and comorbid cardiovascular conditions either as a direct autonomic effect of the disease or due to the side effects of the medications and also because of the higher prevalence of these conditions with advancing age. Supine hypertension is the most common cardiovascular comorbidity, being present in 20–70% of patients with synucleinopathies and NOH.[32,44–47] Physicians treating these patients often confront a difficult clinical dilemma because treatment of one may worsen the other.[33,41,45] Treatment of NOH may take priority in very symptomatic patients in whom the short-term morbidity risk (e.g., falls) is high or in those faster-progressing diseases, such as MSA. However, long-term end-organ damage and cardiovascular risks should remain a concern for patients with longer survival, such as those suffering PAF or PD. In these patients, attempts should be made to control supine hypertension without worsening NOH. Again, nonpharmacologic measures are the first step in the management of supine hypertension: medication adjustments, avoiding the supine position during the day and rising the head of the bed at night, and, in some cases, late-night snacks that promote postprandial hypotension. The use of nighttime short-acting antihypertensives might be considered (e.g., hydralazine, losartan, short-acting nifedipine, or a nitroglycerin patch), but diuretics, alpha-adrenoceptor inhibitors, and central alpha-2 agonists should be avoided. In patients with severe supine hypertension, treatment of NOH with fludrocortisone should be avoided and pyridostigmine and atomoxetine should be preferred over midodrine and droxidopa. The latter 2 can be used if patients are instructed not to lie down for 3–4 hours after a dose[48].

Atrial fibrillation, atrial ectopy, and atrial and left ventricular remodeling are also possibly associated with NOH.[45] Although there is little evidence to base recommendations regarding pharmacologic treatment for these patients, the following can be considered: beta-blockers must be used cautiously in comorbid heart failure or tachyarrhythmias as they may worsen OH; midodrine can potentially worsen bradyarrhythmia; and fludrocortisone is contraindicated in patients with heart failure due to its volume expansion effect. Hypokalemia, which can be seen in up to 50% of patients taking fludrocortisone[49], may worsen arrhythmias[45].

Perioperative management. Because of the loss of baroreflex compensatory mechanisms, patients with NOH may have an exaggerated hypotensive response to blood loss and, conversely, denervation hypersensitivity with increased responses to pressor agents, such as norepinephrine and phenylephrine. Several perioperative precautions must be taken, as has been thoroughly reviewed elsewhere.[50,51] Particular attention should be paid to preoperative hydration and fludrocortisone can be used transiently in preparation for surgery. Intraoperatively and postoperatively, NOH patients are at higher risk to develop both hypertension and hypotension; BP can be affected by mechanical ventilation because of the effect of changes in thoracic pressure on venous return (or pneumoperitoneum in the case of laparoscopic surgery); it can also be affected by exaggerated responses to commonly used drugs. Volume replacement and careful hemodynamic monitoring are advised. Some chronic medications, such as pyridostigmine, can be transiently withheld for safety, but patients on fludrocortisone with doses higher than 0.3 mg q.d. should be treated cautiously as they may have a suppressed hypothalamic–hypophyseal axis. After surgery, with all due precautions, it is important to proceed to early activation of the patient to prevent physical deconditioning that may further impair orthostatic intolerance.

In summary, NOH is common in the elderly, it causes significant morbidity, including falls, can greatly impair quality of life, and is an independent risk factor for increased mortality. In the absence of clinical trial evidence on which to base recommendations, we rely on an understanding of the pathophysiology to guide therapy. In this regard, most of our knowledge in this area, as well as the development of new therapies, comes from studies in synucleinopathies causing primary neurodegeneration of the autonomic nervous system. Hence the importance of understanding these disorders to manage more common causes of NOH.

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DISCLOSURE

I.B. holds a patent on the use of an automated abdominal binder for the treatment of orthostatic hypotension and is a consultant to Theravance Biopharma in the development of treatments for orthostatic hypotension.

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