Orthostatic Hypotension: A Practical Approach to Investigation and Management

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ABSTRACT

The maintenance of blood pressure upon the assumption of upright posture depends on rapid cardiovascular adaptations driven primarily by the autonomic nervous system. Failure of these compensatory mechanisms can result in orthostatic hypotension (OH), defined as sustained reduction in systolic blood pressure > 20 mm Hg or diastolic blood pressure > 10 mm Hg within 3 minutes of standing or > 60° head-up tilt. OH is a common finding, particularly in elderly populations, associated with cardiovascular and cerebrovascular morbidity and mortality. Therefore, it is important to identify OH in the clinical setting. The detection of OH requires blood pressure measurements in the supine and standing positions. A more practical approach in clinics might be measurement of seated and standing blood pressure, but this can produce smaller depressor responses because of reduced gravitational stress. Heart rate responses to standing should be concomitantly measured to assess integrity of baroreflex function. Patients with OH can present with symptoms of cerebral hypoperfusion on standing predisposing to syncope and falls; however, many patients are asymptomatic. When the diagnosis of OH is established, it is important to document potentially deleterious medications and comorbidities and to assess for neurogenic autonomic impairment to establish underlying causes. Treatment should be initiated in a compensatory manner.

The assumption of upright posture induces gravitational blood pooling in the lower extremities to reduce venous return to the heart. In healthy individuals, cardiac output and blood pressure (BP) are maintained upon standing because of activation of autonomic neural and hormonal reflex mechanisms that compensate for impaired venous return. Failure of these compensatory mechanisms can result in orthostatic hypotension (OH), or low BP upon standing (Fig. 1). OH is defined as a sustained reduction of at least 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP within 3 minutes of standing or > 60° head-up tilt. Patients with OH often experience symptoms of cerebral hypoperfusion including lightheadedness, dizziness, blurred vision, fatigue, and headache. The etiology of OH is multifactorial and can include non-neurogenic and neurogenic causes. OH can occur in otherwise healthy people when faced with severe hypovolemic or vasodilatory stress, although it is more common in people with some underlying neurovascular pathology. The incidence of OH increases with age affecting 5%-16% of middle-aged and elderly community dwellers, and more than 50% of elderly patients in nursing homes and geriatric wards. OH...
structured and stepwise approach starting with nonpharmacological interventions (eg, lifestyle modifications and physical countermeasures), and adding pharmacological interventions as needed in patients with severe OH (eg, midodrine, droxidopa, fluadrocortisone). The treatment goal in OH should be to improve symptoms and functional status, and not to target arbitrary blood pressure values.

Additional causes of OH include side effects of medications, anemia, volume loss (eg, dehydration, severe vomiting, or diarrhea), physical deconditioning, benign infections (eg, urinary tract infection), and systemic diseases involving autonomic nerves (eg, amyloidosis, diabetes mellitus, Parkinson disease). Exaggerated orthostatic tachycardia might suggest volume depletion or these other secondary causes. Patients with acute or subacute onset of OH and severe presyncopal symptoms should be evaluated for autoimmune or paraneoplastic syndromes. In rare cases, patients with OH have a primary neurodegenerative disorder (eg, multiple system atrophy, pure autonomic failure, Lewy body dementia). These patients often present with severe OH and lack of compensatory heart rate increase with standing (<15 bpm). Standardized autonomic function testing is recommended to confirm diagnosis of primary neurodegenerative disorders associated with OH.

Treatment of OH

Treatment of OH should involve a structured stepwise approach, which might include nonpharmacological as well as pharmacological interventions (Table 1). The treatment goal for OH patients is to improve symptoms and functional status, and not to achieve target BP values. The need for treatment should be determined on an individual basis with consideration given for OH severity and presence of comorbidities. Patients should maintain a diary of symptoms and orthostatic vital signs to help assess treatment efficacy. There is limited evidence to guide OH treatment, and recommendations are often on the basis of small cross-sectional trials with acute interventions in neurogenic OH. Potential limitations are that these previous studies might not reflect the more common idiopathic OH, have not been validated in large controlled clinical trials, and have not evaluated long-term treatment efficacy.

Nonpharmacological

Medications known to aggravate OH should be discontinued when appropriate. Because OH patients are preload-dependent, nitrates and diuretics should be stopped. Other medications that might worsen or contribute to OH can include dopaminergic drugs, anticholinergic drugs, tricyclic antidepressants, β1-blockers (eg, tamsulosin), and antihypertensive medications. Discontinuation of antihypertensive medications, however, should be approached with...
caution for several reasons. First, although a relationship has been established with use of sympatholytics (eg, α- and β-adrenergic antagonists), the association of other antihypertensive medications with OH is uncertain. Second, studies have shown an increased fall risk in elderly patients with uncontrolled hypertension. Finally, withholding antihypertensive medications can worsen OH by promoting pressure diuresis. Therefore, judicious use of short-acting antihypertensive medications is recommended in patients with OH with close monitoring of orthostatic vital signs and symptoms.

Nonpharmacological approaches should then be initiated as first-line treatment and include physical countermanoeuvres and lifestyle modifications (Table 1). Patients should be educated on use of physical countermanoeuvres to reduce venous pooling such as changing positions gradually, leg-crossing, squatting, and active tensing of leg muscles. Breathing-related countermanoeuvres might also benefit cardiovascular stability in OH patients through actions on the respiratory pump to facilitate venous return to the heart from the abdomen and upper extremities. These respiratory manoeuvres include slow deep breathing and creation of inspiratory resistance through use of an impedance threshold device, inspiratory sniffing, or inspiration through pursed lips.

Nonpharmacological interventions

- Physical countermanoeuvres (eg, standing with legs crossed, squatting, active tensing of leg muscles, breathing-related manoeuvres to increase inspiratory resistance, and avoiding getting up too quickly or standing motionless)
- Compression stockings or abdominal binders (30-40 mm Hg)

Increase central volume
- Increase sodium intake (6-9 g/d)
- Increase water intake (2-3 L/d)
- Raise head of bed during night to prevent pressure natriuresis (6-9 inches)

Other lifestyle modifications
- Eat small frequent meals
- Physical activity such as water exercise, recumbent bicycling, or rowing
- Avoid alcohol consumption
- Avoid situations that increase core body temperature such as prolonged hot showers

Pharmacological interventions

Increase intravascular volume
- Fludrocortisone (0.1-0.2 mg/d, PO)
- Midodrine (2.5-10 mg, PO)
- Droxidopa (100-600 mg, PO)
- Atomoxetine (18 mg, PO)
- Yohimbine (5.4 mg, PO)
- Pyridostigmine (60 mg, PO)
- Octreotide (12.5-25 µg, subcutaneous)
- Pseudoephedrine (30 mg, PO)

Combination therapy
- Fludrocortisone (0.1-0.2 mg/d, PO) and midodrine (5-10 mg, PO)
- Ergotamine (1 mg, PO) and caffeine (100 mg, PO)
- Midodrine (5-10 mg, PO) or pseudoephedrine (30 mg, PO) and water (500 mL)

Custom-fitted thigh or waist-high compression stockings and abdominal binders also reduce venous pooling to improve orthostatic tolerance, when graded pressures of at least 30-40 mm Hg are applied. To improve central volume, increased ingestion of sodium (6-10 g/d) and water (2-3 L/d) is recommended. Rapid ingestion of plain water also serves as a rescue measure in OH (500 mL ingested within 2-3 minutes), by eliciting a sympathetic nervous system-mediated BP elevation for 60-90 minutes. In patients with supine hypertension, elevating the head of the bed (6-9 inches) reduces nocturnal pressure natriuresis to attenuate morning volume depletion. In terms of lifestyle modifications (Table 1), patients should engage in physical activity as tolerated to avoid deconditioning, avoid alcohol, eat small frequent meals to prevent postprandial hypotension, and avoid situations that increase core body temperature to elicit peripheral vasodilation. These nonpharmacological approaches are cost-effective and can be safely combined with pharmacological interventions; however, there is often poor compliance.

Pharmacological

The use of additional pharmacological interventions might be necessitated in patients with severe OH, when nonpharmacological approaches are insufficient to prevent presyncopal symptoms (Table 1). Pharmacological treatment is unlikely to improve outcomes in asymptomatic patients. The presence of hypertension and underlying cardiovascular disease must also be considered.
In patients with hypertension or cardiovascular disease, short-acting pressor agents to increase vascular resistance are preferred. Midodrine was approved by the US Food and Drug Administration for symptomatic OH and improved orthostatic tolerance in controlled clinical trials. Midodrine is a prodrug whose metabolite desglymidodrine stimulates \( \alpha_1 \)-adrenoreceptors in blood vessels to increase vascular resistance. Because midodrine has a short half-life, it can be given as needed 30-45 minutes before upright activities (2.5-10.0 mg orally every 4 hours 3 times per day). Caution is recommended in patients with congestive heart failure and renal failure. Side effects include piloerection, scalp pruritus, and urinary retention. Patients should avoid the supine position within 5 hours of taking midodrine because of the risk of supine hypertension (so it should not be dosed within 4-5 hours of bedtime). Nominal dosing times are 8 AM, 12 PM, and 4 PM.

More recently, the US Food and Drug Administration approved droxidopa for neurogenic OH treatment in the United States (not available in Canada). Droxidopa is a synthetic prodrug that is converted to norepinephrine in the brain and peripheral tissues. Circulating norepinephrine levels are maximally increased at 6 hours after droxidopa dosing, with persistent elevation for 46 hours. Droxidopa is well tolerated and improved orthostatic tolerance in controlled trials in neurogenic OH (100-600 mg orally, 3 times per day). Similar to midodrine, droxidopa should not be taken within 5 hours of bedtime. Caution is recommended in patients with congestive heart failure and chronic renal failure and side effects include headache, dizziness, nausea, and fatigue.

In patients without hypertension or heart failure, fludrocortisone (0.1-0.2 mg/d) is considered first-line pharmacotherapy. Fludrocortisone acts at renal mineralocorticoid receptors to promote sodium and water retention and thus increase intravascular volume. Long-term BP effects of fludrocortisone, however, are attributed to enhanced blood vessel sensitivity to pressor hormones such as norepinephrine and angiotensin II. Patients should be monitored for headaches, volume overload, and hypokalemia. Chronic fludrocortisone can also exacerbate supine hypertension and contribute to end organ damage.

Other medications have shown treatment efficacy in neurogenic OH including pseudoephedrine, atomoxetine (norepinephrine reuptake inhibitor), yohimbine (\( \alpha_2 \)-adrenergic receptor antagonist), pyridostigmine (cholinesterase inhibitor), and octreotide (somatostatin analogue; Table 1). Patients refractory to individual treatments might benefit from combination therapy including fludrocortisone with midodrine, ergotamine with caffeine, midodrine or pseudoephedrine with water bolus, and yohimbine with atomoxetine (Table 1). If patients are unresponsive to these treatment options, referral to a specialized autonomic centre might be necessary.

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