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Orthostatic Hypotension for the Cardiologist

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Structured Abstract

Purpose of review—Orthostatic hypotension (OH) is a phenomenon commonly encountered in a cardiologist's clinical practice that has significant diagnostic and prognostic value for a cardiologist. Given the mounting evidence associating cardiovascular morbidity and mortality with OH, cardiologists will play an increasing role in treating and managing patients with OH.

Recent findings—The ACC, AHA, and HRS recently published consensus guidelines on the diagnosis, treatment, and management of syncope and their instigators, including OH. Additionally, consensus guidelines have also been recently updated, reinforcing the universal definition OH and its closely associated pathologies. Finally, the FDA recently approved droxidopa, a synthetic oral norepinephrine prodrug, in 2014 for the treatment of neurogenic OH, and it represents a safe, effective, and easy to use intervention for neurogenic OH. This represents only the 2nd drug approved by the FDA for OH, the first being midodrine in 1986. A handful of smaller head-to-head studies have pitted not only pharmacologic agents to one another, but also non-pharmacologic interventions to pharmacologic agents. Additionally, recent studies have also reported on more convenient screening tools for OH.

Summary—Though there have been many advances in the management of OH, neurogenic OH remains a chronic, debilitating, and often progressively fatal condition. Cardiologists can play a very important role in optimizing hemodynamics in this patient population to improve quality of life and minimize cardiovascular risk.

Keywords

orthostatic hypotension; neurogenic orthostatic hypotension; autonomic failure; supine hypertension; droxidopa; midodrine

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Introduction

Orthostatic hypotension (OH) is a problem cardiologists commonly encounter in the clinical setting. The etiology can be as simple and reversible as overzealous diuresis, or as troublesome as autonomic nervous system failure secondary to long-standing diabetes mellitus (DM). Regardless of the etiology, OH is the second most common cause of syncope, which is perhaps the most immediately hazardous and dramatic hemodynamic consequence of OH. Syncope leads to hospital admissions in greater than 50% of those older than 80 years of age [1,2]. To complicate matters, severe hypertension (HTN) in the supine position (supine HTN) is a phenomenon observed in over half of neurogenic OH cases, and regulating blood pressures (BP) in these two extremes can be especially challenging, warranting the expertise of a cardiovascular specialist in many cases [3].

OH is associated with significant cardiovascular morbidity and mortality. Not only does OH predicts coronary events, congestive heart failure (CHF), and cardiovascular mortality, the concomitant development of OH in patients with diabetes mellitus (DM) and CHF portends a much poorer prognosis in these disease states [4–8]. A cardiovascular explanation for this association is unclear but may involve structural remodeling of the heart (increased left ventricular hypertrophy, worsening diastolic dysfunction) in OH patients [9].

Understanding the pathophysiology and treatment options of OH can help the cardiologist delineate the etiology of syncope, treat supine HTN, and also enable them to provide better cardiovascular care to those with OH, whatever the etiology may be.

Normal Physiology and Definitions

Normal physiology (Figure 1)

In healthy individuals, assumption of an upright position results in an almost immediate redistribution of up to 1L of blood into the lower extremities and the splanchnic circulation. The resulting decrease in venous return and, consequently, cardiac output is detected by carotid and aortic baroreceptors, causing a surge of catecholamine release from the sympathetic nervous system to both increase cardiac contractility, increase heart rate (HR), and most importantly, produce peripheral vasoconstriction. If this reflex is orchestrated flawlessly, the SBP should decrease by no more than 10 mmHg, the DBP should very slightly *increase*, and there should only be a modest increase in heart rate by 10–20 beats per min (bpm) [10].

Definition

OH is a hemodynamic finding observed during standing (orthostasis) consisting of either a 20 mmHg drop in systolic blood pressure (SBP) or 10 mmHg drop in diastolic blood pressure (DBP) when assuming an upright position after at least 5 minutes supine [10]. In cases of supine HTN (defined as SBP >150 mmHg or DBP >90 mmHg), a drop of 30 mmHg of SBP or 15 mmHg of DBP must be present [10]. OH itself does not imply a specific pathophysiology. Neurogenic orthostatic hypotension (nOH) is a sub-type of OH in which there is evidence of an autonomic neuropathy, with an inability to vasoconstrict

adequately to maintain adequate vascular resistance [10]. Often the physiological reflex tachycardia is blunted or absent in patients with nOH.

Neurogenic vs. non-neurogenic OH

OH can be broadly classified into two categories: nOH or non-neurogenic orthostatic hypotension (non-nOH) [1]. In nOH, the normal physiologic BP and HR response is either severely dysfunctional or outright absent. In conditions such as multiple system atrophy (MSA), pure autonomic failure (PAF), dementia with Lewy bodies, or Parkinson's disease, there is a characteristic profound deficiency in norepinephrine release during standing in over 75% of patients [11,12]. This deficiency in norepinephrine release reflects an inability of sympathetic vasoconstrictor neurons to fire adequately, which is responsible for the lack of peripheral vasoconstriction and consequent hypotension (Figure 1). Peripheral neuropathies such as vitamin B deficiencies, exposure to heavy metals, amyloidosis, certain chemotherapeutic agents, and most importantly diabetes mellitus, which is the most common cause of nOH peripherally, can also suppress the normal BP and HR response to standing [6,13]. Not surprisingly, diabetic patients with OH have higher hemoglobin A1c levels when compared to diabetic patients without OH [14].

Non-nOH causes of OH are often reversible and involve conditions that overwhelm a well-functioning autonomic system with an intact sympathetic nervous system response to standing. These conditions commonly include profound hypovolemia, medication effects, and severe systolic CHF [1]. Intense fluid restriction, overdiuresis, and hemorrhage are all common clinical scenarios cardiologists encounter that can cause hypovolemia to the point OH occurs despite a vigorous sympathetic nervous system response. Drug classes commonly employed by cardiologists such as diuretics, nitroglycerin, calcium channel blockers (CCB), and certain beta-blockers (BB), also pharmacologically antagonize the autonomic system via preload depletion or vasodilation.

In patients with severe CHF who are fluid overloaded, assuming an upright position can prompt a paradoxical effect. Decreasing venous return can increase the cardiac output in these patients by decreasing a right to left ventricular septal bulge. Therefore, in the upright position, the baroreceptors are not activated, and further sympathetic nervous system engagement is not triggered [15].

Diagnosis

Supine-Stand Test

The easiest and most important diagnostic test to evaluate OH is to measure the orthostatic change in blood pressure from a supine position to a standing position. The SBP, DBP, and HR should be recorded after the patient has remained in the supine position for at least 5 minutes. Upon standing, the BP and HR should be taken at 1 min, 3 min and 5 min after standing. OH is present if there is a drop in any BP parameter (either SBP or DBP) that meets the aforementioned criteria at the 3 min or the 5 min mark [10]. The 1 min values can be used if the patient cannot stand long enough for a 3 min standing BP reading. Some studies suggest extending the test period to 10 minutes will increase the sensitivity to

diagnose a milder form of OH, “delayed OH” [16]. If OH is present, the change in HR can be utilized to differentiate between nOH and non-nOH. An increase in HR >20 bpm suggests a non-nOH etiology whereas an increase in HR <15 bpm suggests a nOH etiology [10].

In scenarios where a supine-stand test is not feasible, a sit-stand test can be more convenient and has been recommended as an initial screening tool in these cases [10]. An orthostatic threshold drop of 15 mmHg SBP or 7 mmHg DBP has been shown to have the greatest sensitivity and specificity for identifying OH in this setting [17].

Workup and Interpretation

When both BP and HR are consistent with a diagnosis of nOH, a careful review of the patient’s medical history should be undertaken to rule out non-autonomic causes of a blunted chronotropic response to standing [10]. A cardiologist is well-suited to rule out these causes as several cardiac conditions and medications can be culprits.

An initial 12-lead ECG should be performed to rule out sinus nodal disease, AV block, or any other conduction abnormalities [1]. If a patient has a pacemaker, the device should be interrogated to ensure it is functioning correctly and settings are appropriate. For example, patients with chronic atrial fibrillation and complete AV block with a single ventricular lead will not be able to augment their HR when standing (unless their accelerometer is turned on) and may be more vulnerable to OH. Only when other causes of a blunted chronotropic response are ruled out in the setting of OH can a diagnosis of nOH be reached (see next paragraph). Patients may be particularly sensitive to preload depletion with diuretics or nitrates. Cardiac medications with potent negative chronotropic effects such as BB and potent vasodilators such as hydralazine, alpha-1 antagonists or dihydropyridine (DHP) CCB (e.g. amlodipine or nifedipine) should be scrutinized. Non-cardiac medications such as tamsulosin (an alpha-1 antagonist used for prostatic hypertrophy), morphine, or anti-psychotic drugs should also be identified [18].

Head-up tilt table testing

A head-up tilt table test (HUT) is not always widely available, and is not mandatory to make a diagnosis of nOH [10]. It consists of a platform that allows the patient to be strapped in securely where they can have continuous and simultaneous BP and HR monitoring. The table is then tilted to 60–80 degrees head up (so that patient is almost standing up) after baseline parameters are obtained [13]. It is very useful for individuals who are high risk (known neurodegenerative disease or long-standing uncontrolled DM) and are persistently symptomatic but have only borderline orthostatic parameters on a supine-stand test.

Treatment/Management (Figure 2)

Medication Use Review

The adjustment or discontinuation (when feasible) of medications that predispose to OH is the initial intervention of choice to treat OH [10,18]. A substantial number of these offending agents are medications that cardiologists use on a daily basis. Orthostatic

tachycardia in the setting of OH strongly suggests a hypovolemic state and should prompt reevaluation and adjustment of diuretic therapy [2]. BB with significant alpha-1 receptor antagonism such as carvedilol and labetalol are notorious for worsening OH due to the combination of negative inotropic effects from beta-1 receptor blockade as well as impaired vasoconstriction from vascular smooth muscle alpha-1 receptor blockade. In cases where BB administration is essential, switching these BB with alpha-1 receptor antagonism to a pure beta-blocker is warranted. In contrast to BB, DHP CCB have few mandatory indications and should be best avoided due to their potent vasodilatory effects. In certain cases, such as vasospastic angina, where a CCB can be a useful adjunct, DHP CCB should be switched to verapamil or diltiazem because of less vasodilatory effects and the availability of a shorter duration of action formulation, which can allow for drug free periods during the day when the patient is most symptomatic from OH. Likewise, nitrates should be avoided during the day, to avoid excessive daytime venodilatation during the day. Nitrates should be preferentially be given during the night. Finally, alpha-1 antagonists such as terazosin and doxazosin, especially if administered for hypertension, should be replaced by other anti-hypertensive medications, such as ACE inhibitors or angiotensin-receptor blockers, which are often better tolerated in these patients. If the indication is for benign prostatic hypertrophy, a hormonal agent such as a 5 α -reductase inhibitor is preferable to an alpha-1 antagonist such as tamsulosin.

Non-pharmacologic Interventions

There are several non-pharmacologic interventions that can be used alone, but also in conjunction with pharmacologic agents [2,10]. Patients should be counseled to stand up slowly as slowly standing up over the course of 15 seconds has been shown to blunt the drop in blood pressure [19]. The rapid ingestion of 500 ml of free water in 2–3 min has been shown to increase SBP by an average of 30–40 mmHg for a short period of time, in a phenomenon referred to as the “osmopressor response” [3,20]. In patients without CHF, patients can be instructed to add 1–2 teaspoons of salt daily to their diet to increase fluid retention, and expand the blood volume. The adequacy of salt intake can be assessed by checking 24-hour urinary sodium excretion, which should be >150 mEq when at steady state in the absence of diuretics [10]. We often recommend both the osmopressor response and the dietary salt and water expansion as a part of the initial therapy. Compression garments, including abdominal binders, are especially valuable interventions in patients with heart failure who are fluid restricted. Abdominal binders with mild pressure compression (10 mmHg) or waist-high stockings (in contrast to knee high stockings which are not as effective) of at least 30 mmHg blunt orthostatic BP drop and improve symptoms [10,21]. In fact, a recent study showed that abdominal compression of 40 mmHg was as effective as midodrine [22]. One challenge with abdominal binders is that patients may find it difficult to make them tight enough to generate an adequate compression.

Pharmacologic Interventions

There are a number of pharmacologic agents commonly used to treat OH, but only two are FDA approved: midodrine and droxidopa. Midodrine was approved by the FDA in 1986 and is the most commonly used pharmacologic agent for OH [18,23]. Midodrine is a pro-drug whose metabolite is an alpha-1 adrenergic agonist. Time to peak concentration is roughly 1

hour and the pharmacological effects last up to 4–5 hours [18,24]. A recent phase 4 study in 33 patients demonstrated that midodrine administration, on average, delayed onset of syncopal or presyncopal symptoms during HUT by almost 9 minutes [23]. The patient should not lie down for 4–5 hours after taking a dose of midodrine, and this medication should not be administered within 5 hours of going to bed, as midodrine can worsen supine hypertension. If a patient must nap during the day, they could skip the immediately preceding dose (usually the midday dose) or they could sleep in a recliner with their feet down [10,13]. It is normally given three times daily, at 2.5–15 mg per dose (titrated to effect) every 4 hours x 3 times. Nominal dosing times are 8am, noon, and 4pm.

Droxidopa was recently approved by the FDA after 3 randomized double-blind studies demonstrated impressive improvement in both symptoms as well as BP parameters [25]. Droxidopa is a safe, synthetic prodrug of norepinephrine, reaching peak plasma concentration in 2 hours [26,27]. Droxidopa can be dosed at 100–600 mg per doses, given 2–3 times per day [18]. However, access to this medication is an issue because it is not yet approved in Europe or Canada.

Fludrocortisone is a synthetic aldosterone analogue that treats OH via sodium and water retention. Recently, an oral dose of 0.1mg twice daily (0.2 mg/day in total) was shown to decrease the DBP drop with standing in OH patients by 37% [28]. This agent should be cautiously used in patients with CHF, and the dosage ranges from 0.05–0.3 mg. Higher doses have the potential to suppress the hypothalamic-pituitary axis and glucocorticoid side-effects [18].

Pyridostigmine, an acetylcholinesterase inhibitor that putatively works by augmenting cholinergic tone at the autonomic ganglion thereby increasing residual sympathetic tone, is not considered a first-line agent, but stands out from other agents in that it neither causes significant vasoconstriction nor does it cause fluid retention, making it ideal for patients with CHF [18,28]. However, it only has modest effects on standing BP and a recent study showed that it was no more effective than placebo in decreasing DBP drop with standing [28]. It can be very effective in increasing bowel motility in patients with autonomic failure, who are often prone to severe constipation [10].

Octreotide, erythropoietin, yohimbine, atomoxetine are other pharmacologic agents used for the treatment of OH; they have less robust data to support their use, should be considered second-line pharmacologic agents for the treatment of OH, and should not be routinely prescribed by the cardiologist without additional expertise in managing these patients.

Treatment of concurrent supine hypertension

The simultaneous treatment of OH during the day and supine HTN at night requires implementing key non-pharmacologic measures as well as understanding the unique pharmacokinetic profiles of the various agents involved, namely short acting vasoconstrictors (midodrine or droxidopa) and short acting anti-hypertensives (e.g. nitroglycerin patch, losartan, or eplerenone; Table 1).

The effects of anti-hypertensive medications should only be limited to nighttime, when the patient is supine. Therefore, anti-hypertensives should be administered shortly prior to bedtime, and ideally effects should wear off the next morning prior to the patient rousing. The benefit of using a nitroglycerin patch is that the anti-hypertensive effect of transdermal nitroglycerin dissipates shortly after it is removed. The effects of eplerenone 50mg, when administered at 8pm, maximally reduced BP at 4am, with near return to baseline at 8am [29]. Losartan at 50mg has been shown to decrease supine hypertension and not worsen OH in the morning [13]. At night, the patient should sleep with the head of the bed tilted up to both decrease supine hypertension and also minimize nocturnal supine pressure diuresis, which will obviously worsen OH the next morning [10]. One concern is that patients on anti-hypertensive medications at night might be at higher risks of falls if they have nocturia and get up to void at night. Risk mitigation strategies could include the use of a urinal at night, a bedside commode chair, or even intermittent bladder self-catheterization in some cases.

In the morning, any nitroglycerin patches should be removed prior to getting up. The patient should then take a short-acting vasoconstrictor (midodrine or droxidopa) along with 500 mL of free water (ingested within 2–3 min to exploit the osmopressor phenomenon) [3]. During daytime, the patient should also wear an abdominal binder or waist-high compression garments [10].

Expected Clinical Response and Prognosis

Patients with reversible causes of orthostatic hypotension usually do very well after the culprit is identified and rectified. However, patients with nOH often have a modest improvement in symptoms after institution of these measures (Table 1) that tends to diminish over time with progression of disease. Furthermore, after a diagnosis of autonomic failure, 34% of individuals “phenocover” to MSA or dementia with Lewy bodies/Parkinson’s Disease within 10 years [30]. Median survival after MSA diagnosis is 6–7 years, and 11–12 years for those with Parkinson’s disease and OH [31]. Individuals with nOH secondary to DM also do not fare well, with a 10-year mortality estimated to be upwards of 32% [5].

Conclusions

Given the strong association between OH and cardiovascular disease, the cardiologist plays an important role in the recognition and management of OH patients. Unfortunately, the prognosis of nOH is poor. Therefore, the goal for management of these patients from a cardiologist standpoint is to minimize symptoms and improve quality of life while simultaneously optimizing cardiovascular risk within their expected lifetime horizon [13].

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management and treatment of OH, including the use of droxidopa, the newest agent approved for the treatment of OH.

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Key Points

- Orthostatic hypotension is defined as a drop in systolic blood pressure of 20mmHg or diastolic blood pressure of 10mmHg within 3 minutes of standing.
- There are both reversible and irreversible causes of orthostatic hypotension, and reversible causes are often iatrogenic (medications, hypovolemia).
- Droxidopa and midodrine are both short acting peripheral vasoconstrictors that are FDA approved to treat types of orthostatic hypotension.
- Supine hypertension is a common phenomenon seen in orthostatic hypotension (up to 50%).
- Management of supine hypertension short-acting drugs and approaches to reduce blood pressure only at night.

Figure 1. Normal physiologic reflex and common pathologic or iatrogenic mechanisms causing orthostatic hypotension

Key components of the normal physiologic reflex in rounded rectangles and arrows.

Trapezoid boxes are common pathologic or iatrogenic mechanisms which cause or contribute to orthostatic hypotension. Bolts indicates specific areas in the normal physiologic reflex that are affected by these mechanisms. VD – vasodilators; AF – Autonomic failure; BV – blood volume; PVR – peripheral vascular resistance; BB – beta-blockers, CCB – calcium-channel blockers.

Figure 2. Diagram of stepwise approach to treating orthostatic hypotension and supine hypertension

Key steps in the management of reversible versus non-reversible orthostatic hypotension. Important points include the distinction between reversible versus non-reversible causes, the use of non-pharmacologic interventions prior to addition of pharmacologic interventions, identification of co-existent supine hypertension (HTN) if present, and frequent reassessment of symptoms. Refer to Table 1 for a list of non-pharmacologic and pharmacologic treatments. PAF – pure autonomic failure; MSA – multiple system atrophy; DM – diabetes mellitus

Table 1

Treatment of orthostatic hypotension with concurrent supine hypertension

Orthostatic Hypotension	Treatment	Mechanism	Dose	Administration Time	Duration of Action	Reference
	Rapid consumption of free water over 2–3 min	Osmopressor Response	500 ml	Upon awakening	90 min	[20]
	Compression garment and stockings	Increased cardiac venous return	Pantyhose Style; 30–40 mmHg compression	When Upright	N/A	[22]
	Midodrine	Short-acting, alpha-1 agonist	2.5–15 mg/dose	Every 4 hours as needed while awake (8am, noon, 4pm)	4–5 hours	[18,24]
	Droxidopa	Norepinephrine pro-drug	100–600 mg/dose	TID	4–5 hours	[25,26]
Supine Hypertension	Treatment	Mechanism		Administration Time	Duration of Action	Reference
	Elevation of head of bed	Orthostatic hypotension	20–30 degrees head-up	At bedtime	N/A	[10]
	Carbohydrate-rich snack	Post-prandial hypotension	N/A	At bedtime	~2 hours	[10,13]
	Nitroglycerin patch	Peripheral venodilation	0.1–0.2 mg/hour	Just before bedtime, remove upon awakening	While patch is affixed	[13]
	Losartan	Peripheral vasodilation	50 mg	Just before bedtime	12 hours	[13]
	Eplerenone	Peripheral vasodilation	50 mg	Just before bedtime	12 hours	[29]