Looking for Trouble: Identifying and Treating Hypotension

When it comes to blood pressure (BP), hypertension gets most of the attention. This is not surprising, as an estimated 46% of Americans have the condition and it can have deadly consequences. In 2013 alone, high BP was a primary or contributing cause in almost 1,000 deaths a day.\(^2\)

At the other end of the spectrum, hypotension, although often harmless and easily reversed, can also be dangerous. However, hypotension is frequently overlooked because it can have few or even no symptoms. Moreover, healthcare professionals don't always recognize its manifestations, treat for the condition, or prescribe the latest evidence-based treatments.\(^3\) A 2018 study suggests that a diagnosis of orthostatic hypotension (OH) is “seldom sought in clinical practice”; the researchers add that “this malpractice can lead to adverse and expensive consequences.”\(^4\)

Orthostatic hypotension is the most common form of low BP. Around one-third of people with persistent OH have neurogenic OH (nOH), a sign of sympathetic adrenergic failure, which is associated with conditions like diabetic autonomic neuropathy.\(^3\)

In part because OH can be asymptomatic, estimates of its prevalence range widely, from 5% of people aged 50 years and younger to 30% of people over the age of 70 years.\(^5\) Another issue is a lack of “procedural consistency in measuring OH,” according to Damanti et al.\(^4\)

Researchers who pooled the results of 26 epidemiological studies involving 24,967 community-dwelling older people and 2,694 older people in long-term care settings observed that “[t]here is no standardized method of quantifying symptoms associated with OH, nor an agreement of how severe symptoms would need to be for a positive diagnosis.”\(^6\) But while the methods used to identify OH varied, the researchers found “significant heterogeneity” in both groups: one in five people in the community-dwelling group and approximately one in four long-term residents had OH.

Older people are at risk for a number of reasons, such as reduced baroreflex sensitivity, increased vascular stiffness, reduced ventricular diastolic filling, dehydration, and concentrated capacities of the kidney.\(^7\) Not surprisingly, various researchers have found a link between the prevalence of OH and frailty. In a 2019 study of 693 patients in a geriatric evaluation and management unit, OH was prevalent in 26% and frailty was prevalent in 36%.\(^8\) The association was attenuated after adjusting for physical function but it remained significant for vulnerable subgroups, including women and those patients who were taking multiple medications.

In another 2019 study, the frequency of OH in the frail group was 30%, compared with 17.7% in the robust groups. The relationship was statistically significant even when multiple confounders were considered, including the presence of dementia, hypertension, hemoglobin and albumin levels, and the use of calcium channel blockers, diuretics, antidepressants, and other drugs.\(^7\) However, timing mattered: the connection between frailty and OH was most pronounced when OH was measured during the first minute, compared with measurements taken at three and five minutes.

Orthostatic hypotension is also associated with certain diseases. For instance, approximately 50% of people with Parkinson’s disease, 16% of people with type-1 diabetes, and 25% of people with carotid artery stenosis have OH.\(^9\) Interestingly, studies have also found a strong relationship between OH and hypertension, with a prevalence ranging from 13% to 32%, depending on the population’s age and comorbid medical conditions.\(^9\) Some researchers have found associations between OH and various antihypertensive drugs such as spironolactone, antiparkinson drugs, diuretics, and calcium channel blockers.\(^9\)

### Risks and Consequences

Orthostatic hypotension significantly raises the risk of falls, dementia, cardiovascular disease, and mortality.\(^6\) Regardless of etiology, OH is the second most common cause of syncope—perhaps the most dangerous hemodynamic consequence as it leads to hospital admissions in more than 50% of patients older than 80 years.\(^10\) In 2004, an estimated 80,995 hospitalizations were related to OH, the primary diagnosis in 35% of cases.\(^11,12\) Patients aged 75 or older had the highest annual hospitalization rate—233 per 100,000.

In a sample from the Atherosclerosis Risk in Communities (ARIC) study, researchers prospectively assessed the association between OH and risk of falls in 12,661 participants older than 23 years.\(^13\) After adjusting for a broad range of factors, the researchers found that participants with OH had a greater risk (hazard ratio, 1.30) than those without OH. This risk increased with age, rising to more than 20% in people above the age of 80.

As a result of its somewhat vague symptoms, postprandial hypotension is often overlooked. However, studies suggest that it’s responsible for as many as 15% of fainting-related falls in older adults.\(^14\) Madden et al., noting that it is “logistically impractical” to screen with a meal test all patients who are at risk of falling, nonetheless say that postprandial hypotension should be strongly considered for men and patients who are hypertensive, obese, or have orthostatic intolerance or a low resting BP.\(^14\)

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**KEY RESOURCE:**

**Droxdopa for Hypotension of Different Etiologies: Two Case Reports**

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Orthostatic hypotension is also an underrecognized risk factor in younger, apparently healthy people. In a subgroup analysis of the ARIC study, OH was a predictor of mortality in a group of 6,554 participants without coronary heart disease, stroke, cancer, hypertension, diabetes, or perceived poor health at baseline.9 And in a subgroup analysis of 3,522 apparently healthy men in the Honolulu Heart Program, OH was a significant predictor of four-year mortality.9

Managing an “Invisible” Condition

Identifying OH is obviously important for planning care. But although OH can cause signs and symptoms of cerebral hypoperfusion—e.g., nausea, light-headedness, visual blurring, and syncope—most people have no symptoms. In epidemiological studies of middle-aged and older patients, the majority of patients do not have dizziness on standing.9 In the long-term Cardiovascular Health Study, only 2% of participants had symptomatic OH; 16% had asymptomatic OH. Thus, if patients are screened on the basis of symptoms alone, clinic or office detection of OH could underestimate its prevalence. Asymptomatic OH, however, can be assessed with just a few minutes of seated and standing BP readings.9

Guidelines for the treatment of hypertension recommend periodically assessing for postural hypotension, but they don’t reflect thresholds in risk and may not distinguish among causes.15 For instance, OH is commonly attributed to hypovolemia or neurologic conditions, but one group of researchers documented the presence of subclinical cardiovascular disease (CVD) in patients with OH. They note that the mainstays of OH treatment—such as BP augmentation, increased salt and fluid intake, and de-escalation of antihypertensives—could actually have adverse health implications if the cause of OH is CVD.15

But there are some reasonable actions that can be taken. One is to change how the assessment is done. Researchers at the Johns Hopkins University School of Medicine advise testing for OH within one minute of standing rather than three minutes after a person has been lying down.15 Their findings suggest that waiting three minutes might miss those patients who are at risk.Orthostatic hypotension that occurred within one minute was associated with the highest rate of falls and car crashes; patients who had OH detected within 30 seconds of standing were associated with having the highest rates per 1,000 person-years of fracture, fainting, and death.

Traditional oscillometric approaches may not detect fast transient hypotensive episodes, however. Researchers from St. James’s Hospital in Dublin, Ireland, say misdiagnosis is a very real clinical possibility unless strict protocols and measurement methods are used. They suggest that rapid time-varying responses can only be captured accurately and differentiated from sustained OH by using continuous beat-to-beat measurement methods.10 They do add that it remains unclear which target resting-BP measure would optimally balance the risks of reducing cardiovascular events, falls, and syncope in older patients.

Another early step is to check the drugs, and refrain from titrating upward if the patient has OH. Patients whose OH is overlooked are likely to be undertreated, but not all patients with dizziness have OH. On the other hand, assuming OH on the basis of such symptoms alone—without measuring standing BP—can lead to overtreatment. For some patients, it may be sensible to switch from antihypertensive medications to lifestyle changes.9 On the other hand, a recent meta-analysis of 11 trials found no high-quality evidence to recommend any of the nonpharmacologic methods studied, such as lower limb compression and home-based resistance training, that are often recommended as first-line treatment for OH.17

Most patients with severe symptoms need antihypotensive medicines, which range from diuretics to beta blockers.10 But the efficacy of the medications used to treat low BP has been questioned. Few of them have shown positive results in randomized trials,9 and only two are FDA-approved: droxidopa, a synthetic oral norepinephrine prodrug, was approved in 2014, making it only the second drug to be approved for OH since midodrine’s approval in 1996.14 Droxidopa has been found to improve orthostatic tolerance in patients with neurogenic OH, but its long-term efficacy is “debatable,” according to one researcher.5,18 A 2016 meta-analysis suggested that the drug might have reduced efficacy after eight weeks, although data from a subsequent study indicated that the benefits persisted at three and six months.18 Midodrine has also demonstrated only low to moderate efficacy.5,18

More pharmacotherapeutic choices are needed. In the meantime, clinicians often use drugs such as fludrocortisone and pyridostigmine off-label on a case-by-case basis.18 One group of clinicians reported on using droxidopa, which has been studied extensively in nOH, for a patient with OH associated with diabetic autonomic neuropathy and for another patient with hypotension as a result of autonomic dysfunction associated with rheumatoid arthritis (RA).19 The outcomes were mixed: droxidopa did not prevent persistent syncope in the patient with diabetes, and had no effect in the patient with RA. The authors conclude that their case reports contribute to the literature demonstrating that droxidopa may have varying effects in treating OH of non-neurogenic etiology.

Is Treatment Advancing?

Much of the discussion around the treatment and management of OH is clouded by a lack of agreement about what exactly is “normal.” Opinions differ on which magnitudes of change in BP are abnormal, when those changes should matter, and how to measure them. As with any matter under dispute, it’s important to first define the terms.
The 2011 guidelines on the definition of OH, neurally mediated syncope, and postural tachycardia, which were updated by a multidisciplinary panel of experts, have established a standard definition of OH. But it isn’t an evidence-based clinical guideline and is considered to “lack the explicit timing information needed to define a sustained OH response, thus causing an extreme variability in OH measurements”—even in clinical studies.4

The American College of Cardiologists, American Heart Association, and Heart Rhythm Society recently released their first-ever jointly published consensus guidelines on the diagnosis, treatment, and management of syncope and its instigators, including OH.20 The guidelines include very specific recommendations on the management and treatment of OH.

However, as one author notes: “Consensus criteria also reflect a lumping together of different pathophysiologies that share a final common pathway, for which reason the conclusions may not be generalizable to every patient.” In other words, treatment decisions should be based not only on consensus guidelines, but on the particular medical condition and preferences of the patient.3

Empowering patients to take better care of their health—with the help of evidence-based research, attentive screening, and tailored treatments—could mean that OH will not be a hidden danger for much longer. User-friendly home BP monitors are already helping patients and their healthcare practitioners keep track of their ups and downs. New individualized solutions are on the horizon.3 Microelectronics may lead to a programable, posture-sensing device. Genetic research may help explain how some people’s systems differ in metabolizing drugs, as well as how they regulate sodium excretion and intravascular volume. In the future, routine clinical practice could base treatment decisions not only on BP but also on genotype—taking “individualized medicine” to a new level for patients with OH.3

Although definitions may fluctuate, the patient’s need for practical care remains. New technologies and advances in pharmacological treatments may be close at hand, but taking a few minutes to ask some questions or do a quick test—well, sometimes the old ways are the best.

REFERENCES

ADDITIONAL RESOURCES
2017 ACC/AHA/HRS Guideline for Evaluation and Management of Patients with Syncope
https://www.ahajournals.org/doi/10.1161/CIR.000000000000499

Algorithm for Diagnosing and Managing OH

Is It OH or noH? A Quick, Efficient Screen
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6501706/

A Practical Guide to Active Stand Testing

Talking With Patients About Hypotension
https://www.mayoclinic.org/diseases-conditions/low-blood-pressure/symptoms-causes/syc-20355465

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