Canadian Geriatrics Society

4D-AID: A PRACTICAL APPROACH TO THE ASSESSMENT OF ORTHOSTATIC HYPOTENSION IN OLDER PATIENTS

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Key words:
Postural hypotension, orthostatic, falls, medications, blood pressure

Abstract

Orthostatic Hypotension (OH) is a common geriatric syndrome, usually involving failure of one or more intrinsic mechanisms that help maintain perfusion of the brain during times of orthostatic stress. OH remains underdiagnosed despite the availability of consensus-recognized blood pressure cut-offs, largely due to lack of awareness of the prevalence of this condition in older patients as well as the fact that measurement of postural BP is not considered part of the routine physical examination.

The common causes of OH in older patients are described and the 4D-AID mnemonic, which organizes the approach to OH into a practical and easy-to-remember format for busy clinicians, is presented in the context of an illustrative case.

L'hypotension orthostatique (HO) est un syndrome gériatrique fréquent, impliquant habituellement la défaillance d'un ou de plusieurs mécanismes intrinsèques qui permettent de maintenir la perfusion cérébrale lors des stress orthostatiques. L'HO demeure sous-diagnostiquée malgré la présence de critères bien établis, probablement car la prévalence de ce syndrome est sous-estimée chez les personnes âgées et que la mesure des signes vitaux orthostatiques ne fait pas partie de l'examen physique de routine.

Les causes les plus fréquentes de l'HO dans la population âgée sont décrites dans cet article en utilisant l'acronyme mnémotechnique '4D-AID'. Le '4D-AID' se veut une façon pratique et facile à mémoriser d'évaluer la problématique de l'HO et est présentée ici à l'aide d'un cas clinique.

This article has been peer reviewed.

Conflict of Interest: The authors report no conflicts of interest.

This article was published in May 2016.

Key points

- The need for humans to maintain continuous intracranial perfusion despite the persistent effect of gravity is a concept easily understood by physicians, patients and caregivers – a useful factor when it comes to patient self-monitoring and reporting of symptoms as well as compliance with behavioural management techniques.
- Based on consensus-derived cut-offs, orthostatic hypotension (OH) is defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within three minutes of standing. Because the magnitude of the fall in blood pressure is dependent on the baseline blood pressure, a fall in SBP of 30 mm Hg has recently been adopted for patients with supine hypertension.
- Failure of the heart rate to increase in the setting of OH may be a clue to underlying autonomic pathology (or beta blockade), while exaggerated HR increase is more suggestive of intravascular volume depletion as a contributing factor.
- Timing of testing has been shown to be important due to the variability of blood pressure throughout the day and the observation that patients tend to be most symptomatic from OH in the morning. Other high yield times to test are after meals (due to splanchnic vasodilatation) and when BP medications are expected to have peak effect.
- In spite of well-recognized consensus cut-offs for a blood pressure-based diagnosis of OH, patient-reported symptoms take precedent in situations where patients are symptomatic but lack a "significant" (i.e., consensus-based cut-off) drop in BP upon standing, a situation termed *orthostatic intolerance* (OI).

Introduction

Symptomatic OH represents a significant source of morbidity among both community-dwelling and institutionalized older persons.[1] The standard approach to this common phenomenon taught during medical school is unfortunately fraught with discrepancies over diagnostic technique and intimidating unstructured lists of potential causes.

Much has been learned regarding the pathophysiology that underlies and contributes to the syndrome of OH in the 90 years since its first description in the literature by Bradbury and Eggleston in 1925.[2] Those first case reports involving younger subjects with severe OH likely represented disorders that would be classified today among a group of neurodegenerative conditions that manifest with failure of the autonomic nervous system. While these conditions still exist and should be considered as part of a comprehensive evaluation of OH, the majority of clinically relevant cases of OH seen among our increasingly elderly population are due to much more common aetiologies. The purpose of this article will be to review practical techniques for documenting the presence of OH and to provide a framework for identifying the causes of this common yet often unrecognized geriatric syndrome.

Case

Mr. B is a 72-year-old male being assessed by his family physician. He describes reduced appetite and several falls over the past months. He was last seen six months prior for reassessment of a cholinesterase inhibitor that was started one year prior for a diagnosis of dementia. His CT scan at the time of diagnosis revealed moderate subcortical microangiopathic disease as well as evidence of several old lacunar strokes that he was unaware of. His MoCA at the time of diagnosis was 18/30. For the past year, his wife has been performing all instrumental activities of daily living (ADLs) and helping her husband with some basic ADLs, such as getting dressed.

Past medical history is significant for hypertension, type 2 diabetes (most recent A1c 7.7%), coronary artery disease with previous MI and ischemic cardiomyopathy (with most recent left-ventricular ejection fraction 32%

on echocardiogram 18 months prior), hypothyroidism and BPH. His medications include bisoprolol, perindopril, digoxin, furosemide, ASA, metformin, pantoprazole, levothyroxine, donepezil and tamsulosin. Review of systems reveals that over the past year Mr. B has lost roughly 20 lb due to decreased appetite. When asked about his falls, Mr. B is unable to recall the circumstances, but his wife confirms that most have occurred while getting up to urinate during the night. Mrs. B says she has no concerns during the day since her husband is now using a walker.

On physical exam, BMI is approximately 20. Lying blood pressure is 118/62 mmHg, HR 88 (regular rhythm). BP repeated in the standing position after one minute is 100/55, HR 95 (regular rhythm). Mr. B denies dizziness but reports feeling weak after standing for approximately two minutes and requests to sit back down. He appears to become tremulous and is blinking his eyes and swaying, but still denies dizziness. Mucous membranes appear dry. Cardiovascular examination discloses no jugular venous distension and no peripheral edema. He has a grade II/VI systolic murmur heard best at the left upper sternal border that radiates to the right carotid area. Respiratory examination reveals clear lungs on auscultation. Abdomen is soft with no tenderness. MoCA is now 15/30 and his wife reports the cholinesterase inhibitor has not slowed down the rate of cognitive decline. Routine blood work is unrevealing except for a mild anemia with an elevated MCV of 102.

Physiology – WHY we need to measure postural BP in older patients

The need for humans to maintain continuous intracranial perfusion despite the persistent effect of gravity is a concept easily understood by physicians, patients and caregivers. Standing from a supine position causes approximately 10% to 15% of our blood to pool in the venous beds of the lower extremities and splanchnic system.[3] Early studies of patients with severe OH demonstrated pooling of no more than the normal amount of blood in these patients, suggesting that OH must represent an abnormal response to an expected shift in blood volume.[4] The expected response is triggered by the immediate decrease in cardiac preload that results from blood pooling. This stimulates afferent nerve terminals located in the carotid sinus and aortic arch to trigger a baroreceptor reflex mediated by decreased vagal (parasympathetic) tone and increased sympathetic output, thereby increasing both the cardiac output and systemic vascular tone.[5] In chronic states of reduced intravascular volume and cardiac output, the hormones renin, angiotensin and aldosterone act both on the blood vessels and at the level of the kidneys to maintain blood volume and pressure, and ultimately to preserve cerebral perfusion.[6] Older patients are more prone to hypovolemia due to a loss of ability to conserve water and sodium due to a reduction of renin, angiotensin and aldosterone as well as increased natriuretic peptides. This may be compounded by an age-related decrease in thirst reflex.

Clinical implications – WHEN to measure postural BP

OH becomes clinically relevant when it predisposes to symptoms. In elderly persons, the most feared consequence of OH is falls and potential injury. A fear of falling due to recurrent dizziness or previous falls can result, which effectively worsens existing states of immobility by contributing to deconditioning. Evaluation for OH should be done in all older patients presenting with presyncope, syncope or falls.[7] In our clinical experience, all patients with functional decline, generalized weakness, near falls, falls, postural dizziness and decreased cognition also merit a measurement of postural BP.

Diagnostic technique – HOW to measure postural BP

Unfortunately, there is no simple bedside test to reliably measure cerebral perfusion upon standing.[8] Therefore, clinician inference based on patient reported symptoms, observation and non-invasive peripheral blood pressure measurements allow for the recognition and diagnosis of OH. Based on consensus-derived cut-offs, OH is defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mm Hg or of diastolic blood pressure of 10 mm Hg within three minutes of standing.[9] Because the magnitude of the fall of the blood pressure is dependent on the baseline blood pressure, a fall in SBP of 30 mm Hg has recently been

adopted for patients with supine hypertension.[9] Measurement is typically performed using either a manual or electronic cuff to record blood pressure supine (usually after several minutes in that position to allow for equilibration of blood volume) and after one and three minutes of standing.[10] Failure of the heart rate to increase in the setting of OH may be a clue to underlying autonomic pathology (or beta blockade), while exaggerated HR increase is more suggestive of intravascular volume depletion as a contributing factor. Timing of testing has been shown to be important due to the variability of blood pressure throughout the day and the observation that patients tend to be most symptomatic from OH in the morning.[10] Other high yield times to test are after meals (due to splanchnic vasodilatation) and when BP medications are expected to have peak effect. Consequently, repeat postural BP measurements are essential for confidence in ruling in or ruling out the diagnosis. In spite of well-recognized consensus cut-offs for a blood pressure-based diagnosis of OH, patient-reported symptoms (e.g., postural syncope, presyncope, dizziness, headache, postural unsteadiness etc.) take precedent in situations where patients are symptomatic but lack a "significant" (i.e., consensus-based cut-off) drop in BP upon standing, a situation termed *orthostatic intolerance(OI)*.[11] This goes back to our opening thought in this section, which is that short of a technique for directly measuring a reduction in cerebral perfusion at the bedside, all other maneuvers represent surrogates and therefore must be interpreted in the context of patient symptoms – clinical judgment regarding whether the postural BP drops are causing symptoms supersedes consensus-based cut-offs.

Differential diagnosis – WHAT causes postural hypotension?

The increasing prevalence of OH in the elderly, in part reflects age-related degeneration of the delicate neurologic and endocrine reflex pathways described above, but can also be accounted for by the age-associated accumulation of chronic diseases and medications. The myriad causes of OH can be organized utilizing the 4D-AID mnemonic (Table 1) and are detailed in the subsequent paragraphs of this article. All causes act by blunting one or more of the normal physiologic mechanisms, and thus are best remembered using a pathophysiologic framework.

Table 1: DDX of postural hypotension - 4D-AID acronym

i. **Causes associated with a compensatory tachycardia – 4Ds**

- Deconditioning
- Dysfunctional heart
  - Myocardium (very low left ventricular ejection fraction)
  - Aortic stenosis
- Dehydration
  - Disease (e.g., acute illness, adrenal insufficiency)
  - Dialysis (post-dialysis dry weight too low)
  - Drugs
    - Diuretics
    - Anorexic drugs – narcotics, digoxin, antibiotics, cholinesterase inhibitors
- Drugs – 6 ANTIs
  - Anti-hypertensives
  - Anti-anginals
  - Anti-parkinsonian medications (e.g., levodopa)
  - Anti-depressants (e.g., anti-cholinergic tricyclics)
  - Anti-psychotics (anti-cholinergic effect)
  - Anti-BPH (e.g., terazosin, tamsulosin)

ii. **Causes that present with *lack* of compensatory tachycardia – AID**

- Autonomic dysfunction
  - Diabetic autonomic neuropathy (consider if patient has peripheral neuropathy)
  - Low B12
  - Hypothyroidism
  - ETOH abuse
  - Parkinsonism (Parkinson's disease, progressive supranuclear palsy, multisystem atrophy; e.g., Shy-Drager syndrome)
  - Amyloid
- Idiopathic (Bradbury-Eggleston)
  - Depletion of norepinephrine from sympathetic nerve terminals
- Drugs
  - Beta-blockers

Previously published as 3D-AID in Canadian Family Physician (Reproduced with permission of Canadian Family Physicians (CFP Nov 2010; 56: p1123 – 1129)

Working through the 4D-AID acronym

Deconditioning

OH prevalence increases in populations with prolonged bed rest[12] and low BMI[13]. Several studies have shown higher rates of OH among elderly patients living in nursing homes compared with the community setting, which in part reflects higher degrees of deconditioning and overall frailty among such individuals. OH and OI should be screened for in all elderly individuals deemed to be at least mildly frail.[11]
The following frailty scale can be used to identify who should be screened
(See Faculty of Medicine, Geriatric Research Journal) In the case described above, Mr. B is moderately frail as a result of his underlying cognitive impairment and functional limitations. He is likely also deconditioned based on his weight loss and history of physical inactivity.

Dysfunctional heart
Since the ability to adjust cardiac output and systemic vascular resistance quickly and efficiently during times of orthostatic stress is our primary guard against orthostatic hypotension, it should come as no surprise that patients with cardiac dysfunction experience a higher prevalence of OH. Assessment should include evaluation for left ventricular dysfunction. In this case, Mr. B has known systolic dysfunction due to ischemic cardiomyopathy, which can contribute to his OH.

Aortic stenosis is the most common valvular heart disease in developed countries and disproportionately affects the elderly.[14] Among elderly patients with severe aortic stenosis, 75.6% are symptomatic[14], and the development of syncope or presyncope in these patients is associated with an average survival of only three years without intervention.[15] All patients with orthostatic hypotension should be screened for cardiac murmurs and an echocardiogram should be considered if findings are suggestive of valvular pathology (emedicine.medscape.com/article/150638-clinical#b3). In this case, Mr. B has a murmur suggestive of possible aortic stenosis.

Dehydration
Elderly patients are particularly prone to dehydration as a result of impaired thirst mechanisms and impaired ability of the kidney to retain salt and water during periods of reduced fluid intake or volume loss.[10] The pathologic state of adrenal insufficiency, seen commonly among the elderly in the setting of prolonged exogenous glucocorticoid use as treatment for other conditions, is associated with prominent OH that occurs through essentially the same mechanisms (impaired renal sodium retention) as a consequence of insufficient circulating aldosterone.[16] Volume depletion should be suspected during the assessment of OH when a compensatory HR increase of >15 beats per minute is observed upon standing.[10] However, due to possible underlying autonomic dysfunction, the sensitivity of this finding is reduced and its absence does not rule out volume contraction in the elderly. A high index of suspicion is required for dehydration and subsequent volume contraction in patients presenting with OH and a history of anorexia, medications that reduce intravascular blood volume such as diuretics (both affecting Mr. B in our case) or recent acute illness (i.e., older hospitalized patients as well as seniors presenting to emergency departments should have postural BP routinely monitored).

Drugs
Several classes of medications are closely linked to OH. Most antihypertensive medications directly interfere with the normal hemodynamic homeostatic responses by the cardiovascular system to orthostatic stress.[17] The targets for antihypertensive control must be balanced against the potential for postural hypotension and are reviewed in another article in this journal
(See Canadian Geriatric Society Journal of CME). Anti-anginals (such as nitroglycerin) act by reducing vascular resistance in both venous and arterial vessels. Many drugs possess anti-cholinergic properties, which can produce profound impairments in orthostatic mechanisms through autonomic nervous system disruption. These include antipsychotics such as risperidone, SSRIs such as trazodone, TCAs such as amitriptyline and H2-blockers such as ranitidine. One of the most challenging clinical situations is the patient with Parkinson's disease taking carbidopa-levodopa formulations (e.g., sinemet, prolopa), since both the disease and the therapy are known to cause OH.[5] Commonly used medications to treat symptoms of bladder outlet obstruction from prostatic hypertrophy such as alpha-blockers (terazosin, tamsulosin) directly interfere with the sympathetic vasoconstrictor limb of the baroreceptor reflex and frequently contribute to OH. In our case, Mr. B is taking several medications that may directly worsen OH (perindopril, furosemide and tamsulosin). He is also taking medications that have been associated with anorexia (donepezil and digoxin) and may be contributing to OH indirectly through malnutrition and dehydration. To review other medications that can contribute to anorexia and weight loss see Table 2 in CMAJ.

Autonomic dysfunction
As described in the pathophysiology section above, the autonomic nervous system orchestrates the various cardiovascular responses that act to achieve hemodynamic homeostasis during an orthostatic challenge.

Clues that autonomic dysfunction may be playing a prominent role in the pathogenesis of OH include the presence of autonomic pathology in other organ systems, such as disorders of the bowel and bladder, impotence and anhidrosis and the absence of a compensatory increase in heart rate in the presence of orthostatic hypotension.[5,18] Common underlying conditions that are associated with secondary autonomic pathology include diabetes mellitus, hypothyroidism, vitamin B12 deficiency and alcoholism. Given Mr. B's diabetes, he is at risk for autonomic dysfunction which, in turn, will make him more sensitive to the medications listed above. His use of a PPI[19] (e.g., pantoprazole) and metformin[20] both place him at increased risk of low B12.

Although primary autonomic degenerative disorders are rare in comparison to secondary causes, examination for features of parkinsonism (cogwheel rigidity, resting tremor, bradykinesia), which is seen in many of these disorders (see Table 1), is essential in the assessment of OH.[10]

Conclusion

Although specific consensus-based blood pressure cutoffs are helpful tools in the definition of OH, we must not slavishly adhere to such consensus-based guidelines in lieu of our clinical judgment, recognizing that patients' symptoms are the most important feature and are sufficient to establish the diagnosis in many patients even if their blood pressure drops do not meet consensus-based cut-offs. From the case presented at the beginning of this article, Mr. B should be considered to have OH based on his symptoms and multiple risk factors. The 4D-AID mnemonic introduced in this article provides clinicians with a systematic approach to identifying the contributing causes in complex patients like Mr. B in order to guide management.

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