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# Orthostatic Hypotension and Cardiovascular Risk

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Orthostatic hypotension (OH) results from a failure of neural and circulatory mechanisms to compensate for the reduction in venous return that normally occurs on assuming the upright posture. OH is defined as a fall in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg measured within 3 minutes of standing.[1] OH can result from side effect of medications, intravascular volume loss, systemic diseases that involve autonomic nerves (e.g., diabetes mellitus or amyloidosis), and in rare cases it can be the initial sign of a primary autonomic failure syndrome (multiple system atrophy, pure autonomic failure and Parkinson`s disease). Severe OH can be a dramatic medical condition, with affected patients unable to stand but for few seconds before disabling symptoms of cerebral hypoperfusion and syncope ensue. Asymptomatic OH is a far more common condition, but one that is often unrecognized. It is a frequent finding in the elderly with prevalence reported between 6% to 35% or more, depending on the age group and associated co-morbidities [2;3]Over the last two decades, evidence from cross-sectional and longitudinal epidemiological studies has identified OH as an independent risk factor for cardiovascular morbidity and all-cause mortality.[4] In prospective studies the presence of OH at baseline increased the risk of subsequent adverse outcomes, including stroke,[5] coronary heart disease[6] and all-cause mortality.[2;4;7;8]In this issue of the journal, Franceschini et al.[9] have added chronic kidney disease (CKD) to the list of adverse health outcomes associated with OH. The authors examined the previously reported Atherosclerosis Risk In Communities (ARIC) cohort and found that the presence of OH at baseline increases the risk of subsequent development of CKD, particularly in African Americans, after accounting for known risk factors for CKD including diabetes and hypertension. The figure compares the risk of developing end-stage renal disease attributed to OH, with other risk factors previously reported in the same cohort[10]. It is noteworthy that the presence of OH imparts a risk comparable to or greater than other factors that elicit greater awareness and that are managed more aggressively.

Given the impact of OH, it would seem important to identify it in clinical practice. Adding an upright blood pressure measurement to an office visit would seem a trivial undertaking, but we suspect it is not often done. The definition of OH, and the evidence of it as a risk factor, is based on supine to standing blood pressures, which would be even more difficult to implement. Seated to upright measurements may not be validated in outcome trials, but offer the best hope for detection of OH.

It would be easier to justify routine orthostatic blood pressure measurements if there was an intervention that would either prevent orthostatic hypotension or its consequences. It is important, therefore, to examine the risk factors that lead to OH and the potential

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mechanisms by which it is associated with bad outcomes. It has been argued that the wide swings in blood pressure associated with OH could by themselves contribute to end-organ damage. In this regard, patients with autonomic failure characterized by supine hypertension and severe orthostatic hypotension have decreased renal function as compared to controls.[11] It is not clear, however, if the large blood pressure variations seen in these patients are to blame or if supine hypertension is sufficient to explain these alterations.

The largest determinant of OH is aging.[12]The incidence of OH increases from <5% in the 5th decade of life to about 20% at age >=70. Other risk factors include hypertension, diabetes, Parkinson's disease and carotid arterial disease. All of these risk factors have in common the potential to impair autonomic mechanisms that regulate blood pressure. In particular, baroreflex function is decreased in these conditions. Depressed baroreflex sensitivity has been associated with an increased risk of cardiovascular morbidity and mortality.[1314] Decreased high frequency variability of heart rate, another index of impaired autonomic function, is also an independent risk factor for cardiovascular mortality. We are not aware of epidemiological studies that examined the association between OH and baroreflex sensitivity or heart rate variability, but the evidence points towards an impairment of autonomic function playing a role in the adverse outcomes associated with OH.

Identifying an intervention that would improve autonomic function, avoid OH or prevent its negative consequences, remains a challenge. Pharmacological treatment of symptomatic OH involves mineralocorticoids and pressor agents, but these would be counterproductive in asymptomatic OH and unlikely to improve outcomes. Physical countermeasures (e.g., compression stockings) and lifestyle changes (weight reduction or exercise) are attractive options, but their efficacy is unproven and compliance is likely to be poor in asymptomatic patients. Improving vascular disease with better control of hypertension, hyperglycemia and hyperlipemia should be already part of the management of these patients but treatment directed at these conditions may not necessarily improve OH, and can even induce or worsen it. The one potential intervention at our disposal would be to avoid medications known to be associated with OH (e.g., diuretics or adrenergic blockers), or to impair autonomic function. There is, unfortunately, little evidence-based information that could justify specific guidelines.

In summary, asymptomatic OH is a significant medical problem, particularly in the elderly. As our population ages, the importance of OH as a health care burden is likely to increase.[12] Impaired autonomic function probably contributes to the development of OH and may play a role in its negative consequences. It would be valuable to determine if the presence of OH correlates with non-invasive indices of impaired autonomic function (e.g., baroreflex sensitivity, heart rate spectral analysis). It is likely that asymptomatic OH remains unrecognized in the majority of patients in clinical practice. An effort should be made to detect OH in patients at risk (elderly, patients with hypertension, diabetes mellitus or Parkinson's disease, or receiving multiple medications. Research is needed to determine interventions that may prevent OH or the adverse outcomes associated with it.

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