Orthostatic hypotension: a new cardiac risk factor?

Peter A. Brady*

Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

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This editorial refers to ‘Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies’1, by F. Ricci et al., on page 1609.

Compensatory mechanisms that allow functional and sustained upright posture in humans have evolved over millions of years yet remain poorly understood. Orthostasis, derived from the Greek words arthōs and stāsis, meaning upright or standing, requires sufficient and sustained venous return to the heart that can overcome gravitational pooling of blood in the abdomen, pelvis, and lower extremities, and relies on a complex interplay between autoregulatory cardiovascular, autonomic, and neuroendocrine pathways as well as often subconscious physical counter-manoeuvres such as leg crossing and arm folding, etc. which reduce venous capacitance and increase peripheral resistance to augment venous return.1 Transient or sustained failure of one or more of these mechanisms causes symptoms due to impaired organ perfusion termed orthostatic intolerance.2,3

Within the broad clinical manifestations of orthostatic intolerance, several discrete disorders are recognized: neurocardiogenic (vasovagal) syncope, the postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, chronic fatigue,2,4,5 and fibromyalgia syndromes.6,7 While each of these clinical syndromes is distinct, considerable overlap exists consistent with a unifying pathophysiology. Importantly, common to each of these discrete manifestations of orthostatic intolerance is a very benign long-term prognosis.

Another common but distinct manifestation of orthostatic intolerance which is frequently under-recognized is orthostatic hypotension (OH),8 defined as a sustained reduction of systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg or > 30 mmHg in hypertensive patients within 3 min of assuming an upright position or on head-up tilt testing to at least 60°.9 In current practice, OH is rarely an isolated finding, being most often secondary to neurodegenerative disease such as Parkinsonism, autonomic failure, autoimmune, cardiovascular, endocrine, and metabolic disorders, as well as secondary to dehydration and a variety of pharmacological therapies, most commonly those prescribed for the treatment of hypertension. OH is believed to be common in senescence but is mostly seen in the institutionalized elderly population where its aetiology is multifactorial, rather than in active and otherwise elderly patients, and may occur in some individuals after meals, so-called post-prandial OH.10–12 In each of these conditions, if the assumption is correct that OH is a secondary phenomenon, it would be logical to expect that outcomes in patients with OH would be driven primarily by the underlying cause and not OH itself.

Previously, several small studies reported on an association between OH and incremental higher mortality risk, implying that OH was in some way different from other manifestations of orthostatic intolerance.13 However, many of these studies were small or included widely diverse populations often with inconsistent definitions of OH, and lacked long-term follow-up assessment. Because of these limitations, the hypothesis that OH might be associated with adverse outcomes is yet to be proven.

Ricci and colleagues now revisit this question and present an interesting and thought-provoking meta-analysis of prospective observational studies reporting on the association between prevalent OH, mortality, and incident major adverse cardiac and cerebrovascular events (MACCE) in 13 studies identified between 1966 and 2013.14 Included in their analysis is a population of close to 122 000 patients with a median follow-up of 6 years. The main finding was that prevalent OH is associated with an increased risk of all-cause mortality [relative risk (RR) 1.5, 95% confidence interval (CI) 1.24–1.81], incidence coronary heart disease (RR 1.41, 95% CI 1.22–1.63), and stroke (RR 1.64, 95% CI 1.13–2.37), with the highest risk association being with incident heart failure (RR 2.25, 95% CI 1.52–3.33).

While the authors are to be congratulated on this study, these data have important limitations which the authors acknowledge. First, summary rather than raw data were used, limiting the power of their analysis. Secondly, cardiovascular vs. non-cardiovascular mortality could not be distinguished, which is important given that, at least in the very elderly, therapies that lower blood pressure may act to reduce cardiac events but increase total mortality compared with non-treatment groups. Thirdly, there is wide and inherent variability in age and study populations included, ranging from patients

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2* Corresponding author. Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1 507 284 4045, Fax: +1 507 284 8137, Email: brady.peter@mayo.edu
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who presented to emergency rooms for evaluation, nursing home residents, asymptomatic community-living middle-aged individuals, and patients enrolled pre-dialysis. Importantly, trend data and data on the severity and chronicity of OH are missing, with most studies reporting only a single data point that met the criteria for OH, the definition of which also varied between studies. With these limitations, we can conclude that OH is associated with increased risk but not whether OH is causative or whether more chronic or severe OH, presumably with a greater degree of activation of potentially detrimental neuroendocrine and vascular pathways, is required to effect risk.

To address further whether OH might itself be a risk factor independent of the underlying disease process requires at a minimum a degree of biological plausibility. One could argue that the observed association between OH and all-cause death is simply a consequence of more advanced or aggressive underlying disease, for example rapidly progressive neurodegenerative disorders, which manifest more widespread dysfunction, in which case OH would simply be a marker of the underlying disorder and not a contributor to mortality. Similarly, the association of OH with incident heart failure could be either a consequence of the need for more aggressive pharmacological therapy for an associated condition, such as hypertension, or an indicator of low cardiac output suggesting advanced heart failure. The observed association between OH and incident coronary heart disease and stroke could also be the result of chronic vascular stiffness secondary to longstanding hypertension, perhaps along with diabetes mellitus and diabetic autonomic dysfunction causing OH and transient cerebral hypoperfusion. On this point, the authors speculate that compensatory neuroendocrine mechanisms may also play a role by triggering downstream vascular changes such as platelet adhesion, vascular endothelial injury, and activation of physiological vasoconstrictors such as endothelin-1 and vasopressin, but these arguments cannot be supported by the current study and require further investigation.

The greater association between OH and MACCE seen in younger individuals (aged < 65 years) compared with older individuals is interesting, and the authors again postulate that this may be a consequence of a more severe underlying disease process, or more prolonged exposure to the detrimental effects of OH.

With these limitations in mind, what can the practising clinician take away from the study by Ricci et al.? Certainly, it brings new life to an often forgotten clinical sign. If nothing else, it justifies the routine clinical assessment of OH in any individual undergoing cardiovascular evaluation since it is easy to measure, requires minimal equipment and expense, yet may provide incremental prognostic value. The question as to whether OH could have a more direct detrimental impact, and through what mechanism, is important but unanswered, and deserves further study. Similarly, the potential beneficial impact of therapies targeted to treat OH need to be better understood. In that regard, I would certainly echo the authors’ plea that assessment of OH, its causes and effects should be part of future clinical, epidemiological, and basic investigation in the hope of better understanding this often forgotten physical sign.

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References