Orthostatic hypotension and cardiovascular risk: defining the epidemiological and prognostic relevance

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This editorial refers to ‘Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmö Preventive Project)†, by A. Fedorowski et al. on page 85

An extremely large amount of evidence documents without any doubt that a chronic elevation in blood pressure values represents at any age a major independent risk factor for cerebrovascular, coronary, and also renal disease.1–3 Evidence provided by a less consistent number of studies, however, has shown that also the opposite condition, i.e. a low blood pressure state, may indeed be associated with an increased cardiovascular risk. This is particularly the case for orthostatic hypotension, i.e. the clinical condition defined by international guidelines as that characterized by a blood pressure reduction during the first 3 min of assumption of the orthostatic position ≥ 20 mmHg for systolic and ≥ 10 mmHg for diastolic blood pressure, respectively.4,5 Indeed evidence has been provided that in patients with symptomatic and/or asymptomatic standing-related hypotension, without any evidence of co-existing conditions responsible for autonomic failure, the detection of this condition is associated with an increase in fatal and non-fatal cardiovascular events and also in all-cause mortality.6–8 The evidence, however, has been largely provided in elderly people, and there is much less information available in younger individuals.9,10

Fedorowsky and co-workers have reported the results of a prospective study,11 performed in the context of the Malmö Preventive Project, aimed at defining the prevalence, underlying causes, and prognostic value of orthostatic hypotension in a general Swedish population sample. The main features of the study can be summarized as follows.11 First, the study followed a longitudinal design with a rather long-lasting follow-up (on average 22 years). Secondly, a careful assessment of the subjects enrolled into the study was performed both at baseline and at different time periods during the follow-up. Finally, an accurate data analysis was done to detect the relative prognostic relevance of orthostatic hypotension after correcting the results for possible confounders, such as age and co-morbidities (hypertension/diabetes, etc.).

The study results show that in a large population sample (>30 000 subjects) the prevalence of this pathological condition is quite consistent, amounting on average to 6.2%.11 They also show that a number of variables, such as age, female gender, hypertension, antihypertensive drug treatment, elevated resting heart rate values, diabetes, smoking, and low body mass index, are the conditions more commonly associated with the disease.11 Finally, the study provides evidence on the long-term prognostic relevance of the condition, by showing an increased risk of coronary events and overall mortality rate in patients suffering from orthostatic hypotension, even after correcting the results for confounders.

Several intriguing results of the study deserve to be briefly mentioned and discussed. First, the study makes the diagnosis of orthostatic hypotension on the basis of the blood pressure responses to standing detected during the first minute of the manoeuvre. Does this approach guarantee an accurate and careful assessment of the disease? Based on current guidelines,4,5 the approach seems accurate enough, although some considerations (based on the time-course of the blood pressure response to standing) may suggest that it would be worth focusing more on the circulatory response characterizing the initial 30 s of the manoeuvre, given the more likely chance to have a blood pressure drop in this very initial time period.12 To detect such short-lasting blood pressure changes appropriately, however, the use of beat-to-beat finger or, at least, automatic blood pressure measurements with short time intervals between different evaluations, should be required. Another issue, which is important from a methodological but also a diagnostic viewpoint, refers to the within-subject variability of the haemodynamic responses to standing. In other words, should the diagnosis of the condition be based only on a
single evaluation or should it be based on the average of the responses repeated 2–3 times in a reasonable time window? The question has no answer, given the fact that the diagnosis in the studies performed so far is based only on the evaluation of the haemodynamic response to a single manoeuvre.

Secondly, the authors find that antihypertensive drug treatment was significantly related to the occurrence of orthostatic hypotension, in conjunction with other haemodynamic and non-haemodynamic factors. This is in sharp contrast to the conclusions of another study recently published by some of the authors of the present study, showing that antihypertensive drug treatment [in particular angiotensin-converting enzyme (ACE) inhibitors] may be protective from orthostatic hypotension. It should be noted, however, that the two study populations were not superimposable for their main features, with an age difference of the recruited patients amounting to ~20 years. It is thus not unlikely that the age factor may be important in determining the favourable or unfavourable effects of antihypertensive drug treatment on orthostatic hypotension and that elderly people may, for some unknown reasons, be more protected against antihypertensive drug-induced blood pressure reductions. This possibility, however, seems unlikely considering the well-documented notion that with advancing age the homeostatic mechanisms controlling blood pressure and the speed of the cardiovascular adjustments to a given manoeuvre (such as orthostatic stress or head-up tilting) are progressively less efficient.

Thirdly, the occurrence of orthostatic hypotension was related, among other variables, to the presence of elevated resting heart rate values, underlying once again the importance of the autonomic nervous system for the cardiovascular adjustments to postural changes. The explanation for this relationship is quite simple. Resting tachycardia counts on well-defined pathophysiology and has important clinical implications (Figure 1). From a mechanistic view point, an elevated heart rate means an increased sympathetic cardiac drive at the level of the sinus node coupled with a reduced inhibitory vagal input to the same cardiac region. An elevated heart rate also means, from an operative point of view, a lesser ability of heart rate to increase further in response to a given manoeuvre or intervention. Since during orthostatic stress heart rate increase is of vital importance for maintaining stable blood pressure (particular systolic), its attenuated increase during the manoeuvre may make the patient more prone to develop postural hypotension. In contrast, since the behaviour of diastolic blood pressure during orthostatic stress is less dependent on heart rate, an impairment of the ability of sympathetic neural function to trigger vasoconstriction may be suggested to occur in these patients.

A final comment should be made on the study finding that the risk of coronary heart (but not of cerebrovascular) disease was increased in people suffering from orthostatic hypotension. Some considerations on this relationship should be made, however. Unadjusted data show that cerebrovascular disease risk was also increased in these patients, but an attenuation of the association may be seen after adjustments of other cardiovascular risk factors. This means that, as expected from the common knowledge on the pathophysiology of the cerebral circulation, orthostatic hypotension is linked to cerebrovascular disease risk. The link, however, is weaker than the one associating orthostatic hypotension with coronary artery disease. In this respect, evidence has been provided by the study findings that the diastolic blood pressure drop rather than the systolic drop has a greater relevance for determining the development and progression of coronary events. This is line with the well-known evidence that diastolic blood pressure is a major determinant of coronary blood flow.

**Conflict of interest:** none declared.

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**References**


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**Figure 1.** Association between resting tachycardia and orthostatic hypotension.
Acute and chronic renal artery stenosis

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An 89-year-old woman was admitted for acute left-sided back pain and oliguric acute renal failure. Contrast-enhanced computed tomography of the abdomen demonstrated reduced perfusion of the hypotrophic right kidney (7.5 cm) due to severe stenosis of the right renal artery. There was no uptake of contrast in the left kidney (measuring 9.8 cm) caused by (acute) occlusion of the left renal artery due to a thrombus mass bulging into the aorta (Panels A and B; arrows). Intra-arterial thrombolytic therapy or stent placement was not possible, because the origin of the left renal artery was not visible. Reconstructive vascular surgery was not performed because of severe atherosclerotic disease of aorta and renal artery and patient’s poor performance status. After the start of haemodialysis, patient’s symptoms improved.

However, haemodialysis was stopped after 14 days, according to patient’s wish, because of a dramatic decline in the perceived quality of life status. Two weeks later she died. Autopsy confirmed our pre-mortal diagnosis. Macroscopic examination showed a thrombus mass in the left renal artery, which bulged into the aorta and was superimposed on an atherosclerotic plaque (Panels C and D; arrows). The thrombus was probably formed by rupture of this plaque. More than 70% of the left kidney had a pale appearance consistent with recent infarction. Microscopy of the left kidney showed extensive necrosis of the involved area (Panel E; note the clear demarcation between necrotic tissue (left side) and remaining vital tissue (right side)) due to acute ischaemia caused by the propagated thrombus in the left renal artery (Panel F). Histological examination of the hypotrophic right kidney showed extensive fibrosis with some atrophied tubuli filled with proteineous material (arrowheads) (Panel G).

Here, we describe, in a single patient, acute renal failure due to the combination of a hypotrophic kidney with severely reduced function due to chronic renal artery disease on one side and acute renal artery thrombosis on the other side leading to renal infarction.