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LETTER TO THE EDITOR
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Orthostatic hypertension and adverse clinical outcomes in adults and older people

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Orthostatic hypertension (OHT) is a condition characterized by an increase in blood pressure after assuming the standing position.[1] Nowadays no consensus definition exists, thus OHT prevalence varies among studies (4%–20.3%).[2–6] Studies considering a broad OHT definition (i.e., either a systolic or a diastolic blood pressure increase upon standing) demonstrated the highest prevalence of OHT.[1] However, when any rise in orthostatic blood pressure (without cut-offs) is considered as OHT, people with a normal orthostatic response could be wrongly classified as affected by this pathologic condition. On the contrary, definitions including only a systolic or a diastolic increase in blood pressure could miss some cases of OHT.

The tests used to perform the diagnosis are: active standing, ambulatory blood pressure monitoring and tilt-table.[1] Notwithstanding the lack of validated methods creates uncertainty. In the clinical setting the active standing examination could be biased by the "white coat effect".[1] Automated sphygmomanometers, though widely used, are less sensible than mercury sphygmomanometers in measuring orthostatic blood pressure variations.[7] The level of orthostatic stress applied can be more or less intense (from lying to standing or from sitting to standing); in the last case, some affected people may not be identified. Finally, the recording time after the orthostatic stress (immediately after the stress, one minute or three minutes after the stress) markedly differed across studies. A preconscious increase in blood pressure which is not sustained over time may not bear the same consequences of a prolonged adrenergic activation.

OHT is frequently overlooked in routine clinical practice because many clinicians ignore this condition. Unfortunately, OHT under-diagnosis is not free of potential serious consequences. The pathophysiologic mechanisms that underpin OHT, seem to be implied also in the development of its adverse effects. The sympathetic overdrive [4,5,8,9] responsible for the excessive compensatory reaction to orthostatic stress [4] when associated with blood pressure variability enhances endothelium shear stress. This could favour thrombotic events and cardiovascular morbidity. OHT has been considered as a form of pre-hypertension and has been related to hypertension target organ damage (higher urinary albumin/creatinine ratio and higher BNP levels, higher BNP/ANP ratio, electrocardiographic signs of left ventricular hypertrophy and silent cerebrovascular disease).[5,8,9] Target organ damage is a risk factor for premature cardiovascular events and death. Indeed, OHT has been linked to adverse clinical outcomes,[2,3,6,10–36] thought without a robust evidence.[1] The main source of inconsistency across studies is the absence of a uniform definition of OHT, which also makes the comparison tricky.

Studies on OHT related mortality are extremely heterogeneous. Three studies found that OHT was associated with an increased mortality.[6,19,31] The strongest evidence comes from the study by Veronese who described a higher all cause and cardi-

ovascular related mortality in community dwelling adults with OHT.[6] The study was well conducted with blood pressure measured with mercury sphygmomanometer, with an orthostatic stress from supine to standing, using a cut off of systolic blood pressure increase of 20 mmHg. This result was confirmed in a similar clinical setting by Kostis[19] and by Vellilla-Zancada.[31] However, in the study by Kostis the association of OHT with mortality was present only in unadjusted analyses and became not statistically significant after adjusting for cardiovascular risk factors and comorbidities. In the study by Velilla-Zancada, the association with an increased mortality was present only when considering systolic increase in blood pressure 3 min after standing.[31] On the contrary, six studies found no association between OHT and all-cause mortality.[3,10,11,14,15,17] Anyway, in the study by Curreri, *et al.*,[14] mortality was evaluated as a secondary outcome; thus, this study could have been underpowered for this detection. The study by Davis, *et al.*[15] considered mainly middle-aged people (mean age 50) and the follow-up was probably too short (5 years) to evaluate mortality in a middle-aged population.

Two studies were conducted in nursing homes.[10,17] In such complex setting, the impact of OHT on mortality could have been less relevant compared to the other comorbidities the patients suffered from. Nevertheless, in the study by Agnoletti, *et al.*,[10] cardiovascular morbidity and mortality were higher among nursing home residents suffering from OHT. In the study by Bursztyn, *et al.*,[3] the level of orthostatic stress was mild (from sitting to standing) and possibly insufficient to detect all the cases of OHT. Therefore, some people suffering from OHT may have been wrongly classified as normotensive with an impact on the results. The studies by Alagiakrishnan, *et al.*[11] and Wijkman, *et al.*[34] used lower cut-offs compared to other studies to define OHT. The non-significant findings on mortality could be due to the inclusion of people not really suffering from OHT but just having a preserved orthostatic response in the OHT groups. Indeed, when no cut off is set and any rise in systolic or diastolic blood pressure is considered as OHT, results can be even opposite as in the study by Weiss, *et al.*[33] where mortality was lower in the OHT group.

Studies with different designs confirmed the link between OHT and hypertension. OHT was associated with hypertension,[11,22,24,29] masked hypertension[2,28] and worsen daytime blood pressure profile.[18,32] This relationship was confirmed in normotensive individuals,[24,28,29] hypertensive (with and without treatment)[1,11,18,23,32] and diabetic patients.[22] These findings are in accordance with the previously detected association of OHT with markers of hypertension target organ damage.[5,8,9] Moreover, the relation between OHT and hypertension could be one of the mediators of the association between OHT and cardiovascular morbidity. Other possible pathophysiologic mechanisms of cardiovascular morbidity may be the elevated and frequent activation of the sympathetic nervous system and wide blood pressure oscillations exerting a traumatic effect on blood vessels and increasing atherosclerosis.[4,5,8,9,37]

OHT was found to be associated with nonfatal cardiovascular events leading to hospitalization or to a specific long-term new treatment in insitutionalized older individuals.[10] OHT was also linked to stroke[16,25,35] (though with conflicting results[11,34]), myocardial infarction[26] and peripheral arterial disease.[16]

Eventually, OHT has been related to poor cognitive performance.[14,20,27] Bad blood pressure control promotes cerebral small vessel disease,[9,38–41] which predisposes to micro-bleedings and subcortical lacunar infarctions.[42] These alterations in critical or associative areas of the brain can contribute to the impairment of cognitive performance.[41]

To sum up, it seems that OHT is related to hypertension,[11,22,24,29] abnormal blood pressure patterns[18,32] and masked hypertension,[2,28] which can all predispose to future cardiovascular events. Indeed, an association with some cardiovascular comorbidities, cognitive impairment and mortality has been found, though with some conflicting results.

We need to develop a clear and widely accepted definition of OHT to perform prospective longitudinal studies to clearly assess OHT related adverse outcomes. If future studies confirmed the associations of OHT with adverse clinical outcomes it would be advisable to recommend routine postural change measurement during routine clinical practice to obtain information of prognostic clinical significance.

STATEMENT OF ETHICS

This article complies with the guidelines for human studies. According to the type of article (review) neither patient conflict of interest disclosure nor approval of the institute's committee on human research was necessary. No animal experiment was performed.

DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly to the manuscript and all authors are in agreement with the content of the manuscript. Literature review, data extraction, assessment of the risk of bias: SD, PDR. Data synthesis, analysis of subgroups or subsets: SD, PD, MC. Writing the paper: SD, PDR, MC. Contribution to the revision of the manuscript with important intellectual content: MC.

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