



# Consensus statement on the definition of orthostatic hypertension endorsed by the American Autonomic Society and the Japanese Society of Hypertension

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Received: 11 September 2022 / Accepted: 13 September 2022 / Published online: 29 September 2022  
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## Abstract

We propose a consensus definition of “an exaggerated orthostatic pressor response” in subjects in whom systolic blood pressure increases  $\geq 20$  mmHg when going from supine to standing posture. This definition can be extended for seated to standing measurements. We reserve the term “orthostatic hypertension” for when this pressor response leads to an upright systolic blood pressure  $\geq 140$  mmHg. We believe this consensus definition will help in the study of the pathophysiology, clinical impact, and potential treatment of these entities, and identification of patients who are at greater cardiovascular risk.

**Keywords** Adrenergic · Autonomic nervous system · Baroreflex · Circadian rhythm · Orthostatic hypertension · Orthostatic pressor response · Sympathetic nervous system

## Background

Standing imposes a major hemodynamic burden on the cardiovascular system. In healthy persons, neurohumoral reflex mechanisms, particularly the arterial baroreflex, maintain blood pressure with standing. However, the counterregulatory response overshoots in some people such that blood

pressure increases with standing. This orthostatic pressor response may result in hypertensive blood pressure levels only when standing or further exacerbate arterial hypertension. The condition is often referred to as orthostatic hypertension and appears to be associated with increased cardiovascular risk [1, 2]. Yet, a uniform definition and diagnostic cutoff values of orthostatic hypertension have not been established. In fact, current hypertension guidelines do not cover orthostatic hypertension [3–5]. Moreover, diagnostic criteria of orthostatic hypertension vary from study to study. Therefore, data regarding the prevalence, cardiovascular

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This article is co-published in the journals Clinical Autonomic Research and Hypertension Research, <https://doi.org/10.1007/s10286-022-00897-8> or <https://doi.org/10.1038/s41440-022-01074-0>.

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risk, and management of orthostatic hypertension are difficult to interpret. We propose a new classification distinguishing between an exaggerated orthostatic pressor response and orthostatic hypertension to facilitate research in this area.

## Definitions

- An **exaggerated orthostatic pressor response** is a sustained increase in systolic blood pressure by at least 20 mmHg when changing from the supine to the standing position regardless of absolute blood pressure while standing.
- **Orthostatic hypertension** is defined as an exaggerated orthostatic pressor response associated with systolic blood pressure of at least 140 mmHg while standing.

## Rationale

Our goal was to arrive at a pragmatic definition that could be utilized in the setting of mechanism-oriented studies, epidemiological surveys, and clinical trials. We are aware that the suggested definitions are based on clinical reasoning and normative data rather than cardiovascular risk estimates and that the definitions as well as blood pressure cutoff values may have to be refined in the future. While orthostatic hypertension may be associated with cardiovascular risk as outlined in the sections below, more data are required to allow for a risk-based definition.

In the Malmö Preventive Project, blood pressure after 10 min in the supine position and after 1 min standing was measured in 33,346 persons aged  $45.7 \pm 7.4$  years [6]. On average, systolic blood pressure decreased 1.2 mmHg with a standard deviation of 8.8 mmHg. In the follow-up study to the Malmö Preventive Project, the Malmö Offspring Study [7], among 4019 participants aged  $41.9 \pm 14.5$  years, systolic blood pressure increased by  $1.4 \pm 8.6$  mmHg after 3 min of standing, corroborating Malmö Preventive Project observations. Thus, 20 mmHg systolic blood pressure cutoff value for an exaggerated orthostatic pressor response corresponds to approximately two standard deviations above the population mean.

An increase in diastolic blood pressure on standing can be normal. Moreover, in individuals with excessive orthostatic heart rate increases, cardiac stroke volume may decrease such that pulse pressure is narrowed. The resulting spurious diastolic blood pressure increase is difficult to interpret. The panel, therefore, suggests that systolic blood pressure may be more practical when diagnosing orthostatic hypertension.

A recent publication by an expert group suggested that a systolic blood pressure increase while standing by at least 20 mmHg or above 140 mmHg in otherwise normotensive

persons could serve as criteria for orthostatic hypertension [8]. The limitation of this broad definition is that individuals with upright blood pressure in the normotensive range could be labeled as being “hypertensive.” Even though we cannot exclude that orthostatic blood pressure surges even within the normotensive range can have negative influences on the cardiovascular system, it appears likely that absolute standing blood pressure in the upright posture is more relevant to cardiovascular risk. Therefore, we propose to distinguish between an exaggerated orthostatic pressor response, which may result in normotensive or hypertensive blood pressure while standing, and factual orthostatic hypertension. Among persons with orthostatic hypertension, some may exhibit isolated orthostatic hypertension, which is an exaggerated orthostatic pressor response with hypertensive blood pressure values only while standing. Others may also be hypertensive while supine or seated with further worsening of blood pressure when standing. It is possible that these subgroups require a different diagnostic and therapeutic approach [2, 9].

## Pathophysiology of orthostatic hypertension

When standing, approximately 500–1000 ml blood is pooled below the diaphragm and hydrostatic pressure shifts fluids from the intravascular to the interstitial compartment. In healthy persons, compensatory autonomic reflex mechanisms withdraw cardiac parasympathetic drive and raise cardiac and vascular sympathetic activity, thereby leading to an increase in heart rate, a drop in systolic blood pressure  $< 20$  mmHg, and a small increase in diastolic blood pressure [10, 11]. Small-scale studies suggest that orthostatic hypertension results from an excessive increase in vascular resistance with standing [12]; however, the mechanisms driving orthostatic hypertension may be affected by age [13, 14]. The observation that plasma norepinephrine increases more with standing in patients with orthostatic hypertension suggests that the response is mediated through excessive sympathetic activation with standing [12, 15]. Indeed,  $\alpha$ -adrenoreceptor blockade attenuates orthostatic hypertension [16]. Patients with orthostatic hypertension often feature an extreme dipping pattern in 24 h ambulatory blood pressure recordings [14], and an exaggerated early-morning blood pressure surge [15].

## Epidemiology and cardiovascular risks of orthostatic hypertension

The epidemiology of orthostatic hypertension and the data regarding the cardiovascular risk associated with orthostatic hypotension have been reviewed recently [1]. Briefly, orthostatic hypertension defined as sustained increase in systolic blood pressure  $\geq 20$  mmHg and/or diastolic blood pressure  $\geq 10$  mmHg within 3 min of standing was observed in 5–30% of participants in epidemiological surveys or clinical trials [17–21]. Risk factors for orthostatic hypertension included age, adiposity, arterial hypertension, and diabetes mellitus [22]. An exaggerated orthostatic pressor response with office blood pressure in the normotensive range may precede arterial hypertension in younger people [23]. Among people with arterial hypertension, individuals showing an exaggerated orthostatic pressor response are more likely to exhibit subclinical cerebrovascular disease, peripheral arterial disease, or cerebrovascular disease [15, 24–26]. Orthostatic hypertension was also associated with increased all-cause and cardiovascular mortality [17, 27, 28]. The clinical significance of these findings is difficult to generalize because, in the past, diagnostic criteria for orthostatic were not harmonized.

## Diagnosing orthostatic hypertension

When diagnosing an exaggerated orthostatic pressor response or orthostatic hypertension, blood pressure measurements with a brachial cuff suffice. Pulse rate should also be recorded. Preferably, measurements should be conducted in a quiet surrounding to limit confounding of orthostatic blood pressure responses by external stimuli. Supine blood pressure and heart rate should be measured after 5 min of rest in the supine position. Then, patients should stand up actively. Upright blood pressure and heart rate should be measured after 1, 3, and 5 min, at least, to confirm the persistent character of the blood pressure change. We suggest that the measurements after 3 and 5 min be averaged to determine standing systolic blood pressure. For screening purposes, a single measurement after 3 min may be sufficient.

Beat-to-beat blood pressure and heart rate recordings can be applied in selected patients but are not widely available [8].

We recommend that repeated orthostatic testing should be conducted on a different day to confirm the diagnosis.

Because supine and upright blood pressure measurements may be difficult to conduct in all patients, seated-to-upright measurements may be considered for screening purposes. Since hemodynamic changes when standing up from the seated to the standing position are less compared with

standing up from the supine position, the orthostatic pressor response may be less pronounced such that the sensitivity in detecting orthostatic hypertension may decrease. Similar limitations have been observed when using seated-to-standing measurements when diagnosing orthostatic hypotension [29]. Therefore, we suggest that confirmatory testing be considered with supine-to-standing measurements.

Head-up tilt testing may be considered for persons unable to undergo an active standing test.

## Clinical management

There is no evidence that individuals with an exaggerated orthostatic pressor response and blood pressure within the normal range require antihypertensive therapy. It may be prudent to follow up these patients' blood pressure given the increased risk for progression to arterial hypertension. In patients with isolated orthostatic hypertension in whom blood pressure is only in the hypertensive range while standing, ambulatory blood pressure monitoring may have utility in gauging the overall blood pressure load during the day and detect abnormalities in diurnal blood pressure patterns, such as extreme blood pressure dipping during the night or masked morning hypertension [2, 14]. Patients fulfilling orthostatic hypertension criteria have not been specifically sought for or excluded from blood pressure trials. It appears reasonable to prescribe antihypertensive therapies according to current hypertension guidelines [3–5]. There is no evidence that patients with orthostatic hypertension benefit from a particular drug class in terms of cardiovascular risk protection. Whether diuretics, which could further increase neurohumoral activation while standing, should be avoided in patients with orthostatic hypertension is unclear given the known benefits of such drugs on cardiovascular morbidity and mortality. Overall, there is a need for additional research to guide clinical decision making in patients with an exaggerated orthostatic pressor response and orthostatic hypertension. We hope that a uniform definition will support this endeavor.

**Funding** Open Access funding enabled and organized by Projekt DEAL

## Declarations

**Conflict of interest** J.J. served as advisor for Novo-Nordisk and Bayer, received research support from Boehringer-Ingelheim and Novo-Nordisk, and is co-founder of Eternygen GmbH. He is Editor-in-Chief of Clinical Autonomic Research and International Associate Editor of Hypertension Research but was not involved in editorial handling of this manuscript. I.B. is a consultant for Theravance Biopharma, Takeda Inc., and Amneal Pharmaceuticals, and has a patent for an automated abdominal binder to treat orthostatic hypotension. He is supported by NIH grants R01HL149386 and R01HL161095. V.K., P.N.,

G.G., and A.F. report no conflicts of interest. K.K. is Editor-in-Chief of Hypertension Research but was not involved in editorial handling of this manuscript.

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