Assessment and management of exaggerated blood pressure response to standing and orthostatic hypertension: consensus statement by the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability

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Recent evidence suggests that an exaggerated blood pressure (BP) response to standing (ERTS) is associated with an increased risk of adverse outcomes, both in young and old individuals. In addition, ERTS has been shown to be an independent predictor of masked hypertension. In the vast majority of studies reporting on the prognostic value of orthostatic hypertension (OHT), the definition was based only on systolic office BP measurements. This consensus statement provides recommendations on the assessment and management of individuals with ERTS and/or OHT. ERTS is defined as an orthostatic increase in SBP at least 20 mmHg and OHT as an ERTS with standing SBP at least 140 mmHg. This statement recommends a standardized methodology to assess ERTS, by considering body and arm position, and the number and timing of BP measurements. ERTS/OHT should be confirmed in a second visit, to account for its limited reproducibility. The second assessment should evaluate BP changes from the supine to the standing posture. Ambulatory BP monitoring is recommended in most individuals with ERTS/OHT, especially if they have high-normal seated office BP. Implementation of lifestyle changes and close follow-up are recommended in individuals with ERTS/OHT. Whether specific antihypertensive treatment should be administered in hypertensive patients with ERTS/OHT is unknown. Thus, they should be managed as any other hypertensive patient. Standardized standing BP measurement should be implemented in future epidemiological and interventional studies.

Keywords: blood pressure, hypertension, masked, orthostatic, prognosis, standing

Abbreviations: ABP, ambulatory blood pressure; ABPM, ambulatory blood pressure monitoring; ARIC, Atherosclerosis Risk In Communities; AUROC, area under the receiver-operating-characteristic curve; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CARDIPP, Cardiovascular Risk factors in Patients with Diabetes-a Prospective study in Primary care; CRIC, The Chronic Renal Insufficiency Cohort; CV, cardiovascular; DBP, diastolic blood pressure; ERTS, exaggerated blood pressure response to standing; ESH, European society of hypertension; HARVEST, Hypertension and Ambulatory Recording VEnetia STudy; OHT, orthostatic hypertension; PARTAGE, Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population; PWV, pulse wave velocity; RTS, blood pressure response to standing; SBP, systolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; SPRINT, Systolic Blood Pressure Intervention Trial; WCE, white-coat effect

INTRODUCTION

In most previous hypertension guidelines, including the 2018 guidelines of the European Society of Hypertension (ESH), measurement of blood pressure (BP) on

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standing was recommended only in older people, patients with diabetes, with neurodegenerative disorders, or under antihypertensive treatment, to detect a possible excessive BP fall from lying/sitting to standing [1–3]. However, in the last few years, evidence has been accumulating that also an exaggerated BP increase on standing (ERTS) is associated with an increased risk of adverse outcomes both in young and older individuals [4–7]. The recent 2023 ESH Guidelines have recognized the clinical value of standing BP measurement in the assessment of individuals with hypertension and included orthostatic hypertension (OHT) among the hypertension phenotypes [8]. However, methodological heterogeneity in the assessment of standing BP and the lack of universally accepted definitions of ERTS and OHT made it difficult to establish the actual clinical and prognostic value of these clinical entities. Some authors used ERTS and OHT as interchangeable definitions, others defined OHT only on the basis of BP level on standing, and yet others as a combination of ERTS and standing BP. In addition, most investigators used only SBP to define ERTS/OHT, a minority used DBP, and others a combination of SBP and DBP. Improving the diagnostic testing of the BP response to standing (RTS), harmonizing the definition of ERTS and OHT, and providing a more rational approach to the patient with ERTS/OHT can be of help to prevent or reduce the harmful effects of ERTS/OHT.

The objectives of this consensus statement are to review the available evidence on the association between ERTS/OHT and adverse outcomes, provide a methodological benchmark for a uniform evaluation of RTS, discuss the criteria to be used for a harmonized definition of ERTS and OHT, and provide recommendations for the assessment and management of individuals with ERTS/OHT.

PROGNOSTIC ROLE OF EXAGGERATED BLOOD PRESSURE RESPONSE TO STANDING AND ORTHOSTATIC HYPERTENSION

The recent interest of researchers and clinicians for ERTS and OHT is due to the growing evidence about their independent association with several adverse outcomes, including the development of future hypertension, organ damage, cardiovascular events and all-cause mortality.

PREDICTIVE VALUE FOR FUTURE HYPERTENSION

In a middle-aged cohort of 6591 normotensive healthy men and women from the Atherosclerosis Risk In Communities (ARIC) study, the investigators observed an increased risk of future hypertension, during a 6-year follow-up among participants with both increases and decreases of standing SBP relative to those without SBP changes (four intermediate deciles), even though associations were attenuated after adjusting for confounders [9]. Similar findings were reported in the Coronary Artery Risk Development in Young Adults (CARDIA) study [10] involving 2781 young adults (18–30 years), during 8 years of follow-up. Participants with a SBP increase of more than 5 mmHg in the standing position were more likely to progress to hypertension (12.4%) in comparison to those who experienced a smaller change (±5 mmHg (6.8%; $P < 0.001$). The predictive capacity of SBP RTS was observed also in special populations such as diabetic patients [11]. In 108 newly diabetic normotensive individuals, Nibouche-Hattab *et al.* [11] observed that those who presented OHT, defined as a SBP increase from lying to standing at least 20 mmHg and/or DBP at least 10 mmHg, had the highest rate of incident hypertension (76.2%) after 1 year of follow-up in comparison with those who had a smaller BP response (32.8%) or those with orthostatic hypotension (20%, $P < 0.0008$). These findings were not confirmed by another study in an older population [12], where, after adjusting for seated BP, standing BP was not a significant predictor of future hypertension.

ASSOCIATION WITH HYPERTENSION-MEDIATED ORGAN DAMAGE

A large body of evidence has shown that OHT is often associated with hypertension-mediated organ damage. A positive correlation between orthostatic changes of SBP (SBP increase ≥20 mmHg) and arterial stiffness assessed by pulse wave velocity (PWV) was found by Wu *et al.* [13] in the hypertensive subgroup of a cohort of 1820 individuals. In the Malmö Offspring study [14] involving 3966 middle-aged adults (mean age 42.1 years), Johansson *et al.* [14] observed a U-shaped relationship between SBP changes during standing and aortic stiffness with a significant increase in PWV for both the first and fourth quartiles. In contrast, an inverse relationship was observed for DBP, with a progressive PWV decrease across quartiles of increasing orthostatic DBP change [14].

A strong association has been found between OHT and silent cerebrovascular disease or poorer cognitive performance in the elderly. In a group of 86 elderly hypertensive patients (mean age 67.6 years), Eguchi *et al.* [15] observed a higher number of silent cerebral infarcts in people with SBP RTS at least 10 mmHg than in normotensive individuals or hypertensive patients with normal RTS. Kario *et al.* [7] found a higher prevalence of both silent cerebral infarcts (81%), multiple cerebral infarcts (65%) and advanced deep white matter lesions (62%), in individuals with SBP RTS at least 20 mmHg in comparison with those with lower RTS (48%, $P < 0.01$, 24% $P < 0.001$, and 31% $P < 0.001$, respectively). Similarly, Ryan *et al.* [16] observed a greater orthostatic increase in SBP in elderly patients (mean age 69.9 years) with acute lacunar stroke than in a control group. Curreri *et al.* [17] in a cohort of 1408 elderly patients (mean age 71.4 years), observed that during 4.4 years of follow-up OHT, defined as a rise of at least 20 mmHg in SBP, was a significant risk factor for cognitive decline documented at mini-mental-state evaluation. Similarly in the ELSA- BRASIL study [18], a decline in cognitive function (detected as a reduction in verbal fluency) was found among participants with OHT defined as a SBP increase at least 20 mmHg and/or DBP increase at least 10 mmHg during standing.

Data for renal function are more controversial. Hoshide *et al.* [19], examining 605 hypertensive individuals from the Japan Morning Surge-1 Study, observed that those in the top decile of orthostatic home SBP change (BP increase >7.8 mmHg) had a higher urinary albumin/creatinine ratio in comparison with those in the bottom decile ($P = 0.003$). In a more recent analysis, the same investigators [20] observed that the reduction of the SBP RTS after 6 months of doxazosin intake, was associated with a significant reduction in the prevalence of microalbuminuria (40.7 vs. 28.4%, $P = 0.001$). In contrast, no relationship was found between RTS and albumin excretion rate in the Hypertension and Ambulatory Recording VEnetia STudy (HARVEST) [21].

Conflicting results were also found for cardiac parameters. A higher prevalence of left ventricular hypertrophy at the ECG (46%) was found by Kario *et al.* [7] in people with OHT (defined as a SBP increase ≥20 mmHg during standing), in comparison with those with normal RTS (23%, $P < 0.05$). Similarly, Fan *et al.* [22] observed a higher risk of left ventricular hypertrophy among women in the top quintile of BP response to standing (>15.3 mmHg) in comparison with those with smaller response. In contrast, Eguchi *et al.* [15] observed no significant differences in left ventricle mass according to RTS.

PREDICTIVE VALUE FOR HARD END-POINTS

During the last two decades, convincing evidence has accrued about the prognostic value of ERTS and OHT for major adverse cardiovascular events and mortality, both in normotensive and hypertensive populations. Again in these studies, several different criteria were used to define ERTS and identify individuals with OHT. In most studies, a SBP increase of at least 20 mmHg during standing was used to define ERTS/OHT, but lower SBP threshold levels and a combination of SBP and DBP RTS were used in some studies.

ASSOCIATION WITH CARDIOVASCULAR EVENTS

A U-shaped relationship of RTS with coronary heart disease and lacunar stroke incidence was observed in the above-mentioned ARIC study after 8 years of observation [23]. A similar association was found for stroke and for peripheral artery disease in a large Chinese population, in which these events were more common in the top and bottom quintiles of the RTS distribution [22]. Also, findings in very elderly individuals from the Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE) [24] and from the Normative Aging studies [25] showed that OHT (defined as SBP RTS ≥20 mmHg in the PARTAGE and as DBP RTS ≥10 mmHg in the Normative Aging study) were associated with the presence of nonfatal cardiovascular events. Recent results from the Systolic Blood Pressure Intervention Trial (SPRINT) are consistent with the above data, though the association between OHT (defined as SBP RTS ≥20 mmHg or DBP RTS ≥10 mmHg) and cardiovascular events was found in the intensive but not in the standard treatment group [26,27]. The association between OHT and cerebrovascular events was highlighted in a recent meta-analysis of five studies in which patients with OHT showed a significant 94% increase in the risk of stroke [28]. The predictive value of ERTS for cardiovascular events was found also in the young-to-middle-aged participants of the HARVEST study in which a SBP RTS more than 6.5 mmHg (top decile) was a significant predictor of adverse cardiovascular outcomes during a 17-year follow-up [29].

ASSOCIATION WITH CARDIOVASCULAR AND ALL-CAUSE MORTALITY

Conflicting results have been reported on the relationship between ERTS/OHT and mortality. In the large majority of the studies ERTS was defined using the 20 mmHg SBP cut point. The association with cardiovascular mortality was reported in two studies. A significant increase in risk was observed in the PARTAGE and the SPRINT study, in which OHT was associated with death from cardiac, cerebrovascular, and other vascular causes [24,27]. Meta-analysis of these two studies showed a significant 39% increase in the risk of cardiovascular mortality [28]. The relationship of OHT with all-cause death was investigated in nine studies. An association of OHT with mortality was found in the Pro.V.A [30] and PARTAGE studies [24] (SBP RTS ≥20 mmHg in both studies), in the Systolic Hypertension in the Elderly Program (SHEP) [31] (SBP RTS ≥15 mmHg), and the Velilla-Zancada *et al.* [32] and SPRINT studies [27] (SBP RTS ≥20 mmHg or DBP RTS ≥10 mmHg). The large majority of the participants were elderly. However, some studies found no association between OHT and all-cause mortality [17,33–38]. This may be due to inconsistencies in the criteria used to define OHT and to the different age ranges of the participants. In a meta-analysis including the seven studies that reported time-to-death and used adjusted hazard ratios, there was a significant 21% increase in mortality risk for participants with OHT ($P = 0.007$) [28]. Data in young individuals are missing.

METHOD OF BLOOD PRESSURE MEASUREMENT

There are no agreed recommendations regarding the BP measurement methodology for the detection and confirmation of ERTS/OHT. However, implementing standardized and validated methodology regarding the conditions, body and arm position, number and time interval of measurements and number of visits, is of paramount importance for the accurate assessment of this phenotype and to allow comparison among studies. The recent 2023 ESH Guidelines state that standing BP should be measured at the first visit, and regularly at each visit in selected patients, with at least two BP measurements taken 1 and 3 min after standing [8]. However, no further details are provided.

The measurement conditions for standing BP should follow standard recommendations for sitting office BP measurement (avoiding smoking, caffeine, food and exercise 30 min before, quiet environment with comfortable temperature, and no talking during and between measurements) (Table 1) [1]. The body and arm position are also crucial. From a pathophysiology point of view, BP response to standing may be more pronounced when compared to

TABLE 1. Blood pressure measurement procedure

Sitting/supine BP measurement
No smoking, caffeinated beverages, or exercise for at least 30 min before measurement.
Remain seated or supine for 3–5 min.
No talking by patient or staff throughout the measurement session.
Keep cuff at heart level.
Take three BP readings at 1 min intervals.
Standing BP measurement
Stand up as fast as possible.
Keep the cuff at heart level with arm supported.
Take three BP readings at 1 min intervals starting 1 min after standing.

baseline supine instead of seated BP measurements [6,39]. Yet, in routine clinical practice, assessing BP change from seated to standing position is more feasible for screening. However, when ERTS is suspected, the diagnosis should be confirmed with supine to standing measurements [6,39]. The available studies evaluating the prognostic value of ERTS/OHT present methodological heterogeneity regarding the BP measurement methodology, with almost half of them determining RTS from the supine to standing position and the others from sitting to standing [28]. Interestingly, the same cut-off (SBP ≥20 mmHg) has been used in most of them for defining ERTS [28]. Information on the arm position during standing BP measurement (at the body's side or supported at heart level) is scarce. Specifically, among the studies with prognostic data, two of them reported that 'the forearm was supported at heart level' [22,34], one 'arm at heart level in all postures' [32], one 'arm was relaxed at the side' [40] and one 'arm raised to a position parallel to the floor for 30 sec (for some participants, it was necessary to support the arm in this position for the necessary 30 s)'[37]. Some data suggest that the arm position on standing might affect BP comparisons, with overestimation of BP values when the arm is relaxed at side vs. heart level [41,42]. It is reasonable to suggest that the arm position should be held constant so that to keep the centre of the cuff at heart level in all supine, sitting and standing positions.

In most of the available studies providing prognostic data, duplicate standing BP measurements were taken at 1 and 3 min, whereas in some studies, standing BP was measured between 1 and 2 min [28]; thus, it is reasonable to recommend at least 2 BP measurements 1 and 3 min after standing. However, due to RTS variability, three BP measurements at 1-min intervals would provide a better estimate or RTS [29] especially for research purposes. Other proposals have been made, such as triplicate measurements 1, 3 and 5 min after standing [6].

The presence of OHT needs to be confirmed with additional measurements taken in a separate visit, as data have shown that the reproducibility of the BP response to standing is moderate, if not poor, and the best prognostic value of OHT is obtained with consistent BP response in at least two visits [29,39].

As with all BP measurements, only properly validated upper arm cuff devices should be used, preferably automatic electronic with appropriate cuff size (according to the individual's arm circumference and the manufacturer's instructions) [1].

FOCUS ON ORTHOSTATIC SBP VS. DBP

In the vast majority of studies reporting on the prognostic value of ERTS and OHT, the definition of both entities has been based only on SBP [28]. ERTS/OHT evaluated with DBP alone or combined with SBP has been investigated only in a minority of studies assessing the risk for mortality, myocardial infarction, heart failure or composite outcomes [27,32,33,43]. To assess the clinical relevance of diastolic vs. that of systolic ERTS/OHT, comparing the respective hazard ratios for outcome in studies providing separate results for systolic and diastolic ERST/OHT in the same populations might be useful (Fig. 1) [27,32,33,43]. In the SPRINT study, diastolic OHT (defined as a DBP increase ≥10 mmHg) predicted outcomes in contrast to systolic OHT only in the intensive treatment arm of the study [27]. Yet, the opposite trend was observed for various outcomes in all the other studies (Fig. 1) [32,33,43]. Interestingly, in the Cardiovascular Risk factors in Patients with Diabetes-a Prospective study in Primary care (CARDIPP) study, diastolic OHT (defined as a DBP increase ≥10 mmHg) was associated with lower risk of cardiovascular events compared with patients with normal systolic and diastolic RTS [33]. In a study performed in a predominantly young to middle-aged population, aortic stiffness and central aortic BP gradually decreased across increasing quartiles of orthostatic DBP difference [14]. In contrast, when participants were grouped according to orthostatic SBP difference, aortic stiffness was increased in the bottom and top quartiles compared to the intermediate quartiles [14]. The aforementioned data might suggest differential clinical relevance of ERTS based on SBP or DBP measurements; yet, the characteristics – especially age – of the examined populations differ across the relevant studies which could cause heterogeneity in the pathophysiology mechanisms and the observed associations. Thus, although experts agree that SBP is the most important component from a clinical standpoint, DBP may also be of interest in understanding the pathophysiology and mechanisms of orthostatic BP changes.

DEFINITION OF EXAGGERATED BLOOD PRESSURE RESPONSE TO STANDING

Many different cut-offs have been used in the literature to define ERTS using SBP, DBP or a combination of the two. In most studies, at least 20 mmHg increase was used to define ERTS for SBP [4–8,24,30] and at least 10 mmHg increase for DBP [18,26,32,33]. For the reasons mentioned above, this document will focus on SBP only. The prevalence of a SBP ERTS at least 20 mmHg greatly varied from study to study and increased with increasing age. High prevalence (≥20%) was found in old participants in the PARTAGE study and the ProV.A. study 1 [18,26]. On the contrary, much lower prevalence was reported in young and middle-age individuals, at 1–2% or even lower ERTS rate [13,14,21]. For example, in the Malmö Offspring study, a SBP at least 20 mmHg ERTS was found in 0.8% of participants aged under 44 years and in 2.6% of older individuals [14]. For this reason, in some studies including young individuals, ERTS was defined using a lower SBP cut-off from 5 to 15 mmHg [5,10,29].

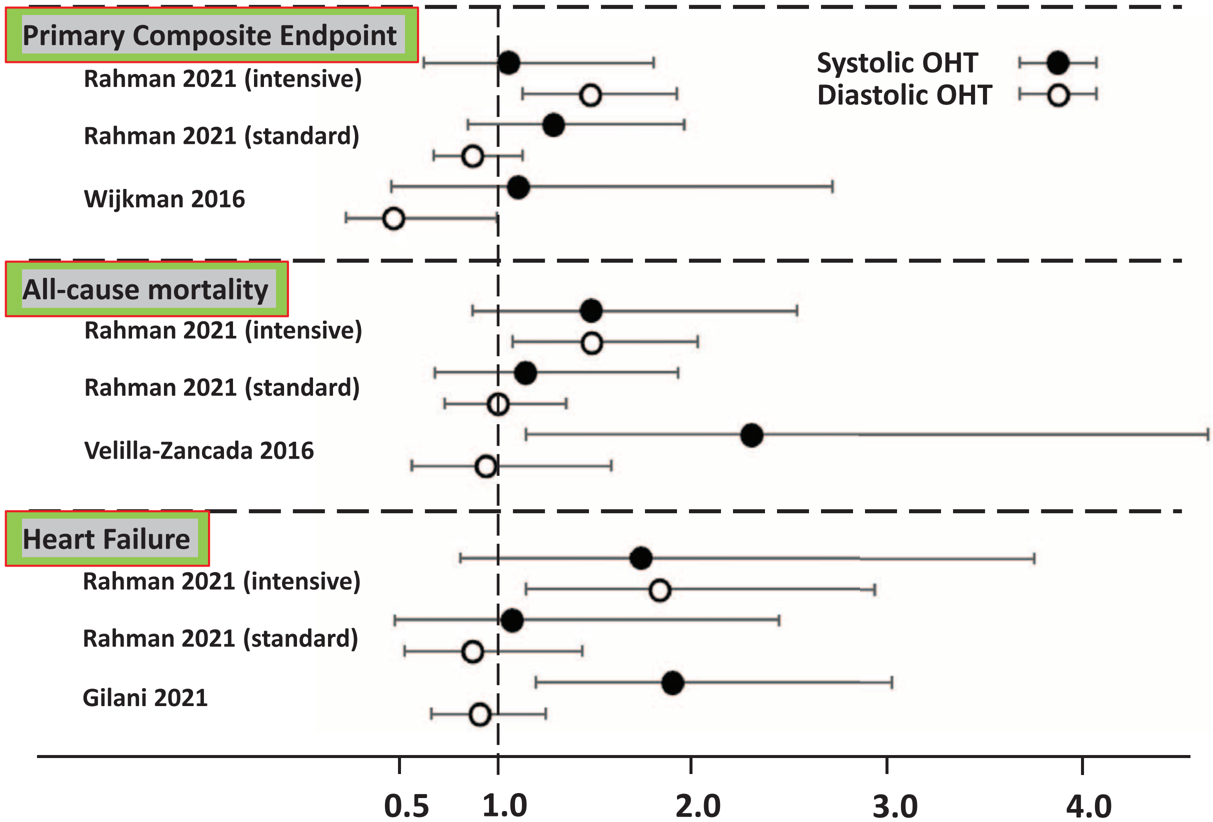

FIGURE 1 Hazard ratios for systolic and diastolic orthostatic hypertension in studies testing the risk of adverse outcomes using both pressures.

A recent document of the American Autonomic Society and the Japanese Society of Hypertension defined ERTS as an orthostatic SBP increase at least 20 mmHg [6] and this definition was endorsed by the 2023 ESH recommendations for the management of arterial hypertension [8]. However, the same experts recognized that in young to middle-aged people, even smaller RTS may have important clinical and prognostic implications. In agreement with the above-mentioned guidelines, the present statement confirms the SBP threshold of 20 mmHg for the definition of ERTS, as lower cut-points could increase the risk of overdiagnosing OHT and lead to overtreatment of people at low cardiovascular risk [4,44].

Although a SBP at least 20 mmHg cut point appears to be reasonable for defining orthostatic hyperreactivity in the elderly, in younger individuals, this cut point may downplay the clinical relevance of lower RTS. In the HARVEST study (mean age 33 years), the prevalence of OHT at baseline was 0.7% according to the above-mentioned criteria [21]. However, in a longitudinal analysis, a SBP RTS at least 6.5 mmHg (upper decile of the distribution) was predictive of cardiovascular events occurring during a 17-year follow-up [29]. In the same line, in the CARDIA study (mean age 27 years), a SBP RTS more than 5 mmHg identified a group of young adults at increased risk of developing hypertension within 8 years [10]. These data suggest that smaller orthostatic SBP increases may identify young people who are hyperreactive to standing, which might be prognostically important. Thus, in younger individuals, the threshold for diagnosing ERTS may be changed when more prognostic data are available.

DEFINITION OF ORTHOSTATIC HYPERTENSION

Similar problems have been encountered in the definition of OHT, due to the large number of different criteria used in the literature. Most investigators have identified OHT on the basis of SBP and/or DBP ERTS with [45,46] or without using absolute values of standing BP [18,26,32,33]. Others have defined OHT as a BP increase from less than 140/90 mmHg in the lying posture to more than 140/90 mmHg on standing [22]. These heterogeneous definitions of OHT represent an important limitation in the interpretation of the results of studies on the association of OHT with cardiovascular events and mortality. The need for standardized OHT criteria has been addressed by the above-mentioned consensus document of the American Autonomic Society and the Japanese Society of Hypertension [6] and more recently by the 2023 ESH Guidelines [8]. According to these statements, OHT should be defined as an ERTS of SBP at least 20 mmHg associated with a standing SBP of at least 140 mmHg. As discussed in the previous section, these criteria may downplay the clinical relevance of lower RTS in younger individuals but have the advantage of providing a harmonized definition to be used in future studies [44].

INFLUENCE OF RESPONSE TO STANDING ON AMBULATORY BLOOD PRESSURE AND RELATED HYPERTENSION PHENOTYPES

Several factors such as smoking, alcohol, anxiety, job stress, intense physical activity and hyper-reactivity to exercise can increase daytime ambulatory BP (ABP) and can induce masked hypertension [47]. Thus, RTS has shown a relationship with several ABP monitoring (ABPM) parameters, such as mean 24 h and daytime BP, BP variability and nocturnal dipping [7,39]. In a recent report, the area under the receiver-operating-characteristic curve (AUROC) was used to evaluate the accuracy of seated and standing BP in diagnosing ambulatory hypertension [48]. When hypertension was defined as average 24-h SBP at least 125 mmHg, standing BP outperformed seated BP in diagnosing ambulatory hypertension [AUROC of standing SBP was 0.81 (95% confidence intervals 0.71–0.92) compared with 0.70 (0.49–0.91) for seated SBP]. In a population of young-to-middle-aged individuals, both SBP RTS ($P = 0.002$) and DBP RTS ($P < 0.001$) showed a significant correlation with average daytime BP [49]. Therefore, RTS can be a simple test to identify people with increased likelihood of elevated ABP and masked hypertension. Conversely, both SBP and DBP RTS are negatively correlated with the white-coat effect (WCE). Data from the HARVEST have shown a strong negative association between WCE and RTS for both SBP and DBP ($R = -0.35$ and -0.27, respectively, both $P < 0.001$) [21]. In the participants grouped into RTS quintiles, a progressive decline in WCE was found from the first to the fifth quintile ($P < 0.0001$) [50]. Recent results from the Chronic Renal Insufficiency Cohort (CRIC) study confirmed those findings [51]. A 5 mmHg postural reduction in SBP or DBP was associated with a 1.46 [0.90, 2.01] and 1.16 [0.36, 1.99] greater systolic WCE.

The relationship of RTS with short-term BP variability is more controversial. In elderly patients, OHT has been found to be associated with high BP variability [7], whereas in younger individuals no such relationship was found [21]. Inconsistency has also been reported for the nocturnal BP fall. A large overlap between OHT and extreme dipping has been reported in old [7] but not in younger individuals [21]. Postural reduction in SBP or DBP was positively associated with greater systolic and diastolic night-to-day ratio in the participants with chronic kidney disease from the CRIC study [51]. In children, ERTS has been associated even with a ‘nondipper’ phenotype [52]. These different patterns of relationship may be explained by the different mechanisms of ERTS according to age. In the elderly, baroreflex dysregulation associated with increased arterial stiffness might be the main mechanisms for ERTS accounting for extreme nocturnal BP dipping and increased BP variability on ABPM [4,5,7]. However, in younger individuals, neurohumoral activation with sympathetic predominance seems to be the driving factor [21]. For the mechanisms accounting for the link between ERTS/OHT and increased cardiovascular risk, we refer the reader to previous reviews [4–6,39].

RELATIONSHIP OF RESPONSE TO STANDING WITH MASKED HYPERTENSION

Masked hypertension is associated with increased risk of adverse cardiovascular outcomes [47] and it is thus important to identify clinical variables that can predict this condition. ERTS has been found to be an independent predictor of masked hypertension in several studies. One longitudinal and three cross-sectional analyses showed that ERTS, defined as an RTS of SBP ranging from 5 to 10 mmHg, is a predictor of masked hypertension diagnosed with either home BP measurement [53] or ABPM [54], even after adjustment for age, sex, BMI, basal SBP and antihypertensive medication. In young to middle-age participants from the HARVEST study, ERTS defined as a SBP increase at least 6.5 mmHg on standing (top decile) was associated with masked hypertension assessed after 3 months with an OR of 2.45 ($P < 0.001$) for hyper vs. normo-reactors [49]. ERTS was present in 16.9% of participants with masked hypertension and was associated with urinary epinephrine ($P = 0.020$). In participants grouped according to RTS and 24-h urinary epinephrine, a four-fold risk of masked hypertension was found in the hyper-reactors with high epinephrine compared to the normoreactors with low epinephrine, suggesting that neurohumoral activation was the driving factor in both conditions. In conclusion, ERTS appears to be a predictor of masked hypertension and a possible indication to perform ABPM, especially in individuals with high-normal seated office BP.

GENERAL RECOMMENDATIONS

ERTS is not a benign clinical entity and the role of ERTS/OHT has been overlooked for long. Hypertension guidelines have recommended measuring orthostatic BP only in elderly individuals or in patients on antihypertensive treatment, aiming at detecting a possible orthostatic fall in BP. The association of OHT with an increased risk of future sustained hypertension [10] and the frequent coexistence with masked hypertension [49,53,54] suggest that BP should be measured in the upright posture, even if seated or supine BP is normal. In hypertension, OHT is often associated with hypertension-mediated organ damage and is a harbinger of adverse cardiovascular outcomes. Thus, orthostatic BP changes should be assessed in all patients with hypertension, irrespective of age or use of antihypertensive drugs, as they can provide additional information on future cardiovascular risk. In untreated patients in the initial phase of the disease, routine standing BP measurements may reinforce the diagnosis of hypertension reducing the number of visits.

MANAGEMENT OF INDIVIDUALS WITH EXAGGERATED BLOOD PRESSURE RESPONSE TO STANDING AND ORTHOSTATIC HYPERTENSION

We recognize that the recommendations provided in this section are the result of an expert-opinion consensus rather than of evidence-based data. When ERTS and/or OHT are detected, orthostatic hyperreactivity should be confirmed with a second assessment on a different visit/day, due to the limited RTS reproducibility [39]. The second active standing test should evaluate the BP change from the supine to the orthostatic posture [6]. ABPM should be performed to have a more detailed picture of the BP changes during standing, preferably using actigraphy. ABPM will provide a more precise estimate of the BP load during daytime hours and information on the diurnal BP rhythm. Extreme nocturnal dipping in elderly patients with a pronounced BP morning surge are frequent features in individuals with ERTS [7], as well as increased short-term BP variability, particularly in old individuals [4,5,7].

Although measurement of standing BP may be helpful in every clinical setting, a different management approach should be considered depending on the level of seated office BP (Fig. 2). If seated BP is normal, there is no evidence from clinical trials that isolated OHT requires antihypertensive treatment. However, considering the increased risk of developing hypertension, nonpharmacological measures and close follow-up should be implemented in all individuals with a standing SBP above the hypertensive criteria, regardless of the level of seated office SBP. If seated office BP is in the high-normal range an ABPM is indicated. Antihypertensive drug treatment should be implemented when CV risk is very high due to previous CV events. In the remaining high-normal BP patients drug treatment can be considered in the presence of masked hypertension with hypertension-mediated organ damage and/or high CV risk [21,50,51]. In individuals with normal ABPM should be performed if readily available.

Whether a specific antihypertensive treatment should be used in hypertensive patients with ERTS/OHT is unknown. No randomized clinical trial has been carried out in this condition and there is no evidence that OHT can benefit from a particular drug class. Small studies have shown that some benefit can be achieved with the use of alpha blockers [20], but the lack of definite evidence suggests that hypertensive patients with ERTS/OHT should be managed in the same way as any other hypertensive patient [6]. Because a decreased preload is one of the mechanisms that may facilitate ERTS, it might be argued that the use of diuretics in OHT is not the most appropriate choice [6]. However, further studies are needed.

GAPS IN EVIDENCE AND FUTURE RESEARCH

Accumulating evidence suggests that ERST and OHT are associated with increased cardiovascular risk. However, studies on the prognostic significance of OHT have been often inconsistent due to heterogeneity in measurement methodology and in diagnostic criteria. Although most studies used SBP to evaluate orthostatic responsiveness, also DBP or their combination have been used, which probably is a major source of inconsistency in the results and interpretation across studies. Considerable disagreement and inconsistencies also pertain to the criteria used to define ERTS/OHT. Harmonized definitions for ERTS and OHT phenotypes should be adopted. In this document, we recommend using the SBP at least 20 mmHg threshold to define ERTS. However, most of the available evidence supporting this threshold stems from investigations

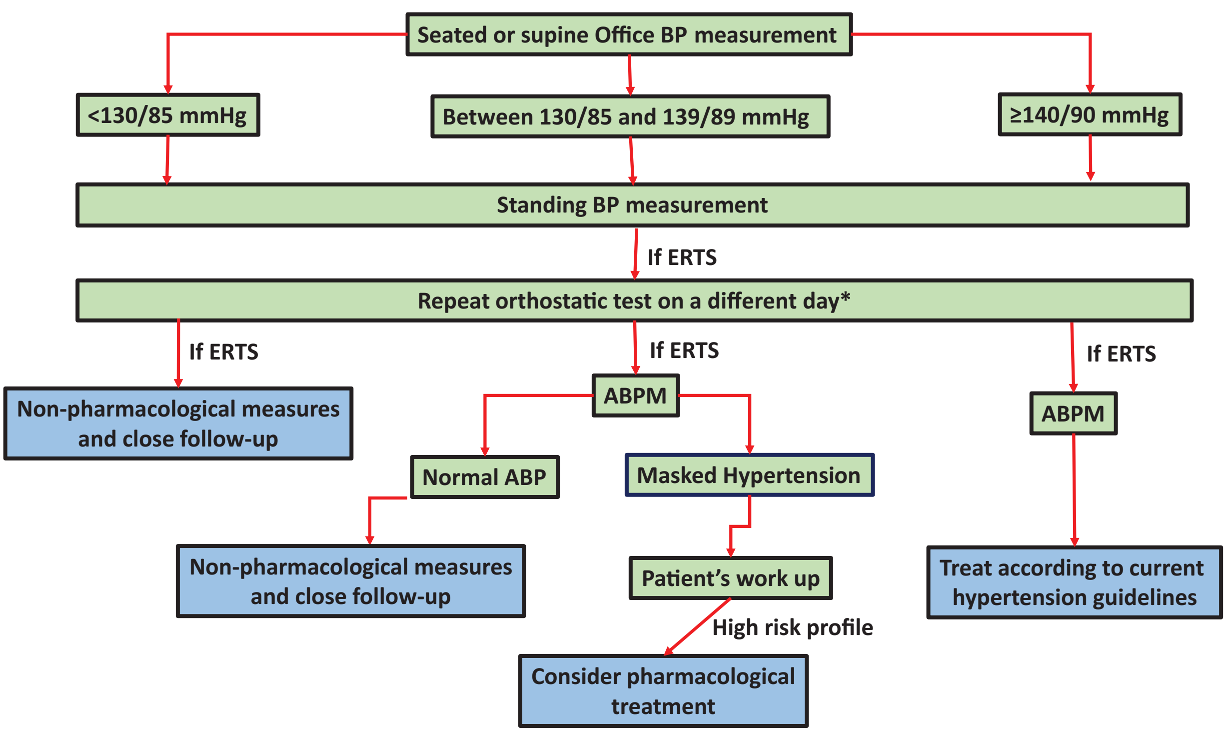

FIGURE 2 Flow-chart for diagnosis of ERTS and management of people with orthostatic hypertension. ABP, ambulatory BP; ABPM, ambulatory BP monitoring; BP, blood pressure; ERTS, exaggerated SBP response to standing (≥20 mmHg). [a]Supine-to-standing BP measurement should be preferred.

performed in middle-aged to elderly individuals in whom prevalences up to 28% have been reported [24]. In the few studies performed in young individuals, much lower orthostatic SBP increases appeared to provide important prognostic information, suggesting that in this age group a lower threshold should be used to identify people hyperreactive to standing. These differing thresholds may reflect a different pathogenesis of OHT according to age.

In light of these gaps in knowledge, we offer methodological and conceptual recommendations for future research in this area.

(1) Both SBP and DBP orthostatic changes should be taken into consideration in future clinical studies. The combination of the two pressures should be tested if associations with outcomes are in the same direction.
(2) SBP and DBP RTS cutoffs should be tested to identify hyperreactors to standing preferably based on outcome data. Separate analyses should be conducted for different age groups.
(3) The role of age should be primarily considered also in mechanistic studies exploring the link of ERST with putative pathogenetic factors.
(4) Assessment of standing BP should be included in future epidemiological studies and in interventional trials.

In longitudinal observational studies, this would allow to monitor trajectories of ERTS throughout life, aiming at investigating their association with cardiovascular and renal outcomes and establishing whether the incremental prognostic value of ERTS can improve diagnosis and management.

In clinical trials, it will be possible to determine whether specific treatments have different effects on seated and standing BP and whether some drug classes are more effective than others in hypertensive patients with OHT (Table 2).

TABLE 2. Consensus points

Definitions
Exaggerated BP response to standing (ERTS) is defined as an increase in SBP $\geq$ 20 mmHg (average of three readings) after assuming the standing posture.**
Orthostatic hypertension (OHT) is defined as an ERTS with SBP $\geq$ 140 mmHg while standing.**
Diagnosis
BP should be measured in the upright posture in every individual at least at the initial visit, even if BP is not increased in the seated or supine position.**
The diagnosis of ERTS should be confirmed on a different visit using the supine-to-standing procedure.**
Orthostatic BP increases <20 mmHg can also be considered clinically important especially in young individuals.*
Management
Ambulatory BP monitoring should be performed in all individuals with ERTS/OHT and high-normal or high seated/supine office BP.*
Implementation of lifestyle changes and close follow-up is recommended in individuals with ERTS.**
Hypertensive patients with ERTS/OHT should be managed using the same treatment strategy as in other hypertensive patients.*

Number of asterisks denotes the strength of recommendation.

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None.

Conflicts of interest

A.K., G.P., G.B., G.S., P.P., R.A. conducted validation studies for various manufacturers and advised manufacturers on device development. J.J. received research support of Boehringer-Ingelheim and Novo-Nordisk, served as advisor for Novo-Nordisk and Theravance, and is co-founder of Eternygen GmbH. I.B. is consultant for Theravance Biopharma, Regeneron Pharmaceutical and Neurawell Therapuetics for drug developments.

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