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Orthostatic Hypertension: A Newcomer Among the Hypertension Phenotypes

Paolo Palatini

ABSTRACT: The prognostic role and the clinical significance of orthostatic hypertension (OHT) remained undefined for long because data were sparse and often inconsistent. In recent years, evidence has been accumulating that OHT is associated with an increased risk of masked and sustained hypertension, hypertension-mediated organ damage, cardiovascular disease, and mortality. Most evidence came from studies in which OHT was defined using systolic blood pressure (BP) whereas the clinical relevance of diastolic OHT is still unclear. Recently, the American Autonomic Society and the Japanese Society of Hypertension defined OHT as an orthostatic systolic BP increase ≥20 mm Hg associated with a systolic BP of at least 140 mm Hg while standing. However, also smaller orthostatic BP increases have shown clinical relevance especially in people ≤45 years of age. A possible limitation of the BP response to standing is poor reproducibility. OHT concordance is better when the between-assessment interval is shorter, when OHT is evaluated using a larger number of BP readings, and if home BP measurement is used. The pathogenetic mechanisms leading to OHT are still controversial and may vary according to age. Excessive neurohumoral activation seems to be the main determinant in younger adults whereas vascular stiffness plays a more important role in older individuals. Conditions associated with higher activity of the sympathetic nervous system and/or baroreflex dysregulation, such as diabetes, essential hypertension, and aging have been found to be often associated with OHT. Measurement of orthostatic BP should be included in routine clinical practice especially in people with high-normal BP.

Key Words: cardiovascular ■ hypertension ■ orthostatic ■ risk ■ standing

Measurement of blood pressure (BP) in the upright posture is recommended by all hypertension guidelines to detect orthostatic hypotension especially in elderly patients.[1] However, a number of studies have shown that also an exaggerated BP response to standing (RTS) is often present in the general population and that it may be of clinical value.[2,3] For years, the prognostic role and the clinical significance of orthostatic hypertension (OHT) remained undefined because data were sparse and often inconsistent. In addition, diagnostic criteria of OHT varied from study to study making it difficult to interpret data regarding the cardiovascular risk associated with this condition.[2,3] In recent years, evidence has been accumulating that OHT is associated with an increased risk of hypertension, hypertension-mediated organ damage, cardiovascular disease, and mortality increasing our knowledge of the pathophysiology, clinical relevance, and prognostic role of this condition. This led some authorities to propose a definition based on both the orthostatic pressor response and the absolute BP levels while standing.[4] Most information on OHT comes from studies performed in elderly subjects whereas much less is known about its prevalence and clinical significance in young individuals. The aim of the present review is to summarize the available evidence regarding the prevalence, reproducibility, diagnosis, pathogenetic mechanisms, and risk of adverse outcomes associated with OHT focusing on potential differences related to age.

DEFINITION AND PREVALENCE OF EXAGGERATED RTS AND OF OHT

Definition of ERTS

A large number of different cut-offs have been used in the literature to define exaggerated RTS (ERTS). Most authors used systolic BP (SBP)[5–11] but some authors

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Nonstandard Abbreviations and Acronyms

ABPM	ambulatory BP monitoring
ARIC	Atherosclerosis Risk in Communities
BP	blood pressure
CARDIPP	Cardiovascular Risk Factors in Patients With Diabetes-a Prospective Study in Primary Care
DBP	diastolic BP
ERTS	exaggerated RTS
HARVEST	Hypertension and Ambulatory Recording Venetia Study
HBPM	home BP measurement
OHT	orthostatic hypertension
PARTAGE	Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population
RTS	response to standing
SBP	systolic BP
SPRINT	Systolic BP Intervention Trial

used diastolic BP (DBP) alone[12,13] or a combination of the 2 pressures.[14–16] In several studies, a ≥20 mm Hg SBP increase[5–11,17–27] and a ≥10 mm Hg DBP increase[14–16,28,29] after standing were used to identify OHT with[30,31] or without using absolute values of standing BP.[14–16,28,29] Recently, the American Autonomic Society and the Japanese Society of Hypertension defined ERTS as a sustained SBP increase by at least 20 mm Hg when changing from the supine to the standing position.[4] The prevalence of an ERTS ≥20 mm Hg greatly varied from study to study. Very low prevalences were found in people ≤45 years of age in either a general population or hypertension studies. In the study by Wu et al[17] in community-dwelling people, no subject younger than 40 years had an RTS ≥20 mm Hg. In the 18- to 45-year-old participants from the HARVEST (Hypertension and Ambulatory Recording Venetia Study), the prevalence of RTS ≥20 mm Hg ranged from 0.6% to 1.2% over 3 separate assessments.[32] In the Malmö Offspring Study, the prevalence was 0.8% in people below 44 years of age and 2.6% in older participants.[33] Other authors used lower SBP cut-offs ranging from 5 to 15 mm Hg.[34,35] Although an ERTS based on the 20 mm Hg cut-off was found to have an important prognostic value in several studies, it should be pointed out that also an RTS that does not reach this SBP level may be clinically relevant especially in young individuals. In a longitudinal analysis of the HARVEST study (mean age, 33 years), an RTS ≥6.5 mm Hg (upper decile of the distribution) was predictive of cardiovascular events occurring during a 17-year follow-up.[36] In the CARDIA study (Coronary Artery Risk Development in Young Adults; mean age, 27 years), an RTS >5 mm Hg identified a group of young adults at increased risk of developing hypertension within 8 years.[37] However, also due to the limited reproducibility of ERTS (see below), it is questionable whether a small SBP increase on standing, even if statistically significant, can be considered prognostically valuable. More evidence is required before definitive conclusions can be drawn.

Definition of OHT

Most studies used only ERTS to identify OHT while only a minority of studies included absolute values of standing BP in the definition. The abovementioned consensus defined OHT as an orthostatic SBP increase ≥20 mm Hg associated with an SBP of at least 140 mm Hg while standing.[4] This definition seems to be suitable especially for its potential impact in clinical practice. It avoids that a person with ERTS without high orthostatic BP may be considered as a hypertensive patient.

METHODOLOGICAL ISSUES

The hemodynamic changes caused by active standing are described in Text S1. To have a reliable estimate of the RTS, BP should be measured starting 1 minute after assuming the upright posture. BP should be measured at least 3× after standing at 1-minute intervals.[2,3,5] Other authorities suggest to measure BP after 1, 3, and 5 minutes.[4] Due to the limited reproducibility of RTS (see below), current guidelines recommend that orthostatic BP testing should be repeated on a different day.[4] Indeed, in a longitudinal analysis of the HARVEST study in which the data obtained during 2 visits performed 2 weeks apart were tested separately, we found that the risk of adverse outcome was greatest for the subjects hyperresponsive at both visits.[36] In clinical practice seated to standing position can be considered to assess RTS for screening purposes because supine and sitting measurements would be difficult to conduct in all patients. However, RTS may be less pronounced when using seated BP and thus guidelines suggest that in subjects with suspected ERTS the diagnosis should be refined with supine to standing measurement.[4]

REPRODUCIBILITY OF OHT

The reproducibility of OHT has been evaluated in only a few studies. In 605 hypertensive subjects 70.2 years of age, Hoshide et al[38] compared the reproducibility of OHT (defined as a RTS >7.8 mm Hg, top decile) identified with clinic versus home BP measurement (HBPM). The concordance in the definition of the orthostatic BP categories evaluated 5× over a 5-month period was good with a Kappa coefficient consistently >0.40 for HBPM, while the concordance in the corresponding definitions obtained by clinic BP remained well below 0.40.

A better reproducibility of RTS evaluated with office BP measurement was found by Moreno Velásquez and Pischon who studied the concordance of OHT within shorter periods (10 and 34 days).[39] Four measurements were used to assess standing SBP, and the intraclass correlation coefficient was used to evaluate the concordance

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between the 2 separate assessments. The coefficient was 0.70 in the NAKO (German National Cohort) pretest and 0.86 in the MetScan study.

The reproducibility of ERTS in young subjects was assessed by our group within the frame of the HARVEST.[40] Concordance differed according to the threshold used and the between-measurement interval (Figure 1; unpublished observations). The level of concordance was the highest (K coefficient, 0.51) when ERTS was defined using an RTS >10 mm Hg assessed 2 weeks apart and was the lowest (K coefficient, 0.20) when ERTS was defined using a RTS >5 mm Hg and the second RTS assessment was performed after 3 months.

The reproducibility of ERTS has been found to be very poor when RTS was remeasured after a long time interval. In 101 normotensive participants from the Shimanami Health Promoting Program, Tabara et al[41] found no concordance at all (K=0.029) when ERTS was remeasured after 2.4 years. However, in the SPRINT (Systolic BP Intervention Trial), participants with OHT at baseline had a higher incidence rate of OHT during the 3.3-year follow-up than those without OHT (incidence rate ratio, 3.18 [95% CI, 3.06–3.31]).[42] However, OHT reproducibility was not studied with K-statistics.

The above data indicate that the reproducibility of ERTS is fair to moderate. Concordance is better when the between-measurement interval is shorter, when RTS is evaluated over a larger number of BP readings, and if HBPM is used. Thus, RTS should be evaluated at least twice on separate days using the average of at least 2 orthostatic readings before making the diagnosis of ERTS. To improve reproducibility, some Japanese investigators developed an automatic BP monitor for the detection of BP changes from sitting to standing at home, which automatically measures BP twice while seated and twice in the standing position, thereby providing a well -standardized measurement of RTS.[43]

ASSOCIATION WITH MASKED HYPERTENSION

Masked hypertension is a condition characterized by normal BP in the doctor's office and high BP outside the office which can be identified with 24-hour ambulatory BP monitoring (ABPM) or HBPM. Data from a large number of studies have shown that masked hypertension is often associated with target organ damage and increased risk of cardiovascular events and mortality.[44,45] Thus, it is important to identify individuals who are at high risk for this condition, with the goal of preventing cardiovascular events in these subjects. Hyperresponsiveness to standing has been found to be associated with masked hypertension in several studies (Figure 2). A cross-sectional investigation of 304 treated hypertensive patients demonstrated that an RTS ≥5 mm Hg on standing is an independent predictor of masked hypertension diagnosed with HBPM. In another cross-sectional study in a general population of 884 individuals assessed with ABPM, the frequency of masked hypertension was

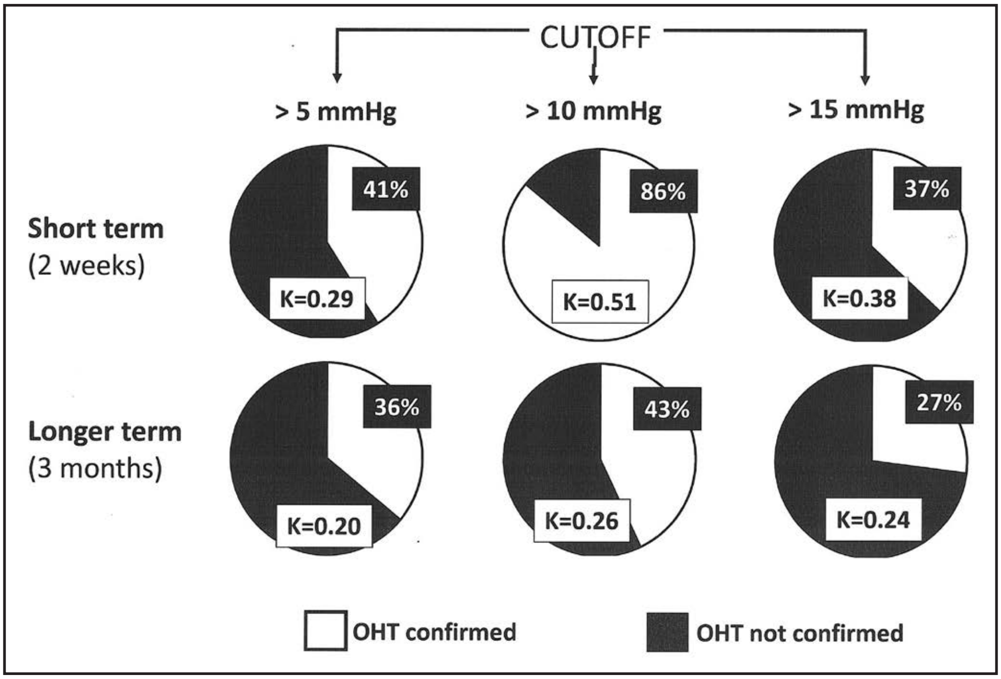

Figure 1. Reproducibility of the systolic blood pressure reaction to standing according to different cut-offs and time intervals between assessments.
Labels indicate percent of subjects in whom orthostatic hypertension (OHT) was confirmed at repeat assessment. Unpublished observations from the HARVEST (Hypertension and Ambulatory Recording Venetia Study). K indicates Kappa coefficient.

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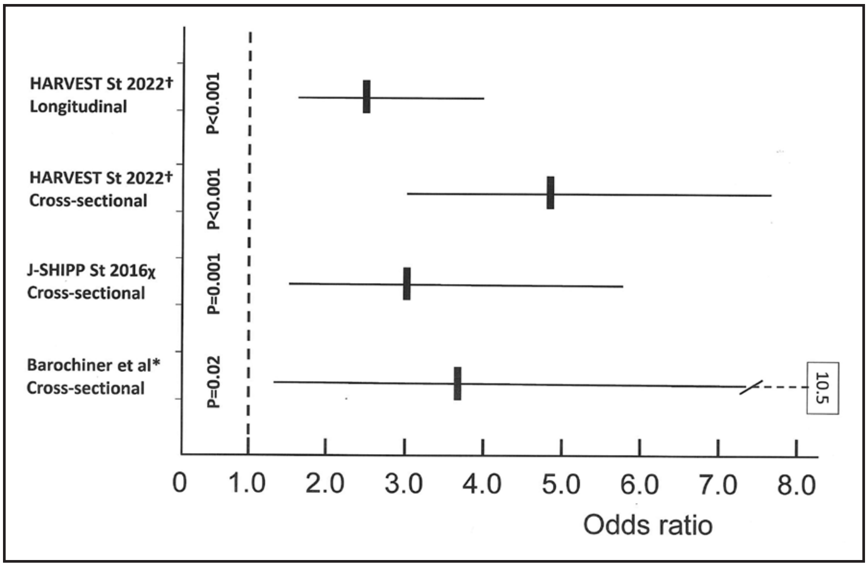

Figure 2. Risk of masked hypertension according to the systolic blood pressure response to standing (high vs normal) in 3 cross-sectional and 1 longitudinal study.
Data are odds ratios and 95% CIs. St indicates study. Cut-off values for high vs normal response are 5 mm Hg in the Barochiner et al study, 10 mm Hg in the J-SHIPP study (Shimanami Health Promoting Program), and 6.5 mm Hg in the HARVEST study. *Barochiner et al[46]; χTabara et al[41]; †Palatini et al.[40]

significantly greater in subjects who showed a postural SBP increase >10 mm Hg 3 minutes after standing (52.1%) compared with controls (27.5%); P=0.001).[41] The association remained significant also after adjustment for antihypertensive medication (P=0.001). Our results obtained with both a cross-sectional and a longitudinal analysis in a larger sample of young-to-middle-aged subjects screened for stage 1 hypertension confirm those previous findings.[40] In a multivariable logistic regression model, baseline ERTS was associated with masked hypertension assessed after 3 months. When the participants were grouped according to ERTS and 24-hour epinephrine output, the risk of masked hypertension for the group of hyperresponders with high epinephrine compared with the normal responders with low epinephrine was even quadrupled suggesting that excessive sympathoadrenal activation may be the linchpin between the 2 conditions. The association between ERTS and masked hypertension was found also cross-sectionally when ERTS and ambulatory BP were both measured after 3 months of follow-up.

ASSOCIATION WITH ABPM PARAMETERS

A methodological drawback of orthostatic BP testing is that RTS measurement follows the measurement of BP in the supine or sitting posture and may thus be influenced by the effect of repeated sequential measurements. A progressive decrease in BP has been shown to occur when multiple measurements are taken over time even in the short term.[47,48] The white-coat effect, as measured from the difference between office and ambulatory BP, is considered a measure of reactivity to the doctor's visit, which tends to attenuate with repeated office BP measurements.[49,50] In the HARVEST study, a high white-coat effect was found to be predictive of a greater BP decline in the short term with the patient in the supine position.[32] Presumably, patients with a greater SBP decline in the recumbent position would also have a larger SBP decline if more BP measurements were made. This suggests that in the subjects with more rapid supine SBP decline and greater white-coat effect the BP increase from lying to standing may be underestimated. Other ABPM parameters showed a relationship with RTS (Text S2).

RISK FACTORS ASSOCIATED WITH OHT

Conditions associated with higher activity of the sympathetic nervous system and baroreflex dysregulation, such as obesity, diabetes, essential hypertension, and aging have been found to be often associated with ERTS or OHT[4,51–57] (Figure 3; Text S3). Also, factors related to BP assessment may influence the RTS. In a recent analysis of the HARVEST, we observed that the level of supine SBP, the SBP decline during the 5-minute supine measurements, and, as reported above, the white-coat effect were modulators of RTS.[32] A higher office BP and a greater BP decline during supine BP measurements were predictors of a lower RTS.

PROGNOSTIC VALUE OF ERTS

In the last few years, a growing body of evidence has documented that ERTS is a significant predictor of several adverse outcomes including the development of hypertension (Text S4),[37,55,58,59] target organ involvement (Text S5),[5,8,9,17,21,23,24,28,32–34,38,52,60–62] cardiovascular events, and mortality.

ASSOCIATION OF ERTS AND OHT WITH HARD END POINTS

Cardiovascular Disease Outcomes

Several studies have shown that ERTS is associated with increased risk of cardiovascular events. In the ARIC

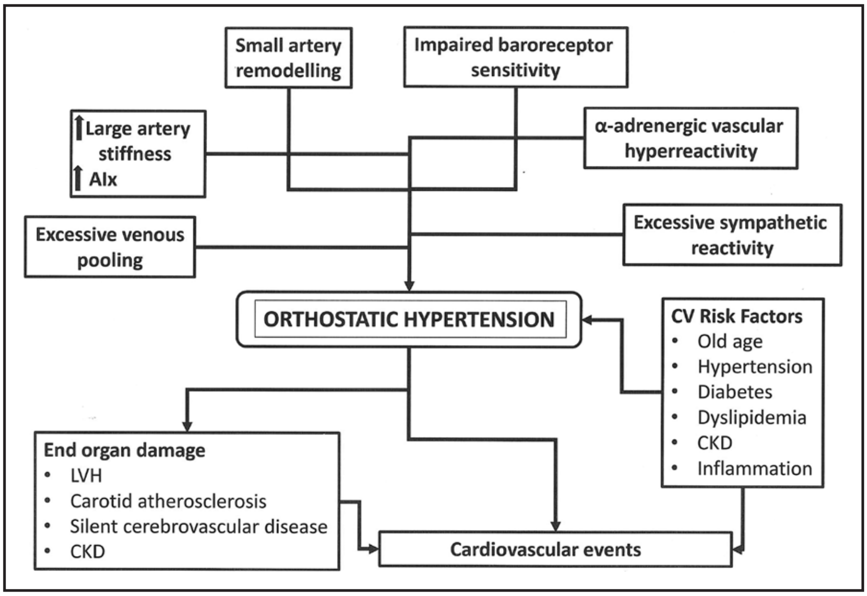

Figure 3. Main mechanisms proposed to underlie orthostatic hypertension. The figure also includes risk factors often associated with orthostatic hypertension and its adverse effects. AIx indicates augmentation index; CV, cardiovascular; CKD, chronic kidney disease; and LVH, left ventricular hypertrophy.

(Atherosclerosis Risk in Communities) Study, both the increase (4.9% versus 4.7%) and decrease (5.0% versus 4.7%) in RTS had a 5% greater predicted risk of developing coronary heart disease after 8 years, which was statistically significant.[57] An increased risk of myocardial infarction was found also in the Normative Aging study.[63] Results from the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study are consistent with the above data.[7] OHT was associated with the presence of nonfatal cardiovascular events leading to hospitalization or a specific long-term new treatment, as well as death from cardiac, cerebrovascular, and other vascular causes.

An increased risk of stroke in patients with OHT has been observed in several studies. In a large Chinese cross-sectional community-based study, both OHT and orthostatic hypotension were associated with stroke.[8] However, in that study, OHT was not associated with the risk of coronary heart disease. In the ARIC study a *U*-shaped association was observed between orthostatic SBP change considered a continuous variable and lacunar stroke incidence (quadratic P=0.004).

In the Chinese study by Fan et al mentioned above, OHT was associated also with peripheral arterial disease with a *U*-shaped relationship between RTS and peripheral vascular involvement.[8]

In the SPRINT, within the intensive treatment group, participants with OHT had a higher risk of developing cardiovascular events compared with participants without OHT. This association was not found within the standard treatment group. Among the participants with OHT, intensive treatment of BP did not reduce the risk of cardiovascular outcomes compared with standard treatment.

All the above studies were performed in middle-aged to elderly subjects. Recent research from the HARVEST investigators has shown that an association of ERTS (defined as the standing-supine SBP difference in the top decile, 6.5 mm Hg) with cardiovascular events may be present also in younger individuals.[36] During a 17-year follow-up, hyperresponsiveness to standing was an independent predictor of adverse cardiovascular outcomes an association, which remained significant even when ambulatory BP data and incident hypertension during the follow-up were included in the Cox model. Epinephrine/creatinine ratio was higher in hyperresponders than normal responders (P=0.005). These data indicate that, in young hypertensive individuals, an SBP RTS much lower (>6.5 mm Hg) than that currently used to define ERTS (≥ 20 mm Hg) is associated with an increased risk of cardiovascular events.

All-Cause Mortality

The relationship between OHT and mortality is controversial because inconsistent data have been reported by different investigators. An independent association of OHT with mortality has been found in 4 studies, which included mainly elderly subjects. In community-dwelling adults, Veronese et al[6] using a 20 mm Hg cut-off of systolic BP to identify people with ERTS found an independent association of OHT with all-cause and cardiovascular mortality. OHT was a predictor of all-cause mortality also in individuals with no hypertension, heart failure, coronary artery disease, or atrial fibrillation.[6] The OHT/mortality association was confirmed by Kostis et al[64] in the participants of the Systolic Hypertension in the Elderly Program, a randomized, double-blind, placebo-controlled clinical trial of the effect of chlorthalidone-based antihypertensive treatment on the rate of occurrence of stroke among older persons with isolated systolic hypertension. A statistically significant association with mortality was found after 17 years of follow-up also after adjusting for cardiovascular risk factors and comorbidities. The increased risk of all-cause mortality associated with OHT was observed in both the active treatment and placebo groups. In a study by Velilla-Zancada et al,[15] an association of OHT with mortality during a 9.4-year follow-up was found only when considering the systolic RTS 3 minutes after standing. In the abovementioned PARTAGE study, an association of OHT with mortality ($P<0.01$) was found after a shorter (2 years) follow-up in subjects with a mean age of 88 years.[7]

At variance with the above reports, some studies found no association between OHT and all-cause mortality.[10,16,20,21,65–67] Inconsistencies in methodology and different age ranges may partly explain these conflicting results. In the study by Davis et al,[66] mainly middle-aged individuals were enrolled. In the Honolulu Heart study, a lower cut-off was used to define OHT compared with the abovementioned studies.[65] In the CARDIPP (Cardiovascular Risk Factors in Patients With Diabetes-a Prospective Study in Primary Care), the definition of OHT was based on a rise of DBP whose association with adverse outcomes is controversial.[16] The same comment applies to the negative study by Weiss et al[67] in which OHT was defined when either systolic or diastolic BP levels upon standing were greater than the supine levels. In the study by Bursztyn et al,[20] the low prevalence of OHT (≤4%) did not enable a meaningful analysis. In conclusion, the majority of data indicate that elderly people with OHT have an increased risk of mortality when the diagnosis is based on an SBP RTS ≥20 mm Hg. No information is available on the risk of OHT-related mortality in young individuals.

DIASTOLIC OHT

Most evidence showing an association of OHT with hypertensive complications and adverse cardiovascular outcomes has come from studies in which OHT was defined using SBP RTS. The clinical relevance of diastolic OHT is unclear as inconsistent results have been obtained in the few studies that investigated this condition. Initially, after the seminal mechanistic study by Streeten et al,[12] focus of the research was put on diastolic OHT. In an old analysis of the HARVEST, the individuals with exaggerated DBP reaction to standing (>11 mm Hg) were characterized by high cardiac index, low total peripheral resistance, and high urinary norepinephrine output.[13] Thus, assessment of the diastolic RTS allowed us to identify a population of young stage 1 hypertensives characterized by a hyperkinetic hemodynamic pattern as a result of increased sympathetic tone. As mentioned above, in the Malmö Offspring Study, RTS showed a different relationship with aortic stiffness according to whether the analysis was based on SBP or DBP.[33] In the participants grouped according to SBP RTS quartiles, PWV was increased in both the bottom and top quartiles. In contrast, PWV gradually and linearly decreased with increasing level of diastolic RTS being lowest in the top quartile (hyperresponders).

In the CARDIPP study, diastolic OHT was defined as a rise of DBP ≥10 mm Hg and was associated with significantly lower risk of cardiovascular events compared with patients with normal systolic and diastolic RTS.[16] In patients admitted to an acute geriatric ward, with a mean age of 81.5 years, Weiss et al found a lower mortality rate in those with OHT defined from SBP and DBP combined than in those with normal RTS.

The above data point to a different clinical significance of ERTS according to whether it is defined using SBP, DBP, or a combination of the 2. Studies that have used SBP and DBP combined to identify people with OHT precluded the possibility of studying the association with adverse outcomes separately for the 2 pressures and could not clarify this controversial issue. It is thus crucial for future studies on the prognostic significance of OHT to use common criteria to identify people with OHT.

MECHANISMS

The mechanisms accounting for the link between OHT and increased cardiovascular risk have been reviewed in excellent and comprehensive articles by Jordan et al[2] and by Kario[52] and are summarized in the Text S6. Excessive neurohumoral activation, baroreflex dysfunction resulting in increased sympathetic activity, exaggerated arteriolar vasoconstriction, and arterial stiffness are considered the most important determinants of OHT (Figure 3).[5,12,22,32,36,40,52,60,68–74] There is general agreement[2–4,52] that the mechanisms driving OHT are affected by age with a cardiac reactive type in younger adults, which may be accompanied by orthostatic tachycardia and a vascular stiffness type in older individuals. It should be pointed out that people with orthostatic hyperresponsiveness may have normal sympathetic activity at rest but increased sympathetic reaction to stressors.

MANAGEMENT OF SUBJECTS WITH ERTS AND OHT

OHT has been an overlooked clinical condition for long. Up to now, hypertension guidelines have recommended to measure BP on standing in elderly subjects and patients on antihypertensive treatment to check for the possible occurrence of orthostatic hypotension. The frequent association with masked hypertension and the increased risk of developing sustained hypertension and cardiovascular events in people with ERTS suggests that BP should be measured in the upright posture in every subject including young individuals. A clinical flow chart including assessment of RTS is

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proposed in Figure 4. RTS measurement appears particularly important in people with high-normal BP values who are more at risk of masked hypertension and OHT. If ERTS (SBP increase from lying to standing ≥20 mm Hg) is confirmed with a second assessment on a different day, ABPM should be performed to have a more detailed picture of the BP changes during standing preferably with the help of an actigraph. If increased morning surge and masked hypertension are detected, a thorough evaluation of the subject's cardiovascular risk profile including assessment of hypertension-mediated organ damage should be made. Antihypertensive treatment should be considered in subjects at high cardiovascular risk. At any rate, close follow-up with repeated visits should be implemented in every subject with ERTS.

There is no agreement over whether a specific antihypertensive treatment should be used in hypertensive patients with ERTS because no randomized clinical trial has been performed in this condition. Although some benefit has been observed with the use of alpha blockers,[60] the lack of definite evidence for a better cardiovascular risk protection with a particular class of drugs suggests that subjects with OHT should be managed in the same way as any other hypertensive patient.[4]

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Studies on the clinical and prognostic significance of OHT and on the pathogenetic mechanisms leading to this condition have been often inconsistent due to methodological heterogeneity (Table S1 through S3). One main aspect, which remained unexplored is whether SBP and DBP postural changes should be used to identify OHT. The large majority of studies have highlighted the role of SBP in evaluating the clinical significance of orthostatic hyperresponsiveness but also DBP RTS has been investigated which often led to conflicting results. Another crucial point that deserves attention is the clinical significance of ERTS in young versus older individuals. The use of the ≥20 mm Hg cut point appears to be appropriate to define orthostatic hyperresponsiveness in middle-aged to elderly individuals in whom a prevalence of ERTS ranging up to 28% has been found. Only a few studies have hitherto been implemented in young individuals, and no study focused on this important issue. It is the opinion of this author that in this age category, the adoption of the 20 mm Hg cut-off might downplay the clinical relevance of smaller orthostatic BP increases. However, in the absence of solid evidence-based information, it is reasonable to use

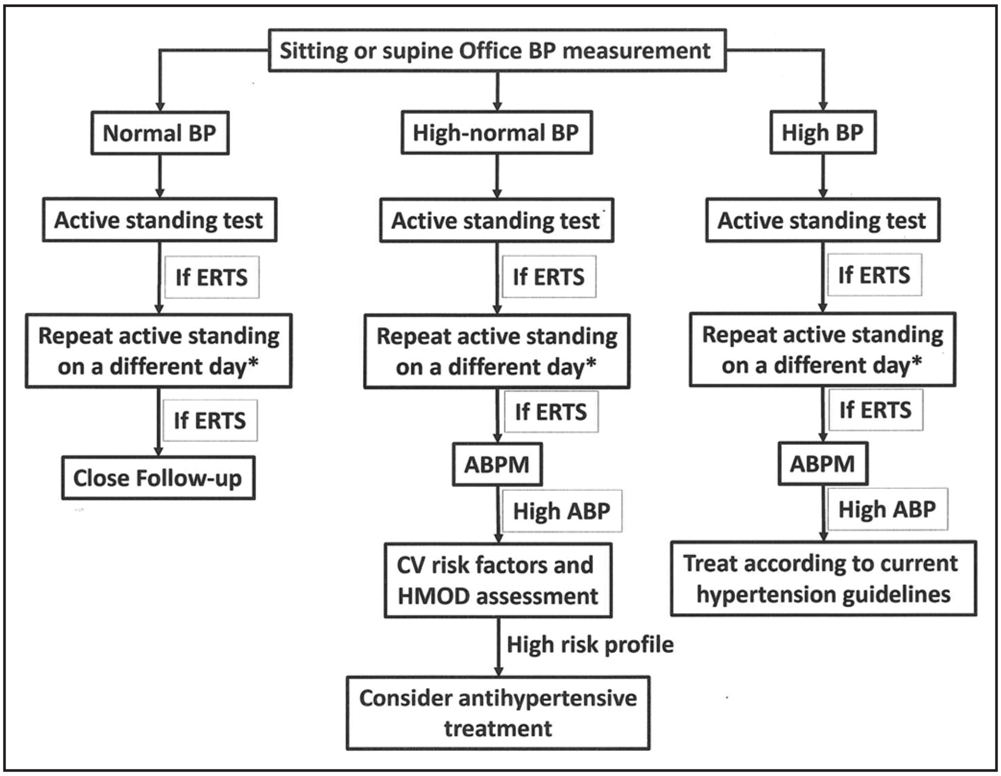

Figure 4. Flow chart for the diagnosis and management of exaggerated systolic blood pressure (BP) response to standing (≥20 mmHg; ERTS).

The algorithm was designed mostly following the recommendations provided by the Consensus document of the American Autonomic Society and the Japanese Society of Hypertension (Jordan et al[4]). ABP indicates ambulatory BP; ABPM, ambulatory BP monitoring; BP, blood pressure; and HMOD, hypertension-mediated organ damage. *For confirmatory testing, supine-to-standing BP measurement should be preferred.

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the definitions of ERTS and of OHT using the criteria suggested by the abovementioned expert consensus in every subject.[4] The pathogenesis of ERTS is multifactorial, and the complex interplay of different mechanisms is likely to differ between young and older subjects. In the former sympatho-adrenergic hyper-reactivity and small artery remodelling may be the main contributors to ERTS whereas in the latter baroreflex dysregulation and arterial stiffness are likely to play a major role.

On the basis of these considerations, I think that the following issues should be the focus of future research in this area:

1. The predictive value of ERTS and OHT for adverse outcomes should be tested for SBP and DBP separately to better clarify the respective mechanistic role and to establish which provides the better prognostic information. This implies that a cut-off should be established also for the definition of DBP ERTS.
2. The association of RTS with adverse outcomes should be tested across the age range trying to identify appropriate definitions of ERTS and OHT for different age groups possibly based on outcome data.
3. The design of treatment trials should be refined including RTS in the assessment of hypertensive patients. Prespecified analyses should be implemented to assess the effect of specific treatments on ERTS and OHT and their relationship with outcomes. This will clarify whether OHT is a leading risk factor for organ damage and cardiovascular events, and whether specific treatments can ameliorate prognosis in patients with this condition.

ARTICLE INFORMATION

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