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REVIEW ARTICLE

Diagnostic criteria for initial orthostatic hypotension: a narrative review

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Abstract

Abnormalities in orthostatic blood pressure changes upon active standing are associated with morbidity, mortality, and reduced quality of life. However, over the last decade, several population-based cohort studies have reported a remarkably high prevalence (between 25 and 70%) of initial orthostatic hypotension (IOH) among elderly individuals. This has raised the question as to whether the orthostatic blood pressure patterns in these community-dwelling elderly should truly be considered as pathological. If not, redefining of the systolic cutoff values for IOH (i.e., a value ≥ 40 mmHg in systolic blood pressure in the first 15 s after standing up) might be necessary to differ between normal aging and true pathology. Therefore, in this narrative review, we provide a critical analysis of the current reference values for the changes in systolic BP in the first 60 s after standing up and discuss how these values should be applied to large population studies. We will address factors that influence the magnitude of the systolic blood pressure changes following active standing and the importance of standardization of the stand-up test, which is a prerequisite for quantitative, between-subject comparisons of the postural hemodynamic response.

Keywords Orthostatic hypotension · Initial orthostatic hypotension · Postural blood pressure changes

Introduction

Orthostatic hypotension (OH) is a common condition that predominantly affects older adults and has a profoundly negative impact on quality of life. OH is also associated with significant morbidity and mortality, making the diagnosis of OH a clinical priority. Classic OH is defined as a *sustained* reduction in systolic blood pressure (BP) of at least 20 mmHg and/or diastolic BP of 10 mmHg within 3 min of standing or head-up tilt to at least 60° (Table 1) [1]. Because approximately 95% of patients with unexplained syncope and orthostatic intolerance can be identified by systolic criteria alone, the systolic cutoff (≥ 20 mmHg) is commonly used in daily practice to define classic OH [2, 3].

In 2011, the American Autonomic Society consensus statement was expanded to include initial orthostatic hypotension (IOH), which was defined as a *transient* BP decrease ≥ 40 mmHg systolic BP and/or ≥ 20 mmHg diastolic BP within 15 s of active standing (Table 1) [1]. In a preliminary study of the Irish Longitudinal Study on Ageing (TILDA), Romero-Ortuno et al. noted that symptoms of orthostatic intolerance such as lightheadedness or presyncope during an active stand test are strongly dependent on systolic BP and not on diastolic BP decline [4]. For these reasons, most recent clinical studies examining IOH used only the systolic cutoff (≥ 40 mmHg) as the more relevant clinical parameter [5–9]. In this review we will focus therefore on the systolic BP changes only.

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Table 1 Currently used cutoffs to define abnormal postural BP changes

Diagnosis	Definition
Classic or sustained orthostatic hypotension (OH)	Sustained reduction in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg within 3 min of standing or HUT [1]
Delayed orthostatic hypotension (DOH)	Sustained reduction in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg beyond 3 min of standing or HUT [1]
Initial orthostatic hypotension (IOH)	Transient BP decrease ≥ 40 mmHg SBP and/or ≥ 20 mmHg DBP within 15 s of active standing [1]
Impaired early BP stabilization	Inability to recover SBP to ≤ 20 mmHg of supine baseline values 30–40 s of standing up, but with recovery within 3 min and thus not meeting the criteria for sustained orthostatic hypotension [7, 10, 19]

SBP systolic blood pressure; *DBP* diastolic blood pressure; *HUT* head-up-tilt table test

IOH, like classic OH, is a sign, a measurement result that may or may not be accompanied by symptoms of orthostatic intolerance [1, 10]. In young adults and healthy physically active older individuals, a rapid recovery to supine values is observed within 20 s after active standing [11–16], but in population-based studies, the recovery in older adults is often delayed [4, 5, 9, 17]. *Impaired early BP stabilization* has been defined as the inability of systolic BP to recover to ≤ 20 mmHg of supine baseline values at 30 s of standing [18, 19]. Note that the term "delayed recovery" is also used to refer to *impaired early BP stabilization* [7, 10, 19]. In this review we will use the term *impaired early BP stabilization* to avoid confusion with delayed orthostatic hypotension (DOH), which refers to hemodynamic responses that meet OH criteria but that occur after 3 min [20, 21]. The delay in BP stabilization in *impaired early BP stabilization* can be considerable, but recovery occurs by definition within 3 min of standing; otherwise criteria would be met for classic OH. An abnormally large initial fall in systolic BP (≥ 40 mmHg) occurs in about 60% of the patients who have impaired early BP stabilization [18].

Several population-based cohort studies, however, have reported a remarkably high prevalence of IOH (between 25 and 70%) using this cutoff [5, 17, 22]. Hence, a recent *Clinical Autonomic Research* editorial raised the question as to whether a redefinition of the systolic cutoff values for IOH (i.e., a value ≥ 40 mmHg in systolic BP) might be necessary in older adults [23]. Therefore, in this narrative review we provide a critical analysis of the current reference values for the changes in systolic BP in the first 60 s after standing up and discuss how these values should be applied to large population studies. We will address factors that influence the magnitude of the systolic BP changes following active standing and the need for standardization of the stand-up test.

Search strategy and selection criteria

In order to provide a critical view, we searched PubMed and OVID for publications in English from 1 May 2016 to 1 May 2021 with the keywords "orthostatic hypotension," "initial orthostatic hypotension," "postural hypotension," and/or "orthostatic blood pressure." In addition, hand searches were performed of our own databases and archives of leading experts in this field. We additionally selected seminal work and reviewed the reference lists of these articles to identify further studies. As this is a narrative review and not a systematic review, searches were not exhaustive and articles were included according to the authors' judgment and based on relevance, quality, rigor, and originality with regard to the topic.

Active standing and passive head-up tilting in young adults

As a starting point, we will address the initial (first 30 s) cardiovascular effects induced by active standing from supine and sitting and by passive head-up tilting in young adults as the physiological platform on which we stand [24].

Head-up tilt results in more gradual changes in heart rate (HR) and BP, whereas active standing is accompanied by a brief immediate increase in BP, followed by a marked decrease in BP with a nadir within 10 s and a recovery of BP within 30 s (Fig. 1). Note that the brief increase in BP and the increase in HR occur instantaneously. The

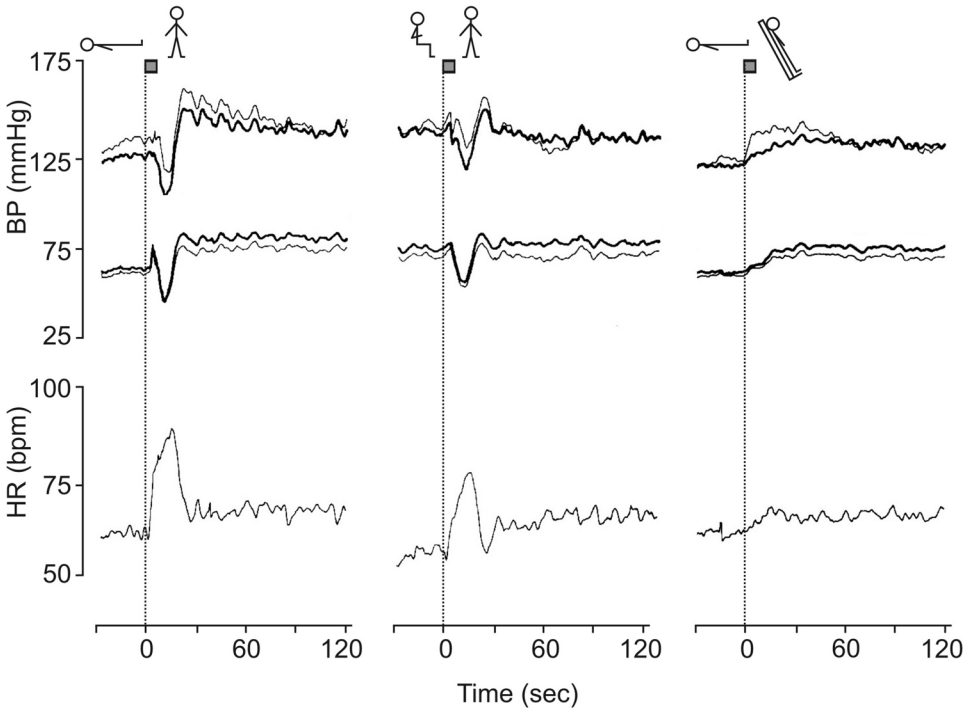

Fig. 1 Hemodynamic responses in three different orthostatic maneuvers. Group average intrabrachial (bold line) and finger (thin lines) blood pressure (BP) and heart rate (HR) responses in 11 male volunteers aged 22–40 years to three orthostatic maneuvers (standing from supine, standing from sitting, and head-up tilting) preceded by a period of at least 5 min supine rest. The time needed to change posture amounted to about 3 s, as is indicated at the top of the dotted vertical line at T = 0. From Imholz et al., with permission [24]

mechanism involved in the transient decrease in BP upon active standing can be attributed to the forceful contractions of leg and abdominal muscles involved in standing up, resulting in an immediate translocation of venous blood towards the heart and thereby increasing right ventricular filling and cardiac output (CO). Since BP is the product of CO and systemic vascular resistance (SVR), the pronounced fall in BP (Fig. 1) upon active standing indicates that rapid vasodilatation in the active muscles has occurred, with a pronounced fall in SVR (Fig. 2) [13, 25]. For a comprehensive review of the physiological mechanisms underlying initial circulatory adjustments in the first 60 s after active standing up, we refer to a recent review by Harms et al. [25]. Of note, the initial circulatory response during active standing from supine and sitting is conspicuously different from the response induced by passive tilting (Fig. 1). As such, while head-up tilt can be useful to evaluate classic OH, it cannot be used to investigate IOH.

Currently used cutoff for the nadir in systolic blood pressure in the first 60 s after standing up

The cutoff value of ≥ 40 mmHg for an abnormally large initial decrease in systolic BP upon standing was established almost three decades ago [26]. The cutoff value is based on studies in the early 1990s with small numbers of participants ($n = 20–40$) using beat-to-beat BP measurement devices [11–14]. One study was performed in healthy teenagers (10–14 years [12]) and two in young adults (22–40 years and 19–28 years, respectively [11, 13]). The fourth study was performed in overall healthy, active older participants (> 70 years) who used no medication [14]. The protocol used in these studies was identical as far as duration of supine rest (5 min) and definition of the trough as the lowest BP value around 10 s after standing up. Participants practiced the standing-up maneuver in order to become familiar with the protocol. The range of the mean fall in systolic BP in the four studies amounted to −20 (SD ± 12) to −26 (± 13) mmHg. The data from the studies by Ten Harkel et al. and Imholz et al. [11, 14] are presented in Fig. 2. The obvious large differences between the circulatory responses in young and older adults will be discussed below.

Based on the values (−20 ± 12 to −26 ± 13 mmHg) obtained in the above-mentioned studies performed in physiological laboratories (in the remainder of this review referred to as "physiological studies") [11–14], a fall in systolic BP ≥ 40 mmHg was considered as a preliminary abnormally large value, even in older adults [26]. This preliminary value of ≥ 40 mmHg established in the early 1990s has been used as a reference up to today [1, 27–30].

High prevalence of IOH in older adults in population studies

Over the last decade, several studies addressing the prevalence of initial BP changes in large cohorts of older adults (in the remainder of this review referred to as "population

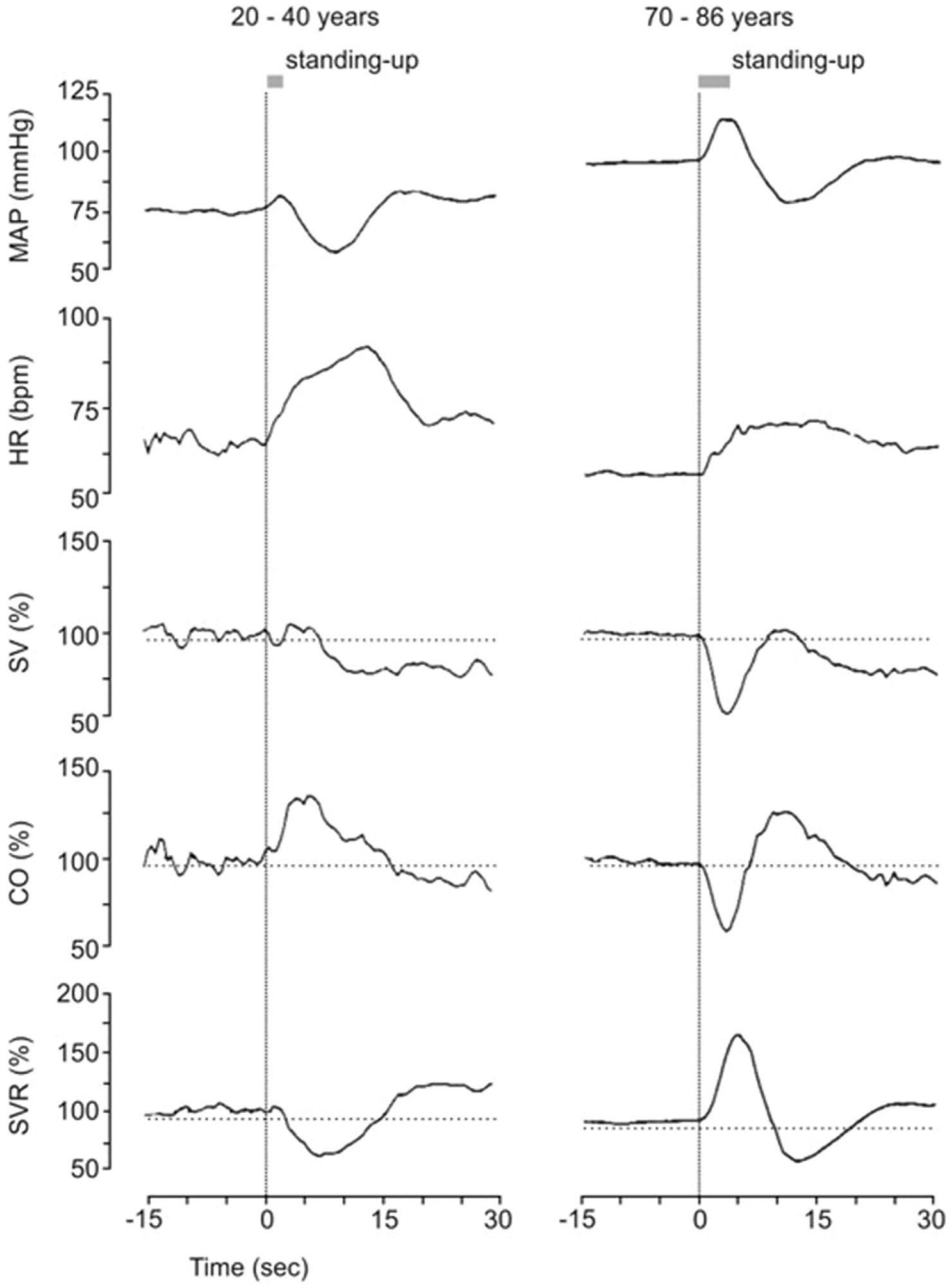

Fig. 2 The effect of age on the initial hemodynamic responses to standing. Group mean finger arterial BP (MAP) and relative changes in stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) during the initial response upon standing. Average responses of 10 young adults (aged 22–40 years] (left panel) and 37 older adults (aged 70–86 years) (right panel) are shown. Duration of standing up is indicated. Revised after ten Harkel et al. and Imholz et al. [11, 24]

studies") have reported a very high number of participants meeting the BP criteria of 40/20 mmHg for IOH [5, 17, 22].

Romero-Ortuno et al. evaluated a community sample of 442 elderly individuals (> 60 years) without dementia or risk factors for autonomic neuropathy and split them into three groups according to clinical signs of frailty [5]. The drop in systolic BP following standing up after lying supine for 10 min was 34.1 (SD ± 17.3), 37.2 (± 18.8), and 37.0 (± 23.8) mmHg in non-frail, pre-frail, and frail elderly, respectively. If symptoms of cerebral hypoperfusion were taken into account, IOH was diagnosed in 12.7%, 22.6%, and 38.7%, respectively.

In the TILDA cohort [17], a large prospective randomly selected population-based study of over 4000 community-dwelling adults aged > 50 years, the systolic fall in BP was much larger than the value of −20 to −26 mmHg in the physiological studies discussed so far [11–14]. Approximately 70% of healthy individuals fulfilled the hemodynamic criteria for IOH (drop in systolic BP ≥ 40 or diastolic BP ≥ 20 mmHg within the first 15 s following standing up after lying supine for 10 min) [17].

Saedon et al. evaluated 1245 Malaysian elderly (mean age 67 years) with a supine BP of 133/69 mmHg on average [22]. After lying supine for 5 min, 25% of the participants

had an initial drop in BP of at least 40/20 mmHg and thus met the BP criteria for IOH.

Taken together, these three studies all report that a very high number of participants met the current BP criteria for IOH [5, 17, 22]. On the one hand, this raises the question as to whether the BP criteria for IOH may need revision, as it appears inappropriate to classify the BP patterns in so many community-dwelling older adults as pathological. On the other hand, however, it also raises the question as to why the results of these recent cohort studies in older adults [5, 17, 22] differ from the physiological studies performed in the early 1990s that formed the basis of the currently used IOH definitions [11–14]. Is this because the physiological studies only included healthy, young individuals (3 out of 4 physiological studies [11–13]) and/or vital healthy elderly without medication (1 out of 4 studies [14]) and therefore presumably do not reflect a random sample of community-dwelling elderly as included in the population studies? Or might there be other factors that affect the magnitude of the initial circulatory response to standing and thus influence comparability between studies? With these questions as a background, we will address factors that influence the magnitude of the initial circulatory response to standing in the next section.

Influence of analysis and performance of a stand-up test on test scores

The following factors will be addressed: (a) data analysis, (b) the duration of supine rest, (c) speed of standing, (d) leg and abdominal muscle tensing, breathing, and straining, (e) standing from supine vs. standing from sitting, (f) time of day and sleep, (g) influence of meals, and (h) medications and substance use. In order to faithfully capture the initial BP responses to standing, beat-to-beat BP recordings are necessary. For review of finger plethysmography BP measurement technology and a practical guide to active stand testing we refer to Finucane et al. 2019 [19].

Data analysis

The computation of supine control values, the immediate increase in BP and the nadir and the recovery of the initial changes in BP following standing up differ markedly between physiological and population studies. As the drop in BP on standing required for the diagnosis of OH is dependent on the baseline value, a valid baseline is an essential component of the investigation [31]. In physiological laboratory studies, a stable baseline is the prerequisite, and averages of 10 s, 30 s, or 60 s are used as supine baseline values [11–14]. In the population studies, the period of −60 to −30 s is used as control because of "motion artifacts" in the BP tracings due to limb movements or (accidental) external pressure being applied to the finger cuff while preparing to stand up [5, 17, 19, 22]. The immediate mechanical increase in BP during the transition time (see section below for details) is included in the analysis in physiological studies (Fig. 2) [11–14], but considered as "noise" in population studies [5, 17, 22]. In the physiological studies, the actual value of the nadir and recovery/overshoot in the first 20 s of a stand-up test are used in the analysis [11–14], whereas in the population studies a computer-calculated running average of mean values or median values of 5–10 s were used to define nadir and overshoot [5, 17, 22]. Running averages of 5 or 10 s will smooth out nadirs and overshoot, and this would decrease the magnitude of the systolic fall [19]. For steady-state BP values after 1, 2, and/or 3 min of standing, a 5-s running average is generally used. This value is based on a finger plethysmography study by Van der Velde et al. that demonstrated that a 5-s average (vs. beat-to-beat 1-, 10-, 15-, 20-, and 30-s averages) showed the best association between OH and history of falls. BP was measured after 1, 2, and 3 min of standing, and the lowest value was used for the analysis [32]. In some studies, the value at 10 s [18] or lowest value within 10 s [9] is used instead of the lowest value within the first 15 s after standing up [1]. The use of a period of 10 s instead of 15 s might underestimate the true magnitude of the BP decline in those with later or longer IOH responses.

Duration of supine rest

Borst et al. noted that in young adults, a longer duration of supine rest (20 min vs. 1 min) resulted in an increase in the fall in systolic BP of 50% (about −20 vs. −30 mmHg) [33]. Ten Harkel et al. compared supine rest periods of 1, 5, and 20 min in young adults. The falls in systolic BP amounted to −8, −20, and −27 mmHg with longer resting periods [11]. In accordance with these studies, following very long supine rest periods (25–30 min), a larger mean fall in systolic BP (about 40 mmHg) is reported in young adults [15, 16, 34]. Likewise, during standing up from the sitting position, a 20-min sit results in a much larger initial drop in systolic BP (−34 mmHg) than a 30-s sit (−12 mmHg) [35]. Of note, in the population studies, the start of supine rest is often recorded after instrumentation, and this setup period should be added to the official period of supine rest. We found no data regarding the influence of the duration of supine rest on the magnitude of the fall in BP in older adults. An increase in the unstretched volume of the dependent veins has been suggested [36] as the mechanism underlying the remarkable strong influence of the duration of supine rest on the magnitude of the initial fall in BP upon active standing [11, 33, 37].

For the purpose of standardization and a practical point of view, we propose that after the beat-to-beat BP measurement device has been installed, the standing-up maneuver is practiced once. After that try-out, we recommend a standard period of 5 min of supine rest prior to the recorded stand-up test, as this appears to be sufficient for BP stabilization and determination of the supine BP values [31]. Longer resting periods should be avoided to prevent an increase in the magnitude of the initial fall in BP which may occur with excessively long supine rest periods [15, 16, 34].

Speed of standing

In healthy young adults, standing up from supine takes less than 3 s [11–13, 15, 16]. In healthy, fit older adults—with assistance if needed—a stand-up takes 3–7 s [14]. Population studies generally ask participants to stand up quickly, and a stand-up time of < 5 s (with physical assistance if needed) is often reported as a goal [5, 7, 9, 17, 22, 38, 39]. However, little information is available on adherence to the preferred quick standing time (< 5 s) in those studies. Insightful information about the standing time in older adults is provided in a study by O'Connor et al. addressing the range of transition times in a sample of 2593 participants in the TILDA study [40]. In the TILDA studies, participants were, if needed, assisted by a research nurse to reach a standing position [17]. Finometer height correction sensors were cleverly used by O'Connor et al. to detect the onset and duration of standing up [40]. The median standing time was 7 s, with a range of 2 to 27 s. In 17% of the participants, the standing time took > 10 s. Transition times much longer than the preferred < 5 s are also reported by De Bruïne et al. [41]. In her study in 24 older adults (mean age 79.3 years, SD ± 7.7), the mean transition time recorded with a stopwatch for a stand-up at the patient's usual pace amounted to 11.5 s. A stand-up as fast as possible took on average 7.05 s. In a study by Mol et al. in 109 older participants with a mean age of 81.7 years, a transition time of 7 s was reported for a stand-up without further assistance [42]. We conclude that an average stand-up time of about 7 s, with values frequently > 10 s, in population studies far exceeds the preferred quick standing time of < 5 s. These long transition times need to be taken into account in the assessment of the initial response to standing in older adults.

No effect was found when comparing a 3- vs. 10-s standing time in young adults [43]. In older adults with a very slow transition time, the fall in systolic BP is attenuated compared to standing up at normal speed. O'Connor found that standing up within 5 s resulted in a drop in systolic BP of −26.4 mmHg, whereas a transition in 20 s was associated with a smaller drop in systolic BP of −15.6 mmHg [40]. Similarly, De Bruïne et al. found a 14 mmHg higher mean systolic BP in the first 0–15 s after standing up in those who stand up very slowly (24 s on average) as compared to normal (11.5 s on average) [41]. Very slow stand-ups [24 s on average] imply that a rise to sit followed by a rise to stand was involved [41]. This factor is likely to be involved in other studies with assisted stand-up times > 10 s and will result in smaller initial falls in BP [44].

Leg and abdominal muscle tensing, breathing, and straining at the onset of standing up

An immediate increase in vasodilation in lower body skeletal vasculature is the main factor causing the fall in SVR underlying IOH. However, immediate increases in arterial pressure and right atrial pressure induced by standing up may also contribute to reflex vasodilation. In the following we will address the effects of (a) leg and abdominal muscle tensing, (b) breathing, and (c) straining on this phenomenon.

(a) Leg and abdominal muscle tensing:

In carefully performed physiological experiments, the BP responses induced by active standing and passive head-up tilting in young adults are highly reproducible (Fig. 3). The responses repeated 10 times in two adults are superimposable [45]. The figure shows that at the onset of standing, a brief immediate increase in BP lasting about 2 s is noted, which is absent at the beginning of head-up tilt. This increase in BP coincided with the period of maximal myogram activity recorded from abdominal and leg muscles during the stand-up [33] and may be attributed to a movement artifact, the reflex effect of (static) exercise, the brief increase in intrathoracic pressure, mechanical compression/kinking of blood vessels, or a combination of these factors. It is unlikely that it is a movement artifact, because all measures designed to limit the arm and cannula movements failed to reduce the BP increase [33]. The immediate increase in BP cannot be of reflex origin because the exercise reflex involves an approximate 2-s neuro-effector delay [46], as illustrated by the arterial pressure increase induced by handgrip performed for 5 s at maximal voluntary force (panel c in Fig. 3). Thus, as an explanation for the immediate BP increase, a brief increase in intrathoracic pressure or compression/kinking of blood vessels, seems most likely.

(b) Breathing:

To evaluate the effects of breathing, Sprangers et al. performed a stand-up test during breath-holding in two young adults measuring BP, right atrial pressure, and esophageal pressure [13]. The subjects were trained to avoid straining. Indeed, monitoring of esophageal pressure showed that neither participant performed a Valsalva-like maneuver during stand-up (Fig. 4). Standing up was accompanied by an abrupt, large tran-

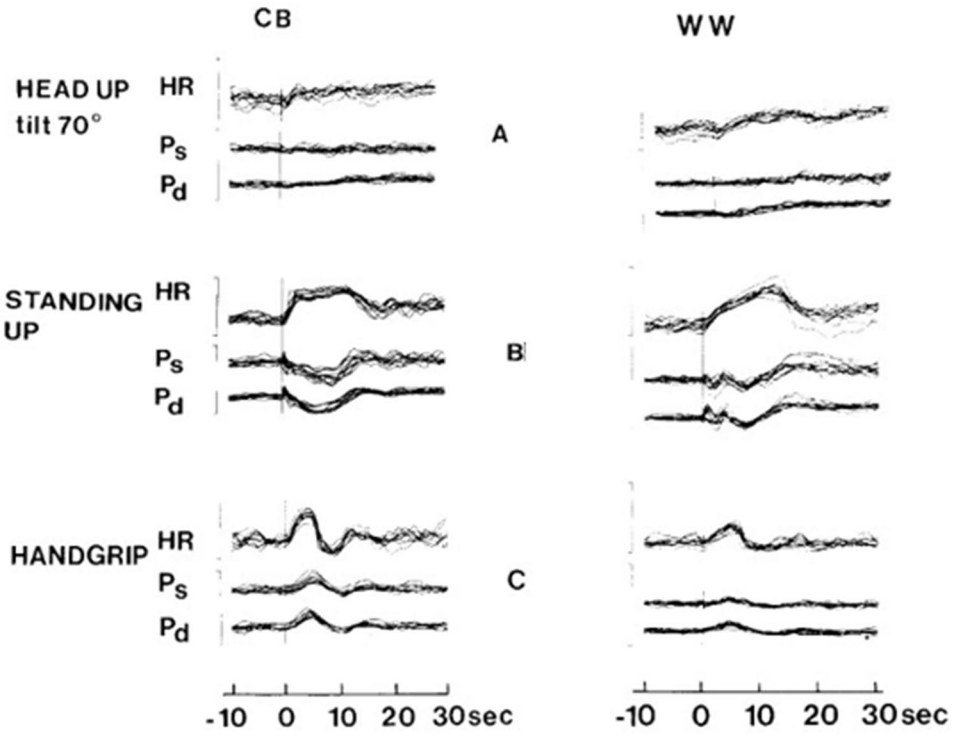

Fig. 3 Reproducibility of orthostatic BP measurements. Cardiovascular changes induced in subjects CB (37 years) and WW (33 years) by 70-degree head-up tilt (**a**), standing up (**b**), and handgrip (**c**). Heart rate (HR) calibration 60–120 beats/min. Systolic (Ps) and diastolic pressure (Pd) calibration 40–180 mmHg. Arterial pressure was measured in the brachial artery with a strain gauge fixed on the upper arm. Note reproducibility within and between subjects of divergent responses to head-up tilt and standing up (From Borst et al. with permission [45])

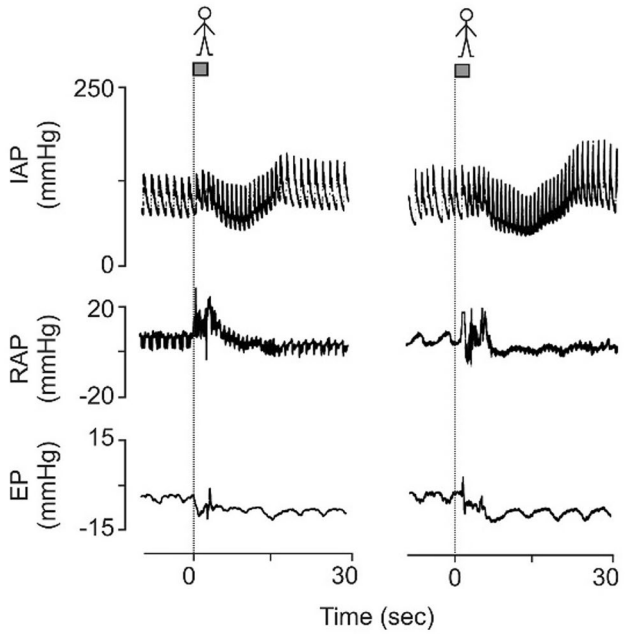

Fig. 4 Esophageal pressure during the standing-up test. Original tracings showing intra-arterial pressure (IAP), right atrial pressure (RAP), and esophageal pressure (EP) transients induced by standing up in two adult subjects. Duration of standing up is indicated (from Sprangers et al., revised [13])

sient increase in right atrial pressure (10–15 mmHg at 3 s) [13] preceding the typical fall in BP that can be attributed to an abrupt increase in venous return due to the forceful contractions of leg and abdominal muscles. These observations indicate that the typical BP response on standing occurs without the effects of breathing. We attribute the very small immediate pressure increase observed at the onset of active standing during breath-holding (diastolic about 10 mmHg, systolic only 2–3 mmHg) in Fig. 4 to mechanical compression/kinking of blood vessels [33]. Of note, the immediate right atrial pressure increase on standing may lead to activation of cardiopulmonary receptors with reflex vasodilation, which may increase the magnitude of the initial fall in BP after standing up [13].

(c) Straining at the onset of standing up:

In the physiological studies without specific breathing instructions [11, 13, 33], a much larger immediate BP increase was observed (10–28 mmHg systolic and 10 mmHg diastolic). We attribute this to unintended straining during standing up, as the rise in intrathoracic pressure (phase 1 of the Valsalva maneuver) is closely followed by the arterial BP (mainly systolic) [47, 48]. We conclude that straining during stand-up is the main factor involved in the immediate transient pressure increase upon active standing. This immediate pressure jump may lead to baroreflex activation and thus peripheral vasodilation, which may increase the magnitude of the initial fall in BP after standing up [33]. To avoid straining, a recent practical guideline recommends asking patients to stand up during inspiration and not to hold their breath [19].

The cardiovascular response to active standing in older adults differs markedly from the response in young adults (Fig. 2) [14, 26]. The initial HR response was blunted as a sign of diminished vagal withdrawal, and the immediate temporary increase in BP was much larger (+17 mmHg in mean arterial pressure [MAP]) and lasted longer (about 7 s) compared to the response in young adults (increase in BP of < 10 mmHg, duration about 3 s) [27, 49]. We attribute the much larger and prolonged BP increase to unintended straining that accompanied the considerable physical activity needed for this age group to stand up quickly. The additional role of vascular stiffness is unclear. At 9.5 s, the immediate increase in BP was followed by a fall of 17 mmHg from baseline. The magnitude of the drop in MAP was similar for young and older adults (−22 mmHg vs. −17 mmHg), with a smaller transient rise in CO together with a less pronounced drop in SVR in the elderly. Importantly, it must be recognized that the stimulus inducing cardiovascular reflex responses are necessarily different across age groups, since the older adults' standing response was accompanied by a pronounced increase in BP [33]. Unfortunately, differences in the stand-up maneuver between younger healthy individuals and elderly cannot be avoided. As such, differences in muscle tensing and unintended straining will inevitably influence the initial BP response and challenge the comparability of hemodynamic changes between individuals. Therefore, a maneuver that can be exerted in a more similar way in both young and elderly may increase comparability between age groups. Standing up from the sitting position can potentially become a viable alternative to improve standardization.

Standing from the supine vs. standing from the sitting position

Standing from the sitting position reflects a common daily activity. It is a simple maneuver and little help is needed to perform it. Obviously, the gravitational stress is less than with standing from supine, but in cases where standing from supine is challenging, it can provide a simple means to assess orthostatic responses that are relevant to typical activities of daily living. The caveat is that the cardiovascular responses are blunted with standing from sitting compared with standing from supine, with the potential to underestimate the severity of any orthostatic deficit in cardiovascular control, particularly in older adults. With supine rest periods of 10–20 min, the systolic BP nadir after standing from supine in 11 young adults was larger than after standing from sitting (−27 mmHg vs. −19 mmHg) and the BP overshoot more pronounced (Fig. 1) [24]. Using 5-min rest periods, almost identical values (−17 mmHg from sitting vs. −19 mmHg from supine) were reported by ten Harkel et al. in 10 young adults (age range 22–40 years) [11], while Fitzgibbon et al. found larger decreases on standing from supine compared to sitting in 77 older adults (age range 69–100 years) [44].

Braam et al. carefully studied the oscillometric BP response after standing from supine and standing from sitting in 148 individuals and noted that the fall after standing from sitting at 1, 2, and 3 min standing was consistently smaller [50]. Lipsitz and coworkers used the initial fall in BP on rising from sitting as a test of cerebral autoregulation, applying an interesting modification of the sit-stand test [51, 52]. After instrumentation, participants sit in a straight-backed chair with their legs elevated at 90 degrees in front of them on a stool. Participants rest for 5 min in this position, then stand upright for 1 min. With this procedure, a fall in MAP of about 20 mmHg at around 10 s after standing is a consistent finding. The time course and magnitude of the systolic BP response in their studies is remarkably similar to the response described in the physiological studies using 5–10 min of supine rest [25].

Standing up from the sitting position may become a viable alternative to standing up from supine. However, as clinical data are scarce and several uncertainties exist (such as the impact of differences in compression/kinking of blood vessels and intra-abdominal pressure between sitting and supine rest), this requires more study.

Time of day and sleep

The peak incidence of vasovagal syncope in the morning and the far more pronounced OH in patients with autonomic failure during morning hours suggests that chronobiological factors (such as relative volume depletion from nocturnal diuresis and not drinking fluid during the night, redistribution of body fluids, and neurohumoral effects) might impair the physiologic response to orthostatic stress in the morning [53–55]. However, Lewis et al. found no diurnal variation in MAP in healthy young adults (mean age 26 years) during active standing at 6:00 and 16:00 [34]. After sleep restriction, a small increase in daytime systolic BP (4–14 mmHg) has been reported [56, 57], but effects on orthostatic tolerance were not observed. As the impact of sleep on orthostatic stress testing may differ between individuals, it is generally recommended that orthostatic testing be performed in the morning, with avoidance of sleep deprivation [19].

Influence of meals

Postural BP changes may be influenced by meals. Ingestion of food (especially high-carbohydrate meals) induces a decrease in splanchnic vascular resistance and an increase in mesenteric artery blood flow, resulting in pooling of blood within the gastrointestinal circulation [58]. In young, healthy individuals, effects on systemic BP are often limited due

to compensatory systemic vasoconstriction and increases in HR [59]. In patients with autonomic dysfunction and elderly individuals, however, systemic BP may decrease within 2 h after eating and induce orthostatic syncope [60]. Therefore, orthostatic testing is preferably performed after an overnight fast or (if an overnight fast is not possible) at least 2 h after the last meal [19].

Medications and substances

Several medications influence the autonomic nervous system and may affect orthostatic BP patterns. Many studies have evaluated the association between medication and classic OH, but placebo-controlled studies of its influence on the initial BP response in the first 60 s after standing up are limited.

Coupland et al. showed that infusion of clonidine lowered supine BP in healthy adults but did not alter the magnitude of the initial drop in BP after standing up as compared to placebo [61]. However, clonidine delayed recovery to baseline systolic BP from 8.1 to 12.3 s. Likewise, Lewis et al. demonstrated in healthy adults (mean age 25 years) that ingestion of the alpha-1 blocker prazosin reduced supine MAP by approximately 15% compared to placebo, but that prazosin did not significantly alter the magnitude of the initial drop in systolic BP or MAP (2 ± 2 mmHg MAP vs. placebo) after standing up [16]. However, unlike placebo, BP failed to recover to supine values after ingestion of prazosin, presumably due to inhibition of the vasoconstrictive response. Thus, although the absolute nadir BP is lower with prazosin or clonidine, this is driven by the reduction in supine BP, as the magnitude of the relative BP drop was similar to placebo. However, the combination of a lower absolute BP nadir and impaired recovery after the initial BP drop contribute to the occurrence of symptomatic cerebral hypoperfusion. Presumably, a similar phenomenon will occur with other alpha blockers, such as doxazosin and tamsulosin (often used by elderly men for benign prostate hyperplasia). As tricyclic antidepressants (TCA) also exhibit alpha-blocking properties [62], a similar phenomenon may occur with these drugs.

Data on other medications and initial BP changes are limited to cross-sectional (non-controlled) association studies and must be interpreted with some caution, as confounding from other patient-related factors may be of influence. In such studies among elderly individuals, beta blockers are associated with increased risk for IOH and classic OH (OR 1.6–3.36) [63, 64]. Most likely this is a result of negative chronotropic and inotropic effects which will hinder counteracting mechanisms that recover BP after the initial drop. In women aged 60–80 years, use of diuretics was associated with an increased risk for classic OH [65]. As diuretics predispose to volume depletion and increased venous capacitance (in particular, loop diuretics), venous return and CO will be reduced, which may delay recovery after the initial drop in BP. In a cross-sectional study among elderly individuals, however, the use of diuretics was not associated with increased risk for IOH [63]. Data from association studies on angiotensin-converting-enzyme inhibitors and angiotensin-II type 1 receptor blockers are conflicting, with some studies having found a small protective effect (attributed to enhanced baroreceptor sensitivity and improved vascular compliance), while others found no effect on OH [8, 66]. Similarly, use of dihydropyridine calcium channel blockers by elderly individuals was associated with OH in some studies [66, 67], while others reported a lower risk for orthostatic BP abnormalities [64].

In the elderly, chronic use of benzodiazepines is associated with lower baseline BP and a larger initial BP drop 10 s after standing up [68]. It has been suggested that stimulation of benzodiazepine-receptor subtypes 2 and 3 results in myorelaxation, enhancing the initial fall in peripheral resistance and increasing venous pooling. Selective serotonin reuptake inhibitors (SSRI) exhibit vasodilation properties (presumably via inhibition of calcium channels) and are associated with a small reduction in HR, resulting in increased risk for OH but to a lesser extent than with TCAs [8, 67]. However, as depression itself is also associated with increased risk for orthostatic BP changes [69], it raises the question as to whether it is the disease or the drug that should be held responsible for this association.

As knowledge on the potential interference of individual drugs on orthostatic hemodynamics is still limited, it is very difficult to predict the impact of combinations of medications on orthostatic BP changes.

As alcohol is a potent vasodilator [70], this should be avoided on the day of testing [19, 71]. Caffeine is able to reduce the postprandial BP drop [72, 73], but its effect on postural BP changes remains unclear [74]. As caffeine has a mild vasoconstrictor effect by blockade of the adenosine receptors and nicotine increases sympathetic nerve activity, it is recommended that caffeine intake and smoking be avoided on the day of testing [19, 71].

Comparing apples to oranges

All the factors addressed above influence the results of individual measurements and thus the comparability between studies. The physiological studies were performed in the well-controlled environment of a hemodynamic laboratory, with a very strict preparation schedule and detailed analyses of the hemodynamic patterns [11–14]. The large population studies, however, are far less "controlled" [5, 17, 22]. Overall physical fitness, ability to stand up quickly, duration of lying supine, and use of medication, as well as

technical aspects in the analyses of hemodynamic patterns, differ from the physiological studies and will all influence the observed nadir BP values to some extent. Although many of these factors may have only a small influence on their own, the combined effect of these small factors may be substantial, resulting in poor reproducibility of the standing-up test. Finucane et al. showed that intra-class correlation for repeated testing after 4–12 weeks (mean 84.3 ± 23.3 days) was only 0.47 for nadir BP values [75]. Belmin et al. found a very large day-to-day variation for BP values after 1 min of standing, with kappa values ranging from 0.12 to 0.47 for the diagnosis of classic OH [76]. Likewise, Moloney et al. found no longitudinal stability of postural BP patterns with repeated testing after 4 years [77]. Surprisingly, in this study the marked initial falls in systolic BP decreased during follow-up in participants with impaired responses. Although limited reproducibility may be attributable to some extent to natural physiological variation over time [78], intra-individual reproducibility was very good in well-controlled physiological studies (Fig. 3) [45]. As such, limited reproducibility will also be related to limited standardization of test conditions. Therefore, reliable comparison of postural BP values between different studies without very strict test protocols appears elusive.

Need for new cutoffs?

Should age-related normative reference data [17] be determined again in specialized laboratories with very strict protocols, taking the marked influence of performance of standing up discussed above into account? From an essentialist view of medical testing the answer is yes, since this is the only way to determine whether the current cutoff is appropriate for all age groups. However, from a person-oriented consequential view, an important question is whether more accurate reference values will benefit patients and improve health outcomes [79].

The key issue is whether a typical clinical history is sufficient to diagnose IOH or whether the documentation of an abnormally large transient fall in systolic BP is needed in addition. If the complaints of transient lightheadedness or (near-)syncope upon active standing are typical, there is hardly a differential diagnosis. Other conditions with "dizziness" and apparent loss of consciousness that may be elicited by standing up, like benign paroxysmal positional vertigo, anxiety, psychogenic pseudo-syncope, and malingering, have a different presentation. Furthermore, an abnormally large initial fall in BP is not associated with unexplained and injurious falls [80, 81], and cognitive and physical performance was even better in the participants with IOH in the population study by Saedon et al. [22]. Considering the lack of malignant causes of syncope for complaints of IOH, we suggest that a typical clinical history of IOH alone is sufficient to reassure the patient by explaining the underlying physiology and advising them to adopt physical counterpressure maneuvers. Beat-to-beat-BP measurements in clinical practice could be helpful to demonstrate the effect of lower body muscle tensing as a physical counterpressure maneuver to the patient [82], but should predominantly be used to convince the patient and not the doctor.

If doctors decide that history-taking alone is inconclusive and that objective determination of orthostatic BP changes is still needed, one needs to realize that one cannot turn his/her doctor's office into a hemodynamic laboratory. In daily clinical practice there are obvious time constraints for performing an orthostatic stress test. Therefore, we advocate that such diagnostic tests (if absolutely needed) be performed in a specialized hemodynamic laboratory with repeated measurements, a very strict preparation schedule regarding diet, sleep, and medication intake, standardization of duration of lying supine, training to stand up quickly enough without unintended Valsalva maneuver, and with very accurate analysis of the hemodynamic patterns.

Both the duration and magnitude of the initial reduction in BP are clinically important. For the time being, the cutoff of 40 mmHg for a fall in systolic BP seems reasonable for supine rest periods of 5 min in teenagers and young adults, but uncertainty exists about this cutoff value in older adults. Standardization of standing up in older adults is problematic (see above). Where an abnormally large fall in systolic BP (≥ 40 mmHg) is documented in the laboratory accompanied by typical complaints, the diagnosis of IOH becomes fully certain. However, an abnormally large systolic fall in BP is only found in about 50% of patients with a typical history [6, 54, 83, 84]. Many specific circumstances that may have contributed to IOH at the time of syncope (very prolonged supine rest, hypovolemia, recent meal, alcohol intake, etc.) are often absent during testing in the laboratory. Moreover, as discussed above, intra-individual reproducibility of the standing-up test is poor [75–77]. Thus, a normal BP drop in the laboratory does not rule out IOH as a cause of a fall or syncope shortly after standing. As such, history-taking should be the cornerstone of diagnosing IOH, with hemodynamic testing under strictly standardized conditions to be used only as an additional tool to confirm the diagnosis.

Conclusions and future directions

Quantitative between-subject comparisons of BP responses in the first 60 s after active standing require standardization of all circumstantial factors that influence the results of individual measurements. A variation in a single factor such as time of day or use of medication may on its own be of little influence, but the sum of several individual

factors may lead to physiologically relevant differences in absolute and relative BP values and thus poor reproducibility. As such, to minimize potential interfering variables, strict standardization of test protocols is a prerequisite for between- and within-subject comparisons and thus a prerequisite for evaluating whether currently used reference values for the changes in systolic BP in the first 60 s after standing up are appropriate. In order to develop the most optimal protocol, pivotal questions need to be answered.

First of all, what is the optimal duration of supine rest? Although the importance of standardization of the period of supine rest to obtain a stable BP has been addressed in several studies, the importance of the length of this period on the initial fall in pressure has not been taken into account. We propose a standard duration of 5 min supine rest (preparation time to connect BP device not included, therefore preferably starting after a single try-out standing-up maneuver has been performed), as 5 min seems to be sufficient for BP stabilization but is short enough to prevent the undesired enhancement of the initial drop which may occur with excessively long supine rest periods.

Secondly, differences in the stand-up maneuver between young healthy adults and frail elderly individuals have rarely been addressed in studies. The impact of physical frailty on this maneuver, including increased duration of standing up, a short sitting period between supine and standing-up position, and more intense physical exertion to stand up, challenges the comparability of the standing-up test between subjects. Standing up from the sitting position (instead of supine position) may be a viable alternative, as this will improve standardization of the standing-up maneuver among all age groups.

Third, as polypharmacy is very common, cross-over studies (instead of associative studies) are needed to provide clear recommendations for how to deal with chronic medication use: should drugs be interrupted for the test, and if so, for how long? Or should reference values be adjusted for use of specific drugs?

Only after establishing the most optimal, internationally applicable, strictly standardized test protocol can new population-based long-term follow-up studies be performed. Such studies will answer the question as to what extent variations in orthostatic BP response (IOH, OH, DOH, or impaired early BP stabilization) and/or other markers for autonomic and cardiovascular function (such as HR and BP variability, arterial stiffness, sympathetic nerve activity [85–87]) are associated with adverse outcomes in the future, including syncope, fractures, development of generalized autonomic dysfunction, and autonomic neurodegenerative diseases. Moreover, optimal cutoffs can be derived to determine which absolute or relative postural BP changes should be considered a variation of normal, but innocent with regard to future outcomes, and which are truly pathological with increased risk for future adverse events.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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