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Review
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Orthostatic hypotension in hypertensive older patients

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Abstract

Orthostatic hypotension (OH) has a significant prevalence in the general population, which increases exponentially with age and determines considerable morbidity and mortality. The older population is prone to frailty and comorbidities, including hypertension requiring treatment, whilst certain antihypertensive classes are proven to precipitate OH. At the same time, OH treatment may determine exacerbation of hypertension, making the therapeutical management of this group of patients a significant challenge. OH can be neurogenic or non-neurogenic. This review summarizes data from current literature on the epidemiology, precipitating medication, prognostic, and treatment of OH in elderly hypertensive patients.

Keywords: orthostatic hypotension, elderly patients, hypertension.

Introduction

Orthostatic hypotension is defined as a persistent drop in systolic blood pressure (SBP) of more than 20 mmHg or diastolic blood pressure of at least 10 mmHg, measured within 3 minutes after assuming orthostatic posture [1]. Patients suffering from orthostatic hypotension can be asymptomatic or present characteristic symptoms as syncope (15% of all syncopes are determined by orthostatic hypotension), dizziness, fatigue, falls, or dementia.

There are two main categories of patients with orthostatic hypotension: older patients without significant autonomic impairment and patients with primary neurodegenerative disorders with severe autonomic failure (neurogenic orthostatic hypertension). This review refers to the first aforementioned group, the older hypertensive patients with orthostatic hypotension. The patients in this group are prone to frailty and falls, have many comorbidities, including hypertension, receive multiple medications, and might be institutionalized [2].

Certain medical situations can determine orthostatic hypotension: hypovolemia as a result of dehydration or bleeding, impaired cardiac output caused by arrhythmia, aortic stenosis or heart failure, or even venous pooling precipitated by fever, heat exposure, prolonged recumbency/standing or postprandial dilation of splanchnic vessels. The importance of determining the cause of hypotension resides in the possibility of customizing its management [3].

Epidemiology

The prevalence of orthostatic hypotension in the elderly population is increased compared to the general population.

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As shown in a recent systematic review of 61 studies, the pooled prevalence for orthostatic hypertension depends on the setting: 17% for community cohorts, 19% for primary care cohorts, and 31% for residential care or nursing homes cohorts. When looking at different pathologies, the highest prevalence was 29% (in patients with dementia (3 cohorts), 25% in patients with Parkinson's disease (7 cohorts), 21% in patients with diabetes mellitus (4 cohorts), 20% in patients with hypertension (20 cohorts) compared to 14% in patients without these conditions (P<0.01 between groups). Increasing age and diabetes were found by multivariable regression modeling as predictors of postural hypotension (P<0.01, P=0.13, respectively; R2=36%) [4].

In a study performed on a large Irish population, the prevalence of orthostatic hypotension increased from 6.9% (95% CI, 5.9%–7.8%) in the total population to 18.5% (95% CI, 9.0%–28.0%) in those aged ≥80 years old [5]. Also, orthostatic hypotension was detected in 50% of the subjects of a prospective study of 844 elderly (≥60 years) residents of nursing homes [6].

A study conducted on inpatients of a geriatric ward (mean age 81.6) determined that 67.9% (332 of 489) patients experienced OH at least once during the day, 34.8% (170 of 489) had OH at least twice (persistent OH) and 33.1%(162) experienced OH only once (variable OH). Diastolic OH was more prevalent than systolic OH (57.3% vs. 43.4%; P<0.001) [7].

A cross-sectional study conducted in Spain on a random 295 patient sample from a health center, aged ≥65 years and hypertensive, recorded a prevalence of orthostatic hypotension of 14.6%. Logistic regression analysis found an association between orthostatic hypotension and higher SPB, orthostatic hypotension, and the presence of orthostatic intolerance symptoms (although only 25.6% of the patients with OH were symptomatic) and between orthostatic hypotension and smoking [8].

A similar prevalence (17.3%) of orthostatic hypotension was found in the group of patients over 60 years from the Systolic Hypertension in the Elderly Program (SHEP) [9].

A cross-sectional analysis of a population-based cohort from Finland (653 home-dwelling elderly individuals) demonstrated a total prevalence of orthostatic hypotension of 34% (n=220), without any significant gender or age differences. The prevalence of orthostatic hypotension was related to the number of hypotension-inducing drugs in regular use (P<0.05). The study also found that it increased with baseline SBP, ranging from 20% with SBP>160 mmHg to 7% in individuals with SBP<120 mmHg [10].

In England, between 2008 and 2017, the number of admissions for orthostatic hypotension has increased by 110% (14658 to 30759), and the greatest increase was in the over 75 years age group (114% 10639 to 22756) [11].

Orthostatic hypotension was found as high as 75.3% in a small study (n=85, age more than 65) done in internal medicine wards in Italy, occasional orthostatic hypotension in 48.2%, and persistent orthostatic hypotension in 27.1%. All patients had diastolic orthostatic hypotension and 57.8% also had systolic orthostatic hypotension. Patients with persistent orthostatic hypotension were older, with a higher percentage of renal failure [12].

A recent study including 65% females admitted to a geriatric clinic with a mean age of 75±8 years, found orthostatic hypotension in 17.3% cases and orthostatic hypertension (defined as an increase in systolic blood pressure of more than 10 mmHg, while the patient was standing up from the supine position) in 7.2% cases [13].

The risk of OH associated with hypertension treatment

Multimorbid elderly patients are prone to polypharmacy and hospitalization, and due to these, they have an increased risk of orthostatic hypotension. Diuretics, alpha-adrenoceptor antagonists, peripheral vasodilators, antiparkinsonian agents, central sympatholytics, and antidepressants are medication classes associated with orthostatic hypotension [14–16].

Diuretics may determine orthostatic hypotension by acute or chronic volume depletion. Furosemide should be recommended just in hypertensive patients that have heart failure. There is evidence that treatment with alpha-adrenergic receptor blockers prescribed for hypertension, urinary retention (terazosin, prazosin), or benign prostatic hypertrophy (tamsulosin) is associated with orthostatic hypotension [17, 18].

Nitrates, hydralazine, phosphodiesterase-5 inhibitors, and calcium channel blockers contribute to orthostatic hypotension or even syncope by vasodilatation [19]. However, there is one calcium channel blocker that was proved not to produce OH. In a recent study of elderly patients with mild-to-moderate Alzheimer's disease, treatment with nilvadipine was not associated with increased incidence of orthostatic hypotension or associated symptoms regardless of baseline blood pressure (BP) and frailty score [20].

Treatment with beta-blockers may also be associated with orthostatic hypotension, thought to be related to impaired tachycardic response to orthostatism [21]. It was determined that central sympatholytic agents, such as clonidine, also precipitate orthostatic hypotension [22].

Prevention of adverse effects determined by uncontrolled hypertension caused by antihypertensive medication can be realized by carefully reviewing it during the hospital stay. Certain antihypertensives such as diuretics, alpha-1 blockers, beta-blockers

should be avoided in elderly patients prone to OH. The association between the use of alfa blockers and beta-blockers and OH has also been shown in the ACCORD study. The association of OH with the use of beta-blockers is concordant with other studies. In these patients, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are the preferred antihypertensive agents [23].

In a study of 994 individuals, residents of a nursing home (77% women, with a mean age of 88±5 years), the prevalence of orthostatic hypotension was 18%. Treated hypertensive patients with SBP≤140 mmHg had a lower prevalence of orthostatic hypotension than patients with SBP>140 mmHg (13 vs. 23%, respectively; P<0.001). Individuals with orthostatic hypotension exhibited higher brachial and central pulse pressure (PP) than individuals without orthostatic hypotension (69±18 vs. 65±16 mmHg, respectively and 57±17 vs. 54±15 mmHg, respectively; P<0.01). In these same individuals, a significant increase in the augmentation index (31.1±14.0 vs. 27.2±13.6%; P<0.01), but not in carotid-femoral pulse wave velocity (cf-PWV) or in peripheral to central pulse pressure amplification (PPA), was observed. Individuals with orthostatic hypotension were treated more frequently with beta-blockers and less frequently with angiotensin receptor blockers or nitrates than individuals without orthostatic hypotension (P<0.05 for both). Therefore, contrary to the general belief, elderly individuals with well-controlled BP (SBP<140 mmHg) show a lower prevalence of orthostatic hypotension, thus constituting an additional argument for efficaciously treating hypertension [24].

Untreated hypertension or interruption of the antihypertensive medication may determine pressure diuresis, causing exacerbation of orthostatic hypotension symptoms, therefore increasing the risk of falls. Orthostatic hypotension exacerbation may also be determined by hypertension through alterations of the sensitivity and response of the baroreflex arc, cerebral autoregulation, and vasoreactivity [25].

Interestingly, in the population of adults with hypertension and diabetes, neither a single time nor a set of measurements of OH was clearly superior regarding the outcomes in the ACCORD study. This finding supports the use of a flexibly timed, single measurement to assess OH in clinical practice [26].

Intensive antihypertensive treatment and orthostatic hypotension

Results from the African American Study of Kidney Disease and Hypertension study (AASK Trial) revealed that a more intensive antihypertensive treatment was not associated with orthostatic hypotension. Thus, the blood pressure (BP) goal of adults with hypertension-related chronic kidney disease (CKD) should not be lowered by concern about causing orthostatic hypotension. However, metoprolol was associated with orthostatic hypotension when compared to ramipril (OR 1.68, 95%CI, 1.15–2.46) or amlodipine (OR 1.94, 95%CI, 1.09–3.44) [27]. The SPRINT study, a multicenter, randomized clinical trial, included 2636 patients aged 75 years or older without diabetes that were randomized to an intense control (target SBP of less than 120 mmHg) (1317 patients), or an SBP target of less than 140mmHg (1319 patients). The primary composite cardiovascular disease outcome included nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. The secondary outcome was all-cause mortality. At a median follow-up of 3.14 years, there was a significantly lower rate of the primary composite outcome (102 events in the intensive treatment group vs. 148 events in the standard treatment group; hazard ratio (HR), 0.66 [95% CI, 0.51–0.85]) and all-cause mortality (73 deaths vs. 107 deaths, respectively; HR, 0.67 [95% CI, 0.49–0.91]). Absolute rates of hypotension were 2.4% in the intensive treatment group vs 1.4% in the standard treatment group (HR, 1.71 [95% CI, 0.97–3.09]), 3.0% vs. 2.4%, respectively, for syncope (HR, 1.23 [95% CI, 0.76–2.00]), 4.0% vs. 2.7% for electrolyte abnormalities (HR, 1.51 [95% CI, 0.99–2.33]), 5.5% vs. 4.0% for acute kidney injury (HR, 1.41 [95% CI, 0.98–2.04]), and 4.9% vs. 5.5% for injurious falls (HR, 0.91 [95% CI, 0.65–1.29]). Orthostatic hypotension was less frequently observed in the intensive treatment group than in the standard treatment group [28].

Orthostatic hypotension was not associated with a higher risk of cardiovascular disease events (hazard ratio 1.06 [95% CI, 0.78–1.44]). An association between orthostatic hypotension with syncope, electrolyte abnormalities, injurious falls, or acute renal failure was not demonstrated. Orthostatic hypotension was associated with hypotension-related hospitalizations or emergency department visits (hazard ratio, 1.77 [95% CI, 1.11–2.82]) and bradycardia (hazard ratio, 1.94 [95% CI, 1.19–3.15]), but these associations did not differ by blood pressure treatment goal. Blood pressure treatment goal had no effect on orthostatic hypotension's association with hypotension and bradycardia. Symptomless orthostatic hypotension during hypertension treatment should not be viewed as a reason to down-titrate therapy even in the setting of a lower blood pressure goal [29].

Age and tight systolic blood pressure control were shown not to be related to orthostatic hypotension incidence according to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. ACCORD BP included 4266 hypertensive and diabetic participants that were followed for a median

of 49.6 months. 20% of the participants in the ACCORD BP Trial had orthostatic hypotension at least at one of the 3 examinations (baseline, 12 months, and 48 months). Independent factors associated with orthostatic hypotension were found: female sex, white race, current smoking, higher baseline systolic BP and hemoglobin A1c, as well as the use of alpha-blockers, beta-blockers, and insulin. The lack of association of orthostatic hypotension with age might be related to the maximum age of the participants (80 years old) and the presence of automatic dysfunction due to longstanding diabetes. Orthostatic hypotension rates were lower at follow-up compared to baseline. The annual stroke rate in the intensive BP treatment group was significantly reduced compared with the standard BP treatment (0.32% versus 0.52% per year, p=0.01), without an increase in the risk of orthostatic hypotension [30].

Orthostatic hypotension, cardiovascular events and mortality

There are several studies showing an association between orthostatic hypotension and increased risk of total mortality and heart failure death and hospitalizations [30–35]. Data from the Malmö Preventive Project in Sweden showed increased total mortality in the general population [31]. In the Honolulu Heart Program, orthostatic hypotension was associated with increased total mortality in a cohort of Japanese American men aged 71 to 93 years old [32]. In Hypertension Detection and Follow-up Program, a particularly strong association between orthostatic hypotension and total mortality was found in the diabetic subset [33].

A few studies demonstrated the association of orthostatic hypotension with a higher rate of coronary events [31–33], and no association between myocardial infarction and orthostatic hypotension was found in the ACCORD study [30].

A higher rate of heart failure was found in patients with OH in the predominantly middle-aged Atherosclerosis Risk in Communities (ARIC) cohort [36] and the participants of the Cardiovascular Health Study (mean age 74 years) [37]. An increased risk of stroke was found in individuals with orthostatic hypotension in ARIC [38], but not in the ACCORD study [30].

Non-lacunar ischemic stroke incidence was associated with an orthostatic decrease of systolic and diastolic blood pressure in Atherosclerosis Risk in Communities Study (12,817 black and white individuals without a history of stroke at baseline and a median follow-up of 18.7 years). Greater lacunar stroke incidence was associated with both orthostatic increases and decreases in systolic blood pressure [39].

The presence of orthostatic hypotension predicted an increased risk of cardiovascular death over 4 years follow-up in a prospective study including 833 adults older than 70 years [40].

In a study conducted at the emergency room (n=814), OH was associated with a significantly higher risk of hospitalization (50.9% vs. 22.9%, p<0.0001). Crude mortality was similar between patients with and without OH (13.8% vs. 8.7%, p<0.06). However, patients older than 75 years with OH had significantly increased mortality (p<0.04) after age-adjusted analysis [41].

A multicenter study of nursing home residents (n=673, mean age 83.8) showed an increased risk of stroke on a two-year follow-up [42].

Another study of 972 institutionalized frail older adults (mean age 88) demonstrated a trend of increased cardiovascular disease morbidity and mortality risk in the 157 patients with OH during a two-year period [43].

A community-based prospective study showed an increased risk of CHD (hazard ratio (HR) 51.31, 95% confidence interval (CI) 51.08–1.57) and all-cause mortality (HR 5 1.22, 95% CI 5 1.09–1.36) in subjects with orthostatic hypertension. These risks are greater in the first (1.80) (95% CI 1.25–2.60) and the third (1.27) tertile of age (95% CI51.11–1.44) [44].

In an observational study that followed 2786 community-dwelling older participants for 4.4 years (261 of them presented OH), participants with orthostatic hypotension were compared to those with orthostatic hypertension or normal changes. During follow-up, 640 subjects died, 83 of them from the group with OH. Orthostatic hypotension was associated with higher non-CVD mortality (HR = 1.19; 95% CI: 1.01–1.60) [45].

The results from the ACCORD trial demonstrate that OH is a predictor of increased mortality and heart failure events among patients with comorbid diabetes and hypertension. OH (late measurements, not at baseline) was associated with increased risk of total death (HR 1.61; 95% confidence interval, 1.11–2.36), with a slightly higher risk of heart failure death or hospitalization (HR 1.85; 95% confidence interval, 1.17–2.93). No significant relationship was found between OH and the combined primary endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death). OH was related to higher total mortality and higher rates of heart failure hospitalization and death [30].

In a 12-year epidemiological population-based study that included 1016 subjects aged ≥65, coronary (20.2% vs. 13.1%, P=0.05), cerebrovascular (13.1% vs. 8.4%, P=0.05), and heart failure (HF) events (20.2% vs. 13.8%, P=0.03) were apparently more incidental in subjects with OH than in those without OH. After adjusting for age, gender, and systolic BP as confounders, OH did not act as a cardiovascular predictor (relative risk for cerebrovascular events 1.33, 95% confidence interval (CI), 0.78–2.2, for coronary events 1.25, CI 0.82–1.88,

for HF 1.07, CI 0.71–1.62, for arrhythmias 0.82, CI 0.40–1.37, and 0.58 for syncope, CI 0.13–2.71). The authors concluded that age and systolic BP were positively associated with OH and fully explained the greater incidence of cardiovascular events and the greater cardiovascular risk observed in subjects with OH [46]. In a study of 471 geriatric patients (mean age 81.5) with acute hospitalization and OH in 34.2% of cases, no impact on mortality or cardiovascular mortality was shown after a follow-up of 3.5 years [47].

Treatment of orthostatic hypotension in elderly hypertensive patients

Risk factors for orthostatic hypotension occurrence in this category of patients include poorly controlled hypertension [48], prescription of three or more antihypertensives and prescription of vasodilators and diuretics [49]. The risk of hypertension and the potential hypotensive effects of medications need to be carefully balanced. Transient OH may occur after introducing antihypertensive medication and usually does not necessitate any intervention. Withdrawal of the antihypertensive medications can even determine exacerbation of OH and falls; therefore, it should not be practiced. It has been shown that in the elderly population with uncontrolled hypertension and OH, the risk of falls is nearly 2.5 times higher [50]. The Systolic Blood Pressure Intervention Trial (SPRINT) even demonstrated a lower incidence of OH in the intensive antihypertensive treatment arm [51].

Control of hypertension should be achieved by opting for the proper antihypertensive agent, preferably a short-acting one [52]. The administration needs to be timed accordingly to the 24-hour blood pressure profile and accommodate patients' functional needs. In elderly patients, antihypertensive treatment starts with monotherapy, and if necessary, a second agent may be carefully added later [53].

The use of a beta-blocker (inhibiting tachycardia induced by orthostatism) or the combination of at least three antihypertensive drugs appear to be the most detrimental, and patients receiving them should be closely monitored [30, 49].

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are less likely to be associated with OH compared with beta-blockers and thiazide diuretics [21, 24, 54, 55].

The first two categories may also improve BP regulation and cerebral blood flow in elderly patients and prevent OH. The starting dose must be low and orthostatic response must be monitored while slowly increasing the dose at 1–2 weeks [50, 56].

The general management of OH begins by searching for treatable causes, for instance, side effects of current medication (including antidepressants and antiparkinsonian medication), dehydration, or anemia. The second step is applying non-pharmacological measures. Salt and water supplementation to increase blood volume is limited for hypertensive patients, although it is helpful in dehydration [57]. Wearing stockings or compression tights with a sufficient level of restraint (class 2 or 3) can be effective, and they should be worn before getting out of bed in the morning. However, their use may be difficult for an older person, and compliance may not be optimal. Abdominal binders can also help with venous pooling [58–60].

Orthostatism should be done slowly, in stages, or even bending forward while doing it (bending forward lowers the head to heart level and improves cerebral perfusion; it also causes abdominal compression and improves venous return) [61].

Patient education about counter-pressure maneuvers engaging the upper and lower limbs (crossing the legs, squatting) can prevent syncope in patients presenting warning symptoms [62, 63].

Sleeping with the head raised at an angle of >10 degrees has been shown to be effective in small observational studies in autonomic failure [64–67], probably by reducing the nocturnal diuresis and natriuresis caused by reduced nocturnal renal perfusion. Pharmacological treatment is the last resort, especially in patients with cardiovascular disease.

Midodrine, an alpha1-adrenergic agent with a short half-life, determines peripheral vasoconstriction and is shown to be effective in three randomized placebo-controlled trials [68–70]. It can be administered when symptoms are debilitating during the day, and the last dose in a day should be administered at least four hours before bedtime. Its use is not recommended at night due to the risk of increasing supine blood pressure, and patients are advised to rest in a sitting position during the daytime. The starting dose is 2.5 mg three times a day, with a progressive 2.5 mg increase per dose each week depending on the response to treatment. Compliance is limited by the need for multiple administrations per day.

Fludrocortisone increases the blood volume by renal sodium retention and is administered once daily 0.1 mg and can be up titrated to 0.3 mg and is used for OH in the general population as monotherapy or with midodrine [71]; however, in elderly patients, it is poorly tolerated, and side effects represent a severe limitation (generalized or localized edema, including pulmonary edema and ascites, as well as aggravated hypertension and hypokalemia). Therefore, it should not be used in patients with heart failure, kidney failure, or hypertension [72].

Other less established therapies for orthostatic hypotension include octreotide in patients presenting postprandial hypotension, erythropoietin in anemia, desmopressin in patients with nocturnal polyuria, and pyridostigmine [66].

Conclusion

Orthostatic hypotension has a significant prevalence in the elderly hypertensive population and an even higher prevalence in those with uncontrolled hypertension. The correlation between orthostatic hypotension and mortality has been confirmed in multiple studies, thus emphasizing its importance as a health issue and the need for screening.

Management of orthostatic hypotension in this particular population is a great challenge since therapeutic resources are limited, and patients need close surveillance. Even with an intensive antihypertensive treatment regimen, there is evidence that the risk of orthostatic hypotension does not increase, thus encouraging hypertension control, an essential measure for cardiovascular risk reduction.

Conflict of interest

The author confirms that there are no conflicts of interest.

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