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ORIGINAL ARTICLE

Orthostatic hypotension in a cohort of hypertensive patients referring to a hypertension clinic

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The prevalence of orthostatic hypotension (OH) in hypertensive patients ranges from 3 to 26%. Drugs are a common cause of non-neurogenic OH. In the present study, we retrospectively evaluated the medical records of 9242 patients with essential hypertension referred to our Hypertension Unit. We analysed data on supine and standing blood pressure values, age, sex, severity of hypertension and therapeutic associations of drugs, commonly used in the treatment of hypertension. OH was present in 957 patients (10.4%). Drug combinations including α-blockers, centrally acting drugs, non-dihydropyridine calcium-channel blockers and diuretics were associated with OH. These pharmacological associations must be administered with caution, especially in hypertensive patients at high risk of OH (elderly or with severe and uncontrolled hypertension). Angiotensin-receptor blocker (ARB) seems to be not related with OH and may have a potential protective effect on the development of OH.

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INTRODUCTION

Orthostatic hypotension (OH) is defined as the reduction in blood pressure (BP) of at least 20 mmHg systolic and/or 10 mm Hg diastolic within 3 min in the upright position. In hypertensive patients, prevalence of OH has been estimated between 3 and 26.5%. OH may be classified into neurogenic and non-neurogenic forms. Non-neurogenic OH is caused by alterations of systems and organs responsible for the metabolic and hemodynamic homeostasis, or by exogenous factors such as medications, alcohol or toxic substances. Drugs are a common cause of non-neurogenic OH and can complicate neurogenic forms. In particular, multiple drug associations with diuretic, sympatholytic and vasodilator effects may result in severe symptomatic forms of OH, especially in the elderly. The aim of the study was to evaluate retrospectively the prevalence of OH in a cohort of essential hypertensive patients referring to our Hypertension clinic and to examine the correlation with antihypertensive drugs, their therapeutic combinations and the associated comorbidities.

MATERIALS AND METHODS

The study is a retrospective evaluation of 9874 essential hypertensive patients (according to the definition of the ESH-ESC guidelines[1]) referred to our Hypertension clinic from 1 January 1989 to 31 December 2008. After exclusion of patients <18 years of age and cases where orthostatic BP values were not available, 9242 subjects were considered. For each patient and for the first visit only, the following variables were considered: systolic (SBP) and diastolic BP (DBP), age (stratified into three groups: 18–39, 40–60 and >60 years), sex, grade of hypertension (1–2–3), BP control, diabetes mellitus (DM), chronic kidney failure (CKD), main antihypertensive drugs, considered both individually and in combination, and total number of antihypertensive drugs taken (stratified into two subgroups: 0–2 and 3–5 drugs). Body mass index (BMI) was calculated as weight (kg)/(height^2(m^2)) $\times 100$. During office evaluations, BP and heart rate were measured with a sphygmomanometer with an appropriate cuff, according to the European Society of Hypertension guidelines. After a 3-min period of supine rest, BP was measured three or more times, 1 min apart, until its stabilization, and then at 1 and 3 min after standing. The average of the last two SBP and DBP values measured in the supine position and the lowest value during standing were considered. Supine hypertension was defined as values $\geqslant 140$ mm Hg SBP and/or $\geqslant 90$ mm Hg DBP in the supine position. The grade of hypertension was defined as reported in the ESH-ESC guidelines. BP control was defined as an ambulatory BP $<140/90$ mm Hg during antihypertensive therapy. OH was defined as the reduction in SBP of at least 20 mm Hg and/or DBP of at least 10 mm Hg within 3 min in the upright position. The presence of DM and CKD was assessed by medical history and results of laboratory tests reported in the medical records (DM was defined as fasting blood glucose >110 mg dl^{-1} or glycated hemoglobin >40 mmol mol^{-1}; CKD was defined as serum creatinine >1.5 mg dl^{-1} or glomerular filtration rate <30 ml min^{-1}). Antihypertensive drugs considered were as follows: ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), diuretics, beta-blockers (BB), dihydropyridine calcium-channel blockers (DHPs), non-dihydropyridine calcium-channel blockers (non-DHP), α-blockers, centrally acting drugs and nitrates. Antihypertensive associations considered were ACEi+diuretics, ACEi+α-blockers, ACEi+centrally acting drugs, ACEi+BB, ACEi+DHP, ACEi +non-DHP, ACEi+nitrates, ARB+diuretics, ARB+nitrates, ARB+centrally acting drugs, ARB+BB, ARB+α-blockers, DHP+ARB, ARB+non-DHP, nitrates +DHP, DHP+diuretics, α-blockers+DHP, DHP+BB, DHP+centrally acting drugs, α-blockers+centrally acting drugs, centrally acting drugs+diuretics, diuretics+α-blockers, BB+diuretics, diuretics+nitrates, BB+centrally acting drugs, BB+nitrates, BB+α-blockers, non-DHP+diuretics, non-DHP+centrally acting drugs, non-DHP+α-blockers, non-DHP+nitrates, nitrates+centrally acting drugs and nitrates+α-blockers. Associations between ACEi and ARB, between DHP and non-DHP and between BB and non-DHP, were not employed in the population considered for the study.

Statistical analysis

All data were decoded and transferred to the V9.1.3 software package SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Quantitative variables (SBP, DBP, heart rate and BMI) were expressed as the mean values and s.d.'s. Qualitative variables (age stratified into three groups, sex, grade of hypertension, BP control, total number of drugs, drugs considered both singularly and in association) were expressed as absolute values and percentage.

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The associations of drugs considered in the study are outlined in the previous chapter. Comparison between subjects with and without OH was performed with Mann–Whitney test for quantitative variables; comparison between subjects with and without OH was performed with X^2-test (replaced by Fisher test for numbers less than 5) for qualitative variables. Logistic regression analysis with the estimation of odds ratios (ORs) was conducted to evaluate the contribution of specific factors to OH, after adjustment for age, grade of hypertension, BP control, CKD, diabetes, antihypertensive drugs (considered individually) and total number of drugs. A P-value < 0.05 was assumed as the level of statistical significance.

Drug associations have been explicated in the previous chapter. Comparison between subjects with and without OH was performed with Mann–Whitney test for quantitative variables; comparison between subjects with and without OH was performed with χ^2 (replaced by Fisher test for numbers less than 5) for qualitative variables. Logistic regression analysis with the estimation of OR was conducted to evaluate the contribution of specific factors to OH, after adjustment for age, grade of hypertension, BP control, CKD, diabetes, antihypertensive drugs (considered individually) and total number of drugs. A P-value < 0.05 was assumed as the level of statistical significance.

RESULTS

Of the 9242 patients, 19.2% were 18–39 years of age, 49.5% were 40–60 years and 31.3% were older than 60 years. In all, 520 patients (5.4%) were older than 75 years. Essential hypertensive patients with OH were 957 (10.4%).

Over 60 years, the prevalence of OH was 13.4% and in subjects of 40–60 years was 9.2%, compared with subjects aged 18–39 years (6%; $P < 0.0001$). OH was more frequent in females (11.2%) than in males (9.5%) ($P = 0.0080$). The mean BMI was 26.7 ± 4.5 kg m^{-2} in patients with OH and 26.5 ± 4.7 kg m^{-2} in patients without OH ($P = 0.1999$). In all, 8.2% of subjects with OH had DM ($P < 0.0001$) and 3.1% had CKD ($P < 0.0001$). In all, 248 patients with OH (25.9%) were not taking antihypertensive medication; this subgroup of patients did not differ in terms of anthropometric variables from those with OH taking antihypertensive treatment (data not shown).

In Table 1, we reported anthropometric variables (mean SBP, DBP, heart rate in supine and standing positions, age, sex, grade of hypertension, BP control and number of drugs) and the prevalence of antihypertensive drugs in patients with or without OH. The intake of any drugs, except ARB, was higher in subjects with OH compared with those without OH.

Logistic regression analysis was performed to identify independent factors associated with OH (Table 2). OH was significantly related to advanced age, high grades of hypertension and presence of CKD and DM. OH was also related to any drugs except ARB. Achievement of BP control was not associated with OH.

In Table 3 we report the logistic regression analysis performed to identify drug combinations associated with OH, after adjustment for age, sex, BP control, grade of hypertension, diabetes and CKD, antihypertensive drugs individually considered and total number of drugs (stratified into two groups: 0–2 and 3–5 medications). The following drug associations were identified as independent factors associated with OH: ACEi+diuretics, DHP+α-blockers, non-DHP+diuretics, α-blockers+centrally acting drugs and BB+α-blockers.

Table 1. Anthropometric variables and antihypertensive therapy in patients with and without OH

	With OH (n = *957*)	*Without OH* (n = *8285*)	P-*value*
SBP supine (mm Hg) mean ± s.d.	172.4 ± 25.6	152.8 ± 21.5	< 0.0001
DBP supine (mm Hg) mean ± s.d.	100.7 ± 14.6	93.4 ± 11.5	< 0.0001
SBP standing (mm Hg) mean ± s.d.	154.1 ± 25.2	151.8 ± 21.9	0.0208
DBP standing (mm Hg) mean ± s.d.	93.2 ± 14.5	94.2 ± 11.7	0.01
HR supine (bpm) mean ± s.d.	77.4 ± 13.2	76.6 ± 12.5	0.0919
HR standing (bpm) mean ± s.d.	76.8 ± 13.8	74.1 ± 12.3	0.0028
Age *n* (%)			< 0.0001
18–39	112 (11.7%)	1657 (20%)	
40–60	441 (46.1%)	4134 (49.9%)	
> 60	404 (42.2%)	2494 (30.1%)	
Sex *n* (%)			0.008
Female	532 (55.6%)	4231 (51.1%)	
Male	425 (44.4%)	4054 (48.9%)	
Grade of hypertension *n* (%)			< 0.0001
Normal	42 (4.4%)	1344 (16.2%)	
1	102 (10.7%)	2144 (25.9%)	
2	234 (24.5%)	2184 (26.4%)	
3	468 (48.9%)	1516 (18.3%)	
ISH	109 (11.4%)	1068 (12.9%)	
Blood pressure control *n* (%)			< 0.0001
Yes	42 (4.4%)	1368 (16.5%)	
No	915 (95.6%)	6917 (83.5%)	
Total number of drugs *n* (%)			< 0.0001
0	248 (25.9%)	2814 (34%)	
1	213 (22.3%)	2281 (27.5%)	
2	253 (26.4%)	1871 (22.6%)	
3	172 (18%)	1011 (12.2%)	
4	60 (6.3%)	279 (3.4%)	
5	11 (1.1%)	29 (0.4%)	
ACEi *n* (%)	350 (36.6%)	2572 (31%)	0.0005
ARB *n* (%)	87 (9.1%)	917 (11.1%)	0.0062
Diuretics *n* (%)	324 (33.6%)	2101 (25.6%)	< 0.0001
DHP *n* (%)	260 (27.2%)	1783 (21.5%)	< 0.0001
Non-DHP *n* (%)	30 (3.1%)	113 (1.4%)	< 0.0001
BB *n* (%)	225 (23.5%)	1710 (21%)	0.0387
α-blockers *n* (%)	158 (16.5%)	758 (9.1%)	< 0.0001
Centrally acting drugs *n* (%)	90 (9.4%)	373 (4.5%)	< 0.0001
Nitrates *n* (%)	6 (0.6%)	55 (0.7%)	0.1653

Abbreviations: ACEi, ACE inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CKD, chronic kidney disease; DBP, diastolic blood pressure; DHP, dihydropyridine calcium-channel blockers; DM, diabetes mellitus; HR, heart rate; ISH, isolated systolic hypertension; non-DHP, non-dihydropyridine calcium-channel blockers; OH, orthostatic hypotension; SBP, systolic blood pressure. Comparison was made with X^2 analysis.

DISCUSSION

In our study, hypertensive patients with OH were older, had a high supine BP, a severe grade of hypertension and a poor BP control. They were often affected by diabetes and CKD, and were under vasoactive polytherapy. Diuretics, α-blockers, centrally acting drugs, BB and non-DHP were more often associated with OH. No correlation was found between OH and ARB. Owing to the type of study (retrospective analysis), it was not possible to evaluate a causal or temporal relationship between specific medications and OH.

OH, anthropometric variables, comorbidities, supine hypertension and BP control

In accordance with previous studies,[2–6] the prevalence of OH was of 10.4% in our cohort of essential hypertensive patients and was increased in those aged > 60 years. In the elderly, independent of therapies, OH has been attributed to a decreased baroreceptor

Table 2. Logistic regression analysis using OH as dependent factor

	OR	P-*value*	*IC 95%*
Age[a]	1.14	0.038	1.09–1.30
Female sex	1.15	0.107	0.97–1.37
Grade of hypertension[b]	1.59	< 0.0001	1.45–1.74
Blood pressure control	0.32	0.002	0.16–0.67
DM	2.16	< 0.0001	1.52–3.08
CKD	3.66	0.0003	1.80–7.45
ACEi	1.03	0.801	0.84–1.25
Diuretics	1.29	0.026	1.03–1.61
ARB	0.44	0.0009	0.28–0.72
α-blockers	1.6	0.0003	1.24–2.07
Centrally acting drugs	1.58	0.004	1.16–2.15
BB	1.28	0.03	1.03–1.59
Non-DHP	1.15	0.047	1.04–1.41
DHP	1.15	0.185	0.94–1.42
Total number of drugs	0.83	0.256	0.59–1.15

Abbreviations: ACEi, ACE inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CKD, chronic kidney disease; DHP, dihydropyridine calcium-channel blockers; DM, diabetes mellitus; non-DHP, non-dihydropyridine calcium-channel blockers; OH, orthostatic hypotension; OR, odds ratio. Total number of drugs was stratified into two groups: 0–2 and 3–5 drugs. [a]Increase in odds of OH for each group of 20 years. [b]Increase in odds of OH for each grade of hypertension (according to the ESH Guideline 2007).

Table 3. Logistic regression analysis (adjusted for age, grade of hypertension, BP control, chronic renal failure, diabetes, antihypertensive drugs individually considered and total number) to identify drug combinations associated with OH

Antihypertensive drug associations (n)	*OR*	P-*value (IC 95%)*
ACEi+diuretic (1229)	1.47	0.006 (1.12–1.93)
ACEi+BB (647)	1.39	0.057 (0.99–1.96)
ACEi+centrally acting drug (186)	1.45	0.124 (0.90–2.31)
ACEi+α-blocker (360)	1.33	0.158 (0.9–1.97)
ACEi+DHP (110)	0.99	0.936 (0.71–1.37)
ACEi+non-DHP (62)	1.68	0.181 (0.79–3.6)
DHP+diuretic (735)	1.13	0.481 (0.80–1.60)
DHP+centrally acting drug (151)	1.38	0.137 (0.88–2.47)
DHP+BB (490)	1.49	0.07 (0.93–2.15)
DHP+α-blocker (254)	1.63	0.025 (1.16–2.49)
non-DHP+diuretic (59)	2.28	0.04 (1.03–5.00)
α-blocker+centrally acting drug (78)	1.85	0.047 (1.08–3.47)
Diuretic+centrally acting drug (197)	1.56	0.068 (0.97–2.49)
Diuretic+α-blocker (329)	1.22	0.378 (0.79–1.88)
Diuretic+BB (764)	1.22	0.252 (0.87–1.71)
BB+centrally acting drug (103)	1.67	0.109 (0.89–3.11)
BB+α-blocker (224)	1.71	0.019 (1.09–2.69)

Abbreviations: ACEi, ACE inhibitors; BB, beta-blockers; DHP, dihydropyridine calcium-channel blockers; non-DHP, non-dihydropyridine calcium-channel blockers; OR, odds ratio. Data on angiotensin receptor blockers and nitrates not shown.

and autonomic function in the upright position, a reduced cardiac and vascular response to α- and β-adrenergic stimuli, an increased stiffness of the vessels and cardiac chambers and, frequently, a depletion of plasma volume due to reduced fluid intake and renin–angiotensin–aldosterone system dysfunction.

In our study we did not detect a significant correlation between OH and low BMI, found by other authors. The difference may be related to the different BMI values, age and ethnicity considered in other studies.[7]

In our analysis, DM was significantly related to OH. The role of long-standing and poorly controlled hyperglycemia in the development of severe autonomic neuropathy with OH in diabetic patients has been well described.[8–10] In our study, CKD is significantly related to OH. In a previous cohort study[11] OH was shown to predict CKD (increased albuminuria) in middle-aged persons; the authors assumed that OH could lead to alterations of renal perfusion, autoregulation of renal microcirculation and renal function. On the other hand, patients with CKD may also develop OH secondary to other factors, such as uremic autonomic neuropathy, diuretic and vasoactive therapy and volume depletion during dialysis therapy.

A significant relationship between supine hypertension and OH has been confirmed in our analysis. This condition is reported in many other studies.[6,7,12–14] In hypertensive subjects the increased vascular stiffness contributes to the development of both OH and systolic hypertension. In two studies, the first conducted on elderly patients[15] and the second comparing hypertensive and normotensive individuals,[3] a higher prevalence of OH was described in high-grade hypertensives compared with normotensives or mild hypertensives. In a study by Kamaruzzaman *et al.*,[16] uncontrolled hypertension was an independent risk factor for OH in a cohort of old women.

In our study we showed that the achievement of BP control was present in a small percentage of patients with OH and, in logistic regression analysis, was not associated with OH. This finding is in agreement with the study of Masuo *et al.*,[17] in which a reduction in orthostatic hypotensive episodes was described in hypertensive subjects achieving BP control with an appropriate antihypertensive therapy.

OH and antihypertensive drugs

In our study, the prevalence of OH increased significantly with the number of antihypertensive drugs. In two previous studies, the first conducted in elderly patients[18] and the second in elderly women,[16] treatment with three or more antihypertensive drugs predicted OH. In another study on 47 elderly hypertensives,[19] OH frequency was reduced from 23 to 11% within 12 months after pharmacological antihypertensive treatment washout.

In our study, we found a significant correlation between OH and treatments with diuretics, non-DHP, α-blockers, centrally active drugs and BB, confirmed also as independent risk factors with the regression analysis.

An association between OH and calcium-channel blockers (DHP and non-DHP) has been described in some studies.[15,20–22] DHP use did not correlate with OH in other studies.[23] The correlation between OH and non-DHP reported in our study may be related to a reduced cardiac output in the absence of an appropriate chronotropic compensation in orthostatism, in agreement with a previous study.[2]

The increased prevalence of OH with α-blockers therapy found in our study is in agreement with several previous reports.[3,16] Development of OH during α-blocker therapy may be sustained by concomitant plasma volume depletion and absence of peripheral vasoconstriction in the upright position.[24]

Association between OH and centrally acting drugs (clonidine) depends on the inhibitory action on sympathetic tone or by the fact that these drugs are often prescribed in polytherapy, in patients with severe and resistant hypertension. Studies regarding the association between OH and the use of this pharmacological class in essential hypertension are lacking.

Clinical studies on the association between ACEi and OH have produced contradictory results. In a study by Poon *et al.*,[18] an association between OH and ACEi in an elderly population was reported, whereas in a study by Fedorowski *et al.*[3] a decreased prevalence of OH in hypertensive patients under ACEi was found, possibly because of the protective effect of ACEi on kidney function.

ARBs have not been significantly related to OH, when compared with other drugs.[25,26] The data are confirmed in our study. Further studies are warranted to evaluate a potential protective effect of ARB against the development of OH in essential hypertensives.

As regards OH, the diverse effect of ACEi and ARB shown in our study may be secondary to a different pharmacokinetic profile (ARB reaching the peak of action more slowly compared with short half-life ACEi).[27,28] Furthermore, it is not known whether different effects of these drugs (ACEi and ARB) on other neurohormonal systems (for example, bradykinin) may have a role in altering orthostatic BP homeostasis.

In population studies, different results about the association between diuretics and OH have been reported. In some studies, diuretic therapy did not correlate significantly with OH.[8,12,29,30] In a study by Poon *et al.*[18] on elderly patients, an increased prevalence of OH was detected during loop diuretics and thiazide treatment. In hypertensives, Fedorowski *et al.*[3] found a significant correlation between OH and spironolactone intake only. In our analysis, it was not possible to distinguish between the various subclasses of diuretics. Whether considered individually or in combination with other antihypertensive drugs, they were significantly associated with OH.

In some studies, BBs are not significantly associated with OH;[15,21] in the study of Cleophas *et al.*,[31] treatment with nebivolol offsets the decrease in pulse pressure while standing in a large cohort of elderly hypertensives with mild hypertension. In other studies,[2,16] a correlation between BB and the onset of OH was reported, especially in elderly individuals with age-related baroreceptor dysfunction. Some α–β nonselective BBs, such as carvedilol and labetalol, may also inhibit α-adrenergic receptor, resulting in vasodilation and OH. In our study, BBs were significantly associated with OH, although it was not possible to analyse the individual classes.

In our study, we did not find any significant association between OH and nitrates, as confirmed by other clinical studies. The small number of hypertensive patients treated with this drug may have affected the result.

OH and drug associations

In the literature, there is a scarce number of epidemiological studies on the correlation between OH and antihypertensive drug combinations.[32] In our analysis we have considered the different associations of antihypertensive drugs employed in the cohort. We found that drug combinations including α-blockers, centrally acting drugs, non-DHP and diuretics were associated with OH. The correlation between OH and non-DHP plus diuretics may be secondary to a lack of compensatory chronotropic response in the upright position together with a certain degree of intravascular volume depletion. The associations of OH and DHP plus α-blocker or α-blocker plus centrally acting drug may be ascribed to the synergic effects of drugs characterized by the same mechanism of action (peripheral arterial vasodilatation). The association between BB (in particular nonselective labetalol and carvedilol) and α-blockers may also determine a synergic peripheral vasodilation and, consequently, OH secondary to excessive venous pooling. Diuretic therapy, in combination with ACEi, may be related to OH, secondary to vasodilatation plus plasma volume depletion.

Limitations of the study

The study was conducted on a selected population referred to the Hypertension clinic. The study is a retrospective analysis; therefore, it was not possible to evaluate a causal or temporal relationship between specific medications or comorbidities and OH. The following factors may have led to an overestimation of the prevalence of OH or the contribution of antihypertensive drugs to the development of OH: there are no data available about other therapies and medications with hypotensive effect (that is, antidepressants and dopaminergic drugs), single classes of antihypertensive drugs, type and severity of DM and CKD. Moreover, we have not considered other primary or secondary neurological diseases characterized by neurogenic OH (that is, Parkinson's disease and multiple system atrophy). No data were available about other cardiac or cerebral comorbidities associated with hypertension (that is, ischemic heart disease, congestive heart failure or cerebrovascular events). Unfortunately, no data were available about OH symptoms, although several studies have reported higher mortality and morbidity in different populations with OH, independent of symptoms.[7,29,33] Finally, we did not consider delayed forms of OH (measurements of OH after 3 min of standing were not performed in the outpatients' visits).

CONCLUSIONS

In hypertensive patients referring to a Hypertension Clinic, OH was related to advanced age, high supine BP, high grade of hypertension and inadequate BP control during antihypertensive treatment. Polytherapy was associated to an increased prevalence of OH.

What is known about topic

- Non-neurogenic orthostatic hypotension is a common finding in essential hypertensive patients under antihypertensive therapy.
- Orthostatic hypotension is related to cardio- and cerebrovascular morbidity and mortality, especially in elderly and diabetic patients.

What this study adds

- The present study analyzes the association between orthostatic hypotension and therapeutic combinations of antihypertensive drugs, not only with single classes.
- This study describes anthropological features, comorbidities and therapies of a selected population referring to a Hypertension Clinic and identify high-risk factors related to orthostatic hypotension in these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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