Risk Factors for Orthostatic Hypotension: Differences Between Elderly Men and Women

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BACKGROUND
Orthostatic hypotension (OH) occurs when mechanisms regulating blood pressure (BP) levels after standing-up are altered. It is unclear how prevalence and risk factors for OH are different between sexes. We aimed to investigate sex differences in prevalence and risk factors for OH elderly individuals.

METHODS
We included 882 participants from Maracaibo Aging Study. OH was a sustained reduction of ≥20 mm Hg in systolic BP, ≥10 mm Hg in diastolic BP, or both, after 3 minutes of changing positions from supine to standing. Multivariable logistic regression models were used to examine the relationships among risk factors for OH in men and women considering interaction sex-term and stratified by sex.

RESULTS
The mean age was 66.7 ± 8.5 years, being similar by sex. Women and men 55–74 years had similar prevalence of OH+ (18.5% vs. 20.9%, respectively). After 75 years, the proportion of women with OH+ was lower than men (11% vs. 30%, respectively). Hypertension, specifically systolic BP ≥140 mm Hg, and high pulse pressure (PP) were related with OH+ accounted by interaction sex-term, while diastolic BP ≥90 mm Hg, antihypertensive treatment, body mass index (BMI), diabetes mellitus and age were not. Systolic BP ≥140 mm Hg increases the risk of OH only among women, while BMI showed an inverse association in both sexes.

CONCLUSIONS
Although the prevalence of OH is similar in both sexes, there are different risk factors associated by sex. Systolic BP ≥140 mm Hg was associated with increased risk of OH only with women while BMI was a protective factor for OH in men and women.

Keywords: blood pressure; Hispanic; hypertension; Latin America; orthostatic hypotension; prevalence; risk factors.

doi:10.1093/ajh/hpy050

Orthostatic hypotension (OH) is an exaggerated drop in systemic blood pressure (BP) levels after standing up from a supine or sitting position,[1] attributed to a failure on the cardiovascular and neurological adaptive mechanisms to maintain BP.[2] Although common in the elderly, the prevalence of OH ranges from 5% to 30% in community living individuals[3,4] and it is known as an independent risk factor for cardiovascular morbidity and mortality.[1,5,6]

Common cardiovascular risk factors such as aging,[7] diabetes mellitus,[8] and hypertension[9] have been associated with the presence of OH. Many of these associations are based on the assumption that risk factors do not significantly differ between men and women. Because evidence indicates that there are differences according to sex in the BP regulation,[10,11] diabetes pathophysiology,[12] and vascular aging,[13] it is likely that the physiological mechanisms involved in the

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Initially submitted January 3, 2018; date of first revision March 6, 2018; accepted for publication March 29, 2018; online publication March 30, 2018

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presence of OH differ by sex. In addition, the risk for cardiovascular morbidity and mortality associated with OH varies between men and women,[14] suggesting that there might be sex differences in the clinical outcomes related with OH. Therefore, it is important to examine the sex-differences in risk factors associated with OH.

To examine prevalence of OH and associated risk factors in elderly men and women, we examined a subset of 882 individuals from the Maracaibo Aging Study (MAS), a longitudinal population-based study of Latin Americans. To our knowledge, there are no population-based studies examining the prevalence of OH in the elderly from Latin America. Further, OH prevalence rates are needed, particularly in Latin America where cardiovascular diseases represent the main cause of death and this is expected to increase in the future.[15,16] Unlike other studies of aging, the MAS participants were recruited at relatively younger age (≥55 years of age), thereby providing information on age-related conditions in mid- to- late-life adults. Finally, because MAS participants exhibit a high burden of hypertension,[17] we reasoned that they would provide an exceptionally rich sample to address the importance cardiovascular risk factors in OH at older age.

MATERIALS AND METHODS

Study population

The MAS is a multidisciplinary study of age-related conditions that includes assessment of cognition, cardiovascular, and metabolic traits.[18] The original cohort includes 2,439 subjects ≥55 years of age residents of Santa Lucía in Maracaibo, Venezuela recruited from January 1998 to August 2001. The present study included a subset of participants (n = 882), who completed the OH measurement protocol that included BP measures obtained at supine position and the first and third minutes according to the first consensus on diagnosis of OH.[19] Of the 2,439 participants, 102 participants did not have supine BP measures, 63 participants did not have BP measures obtained at the first minute and 1,277 participants did not have at the third minute. No one was excluded for not having BP measured at the fifth minute. Comparison of the study sample and the original cohort is included in Supplementary Table S1. The ethics review board of the Cardiovascular Institute, University of Zulia, and Columbia University approved the study, and informed consent was obtained from all participants.

OH assessments

All BP recordings were measured using the same oscillometric device (Dinamap 8100, Critikon Inc., Tampa, FL, USA) with an appropriate size cuff around the right arm and the cuff at the heart level. The OH protocol included supine BP and standing BP measurements registered after 1, 3, and 5 minutes in the upright standing position. Supine BP was measured after 5 minutes of rest. We defined OH based on the latest recommendations of the American Autonomic Society and American Academy of Neurology[20]: a sustained reduction of systolic BP >20 mm Hg or diastolic BP >10 mm Hg within 3 minutes of standing, i.e., both at 1 and 3 minutes, when comparing BP from supine to standing.

Conventional BP measurements

Conventional BP was measured with the subject in a sitting position. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, or receiving antihypertensive medication. Information on the class of antihypertensive drugs (ACE-inhibitors, beta-blockers, calcium channel blockers, and diuretics) and dosage was collected. Controlled hypertension was defined as a systolic BP <140 mm Hg or a diastolic BP <90 mm Hg, among those receiving antihypertensive treatment. Pulse pressure (PP) was defined as the difference between brachial systolic and diastolic BP levels. Although there is not a broadly accepted threshold for defining high PP levels, a cutoff of 65 mm Hg or more for high PP has been suggested[21] and we adopted that level.

Other clinical information

Participants underwent standardized physical and clinical evaluations. Laboratory assessments included hematology and blood biochemistry. Body mass index (BMI) was weight (kg) divided by the square of height (m^2). Diabetes was defined as fasting glucose level ≥126 mg/dl, self-reported use of glucose-lowering medication, or self-reported history of diabetes. To determine the accuracy of self-report for diabetes, we computed sensitivity and specificity of self-report vs. glucose measurements for individuals with data on both. Using fasting glucose level as the gold standard, sensitivity was 77% and specificity was 97%. History of cardiovascular events was defined as myocardial infarction, stroke, coronary bypass, angina pectoris, or congestive heart failure. Among the causes of OH available for MAS participants, we had information on extrapyramidal symptoms (such as bradykinesia, rigidity, and tremor), use of central nervous system drugs (included antiparkinsonian drugs, antidepressants, and antipsychotics treatment), anemia (hemoglobin and hematocrit), alcohol intake, presence of Parkinson's disease, and dementias (Alzheimer's disease, vascular dementia, and levy body dementia).

Statistical analyses

Descriptive information is presented as mean standard deviation (±), and frequency and percentage (%). The prevalence of OH was estimated in the total population and by age groups (55–64, 65–74, and ≥75 years). Significance differences of continuous data among two groups variables were evaluated using a two-tailed independent t-test. Dichotomous variables were compared using the chi-squared test. We compared the characteristics between individuals with OH+ and OH− by sex. The examination of variables as risk factors was performed by selecting those variables with a P value less than 0.1 in the comparison of characteristics between OH+ and OH−. For analysis of the sex-effect on the association between risk factors and OH+, we performed interaction term analysis using multivariate logistic regression modeling for each risk factor. Seven models were created (i) model 1: systolic BP ≥140 mm Hg × sex; (ii) model 2: diastolic BP≥90 mm Hg × sex; (iii) model 3: PP × sex; (iv) model 4: antihypertensive treatment × sex; (v) model 5:

BMI × sex; (vi) model 6: diabetes mellitus × sex; and (vii) model 7: age × sex. Each model was adjusted by systolic BP ≥140 mm Hg, diastolic BP≥90 mm Hg, PP, antihypertensive medication, BMI, diabetes mellitus, and age. Because of the high proportion of participants with high PP in our study population, we repeated the same seven models expressed above, using PP as a dichotomous variable (normal and high PP) based on its cut-off as well.[21] To observe the specific relationship between sex and different risk factors for OH+, we performed stratified analyses by sex. Because PP is calculated based on systolic and diastolic BP levels, it is assumed that a multicollinearity effect could be presented between the independent variables. Variance inflation factors were monitored and were less than 2 in all models, ensuring lack of multicollinearity among the independent variables.[22] All analyses were performed using SPSS for Windows, version 23.0 (IBM Corp; Armonk, NY).Statistical significance was accepted at P <0.05 for two-tailed tests.

RESULTS

Characteristics of the total population and stratified by sex

A total subset of 882 individuals was assessed. The average age of study participants was 66.7 ± 8.5 years and 62.0% were women (Table 1). Around a third part of the participants were smokers, reported alcohol intake, were obese and had history of cardiovascular diseases. Overall prevalence of diabetes mellitus was 18.6% and hypertension was 80.4%, with 25.6% of hypertensive subjects being treated and 2.7% controlled. When comparing by sex, women OH+ were less likely to be obese, and more likely to have hypertension and high PP in comparison to women OH−. Of those women receiving antihypertensive treatment, all with uncontrolled hypertension had OH, while none with controlled BP had OH+. These associations were not consistent among men. Men OH+ tended to be older than those OH−, and were less likely to be obese. When comparing women OH+ vs. men OH+, we

Table 1. Characteristics of the total population and between orthostatic hypotension stratified by sex

		Women (n = 547)			Men (n = 330)		
	Total	OH+	OH−		OH+	OH−	
Characteristics	(n = 882)	(n = 101)	(n = 446)	P value[a]	(n = 69)	(n = 261)	P value[a]
Age, years	66.7 ± 8.5	66.4 ± 7.8	67.2 ± 8.9	0.394	67.8 ± 8.7	65.6 ± 7.9	**0.051**
Education, years	6.7 ± 4.3	5.4 ± 3.7	3.3 ± 4.2	**0.036**	6.8 ± 3.4	7.8 ± 4.6	0.092
Smoking, n (%)	265 (30.0)	26 (25.7)	93 (20.9)	0.287	26 (37.7)	118 (45.2)	0.262
Alcohol intake, n (%)	309 (35.0)	14 (14.1)	84 (19.1)	0.245	43 (62.3)	165 (63.7)	0.832
BMI (kg/m^2)	27.9 ± 5.4	27.3 ± 5.4	28.3 ± 5.7	0.094	25.5 ± 5.3	27.9 ± 4.9	**0.001**
Total cholesterol levels, mg/dl	164.6 ± 58.6	174.4 ± 58.9	173.1 ± 55.8	0.885	154.0 ± 52.9	150.2 ± 59.9	0.724
Triacylglycerides levels, mg/dl	186.3 ± 135.0	161.3 ± 78.3	172.9 ± 110.1	0.477	188.1 ± 129.0	208.9 ± 166.3	0.477
Creatinine levels, mg/dl	1.0 ± 0.4	0.9 ± 0.4	0.9 ± 0.3	0.731	1.0 ± 0.3	1.1 ± 0.4	0.401
Hemoglobin levels, g/dl	12.4 ± 1.7	12.0 ± 1.5	12.0 ± 1.5	0.695	12.9 ± 1.9	13.0 ± 1.7	0.758
Hematocrit	39.2 ± 4.0	38.0 ± 3.6	38.2 ± 3.4	0.567	40.3 ± 4.3	41.0 ± 4.41	0.241
Diabetes mellitus, n (%)	164 (18.6)	24 (23.8)	76 (17.0)	0.115	18 (26.1)	46 (17.6)	0.114
Hypertension, n (%)	709 (80.4)	92 (91.1)	348 (78.0)	**0.003**	51 (73.9)	210 (80.5)	0.234
Treated, n (%)	226 (25.6)	28 (30.4)	121 (34.9)	0.424	16 (31.4)	59 (28.2)	0.657
Controlled, n (%)	24 (2.7)	0 (0)	14 (11.6)	0.059	4 (25.0)	5 (8.8)	0.081
SBP ≥ 140 mm Hg, n (%)	677 (76.8)	92 (91.1)	332 (74.4)	**0.001**	47 (68.1)	202 (77.4)	0.111
DBP ≥ 90 mm Hg, n (%)	296 (33.6)	30 (29.7)	131 (29.4)	0.947	25 (36.2)	108 (41.4)	0.438
PP, mm Hg	79.1 ± 24.1	84.9 ± 20.9	81.2 ± 26.1	0.183	73.7 ± 21.2	74.8 ± 21.9	0.706
PP ≥ 65 mm Hg, n (%)	629 (71.3)	89 (88.1)	321 (72.0)	**0.001**	45 (65.2)	171 (65.5)	0.963
History of cardiovascular disease, n (%)	231 (26.2)	21 (20.8)	116 (26.0)	0.275	19 (27.5)	74 (28.4)	0.893
History of Parkinson's disease, n (%)	6 (0.7)	2 (2.0)	2 (0.4)	0.103	0 (0)	2 (0.8)	0.465
Extrapyramidal symptoms, n (%)	70 (7.9)	6 (5.9)	32 (7.2)	0.656	8 (11.6)	24 (9.2)	0.556
Dementia, n (%)	80 (9.1)	12 (11.9)	46 (10.3)	0.644	4 (5.8)	18 (6.9)	0.739
Use of CNS medications, n (%)	13 (1.5)	3 (3.0)	6 (1.3)	0.248	1 (1.4)	3 (1.2)	0.845

Quantitative data is presented as mean and standard deviation (±) and qualitative data as frequencies and percentages. Diabetes is defined based on serum glucose levels ≥126 mg/dl, medication treatment or self-report; hypertension was a SBP or DBP ≥140/90 mm Hg or antihypertensive drug treatment intake. Bold text indicates a statistically significant difference with a P-value less than 0.05. Abbreviations: BMI, body mass index; CNS, central nervous system; OH, orthostatic hypotension; PP, pulse pressure.

[a]P value of the comparison of the baseline information between individuals with and without OH.

found that women had fewer years of formal education, fewer alcohol intake rates, lower creatinine levels, and higher systolic BP and PP levels than men (Supplementary Table S3). Hemoglobin and hematocrit levels (proxy for anemia, hypovolemia), antihypertensive medications and central nervous system medications, diabetes mellitus, Parkinson's disease, dementia, and history of cardiovascular diseases were not significantly different between OH+ and OH− (Table 1).

Orthostatic changes in systolic and diastolic BP

Subjects OH+ had an average sitting systolic BP of 165.3 ± 28.3 which was not different from those OH− (Figure 1). However, after 5 minutes in a supine position, systolic BP levels among subjects OH+ increased by 6 mm Hg, while individuals OH−, exhibited a drop in systolic BP levels of 8 mm Hg ($P = 0.001$). After 1 and 3 minutes of standing, individuals OH+ had a drop in systolic BP of 17% and 15%, equivalent to 29 and 25 mm Hg, respectively. In contrast, individuals OH− drop an average of 4.9 mm Hg at 1 minute of standing and there was no drop on their BP after 3 minutes. This pattern was the same for men and women, and was also exhibited when diastolic BP was assessed (Supplementary Table S2).

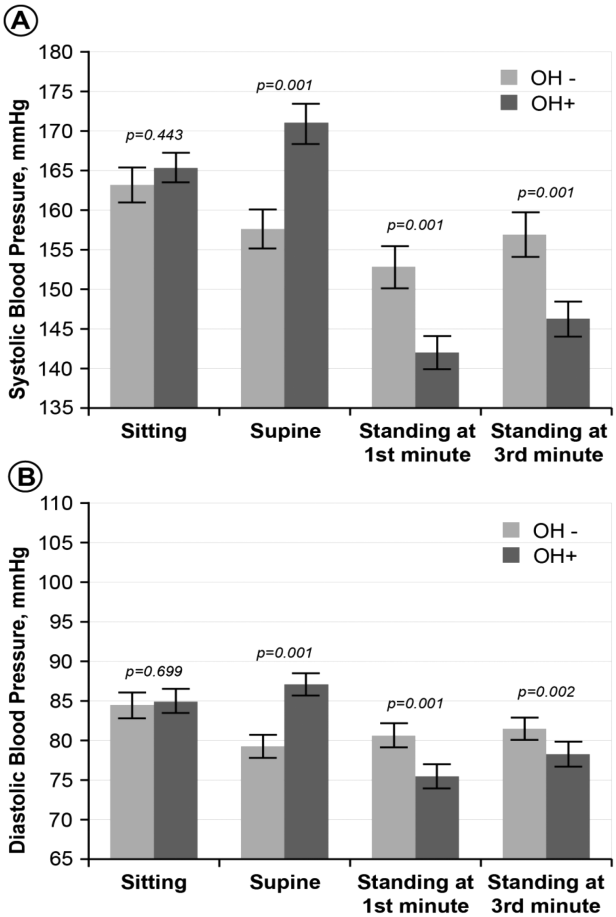

Figure 1. Orthostatic changes in systolic (upper panel) and diastolic (lower panel) blood pressure after standing from supine or sitting position.

Prevalence of OH by age and sex

Overall prevalence of OH+ in the sample population was 19.3% (170 of 882 participants), with no difference between sexes. However, when divided by age and sex groups, the proportion of participants OH+ was similar for women and men <75 years of age but was significantly higher in men than in women ≥75 years (Figure 2).

Risk factors associated with OH

Effect of sex-interaction on the association between risk factors and OH are shown in Table 2 and Supplementary Table S4. In Table 2, each model was adjusted by systolic BP ≥140 mm Hg, diastolic BP≥90 mm Hg, PP, antihypertensive medication, BMI, diabetes mellitus, and age, while in Supplementary Table S4 we included the same confounders but we added PP based on its clinical cutoff.[21] Systolic BP ≥140 mm Hg alone was not associated with increased risk of OH (odds ratio (OR) = 0.87; 95% confidence interval (CI) = 0.46–1.64; $P = 0.678$) while accounted for interaction sex-term, systolic BP ≥140 mm Hg was significantly associated (OR = 4.53; 95% CI = 1.94–10.58; $P = 0.0001$). The same association persisted in Supplementary Table S4 when hypertension was adjusted by high PP. Continuous PP was not significantly associated with OH (Table 2), but high PP (categorical) was associated with OH while accounted for interaction sex-term (high PP = 0.939 and for high PP × sex = 0.014). In both Table 2 and Supplementary Table S4, the association between BMI and OH+ lost its significance when sex was included as an interaction term (P for BMI = 0.0001 and for BMI × sex = 0.779 and 0.512). Diastolic BP ≥90 mm Hg, antihypertensive treatment, diabetes mellitus, and age

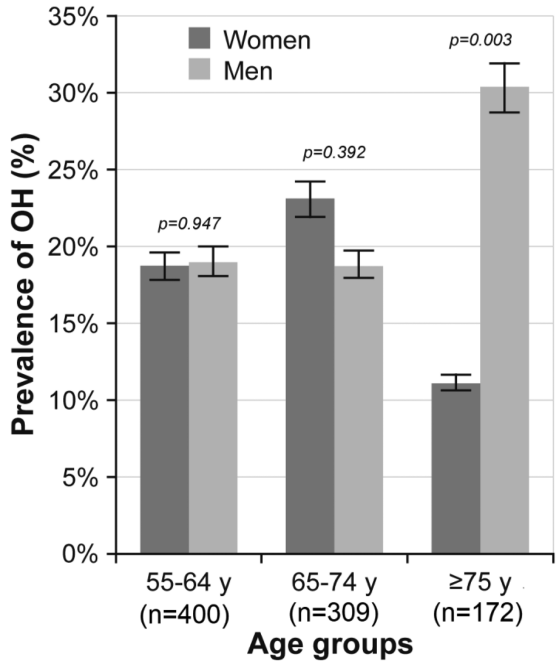

Figure 2. Age and sex-specific prevalence of orthostatic hypotension. Dark gray: women; light gray: men. *P value of the comparison between men and women in each age group.

Table 2. Multivariate logistic regression models with two-way interaction terms to determine the effect of sex and risk factors for orthostatic hypotension

Variables	OR (95% CI)	*P* value
Model 1		
SBP ≥ 140	0.87 (0.46–1.64)	0.678
SBP ≥ 140 × sex	4.53 (1.94–10.58)	<0.0001
Model 2		
DBP ≥ 90	0.72 (0.44–1.18)	0.201
DBP ≥ 90 × sex	1.22 (0.79–1.89)	0.367
Model 3		
Pulse pressure	0.99 (0.98–1.00)	0.647
Pulse pressure × sex	0.99 (0.99–1.00)	0.745
Model 4		
Antihypertensive treatment	0.97 (0.60 – 1.57)	0.974
Antihypertensive treatment × sex	1.13 (0.75 – 1.70)	0.546
Model 5		
BMI	0.93 (0.90–0.97)	<0.0001
BMI × sex	0.99 (0.98–1.01)	0.779
Model 6		
Diabetes mellitus	1.52 (0.74–2.47)	0.090
Diabetes mellitus × sex	1.12 (0.74–1.67)	0.579
Model 7		
Age	0.99 (0.97–1.00)	0.570
Age × sex	0.99 (0.99–1.01)	0.360

Each model was adjusted by hypertension, antihypertensive treatment, pulse pressure, BMI, diabetes mellitus and age. Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.

were not associated with OH+ in either alone or accounted for interaction sex-term.

Stratified analyses by sex demonstrated which sex reported the risk factor associated with OH+ (Table 3). Univariate regression analyses showed that systolic BP ≥140 mm Hg (P = 0.001) was a significant risk factors for OH+ only in women, while BMI was protective for both sexes. In the multivariate analyses, systolic BP ≥140 mm Hg remained as a significant risk factor in women. BMI remained significantly associated with lower risk of OH+ for both sexes even after adjustment for confounding variables.

DISCUSSION

The high prevalence of OH in our cohort (19.3%) was consistent with other studies that examined elderly populations and used similar OH definitions,[23–25] even though no comparable studies included Hispanics. Prevalence of OH was generally constant and similar between younger men and women, but increased significantly in men and decreased in women older than 75 years. Due to the cross-sectional nature of our study, we are not able to assess if that difference was due to selective mortality. We did not have a large enough sample to assess whether the prevalence remains constant in octogenarians as previously suggested.[23,26]

Vascular risk factors for OH and sex differences

Our results showed that hypertension was an independent risk factor for OH in women, but not in men. Some studies have identified hypertension as risk factor for OH,[8,27] being uncontrolled hypertensive individuals more likely to have OH.[26,28] We also found that the increased risk of OH was directly associated with the systolic BP levels as other studies.[26,29] However, the PARTAGE study of 994 individuals

Table 3. Univariate and multivariate logistic regression models to determine risk factors associated with orthostatic hypotension

	Women		Men	
	Univariate	Multivariate	Univariate	Multivariate
Risk factors	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vascular risk factors				
SBP ≥ 140	3.51 (1.71–7.18)†	5.25 (2.30–11.97)‡	0.62 (0.34–1.11)	0.57 (0.24–1.34)
DBP≥ 90	1.01 (0.63–1.63)	0.75 (0.45–1.25)	0.80 (0.46–1.39)	1.15 (0.59–2.23)
PP	1.00 (0.99–1.01)	0.99 (0.98–1.00)	0.99 (0.98–1.01)	0.99 (0.98–1.01)
Antihypertensive treatment	1.02 (0.63–1.66)	0.89 (0.52–1.51)	1.03 (0.55–1.94)	1.25 (0.61–2.56)
Metabolic risk factors				
BMI	0.96 (0.92–1.00)	0.95 (0.91–0.99)*	0.90 (0.85–0.95)‡	0.91 (0.85–0.96)†
Diabetes mellitus	1.51 (0.90–2.55)	1.65 (0.95–2.88)	1.65 (0.88–3.08)	1.68 (0.86–3.29)
Demographic risk factors				
Age	0.98 (0.96–1.01)	0.97 (0.94–0.99)*	1.03 (1.00–1.06)*	1.02 (0.98–1.06)

Univariate analyses explore the associations between individual risk factors and OH. Multivariate models included all the listed risk factors in the same regression model. *P < 0.05; †P < 0.01; ‡P < 0.001. Abbreviations: OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index.

aged ≥80 years found no significant difference in hypertension rates between OH+ and OH−[26] individuals. High PP also increased the risk of OH, only in women. However, when PP was added as a continuous variable, it lost significance suggesting that high PP is secondary to hypertension as a risk factor for OH. Previous population-based studies among elderly, suggested that arterial stiffness, the main underlying factor of high PP, is independently related to OH,[30] and that postmenopausal women have stiffer large vessels than age-matched males, tending to present higher PP than men.[31] Nevertheless, the association between high PP and OH remains unclear.

The sex-specific differences in risk factors for OH have several possible explanations. First, although the rate of hypertension was the same for men and women, the prevalence of both high PP and isolated systolic hypertension was significantly higher in women than in men. Second, postmenopausal women have stiffer large vessels and tend to present higher central PP than age-matched males.[31] Furthermore, women have lower baroreflex sensitivity and greater carotid aorta stiffening than men,[32] which may compromise the cushioning of BP during postural changes.[30,33]

BMI and OH

We found an inverse relationship between BMI and OH in both men and women, in agreement with previous studies,[34] including studies that used beat-to-beat technology or the head-up tilt test to assess OH.[35,36] A study of patients with Parkinson's disease suggested two possible mechanisms for the association between BMI and OH: (i) patients with lower BMI might have reduced autonomic function, due to alterations of the sympathetic nervous system[35]; and (ii) levels of leptin, a hormone produced by fat cells, are low in patients with lower BMI, possibly mediating the inhibition of sympathetic excitation.[35] Our results showed a stronger relationship between BMI and OH in men than in women. In men, BMI is a major determinant of sympathetic nervous system activity, independent of BP level and age, while sympathetic nervous system activity in women is directly linked to BP.[37]

The present study has some potential limitations. First, the cross-sectional design precluded causal interpretation of the results. Second, we used conventional BP measurements, rather than 24-hour ambulatory BP monitoring, which might have resulted in overestimation of the prevalence of hypertension. Third, diabetes was operationalized using fasting glucose measurement, self-reported use of glucose-lowering medication, or self-reported history of diabetes, repeated fasting plasma glucose measurements were not available, this could have resulted in an underestimation of the prevalence of diabetes. Fourth, we did not assess OH using the head-up tilt test. However, we used the most common method used in clinical practice, and the strictest and most accepted diagnostic definition of OH.

In conclusion, the results of our study provide new information about sex-specific differences in vascular aging and the regulation of the autonomic nervous system. Future studies should evaluate whether these relationships are causal by using incident, rather than prevalent, data.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

ACKNOWLEDGMENTS

This work was supported by grants 1R01AG036469-01A1 and R03AG054186 from the National Institutes of Health, National Institute of Aging and Fogarty International Center and (Maestre, Terwilliger, Lee). We thank all of the staff at the Laboratory of Neurosciences, University of Zulia Research Centre, for facilitating assessment of MAS participants throughout the study. We would like to thank Lenys Araujo for taking the BP measurements for the OH protocol. We also thank Maria Zenaida Castellano and Sonia Pineda for the mapping of the community and maintenance of the database. We also acknowledge the South Texas Diabetes and Obesity Institute (STDOI) for support in preparation of this report.

DISCLOSURE

The authors declared no conflict of interest.

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