Orthostatic Hypotension and the Incidence of Coronary Heart Disease: The Atherosclerosis Risk in Communities Study

Kathryn M. Rose, Herman A. Tyroler, Christopher J. Nardo, Donna K. Arnett, Kathleen C. Light, Wayne Rosamond, A. Richey Sharrett, and Moyses Szklo

We examined the association between orthostatic hypotension (OH) at baseline examination (1987–1989) and the incidence of coronary heart disease (CHD) over an average of 6 years, among 12,433 black and white middle-aged men and women participating in the Atherosclerosis Risk in Communities (ARIC) study. OH was defined as a SBP decrease ≥ 20 mm Hg or a DBP decrease ≥ 10 mm Hg after changing from supine to standing. CHD events included definite or probable myocardial infarctions (MI), silent MI, and fatal CHD. Five percent of participants had OH. Prevalence increased with advancing age and was more common among those with cardiovascular disease (CVD)-related comorbidities and risk factors. Those with OH had an increased risk of CHD (hazard ratio [HR] = 3.49, 95% confidence interval [CI] = 2.58, 4.73). This association was attenuated after controlling for age, ethnicity, gender, comorbid conditions, and CVD risk factors (HR = 1.85, 95% CI = 1.31, 2.63). Am J Hypertens 2000;13:571–578 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Orthostatic hypotension, CHD, middle-age.

Upon standing, arterial blood pressure normally increases. However, as blood pools in the lower extremities, cardiac output decreases and a sharp, transient blood pressure decrease occurs. Baroreceptor relaxation and sympathetic stimulation lead to increased heart rate, catecholamine excretion, vasoconstriction, total peripheral resistance, and cardiac output. Although systolic blood pressure (SBP) tends to restabilize at prestanding levels and diastolic blood pressure (DBP) at slightly higher than prestanding levels, many have standing blood pressures higher or lower than when seated or supine. Orthostatic hypotension (OH) occurs when standing blood pressure remains sharply below prestanding levels. More common in the elderly, it is asso-
associated with dizziness, syncope, and falls. Other risk factors include diabetes, certain medications (diuretics, other antihypertensive medications, alcohol), and Parkinson’s disease and Shy-Drager Syndrome. Studies have not consistently defined OH. A recent consensus conference proposed the following definition: a SBP decrease ≥ 20 mm Hg or a DBP decrease ≥ 10 mm Hg within 3 min of standing. If adopted, this definition will improve comparability across studies.

Associations of OH with CHD risk factors have been examined in high-risk populations. Although positive associations generally were noted between OH and age and elevated blood pressure, associations with diabetes, antihypertensive medications, atherosclerosis, gender, and ethnicity have been less consistent or infrequently investigated. Ten-year vascular mortality was higher among members of an elderly cohort who at baseline had strong DBP decreases after standing. Both a higher prevalence of MI among those with OH and no difference in the prevalence of MI by OH status have been reported.

Our purpose was to determine if OH was associated with an increased 6-year incidence of CHD and the extent to which this association was explained by CVD risk factors and comorbidities. A secondary purpose was to determine the prevalence of OH and the variation of CVD risk factor levels by OH status.

**MATERIALS AND METHODS**

Participants Participants were from the baseline examination (1987–1989) of the ARIC study, designed to investigate the natural history and etiology of atherosclerosis. Probability samples of men and women ages 45 to 64 years were taken in four communities: Forsyth County, North Carolina; Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi. Blacks were oversampled in Forsyth and sampled exclusively in Jackson to ensure that race-specific estimates were possible. All participants gave written informed consent. Response rates were 46% in Jackson and between 65% and 67% in the other communities. A comparison of respondents to nonrespondents and an account of the design and procedures have been published.

Of 15,792 baseline participants, we excluded the following: ethnicity other than black or white (n = 48) and those with prevalent (n = 771) or unknown (n = 345) CHD status. Of the 14,628 eligible participants, we excluded those with missing sitting SBP data (n = 5) and those who had their examination before the inclusion of the postural change examination (N = 2190). Thus, 12,433 eligible participants remained.

**Study Variables** A certified ARIC sonographer measured supine and standing blood pressure with a Dnamap1846-SX automated oscillometric device. It has high within-subject reliability and is comparable to Doppler ultrasound measurement. Supine and standing blood pressure measurements were always taken on the same arm as seated measurements (right arm, unless there was a medical contraindication). Given that the device was automated, the number of measurements (as many as five) varied across participants. After 20 min of supine rest, measurements were taken for 2 min. Participants were then instructed to stand. To prevent cuff slippage and to assure a standard, comfortable position, participants were asked to bend their elbows and to support the hand of the cuffed arm with their other hand. When their feet touched the ground, standing measurements were taken for 2 min. Postural blood pressure change was calculated as the average of the supine minus the average of the standing blood pressure measurements. We excluded the first standing measurement because blood pressure restabilization occurs during the first 30 s after standing. Participants were classified using the consensus definition (OH = ≥ 20 mm Hg drop in SBP or ≥ 10 mm Hg drop in DBP).

Event classification criteria were previously described. Incident CHD events were identified through December 1994. Each year, potential CHD hospitalizations were ascertained by telephone interview and review of records. For CHD-related hospitalizations, symptoms and cardiac enzyme information was abstracted from discharge summaries. The Minnesota Code was used to code up to three electrocardiograms (ECG) per hospitalization. Waveforms were evaluated using a side-by-side comparison of paired tracings and measurement of specific differences. Out-of-hospital deaths were evaluated using death certificates, family interviews, physician questionnaires, and coroner reports. Serial ECG from follow-up visits were evaluated for evidence of silent MI (major or minor Q-wave with ischemic ST-T changes or NOVACODE criteria, with confirmation by side-by-side visual ECG comparisons). CHD events included definite or probable hospitalized MI, silent MI, and fatal CHD. Time-to-event was calculated as the interval between the baseline examination and event date, except for silent MI, where the midpoint between the two visits when the silent MI was detected was used.

Three sitting blood pressure measurements were taken using a standardized protocol and the last two were averaged. Hypertension was defined as an SBP ≥ 140 mm Hg or a DBP ≥ 90 mm Hg, or self-reported use of medications to treat high blood pressure during the previous 2 weeks. Participants who brought in their medications were classified based on use of classes of antihypertensive drugs: β-blockers, ACE-inhibitors, calcium channel blockers, diuretics,
Participants also were classified based on self-reported current use of chest pain and blood sugar control medications.

Diabetes was defined as nonfasting glucose > 11.1 mmol/L, fasting glucose ≥ 7 mmol/L, a self-reported history of diabetes, or current use of diabetes medications. Smoking was categorized as former, current, and never smoker. A series of questions about consumption of beer, wine, and liquor were used to estimate alcohol consumption (g/week). Height and weight were measured using standardized protocols and body mass index (BMI) calculated as kg/m². Education was classified as less than high school diploma, high school diploma, or at least some college. High-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) (mmol/L) were determined using standardized methods. Noninvasive measures of atherosclerosis included the ratio of ankle to brachial SBP (ABI) and a measure of lower extremity artery disease (LEAD), and carotid artery intima-media thickness (IMT). ABI values < 0.90 were classified as LEAD. IMT was determined using B-mode ultrasound procedures. The IMT of 1-cm segments of the near and far walls of six sites (distal common carotid artery, carotid bifurcation, and proximal centimeter of right and left internal carotid artery) were averaged to index atherosclerosis.

Analyses Analyses were conducted using SAS. Age-specific and age-adjusted (to mean age) OH prevalences were calculated overall, and for each ethnic-gender group. Risk factor levels and 95% confidence intervals (CI) were calculated by OH status, controlling for age, ethnicity, and gender. The association between postural blood pressure change and incident CHD was modeled using proportional hazards (PH) regression. The PH assumption was tested by comparing estimated −ln(−ln) survivor curves of those with and without OH; curves were roughly parallel. Crude and age-, gender-, and ethnicity-adjusted PH models were performed. Next, we controlled for conditions potentially associated with OH (SBP, antihypertensive medications, diabetes, IMT, ABI) and selected CVD risk factors (BMI, education, HDL, LDL, physical activity, alcohol, smoking). A final set of models substituted use of specific antihypertensive and other medications.

We evaluated whether the association between OH and CHD differed between those with and without comorbid conditions (eg, diabetes, hypertension, smoking status, peripheral vascular disease [low ABI], atherosclerosis [thick IMT]). Stratified analyses were done to compare HR between those with and without each comorbid condition; they did not differ substantially (data not shown). Next, a statistical assessment of effect modification was performed by including interaction terms of OH with covariates included in the final model using a Likelihood Ratio Test. The likelihood estimate from the model with interaction terms did not significantly differ from the model without interaction terms (P < .10). Thus, based on these results, only overall models are presented.

RESULTS Participants’ age averaged 54 years. Approximately 57% were women and 28% were black. Twenty-two percent had less than a high school education and 37% had education beyond high school. On follow-up averaging 6 years, 346 CHD events occurred (4.6 per 1000 person-years of follow-up).

Average blood pressures (SBP/DBP mm Hg) were as follows: supine: 125.1/72.5; standing: 124.8/75.5. Average postural SBP change was −0.35 (+10.7) mm Hg and average DBP change was 3.0 (+5.7) mm Hg.

Table 1 presents age-specific, crude and age-adjusted OH prevalence estimates. As age increased, OH prevalence increased.
blacks than whites; overall, this difference was significant (6.4% vs 4.4%, \( P < .0001 \)).

Table 2 presents the age-, gender-, and ethnicity-adjusted means (proportions) of CVD risk factors by OH status. Those with OH were, on average, more than 3 years older and more likely to have low educational attainment than were those without OH. Average BMI, alcohol consumption, and physical activity did not vary by OH status. Less favorable lipid profiles, a higher prevalence of smoking, and higher blood pressures were noted among those with OH.

Age-, gender-, and ethnicity-adjusted means (proportions) for conditions potentially associated with OH are presented in Table 3. Those with OH were almost twice as likely to be diabetic as were those without OH; diabetics with OH were more likely to report current use of drugs to control blood sugar than were those without OH. Those with OH were 1.5 times more likely to be hypertensive than were those without OH. Among hypertensives, neither use of antihypertensive medication nor use of specific classes of medications was associated with OH status. Among normotensives, use of calcium-channel and \( \beta \)-blockers was significantly more common among those with OH; use of ACE inhibitors was not evaluated due to the small numbers reported. Self-reported use of antianginal drugs did not vary by OH status. Those with OH were almost three times more likely to have LEAD; likewise, mean IMT was greater among those with OH.

Table 4 presents results of PH regression models of the OH-incident CHD association. In the unadjusted model, those with OH had an increased risk of developing CHD (hazard ratio [HR] = 3.49, 95% confidence interval [CI] = 2.58, 4.73). This association was attenuated after controlling for age, gender, and ethnicity (HR = 2.91, 95% CI = 2.14, 3.95) and further reduced after controlling for SBP, antihypertensive medication use, diabetes, ABI, and IMT (HR = 2.01, 95% CI = 1.44, 2.82). Adjustment for HDL, LDL, and smoking led to modest reductions (HR = 1.85, 95% CI = 1.31, 2.63). Education, alcohol, BMI, and physical activity were not retained in the final model, as they did not influence the HR.

A PH model substituting specific antihypertensive medications for any overall use of antihypertensive medications produced virtually equivalent results to adjusted model 3 (HR = 1.88, 95% CI = 1.32, 2.67). Adding current use of antianginal and blood sugar control drugs to the model did not influence this association (1.85, 95% CI = 1.30, 2.63).

**DISCUSSION**

Five percent of participants, who were middle-aged and free of CHD at baseline, had OH. As previously reported, \(^9,10,13,14\) prevalence increased with increasing age. This is probably partly attributable to the higher rates of conditions associated with autonomic dysfunction and peripheral neuropathies. However, aging per se also may be associated with autonomic function decline.\(^13\) Consistent with earlier reports,\(^10,16\) we found no gender differences in OH prevalence. OH was more common among blacks than whites. In older populations a higher prevalence of OH among whites\(^6\) and no significant variation by ethnicity\(^10\) have been reported. Blacks in our middle-aged population had markedly higher prevalences of comorbid conditions than whites. If such conditions are weaker...
predictors of OH in the elderly, it could explain the different associations across studies.

As previously reported, in our study those with OH had less favorable lipid levels. In contrast to earlier studies, those with OH were more likely to currently smoke, whereas BMI, alcohol intake, and physical activity did not vary by OH status. Associations of BMI with OH in previous studies are inconclusive, though associations of OH with alcohol and physical activity, although associated with OH in experimental studies, were not considered in the studies reviewed. Our findings of higher mean SBP and DBP among those with OH were consistent with most previous reports. Studies investigating associations of antihypertensive medications with OH have been inconsistent. In the current study, modest but not significant differences in the prevalence of OH were noted among hypertensives for the major classes of drugs used to treat hypertension, whereas among normotensives, calcium channel and β-blocker use was more common among those with OH. In community-dwelling populations, such as those represented in ARIC, most individuals are ad-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Orthostatic Hypotension Status (Mean% ± SE)</th>
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<tbody>
<tr>
<td></td>
<td>Yes, N = 614 (4.9%)</td>
</tr>
<tr>
<td></td>
<td>No, N = 11819 (95.1%)</td>
</tr>
<tr>
<td>P Value</td>
<td></td>
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<tr>
<td>Diabetes (%)</td>
<td>18.2 (15.3, 21.5)</td>
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<tr>
<td>Diabetics using blood sugar control drugs (%)</td>
<td>10.8 (10.2, 11.5)</td>
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<tr>
<td>Hypertension (%)</td>
<td>53.7 (49.2, 58.1)</td>
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<tr>
<td>Proportion of all hypertensives reporting use of medications to control high blood pressure (%)</td>
<td>75.0 (70.2, 79.2)</td>
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<tr>
<td>Proportion of all hypertensives using specific medications (%)</td>
<td>70.9 (69.4, 72.3)</td>
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<tr>
<td>ACE inhibitors</td>
<td>10.5 (7.7, 14.3)</td>
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<tr>
<td>β-blockers</td>
<td>26.5 (22.0, 31.5)</td>
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<tr>
<td>Calcium channel blockers</td>
<td>7.5 (5.2, 10.7)</td>
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<tr>
<td>Diuretics</td>
<td>44.3 (39.1, 49.6)</td>
</tr>
<tr>
<td>Other</td>
<td>22.1 (18.0, 26.9)</td>
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<tr>
<td>Proportion of normotensives† using selected medications (%)</td>
<td>1.6 (1.3, 1.9)</td>
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<tr>
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<td>4.9 (2.8, 8.5)</td>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Diuretics</td>
<td>3.0 (2.8, 8.8)</td>
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<tr>
<td>Antianginal drug use (%)</td>
<td>2.2 (1.4, 3.5)</td>
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<tr>
<td>Indices of atherosclerosis</td>
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<td>Ankle-branchial index (% ≤ 90)</td>
<td>2.7 (2.4, 3.0)</td>
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<tr>
<td>Intima-media thickness (mm)</td>
<td>0.80 (0.79, 0.81)</td>
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<tr>
<td>P Value</td>
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* All proportions and means have been adjusted to age, gender, and ethnicity. NS for variables vary due to missing data.
† Normotensives included those participants with systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg and those who did not report use of medications to treat high blood pressure during the previous 2 weeks. Thus, they were assumed to be using these medications to treat other conditions.
ACE = angiotensin-converting enzyme; BP = blood pressure.
adjusted to their medications; however, in patient populations, individuals may seek care because of acute medication-related side effects. In addition, drug-induced OH may occur primarily in elderly individuals using multiple medications.31

Those with OH were almost twice as likely to be diabetic as were those without OH. In the Hypertension Detection Follow-up Project, a similar excess occurrence was noted among those with systolic OH.9 However, differences in diabetes prevalence by OH status were not found among the elderly.7,10 OH was strongly associated with atherosclerosis in this study, which might be related to the reduction in elasticity in high-capacitance arteries with atherosclerosis. An earlier study of the elderly also noted thicker IMT but no variation in ABI by OH status12; use of different cutoff points in the earlier study may explain the difference.

Orthostatic hypotension was associated with a strong increased risk of incident CHD in ARIC. Almost half of this association was explained by controlling for comorbid conditions, indices of atherosclerosis, and CVD risk factors. However, a moderate significant increased risk of CHD persisted after controlling for these factors. With postural blood pressure change there is rapid displacement of blood volume to the lower body. Between 25% and 30% of thoracic blood volume may be displaced during orthostasis.2 Furthermore, both cerebral1,13 and myocardial16 ischemia may occur during OH. Thus, OH could plausibly trigger a CHD event via the acute physiologic changes that accompany it.

Atherosclerosis was not completely controlled for in our study, as measures were limited to two sites (midextracranial carotids [IMT] and arteries of one lower extremity [ABI]). Despite similarities, the extent of atherosclerosis in arteries at one site may not accurately reflect the condition of arteries at other sites32 or of the general arterial system.33 If atherosclerosis in large-capacitance arteries is more strongly associated with OH than atherosclerosis at the sites measured, it is possible that some of the residual effect was due to its incomplete control.

Orthostatic hypotension is clinically diagnosed when patients present with symptoms. However, data from an elderly population suggest that most individuals with OH are asymptomatic.10 In our study, dizziness upon standing did not vary significantly by OH status (11.3% for those with OH and 9.4% for those without OH). Thus, established guidelines would be important for effective clinical screening. In the current study, there was a rest period ≥ 20 min before the supine blood pressure measurement, a time sufficient to decrease temporary elevations caused by the stress of being in a clinical setting.34 Likewise, standing measurements were taken within 2 min of standing, which is within the guidelines suggested by the consensus definition.15 The use of the automated Dinamap device reduces concern about measurement error. However, although it allowed for multiple supine and standing blood pressure measurements, the number of measurements (maximum of five) varied across subjects. This is of particular concern for standing measurements, as blood pressure fluctuations occur immediately upon standing.2,35 By eliminating the first standing measurement from our calculation, we hopefully limited measurements to those occurring after the transition period.

Postural blood pressure change data were not available for 2190 individuals who underwent their physical examination before the inclusion of the ultrasound segment. This probably did not lead to systematic bias, as examination dates were randomly assigned. Also, in earlier, related work, major differences in CVD risk factors by inclusion status were not noted.36

The ARIC study was designed to be representative of the communities from which the samples were drawn. However, those who participate in studies may have more favorable health and socioeconomic profiles than do the populations from which they are sampled. This is of particular concern for blacks, who had the lowest participation rates. Thus, caution should be taken when extrapolating these findings to the general population.

To our knowledge, this is the first study to report on the prevalence and CVD-related correlates of OH and on the association between OH and incident CHD in a healthy, biracial, middle-aged cohort. Given that the study was large, there was adequate power to simultaneously control for risk factors that potentially explained the association of OH with CHD. Although OH was more common among those with comorbid conditions and preclinical atherosclerosis, the association of OH with CHD did not vary substantially between those with and without any of the comorbid conditions considered (eg, diabetes, hypertension). Furthermore, when adjusted model 3 (Table 4) was repeated including only the 4973 participants who at baseline had no existing comorbid conditions (hypertension, diabetes, low ABI [ABI < 0.90], thick IMT [IMT > 1.0], current smoking), results were of a similar magnitude (HR = 1.71, 95% CI = 0.42, 7.2) to those obtained in the full sample (HR = 1.85, 95% CI = 1.3, 2.6). The confidence interval in the healthy subsample included 1.0; however, this probably reflects the small number of CHD events that occurred in this subgroup.

In summary, OH occurred in 5% of the ARIC cohort. It was more common among individuals with elevated CVD risk factors and among those with diabetes and atherosclerosis. Persons with OH had an increased risk of incident CHD that was not limited to those with or completely explained by CVD risk factors. Inclusion of an assessment for OH in future stud-
ies could improve our understanding of the mechanisms by which OH may influence CHD risk.

ACKNOWLEDGMENTS

We thank ARIC staff at the University of North Carolina at Chapel Hill, University of Mississippi Medical Center, Johns Hopkins University, University of Minnesota, University of Texas Medical School, and the Wake Forest University Baptist Medical Center.

REFERENCES


