Pulse Pressures and Subclinical Cardiovascular Disease in the Multi-Ethnic Study of Atherosclerosis

Ginger J. Winston, Walter Palmas, Joao Lima, Joseph F. Polak, Alain G. Bértoli, Gregory Burke, John Eng, Rebecca Gottesman, and Steven Shea

**BACKGROUND**

Brachial pulse pressure (PP) has been found to be associated with markers of subclinical cardiovascular disease, including carotid intima-media thickness and left-ventricular mass index (LVMI), but it is unclear whether these associations are independent of traditional cardiovascular risk factors and of the steady, nonpulsatile component of blood pressure (BP). Moreover, it is unknown whether these associations are modified by gender, age, or race/ethnicity.

**METHODS**

We used multivariate linear regression models to assess the relationship between brachial PP and three markers of subclinical cardiovascular disease (CVD) (common carotid intima–media thickness (CC-IMT), internal carotid intima–media thickness (IC-IMT), and LVMI) in four race/ethnic groups in the Multi-Ethnic Study of Atherosclerosis. The models were adjusted for traditional Framingham risk factors (age, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, diabetes, smoking status), use of lipid-lowering medication, use of antihypertensive medication, study site, and mean arterial pressure (MAP).

**RESULTS**

The assessment was done on 6,776 participants (2,612 non-Hispanic white, 1,870 African-American, 1,494 Hispanic, and 800 Chinese persons). The associations between brachial PP and CC-IMT, IC-IMT, and LVMI were significant in fully adjusted models. The three subclinical markers also showed significant interactions with gender ($P < 0.0001$), with stronger interactions in men. There was an interaction with age for LVMI ($P = 0.004$) and IC-IMT ($P = 0.008$). Race/ethnicity modified the association of PP with CC-IMT.

**CONCLUSIONS**

Brachial PP was independently associated with subclinical CVD after adjustment for cardiovascular risk factors and mean arterial pressure (MAP). The strength of the association differed significantly for strata of gender, age, and race/ethnicity.

Keywords: pulse pressure; subclinical cardiovascular disease; carotid intima–media thickness; left ventricular mass index; aging; hypertension; arterial stiffness; blood pressure.

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Pulse pressure (PP), which is the difference between the systolic and diastolic blood pressures (BPs), represents the pulsatile component of blood flow. It denotes arterial compliance and the reflective properties of blood flow related to vessel branching. Pulse pressure increases concomitantly with aging and loss of arterial elasticity. It has therefore been of interest as a predictor of clinical events related to cardiovascular disease (CVD) and as a correlate of markers of subclinical CVD. However, values of PP have been shown to vary significantly according to population demographics. Pulse pressure increases with age and women tend to have higher levels of PP than do men, a difference noticeable after midlife. Furthermore, a recent examination of risk factors for CVD among Hispanic, African-American, Chinese, and non-Hispanic white participants with diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA) revealed racial and ethnic differences in PP. Therefore, it is of interest to examine whether the association of PP with subclinical CVD varies according to age, gender, and race/ethnicity. The MESA study allows a unique opportunity to address this question in a population-based cohort that underwent a comprehensive baseline evaluation, including testing for traditional and non-traditional risk factors.
novel risk factors for CVD as well as ultrasonographic measurements of carotid intima–media thickness and the evaluation of left-ventricular (LV) mass with cardiac magnetic resonance imaging (MRI).

Available data consistently suggest that central aortic BP has a stronger association with CVD than does peripheral BP. For example, the Conduit Artery Function Evaluation (CAFE), a substudy within the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), showed that despite having a similar effect on brachial PP, treatment with amlodipine with or without perindopril resulted in better central aortic pressures and cardiovascular outcomes than did treatment with atenolol with or without a thiazide diuretic. However, measurements of brachial arterial BP remain the cornerstone of the clinical evaluation and management of hypertension. Therefore, we examined the relationships of brachial PP with common carotid intima-media thickness (CC-IMT), internal carotid intima-media thickness (IC-IMT), and left-ventricular mass index (LVMI) after adjustment for cardiovascular risk factors and mean arterial pressure (MAP), a measure of the nonpulsatile component of BP, in both men and women, across age groups, and in four racial/ethnic groups (non-Hispanic white, Chinese, African-American, and Hispanic) in MESA. Common carotid intima–media thickness and IC-IMT were examined separately because they may provide different prognostic information; CC-IMT has been shown to be a better predictor of stroke, whereas IC-IMT appears to be a better predictor of myocardial infarction (MI).

METHODS

The Multi-Ethnic Study of Atherosclerosis is a multicenter cohort study of subclinical cardiovascular disease (CVD) and its progression in 6,814 men and women ranging in age from 45–84 years who were without clinical evidence of CVD at the time of enrollment in the study. The baseline examination for MESA was conducted from July 15, 2000 through August 15, 2002. Subjects were recruited from six communities in the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, in New York City, NY; and St. Paul, MN). Participants were self-identified as non-Hispanic white (38%), African-American (28%), Hispanic (22%), or Asian of primarily Chinese descent (12%). The design and recruitment methods for MESA have been reported in detail elsewhere. The study was approved by the institutional review boards of all participating institutions, and all MESA participants provided informed consent.

Methods of Data Collection

All data were from the first MESA examination period, of July 15, 2000 through August 15, 2002. Demographic data including race/ethnicity were obtained through structured questionnaires. Data about medication use during the 2 weeks before each examination visit was obtained by interview. Medications were classified as antihypertensive, lipid-lowering, or glucose-control agents. Smoking status (classified as never-, current, or former smoker) was determined through questionnaire responses. Blood samples were collected according to a standardized procedure after an overnight fast. The BP of participants in the resting, seated position was measured three times in the right arm with a Dinamap model Pro 100 automated sphygmomanometer (GE Healthcare, Port Washington, NY) according to a standardized protocol. The average of the second and third measures was used in the analyses of the study data. Cardiac MRI was performed with 1.5-T magnet scanners with determination of LV mass and volume as previously described. Cine images for LV mass were read centrally at the Department of Radiology of the Johns Hopkins University School of Medicine and were estimated in grams. High-resolution B-mode ultrasound images of the right and left near and far walls of the common carotid and internal carotid arteries were obtained with a Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, Wisconsin). Carotid ultrasound images were read at the Department of Radiology of the Tufts Medical Center, Boston, Massachusetts. Maximal intima–media thickness of the internal and common carotid arteries sites were recorded as the mean of the maximum intima–media thickness of the near and far walls of the right and left sides of the respective vessels. Measurements were made of the thickness of the near and far walls of the right and left internal and common carotid arteries. The larger values for both the right and left sides were then used to calculate the mean IMT for that site (either internal or common carotid arteries).

Definition of Variables

Low-density lipoprotein (LDL)-cholesterol was calculated with the Friedewald formula. Values of LDL cholesterol were excluded from data analysis if the serum triglyceride concentration was >400 mg/dl. Diabetes was defined as the self-reported use of insulin or of an oral hypoglycemic agent or both, or a fasting blood glucose of ≥126 mg/dl. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg, or as self-reported hypertension and the use of antihypertensive medication. Pulse pressure was defined as the difference between SBP and DBP. Mean arterial pressure was defined as DBP + (SBP – DBP)/3. Left-ventricular mass was indexed by body surface area (BSA) as

\[
\text{LV mass indexed by BSA (m^3)} = 0.20247 \times \text{height (m)^{0.725}} \times \text{weight (kg)^{0.425}}
\]

and in this paper, the abbreviation LVMI refers to LV mass indexed by BSA. Because LVMI does not completely remove the correlation of LV mass with weight and height, we also examined the association of PP with predicted LV mass, estimated as

\[
\text{Predicted LV mass} = 100 \times \text{LV mass}/(A \times \text{height}^{0.561} \times \text{weight}^{0.669})
\]

where A = 6.82 for women and 8.17 for men, with mass in grams, height in meters, and weight in kilograms. Using predicted LV mass as the outcome provided results similar to those we report for LVMI. Pressure pulsatility was defined as brachial PP divided by MAP.

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Statistical Analysis

Clinical characteristics of the sample were first compared for male and female gender and among quartiles of PP (< 40 mm Hg, 40 < PP ≤ 50 mm Hg, 50 < PP ≤ 60 mm Hg, and > 60 mm Hg), with the use of analysis of variance (ANOVA), t-tests, and chi-squared tests as appropriate. Multivariate linear regression models were then used to assess the relationship between PP and measures of subclinical CVD (LVMI, CC-IMT, and IC-IMT), through the PROC GENMOD procedure in SAS (SAS Institute, Cary, NC). These models were adjusted for age, gender, race/ethnicity, MESA site, LDL-cholesterol, HDL-cholesterol, use of lipid-lowering medication, diabetes mellitus, smoking status, use of antihypertensive medication, and MAP. We examined the collinearity of SBP and PP as covariates in models with LVMI, CC-IMT, or IC-IMT as the dependent variable. The examination of collinearity revealed that SBP and PP were highly collinear (variance proportion > 0.5 for the largest condition index).22 Therefore, we did not include SBP as a covariate in our models. Instead, we adjusted for MAP, an approach previously used by other investigators.6,7 Effect modifications by age, gender, and race/ethnicity were tested by using multiplicative interaction terms in fully adjusted models. In the models in which interactions were assessed, age, in 10-year intervals, was entered as a categorical variable. These models included indicator variables for the eight gender/race groups in the study and were adjusted for all of the covariates named above. Multivariate linear regression models were also used in post-hoc analyses to assess the relationship between pressure pulsatility (brachial PP/MAP) and the three markers of subclinical CVD included in the study, with adjustment for the same covariates as in the prespecified analyses for PP. All analyses were done with SAS version 9.2.

RESULTS

Among the 6,814 participants in MESA, 6,776 were included in the analysis. We excluded participants for whom measures of all three outcome variables (CC-IMT, IC-IMT and LVMI) were missing at the baseline examination. Measurements of LV mass were available for 5,004 participants, CC-IMT measurements for 6,726, and IC-IMT measurements for 6,629. Table 1 presents the demographic and clinical characteristics of the sample. Women were more likely than men to have hypertension (P = 0.003), whereas men were more likely to have diabetes (P = 0.002). Mean LVMI was higher among men (P < 0.0001), as were also mean CC-IMT and IC-IMT (P < 0.0001). Table 2 shows clinical characteristics classified by quartiles of PP. A higher percentage of women than of men had a PP > 50 mm Hg. Pulse pressure increased with age. Mean LVMI, CC-IMT, and IC-IMT were greater at higher quartiles of PP (P < 0.0001). Table 3 shows the differences in CC-IMT, IC-IMT, and LVMI per 10 mm Hg increment in PP after adjustment for covariates. Statistically significant interactions of PP by gender were found in fully adjusted models for all three subclinical markers (CC-IMT, P = 0.002; IC-IMT, P = 0.002; LVMI, P = 0.004), with men showing stronger interactions. The results in Table 3 are therefore shown separately for men and women.

There was also an effect modification by age category (< 50 years, 50–59 years, > 59 years) in the fully adjusted model that was used to examine the relationship between LVMI and PP (P = 0.004), with LVMI showing a stronger association with PP in the younger age groups in the study. This effect modification by age differed further by gender (P = 0.01 for the three-way interaction among age, gender, and PP). The association of PP with LVMI was stronger in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n = 3,579)</th>
<th>Men (n = 3,197)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>62.1 (10.3)</td>
<td>62.2 (10.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (SD)</td>
<td>127 (23)</td>
<td>126 (19)</td>
<td>0.055</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (SD)</td>
<td>69 (10)</td>
<td>75 (9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1,662 (46)</td>
<td>1,370 (43)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg (SD)</td>
<td>88 (13)</td>
<td>92 (12)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Brachial pulse pressure, mmHg (SD)</td>
<td>58 (18)</td>
<td>51 (15)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>406 (11)</td>
<td>447 (14)</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL-cholesterol mg/dl (SD)</td>
<td>117.7 (31.9)</td>
<td>116.7 (31.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL-cholesterol mg/dl (SD)</td>
<td>56.2 (15.3)</td>
<td>45.0 (11.8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean LVMI, body surface area in g/m² (SD)</td>
<td>70.8 (12.6)</td>
<td>85.8 (16.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean CC-IMT, mm (SD)</td>
<td>0.849 (0.003)</td>
<td>0.894 (0.20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean IC-IMT, mm (SD)</td>
<td>1.013 (0.58)</td>
<td>1.140 (0.63)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Hypertensive is defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, a self-report of hypertension, or the use of antihypertensive medication.

Abbreviations: CC-IMT, common carotid intima–media thickness; HDL, high-density lipoprotein; IC-IMT, internal carotid intima–media thickness; LDL, low-density lipoprotein; LVMI, left-ventricular mass index.
women than in men in the younger age category (with age > 59 years as the referent group, the association of LVMI with PP in participants < 50 years was 4.0 gm vs. 2.0 gm per 10 mm Hg PP for women vs. men, whereas in participants of age 50–59 years it was 3.3 gm vs. 2.1 gm per 10 mm Hg pulse pressure for women vs. men, respectively (Supplementary Figures S1 and S2).

There was also an interaction-by-age category for the relationship between CC-IMT and PP ($P = 0.059$). Pulse pressure was more strongly associated with CC-IMT in
older subjects (with age < 50 years as the referent group, CC-IMT for subjects aged 50–59 years was 0.05 mm greater per 10 mm Hg of PP, whereas for those aged > 59 years it was 0.14 mm greater per 10 mm Hg of PP (Supplementary Figure S3). Similarly, there was an effect modification by age category in the relationship between PP and IC-IMT ($P = 0.008$), with PP more strongly associated with IC-IMT in older subjects (with age group < 50 years as the referent group, IC-IMT was 0.10 mm greater per 10 mm Hg increase in PP for subjects aged 50–59 years, whereas for subjects aged > 59 years IC-IMT was 0.57 mm greater per 10 mm Hg of PP (Supplementary Figure S4). Contrary to the findings noted above for LVMi, there was no evidence of a three-way interaction with age and gender for the relationship between PP and CC-IMT or PP and IC-IMT.

In fully adjusted nonstratified models, there was a significant interaction by race for the relationship of PP with CC-IMT ($P = 0.0001$), but this was not so for IC-IMT or LVMi. Table 4 shows the difference in CC-IMT per 10 mm Hg of PP in the four racial/ethnic groups in the study, with highly significant associations in all four groups after adjustment for covariates. There was a weaker association between CC-IMT and PP for Hispanics than for the other racial/ethnic groups in the study. In post-hoc analyses, the relationships between pressure pulsatility and the three subclinical cardiovascular markers were examined in fully adjusted multivariate regression models. The findings were similar to those described above for PP (Supplementary Table S1). There was an interaction between pressure pulsatility and gender in the fully adjusted models for CC-IMT, IC-IMT, and LVMi ($P = 0.002, 0.004,$ and 0.006, respectively). There was also an interaction by race/ethnicity in the relationship between pressure pulsatility and CC-IMT ($P = 0.0007$), and an interaction by age in the relationship between pressure pulsatility and both IC-IMT ($P = 0.0002$) and LVMi ($P = 0.04$).

**DISCUSSION**

We found an independent relationship between brachial PP and markers of subclinical CVD (CC-IMT, IC-IMT, and LVMI) after adjustment for traditional risk factors for CVD and MAP. Gender, age, and race/ethnicity were significant modifiers of these relationships, with stronger associations between PP and the three markers of subclinical CVD among men than among women.

In general, our findings confirm and extend previous reports of an association between PP and subclinical CVD. Greater PP was associated with a greater increase in CC-IMT over 4 years in middle-aged men from eastern Finland, after controlling for age, lipid treatment, serum HDL and smoking. Viazzi et al., in a study of 333 untreated subjects with primary hypertension enrolled in an outpatient clinical setting, found that PP was an independent predictor of LVMI and carotid intima–media thickness after adjustment for age, gender, body mass index (BMI), and the albumin-to-creatinine ratio. A recent study found that increased arterial stiffness, measured as PP/stroke volume indexed to height, was associated with increased carotid plaque burden after adjustment for traditional cardiac risk factors. Our study expands on these studies by examining a diverse racial/ethnic cohort with and without hypertension, and analyzing both IC-IMT and CC-IMT as markers of subclinical CVD. We were able to confirm the independent association of PP with CC-IMT, IC-IMT, and LVMI after comprehensive adjustment for an extensive set of covariates, and across gender, age, and racial/ethnic groups. Our analyses showed effect modification by gender, with a stronger association among men than among women between the three markers of subclinical CVD used in our study and PP. This is a novel finding. Previous studies that examined the association between PP and these subclinical markers did not discuss the possibility of a gender interaction. Whether this effect modification may also apply to the relationship between PP and major cardiovascular events remains unclear. Interestingly, a study by Regnault et al. showed that a decrease in PP amplification (estimated as the ratio of brachial PP to carotid PP) had a stronger association with all-cause and cardiovascular mortality in women than in men. However, our analyses were limited to brachial PP, and we therefore cannot draw comparisons with their results. The Cardiovascular Study in the Elderly (CASTEL) showed that PP was independently predictive of CV mortality in elderly women but not in men; however, a limitation of the study was that no BP variable was independently predictive of mortality in men. This may have been because men with increased risk of CVD because of higher BP had died at an earlier age and therefore were not enrolled.

We also report effect modification by age, which to the best of our knowledge has not previously been reported. It

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**Table 4. Difference in common carotid intima–media thickness per 10 mm Hg increase in pulse pressure in four racial/ethnic groups, adjusted for covariates**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta coefficient</th>
<th>95% CI</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white (n = 2,612)</td>
<td>0.026</td>
<td>0.020, 0.032</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Chinese (n = 800)</td>
<td>0.033</td>
<td>0.023, 0.043</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>African-American (n = 1,870)</td>
<td>0.025</td>
<td>0.019, 0.032</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hispanic (n = 1,494)</td>
<td>0.016</td>
<td>0.008, 0.02</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Covariates are age, gender, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, diabetes mellitus, lipid lowering medication, anti-hypertensive medication, smoking status, mean arterial pressure, and study site in the Multi-Ethnic Study of Atherosclerosis.
is known that the stiffness of larger arteries increases with age and that this contributes to higher mean PP values in the elderly. Moreover, PP is a stronger predictor of coronary heart disease in persons older than 59 years of age than is either SBP or DBP. In our study, the association of PP with measurements of intima–media thickness (IMT) was stronger in older than in younger subjects. This may reflect the coexistence of cumulative atherosclerosis with greater arterial stiffness because of vessel aging. Of note is that this directionality for the effect modification by age of the relationship of IMT with PP was the opposite of that for LVMI with PP, with a stronger association in younger than in older age groups. This could be related to cardiac remodeling with age, because LV mass tends to decrease in the elderly.

The interaction by race/ethnicity was limited to the relationship between PP and CC-IMT. Race has been shown to be an independent predictor of CC-IMT in young adults. African-Americans have been shown to have a greater CC-IMT than that of whites, with no difference in IC-IMT in the two racial groups. Published data indicate that Hispanics have a smaller CC-IMT than do non-Hispanic whites, without any significant difference in the two groups' IC-IMT. Our data do suggest a weaker association between CC-IMT and PP for Hispanics than for other racial/ethnic groups, particularly when compared with Chinese participants. We are not aware of any data suggesting a biologically plausible explanation for this observation.

Limitations of our analysis include its cross-sectional design, self-reported use of medication, and absence of information about patient adherence to medication regimens. Our study is also limited to measurements of brachial artery BP; whereas central PP has been shown to more accurately reflect vascular load on the left ventricle and on the cerebral and coronary vasculature than does brachial PP. Furthermore, as previously discussed, the CAFE study showed that an antihypertensive treatment that reduces cardiovascular risk may be associated with changes in central aortic PP without any appreciable difference in brachial PP. Thus, measurements of central BP appear to hold great promise in the assessment and management of hypertension. However, brachial PP remains relevant because it is most readily measured in the standard clinical setting. Another limitation of our study is that we were unable to account for the use of specific antihypertensive medications, even though systolic and diastolic pressures can be affected differentially by different antihypertensive medications. Additionally, our study was limited in that the collinearity of SBP and PP precluded the simultaneous inclusion of both of these measures of BP in the same multivariate models. Lastly, observational cross-sectional studies do not support conclusions about the causality or directionality of effects. This limitation applies to interpretation of the associations reported in our study. Strengths of our analysis include the large study size and data on four major race/ethnic groups.

In conclusion, we found an independent association of PP with CC-IMT, IC-IMT, and LVMI, respectively, after comprehensive adjustment for cardiovascular risk factors and MAP. Our findings also confirm the importance of PP as a predictor of subclinical cardiovascular risk among patients of different gender, age, and racial/ethnic group. The associations with PP were stronger in men, and varied by age group and, to a lesser extent, by race/ethnicity. It is not known whether the strength of the association between PP and major cardiovascular events also varies across categories of age, gender, and race/ethnicity, and this warrants further examination.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

Winston et al.


