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Sex-Specific Association of Age with Carotid Artery Distensibility: Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: Older women have a higher prevalence of systolic hypertension than do men; however, whether or not this relates to arterial properties, such as distensibility coefficient (DC), is not known. We examined whether the association of carotid artery DC with age differed by sex in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: B-mode ultrasound-measured carotid diameters and brachial pressures were obtained from 6359 participants (53% female, 38% white, 12% Chinese, 27% black, 22% Hispanic, aged 45–85 years) of the MESA baseline examination. The within-individual slopes of 2log(diameter) vs. blood pressure fit using mixed models (MM) are interpreted as the DC, and interaction terms are interpreted as differences in DC. The MM calculation allows for correction of the confounding caused by the association of age, sex, and race with blood pressure, the denominator in the calculation of DC.

Results: DC was associated with age, sex, and race (all $p < 0.001$). Women had a greater age-related lowering of DC compared to men (2.52×10^{-5} vs. 2.16×10^{-5}/mm Hg lower DC per year of age, $p = 0.006$). Mean diameter of carotid arteries was greater with age ($p < 0.001$); this association also was significantly stronger in women compared to men (0.24% vs. 0.14% larger mean carotid diameter per year of age, $p < 0.001$).

Conclusions: Greater stiffening and enlargement of arteries are seen in older women compared to older men. This implies that the afterload on the heart of older women is likely to be greater than that among older men.

Introduction

The stiffening of arteries throughout life is thought to underlie the pathogenesis of such diseases as hypertension[1] and heart failure[2] that are associated with aging. Older women have a greater prevalence of hypertension than do older men.[3] It is not known, however, if this difference of aging by sex is because of sex differences in the stiffness of arteries at different ages.

The material properties of arteries (related to stiffness and compliance) may be measured invasively,[4] but this is not possible in large studies where sex by age interaction can be assessed. Therefore, direct noninvasive imaging of arteries is often used. The systolic and diastolic diameters of the carotid artery obtained by ultrasound and the simultaneous measure of systolic and diastolic brachial artery pressure[5] allow the investigator to determine the distensibility coefficient (DC) in the linear approximation. If epidemiologic associations of these material properties with other variables are sought, however, variables that are associated with only one or the other of the component variables (i.e., systolic or diastolic diameters, systolic or diastolic pressures) may erroneously appear to be associated with the material properties of the arteries.[6] Because the diameters and pressures are a part of a nonlinear calculation of DC, usual linear regression methods to adjust for confounding is not appropriate. A recent publication shows association of incident coronary disease and stroke with carotid artery stiffness measures, and this association is either fully or greatly attenuated by linear adjustment by blood pressure (BP) measures, likely due to overadjustment.[7]

We have analyzed Multi-Ethnic Study of Atherosclerosis (MESA) data using mixed model (MM) statistical methods that appropriately correct for such confounding to test for

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differences in the material properties of arteries between groups using these methods. Our aim is to determine if there is a difference in the relationship of age with the distensibility of arteries by sex, adjusting for BP levels in the population-based MESA.

Materials and Methods

Study population

We used baseline data from the MESA. The design of MESA, a study of the prevalence and progression of subclinical atherosclerosis, has been described previously.[8] Briefly, 6814 individuals, all free of clinical cardiovascular disease (CVD) at baseline, aged 45–85 years, of four ethnicities (Caucasian, Chinese, Hispanic, and African American), were enrolled at six U.S. sites. Of these, 6359 participants had carotid ultrasound data adequate for the calculation of carotid artery distensibility and compliance.

B-mode ultrasound and brachial BP measurements

Detailed methods have been published previously.[9] A 20-second B-mode ultrasound recording including a longitudinal section of the distal right common carotid artery was acquired using a Logiq 700 machine (General Electric Medical Systems). Single measures of brachial systolic and diastolic BPs were obtained simultaneously (DINAMAPP System, GE Medical systems). This single measurement corresponded well with a three-measure average of seated BP (Pearson correlation coefficients: systolic 0.78, diastolic 0.74, pulse pressure 0.78). Ultrasound images were analyzed and interpreted by the MESA ultrasound reading center, located at Tufts Medical Center, Boston, MA, which used edge-detection software to extract the carotid artery diameters in the images. Systolic and diastolic diameters were determined as the largest and smallest diameters during the cardiac cycle. For the DC (calculated using the linear approximation in Supplementary Table S1 available online at www.liebertonline.com), the repeat-study class correlation coefficient was 0.71, and the repeat-reading class correlation was 0.68.[9]

Statistical methods

The traditional method of calculating DC is as follows:

$$\frac{2}{\overline{D}} \times \frac{\Delta D}{\Delta P}$$

where D represents the diameter of the artery, P represents the BP within the artery, Δ represents the difference between systolic and diastolic measurements, and $\overline{D}$ represents the appropriate mean value of the diameter. In practice, $\overline{D}$ may be approximated to the systolic or diastolic diameter.[5]

We used MM regression where diameters and BP were modeled; thus, DC and differences in DC were estimated within the model, appropriately adjusted for confounders. This allows for disentangled estimation of the associations of independent variables with diameter alone and with distensibility. This contrasts with calculation of DC outside the statistical model, when the association and confounding of diameter and distensibility are entangled.

Differences in DC were estimated in the multivariate model, which allowed for adjustment for the confounding of BP by covariates. For a single binary covariate (e.g., F = 0 if male, 1 if female), the model would be specified as:

$$[2\times\log(D)]_{ij} = \beta_0 + \beta_1\overline{P}_j + \beta_2(\overline{P}_j - P_{ij}) + \beta_3 F\times\overline{P}_j + \beta_4 F\times(\overline{P}_j - P_{ij}) + \gamma_j + \eta(\overline{P}_j - P_{ij}) + \varepsilon_{ij}$$

for the ith condition (diastole or systole) of the jth individual. Random effects are estimated for the average log-diameters (log-diameter at the average of the systolic and diastolic pressure for each individual) and the slope of the log-diameter to pressure slope for every individual, which is determined using diastolic and systolic pressure (γ and η, respectively). The coefficients β_3 and β_4 can be interpreted as the fixed-effect association of the binary covariate with the mean diameter and the fixed-effect difference in slopes (i.e., the material properties of the artery) associated with the covariate. This specification can be generalized to any categorical or linear continuous covariate.

A detailed explanation of the MM regression is provided as Supplementary material (available online at www.liebertonline.com). Models with age (centered at 65 years), sex, race, and height were evaluated. First-order (two-way) interactions between age, sex, and race were also evaluated. Only significant interactions ($p < 0.05$) were retained.

The MM-estimated DC for every individual from best linear unbiased predicted (BLUP) values was compared with the traditionally calculated DC. The mean of the MM DC was numerically close to the mean of traditionally calculated DC (0.0025 vs. 0.0025), although the standard deviation (SD) was smaller (0.0006 vs. 0.0011), showing a shrinkage of variation due to the MM estimation. The Spearman correlation of the traditionally calculated DC with model-fitted DC was 0.81. In sensitivity analysis, the final regression models were further adjusted for education (as a proxy for socioeconomic status [SES]) and the use of BP medications to check for possible confounding. Another model excluding individuals using BP medications was also evaluated.

Results

Population characteristics

The MESA population has been described previously.[10] The demographic and clinical profile of the participants included in this analysis are shown in Table 1.

Age, sex, and race associations of the distensibility coefficient

The MM simultaneously assesses the association of covariables with mean arterial diameter and the D.C. Age, sex, race, and the age-sex interaction had significant associations in the regression analysis (Table 2). In addition, the arterial diameter at the average of systolic and diastolic pressures is larger in older persons, but this association is significantly greater in women than men. Ethnic differences in diameter are also seen, with Chinese having the smallest diameter and Hispanics having the largest diameter. Supplementary Table S2 (available online at www.liebertonline.com) shows that adjusting for the traditional risk factors, smoking, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels, and current diabetes, does not change the levels of significance for any of these results. Supplementary Table S3

Table 1. Demographic and Cardiovascular Risk Characteristics of Sample, by Race/Ethnicity

	Caucasian American	*Chinese American*	*African American*	*Hispanic American*
n	2435	773	1732	1419
Age (years)	62.6 ± 10.3	62.4 ± 10.4	62.3 ± 10.1	61.3 ± 10.3
Males	1176 (48%)	377 (49%)	773 (45%)	693 (49%)
Height (cm)	169.0 ± 9.7	161.6 ± 8.6	168.3 ± 9.7	161.9 ± 10.3
SBP (mm Hg)	123.4 ± 20.5	124.4 ± 21.6	131.8 ± 21.7	126.6 ± 21.8
DBP (mm Hg)	70.2 ± 10.0	71.9 ± 9.4	74.6 ± 10.2	71.6 ± 10.1
Antihypertensive use	632 (26%)	214 (28%)	819 (47%)	415 (29%)
Type 2 DM	144 (6%)	104 (13%)	302 (18%)	243 (17%)
Current smokers	285 (12%)	44 (6%)	306 (18%)	190 (13%)
TC (mg/dL)	195.5 ± 35.2	192.4 ± 34.7	189.5 ± 36.4	197.8 ± 37.3
HDL-C (mg/dL)	52.1 ± 15.5	49.7 ± 12.9	52.5 ± 15.3	47.6 ± 13.1

Mean ± standard deviation (SD) or number (%).

DBP, diastolic blood pressure; DM, diabetes mellitus, using American Diabetes Association 2003 criteria; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, serum total cholesterol.

(available online at www.liebertonline.com) shows various models assessing the association of carotid diameters and pressures with age, sex, and race. These traditional linear models with DC as the dependent variable include BP as a covariate, which results in overadjustment.

The age-sex interaction found in the mixed model is graphically illustrated in Figure 1, where model-calculated DCs, adjusted for race distribution and mean height (166 cm) are plotted against age among women and men. In both men and women, the DCs are lower with greater age. Although the DCs in men and women have similar values in the age range 45–60 years (confidence intervals [CI] overlap), at older ages, the DCs in women are lower than those in men. Because numerical measures of DC are not intuitive, Figure 1 illustrates the sex interaction in age equivalents. A difference of 10 chronologic years results in a reduced distensibility equivalent of 11.6 years in women compared to 10 years in men.

In sensitivity analyses, there was no difference in significant associations in the MM after addition of education and use of BP medications to the model. When analyses were restricted to 4279 individuals who were not using BP medications, all associations remained significant except for one: the difference between DC of men compared to women at age 65 was no longer significant (beta $= 3.59 \times 10^{-5}$, $p = 0.16$); however, the magnitude of the point estimate was similar to that tabulated for the main analysis. The association of traditionally calculated DC with age, sex, race, and the age-sex interaction is contrasted with the MM results in the supplementary material (available online at www.liebertonline.com).

Discussion

We have shown significant sex-age interaction in association with both DC and mean carotid artery diameter in a large well-characterized multi-ethnic population-based study. Our findings are consistent with those of Redfield et al.,[11] who found that vascular and systolic and diastolic ventricular elastance was more steeply associated with age in women than men in Olmsted County, Minnesota.

Using appropriate MM statistical methods, we were able to show associations of DC with covariates with two distinct advantages over using traditional calculations of DC: (1) the associations in our models were adjusted for BP levels, which

Table 2. Association of Age, Sex, and Race with Carotid Artery Distensibility Coefficient and Diameter

Covariate	*Difference in DC (2*slope) mm Hg^{-1}*	*% Larger carotid diameter (intercept)*
	Beta coefficients (95% CI)	
Sex (male vs. female) at 65 years of age	$8.24\ (0.62\text{-}15.8) \times 10^{-5}$	4.83 (3.99-5.69)%
Age (difference per year among females)	$-5.04\ (-5.38\text{-}-4.70) \times 10^{-5}$	0.24 (0.20-0.28)%
Difference in age-associated slope between men and women	$7.14\ (2.10\text{-}12.2) \times 10^{-6}$	−0.10 (−0.15-−0.04)%
Height (difference per cm of height)	$3.08\ (-0.98\text{-}7.14) \times 10^{-6}$	0.19 (0.15-0.24)%
White	Reference	Reference
Chinese vs. White	$-1.88\ (-2.81\text{-}-0.96) \times 10^{-4}$	−3.77 (−2.78-−4.75)%
African American vs. White	$-3.06\ (-3.70\text{-}-2.42) \times 10^{-4}$	−0.09 (−0.81-0.62)%
Hispanic vs. White	$-2.81\ (-3.55\text{-}-2.07) \times 10^{-4}$	1.15 (0.33-1.97)%
Overall test for race/ethnicity	$p = 7.6 \times 10^{-23}$	$p = 1.1 \times 10^{-13}$

Intercept: mixed model intercept coefficient corresponding to group difference between geometric means in percent; slope: mixed model slope coefficient corresponding to distensibility coefficient difference by group; 2*slope = difference in distensibility coefficient; to allow for judging of magnitude of coefficients, the standard deviation (SD) of distensibility coefficient $= 1.1 \times 10^{-3}$; for example, the beta coefficient for age in women is -5.04×10^{-5}/mm Hg. This means that, on average, keeping other covariates constant, if 2 women differ 1 year in age, the older would have DC lower by -5.04×10^{-5}/mm Hg, which corresponds to 0.045 SD units. The SI unit for distensibility, kPa^{-1} = 7.5 mm Hg^{-1}.

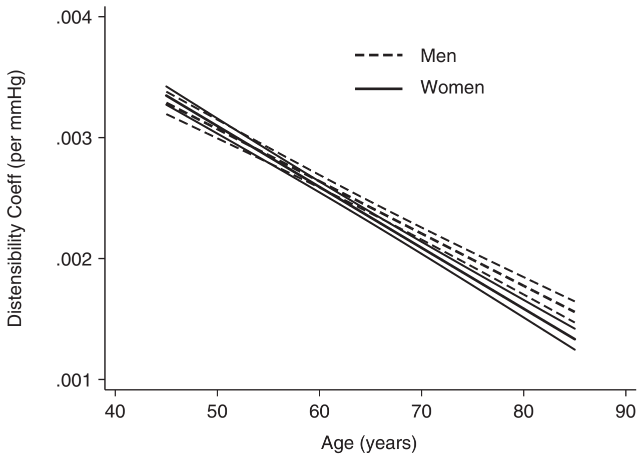

FIG. 1. Fitted age-distensibility coefficient relationship for men (dashed lines) and women (solid lines), adjusted for race and mean height (166 cm), and their 95% confidence intervals calculated using mixed model analysis.

is not possible for traditionally calculated DC, where BPs are part of the nonlinear calculation and (2) using our analytic model, the MM also provides estimates of association with mean carotid artery diameter, which has been shown to be associated with carotid atherosclerosis.[12] Our results show that MM analysis can detect significant associations that have been previously published using within-participant calculation of DC[9] in the same study dataset.

Although our analysis reproduced the findings of Blaha et al.[9] for some covariates, we also contribute several important new findings. We have shown interethnic differences in mean carotid artery diameters that have not been reported previously. Whereas the sex differences in arterial diameters are expected, the age-sex interaction is novel. Older women have larger arterial diameters than young women, and this age association is steeper than the age association among men. Also, the age-sex interaction in DC means that older women have stiffer arteries than older men. To give a sense of the magnitude of the differences, we use the unadjusted hazard ratios for stroke associated with lower distensibility reported by Yang et al.[7]: because of differences in DC, women who are 10 years older would have a 30.4% higher hazard of stroke than their younger counterparts, whereas men with the same age difference would have a 25.6% higher hazard of stroke. In addition, the afterload on the heart of older women is likely to be greater than that among older men. This may help to explain why older women predominate among patients with heart failure with preserved systolic function.[13] It may also have a part in explaining why although the absolute mortality rate is higher in men than women, the rate of increase of total heart disease mortality in men >45 years rises less steeply than in women.[14]

Because this is a cross-sectional, observational study, we are circumspect about clinical and treatment-related implications of this finding. It is noteworthy that current antihypertensive drugs of choice have somewhat lower effectiveness in women compared to men in the prevention of death in heart failure.[15] It is possible that drugs that improve arterial distensibility might be more efficacious in prevention of heart failure mortality in women.[16]

Strengths and limitations

The large multi-ethnic database of both men and women with a large range of ages collected using rigorous measurement standards is a significant strength of this study. A limitation of this study is that the arterial diameter imaging was of the carotid artery, but pressure measurement was performed in the brachial artery. There was no invasive gold standard measurement of distensibility. However, the aim of study was to analyze the kind of noninvasive measurement practical in large-scale studies, such as MESA, which have been reported in current published literature,[9] rather than comparison with a gold standard measurement.

Conclusions

We have shown sex and ethnic differences in the diameter and distensibility of the carotid artery, with adjustment for confounding by BP. Furthermore, we have shown a sex-age interaction that can be hypothesized to have worse consequences of arterial stiffness among older women compared to older men. The biologic underpinnings of these strong findings and whether they translate into differences in heart failure and other cardiovascular outcomes remain to be determined by future research.

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Disclosure Statement

The authors have no conflicts of interest to report.

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