Longitudinal Effects of a Decade of Aging on Carotid Artery Stiffness

The Multiethnic Study of Atherosclerosis

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Background and Purpose—Arterial stiffening is associated with hypertension, stroke, and cognitive decline; however, the effects of aging and cardiovascular disease risk factors on carotid artery stiffening have not been assessed prospectively in a large multiethnic longitudinal study.

Methods—Distensibility coefficient and the Young's elastic modulus (YEM) of the right common carotid artery were calculated at baseline and after a mean of 9.4 (standard deviation [SD], 0.5) years in 2650 participants. Effects of age and cardiovascular disease risk factors were evaluated by multivariable mixed regression and ANCOVA models.

Results—At baseline, participants were 59.9 (SD, 9.4) years old (53% women; 25% black, 22% Hispanic, 14% Chinese). YEM increased from 1581 (SD, 927) to 1749 (SD, 1306) mm Hg ($P<0.0001$), and distensibility coefficient decreased from 3.1 (SD, 1.3) to 2.7 (SD, 1.1)$\times 10^{-3}$ mm Hg^{-1} ($P<0.001$), indicating progressive arterial stiffening. YEM increased more among participants who were aged >75 years old at baseline ($P<0.0001$). In multivariable analyses, older age and less education independently predicted worsening YEM and distensibility coefficient. Stopping antihypertensive medication during the study period predicted more severe worsening of YEM (β=360.2 mm Hg; P=0.008). Starting antihypertensive medication after examination 1 was predictive of improvements in distensibility coefficient ($\beta=1.1\times10^{-4}$ mm Hg^{-1}; P=0.024).

Conclusions—Arterial stiffening accelerates with advanced age. Older individuals experience greater increases in YEM than do younger adults, even after considering the effects of traditional risk factors. Treating hypertension may slow the progressive decline in carotid artery distensibility observed with aging and improve cerebrovascular health. **(*Stroke*. 2014;45:48-53.)**

Key Words: aging ■ carotid arteries ■ elasticity ■ hypertension

Stroke, cognitive decline, and conventional cardiovascular disease (CVD) risk factors have been associated with increased arterial stiffness in cross-sectional analyses[1–4]; however, much less is known about the longitudinal relationships between traditional CVD risk factors and changes in arterial dynamics. Increases in arterial stiffness with aging are caused by fragmentation of elastin fibers and a decrease in the elastin-to-collagen ratio in the walls of large arteries.[5–7] This process may underlie the development of hypertension and its complications[5] because a more rigid arterial tree is less able to accommodate large pulsatile blood volumes. Treatment of systolic blood pressure (SBP) reduces cardiac and cerebral vascular events in elderly populations; however, no longitudinal observational studies have described the effects of hypertension and treatment of hypertension on the progression of local arterial stiffness for a decade.[1,8,9]

To our knowledge, this is the first large study to evaluate the longitudinal associations among aging, traditional CVD risk factors, and changes in carotid distensibility and elasticity in a diverse cohort without clinically evident CVD.

Materials and Methods

Study Participants and Design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a large prospective cohort study investigating the prevalence, causes, and progression of subclinical CVD. MESA has a population-based sample of 6814 men and women aged 45 to 84 years, free of known CVD at baseline, recruited from 6 United States communities. The study objectives and design have been published previously.[10] All participants gave informed consent for the study protocol, which was approved by the Institutional Review Boards of the ultrasound reading center and all MESA field centers.

The present analyses were prespecified and include a subset of MESA participants with valid carotid distensibility measurements

Received July 15, 2013; accepted October 8, 2013.

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A full list of participating Multiethnic Study of Atherosclerosis (MESA) investigators and institutions can be found at http://www.mesa-nhlbi.org.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002649/-/DC1.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.002649**

at examination 1 (baseline) and examination 5 who were not missing pertinent examination 1 covariates (n=2650; online-only Data Supplement A: Flow diagram). Demographic, medical history, and laboratory data for the present study were obtained from the first (July 2000 to August 2002) and fifth (January 2012 to February 2012) examinations of the cohort. Hypertension was defined as SBP ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or use of antiglycemic medications. Impaired fasting glucose was defined as blood glucose 100 to 125 mg/dL. Total and high-density lipoprotein cholesterol levels were measured after a 12-hour fast. Low-density lipoprotein cholesterol was calculated. The Young's elastic modulus (YEM) and carotid distensibility coefficient (DC) were calculated using standard formulae (online-only Data Supplement B).

B-Mode Ultrasound and Brachial Blood Pressure Measurements

At examination 1, B-mode ultrasound video-loop recordings of a longitudinal section of the distal right common carotid artery were recorded on videotape using a Logiq 700 ultrasound system (General Electric Medical Systems; transducer frequency 13 MHz). Video images were digitized at high resolution and frame rates using a medical digital recording device (PACSGEAR, Pleasanton, CA), which were converted into DICOM-compatible digital records. At examination 5, a similar protocol was performed using the same ultrasound and digitizing equipment; however, the video output was directly digitized using the same medical digital recording settings without use of videotape. Certified and trained sonographers from all 6 MESA sites used selected reference images from examination 1 to try to match the scanning conditions of the initial study, including common carotid artery display depth, angle of approach, surrounding tissues and internal landmarks, degree of jugular venous distension, and ultrasound system settings. After 10 minutes of rest in the supine position and immediately before ultrasound image acquisition, repeated measures of brachial blood pressures were obtained using a standardized protocol with an automated upper arm sphygmomanometer (DINAMAP; GE Medical Systems, Milwaukee, WI). Ultrasound images were reviewed and interpreted by the MESA Carotid Ultrasound Reading Center (the University of Wisconsin Atherosclerosis Imaging Research Program, Madison, WI). Systolic and diastolic diameters were determined as the largest and smallest diameters during the cardiac cycle. All measurements were made manually and performed in triplicate from 2 to 3 consecutive cardiac cycles. Internal and external artery diameters were measured using Access Point Web version 3.0 (Freeland Systems, Westminster, CO). Measurement reproducibility was excellent (online-only Data Supplement C).

Statistical Analysis

Results are reported as mean (standard deviation [SD]) for continuous variables or percentages for categorical variables. Paired *t* tests were used to compare the continuous characteristics of baseline and examination 5. The McNemar and Bhapkar tests were used for dichotomous and multicategory variables, respectively. ANOVA was used to assess ethnic differences in continuous variables, and χ^2 tests were used for categorical variables.

A repeated-measures mixed model, adjusted for risk factors, was used to estimate mean YEM and DC at baseline and examination 5, as well as their changes between baseline and examination 5. Baseline age was classified into 4 decades (ages 45–54, 55–64, 65–74, and 75–84 years). Age and study examination were specified as class variables, and the interaction of examination and age group was included in the models to allow evaluation of whether the differences between examinations differed by age.

Differences between baseline and examination 5 measures were examined using ANCOVA, adjusting for risk factors, with and without adjustment for baseline stiffness measures to account for the fact that in subjects with high levels of stiffness at baseline, the independent variables may have less of an effect on progression of YEM and DC, which are referred to as ceiling effects for YEM or floor effects for DC. Because the results of both models were similar, the adjusted data are presented. The models that were not adjusted for baseline are provided in Tables I and II in the online-only Data Supplement. Sequential ANCOVA models were performed as unadjusted or adjusted for age, sex, ethnicity, study site, and baseline CVD risk factors (body mass index, diabetes mellitus status, SBP, use of antihypertensive medication, lipids, use of lipid-lowering medications, physical activity, and smoking status), and then adjusted for antihypertensive medication use at examination 1 and examination 5. All analyses were performed with the use of SAS (version 9.3; SAS Institute, Cary, NC).

Results

Participant Characteristics

At baseline, participants were a mean of 59.9 (SD, 9.4) years old, 53% were women, 39% were white, 25% were black, 22% were Hispanic, and 14% were Chinese. Most participants (68.9%) graduated from high school, 17.2% had some high school education, and 13.8% had no high school education. The mean follow-up was 9.5 (SD, 0.5) years. Baseline and examination 5 characteristics, including the prevalence of CVD risk factors, are shown in Table 1. Pulse pressure, carotid wall thickness, and arterial diameter increased with age (all $P<0.0001$) and were greatest in the oldest age group. Older subjects had greater increases in end-diastolic internal diameter (75–84 years, 0.020 cm; 65–74 years, 0.022 cm; 55–64 years, 0.019 cm; 45–54 years, 0.017 cm; $P=0.02$) but less wall thickening (75–84 years, 0.011 cm; 65–74 years, 0.014 cm; 55–64 years, 0.016 cm; 45–54 years, 0.018 cm; $P<0.0001$) compared with younger subjects.

Young's Elastic Modulus

Mean YEM increased from 1581 (SD, 927) to 1749 (SD, 1306) mm Hg ($P<0.0001$) during the study period, indicating progressive arterial stiffening. YEM increased significantly more among older participants and was especially prominent in those aged >75 years at baseline, indicating an accelerated rate of arterial stiffening in this group ($P<0.0001$; Figure 1). Older age independently predicted an accelerated increase in YEM from examination 1 to examination 5 ($P<0.0001$). Use of antihypertensive medications at baseline predicted more of an accelerated rate of increase in YEM; higher education level predicted slower progression of YEM (Table 2). Other traditional CVD risk factors, including lipid levels, diabetes mellitus status, body mass index, and smoking status, were not independent predictors of change in YEM (all $P>0.05$).

Distensibility Coefficient

Mean DC decreased from 3.1 (SD, 1.3) to 2.7 (SD, 1.1) 10^{-3} mm Hg^{-1} ($P<0.001$), also indicating progressive arterial stiffening (Table 1). Older age was an independent predictor of worsening DC ($P<0.0001$), even after adjustment for socioeconomic factors and CVD risk factors (Table 3). However, the magnitude of DC changes between participants in the oldest and younger age groups was similar (all $P>0.05$; Figure 2). Chinese ethnicity, treated diabetes mellitus, and higher SBP also were independent predictors of an accelerated decrease in DC. As with YEM, higher education level independently predicted a higher DC corresponding to more compliant arteries (Table 3).

Table 1. Participant Characteristics at Baseline and Examination 5

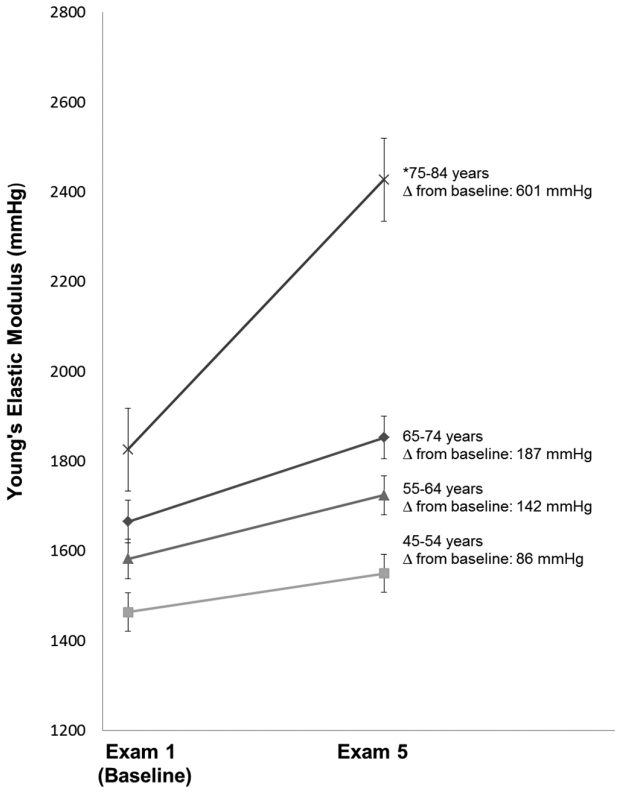
n=2650	Baseline	Examination 5	*P* Value
Age, y	59.9 (9.4)	69.3 (9.3)	<0.0001
Female (%)	1414 (53.4)		NA
Ethnicity (%)			
White	1039 (39.2)		NA
Black	660 (24.9)		
Chinese	380 (14.3)		
Hispanic	571 (21.6)		
Blood pressure parameters, mm Hg			
SBP	123.3 (20.0)	123.6 (20.5)	0.42
DBP	71.7 (10.1)	68.4 (10.2)	<0.0001
Pulse pressure	51.6 (15.6)	55.3 (17.3)	<0.0001
Hypertension (%)	1118 (42.2)	1596 (60.3)	<0.0001
HTN meds (%)	864 (32.6)	1390 (52.5)	<0.0001
Diabetes mellitus status, %			
IFG	317 (12.0)	557 (21.1)	<0.0001
Untreated	42 (1.6)	41 (1.6)	
Treated	181 (6.8)	420 (15.9)	
Lipids, mg/dL			
Total cholesterol	194.1 (34.9)	183.7 (36.7)	<0.0001
Low-density lipoprotein cholesterol	117.2 (30.5)	105.9 (32.0)	<0.0001
High-density lipoprotein cholesterol	51.5 (15.1)	56.5 (17.2)	<0.0001
Triglycerides	127.7 (81.7)	107.9 (60.7)	<0.0001
Lipid-lowering meds, %	400 (15.1)	993 (37.5)	<0.0001
BMI, kg/m^2	27.7 (5.0)	27.9 (5.3)	<0.0001
Waist, cm	96.2 (13.7)	97.8 (13.7)	<0.0001
Smoking, %			
Former	940 (35.5)	1205 (45.7)	<0.0001
Current	297 (11.2)	194 (7.4)	
YEM, mm Hg	1581 (927)	1749 (1306)	<0.0001
DC, 10^{-3} mm Hg^{-1}	3.1 (1.3)	2.7 (1.1)	<0.0001
Carotid wall thickness, cm	0.147 (0.030)	0.163 (0.033)	<0.0001
PSI diameter, cm	0.627 (0.074)	0.644 (0.080)	<0.0001
EDI diameter, cm	0.581 (0.070)	0.599 (0.076)	<0.0001

All values are mean (SD) unless noted otherwise. *P* values for continuous variables are from paired *t* tests and for categorical variables from McNemar or Bhapkar test. BMI indicates body mass index; DBP, diastolic blood pressure; DC, distensibility coefficient; EDI, end-diastolic internal diameter; HTN, hypertension; IFG, impaired fasting glucose; meds, medication; NA, not applicable; PSI, peak-systolic internal; SBP, systolic blood pressure; and YEM, Young's elastic modulus.

Associations With CVD Risk Factors

As in Table 1, there were significant increases in body mass index, waist circumference, rates of diabetes mellitus, and percentage of participants using lipid-lowering and antihypertensive therapies from examination 1 to examination 5 (all $P<0.0001$). Sex was not a significant predictor of change in YEM or DC. Menopausal status did not predict changes in DC or YEM in analyses restricted to women.

Use of antihypertensive medication at baseline was independently associated with an increase in YEM. Higher baseline SBP predicted worsening DC. To further explore relationships among medication use, blood pressure, and arterial stiffness, models were created that evaluated changes in the use of antihypertensive therapy from examination 1 to examination 5. Stopping antihypertensive medication was a strong independent predictor of accelerating YEM ($P=0.008$), although only 84 participants (3.1%) stopped antihypertensive medications between examinations 1 and 5. After adding examination 5 treatment to the model, SBP ($P=0.043$) and being a former smoker ($P=0.049$) predicted changes in YEM (Table 2). For DC, starting on antihypertensive therapy independently predicted an improvement in DC ($P=0.024$) after adjusting for baseline DC. Similar findings regarding changes in YEM and DC were detected in sensitivity analyses that included antihypertensive medication treatment at MESA examinations 2, 3, and 4 (data not shown). Follow-up time was not an independent predictor of change in YEM. For DC, follow-up time was an independent predictor ($\beta=-1.2\times10^{-4}$ mm Hg^{-1}; $P=0.004$);



*p<0.0001 for change from baseline compared to all other age groups

Figure 1. Change in Young's elastic modulus from baseline to examination 5.

however, its addition to the models did not change the magnitude of the associations or level of significance of the other variables (data not shown).

Differences in DC and YEM by Ethnicity

Differences among ethnic groups at baseline and examination 5 are shown in Table III in the online-only Data Supplement. Baseline YEM was significantly higher (worse) in black (1630 [SD, 1023] mm Hg), Chinese (1733 [SD, 996] mm Hg), and Hispanic (1687 [SD, 908] mm Hg) participants compared with white participants (1436 [SD, 823] mm Hg; all $P<0.0001$). Baseline DC was higher (better) in white participants compared with other ethnicities ($P<0.0001$). Age was similar across ethnic groups ($P=0.359$). Black participants had higher baseline and examination 5 SBP and diastolic blood pressure compared with other groups ($P<0.0001$). Hispanic participants had higher blood pressures than white and Chinese participants (all $P<0.05$); however, average SBP and diastolic blood pressure of all ethnic groups were not in the hypertensive range. All ethnic groups experienced progressive stiffening at a similar rate, with no significant differences in change in YEM ($P=0.246$) or DC ($P=0.233$) from examinations 1 to 5.

At baseline, nonwhite ethnic groups started with stiffer arteries (YEM and DC); however, in the repeated-measures models, only white ($P=0.002$) and black ($P=0.01$) participants exhibited a significant age group and examination interaction. The change in YEM in the oldest Hispanic and Chinese participants was not statistically significantly different from the younger age groups (all $P\geq0.07$; Figure I in the online-only Data Supplement). Change in DC was not significantly different between participants in the oldest age group compared with younger participants in any ethnic group (all $P\geq0.2$; Figure II in the online-only Data Supplement).

Table 2. Multivariate ANCOVA Regression Models for Change in Young's Elastic Modulus*

Significant Predictors	β	*P* Value
Model 1		
R^2=0.148		
Age	16.5	<0.0001
Education level (compared with those who did not graduate high school)		
High school graduate	−235.8	0.007
More than high school	−243.1	0.003
Use of antihypertensive medication at baseline	175.8	0.001
Model 2		
R^2=0.150		
Age	16.8	<0.001
Education level (compared with those who did not graduate high school)		
High school graduate	−236.4	0.007
More than high school	−243.0	0.003
Former smoker at baseline	−101.1	0.050
Baseline systolic blood pressure (per mm Hg)	2.8	0.043
Stopping antihypertensive medication	360.2	0.008

Model 1: Age, sex, race, study site, socioeconomic factors (education level, income), and traditional cardiovascular disease risk factors (systolic blood pressure, diabetes mellitus status, smoking status, total cholesterol, high-density lipoprotein cholesterol, body mass index, and physical activity level), and treatment of traditional cardiovascular risk factors at baseline (use of antihypertensive medications, use of lipid-lowering medications). Model 2: Model 1 plus exchanging the variable use of antihypertensive medication at baseline with 4 categories: (1) never treated with antihypertensive medication (untreated at examination 1 and examination 5), the reference group; (2) continued use of antihypertensive medication (treated at examination 1 and treated at examination 5); (3) starting antihypertensive medication (untreated at examination 1, treated at examination 5); and (4) stopping antihypertensive medications (treated at examination 1, untreated at examination 5).

*Models shown are adjusted for baseline Young's elastic modulus.

Discussion

Although cross-sectional studies have demonstrated higher arterial stiffness with increasing age,[2,5,6] longitudinal changes in arterial stiffness for nearly a decade of aging have not been described in a large multiethnic population. The values obtained for YEM and DC are similar to those that have been reported elsewhere.[2,6] Previous longitudinal studies that evaluated changes in carotid artery stiffness parameters were small,[11] of short duration,[11–14] and were performed in younger, more homogeneous populations.[12–14] Our study confirmed a strong cross-sectional association between older age and arterial stiffness but also identified a longitudinal increase in arterial stiffness that was especially prominent in older participants. Importantly, more rapid stiffening (increased YEM) was observed among the oldest participants and for participants who discontinued antihypertensive medication. Lower baseline SBP and longitudinal use of antihypertensive medications were associated with slower progression of arterial stiffness. Reduced carotid arterial stiffness could translate into reduced

Table 3. Multivariate ANCOVA Regression Models for Change in Distensibility Coefficient*

Significant Predictors	β	*P* Value
Model 1		
R^2=0.359		
Age	-2.2×10^{-5}	<0.0001
Chinese	-1.9×10^{-4}	0.006
Study site		
University of Minnesota	3.1×10^{-4}	<0.0001
University of California, Los Angeles	1.6×10^{-4}	0.025
Education level (compared with those who did not graduate high school)		
More than high school	1.7×10^{-4}	0.006
Baseline systolic blood pressure (per mm Hg)	-2.8×10^{-6}	0.007
Treated diabetes mellitus at baseline	-1.6×10^{-4}	0.029
Model 2		
R^2=0.361		
Age	-2.2×10^{-5}	<0.0001
Chinese	-1.9×10^{-4}	0.006
Study site		
University of Minnesota	3.1×10^{-4}	<0.0001
Education level (compared with those who did not graduate high school)		
More than high school	1.7×10^{-4}	0.007
Baseline systolic blood pressure (per mm Hg)	-3.6×10^{-6}	0.001
Starting antihypertensive medication	1.1×10^{-4}	0.024
Treated diabetes mellitus at baseline	-1.8×10^{-4}	0.018

Model 1: Age, sex, race, study site, socioeconomic factors (education level, income), and traditional cardiovascular disease risk factors (systolic blood pressure, diabetes mellitus status, smoking status, total cholesterol, high-density lipoprotein cholesterol, body mass index, and physical activity level) and treatment of traditional cardiovascular risk factors at baseline (use of antihypertensive medications, use of lipid-lowering medications). Model 2: Model 1 plus exchanging the variable use of antihypertensive medication at baseline with 4 categories: (1) never treated with antihypertensive medication (untreated at examination 1 and examination 5), the reference group; (2) continued use of antihypertensive medication (treated at examination 1 and treated at examination 5); (3) starting antihypertensive medication (untreated at examination 1, treated at examination 5); and (4) stopping antihypertensive medications (treated at examination 1, untreated at examination 5).

*Models shown are adjusted for baseline distensibility coefficient.

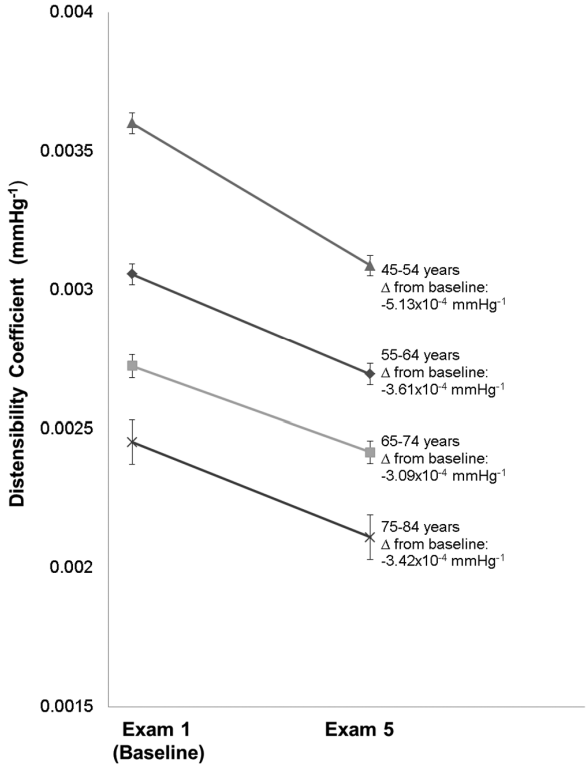


Figure 2. Change in distensibility coefficient from baseline to examination 5.

risk for stroke and cognitive dysfunction because stiffer arteries do not dampen pulse wave transmissions that may amplify more deeply toward cerebral capillaries.[7]

Our data suggest that the pathophysiological processes that underlie progressive arterial stiffening do not evolve linearly. YEM, but not DC, increased most rapidly in the oldest participants. Older individuals had a disproportionate increase in arterial diameter relative to wall thickness. YEM detected adverse arterial remodeling with aging because it accounts for wall thickness, whereas change in DC among older participants seemed to be blunted because of floor effects; those who started with the stiffest arteries (lowest DC) had less physiological room for change and ultimately less progression of DC because they had larger arterial diameters and wider pulse pressures at baseline.

Previous cross-sectional analysis of distensibility measures in the MESA cohort found associations with traditional CVD risk factors including sex, ethnicity, smoking, diabetes mellitus, and lipid levels but not treatment of hypertension.[2,3] Socioeconomic status and health care access have also been associated with CVD risk in MESA.[15] Baseline YEM and DC were significantly worse in nonwhite participants, but progression rates did not differ by race. Racial differences in the prevalence of hypertension may explain this observation, at least in part. Also, ethnicity was an independent predictor of change in DC but not in YEM. The major difference between the stiffness parameters used in this study is that YEM includes wall thickness weighted for end-diastolic diameter. Wall thickness had highly significant associations (P<0.0001) with YEM and DC however, when it was included in the models for YEM and DC (not shown), it had little effect, suggesting that the effect of differences in wall thickness between ethnic groups is minimal. Regardless, the oldest participants in all ethnic groups showed a pronounced increase in YEM over time, although it was most prominent in black and white participants after adding an age and examination interaction term.

Hypertension and its treatment seem to play a greater role in the progression of arterial stiffness over 10 years. Starting or stopping antihypertensive medications between examinations 1 and 5 was associated with changes in arterial distensibility, suggesting that examining the effects of treatment of blood pressure at a single time point is inadequate to explain these complex relationships. Our data also suggest that continuing to treat hypertension restricts adverse changes in arterial stiffness, especially in the older individuals. Clinicians often hesitate to treat hypertension in elderly patients because of concerns regarding adverse events, despite the fact that treatment has been shown to reduce risk of stroke, myocardial infarction, heart failure, CVD death, and all-cause mortality.[16,17] Use of

antihypertensive medications in older patients may reduce clinical events by slowing the progressive arterial stiffness that accompanies aging and its resulting end-organ damage. Arterial stiffening is also associated with cognitive decline and may be a target for reducing dementia by improving cerebrovascular health.[1,4]

Limitations

The reported associations cannot confirm causation; longitudinal follow-up from clinical trials of antihypertensive therapy is needed to confirm the effects of therapy we observed. Our participants were a subset of the MESA study; there may be a bias based on survival to examination 5. Those who participated in examination 5 were healthier and less likely to have a nonfatal CVD event than the original MESA cohort; however, this would create a null bias. Brachial artery blood pressures were considered as surrogates for carotid arterial pressures. Although a standard practice in epidemiological studies, brachial measurements can overestimate central pressures, although this difference is smaller in older participants and would amplify the null bias.[18,19] SBP may confound our analyses because it was used to generate the blood pressures used in the YEM and DC equations.

Conclusions

Carotid arterial stiffening accelerates with advanced age. Older individuals experience greater increases in YEM than do younger adults, even after considering the effects of traditional CVD risk factors. Baseline YEM and DC were significantly worse in nonwhite participants, but progression rates did not differ by ethnicity. Higher baseline blood pressure predicted increases in arterial stiffness for a decade. Stopping antihypertensive therapy was associated with increased arterial stiffening; longitudinal use of antihypertensive medications slowed its progression, especially in elderly participants. Treatment of hypertension restricts the progressive decline in carotid artery distensibility observed with aging. These findings support treatment of hypertension in older adults and may provide a new target for improving cerebrovascular health.

Sources of Funding

This work was supported by contracts HC95159-HC95169 and HL07936 from the National Heart, Lung, and Blood Institute, grant ES015915 from the National Institute of Environmental Health Sciences, and grants RR024156 and RR025005 from the National Center for Research Resources. This publication was developed under Science to Achieve Results research assistance agreement RD831697 from the Environmental Protection Agency. It has not been formally reviewed by the Environmental Protection Agency. The views expressed in this document are solely those of the authors. The Environmental Protection Agency does not endorse any products or commercial services mentioned in this publication. Dr Gepner was supported, in part, by a Ruth L. Kirschstein National Research Service Award from the National Heart, Lung, and Blood Institute to the University of Wisconsin-Madison Cardiovascular Research Center (T32HL07936). E.K. Hom was supported by the University of Washington Biostatistics, Epidemiologic, and Bioinformatic Training in Environmental Health Training Grant, which is sponsored by the National Institute of Environmental Health Sciences (T32ES015459).

Disclosures

Dr Stein is a member of the Wisconsin Alumni Research Foundation. The other authors report no conflicts.

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