Aortic Distensibility and Retinal Arteriolar Narrowing
The Multi-Ethnic Study of Atherosclerosis

Ning Cheung, A. Richey Sharrett, Ronald Klein, Michael H. Criqui, F.M. Amirul Islam, Katarzyna J. Macura, Mary Frances Cotch, Barbara E.K. Klein, Tien Y. Wong

Abstract—Increased aortic stiffness and retinal arteriolar narrowing are subclinical vascular effects of chronic hypertension and predict future cardiovascular events. The relationship between these 2 vascular measures is uncertain and is examined in the Multi-Ethnic Study of Atherosclerosis. This cross-sectional analysis involves 3425 participants (aged 45 to 85 years) free of clinical cardiovascular disease. Retinal vascular caliber was quantified from digital retinal photographs using standardized protocols. Aortic distensibility was determined from chest MRI. After controlling for age, squared age, gender, race, study center, height, weight, heart rate, cigarette smoking, and current systolic blood pressure, use of antihypertensive medications, diabetes, fasting glucose, lipid profile, and C-reactive protein, reduced aortic distensibility (first versus fourth distensibility quartile) was associated with increased odds of retinal arteriolar narrowing (odds ratio: 1.72; 95% CI: 1.15 to 2.58, comparing lowest to highest quartile of arteriolar caliber). Further adjustments for atherosclerotic measures (carotid intima-media thickness, coronary calcium score, and ankle brachial index) had minimal impact on this association (odds ratio: 1.70; 95% CI: 1.13 to 2.55). Reduced aortic distensibility was not associated with retinal venular caliber. We conclude that increased aortic stiffness is associated with retinal arteriolar narrowing, independent of measured blood pressure levels and vascular risk factors. These data suggest that changes in the microvasculature may play a role linking aortic stiffness with clinical cardiovascular events. (Hypertension. 2007;50:617-622.)

Key Words: population science ■ microcirculation ■ arterial compliance ■ imaging ■ risk factors

By virtue of its elastic properties and proximity to the heart, the aorta acts as an important modulator of the entire cardiovascular system, buffering the intermittent pulsatile cardiac output to provide steady flow to capillary beds. Aortic distensibility plays a key role in maintaining normal left ventricular function and coronary blood flow.

Normal aortic function is compromised when the aorta loses its elasticity, resulting in stiffening of the aorta. There is growing evidence that aortic stiffness is a subclinical marker of early atherosclerosis and predicts future risk of hypertension and cardiovascular events, independent of traditional risk factors. Some studies suggest that aortic stiffness is also associated with microvascular disease. In the Framingham Heart Study, aortic stiffness was associated with blunted microvascular reactivity to ischemic stress, independent of conventional cardiovascular risk factors. Other studies found associations of aortic stiffness with microvascular disease in the heart, brain, and kidneys. These observations support the hypothesis that aortic stiffness may exert an adverse influence on the microcirculation, predisposing the development of cardiovascular disease.

Retinal arteriolar narrowing and other retinaopathy signs (eg, retinal hemorrhages and microaneurysms) are changes in the retinal microvasculature associated with elevated blood pressure. These retinal microvascular changes have been shown to predict hypertension and clinical cardiovascular diseases, independent of known risk factors. In this study, we tested the hypothesis that aortic stiffness, quantified from chest MRI, is associated with retinal arteriolar narrowing in a large multiethnic population–based cohort of people without clinical cardiovascular disease.

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis is a prospective cohort study of men and women aged 45 to 84 years without history of clinical cardiovascular disease, sampled from 6 US communities. In brief, there were 6814 participants at the first examination (July 2005; first decision April 21, 2007; revision accepted July 22, 2007.

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2000 to July 2002), when cardiac MRI was performed. Fundus photography was performed at the second examination (August 2002 to January 2004), which occurred immediately after the baseline examination.31,32 At the second examination, 6237 participants (92%) returned, 6147 had retinal photography, and 5979 had photographs that were suitable for measurement of retinal vascular caliber. Of these, we excluded 255 persons without cardiac MRI data, leaving 3425 participants for the current analysis. Reasons for nonparticipation for MRI studies include participant refusals, MRI contraindications, and other technical problems.

The tenets of the Declaration of Helsinki were observed, and institutional review board approval was granted at each study site. Written informed consent was obtained from each participant. All of the procedures followed were in accordance with institutional guidelines.

Retinal Photography and Retinal Vascular Measurements
Fundus photography was performed at each site, according to a standardized protocol described elsewhere.31,32 Both eyes of each participant were photographed with a 45° digital nonmydriatic camera. Trained graders who were masked to participants’ characteristics evaluated all of the images.

Retinal vascular caliber was measured with a computer-based program based on a previously validated protocol.33–35 For this study, photographs in the right eye were selected for measurement. The left eye photographs were used if retinal vascular caliber could not be measured in the right eye. For each photograph, all of the arterioles and venules coursing through an area 0.5 to 1 disc in diameter from the optic disc margin were measured and summarized as the central retinal arteriolar equivalents (CRAEs) and central retinal venular equivalents (CRVEs) using formulas described elsewhere.31,32 These equivalents represented the average of projected calibers for the central retinal vessels, measured away from the optic disc. Reproducibility of retinal vascular measurements has been reported, with intragrader and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99.31,32

In addition to retinal vascular caliber measurements, retinopathy signs were graded using a standardized protocol31 and considered to be present if any characteristic lesion, as defined by the Early Treatment Diabetic Retinopathy Study severity scale,37 was present: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. The presence of focal arteriolar narrowing and arteriovenous nicking was also examined.

MRI Protocols and Aortic Distensibility Measurement
MRI was performed using a 1.5-T whole-body MRI systems, Signa CVI or Signa LX (General Electric Medical Systems), at the first examination. The receiver coil used was a 4-element phased-array coil placed on the anterior and posterior surfaces of the chest. For evaluation of aortic distensibility, MRI scans of the aorta were obtained using gradient echo phase-contrast cine MRI with ECG gating. Images of the ascending and descending aorta were obtained in the transverse plane at the level of the right pulmonary artery perpendicular to the vessel lumen. Imaging parameters were as follows: repetition time: 10 ms; echo time, 1.9 ms; field of view, 34 cm; slice thickness, 8 mm; matrix: 256×224; 2 signal averages; temporal resolution, 20 ms; velocity encoding gradient: 150 cm/s; and receiver bandwidth: ±32 kHz. Aortic wall measurements were performed using the Magnetic Resonance Analytical Software System 4.2 (Medis).

For calculation of aortic distensibility, the following formula was used: aortic distensibility = (maximum area − minimum area)/[(Minimum area)×P]×1000, where *P is the pulse pressure.36 Pulse pressure was the difference between systolic and diastolic measurements of blood pressure. Blood pressure was measured immediately before and after the MRI aortic measurements while the patient was in the supine position in the MRI scanner; the average systolic and diastolic values were then used to calculate pulse pressure. The minimum and maximum cross-sectional areas of the ascending aorta were determined using an automated contour routine using the software FLOW (Medis).

Assessment of Cardiovascular Risk Factors
All of the participants underwent an interview and assessment of cardiovascular risk factors at both baseline and second examination.29,30 Resting blood pressure was measured using standardized protocol, and hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medications. Fasting (>8 hours) blood samples were drawn from all of the participants to measure the serum glucose, glycosylated hemoglobin (HbA1c), lipids and lipoproteins, and systemic inflammatory markers, such as C-reactive protein.29 Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L (126 mg/dL) or use of insulin or oral hypoglycemic medication. Participants underwent an extensive assessment of atherosclerotic disease. Detailed procedures regarding collection of data for various atherosclerotic measures, including coronary artery calcification, carotid arterial intima-media thickness, and ankle-brachial index, have been described elsewhere.38

Statistical Analysis
Summary measures of retinal vascular caliber (CRAE and CRVE) were categorized into quartiles and retinopathy as absent or present for analysis. ANOVA or independent sample t test was used to compare the characteristics between included and excluded participants and between participants with lowest and highest quartile of aortic distensibility. The distribution of aortic distensibility data was skewed, and, therefore, the data were transformed to logarithmic scale. To include participants with aortic distensibility of 0 (n = 37), a value of 1 was added to the aortic distensibility measurements for all of the participants before logarithmic transformation. The distribution of CRAE and CRVE by aortic distensibility was determined using ANCOVA models.

Multinomial logistic regression models were used to determine the odds of decreasing CRAE and CRVE quartiles (with the fourth quartile as reference) in association with reduced aortic distensibility (first versus fourth quartile). We constructed 3 models: model 1 included adjustments for age, squared age, gender, race, study center, height weight, and heart rate; model 2 had additional adjustments for vascular risk factors; and model 3 had additional adjustments for atherosclerotic measures. Logistic regression was used to examine the association between aortic distensibility and retinopathy.

In supplementary analysis, we examined the associations stratified by age groups (younger [<65 years] and older [≥65 years] persons), racial groups, diabetes, and hypertension. We also tested for any interactions among these variables. All of the analyses were performed in SPSS 12.0.1 (SPSS Inc).

Results
Participants’ characteristics by the highest and lowest quartiles of aortic distensibility and differences in characteristics between included and excluded participants are outlined in Table 1. The high exclusion rate was primarily because of participant’s refusal to participate in MRI examination because of the need for intravenous contrast administration. Compared with those without aortic distensibility data, participants in our study were younger and more likely to be men, whites, African Americans, Chinese, current cigarette smokers, and to have hypertension and higher levels of serum cholesterol.

The Figure shows the crude relationship between aortic distensibility and retinal vascular caliber. Significant trends of reducing aortic distensibility with decreasing CRAE (P for trend < 0.001) and CRVE (P for trend = 0.001) were noted.
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Table 1. Participant Characteristics and Aortic Distensibility: The Multi-Ethnic Study of Atherosclerosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Excluded Participants (N=2722)</th>
<th>Included Participants (N=3425)</th>
<th>AD (Q1) (N=858)</th>
<th>AD (Q4) (N=855)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>930</td>
<td>1501</td>
<td>379</td>
<td>366</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>696</td>
<td>970</td>
<td>284</td>
<td>181</td>
<td>0.17</td>
</tr>
<tr>
<td>Hispanics</td>
<td>757</td>
<td>569</td>
<td>125</td>
<td>180</td>
<td>0.09</td>
</tr>
<tr>
<td>Chinese</td>
<td>339</td>
<td>385</td>
<td>70</td>
<td>128</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender, Men</td>
<td>1360</td>
<td>1571</td>
<td>364</td>
<td>397</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, y*</td>
<td>65.4</td>
<td>62.0</td>
<td>66.1</td>
<td>55.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose, mg/dL*</td>
<td>107.6</td>
<td>103.4</td>
<td>106.6</td>
<td>101.3</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>126.2</td>
<td>122.9</td>
<td>132.5</td>
<td>113.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>29.0</td>
<td>27.9</td>
<td>27.8</td>
<td>27.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL*</td>
<td>188.8</td>
<td>193.4</td>
<td>192.5</td>
<td>195.2</td>
<td>0.40</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL*</td>
<td>50.8</td>
<td>52.7</td>
<td>53.2</td>
<td>52.0</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL*</td>
<td>111.7</td>
<td>115.1</td>
<td>113.4</td>
<td>116.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>134.6</td>
<td>129.1</td>
<td>130.6</td>
<td>133.8</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP, mg/L*</td>
<td>1.99</td>
<td>3.17</td>
<td>2.05</td>
<td>1.61</td>
<td>0.01</td>
</tr>
</tbody>
</table>

AD indicates aortic distensibility; Q1, lowest quartile; Q4, highest quartile; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CRP, C-reactive protein. Data shown as numbers and proportions (%) unless otherwise specified.

*Data are means and SDs.

Tests for interactions with age groups (P=0.81), gender (P=0.22), race/ethnicity (P=0.17), diabetes (P=0.82), hypertension (P=0.91), and coronary artery calcification status (P=0.09) did not show any statistically significant interactions (P<0.05). Finally, retinopathy and other less common retinal vascular abnormalities, including focal arteriolar narrowing and arteriovenous nicking, were also examined, but reduced aortic distensibility was not associated with these retinal vascular changes in multivariate analysis (data not shown).

Discussion

In this study among persons free of clinical cardiovascular disease, we demonstrate an association between reduced aortic distensibility, a sign of aortic stiffening, and retinal arteriolar narrowing, a vascular effect of hypertension,22–24 that has been found to predict clinical cardiovascular events.21,25,27 This association was independent of age, blood pressure, diabetes, measures of atherosclerosis, and other vascular risk factors.

Our findings are in keeping with data from the Atherosclerosis Risk in Communities Study, which showed an association between increased carotid artery stiffness, determined from ultrasound examinations, and smaller arteriole:venule ratio (AVR), suggested to reflect retinal arteriolar narrowing.40 This finding, similar to ours, was independent of age, blood pressure, and other risk factors. However, the use of AVR has an important limitation in that both narrowing of the
retinal arterioles and widening of the venules can produce a smaller AVR.\textsuperscript{41} Our study now confirms that increased aortic stiffness, as quantified from MRI, was associated with narrower retinal arteriolar caliber rather than wider retinal venular caliber. These data add to previous investigations that have shown aortic stiffness to be associated with microvascular dysfunction\textsuperscript{15} and clinical microvascular diseases, such as microvascular angina and nephropathy.\textsuperscript{16–19}

We showed that, in analysis controlling for vascular risk factors and measures of atherosclerosis, the association of aortic stiffness and retinal arteriolar narrowing was weakened but remained statistically significant, suggesting that the effects of these risk factors and atherosclerotic processes do not completely explain this association. An alternative explanation, supported by the known inverse relationship between pulse pressure and retinal arteriolar caliber,\textsuperscript{20} is that aortic stiffness increases pulse pressure, which, in turn, causes narrowing of the retinal arterioles. This may be linked to a previous hypothesis that exposure of small vessels to highly pulsatile pressure and flow is a potentially important patho-

Table 2. Multinomial Logistic Regression of Retinal Vascular Caliber by Aortic Distensibility

<table>
<thead>
<tr>
<th>Aortic Distensibility</th>
<th>OR (95% CIs) CRAE/CRVE Quartiles*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Quartile</td>
</tr>
<tr>
<td>CRAE</td>
<td></td>
</tr>
<tr>
<td>Age-gender-race†</td>
<td>2.48 (1.72 to 3.60)</td>
</tr>
<tr>
<td>Vascular risk factors‡</td>
<td>1.72 (1.15 to 2.58)</td>
</tr>
<tr>
<td>Measures of atherosclerosis§</td>
<td>1.70 (1.13 to 2.55)</td>
</tr>
<tr>
<td>CRVE</td>
<td></td>
</tr>
<tr>
<td>Age-gender-race†</td>
<td>0.98 (0.68 to 1.43)</td>
</tr>
<tr>
<td>Vascular risk factors‡</td>
<td>0.96 (0.64 to 1.44)</td>
</tr>
<tr>
<td>Measures of atherosclerosis§</td>
<td>0.98 (0.65 to 1.47)</td>
</tr>
</tbody>
</table>

Ref indicates reference.

*Multinomial logistic regression of decreasing quartiles of CRAE and CRVE equivalents.

†Model 1: OR (95% CI) adjusted for age, squared age, gender, race, study center, height, weight, and heart rate.
‡Model 2: model 1 plus adjustments for systolic blood pressure at examinations 1 and 2, use of antihypertensive medications, diabetes, serum glucose, total and high-density lipoprotein cholesterol, triglycerides, cigarette smoking status, and C-reactive protein.
§Model 3: model 2 plus common carotid intima-media thickness, coronary artery calcium, and ankle-arm index.
physiological mechanism underlying the associations of aortic stiffening with renal and cerebral microvascular diseases.14

In subgroup analyses, the association between increased aortic stiffness and retinal arteriolar narrowing was weaker and not statistically significant in women and in Chinese. There was also no positive association seen in Hispanics. Although the reasons for these observations are not apparent, the sample size was reduced in these subgroup analyses, and there were no statistically significant interactions with gender or race/ethnicity.

Strengths of our study include its large, multiethnic, and population-based design with all of the participants free of clinical cardiovascular disease at baseline, use of a previously validated computer-based technique to quantify retinal vascular caliber, and standardized evaluation of retinopathy with high proportion of gradable digital fundus photographs, as well as the use of MRI, a robust imaging technology for accurate assessment of aortic distensibility, which has been shown to have better quality of validation and less operator bias compared with other methods of quantifying aortic stiffness.42 However, the present study must be interpreted within the context of its potential limitations and the choices that we made in our epidemiological and statistical approach. First, because of the cross-sectional design of our study, the temporal sequence of reported associations cannot be verified and needs to be further elucidated in future prospective studies. Second, a significant proportion of participants were excluded because of unavailability of aortic MRI data. These participants demonstrate several differences in characteristics (Table 1), indicating that the possibility of selection bias cannot be totally excluded. Because the calculation of aortic stiffness in our study was based on the use of peripheral pulse pressure, it may not exactly represent the central aortic stiffness. Lastly, at the time of this study, the Multi-Ethnic Study of Atherosclerosis did not have available data on ocular factors that may affect measurement of retinal vascular caliber, such as refractive error44 and axial length.43 These factors, nevertheless, have been shown to have only a small impact on the measurement of absolute retinal vascular caliber and may not affect the association between retinal vascular caliber and cardiovascular disease in the epidemiological study setting.44

Perspectives
In summary, in a cohort free of clinical cardiovascular disease, we show an association between increased aortic stiffness and retinal arteriolar narrowing, independent of age, measured blood pressure, and other risk factors. Both aortic stiffness12,13,45 and retinal arteriolar narrowing21,25,27 have been shown to predict clinical cardiovascular outcomes. Our findings are consistent with the hypothesis that aortic stiffness may exert an adverse influence on the microcirculation,14 predisposing the development of cardiovascular disease attributable to microvascular injury.

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Disclosures
None.

References
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