Relationship Between Carotid Artery Stiffness and Retinal Arteriolar Narrowing in Healthy Middle-Aged Persons

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Background and Purpose—Both carotid atherosclerosis and cerebral arteriolosclerosis are associated with stroke. However, the relationship between carotid atherosclerosis and cerebral arteriolosclerosis is unknown. We examined the association between carotid artery stiffness, a marker of early atherosclerosis, and retinal arteriolar narrowing, a marker of arteriolosclerosis, in healthy middle-aged people.

Methods—This population-based, cross-sectional study involved 8031 men and women 45 to 64 years of age. Carotid arterial stiffness was estimated from high-resolution ultrasonic echo tracking of the left common carotid artery and was defined as adjusted arterial diameter change (AADC, μ, adjusted for diastolic blood pressure, pulse pressure and pulse pressure squared, and diastolic arterial diameter and height, with smaller AADC reflecting greater arterial stiffness). Generalized retinal arteriolar narrowing was estimated from measurements of diameters of retinal vessels from digitized retinal photographs and summarized as the arteriole-to-venule ratio (AVR, with smaller AVR indicating greater retinal arteriolar narrowing).

Results—After controlling for age, sex, ethnicity, hypertension, diabetes, and cigarette smoking, decreasing AADC was associated with decreasing AVR. The mean AADCs, comparing the lowest and highest quartiles of AVR, were 394 (SE, 4) and 409 (SE, 4) μ, respectively (P<0.01). The pattern of the graded association between carotid arterial stiffness and generalized retinal arteriolar narrowing was similar among persons with and without hypertension.

Conclusions—Greater stiffness of the carotid arteries is related to generalized narrowing of the retinal arterioles independent of blood pressure and other vascular factors. This supports a relationship between macrovascular and microvascular disease processes important in stroke pathogenesis. (Stroke. 2004;35:837-842.)

Key Words: blood pressure ■ carotid arteries ■ carotid stenosis ■ sclerosis

Macrovascular processes involving the carotid arteries and microvascular processes involving the cerebral arterioles are known to contribute to the pathogenesis and risk of stroke. However, little is known about the relationship between carotid atherosclerosis and cerebral arteriolosclerosis. The loss of elasticity in medium and large arteries is an early manifestation of atherosclerosis. Decreased elasticity, or increased stiffness, has long been considered intrinsic to the aging process of the arterial wall. However, there is evidence that, independent of age, arterial stiffness is associated with a variety of vascular risk factors such as hypertension, diabetes, and cigarette smoking. New data suggest that arterial stiffness is independently associated with increased risk of ischemic stroke and cardiovascular mortality. Nevertheless, the pathogenesis of arterial stiffness remains uncertain. An association between arterial stiffness and atherosclerosis has been found in some but not all studies. An explanation for this conflicting evidence is not available. Microvascular processes (eg, diseases of vaso vasorum) may also contribute to the loss of arterial elasticity. However, to the best of our knowledge, there have been no studies directly linking microvascular disease with arterial stiffness.

The retinal arterioles provide a unique opportunity to study the associations of cerebral microvascular disease because they can be viewed noninvasively and have anatomy, physiology, and embryology similar to those of the cerebral arterioles. Narrowing of the retinal arterioles has been shown to be associated with persistently elevated blood pressure (BP)23,24 and inflammation25 and predicts stroke independently of stroke risk factors. This provides support to the concept that cerebral microvascular disease may play an independent role in stroke pathogenesis.

The purpose of this investigation is to examine the association between stiffness of the common carotid artery and...
narrowing of the retinal arterioles in a population of healthy middle-aged persons.

Methods

Study Population

The population for this study was drawn from the 15,792 individuals who participated in the Atherosclerosis Risk in Communities (ARIC) study, a longitudinal study of cardiovascular disease. The ARIC cohort was selected as a probability sample of men and women between 45 and 64 years of age at 4 study centers in the United States: Forsyth County, North Carolina; Jackson, Mississippi (blacks only); suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Details of sampling, study design, and cohort examination procedures have been published. Eligible participants were interviewed at home and then were invited to a baseline clinical examination in 1987 to 1989, with a second examination 3 years later (93% return rate) and a third 6 years later (86% return rate).

In the ARIC cohort, arterial elasticity was assessed in 11,478 participants (73% of the entire cohort). These participants contributed to the arterial elasticity study cohort, of which 9% were assessed during the initial examination and 91% during their second examination. Of these 11,478 participants, 3,447 were excluded because of nonparticipation in the third examination (during which generalized retinal arteriolar narrowing was assessed via retinal photography), ethnicity other than white or black, or ungradeable retinal photographs. Therefore, the final effective sample size for this report is 8,031 individuals.

Measurement of Carotid Arterial Stiffness

The procedures for the collection and evaluation of common carotid arterial diameter and functional data in the ARIC study have been published extensively. Briefly, for this study, we used the arterial diameter data collected on the left common carotid artery (1 cm below the origin of the carotid bulb) during B-mode ultrasound examination of the carotid arteries. This method uses noninvasive ultrasonic echo-tracking methods carried out by centrally trained and certified sonographers. Data were collected after the participants had rested in a supine position for at least 20 minutes. With the transducer held securely by a mechanical transducer holder, transducer angulation was adjusted to maximize near-wall and far-wall media-adventitia echoes. Electronic gates were moved to track the 2 interfaces and the distance between them as a function of time visualized for the consecutive cardiac cycles. These data were digitized by an analog-to-digital converter and stored on floppy diskettes. Diskettes were sent to the ARIC Ultrasound Reading Center, where arterial diameter data were estimated as the average over as many cardiac cycles as possible (maximum, 10; average, 5.5). The arterial diameter data were read by trained and certified ultrasound readers in a central location subject to regular quality control monitoring, retraining, and recertification. The readers were masked to the identity and other cardiovascular health profiles of the participant. The following left carotid arterial diameter parameters during cardiac cycles were used for this analysis: systolic carotid arterial diameter, diastolic diameter, and the change in carotid arterial diameter between systole and diastole. Concurrent brachial BP was measured every 30 seconds with an automated oscillometric device (1846SX Dinamap), and the average of 2 BP measures before the completion of ultrasound examination was used to calculate arterial stiffness indices.

From these diameter and BP data, the following parameters, needed for estimating arterial elasticity, were assembled for the entire ARIC cohort: average diastolic arterial diameter, average systolic arterial diameter, average diameter change, diastolic BP, systolic BP, and pulse pressure (systolic minus diastolic BP). The BP-adjusted arterial diameter change (AADC; strain) as a dependent variable and other BP-related variables (diastolic BP, pulse pressure, pulse pressure squared, height, and diastolic arterial diameter) as covariates to be adjusted for, Details concerning the rationale for this adjustment, how AADC compares with other conventional methods of estimating arterial stiffness (pulse-wave velocity or ultrasound-measured elastic modulus to obtain stress-strain curves), and the reproducibility of these measurements are presented elsewhere.

Measuring Retinal Arteriolar Narrowing

Procedures for retinal photography performed at the third examination and its grading have been reported. Briefly, after 5 minutes of dark adaptation, a 45° degree retinal photograph was taken of a randomly selected eye, centered on the region of the optic disc and the macula, with an automatic-focus camera. These photographs were sent for grading at the ARIC Retinal Reading Center at the University of Wisconsin, Madison. The photographs were digitized by a high-resolution scanner, and the diameters of individual arterioles and venules coursing through a specified zone (1/2 (750 μm) to 1 (1500 μm) disk diameter from the optic disc margin were measured on the computer monitor by trained graders masked to subject identity. The branches of arterioles were also measured when possible if the measurement of the trunk arteriolar diameter was ≥85 μm. The individual arteriolar and venular diameters (and branch measurements) were combined into summary measures (in μm) according to a formula described elsewhere and expressed as an arteriole-to-venule ratio (AVR). The AVR accounts for magnification differences between photographs and is distributed normally in the general population. An AVR of 1.0 indicates that retinal arteriolar diameters were on average the same as venular diameters, whereas a smaller AVR represents narrower arterioles because venular diameters vary little with BP. The intragrader and intergrader reliability coefficients for AVR were 0.84 and 0.79, respectively. Trained graders also evaluated retinal photographs using a “light box” for focal retinal lesions, including arteriovenous nicking, focal arteriolar narrowing, and signs of retinopathy (eg, microaneurysms, retinal hemorrhages), according to standardized protocols.

Other Covariates

Information on age, ethnicity, sex, education levels, and cigarette smoking status was obtained from standardized questionnaires administered by trained interviewers. Body mass index was calculated as weight (kg) divided by height (m) squared. Fasting serum total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured by an enzymatic procedure with a Cobas centrifuge analyzer (Hoffman-La Roche). HDL cholesterol was measured after precipitation of apolipoprotein B–containing lipoproteins. Low-density lipoprotein (LDL) cholesterol was calculated in participants with triglycerides <400 mg/dL as total cholesterol minus HDL cholesterol plus 1/5 of triglycerides. Diabetes mellitus was defined as fasting (8 hours) serum glucose ≥140 mg/dL, glucose ≥200 mg/dL if fasting <8 hours, history of physician-diagnosed diabetes, or use of an oral hypoglycemic agent or insulin. At every examination, sitting BP was measured 3 times for each participant with a random-zero sphygmomanometer after a 5-minute rest by trained technicians following a standardized protocol. The systolic and fifth-phase diastolic BP measurements used in this report are the average of the second and third readings. Study participants were asked to bring all medications, vitamins, and supplements taken in the 2 weeks before the examination. The information on pharmacological treatment of hypertension is based on the participant’s self-reported use of any medication to treat high BP and the transcription and coding of all medication names. Prevalent hypertension at the examination of arterial stiffness was defined as diastolic BP ≥90 mm Hg, systolic BP ≥140 mm Hg, or use of antihypertensive medication.

Statistical Analysis

Mean and SD values for major continuous covariates and proportions for major categorical covariates were obtained for the entire study population and were stratified by ethnicity and sex. Analysis of covariance (ANCOVA) was used to estimate the adjusted means and SE of carotid arterial elasticity, as measured by AADC, and
generalized retinal arteriolar narrowing, as measured by the retinal AVR, and to test differences in the mean AADC across quartiles of AVR. Similar ANCOVA models were used to estimate the adjusted means of AVR by quartiles of AADC. As a result, all associations obtained were adjusted for age, sex, ethnicity-center, height, diastolic carotid arterial diameter, diabetes, hypertension status, and smoking status. All analyses were performed and reported on the entire study population and in subgroups stratified by hypertension status. Interactions with hypertension and other covariates were tested by inclusion of cross-product terms in linear regression models of AVR and AADC. SAS (SAS Institute) software was used for all statistical analyses.

Results

The characteristics of the study population at the time of arterial stiffness measurement according to ethnicity and sex are presented in Table 1. The mean age of the study population was 56 years; 15.6% were black; and 56% were women. The major characteristics of these 4 ethnicity-sex groups are similar to those found in the entire ARIC cohort sample. The mean±SD of AADC and AVR were 404±127 μ and 0.844±0.078 mm, respectively.

Table 2 presents mean levels of retinal AVR and carotid ADC (unadjusted for any covariates) in relationship to major cardiovascular disease risk factors. Persons with smaller AVR (representing narrower arterioles) were older. Men have larger ADC but smaller AVR than women, and blacks have smaller AVR than whites but similar ADC. Both AVR and ADC are associated with age, hypertension, BP, triglycerides, coronary heart disease, and diabetes in the same direction, but the association with diabetes is much stronger for AVR than for ADC. Total cholesterol and education are associated with ADC but not with AVR. We found that smokers tend to have smaller AVR but larger ADC than nonsmokers (see Table 2).

We examined the mean levels of carotid arterial elasticity across quartile levels of AVR (the Figure). After adjustment for age, sex, ethnicity-center, BP/arterial size–related variables (diastolic BP, pulse pressure and its squared term, height, and diastolic carotid arterial diameter), diabetes, hypertension status, and smoking status, lower AADC (indicative of increased carotid artery stiffness) was associated with lower AVR (increased arteriolar narrowing). The identically adjusted mean±SE AADCs comparing the lowest and highest quartiles of AVR were 394±4 and 409±4 μ, respectively (P<0.01). This pattern was similar in people with and without hypertension (for test of a linear trend across the quartiles, P<0.01 for both groups). Additional analysis was performed to further adjust for fasting glucose and insulin in the statistical model used to estimate the associations between AVR and AADC (the Figure). The pattern of association was not meaningfully changed; eg, the mean AADC in the lowest quartile of AVR group changed from 394 to 395 μ and mean AADC in the highest quartile of AVR group remained

### Table 1. Mean±SD and Proportions of Main Variables in the Study Population by Ethnicity and Sex: The ARIC Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=8031)</th>
<th>BF (n=946)</th>
<th>BM (n=577)</th>
<th>WF (n=3549)</th>
<th>WM (n=2959)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.2±5.7</td>
<td>55.1±5.3</td>
<td>55.3±5.8</td>
<td>56.2±5.7</td>
<td>56.8±5.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.6±9.3</td>
<td>163.8±6.0</td>
<td>176.8±6.7</td>
<td>162.1±5.9</td>
<td>176.4±6.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3±4.7</td>
<td>30.2±5.9</td>
<td>27.4±4.2</td>
<td>26.4±5.0</td>
<td>27.3±3.6</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>17.3</td>
<td>32.9</td>
<td>33.0</td>
<td>13.1</td>
<td>14.4</td>
</tr>
<tr>
<td>High school</td>
<td>43.1</td>
<td>31.1</td>
<td>27.5</td>
<td>52.0</td>
<td>39.3</td>
</tr>
<tr>
<td>More than high school</td>
<td>39.6</td>
<td>36.0</td>
<td>39.5</td>
<td>35.0</td>
<td>46.3</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>41.8</td>
<td>58.1</td>
<td>27.7</td>
<td>50.4</td>
<td>29.1</td>
</tr>
<tr>
<td>Former</td>
<td>37.8</td>
<td>22.2</td>
<td>39.7</td>
<td>30.0</td>
<td>51.8</td>
</tr>
<tr>
<td>Current</td>
<td>20.4</td>
<td>19.7</td>
<td>32.6</td>
<td>19.6</td>
<td>19.2</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>122.1±17.7</td>
<td>129.9±21.4</td>
<td>130.2±18.8</td>
<td>117.6±16.9</td>
<td>123.5±15.2</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71.8±9.3</td>
<td>73.8±9.5</td>
<td>78.9±9.09</td>
<td>67.4±8.3</td>
<td>75.2±7.7</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>50.3±13.1</td>
<td>56.0±16.3</td>
<td>51.3±13.4</td>
<td>50.2±13.2</td>
<td>48.3±11.2</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>100.3±35.0</td>
<td>119.6±54.0</td>
<td>119.9±49.5</td>
<td>104.2±29.0</td>
<td>110.1±28.9</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>209.5±38.6</td>
<td>212.2±41.1</td>
<td>204.5±39.4</td>
<td>214.2±39.0</td>
<td>204.1±36.2</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.2±16.7</td>
<td>57.2±16.8</td>
<td>48.1±15.8</td>
<td>56.2±16.5</td>
<td>41.4±12.2</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>133.1±36.3</td>
<td>133.5±39.6</td>
<td>133.7±38.7</td>
<td>131.8±37.3</td>
<td>134.4±33.4</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>132.3±82.4</td>
<td>108.2±68.8</td>
<td>114.5±75.9</td>
<td>132.0±81.3</td>
<td>143.7±86.6</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>30.6</td>
<td>50.4</td>
<td>46.1</td>
<td>24.7</td>
<td>28.2</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.7</td>
<td>13.8</td>
<td>13.5</td>
<td>5.3</td>
<td>7.5</td>
</tr>
<tr>
<td>History of CHD, %</td>
<td>5.6</td>
<td>3.6</td>
<td>5.4</td>
<td>2.6</td>
<td>9.7</td>
</tr>
<tr>
<td>AADC, μ</td>
<td>404±127</td>
<td>399±126</td>
<td>416±138</td>
<td>398±120</td>
<td>410±134</td>
</tr>
<tr>
<td>AVR</td>
<td>0.844±0.078</td>
<td>0.834±0.077</td>
<td>0.821±0.077</td>
<td>0.859±0.078</td>
<td>0.835±0.076</td>
</tr>
</tbody>
</table>

B indicates black; F, female; M, male; W, white; BMI, body mass index; and CHD, coronary heart disease.
unchanged (409 μ).

We also performed an analysis to estimate the mean levels of AVR according to quartiles of arterial elasticity, adjusting for age, sex, ethnicity-center, BP/arterial size-related variables (diastolic BP, pulse pressure and its squared term, height, and diastolic carotid arterial diameter), diabetes, hypertension status, and smoking status. The adjusted means of AVR from the highest to lowest quartiles of AADC were 0.841 ± 0.002, 0.837 ± 0.002, 0.836 ± 0.002, and 0.833 ± 0.002 (test of a linear trend across the quartiles, \( P<0.01 \)). The pattern also did not differ substantially by hypertension status (data not shown).

We defined generalized retinal arteriolar narrowing as the lowest 20th percentile of the AVR distribution in the population (AVR <0.77 as the cut point). After adjustment for similar factors, the odds ratio for generalized retinal arteriolar narrowing was 1.12 (95% confidence interval, 1.05 to 1.19) for each 1-SD (127 μ) decrease in AADC.

The AADC-AVR association was tested for interactions with ethnicity, hypertension and diabetes status, antihypertensive medication use, and cigarette smoking. No statistically significant interactions \( (P<0.10) \) were found (data not shown).

### Discussion

In this population-based study of healthy middle-aged men and women, we showed that increased carotid artery stiffness, as measured by ultrasonic echo tracking of the change in its diameter, was associated with increased retinal arteriolar narrowing, as quantified from retinal photographs. In general, each 1-SD decrease in carotid artery elasticity was associated with a 12% increase in odds of generalized retinal arteriolar narrowing. This association was independent of age, sex, race, BP, diabetes, cigarette smoking, and carotid artery diameter; was seen in persons with and without hypertension; and was not modified by diabetes or cigarette smoking.

The observed association between carotid arterial stiffness and generalized arteriolar narrowing may provide important insights into the interrelationship between large- and small-vessel disease processes involved in cerebrovascular disease. In the ARIC study, we have previously shown that generalized retinal arteriolar narrowing is associated with incident clinical stroke,\(^5\) cognitive function impairment,\(^6\) and subclinical white matter lesions defined by MRI,\(^6\) independent of BP, common carotid artery intima-media thickness, diabetes, and other stroke risk factors. The ARIC study did not have cerebral imaging data on all participants to determine whether generalized arteriolar narrowing was specifically associated with lacunar infarction defined by MRI. However, other investigators have shown that generalized arteriolar narrowing and other arteriolar changes are associated with lacunar infarction.\(^7\) Thus, taken together, these observations suggest that generalized arteriolar narrowing is a marker of cerebral small-vessel disease. Carotid stiffness, in contrast, is an early manifestation of large-vessel atherosclerotic disease and has been associated with stroke.\(^1\) The present findings suggest that common antecedents may contribute toward both macrovascular processes in the carotid arteries and microvascular processes in the cerebral arterioles. These would include risk factors associated with both arterial stiffness and generalized retinal arteriolar narrowing such as hypertension,\(^5\) diabetes,\(^6\) cigarette smoking,\(^9\) and cigarette smoking.\(^9\) Our study shows that hypercholesterolemia, an established risk factor for atherosclerosis, is associated with loss of
elasticity but not associated with arteriolar narrowing (Table 2), in keeping with the concept that dyslipidemia is a stronger risk factor for macrovascular disease. However, we note that other studies have not found an association between hypercholesterolemia and arterial stiffness.39

This association may also reflect the effects of microvascular disease on the development of arterial wall stiffness in medium and large arteries. In favor of this hypothesis, experimental data show that impairment of microvascular flow in the vasa vasorum alters the structure and function of arterial walls and reduces the elastic properties of these vessels.21,22 The present data may provide clinical evidence to support this hypothesis. Alternatively, increased arterial stiffness, possibly via elevated systolic BP, may contribute to a narrowing of the retinal arterioles. Arterial stiffness in large and medium arteries and its effect on the kidneys may precede the development of arterial hypertension. We have previously shown in the ARIC study, in BP-adjusted models, a graded, temporal relationship between baseline loss of arterial elasticity and the subsequent development of clinical hypertension31 and a strong association between generalized arteriolar narrowing and past BP, independent of current BP levels.24

However, it is possible that carotid arterial stiffness and generalized retinal arteriolar narrowing occur independently without a causal interrelationship. We note that the data presented are cross-sectional and that carotid arterial elasticity was assessed 3 to 6 years before the retinal photography. The temporal interrelationship between the elastic properties of the large arteries and the development of narrowing in small vessels (or the link between microvascular processes and occurrence of arterial stiffness) can be thoroughly investigated only by the use of longitudinal studies.

Other limitations of this study also warrant consideration. First, selection bias may have obscured or enhanced these associations. A number of photographs were ungradeable largely because pharmacological pupil dilation was not performed. For example, if persons with both arterial stiffness and generalized retinal arteriolar narrowing were more likely to have been excluded because of ungradeable photographs, the observed association could be falsely attenuated. Second, the effect of long-standing hypertension on both carotid arterial stiffness and retinal arteriolar narrowing is likely substantial and may not be completely eliminated despite our adjustment for hypertension and BP, resulting in residual confounding in these associations. Additionally, because elevated pulse pressure may be secondary to increased arterial stiffness, adjustment for pulse pressure in the calculation of AADC may have resulted in overadjustment. On the other hand, to obtain a measure of stiffness in the ARIC study data, AADC must be adjusted for pulse pressure, and because the association is nonlinear (Starling’s law), the adjustment must have a quadratic term. Our method of estimating AADC would not be representative of stiffness without these BP adjustments. Thus, the BP adjustment is not considered an overadjustment but is conceptually necessary. However, the strengths of the present study include a representative, population-based sample; quantitative and masked evaluation of arterial stiffness and retinal arteriolar diameters; and standardized ascertainment of BP and other risk factors.

In conclusion, we demonstrate an association between carotid arterial stiffness and retinal arteriolar narrowing in a population of largely healthy middle-aged persons independent of hypertension and other factors. These data suggest a link between 2 measures of macrovascular and microvascular disease important in stroke pathogenesis. Our data suggest that effective preventive and therapeutic strategies may have to target risk factors affecting multiple vascular beds. Hypertension and diabetes, because of their strong link with both large- and small-vessel disease, are examples of such risk factors.
Acknowledgments

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References

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