Arterial Enlargement in the Atherosclerosis Risk in Communities (ARIC) Cohort

In Vivo Quantification of Carotid Arterial Enlargement

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Background and Purpose The relation between arterial wall (intimal-medial) thickness and lumen narrowing is complex and has previously been studied predominantly at autopsy. B-mode ultrasound affords the opportunity to visualize both wall and lumen of the extracranial carotid arteries in vivo. Several studies have quantified the relation of various independent variables to wall thickness of carotid arteries in population-based samples, but the relation of age and wall thickness to interadventitial and lumen diameter has not previously been investigated in these samples.

Methods We used B-mode ultrasound to quantify the relation of arterial lumen diameter to age, arterial wall thickness, and arterial size (interadventitial diameter) of the extracranial carotid artery in 13,711 members of the Atherosclerosis Risk in Communities (ARIC) cohort.

Results Men had greater interadventitial diameters, thicker walls, and wider lumens than women. Wall thicknesses of the common carotid artery were greater by 21% in men and 22% in women aged 60 to 64 years compared with those aged 45 to 49 years (P<.001). However, lumen diameters were also greater in older individuals because interadventitial diameters were greater. Wall thickness of the internal carotid artery was also associated positively with age, but the lumen diameter of the internal carotid artery was smaller in older individuals. Diameters of the carotid artery segments also differed in their relation to arterial wall thickening. The lumen of the internal carotid artery was uniformly progressively narrower with increasing wall thickness. For the common carotid artery greater wall thickness bore only a small correlation with narrower lumen diameter for thickening of the arterial wall up to 1.2 mm, but the association was more marked for the range of thicknesses between 1.2 mm and 2.5 mm.

Conclusions When arterial enlargement accompanies increased wall thickness, less lumen constriction results than expected. Quantification of these complex relations in vivo may provide new insight into the pathogenesis of symptoms related to cardiovascular disease. Narrowing of the internal carotid artery lumen associated with thicker walls is consistent with the observation that stenosis develops in this region and often leads to symptoms. (Stroke. 1994;25:1354-1359.)

Key Words • aging • ultrasonics • arterial occlusive diseases • carotid arteries • gender

Validation of B-mode and Doppler ultrasound methods for imaging extracranial carotid arteries has provided an important opportunity for investigators to quantify wall thickness (intimal-medial thickness) of the extracranial carotid arteries,1-6 to relate wall thickness to prevalent7,8 and incident9 cardiovascular disease and to cardiovascular disease risk factors,1-7,9-13 and to identify determinants of progression.14 Although this approach is particularly rewarding for the study of the relation of risk factors to arterial disease, the relation of arterial disease to symptom development is not only a function of wall thickening but is additionally related to lumen compromise.15-19 This has been examined most carefully in coronary arteries, and even patients with mild compromise of the coronary artery lumen have a worse prognosis than patients with normal angiograms20; thus, the important relation of mildly obstructive disease to myocardial infarction has recently been explored.21,22 The internal carotid artery and bifurcation more often show stenosis that may result in symptoms compared with the common carotid artery. Extensive literature supports the observation that wall thickening is not synonymous with compromise of the lumen but rather that certain physical principles mandate a positive relation between the outer or interadventitial diameter of the artery and its wall thickness.23 Clinical trials in animals have shown that the initial response of arteries to atherosclerosis is to enlarge or "compensate," increasing the circumference described by the external elastic lamina and preserving the lumen diameter.24 Autopsy studies have provided a qualitative description of arterial compensation in humans25,26; however, there is no quantitative information on the prevalence of this phenomenon in free-living individuals or its relation to age. Arterial enlargement may be involved in symptom development: individuals who are unable to compensate for atherosclerosis may develop stenosis and symptoms sooner than those who are able to compensate. Individual differences or differences between arterial segments in the ability to compensate have not been explored in free-living individuals.

The Atherosclerosis Risk in Communities (ARIC) study affords a unique opportunity to describe the
prevalence of arterial compensation in a population-based sample and to evaluate its relation to wall thickness, demographic factors, and various risk factors. This communication provides evidence for arterial compensation in vivo and explores the quantitative importance of the phenomenon.

Subjects and Methods

The ARIC cohort has been described previously and consists of a probability sample of 15,800 men and women aged 45 to 64 years from four US communities. In three of the four communities the demographic composition of the ARIC cohort reflects that of the community, and the fourth community is made up of black residents of Jackson, Miss. Details of the selection of this cohort have been published.

Ultrasound methods in ARIC have been previously described and consist of a standardized baseline examination of the left and right carotid arteries with measurements of 1-cm lengths of the near and far wall in the common carotid, the bifurcation, and the internal carotid artery. In this study the common carotid artery is defined as the distal 1.0-cm straight portion of the common carotid artery, the bifurcation as the 1.0-cm portion of the artery just below the flow divider, and the internal carotid as the 1.0-cm portion of the artery distal to the flow divider. Ultrasound tapes are digitized and read in a central laboratory by trained and certified readers who attempt to identify the following four boundaries in each segment from the optimal interrogation angle: the adventitia-media interface at the near wall (interface 2); the intima-lumen boundary at the near wall (interface 3); the lumen-intima boundary at the far wall (interface 4); and the media-adventitia boundary at the far wall (interface 5). Intima-media thickness is defined as 2-3 or 4-5 on the near wall and far wall, respectively (Fig 1); however, because the ARIC protocol was designed to focus on the far wall, near wall measurements are often missing and have not been used in this analysis. As described, not all participants have measurements of wall thickness, interadventitial diameter, or estimated lumen due to poor visualization of the relevant interfaces. Nonblack and nonwhite participants were excluded from the analysis. Of the remaining 15,739 ARIC participants, 71% of men and 70% of women had images suitable for estimation of the lumen diameter in the left common carotid artery, and 36% of men and 33% of women had images suitable for estimation of the lumen diameter in the left internal carotid artery. In all, 13,711 individuals had images that were suitable for estimating the lumen diameter in either the common carotid or the internal carotid or both segments. Interface visualization is slightly poorer in those who are more obese with deeper carotid arteries, but we have not found any other factors that are systematically different in those with missing values compared with those whose lumens could be measured, and we do not anticipate that exclusion of those with missing diameter estimates would bias the relations of diameter to wall thickness that are the focus of this report.

Wall thicknesses, lumen diameters, and arterial diameters were compared in men and women and between the internal and common carotid arteries using unpaired (men versus women) and paired (internal versus common carotid) t tests. Mean values of the specified diameters and thicknesses were calculated in men and women for 5-year age groups after adjusting for height using ANCOVA and were calculated for all ages after adjustment for age and height using ANCOVA. For descriptive purposes lumen diameters and interadventitial diameters were calculated in categories of wall thickness and adjusted for age using ANCOVA. The association of wall thickness with lumen diameters and interadventitial diameters was also estimated using a multiple linear regression model with age, wall thickness, and the square of wall thickness as independent variables. The effect on interadventitial diameter and lumen of wall thickness of 0.5 mm compared with 2.5 mm was estimated using the multiple linear regression model. The effect was described as a percent change using the estimated difference divided by the age and height means in the Table.

Results

An initial exploration of the data uncovered a positive association between height and interadventitial diame-
Height-Adjusted Means for Arterial Wall Thickness, Interadventitial Diameter, and Lumen Diameter by Age, Sex, and Arterial Segment

<table>
<thead>
<tr>
<th>Age, y</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WT</td>
<td>IA</td>
<td>LUM</td>
<td>WT</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>.77</td>
<td>7.78</td>
<td>6.24</td>
<td>.81</td>
</tr>
<tr>
<td>No.</td>
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<td>1473</td>
<td>1028</td>
<td>1258</td>
</tr>
<tr>
<td>Women</td>
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<td>5.79</td>
<td>.73</td>
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<tr>
<td>No.</td>
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<td>2114</td>
<td>1789</td>
<td>1930</td>
</tr>
<tr>
<td>Internal</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>6.91</td>
<td>.84</td>
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<tr>
<td>No.</td>
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<td>615</td>
<td>693</td>
<td>636</td>
</tr>
<tr>
<td>Women</td>
<td>.68</td>
<td>7.76</td>
<td>6.47</td>
<td>.75</td>
</tr>
<tr>
<td>No.</td>
<td>593</td>
<td>666</td>
<td>511</td>
<td>642</td>
</tr>
</tbody>
</table>

**WT** indicates maximum far wall arterial intimal-medial thickness; **IA**, interadventitial diameter; and **LUM**, lumen diameter = interadventitial diameter - 2 × maximum far wall thickness. Measurements are expressed in millimeters. ANCOVA was used to estimate adjusted means using total average height so that the means are comparable between men and women.

Age-adjusted values for men greater than those for women for wall thickness, interadventitial diameter, and lumen, *P* < .001.

ters and between height and lumen in men and women (difference of 0.2 mm to 0.4 mm in diameter for 10-cm difference in height; *P* < .0001 for men and women, common and internal carotid arteries), and artery dimension data have been adjusted accordingly. The Table presents the height-adjusted mean wall thickness, interadventitial diameter, and lumen diameter in the common carotid and internal carotid arteries of men and women in four age groupings of the ARIC sample as well as for all ages combined. As has been previously described, the mean wall thickness of the internal carotid artery exceeded that of the common carotid artery, was greater at both sites in men compared with women, and was greater in older individuals. The Table further demonstrates that the interadventitial diameters and lumen diameters of these arteries in men exceeded those in women. For both men and women the average lumen and interadventitial diameter were greater in the internal carotid than in the common carotid artery (*P* < .001).

Compared with individuals aged 45 to 49 years, height-adjusted wall thicknesses of the common carotid arteries of individuals aged 60 to 64 years were 21% (0.16 mm) and 22% (0.15 mm) greater for men and women, respectively, interadventitial diameters were 7% (0.51 mm) and 8% (0.57 mm) greater, and lumen diameters were 3% (0.21 mm) and 5% (0.30 mm) greater in men and women, respectively (*P* < .001). The wall thicknesses of the internal carotid arteries of older individuals were also greater than those of younger individuals, but this was not correlated with greater internal carotid interadventitial diameters, and therefore the lumen diameters were narrower by 8% (0.59 mm) and 3% (0.20 mm) in older compared with younger men and women, respectively (*P* < .01). The association of age with decreased lumen diameter in the internal carotid artery was more pronounced in men than in women.

Fig 2 presents the relation of wall thickness to interadventitial diameter and lumen diameter in the internal carotid and the common carotid arteries in men and women. For both the common and the internal carotid arteries in both men and women, thicker arterial walls were associated with greater interadventitial di-
ameters, but the association of artery walls and lumen diameters was more complex.

The association of wall thickness with interadventitial diameter was more pronounced in the common carotid than in the internal carotid artery. For example, in the common carotid artery, mean interadventitial diameters associated with wall thicknesses of 2.5 mm were 20% greater in men and 23% greater in women than interadventitial diameters associated with wall thickness of 0.5 mm. These estimates are from linear regression models using age, wall thickness, and wall thickness squared as independent variables and are statistically significant ($P < .001$). For the internal carotid artery a comparable difference in wall thickness was associated with a smaller increase in interadventitial diameter of only 5% in both men and women ($P < .001$).

The association of wall thickness with lumen diameter varied by arterial segment. In the internal carotid artery, the association appeared to be uniform over a wide range of wall thickness (Fig 2). Lumens were 54% narrower in men and 57% narrower in women in association with walls of 2.5-mm thickness compared with walls of 0.5-mm thickness. In the common carotid artery, the comparable reduction in lumen diameter associated with walls of increasing thickness was 38% in men and 39% in women. However, in the common carotid artery compromise of the lumen was more markedly progressive at wall thicknesses greater than 1.2 mm (Fig 2). This variability in association of lumen and wall thickness appears in the regression models with a larger coefficient for the quadratic term for wall thickness in the common than in the internal carotid artery. In magnitude it is reflected in only a 6% smaller lumen of the common carotid artery in men and an 8% smaller lumen in women associated with a difference in wall thicknesses from 0.5 to 1.19 mm and with a more marked decrease in lumen diameter of 32% in men and 31% in women associated with a difference in wall thickness from 1.2 to 2.5 mm.

**Discussion**

Development of methodology for noninvasively imaging the extracranial carotid arteries in vivo has afforded investigators a unique opportunity to establish normative data for thickness of the arterial wall (intimal-medial thickness) and to relate arterial wall thickness to demographic factors,14-16 to cardiovascular risk factors,17-19 and to symptomatic cardiovascular disease.20 However, symptomatic atherosclerotic vascular disease may be related to lumen compromise as well as thickening of the arterial wall. Early studies of patients with coronary artery disease showed that even disease that only minimally obstructs the lumen leads to worse prognosis than that associated with normal coronary arteries,20 and more recently the wall of the minimally obstructive but atherosclerotic coronary vessel has been shown to be a site of predilection for thrombosis.21 Others have demonstrated that obstructive coronary disease is strongly associated with symptoms.22 However, there is only a loose relation between wall thickening and lumen stenosis: several authors have observed a tendency for interadventitial diameters and lumen diameters to increase rather than decrease with increasing wall thickness of the coronary arteries,22,23 and clinical trials in nonhuman primates have confirmed that the initial response to cholesterol feeding is for the artery to develop atherosclerosis and dilate rather than constrict.24 The observation that atherosclerotic arteries dilate is not new,25 but the more recent observations more carefully quantify the extent to which interadventitial enlargement is associated with wall thickening. To our knowledge there are no previous studies of the relation of wall thickening to lumen diameter in the carotid arteries.

Our data demonstrate a weaker association in vivo between narrow arterial lumens and thick arterial walls in the common carotid artery than in the internal carotid artery. In the common carotid artery, individuals with thicker artery walls also had increased interadventitial diameter and little compromise of the lumen in artery walls of up to 1.2 mm in thickness. For individuals whose common carotid arterial wall thicknesses ranged from 1.2 mm to 2.5 mm, interadventitial diameters continued to show a positive association with wall thickness (though of lesser magnitude), and lumens of these arteries narrowed more dramatically as association with thicker walls. In contrast, in the internal carotid artery, increments in wall thickness were associated with little increase in interadventitial diameter and with progressive narrowing of the lumen. We have no explanation for this difference between the common carotid artery and the internal carotid artery, although it is consistent with clinical experience that the internal carotid is more often the site of stenosis and symptoms than the common carotid. It is well known that the internal carotid artery and the common carotid artery are different histologically: the former is a muscular artery, whereas the latter is an elastic artery.26 The arteries differ physiologically as well, in that the internal carotid artery is less distensible than the common.27 We are unaware of studies comparing elastic with muscular arteries for their ability to compensate for thickening of the arterial wall. The coronary artery has been shown to behave like the common carotid artery in the sense that the most usual response of the coronary artery to atherosclerosis is to dilate.25,26 It is also evident that the internal carotid and the common carotid arteries differ in their exposure to turbulent flow; perhaps an interactive effect of flow with risk factors is responsible for the difference in ability to compensate expressed by the common and internal carotid arteries. Irrespective of the nature of the factors that promote its dysfunction, it is likely that arterial remodeling ultimately depends on growth factors and other factors whose activities are promoted in the setting of disruption of endothelial integrity.28

Although we have discussed the ability of arteries to compensate for thickened walls, considerable literature suggests that, based on physical principles, larger arteries are likely to be accompanied by thicker walls,29 and we believe that these physical principles may be at least partly responsible for the greater wall thickness in tall compared with short individuals and in men compared with women.

Older individuals in this sample had thicker common carotid artery walls but also larger lumens related to a greater interadventitial diameter. This association of increased lumen with age was not seen in the internal carotid artery, where age was associated with a decreased lumen in men and (to a lesser extent) in women.
Investigators have previously related symptom development and risk factors to stenosis of the coronary arteries. Our data suggest that because of the loose relation of lumen stenosis to wall thickening, investigations attempting to define the relation of risk factors to arterial disease should focus attention on the arterial wall and that there may be inherent pitfalls for studies that attempt to relate risk factors to arterial disease using measurements of lumen diameter (eg, angiography, Doppler ultrasound). On the other hand, a focus on the lumen may be appropriate for investigators wishing to relate arterial disease to symptom development. Although wall thickening is a common and perhaps universal response to age and other risk factors, narrowing of the arterial lumen (at least of the common carotid and coronary arteries) is less prevalent. The ability of individuals and of certain arteries to remodel in the face of the commonplace occurrence of wall thickening may importantly reduce the expression of symptoms related to atherosclerotic arteries. It is well known that the internal carotid artery (which our data shows does not remodel but rather develops stenosis with increasing wall thickness) is more commonly associated with symptom development than the common carotid artery. We believe that estimation of lumen diameter or of wall thickness separately only partly describes arterial disease, and analysis should take both into consideration to better understand pathophysiology.

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