Carotid Arterial Structure in Patients With Documented Coronary Artery Disease and Disease-Free Control Subjects

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Background—Although atherosclerosis often leads to lumen narrowing and symptomatic cardiovascular disease, it is now recognized that arteries have the potential to compensate by enlarging in response to atherosclerosis. We tested the hypotheses that carotid arterial interadventitial (IA) and lumen diameters were related to wall thickness and that carotid arterial diameters of individuals with coronary artery disease (CAD) differed from those of CAD-free controls.

Methods and Results—We measured lumen diameter, IA diameter, and intima-media thickness (IMT) using B-mode ultrasound in the common and internal carotid arteries of 141 CAD case patients and 139 disease-free control subjects. Common carotid IA diameter was greater in CAD cases than controls after adjustment for age, height, and sex (P<0.01). Common carotid lumen diameter was marginally larger in individuals with greater IMT (P=0.06) but was not associated with case status. Conversely, mean internal carotid IA and lumen diameters were smaller in CAD cases than controls in both univariable and multivariable models (both P<0.001), and lumina were smaller in individuals with greater IMT. Despite these cross-sectional differences in carotid artery dimensions, we were unable to detect any statistically significant interactive effects of CAD case status on the association of IMT with arterial dimensions.

Conclusions—Internal carotid artery lumen and IA diameters are both smaller in CAD cases than controls. The association of increased IMT with arterial dimensions varies in a manner that is segment-specific for the common and internal carotid arteries. (Circulation. 2003;107:1146-1151.)

Key Words: carotid arteries ■ atherosclerosis ■ coronary disease ■ compensation

Although atherosclerosis may advance to obstruct the artery lumen, the relationship between lumen stenosis and intima-media thickening (IMT) per se is often counterintuitive. Indeed, a growing body of evidence suggests that arteries have the potential to enlarge and thus compensate for atherosclerosis, thereby preserving lumen diameter and vital blood flow. Moreover, arterial compensation during development of subclinical atherosclerosis may influence whether clinical presentation of vascular disease comes in the form of a chronic, stable condition such as exercise-induced angina (related to stenosis) or a life-threatening acute coronary syndrome (related to rupture of a nonocclusive unstable plaque).

In a seminal 1988 report, Glagov et al demonstrated the compensatory remodeling effect in autopsy specimens of the left main coronary artery. These cross-sectional studies suggested that adaptive enlargement could effectively preserve lumen area until atherosclerosis overcame the arterial compensatory response (~40% lumen stenosis according to Glagov et al). Quantitative postmortem studies of coronary artery dimensions in humans and cholesterol-fed monkeys further suggested that lumen area could be preserved even in severely diseased arteries. Subsequently, noninvasive B-mode ultrasound was used to investigate carotid artery remodeling in vivo in the population-based Atherosclerosis Risk in Communities (ARIC) Study. The cross-sectional ARIC data in healthy individuals suggested that carotid artery lumina are larger in individuals with a modest degree of wall thickening; however, smaller lumina were found in association with more severe wall thickening. Furthermore, longitudinal studies have demonstrated the direct relationship between atherosclerotic thickening and arterial enlargement; in individuals with carotid plaques that progressed during follow-up, arterial dilatation accompanied increased IMT, but arterial dimensions were unchanged in participants whose atherosclerosis was stable. Likewise, serial studies using quantitative coronary angiography have shown significant lumen enlargement with progression of atherosclerosis, and these studies also demonstrated that aggressive risk factor treatment inhibits progression and enhances lumen enlargement.
The role of arterial remodeling in the development of symptomatic vascular disease remains poorly understood. Autopsy data suggested little, if any, association of lumen area with atherosclerotic wall thickening in patients with a history of coronary heart disease, whereas lumen area was increased in association with atherosclerosis in patients free of symptomatic coronary heart disease.\(^2\) On the basis of these data, the hypothesis was advanced that arterial enlargement could explain susceptibility to or protection against symptomatic disease.\(^2\) Unfortunately, the study of coronary artery remodeling has been impeded by the lack of noninvasive methods for quantifying atherosclerosis and the resultant restriction of investigation to specimens obtained at autopsy or to patients undergoing angiography for suspected coronary artery disease (CAD). In symptomatic individuals, the contribution of arterial remodeling may be difficult to assess retrospectively because of the severity of disease and/or complications associated with atherosclerosis.\(^3,9\)

B-mode ultrasound measures of asymptomatic carotid artery atherosclerosis are associated with prevalent coronary heart disease\(^5,13\) and allow noninvasive study of associations of arterial walls with lumen dimensions in vivo.\(^1\) Therefore, we used B-mode ultrasound to test the hypothesis that associations of IMT with arterial dimensions are different in individuals with obstructive CAD compared with CAD-free controls.

### Methods

#### Patient Population

Participants were recruited for the Carotid Artery Follow-up Study (CAFUS) from patients undergoing coronary angiography at Wake Forest University Baptist Medical Center as previously described.\(^1-13\) Potentially eligible CAD case patients (cases) (≥50% stenosis of ≥1 coronary vessels) and control subjects (controls) (no coronary lumen irregularities) were recruited, and “nonobstructive” patients (coronary stenoses of <50%) were excluded. Equal numbers of male cases (n=71) and controls (n=69) and female cases (n=70) and controls (n=70) were recruited according to a stratified random sampling strategy. Patients were excluded who were <45 years old, were clinically unstable (eg, myocardial infarction within the last 6 weeks), or who had previously had coronary bypass surgery, angioplasty, or carotid endarterectomy. Use of certain medications (lipid-lowering drugs, thyroid medication, or cortisone) or the presence of certain clinical conditions (hepatic disease, alcohol abuse, cancer, or renal failure) that could alter plasma lipids were also reasons for exclusion. All patients provided informed consent to participate in the study, and the protocol was approved by the Institutional Review Board of Wake Forest University School of Medicine.

#### Clinical Evaluation

Medical history, vascular disease risk factors, menopausal status, and medication use were elicited during an outpatient clinic visit 6 to 8 weeks after catheterization. During the visit, height, weight, and blood pressure were measured and blood was drawn for laboratory analyses. Detailed descriptions of laboratory analyses for the present study have been published previously.\(^1-13\)

#### Ultrasound

The ultrasound methodology for this study has been described extensively.\(^1-13\) In brief, a Biosound 2000 II spectral analysis high-resolution ultrasound unit equipped with an 8-MHz transducer was used for all examinations, and images were recorded on S-VHS videotapes for offline analysis. Sonographers and readers were certified, and regular quality control was performed.

Arterial IMT and dimensions were measured semiautomatically as detailed previously using customized software developed by the California Institute of Technology/Jet Propulsion Laboratory.\(^11-13\) For the present analysis, 2 carotid segments were identified on both the left and right sides: the distal 1 cm of the common carotid proximal to the bifurcation and the proximal 1 cm of the internal carotid. The sonographer identified 2 interfaces on each wall: on the near wall, the first interface (interface 2) is the adventitial-medial boundary, and the second (interface 3) is the intima-lumen boundary; on the far wall, the first interface (interface 4) is the lumen-intima boundary, and the second (interface 5) is the media-adventitia boundary. Thus, 2 to 3 and 4 to 5 define IMT on the near and far walls, respectively. The sonographer optimized the near and far walls separately (multiple focus zones) to define the maximum IMT for each of the 8 sites.

Arterial dimensions were measured at the maximum 2 to 3 or 4 to 5 IMT within each segment. Reference points were placed at interfaces 2, 3, 4, and 5 when available, and the distance was computed between interfaces 2 and 3 (near-wall IMT), 4 and 5 (far-wall IMT), 3 and 4 (lumen), and 2 and 5 (interadventitial [IA] diameter). In some cases, because of the tortuosity of the internal segment, the intima/lumen interface (interface 3 or 4) opposing the site of maximum IMT could not be visualized, and direct lumen measurement was not possible. If interfaces adjacent to this site (with missing intima/lumen interface) were defined, readers were instructed to measure the IMT there after recording the maximum IMT and IA diameter measurements. In such circumstances, an indirect measurement of lumen diameter was computed by subtracting the adjacent IMT plus the maximum IMT from the IA diameter measured at the maximum IMT site.

### Statistical Analysis

Preliminary analyses suggested no differences in the distributions of IMT, lumen diameter, and IA diameter for right versus left carotid artery; therefore, the mean of right- and left-side measures was analyzed for each variable. For data presentation and analysis, age and IMT were categorized separately into quartiles by ranking these data without regard to CAD status. General linear regression models (SAS GLM procedure) were used to test associations between arterial dimensions and case-control status, age quartile, and IMT quartile.\(^14\) For arterial measures, means and SEMs (SAS least-square means procedure) are reported after adjustment for age, sex, and, where appropriate, IMT. Because physical stature is known to contribute to arterial diameter,\(^7\) height was included in all multivariable models for arterial dimensions.

### Results

#### Association of Arterial Dimensions With Age and CAD

As shown in the Table, age was associated with structural measures (IMT, IA diameter, and lumen diameter) similarly in CAD cases and controls with the exception of the association between age and internal carotid lumen diameter. Among all participants, both common and internal carotid IMTs were greater in each quartile of increasing age (\(P<0.01\) for each artery segment, adjusted for CAD status). In the common carotid artery, both lumen and IA diameter were greater in association with age (\(P=0.003\) and \(P<0.001\), respectively, adjusted for CAD status and height). Associations of age with common carotid lumen or IA diameter did not differ by case status (tests of CAD status–by-age interactions were not significant). In contrast, internal carotid IA diameter was not associated with age (\(P=0.17\) adjusted for CAD status and height), whereas lumen diameter was smaller.
in older individuals ($P=0.002$), and the association varied by CAD case status ($P_{interaction}=0.005$).

**Case-Control Differences in Arterial Dimensions**

The Table shows that, among all participants, height-adjusted common carotid IA diameter was greater in CAD cases than controls ($P=0.004$), whereas lumen diameters did not differ between cases and controls. Overall, CAD cases had reduced internal carotid lumen and IA diameters compared with controls ($P<0.001$ and $P=0.01$, respectively) despite markedly greater IMT in the former. The relationships between arterial diameters and case status were essentially unaffected by adjustment for age and sex (data not shown). In the internal carotid, associations of prevalent CAD with smaller IA and lumen diameters persisted ($P<0.01$ and $P<0.001$, respectively) in multivariable models that included age, sex, and IMT.

**Associations of Lumen and IA Diameter With IMT**

Figures 1 and 2 depict the relationships between IMT and lumen and IA diameters in the common and internal carotid arteries, respectively. Figure 1 demonstrates that age- and height-adjusted common carotid IA diameters were larger

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<th>Arterial Measures* (mm) for CAD Cases and Controls by Quartiles of Age</th>
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*Mean±SEM; lumen and IA diameters adjusted for height; IMT unadjusted.
†P for age trend.
‡P for age-by–case status interaction.
§P for case-control comparison.
with each quartile of increasing IMT in both cases and controls. Common carotid IA diameter was strongly associated with IMT (P<0.001 for age, height, and CAD status--adjusted model), and the association was consistent in cases and controls (P=0.79 for case status by IMT interaction). The marginally significant association of common carotid lumen diameter with increased IMT (P=0.06) likewise did not vary by CAD status (P_{interaction}=0.98).

As suggested by Figure 2, internal carotid IA diameter was not associated with IMT (P=0.27 for age, height, and CAD status--adjusted model). However, internal carotid lumen diameter was smaller in individuals with greater IMT (P<0.01 for age, height, and CAD status--adjusted model). The trend was present in CAD cases and controls alike, with lumen diameter smaller by almost 1 mm in patients in the lowest compared with those in the highest quartile of IMT (6.53±0.16 versus 5.59±0.16 mm, P<0.001, in the lowest and highest quartiles, respectively, adjusted for age, height, and CAD status). Mean internal carotid lumen diameters for CAD cases tended to be smaller than those of controls at each IMT cut-point; however, within quartiles, case-control comparisons reached significance only in the upper quartile of IMT. Within the internal carotid, CAD cases and disease-free controls showed similar associations of lumen and IA diameter with IMT (P=0.32 and 0.28 for tests of CAD status--by-IMT interaction for lumen and IA, respectively).

Discussion

Segment-specific associations of carotid artery dimensions with IMT were reported previously in a cross-sectional analysis of data from the population-based ARIC study. Common carotid wall thickening in the ARIC study was associated with larger IA diameters in both men and women; however, there was no significant association between IMT and IA diameter in the internal segment. The ARIC analysis suggested that common carotid lumina were smaller only when mean far wall IMT exceeded 1.2 mm (observed in 1.5% of women and 3.2% of men), but internal carotid lumina were smaller over a broad range of increasing IMT.

The present study describes segment-specific differences in carotid artery lumens and IA dimensions in individuals with obstructive CAD and CAD-free controls. Although common carotid IMT was greater in CAD cases than controls (as previously reported), IA diameters were increased proportionately; thus, lumen diameters were similar in CAD cases and controls. In the internal carotid, CAD cases also had greater IMT than controls, but both lumen and IA diameters of the internal segment were significantly smaller in cases than controls.

Of interest, Pasterkamp et al reported what the authors called “paradoxic constrictive” femoral arteries associated with atherosclerosis. Their cross-sectional study suggested that stenoses of <25% were most often associated with local arterial enlargement in the femoral arteries, whereas reduced arterial diameter accompanied more significant stenoses. A previous longitudinal study using B-mode ultrasound also suggested that the absence of compensatory enlargement contributed to lumen compromise during rapid focal progression of carotid plaques in areas of high hemodynamic forces such as the internal carotid. The cross-sectional design of the present study does not permit us to determine whether case-control differences in internal carotid IA diameters accompanied atherosclerosis or whether individuals with CAD had smaller internal carotid arteries ab initio.

Because previous studies have described associations of age, sex, physical stature, and arterial diameters, we adjusted for these factors in multivariable models. These covariates explained neither the case-control differences in arterial dimensions nor the segment-specific associations of IMT with arterial dimensions. Moreover, inclusion of IMT in multivariable models failed to explain reduced internal carotid luminal and IA diameters associated with prevalent CAD. Pasterkamp et al also reported that reductions in femoral artery lumen and IA diameters were not explained by increased IMT.

It has been postulated that variation in the compensatory remodeling mechanism could influence individual susceptibility to developing symptomatic, obstructive cardiovascular disease. Indeed, we found that participants with prevalent CAD had smaller mean internal carotid lumen and IA diameters than disease-free controls; however, we could detect no statistically significant effect of case status on the association of IMT with either lumen or IA diameter (P>0.2 for tests of interactive effects of case status on association of IMT with lumen and IA diameters). It is possible that our
sample size limits the statistical power to detect interactive effects with case status, although Figures 1 and 2 suggest that large differences in the association of carotid artery atherosclerosis with arterial dimensions are unlikely between CAD cases and controls.

Anatomic and physiological differences in the carotid segments may partially explain segment-specific differences in associations of arterial dimensions with IMT. The internal carotid is a muscular artery, whereas the common segment is an elastic conducting artery. Elastic arteries, such as the common carotid, are exposed to relatively high blood pressure and laminar blood flow, ostensibly curtailing intima exposure to circulating risk factors. Within the internal carotid, turbulent blood flow and locally reduced shear stress prevail and advanced plaques are more frequent. Longitudinal follow-up suggests that procoagulant risk factors such as fibrinogen and lipoprotein(a) contribute to rapid focal progression of atherosclerosis in the internal carotid, where blood flow is turbulent. Moreover, these data showed that rapid focal atherosclerosis progression within the internal carotid favored lumen narrowing over arterial enlargement and lumen preservation. In both the coronary and carotid artery systems, associations between atherosclerosis and lumen and IA dimensions are probably modulated by myriad growth factors, cytokines, and enzymes secreted from both resident cells and cells recruited from the circulation.

Although confirmation in longitudinal trials is needed, the present data suggest that differences in arterial enlargement may contribute to carotid segment-specific variation in the occurrence of occlusive lumen stenosis. Common carotid occlusion is rare, accounting for <1% of carotid disease cases. The present data, as well as cross-sectional ARIC data, suggest that increased common carotid IMT is strongly associated with enlarged IA diameter and little or no decrease in lumen diameter. However, at the other extreme, our data suggest that increased internal carotid IMT is associated with decreased lumen diameter in the absence of IA diameter enlargement.

Fishcr et al noted in the early 1950s that internal carotid stenosis and occlusion were more frequent than previously believed. These data provide a methodological basis for the present study. The Framingham Study, researchers found that among asymptomatic participants >65 years old, 8% had significant carotid stenosis >50%. Although the carotid arteries are the source of perhaps only 20% of all ischemic strokes, overall stroke incidence in asymptomatic patients with significant carotid lumen stenosis ranges from ~2% to 8% per year, depending on the degree of lumen obstruction. Moreover, longitudinal follow-up within the ARIC and Cardiovascular Health Study populations suggests a graded increase in risk of incident ischemic stroke with increasing carotid IMT measured by B-mode ultrasound. The present data are consistent with the hypothesis that part of the risk of occlusive disease within the internal carotid is related to a relative lack of compensatory enlargement in that segment.

**Study Limitations**

The present study is cross-sectional in design and used B-mode ultrasound; therefore, some caveats apply. Because carotid atherosclerosis is eccentric in nature, the angle of interrogation is critical in studies using longitudinal B-mode ultrasound imaging protocols. As such, we cannot be certain that lumen diameter accurately reflects cross-sectional lumen area. Moreover, because arterial dimensions were measured at the site of maximum IMT, it is possible that variation in the location of plaque development (proximally versus distally) could have affected our findings. Also, the design of the present study does not permit us to address the temporal relationships between atherosclerosis and arterial diameter; however, longitudinal studies suggest that arterial remodeling accompanies significant progression of atherosclerosis in both the carotid and coronary arteries. Moreover, our data probably reflect arterial dimensions in relatively early, asymptomatic carotid atherosclerosis, and with progression or complication of disease, associations may differ.

**Conclusions**

Common carotid atherosclerosis is associated with larger IA diameter and no reduction in lumen diameter. Conversely, in the internal carotid, greater IMT is associated with smaller lumina in the absence of IA diameter enlargement. Case-control comparisons suggest differences in arterial dimensions: common carotid IA diameter was greater in cases than controls, whereas internal carotid lumen and IA diameter were both reduced in CAD cases compared with controls. However, interactive effects of case status on the associations between IMT and arterial dimensions did not reach significance. Although these data require confirmation in a longitudinal study, they are consistent with the concept that lack of arterial enlargement of the internal carotid during atherosclerosis progression partly explains the well-documented association of this carotid segment with symptomatic cardiovascular disease.

**Acknowledgments**

This study was supported by grants HL-35333 and HL-59503 from the National Heart, Lung, and Blood Institute and by the General Clinical Research Center of the Wake Forest University School of Medicine (MO1 RR-07122).

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_Circulation_. 2003;107:1146-1151; originally published online February 10, 2003; doi: 10.1161/01.CIR.0000051461.92839.F7
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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