Relations of Intimal-Medial Thickness Among Sites Within the Carotid Artery as Evaluated by B-Mode Ultrasound

George Howard, DrPH; Gregory L. Burke, MD; Gregory W. Evans, MS; John R. Crouse III, MD; Ward Riley, PhD; Donna Arnett, PhD;
Regina de Lacy, MS; Gerardo Heiss, MD, PhD; for the ARIC Investigators

Background and Purpose B-mode ultrasound is a widely used technique for the clinical and epidemiological assessment of carotid atherosclerosis. This article describes the relation between arterial intimal-medial thickness (IMT) at different sites within the extracranial carotid artery.

Methods IMT was measured by B-mode real-time ultrasound as an index of atherosclerotic involvement in the extracranial carotid arteries as part of the population-based Atherosclerosis Risk in Communities (ARIC) study. The relation between IMT at different sites was described by correlation coefficients and percentile regression techniques based on between 4034 and 9386 pairs of measurements (variation in sample size depending on the paired sites).

Results Increased IMT at one site was associated with increased IMT at other sites. The correlation between right and left IMT at the same anatomic location in the carotid artery ranged from .34 to .49; the correlation at different anatomic locations in the carotid artery on the same side ranged from .25 to .43. The distribution of IMT, described by the percentiles of IMT at the inference site as a function of IMT at the index site, showed constricted percentiles of IMT at the inference site for small IMT at the index site and an increase in the spread of percentiles with increasing IMT.

Conclusions Although increased carotid IMT at one site is positively associated with thickened walls at other carotid sites, the ability to accurately predict wall thickness at a site given the wall thickness at other sites is modest. The general association between sites supports the systemic nature of atherosclerosis, while the lack of tight agreement between sites supports the focal nature of the atherosclerotic process.

Key Words • atherosclerosis • carotid arteries • ultrasonics

The use of B-mode real-time ultrasound to assess atherosclerosis has been increasing in both epidemiological studies and clinical trials. This technology offers the opportunity to reliably assess intimal-medial thickness (IMT) in the carotid and other superficial arterial beds. Gaining an understanding of the relation of IMT among arterial sites allows a better understanding of the development and progression of atherosclerosis and enables investigators to better establish which arterial sites may be most useful as an index of atherosclerosis for clinical trials and epidemiological studies.

The International Atherosclerosis Project, an autopsy-based project that studies the extent of atherosclerotic involvement in the carotid bed,1–7 observed raised fibrous plaques in the carotid arteries of nearly all adult subjects. Major cardiovascular risk factors (including diabetes and hypertension) were associated with the proportion of surface area involved in atherosclerosis in the carotid arteries, intracranial arteries, the aorta, and the coronary arteries.1,4 These autopsy studies observed a stronger association between the amount of surface area involved in raised lesions between contralateral carotid arteries than between the carotid and either coronary arteries or the aorta.7

Most studies using ultrasound to assess the extent of atherosclerosis have focused on evaluation of the carotid rather than peripheral artery bed.8–14 Since imaging the more distal sites of the extracranial carotid bed is more difficult, some investigators have restricted ultrasound evaluation of atherosclerosis to the common carotid artery (CCA) segment.10–12 However, early atherosclerotic lesions are demonstrably more frequent in the distal parts of the carotid bed.12 Information on the relation among IMT at different carotid sites would permit a more complete understanding of the usefulness of specific sites as indexes of atherosclerosis. This article describes the distribution of IMT, assessed bilaterally by B-mode ultrasound, at sites in the CCA, bifurcation, and internal carotid artery (ICA) as a function of the IMT at other sites in the same arterial bed.

Subjects and Methods

The Atherosclerosis Risk in Communities (ARIC) cohort is a population-based probability sample of 15 800 participants aged 45 to 64 years sampled from four US communities.8 From May 15, 1987, through December 1989, 14 106 carotid B-mode real-time ultrasound examinations were performed as part of the baseline examination. The reduced sample size (14 106
versus 15,800) reflects technical difficulties during "early" ultrasound examinations in the ARIC study (those before May 15, 1987). The IMT was measured in the far (deeper) wall of three segments of the right and left extracranial carotid arteries: (1) the 1-cm segment proximal to the dilation of the carotid bulb, which will be referred to as the CCA; (2) the 1-cm segment proximal to the flow divider, referred to as the bifurcation; and (3) the 1-cm segment in the internal branch distal to the flow divider, referred to as the ICA. In each of these segments, 11 measurements of the IMT of the far wall were attempted at 1-mm increments, and for purposes of this analysis, the IMT at each segment was estimated as the mean of these 11 measurements. Ultrasound examinations were performed using the Biosound 2000IIsa, with a nominal center transducer frequency of 8 MHz. The images were evaluated in a central reading facility with computer-assisted reading stations. Details of the scanning and reading procedures are described elsewhere.16,17

At any carotid segment, it was not always possible to visualize the far wall intimal-medial boundary sufficiently to measure IMT. Because images are more difficult to obtain in more distal segments, the proportion of participants with visualized walls was greatest at the CCA (79% visualized), followed by the bifurcation (59% visualized), and least at the ICA (41% visualized).

The relation of IMT between select pairs of sites was described by the Pearson correlation coefficient and regression techniques. The commonly used technique of ordinary least-squares (OLS) regression, or "linear regression," is used in a wide variety of settings to describe the mean value of one factor as a function of a second factor. However, this technique does not provide information on the distribution (or spread) of the data points about the predicted mean line. In this report, OLS regression was used to describe the relation of the mean value of IMT at one arterial site ("inference site") as a function of IMT at another site ("index site"). In addition, the asymmetrical residual weighting approach described by Efron18 was used to describe the relation between the percentiles (or spread) of IMT at the inference site as a function of wall thickness at an index site. To allow curvature of the OLS and percentile regression estimates, a quadratic model was fit relating the IMT at the index site to the IMT at the inference site (IMT_inference = β0 + β1IMT_index + β2IMT_index^2). Percentile regression lines were estimated for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. Results are presented graphically and as a table of estimated IMTpercentiles for the inference site at 0.25-mm increments of IMT at the index site. For example, for a CCA IMT of 0.50 mm, 80% of the values at the bifurcation were observed between the values of 0.47 mm (10th percentile) and 0.98 mm (90th percentile), a range of 0.51 mm. However, for a CCA IMT of 1.5 mm, 80% of the bifurcation IMT values are expected to be between 0.84 mm and 1.95 mm, a range of 1.11 mm.

Fig 2 shows the estimated percentiles of IMT on the right CCA, bifurcation, and ICA as a function of IMT on the corresponding left CCA, bifurcation, or ICA. These percentiles also show a fan pattern, with the upper percentiles of IMT at the inference site exhibiting steeper slopes than the lower percentiles. Table 3 provides the point estimates of the IMT on the right (inference) side as a function of thickness on the left (index). Again, as the IMT increases on the index (left) side, the range of the inference (right) IMT increases. For example, if the left bifurcation has an IMT of 0.50 mm, 80% of the IMT values on the right side are between 0.48 mm and 1.00 mm, a range of 0.52 mm. If the left bifurcation has an IMT of 2.00 mm, 80% of the IMT values at the right bifurcation are between 0.70 mm and 2.01 mm, a range of 1.31 mm.

**Table 1. Correlation Coefficients Between Carotid Sites**

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCA</td>
<td>BIF</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>.38</td>
<td>.30</td>
</tr>
<tr>
<td></td>
<td>(7311)</td>
<td>(5035)</td>
</tr>
<tr>
<td>BIF</td>
<td>.41</td>
<td>.31</td>
</tr>
<tr>
<td></td>
<td>(4186)</td>
<td>(5748)</td>
</tr>
<tr>
<td>ICA</td>
<td>.26</td>
<td>.30</td>
</tr>
<tr>
<td></td>
<td>(4884)</td>
<td>(4034)</td>
</tr>
</tbody>
</table>

CCA indicates common carotid artery; BIF, bifurcation; and ICA, internal carotid artery. Values are Pearson correlation coefficients. Numbers in parentheses are sample size in pairwise calculations.

**Discussion**

A number of risk factors (ie, hypertension, diabetes, hyperlipidemia, and smoking) are associated with the development of atherosclerosis, presumably affecting the entire vascular system. However, atherosclerotic plaques may occur in a particular segment of the arterial tree (such as bifurcations), while other segments remain relatively disease free.19,20 These manifestations have also been observed in the coronary bed, where the...
extent and location of coronary vessels affected by atherosclerosis vary between patients. Here also the risk factors are generally associated with extent as well as severity of disease, and there is a predisposition for proximal left anterior descending disease at branch points. To accommodate both systemic and anatomic manifestations of disease in the carotid bed, Crouse et al developed two scales for the measurement of atherosclerosis: a "severity" measure, which is an index of the greatest IMT, and an "extent" measure, which is the average IMT across the carotid bed. Similar atherosclerosis extent end points have been used in recent epidemiological studies and clinical trials.

The results in this report support the existence of systemic, anatomic, and focal development of atherosclerosis within the carotid bed. We provide population-based, in vivo evidence that with increasing IMT at one site in the carotid bed there is an increase in the average (mean or median) IMT at other sites, supporting the systemic nature of atherosclerosis. The higher correlations between the ipsilateral bifurcation and ICA, compared with the correlation of either with the CCA,

TABLE 2. Percentiles of Wall Thickness at an Inference Site as a Function of Thickness at an Index Site in the Ipsilateral Carotid Artery

<table>
<thead>
<tr>
<th>Index Site</th>
<th>BIF (%)</th>
<th>ICA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>CCA</td>
<td>0.25</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>0.72</td>
</tr>
<tr>
<td>BIF</td>
<td>0.25</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>0.48</td>
</tr>
</tbody>
</table>

BIF indicates bifurcation; ICA, internal carotid artery; and CCA, common carotid artery. Values are shown for left carotid artery in millimeters. For example, if the CCA has a thickness of 0.25 mm, then the 25th percentile of wall thickness at the BIF is 0.36 mm; if the CCA is 0.5 mm, then the 25th percentile of wall thickness at the BIF is 0.55 mm; and if the CCA is 0.75 mm, then the 25th percentile of wall thickness is 0.71 mm.
reflect the previously reported development of plaque at and above the carotid bifurcation, thereby supporting the anatomic predilection of atherosclerosis. The anatomic nature of atherosclerosis is also reflected in consistently greater average IMT in the bifurcation and ICA compared with the CCA. However, the frequent discrepancies in IMT between sites also provide evidence for the focal nature of atherosclerosis.

Generally, a relatively thin IMT at one site implies that the IMT at other sites is likely to be relatively thin. For example, if the left CCA has an IMT of 0.75 mm, there is a 90% chance that the right CCA is below 0.89 mm, the left bifurcation is less than 1.29 mm, and the left ICA is less than 1.12 mm. However, the divergence of the percentiles with increasing IMT implies that if one site has a relatively thick IMT there is more uncertainty about the IMT at other ipsilateral as well as contralateral sites. As an example, for a mean left CCA IMT of 1.5 mm, a relatively wide interval between the 5th and 95th percentiles was observed for other sites, ranging from 0.72 mm to 2.29 mm for the left bifurcation. Thus, the group characterized by a thick IMT at one site was composed of individuals whose wall thickness at other sites ranged from those with quite thin (or plaque-free) segments to those with quite thick (likely atherosclerotic) segments. These data provide a measure of the extent to which sites within the carotid bed are focally distinct. In addition, although the correlation between the left and right CCA was the highest observed between sites (r=0.49), it was itself fairly low, further emphasizing a focal component to the development of atherosclerosis.

One potential reason for the relatively poor correlation between sites would be a measurement error at individual sites. However, this measurement error is unlikely to play a major role in these data, as the estimated reliability coefficient for measurements within sonographer and within reader range from 0.80 (for the left CCA) to 0.92 (for the right ICA). Under a number of assumptions, these reliability coefficients can be used to calculate an "inflation" factor by which the observed correlations underestimate the true correlations. These inflation factors for the correlations provided in Table 1 range from 9% to 27%. With this adjustment, the largest estimated correlation would be the correlation between the left bifurcation and ICA, which would be inflated 26% to 0.51 (0.41×1.26=0.51). Even with this inflation, the percentage of the variance explained between these sites is only 26% (0.51×0.51=0.26). Hence, even after an adjustment for measurement error there is relatively poor correlation between the IMT measured at the carotid sites.

Systemic and anatomic characterizations of atherosclerosis are well known to students of atherosclerosis. The systemic nature of atherosclerosis presumably reflects uniform effects of risk factors on the artery wall and supports public health measures to control blood pressure, modify smoking habits, and lower cholesterol levels. Correlation between atherosclerosis of the coronary and cerebral arteries also reflects the systemic nature of the disease. Atherosclerosis is also typically characterized by its anatomic distribution and is particularly likely to occur at branch points such as the ostia of vessels leading from the coronary arteries or at the bifurcation of the carotid. It is thought that turbulence at these sites predisposes the vessel to accelerated disease development, and in the extracranial carotid arteries there is additional evidence for differences in the histological character of the CCA compared with the ICA. A substantial portion of the variability in wall thickness of the CCAs can be attributed to focal effects rather than effects that are systemic (since left and right CCAs were evaluated in the same individual) or segmental (since both CCAs are at the same anatomic location).

The ARIC study is a population-based cohort of middle-aged adults, and hence relatively few of these participants have clinically significant increases in arterial wall thickness. We assume that the majority of individuals lacking more advanced atherosclerotic lesions have relatively thin IMT at all the arterial sites measured; when a large IMT is observed it is likely that the person has more advanced atherosclerotic lesions. In the latter case, there is a wider range of IMT values at other sites, reflecting a broader range of atherosclerotic involvement. If a smaller IMT is observed, it is either an observation in an individual without advanced lesions (where all sites are thin) or a site without advanced lesions in an individual with lesions at other sites. However, the large proportion of participants without advanced atherosclerotic lesions dominates in this range of observed IMT, and as such the IMTs at other sites are likely to be small. Hence, the divergent...
pattern in the percentiles of wall thickness at the inference site as a function of the thickness at the index site is consistent with the observation that persons without advanced lesions (who have uniformly thin walls at other sites) dominate the small IMT range, while those with more advanced lesions (who have a range of thickness at other sites) dominate at large IMT values. However, it should be noted that approximately the same number (but not proportion) of relatively thick IMT values exist for thin as for thick IMT values at the index site (Figs 1 and 2).

For a variety of reasons, some investigators who have used B-mode to quantify atherosclerosis in epidemiological studies have focused on the CCA segment.\textsuperscript{10-12} The CCA is easier to image because it is relatively close to and parallel to the skin surface. In addition, because of its nearly circular cross section, it is easy and accurate to quantify the IMT. These investigators have found the IMT of the CCA to be related to a variety of risk factors.\textsuperscript{10,11} However, clinical attention focuses more on the bifurcation and ICA sites because they are the sites where atherosclerotic lesions are seen more frequently and the locations of the most severe lesions. Our data suggest there may be a loss of power in restricting evaluations to the CCA segments, since by increasing the number of sampled anatomic regions the presence of thicker IMT and lesions is more likely to be detected. However, its systemic nature, which has been documented through the significant correlations (correlations ranging from .25 to .38), makes the use of the CCA as an index of IMT in epidemiological studies scientifically reasonable given a sufficient sample size.

When the reading protocol for the ARIC study was designed, explicit instructions were provided to the readers to avoid recording IMT measurements when they were not confident of the wall measurements. While this approach has led to high-quality and repeatable data, it has generated a considerable number of sites where no measurements were made (resulting in "missing data"). Of the 14 106 measurements at-
tempted, the scanning and reading procedures in the ARIC study have generated relatively complete data for the CCA (79% evaluated), although there is a considerable amount of missing data for the bifurcations (59% evaluated) and ICAs (41% evaluated). If the ability to visualize an arterial segment was related to the wall thickness at that site, the missing data could result in an underestimation of the true correlations between sites. There is, in fact, some reason to believe that visualization and thickness of arterial segments are related in the ARIC data. Analysis of factors associated with visualization suggests that visualization rates may be lower in obese participants, who would also be expected to have thicker arterial walls. At the same time, quality control studies involving repeated scans suggest that thin walls also may be visualized slightly less often than the norm. The relation between visualization and wall thickness appears to be relatively weak, however, since standardized estimates of observed wall thickness accounted for less than 1% of the variation in the number of sites visualized per participant in race- and sex-adjusted analyses focusing on participants with at least one visualized site (>95% of all participants). Furthermore, participant age, traditionally one of the strongest correlates of IMT, was also able to account for less than 1% of the variation in the number of sites visualized per participant in race- and sex-adjusted analyses. Thus, it appears that factors unrelated to wall thickness are primarily responsible for missing ultrasound data in the ARIC study. Because we expect that any biases in estimated correlation coefficients resulting from missing data are likely to be small.

Because of the relatively large sample size of the ARIC study (14,106 baseline ultrasound examinations), there are numerous options to provide an index of atherosclerosis even in the presence of missing data. The large sample size of the ARIC study can greatly offset the loss of power that would result from using the CCA as the index of atherosclerosis for a participant, and its use has some attraction. The focal nature of atherosclerosis documented herein suggests that “severity” measures based on a single site may misrepresent the burden of disease for a patient. To accommodate the focal nature of atherosclerosis documented in this report, the study has generally quantified atherosclerotic involvement of participants by the mean across sites. This approach follows the “extent” measurements previously suggested by Crouse et al.22 The extent of missing data introduces problems in the calculation of the mean for the patient, which can be addressed by the use of maximum likelihood statistical methods. This approach uses the observed differences in the mean wall thickness between sites and the correlational structure of the sites to provide an adjusted wall thickness measure, which accounts for the pattern of the missing data for the participant. Under the assumption that the data are missing at random (ie, absence is not related to the true, unobserved IMT after control for observed IMT values and any covariates), these methods provide unbiased estimates of IMT and maximize precision. Unfortunately, these techniques are not suitable for questions involving the distributions (as opposed to mean values) and could not be applied to the present study.

We believe that the benefits of maximum likelihood techniques, which use data from all six carotid sites, are generally superior to approaches focusing only on the CCA because the clinical significance of disease in more distal segments of the extracranial carotid arteries, together with the predilection of disease for more distal anatomic locations and the focal nature of disease presented in this report, argues in favor of an aggregate description of IMT to define its association with risk factors. The possibility that there may be interactive effects of risk factors at different anatomic sites also argues for the measurement of all extracranial carotid artery sites. Whether the relation of extent of disease to clinical cerebrovascular or coronary heart disease outcomes is as strong or stronger than that of disease severity is unknown and of considerable consequence.

Acknowledgments

This study was supported by contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.

References

Howard et al  Carotid Artery Wall Thickness 1587


Relations of intimal-medial thickness among sites within the carotid artery as evaluated by B-mode ultrasound. ARIC Investigators. Atherosclerosis Risk in Communities. G Howard, G L Burke, G W Evans, J R Crouse, 3rd, W Riley, D Arnett, R de Lacy and G Heiss

 Stroke. 1994;25:1581-1587
doi: 10.1161/01.STR.25.8.1581

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/8/1581

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/