Segment-Specific Associations of Carotid Intima-Media Thickness With Cardiovascular Risk Factors
The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Background and Purpose—We propose to study possible differences in the associations between risk factors for cardiovascular disease (myocardial infarction and stroke) and carotid intima-media thickness (IMT) measurements made at 3 different levels of the carotid bifurcation.

Methods—We conducted a cross-sectional study of a cohort of whites and blacks of both genders with a mean age of 45 years. Traditional cardiovascular risk factors were determined in cohort members. Carotid IMT was measured from high-resolution B-mode ultrasound images at 3 levels: the common carotid artery, the carotid artery bulb (bulb), and the internal carotid artery. Associations with risk factors were evaluated by multivariate linear regression analyses.

Results—Of 3258 who underwent carotid IMT measurements, common carotid artery, bulb, and internal carotid artery IMT were measured at all 3 separate levels in 3023 (92.7%). A large proportion of the variability of common carotid artery IMT was explained by cardiovascular risk factors (26.8%) but less so for the bulb (11.2%) and internal carotid artery (8.0%). Carotid IMT was consistently associated with age, low-density lipoprotein cholesterol, smoking, and hypertension in all segments. Associations with fasting glucose and diastolic blood pressure were stronger for common carotid artery than for the other segments. Hypertension, diabetes, and current smoking had qualitatively stronger associations with bulb IMT and low-density lipoprotein cholesterol with internal carotid artery IMT.

Conclusion—In our cohort of relatively young white and black men and women, a greater proportion of the variability in common carotid IMT can be explained by traditional cardiovascular risk factors than for the carotid artery bulb and internal carotid arteries. (Stroke. 2010;41:9-15.)

Key Words: carotid intimal medial thickness ■ carotid ultrasound ■ risk factors

Carotid wall intima-media thickness (IMT) measured with high-resolution B-mode ultrasound has been recognized as a surrogate measure of atherosclerosis.1 Prior studies have shown carotid IMT measurements to be associated with cardiovascular risk factors 2 and cardiovascular outcomes.3-7 They serve as a useful index of subclinical cardiovascular disease.8

Carotid IMT has been used as an outcome measure, serving as a surrogate for atherosclerotic burden. However, measurements of the carotid artery wall can be obtained at very distinct sites near the carotid artery bifurcation: the common carotid artery proper just before it bifurcates; the carotid bulb, where the common carotid artery dilates as it bifurcates; and the internal carotid artery proper that is above the level of the bifurcation. Although these separate carotid IMT segments can be added up to generate a single composite score,9 each of these segments may actually have distinct associations with cardiovascular risk factors.2,10 Previous large epidemiological studies were limited by data that were either incomplete for the various carotid segments11,12 or older age range of the individuals under study.2

The geometry of the carotid artery bifurcation is such that shear stress rates are oscillatory in the bifurcation proper and show a more cyclically constant lumen to intima gradient in the common carotid artery.13,14 It is believed that this might explain the differences in cellular constituents noted in the
carotid artery, specifically a preponderance of foam cell in the common carotid artery wall and more typical cholesterol-rich plaques in the carotid bifurcation. Based on these differences, we believed that blood pressure might have stronger associations with the common carotid artery IMT than other segments, whereas cholesterol would possibly be more strongly associated with the carotid bulb and internal carotid artery (ICA) IMT.

We studied this possibility by investigating the associations between cardiovascular risk factors and carotid IMT at 3 separate segments of the carotid artery using data from a large population-based cohort of black and white adults in the United States.

Materials and Methods

General Methods

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a multicenter cohort study sponsored by the National Heart, Lung, and Blood Institute. The cohort was mostly recruited from the general population in Birmingham, Ala, Chicago, Ill, Minneapolis, Minn, and a random subset of members of a medical plan in Oakland, Calif. The detailed methods, instruments, and quality control procedures are described elsewhere. Briefly, a total of 5115 black and white men and women were recruited for the baseline (Year 0) examination in 1985 to 1986 with 3549 (72%) returning in 2005 to 2006 for the Year 20 examination. We report on the results of IMT measurement and risk factor assessments made at the Year 20 examination.

During the examinations, cardiovascular risk factors were determined according to standard approaches. Briefly, blood pressure, height, and weight were measured by centrally trained staff. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Smoking status was assessed using a standardized questionnaire. The presence of diabetes was defined as fasting glucose ≥126 mg/dL, or taking insulin and/or oral hypoglycemic agents. Venous blood was stored at −70°C. Both fasting glucose and fasting lipid profile (triglycerides, total cholesterol, and high-density lipoprotein cholesterol [HDL-C]) were measured using a standard laboratory technique. Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald approximation (total cholesterol−HDL-C−triglycerides/5, when triglycerides was no more than 400 mg/dL). Hypertension was defined as a seated resting systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or a history of taking antihypertensive medications.

Ultrasound Studies

Ultrasound studies were acquired according to a standard protocol using a GE-Logiq-700 (Issaquah, Ill). A high-resolution M12L transducer operating at a frequency of 13 MHz was used to image the common carotid artery and a 9-MHz frequency for the carotid artery bulb and proximal internal carotid arteries. Sonographers were trained centrally and then underwent a certification process.

Image acquisition was made at end diastole by a certified sonographer selecting the image with the lowest arterial diameter and then saving the selected images on a super VHS videotape. The image series used to select the images were also recorded so that the selection could subsequently be confirmed during the reading process. On each side, one image was obtained at the level of the common carotid before the bifurcation. Two images were then acquired at the carotid artery bulb, and 2 images were obtained in the proximal 2 cm of the ICA proper after the flow divider (Figure). The first image was taken at approximately 45° to the horizontal, whereas the second was set more vertical near to 20° to 25°.

A certified reader reviewed the videotape and digitized images with the aid of an image analysis workstation. The software integrated validated image analysis algorithms interfaced with an Access database to store the IMT measurements. The high-resolution images of the different carotid artery segments were used to calculate the IMT of the far or near wall on each image after the operator traced the respective lumen–intima and media–adventitia interfaces over a 1-cm distance with the aid of a Wacom imaging tablet. Any atherosclerotic plaque was included as part of the intima media and a note was made about the extent of stenosis that existed anywhere in the right or left carotid artery. The mean of the maximum wall thickness of the respective carotid artery segment was defined as the mean of the mean near and far wall thickness for each of the images taken on the left and right sides, 4 for the common carotid arteries and 8 segments for the bulb and ICAs, respectively. Carotid ultrasound studies were acquired in 3258 of the 3549 (91.8%) participants seen in the clinics. Pearson correlation coefficients based on 58 replicate studies were 0.86 for the common carotid artery, 0.72 for the bulb, and 0.88 for the ICA.

Statistical Analyses

Associations between dichotomous cardiovascular risk factors and carotid IMT were examined using the χ² test. Linear regression models were used to evaluate the strength of associations between individual risk factors and IMT measures. Three separate multivariable linear regression models were created to evaluate the strength of associations between cardiovascular risk factors and carotid IMT in each of the 3 carotid artery segments. All cardiovascular risk factors, including age and race/gender (white female serving as the referent) were entered into the model as candidate variables. Total cholesterol was not used in the final model due to collinearity with LDL-C and HDL-C levels. Multivariable models were generated separately with the full set of IMT measurements available at each level (3254 in the common carotid artery, 3182 in the bulb, and 3064 in the ICA). A separate set of 3 multivariable models was generated for a data set in which IMT measurements were available at all 3 levels of the carotid artery (n=3023). All analyses were done with standard statistical package using SAS Version 9.1 (SAS Institute, Cary, NC). Associations were considered statistically significant at the P≤0.05 level.

Results

Table 1 summarizes the basic demographics of study participants and consisted of 43% males and 46% blacks. The mean age was 45.2 years (±3.63 years SD). Data completeness for carotid artery IMT measurements was 99.9% at the common carotid artery (3254 of 3258), 97.7% at the carotid artery bulb (3182 of 3258), and 94% at the ICA (3064 of 3258). The bivariate associations between carotid IMT and cardiovascular risk factors are shown in Tables 2 and 3. Associations of segment-specific carotid IMT with dichotomous variables all reached statistical significance (P<0.002) with the exception of bulb maximum IMT and race (P=0.08) and ICA maximum IMT and race (P=0.07). The strength of the association between all continuous risk factors and the
IMT measured in the 3 different segments was significant at the $P<0.0001$ level.

Results of the multivariable models evaluating the strength of the associations between cardiovascular risk factors and IMT in individual segments of the carotid artery are shown in Table 4. Although a total of 3023 participants had IMT measurements available at all 3 levels (92.7%), the analyses were limited to the 2920 with complete risk factor profiles. Cardiovascular risk factors explained 26.8% of the variability for common carotid artery (CCA) IMT, whereas they explained only 11.2% of the variability for bulb IMT and 8.0% of the variability for ICA IMT. IMT measured in all 3 levels of the carotid artery had significant associations with age, smoking, LDL-C, hypertension, and male gender. Significant associations of IMT with fasting glucose and diastolic blood pressure (inverse association) were only seen for the CCA IMT. Diabetes was only significantly associated with bulb IMT. We noted a negative association of CCA IMT with diastolic blood pressure and positive association with systolic blood pressure when both pressure measurements were in the same model. Separate analyses with systolic and diastolic pressures entered separately in multivariable models showed positive associations for both and a stronger association for CCA IMT than for the other segments (data not shown).

Qualitatively, bulb IMT appeared to have stronger associations (greater partial $R^2$ and standardized $\beta$) with smoking and hypertension than for the other levels and was the only IMT value significantly associated with diabetes. LDL-C also showed qualitatively stronger associations with the ICA IMT than for the other levels. Age, race, gender, body mass index, and systolic blood pressure also had a qualitatively stronger association with CCA IMT than for the other levels.

The pattern of associations between IMT values in the different segments were similar for models in which fasting glucose levels were not included in the multivariable models (results not shown).

### Discussion

This study sought to determine whether there is a segment-specific effect between carotid artery wall thickness (IMT) measurements and cardiovascular risk factors. Our results indicate that, overall, mean of the maximum IMT in the CCA is more strongly associated with cardiovascular risk...
factors than IMT measurements made in the carotid artery bulb or ICA.

We have found stronger associations for blood pressure in the CCA than for other segments. This association was seen when systolic and diastolic pressure were both included in the models. We believe that the negative association with diastolic blood pressure is due to the effects of pulse pressure. When systolic and diastolic pressures are entered into separate models, both have positive associations with IMT. The bulb and ICA IMT have qualitatively stronger associations

### Table 3. Bivariate Associations Between Continuous Variables Shown and Respective IMT Values at the 3 Levels in the Carotid Artery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CCA Mean of the Maximum IMT</th>
<th>Bulb Mean of the Maximum IMT</th>
<th>ICA Mean of the Maximum IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coefficient</td>
<td>R²</td>
<td>N</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.0078</td>
<td>0.051</td>
<td>3254</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>0.00032</td>
<td>0.008</td>
<td>3220</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>0.00224</td>
<td>0.021</td>
<td>3220</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>0.00054</td>
<td>0.019</td>
<td>3187</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>−0.00147</td>
<td>0.039</td>
<td>3220</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.00275</td>
<td>0.101</td>
<td>3252</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.0031</td>
<td>0.073</td>
<td>3252</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.0010</td>
<td>0.042</td>
<td>3216</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.0049</td>
<td>0.079</td>
<td>3242</td>
</tr>
</tbody>
</table>

Associations are expressed as proportion variability explained (R²). The numbers in the column N refer to no. of participants in whom data are available. These associations are nonsignificant. All associations significant at P<0.0001.

### Table 4. Associations Between Risk Factors and Maximum IMT Measured in the 3 Separate Segments of the Carotid Artery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CCA Mean of the Maximum IMT</th>
<th>Bulb Mean of the Maximum IMT</th>
<th>ICA Mean of the Maximum IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>Standardized β</td>
<td>Partial R²</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.0079</td>
<td>0.2264</td>
<td>0.0611</td>
</tr>
<tr>
<td>Black male</td>
<td>0.0843</td>
<td>0.2513</td>
<td>0.0517</td>
</tr>
<tr>
<td>Black female</td>
<td>0.0495</td>
<td>0.1742</td>
<td>0.0241</td>
</tr>
<tr>
<td>White male</td>
<td>0.0326</td>
<td>0.1131</td>
<td>0.0104</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>0.0167</td>
<td>0.0536</td>
<td>0.0028</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.0020</td>
<td>0.2233</td>
<td>0.0185</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−0.0011</td>
<td>−0.0961</td>
<td>0.0034</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>0.000056</td>
<td>0.0262</td>
<td>0.0007</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>0.00029</td>
<td>0.0721</td>
<td>0.0066</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>−0.00031</td>
<td>−0.0409</td>
<td>0.0015</td>
</tr>
<tr>
<td>Diabetes‡</td>
<td>0.0187</td>
<td>0.0352</td>
<td>0.0009</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>0.00030</td>
<td>0.0565</td>
<td>0.0024</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.0031</td>
<td>0.1684</td>
<td>0.0268</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.0183</td>
<td>0.0562</td>
<td>0.0039</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>0.0066</td>
<td>0.0208</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total model R²</td>
<td>0.268</td>
<td>0.112</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Results for each segment are presented by separate multivariable models where all of the listed risk factors are included.
†Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or on medication for hypertension.
‡Defined as fasting blood glucose ≥126 mg/dL or taking insulin and/or oral hypoglycemic agents.
§Negative coefficient indicates an effect linked to pulse pressure given the presence of systolic pressure.

Values in bold correspond to factors that contribute significantly to the individual models at P<0.05. Only the 2920 individuals with complete risk factor profiles from among the 3023 with IMT measurements in all 3 segments are included in the model. Some of the missing data are due to the exclusion of individuals with elevated triglyceride levels (≥400 mg/dL) given use of the Friedewald equation to derive LDL-C (n=29).
with cholesterol than those of the CCA. Smoking and diabetes have stronger associations with the carotid bulb IMT than the CCA.

Differences in the strength of the association between IMT measurements in the different carotid artery segments and cardiovascular risk factors were described by O’Leary et al in a 2-segment protocol. Similar to our findings, associations with blood pressure were stronger for CCA IMT than for bulb/ICA IMT, whereas the reverse was true for smoking status in adults aged ≥65 years. No comment was made on a differential effect of diabetes. Our findings might reflect a high prevalence of patients with Type 1 diabetes given the age distribution of our cohort. Our findings, although similar, show other qualitative differences. O’Leary et al showed that 18% of the CCA IMT and 17% of the proximal ICA IMT variability could be explained by cardiovascular risk factors. Our results show that 27% of the CCA variability can be explained by cardiovascular risk factors. This decreases in the carotid artery bulb, in which 11% of the variability can be explained and lower than the 17% reported by O’Leary et al. In our study, we also imaged at a higher level above the carotid artery bifurcation. We found that 8% of the variability of IMT in this segment was explained by traditional cardiovascular risk factors. Our image acquisition protocol resembles the ones used in the Atherosclerosis Risk in Communities (ARIC) study and of the Rotterdam study. Data from ARIC have shown that strong correlations exist between IMT measurements in the different segments of the carotid artery. However, segment-specific differences in the associations of IMT with risk factors have been poorly studied with the exception of the association between age and IMT. We were able to obtain IMT measurements in a much greater proportion of the carotid artery segments than was done in ARIC or in the Rotterdam study. In the Rotterdam study, although CCA IMT data were available in 96% of individuals, only 64% were available for the bulb and 31% for the ICA. In ARIC, CCA IMT was measurable in 79% of individuals in the CCA, 59% for the carotid bulb, and 41% for the ICA. We believe that the level of completeness of our IMT data helped unmask segment-specific differences in the association between IMT and risk factors.

An explanation for the differences in the association between risk factors and IMT measured in different segments is likely linked to bifurcation geometry and differences in hemodynamics such as discussed by Malek et al for shear stress and shear rates near the lumen of the CCA and the widened carotid artery bulb. The carotid bifurcation has a more complex oscillatory low shear stress that promotes the primary deposition of LDL-C in the wall. These processes ultimately affect the cellular constituent of the artery wall. A preponderance of foam cells is observed in the CCA wall, whereas more complex plaques are seen at the bifurcation. The segmental differences in the associations between risk factors and IMT are likely secondary to these basic pathophysiological differences. The complex interactions among blood pressure, blood flow, and cholesterol deposition in the arterial wall make it difficult to isolate individual contributions based only on cross-sectional associations.

A limitation of our study is the relatively young age of our cohort given that the prevalence of cardiac and vascular disease increases in older individuals. Although this would seem to be a major limitation, pathological studies of young subjects dying from noncardiac-associated events in the Pathological Determinants of Atherosclerosis in Youth (PDAY) Study have confirmed the high prevalence of subclinical disease. A recent comparison between our cohort and this large autopsy study has shown similar associations in risk factor distributions.

Other authors have investigated possible differences in the associations between cardiovascular disease and IMT in the different carotid artery segments. Espeland et al showed differences in the strength of the associations of IMT in the 3 carotid segments with age, hypertension, body mass index in women, and coronary artery disease status. We also noted associations with body mass index in both the CCA and the ICA and qualitative differences in the associations of segment-based IMT measurements with blood pressure and race. Tell et al noted, as we do, that age, hypertension, and cigarette smoking were similarly associated with all segments and that differences were seen for gender and diabetes. We also observed significant associations between diabetes and IMT in the CCA and carotid artery bulb, whereas fasting glucose levels were associated only with the common carotid IMT. However, in the study by Tell et al, the breakdown of carotid artery levels did not conform to the 3 segments of the carotid artery that we evaluated. Schott et al indicated in their study that risk factors might differentially affect IMT in the CCA, bulb, and ICA. In our multivariable models, systolic blood pressure showed stronger associations with CCA IMT and bulb IMT, whereas smoking was qualitatively stronger for the bulb IMT. Contrary to our own results, these authors did not show a positive association between age and either ICA IMT or bulb IMT.

Site-specific differences in the associations between risk factors and IMT have also been seen in protocols that look at CCA IMT compared with wall thickness measurements that combine levels in the bulb and the ICA. In the Vascular Aging Study (EVA) study, carotid plaques were defined as bulb/ICA IMT of >2 mm. Diabetes and current smoking were significantly associated with CCA IMT and not plaques (a rough equivalent of bulb and ICA IMT). The strength of the association might have been lost due to the use of plaque as a dichotomized measure of bulb/ICA IMT rather than a continuous measure of IMT as we did. There were strong associations between plaques and cholesterol levels. For LDL-C, we also observed a qualitative increase in the strength of the associations between LDL-C and IMT from the CCA to the ICA. Contrary to our study, the San Antonio study showed that in Hispanics, smoking was associated with ICA IMT and not CCA IMT; total cholesterol was more strongly associated with CCA IMT than for ICA IMT. We also note a qualitatively stronger association between bulb IMT and smoking than for the CCA or ICA. The observation for
LDL-C is opposite to the one we observe. Like in our study, blood pressure was more strongly associated with CCA IMT than with ICA IMT. Data completeness in the San Antonio study was similar to that of our study. Our study as well as others suggests that segment-specific differences exist in the associations between cardiovascular risk factors and IMT. These differences might also translate into differences in clinical outcomes. At this stage of the CARDIA study, the incident number of cardiovascular events is still too low for such an evaluation.

Carotid IMT is viewed as a potential tool for evaluating overall cardiovascular risk. Based on our data, recommendations to adopt only common carotid IMT as a marker of subclinical disease and of cardiovascular risk might be too low for such an evaluation.

Conclusions

We conclude that carotid IMT measurements made in the CCA, carotid artery bulb, and ICA are all associated with cardiovascular risk factors. Although some cardiovascular risk factors show qualitatively stronger associations with IMT measured in the bulb or ICA, the CCA IMT best reflects overall exposure to traditional cardiovascular risk factors.

Sources of Funding

The CARDIA Study is supported by contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050, and N01-HC-95095 from the National Heart, Lung, and Blood Institute (NHLBI). J.F.P. is partly supported by NHLBI R01 HL069003 and HL081352.

Disclosures

D.H.O. serves as a consultant to Sanofi-Aventis and Astra Zeneca and owns stock in Medpace, Inc.

References


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Stroke. 2010;41:9-15; originally published online November 12, 2009;
doi: 10.1161/STROKEAHA.109.566596

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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