Relationship Between Intima-Media Thickness in the Common Carotid Artery and Atherosclerosis in the Carotid Bifurcation

Stefan Rosfors, MD, PhD; Staffan Hallerstam, MD; Kerstin Jensen-Urstad, MD, PhD; Maria Zetterling, MD; Christian Carlström, MD

Background and Purpose—An increase in intima-media thickness (IMT) in the common carotid artery (CCA) is commonly used as a marker of atherosclerosis. The purpose of this study was to investigate the relationship between IMT in the CCA and atherosclerosis in the carotid bifurcation.

Methods—182 consecutive patients (mean age, 67 years) referred for carotid duplex scanning were included. We measured IMT and classified plaques by means of a high-resolution ultrasound technique.

Results—IMT was correlated to age, male gender, ischemic heart disease, and presence of plaques or stenoses in any of the carotid bifurcations. In men, IMT was larger on the left than on the right side. Plaques were seen in 163 carotid bifurcations, in 45 of these with >50% stenosis. On the left side but not on the right, there was a correlation between IMT in the CCA and presence of plaques or stenoses in the carotid bifurcation. Echogenic plaques were more common than echolucent, but the latter caused significantly more stenoses. No relationship was found between plaque echogenicity and IMT.

Conclusions—IMT of the CCA is correlated to the degree of atherosclerosis in the carotid bifurcations in general and on the left side also to the presence of plaques or stenoses in the left carotid bifurcation. Our results support earlier observations suggesting faster development of carotid atherosclerosis on the left than on the right side. Echogenic plaques were more common and generally smaller than echolucent plaques, but there was no correlation between plaque echogenicity and IMT. (Stroke. 1998;29:1378-1382.)

Key Words: aging ■ atherosclerosis ■ carotid arteries ■ ultrasonography, Doppler

One of the main sources of cerebral thromboembolism is the carotid bifurcation. Following cardiogenic embolism, it is the second largest cause of stroke or transient ischemic attacks. Because the carotid bifurcation is highly amenable to ultrasound imaging and Doppler analysis, this technique (ie, duplex ultrasound) has contributed significantly to our knowledge in this field. Recent studies have shown that not only the degree of narrowing but also the ultrasonographic appearance of the atherosclerotic plaque is of importance in this respect.1–3

High-resolution ultrasound is also commonly used to measure intima-media thickness (IMT) of the distal common carotid artery (CCA) below the carotid bifurcation.4–5 The intima-media complex in the distal CCA starts to thicken early in the atherosclerotic process,6 even though plaques are seen infrequently at this location. An increased IMT may predict future atherosclerotic morbidity, as it for example has been shown to correlate with the likelihood of acute coronary events.8 Moreover, in asymptomatic subjects a correlation has been shown between IMT and the presence of plaques in the femoral or carotid bifurcations5 and between IMT and number of carotid artery plaques.7 However, less is known regarding the relationship between IMT and the presence of carotid artery stenosis. Prior to this, no study has been designed to evaluate the morphologic appearance of the carotid plaques and its relationship to the wall thickness in patients with various degrees of atherosclerotic disease.

In the present ultrasonographic study atherosclerotic disease of the carotid bifurcation and IMT in the distal CCA were evaluated in a consecutive series of patients referred for carotid duplex examination. Our particular aim was to describe and further investigate the relationship between IMT and the extent of carotid artery disease with special attention to plaque occurrence, plaque morphology and formation of stenoses.

Subjects and Methods

Patients
All patients referred for carotid duplex scanning to the Vascular Laboratory at the Department of Clinical Physiology at Stockholm...
Söder Hospital during a 2-month period were entered in a prospective study of carotid vessel wall disease approved by the local ethic committee. Patients seen after carotid endarterectomy (n=4) and those with poor ultrasonographic recording quality with no clear delineation of the intima-media complex (n=6) were excluded. Thus, a consecutive series of 182 patients were included (90 men and 92 women; mean age, 67 [range, 37 to 88] years). One hundred fourteen patients (63%) were referred from the Department of Neurology, 39 patients (21%) from other departments within the hospital (mainly vascular surgery and internal medicine), and 29 patients (16%) from physicians outside the hospital.

Risk factors for cerebralvascular disease known at the time of the examination were searched for in the patients’ records and in other examinations, including ECG and echocardiography (performed in most of the cases). One or more risk factors (hypertension, ischemic heart disease, diabetes mellitus, peripheral artery disease, or blood lipid disorder) were found in 96 patients (53%). Twenty-seven percent had hypertension, 30% had ischemic heart disease, and 8% had diabetes.

**Duplex Ultrasonography**

Color duplex ultrasound scanning was performed with an Acuson 128XP with 5- or 7-MHz linear-array transducers. The carotid arteries were scanned, and tape recordings were made of vessel walls and blood flow velocities in all segments. A blood flow velocity >1.2 m/s was used to define a stenosis with >50% lumen diameter reduction.10,11

At the end of the examination IMT was measured on both sides. The subject’s head was tilted to get the common carotid artery just proximal to the bulb placed horizontally across the screen. The 7-MHz probe was used together with the resolution box function of the system, and settings were made to get an optimal picture of the proximal to the bulb placed horizontally across the screen. Magnified pictures were frozen incident with the R wave on the ECG. Only the far walls of the artery were used for calculation. The IMT was defined as the distance between the leading edge of the luminal echo to the leading edge of the media/adventitia echo.12 IMT was measured over a length of 1 cm just proximal to the bulb. This was accomplished by use of the calipers and the trace function of the ultrasound system and calculation of the mean IMT over this length.13 We never included plaques that were classified in a blinded manner by the same operator twice within 1 week. Evaluation through the use of $\kappa$ statistics showed a good agreement between these 2 analyses, with a weighted $\kappa$ value of 0.75.14 The strength of agreement was slightly better ($\kappa$ value, 0.80) when the comparison was restricted to only 2 groups (ie, echolucent 1 and 2 versus echogenic 3 and 4).

**Results**

**Intima-Media Measurements**

IMT measurements are presented for each side separately and as IMT\_mean (=right+left/2). IMT was significantly larger on the left side compared with the right ($P<0.01$). There was a positive linear relationship between IMT\_mean and age ($r=0.48$; $P<0.001$). The correlation between IMT\_mean and the presence of risk factors for cerebralvascular disease was eliminated when age was included in the regression analysis. When hypertension, ischemic heart disease, and diabetes mellitus were tested together with age in a multiple regression analysis, only ischemic heart disease had an independent significant effect on the thickness of the intima-media complex ($P<0.05$).

**Carotid Artery Disease**

Plaques were seen in 163 carotid bifurcations in 103 patients. In 45 of these bifurcations, the plaque caused a >50% stenosis of the internal carotid artery, including 7 total occlusions. Echogenic plaques (types 3 and 4; n=94) were more common than echolucent (types 1 and 2; n=57) ($P<0.001$). There was no significant side difference regarding the occurrence of plaques or stenoses, although 5 of 7 occlusions were left sided. Stenoses were more frequently seen together with echolucent (24 of 57) than with echogenic (14 of 94) plaques ($P<0.001$). In echolucent plaques but not

<table>
<thead>
<tr>
<th>TABLE 1. Intima-Media Thickness in the Distal Common Carotid Artery Measured by Ultrasonography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age, median years (range)</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>No. of patients with risk factors (%)</td>
</tr>
<tr>
<td>IMT_left, mm</td>
</tr>
<tr>
<td>IMT_right, mm</td>
</tr>
<tr>
<td>IMT_mean, mm</td>
</tr>
</tbody>
</table>

Ranges in parentheses are 95% confidence intervals. IMT indicates intima-media thickness.

Intraoperator variability for plaque characterization was evaluated by analysis of 40 randomly selected plaques that were classified in a blinded manner by the same operator twice within 1 week. Evaluation through the use of $\kappa$ statistics showed a good agreement between these 2 analyses, with a weighted $\kappa$ value of 0.75.15 The strength of agreement was slightly better ($\kappa$ value, 0.80) when the comparison was restricted to only 2 groups (ie, echolucent 1 and 2 versus echogenic 3 and 4).

**Statistical Methods**

Data are presented as mean and 95% confidence interval (CI). Paired or unpaired, 2-sided Student $t$ tests were used for comparison of IMT measures. When more than 2 groups were compared, this was done with analyses of variance. If the $F$ test demonstrated a significant difference between the groups, each pair of means was compared with the Duncan test. The $\chi^2$ test with Yates correction was used for comparison of proportions. Regression or multiple regression analyses were used to characterize relationships between variables. Statistical significance was inferred at $P<0.05$.  

Intraoperator variability for plaque characterization was evaluated by analysis of 40 randomly selected plaques that were classified in a blinded manner by the same operator twice within 1 week. Evaluation through the use of $\kappa$ statistics showed a good agreement between these 2 analyses, with a weighted $\kappa$ value of 0.75.15 The strength of agreement was slightly better ($\kappa$ value, 0.80) when the comparison was restricted to only 2 groups (ie, echolucent 1 and 2 versus echogenic 3 and 4).
in echogenic, the stenoses were dominantly left sided \((P<0.05)\). Plaque morphology results are summarized in Table 2.

**Relationship Between IMT and Carotid Plaques**

In a multiple regression model, only age, gender, and the presence of stenosis on any side correlated independently with IMTmean, thus explaining approximately 40% of the IMT variance. The relative contribution of each variable is shown in Table 3. There was no relationship between plaque echogenicity and IMT. The highest IMT values were seen in carotid arteries with heterogenic plaques (types 2 and 3). The same results were obtained if the analysis was restricted only to plaques causing a stenosis (see Table 2). However, there was a wide overlap regarding IMT in the different groups of plaque morphology, and ANOVA revealed no statistically significant difference.

IMTmean was significantly higher in patients with plaques on any side, even after adjustment for age, gender and ischemic heart disease \((P<0.05)\). An even more evident difference was seen when IMTmean was compared for patients with and without stenoses on any side \((P<0.001, \text{after adjustment for age, gender and ischemic heart disease})\). In univariate analyses regarding IMTmean and age the estimated progression rate of IMT was 0.010 mm/y for patients with plaques and 0.006 mm/y for patients without plaques. IMTmean with increasing degree of carotid artery disease is shown in the Figure. Patients with small plaques, ie, without stenoses, had thicker IM than those without plaques \((P<0.05)\), and thinner IM than those with larger plaques causing stenoses \((P<0.001)\). Of subjects with an IMTmean \(\geq 0.8\) mm, 68% had plaques and 31% had stenoses in at least one of the carotid bifurcations (Table 4).

IMTright for patients with a plaque \((n=87)\) or a stenosis \((n=20)\) on the same side was 0.86 mm (CI, 0.81 to 0.90) and 0.92 mm (CI, 0.78 to 1.05), respectively. In a multiple regression analysis, with adjustment for age and gender, no significant relationship was found between IMTright and the presence of a right-sided plaque or stenosis. Of subjects with an IMTright \(\geq 0.8\) mm, 55% had a plaque and 12% had a stenosis in the right carotid bifurcation (Table 5).

IMTleft for patients with a plaque \((n=76)\) or a stenosis \((n=25)\) on the same side was 0.98 mm (CI, 0.90 to 1.05) and 1.09 mm (CI, 0.95 to 1.23), respectively. After adjustment for age and gender, there still was a significant relationship between IMTleft and the presence of a left-sided plaque or stenosis \((P=0.009)\) or stenosis \((P=0.002)\). Of subjects with an IMTleft \(\geq 0.8\) mm, 53% had a plaque and 20% had a stenosis in the left carotid bifurcation (Table 6).

**TABLE 2. Ultrasonographic Evaluation of Plaque Morphology (Types 1–5) and Intima-Media Thickness in the Common Carotid Artery in 182 Patients (364 Carotid Bifurcations)**

<table>
<thead>
<tr>
<th>Plaque Morphology Type</th>
<th>Total</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bifurcations</td>
<td>163</td>
<td>26</td>
<td>31</td>
<td>46</td>
<td>48</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Side (right/left)</td>
<td></td>
<td>15/11</td>
<td>15/16</td>
<td>26/20</td>
<td>25/23</td>
<td>6/6</td>
<td></td>
</tr>
<tr>
<td>IMT_{plaques}, mm</td>
<td></td>
<td>0.84</td>
<td>0.98</td>
<td>0.93</td>
<td>0.89</td>
<td>0.90</td>
<td>0.91</td>
</tr>
<tr>
<td>((n=163))</td>
<td></td>
<td>(0.74–0.93)</td>
<td>(0.86–1.11)</td>
<td>(0.86–1.00)</td>
<td>(0.81–0.97)</td>
<td>(0.77–1.03)</td>
<td>(0.87–0.95)</td>
</tr>
<tr>
<td>No. of stenoses (&gt;50%)</td>
<td>45</td>
<td>11</td>
<td>13</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Side (right/left)</td>
<td></td>
<td>5/6</td>
<td>3/10</td>
<td>5/4</td>
<td>3/2</td>
<td>4/3</td>
<td>20/25</td>
</tr>
<tr>
<td>IMT_{stenosis}, mm</td>
<td></td>
<td>0.89</td>
<td>1.22</td>
<td>0.95</td>
<td>0.93</td>
<td>0.97</td>
<td>1.01</td>
</tr>
<tr>
<td>((n=45))</td>
<td></td>
<td>(0.67–1.10)</td>
<td>(1.00–1.45)</td>
<td>(0.81–1.09)</td>
<td>(0.78–1.07)</td>
<td>(0.77–1.17)</td>
<td>(0.91–1.12)</td>
</tr>
</tbody>
</table>

Ranges in parentheses are 95% confidence intervals. IMT indicates intima-media thickness in the distal common carotid artery on the side of the plaque (IMT_{plaques}) or on the side of the stenosis (IMT_{stenosis}).

**TABLE 3. Summary of Best Multivariate Model for Prediction of Mean Intima-Media Thickness in the Common Carotid Artery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>(b)</th>
<th>SE</th>
<th>B</th>
<th>SE</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.398</td>
<td>0.066</td>
<td>0.007</td>
<td>0.001</td>
<td>0.0000</td>
</tr>
<tr>
<td>Gender</td>
<td>0.222</td>
<td>0.061</td>
<td>0.090</td>
<td>0.025</td>
<td>0.0003</td>
</tr>
<tr>
<td>Stenosis on any side</td>
<td>0.253</td>
<td>0.068</td>
<td>0.124</td>
<td>0.034</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.070</td>
<td>0.077</td>
<td>0.031</td>
<td>0.034</td>
<td>0.3665</td>
</tr>
<tr>
<td>Plaque on any side</td>
<td>0.035</td>
<td>0.072</td>
<td>0.144</td>
<td>0.029</td>
<td>0.6243</td>
</tr>
<tr>
<td>Any risk factor present</td>
<td>0.036</td>
<td>0.076</td>
<td>0.147</td>
<td>0.031</td>
<td>0.6308</td>
</tr>
</tbody>
</table>

\(b\) is the standardized regression coefficient whereas B is the raw regression coefficient. The magnitude of \(b\) allows comparison of the relative contribution of each variable in the prediction of the dependent variable. SE is the standard error for \(b\) and B, respectively. Multiple R=0.62 \((P<0.001)\).
TABLE 4. Number of Subjects with Plaques and Stenoses in the Carotid Bifurcation in Relation to the Mean Intima-Media Thickness of the Right and Left Common Carotid Arteries (IMTmean)

<table>
<thead>
<tr>
<th>IMTmean</th>
<th>No. of Subjects</th>
<th>Plaque (Any Side)</th>
<th>Stenosis (Any Side)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.60 mm</td>
<td>13</td>
<td>4 (31%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>0.60–0.79 mm</td>
<td>73</td>
<td>34 (47%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>0.80–0.99 mm</td>
<td>67</td>
<td>40 (60%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>≥1.00 mm</td>
<td>29</td>
<td>25 (86%)</td>
<td>16 (55%)</td>
</tr>
</tbody>
</table>

**Discussion**

In this study of carotid artery wall disease we focused our attention on the thickness of the intima-media complex in the CCA and the morphological appearance of atherosclerotic plaques in the carotid bifurcation. Our results show a correlation between IMTmean in the CCA and the occurrence of plaques and/or stenoses in any of the bifurcations, with the thickest IM in those with more advanced atherosclerosis in the carotid bifurcations.

When the left and right sides were analyzed separately, a correlation between IMT and presence of plaques/stenoses on the ipsilateral side was found only on the left side. There was a side difference, with thicker IMT on the left side in men but not in women. A side difference between IMT on the left and right sides has been described earlier, strongly suggesting that this was not a chance finding. One proposed explanation has been that atherosclerosis develops faster on the left side because of the anatomic difference between the sides and thus different shear stress conditions. The discrepancy between men and women in the present study might be from the fact that men develop atherosclerosis at an earlier age than women. IMT was generally larger in men than in women, an observation also found in other studies of similar design in the age group 60 to 70 years but not in healthy subjects of lower ages.

The recent interest in ultrasonographic classification of different plaque types is based on the increasing number of observations demonstrating that stenoses caused by echolucent plaques are more prone to embolization and development of ipsilateral hemispheric symptoms than are echogenic plaques. In our study echogenic plaques were more common than echoluent. However, echogenic plaques were in general smaller than echoluent plaques; thus, the latter caused significantly more stenoses. Whether this is caused by bleeding into the plaque, more advanced disease with more lipid deposition, or both remains unclear. The carotid arteriies with the thickest IM were those with type 2 plaques in the carotid bifurcation, although the difference between IMT in the groups of plaque morphology did not reach statistical significance. Type 2 plaques contain a mixture of calcification and a significant amount of echoluent material, such as hemorrhage and/or lipids. They can be classified as both heterogeneous and echoluent and might represent a more advanced stage of atherosclerosis. Type 2 plaques causing stenoses, but not type 2 plaques in general, were predominantly left sided. Moreover, 5 of 7 carotid occlusions were found on the left side. These observations support the hypothesis stated above regarding side difference in the development of atherosclerosis.

In our study of elderly patients (median age, 69 years), age was still the most important factor for determining IMT. The strong correlation between age and IMT has earlier been established in groups of patients/subjects with mean ages of 40 to 50 years as well as in elderly patients/subjects with mean ages of 60 to 70 years. Using the same technique and equipment as in the present study, we found IMTmean to be 0.56 mm in healthy subjects of mean age 40 years without carotid plaques compared with 0.77 mm in plaque-free subjects of mean age 62 years in the present study. Our estimated rates of progression of IMT for patients with and without plaques (0.010 mm/y and 0.006 mm/y, respectively) fits well with those documented in a recent report. However, various progression rates are given in the literature, highlighting the importance of a standardized technique for IMT measurements to provide better possibilities for the comparison of study results. In the present study we used the most common approach so far: measurement of the mean thickness over a 1-cm length of the far wall of the distal common carotid artery.

Veller et al described a plaque incidence in carotid or femoral arteries of 95% if IMTmean exceeded 0.8 mm in a group of symptom-free, healthy volunteers. In our elderly and more diseased patient group, carotid plaques were found in 68% of those with IMTmean ≥0.8 mm and in 86% of those with IMTmean ≥1 mm. Plaques in the femoral arteries might explain this difference.

Regarding risk factors for cerebrovascular disease, we found an independent relationship only between IMT and ischemic heart disease, which might demonstrate that other common risk factors lose some of their importance as age increases. A limitation of our study is the lack of measurement of blood lipid levels and lack of adjustment for smoking habits. It is, however, worth noting that a study by Fabris et al showed that the association between risk factors and
Carotid atherosclerosis decreased with age and that a correlation between carotid atherosclerosis and cholesterol levels and cigarette smoking existed in younger but not in elderly subjects. The correlations with IMT and ischemic heart disease and male gender found in our study fit with the previously described observation of higher subsequent risk of acute coronary events in males with increased IMT.  

In conclusion, we found the IMT of the CCA to be correlated to the degree of atherothrombosis in the carotid bifurcations in general and on the left side also to local atherosclerosis in the left carotid bifurcation. Echogenic plaques in the carotid bifurcation were more common than echolucent, but the latter caused significantly more stenoses with a predominance of the left side. We found no correlation between IMT and plaque echogenicity. Our results support earlier observations that suggest faster development of carotid atherosclerosis on the left than on the right side.

Acknowledgments
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References
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