Extracranial Carotid Atherosclerosis in Patients with and without Transient Ischemic Attacks and Coronary Artery Disease

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We examined the extent of extracranial carotid atherosclerosis as evaluated by a B-mode ultrasound score in four groups of hospitalized patients: hospital controls free of both cerebrovascular symptoms and coronary atherosclerosis (HC, n=245); patients with coronary atherosclerosis but without cerebrovascular symptoms (CAD, n=382); patients with transient ischemic attacks but asymptomatic for coronary atherosclerosis (TIA, n=107); and patients having both transient ischemic attacks and symptomatic coronary events (TIA+CAD, n=39). The unadjusted B-mode scores were lowest for the HC group, intermediate for the CAD group, and highest for the TIA or TIA+CAD groups (no difference between these two groups). However, after adjustment for age (or age and other risk factors), we could find no significant differences among the CAD, TIA, and TIA+CAD groups, while the HC group had significantly lower adjusted scores. These data suggest that 1) accentuated development of carotid atherosclerosis is associated with both TIA and CAD and 2) the apparent differences in extracranial carotid atherosclerosis between coronary and cerebrovascular patients are partly attributable to differences in risk factor profiles (most notably age). The potentially accentuated rate of development of extracranial atherosclerosis in patients with CAD mandates a low threshold for cerebrovascular evaluation in CAD patients. (Arteriosclerosis 10:714-719, September/October 1990)

The important studies of Roederer et al. have established carotid atherosclerosis as an important precursor of stroke in patients with transient ischemic attacks (TIAs). As a result, the extent of carotid atherosclerosis is routinely evaluated in patients experiencing cerebrovascular events. As such, data describing its extent and severity in such patients are readily available. However, because of the inherent danger of invasive carotid imaging techniques such as angiography, the cost of noninvasive imaging techniques such as B-mode or Doppler ultrasound, and the scant availability of symptom-free volunteers who will submit to carotid evaluations, remarkably little is known about the extent of carotid atherosclerosis in individuals asymptomatic for cerebrovascular disease.

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We know of only two studies which compared in vivo carotid atherosclerosis by using cerebrovascular angiography in totally asymptomatic persons (prisoners) and in patients with cerebrovascular disease. Although these studies did report more extensive disease in symptomatic than in asymptomatic volunteers, they concluded, "since... a majority of healthy asymptomatic individuals have significant arterial abnormalities in the neck vessels, interpreting such lesions in patients with cerebrovascular insufficiency must be carried out cautiously." Harrison and Marshall also reported higher rates of irregular wall characteristics, stenosis, or occlusion in TIA and cerebral infarction patients than in controls (cerebral tumor patients).

Autopsy information contrasting the extent and severity of carotid atherosclerosis in symptomatic individuals to those in their asymptomatic counterparts is also available from the International Atherosclerosis Project (IAP), which reported more extensive cerebrovascular atherosclerosis in individuals with autopsy evidence of cerebral infarction or hemorrhage as compared to individuals free of these conditions. Masuda et al. reported that the extent of intracerebral atherosclerosis was greater for patients with cerebral infarctions, as compared to those with cerebral hemorrhage or those who were stroke free. However, although autopsy studies offer the strength of diagnostic certainty of both carotid atherosclerosis and cerebral infarction, these studies have two major drawbacks: 1) difficulty in estimating stenosis from autopsy material and 2) selection bias. Furthermore, such studies cannot be used to assess carotid atherosclerosis in nonfatal TIA.
In this study, noninvasive imaging techniques were used to compare the extent of carotid atherosclerosis in TIA patients to that of patients asymptomatic for cerebrovascular disease. Because autopsy studies, including the IAP,\textsuperscript{5,6} have suggested a correlation between coronary and carotid atherosclerosis, we categorized the TIA patients into those with and those without symptoms of coronary artery disease (CAD), and we compared them to patients free of TIA with and without angiographically defined CAD. We examined the reasonable assumption that individuals who are asymptomatic for TIA but who have documented CAD may be an intermediate group with respect to carotid atherosclerosis. Finally, the article examines whether individuals symptomatic for cerebrovascular disease and having evidence of CAD have more advanced carotid atherosclerosis than those with either TIA or CAD only. The availability of TIA patients and neurologically asymptomatic patients with or without CAD in the same ultrasound laboratory provided us with the opportunity to compare the extent of extracranial atherosclerosis in these groups.

Methods

This article contrasts the extent of carotid atherosclerosis as evaluated by B-mode real-time ultrasound in four groups of patients:

1. **Hospital Controls (HC)**

These patients were determined at the time of diagnostic coronary angiography to be free of coronary atherosclerosis and asymptomatic for cerebrovascular disease.

2. **Coronary Artery Disease (CAD)**

These patients were determined at the time of diagnostic coronary angiography to have greater than 50% stenosis of any one major vessel, but they were asymptomatic for cerebrovascular disease.

3. **Transient Ischemic Attack (TIA)**

These patients were hospitalized for treatment of TIA but were asymptomatic for coronary atherosclerosis.

4. **Both Coronary and Cerebrovascular Disease (TIA+CAD)**

These patients were hospitalized for treatment of TIA and were found to have evidence of coronary atherosclerosis (history of myocardial infarction, angioplasty, or coronary bypass surgery).

The HC and CAD groups were recruited as part of an ongoing project in the Special Center of Research in Atherosclerosis. From all admissions for coronary angiography to North Carolina Baptist Hospital between March 1983 and December 1986, 627 patients were selected for inclusion in this study by a stratified random sampling strategy designed to admit men and women above and below the age of 50 at the same rate. Details of this selection process are provided elsewhere.\textsuperscript{8} All patients with a history of stroke or TIA, as well as those with a previous endarterectomy, were excluded. These patients underwent coronary angiography for evaluation of chest pain (73%), valvular heart disease (20%), and arrhythmias, heart failure, congestive heart disease, and other problems (7%). A standard questionnaire assessing traditional and nontraditional risk factors for cerebrovascular and coronary disease, including history of hypertension, diabetes, and smoking behavior was administered by trained interviewers during hospitalization.

Patients were considered to have CAD if angiography revealed more than 50% stenosis in any coronary artery. Patients in the HC group had normal coronary arteries (no evidence of stenosis or luminal irregularities).

The two TIA groups consisted of both white (\% of the patients) and black (\% of the patients) patients discharged between 1983 and 1988 from North Carolina Baptist Hospital with a diagnosis of TIA. The selection process for these groups is provided elsewhere\textsuperscript{9} in a report detailing black/white differences in TIA. Instead of focusing on racial differences, we considered these patients as a whole group in this analysis. Data on risk factors and concomitant diseases were obtained through a combination of retrospective chart review and patient interview. The group of patients with TIA described above was divided into two subgroups: 1) those with a history of CAD (TIA+CAD) and 2) those with no such coronary disease history (TIA). Patients were considered to have a positive history of CAD if they reported a previous myocardial infarction, bypass surgery, or angioplasty.

All patients provided informed consent to participate in the studies reported here, which were approved after review by the Institutional Review Board of Bowman Gray School of Medicine.

All patients were evaluated in the clinical ultrasound laboratory. Scoring techniques described elsewhere\textsuperscript{9,10} (with one modification) were applied to the results of the B-mode ultrasound investigation to provide a summary score representing the extent of carotid atherosclerosis. Measurements of wall thickness were made at six sites in each carotid artery (near and far wall \( \leq 5 \text{ mm} \) above the flow divider in the internal carotid artery, near and far wall \( \leq 5 \text{ mm} \) below the flow divider, and near and far wall \( >5 \text{ mm} \) but \( \leq 15 \text{ mm} \) below the flow divider). The wall thickness measurements were summed to obtain an "extent score" as previously described.\textsuperscript{9,10}

Analysis of variance (ANOVA) was used to test for overall differences in the "unadjusted" B-mode scores, and when a significant difference was found, pairwise t tests were applied to identify pair(s) of groups contributing most strongly to the overall significance. This analysis was then repeated on B-mode scores adjusted for age, providing a comparison as if all patients were of the same age (59.09 years, the mean for all groups). Finally, the B-mode scores were adjusted for other cardiovascular risk factors by fitting a multivariable linear regression model predicting the B-mode score by use of the diagnosis group and the patient's age, race, sex, and history of hypertension and diabetes. A backwards stepwise procedure was used to sequentially remove nonsignificant covariates (\( p >0.05 \)), and when only significant covariates remained, the significance of interaction terms was considered in a forward stepwise manner. This best model was used to adjust the B-mode scores to represent a "typical" patient (having similar covariate values on all factors but group membership). ANOVA was then used to...
Table 1. Description of Patient Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HC</th>
<th>CAD</th>
<th>TIA</th>
<th>TIA+CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>245</td>
<td>382</td>
<td>107</td>
<td>39</td>
</tr>
<tr>
<td>Mean age</td>
<td>55</td>
<td>58</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>% Black</td>
<td>5</td>
<td>4</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>% Male</td>
<td>43</td>
<td>63</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>% Ever smoker</td>
<td>48</td>
<td>68</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>% Diabetes mellitus</td>
<td>6</td>
<td>19</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>42</td>
<td>57</td>
<td>53</td>
<td>61</td>
</tr>
</tbody>
</table>

HC = hospital controls, CAD = coronary artery disease patients, TIA = transient ischemic attack patients, TIA+CAD = patients with both TIA and CAD.

Controlling for the effects of age through covariance analysis removed most of the difference in carotid atherosclerosis extent between CAD and TIA or TIA+CAD (Figure 2). ANOVA indicated that mean age-adjusted scores (adjusted to the overall average age of 59.05 years) continued to differ significantly among the four groups (p < 0.0001). However, pairwise comparisons indicated that the effect was concentrated in the HC group, which had a significantly lower mean age-adjusted B-mode score than any other group (p < 0.0001 in all cases), while no differences could be detected between the mean age-adjusted B-mode scores of the CAD, TIA, and TIA+CAD groups (p > 0.14 in all cases). In fact, the mean age-adjusted B-mode score for the CAD group (8.8 mm) was slightly higher than for the TIA groups (8.3 mm).

We also used multivariable covariance analysis to evaluate the relationship of B-mode score to group membership and the patient's age, race, sex, smoking status, and history of hypertension and diabetes. In addition to the patient's group (p = 0.0025), the patient's age (p < 0.0001), diabetes (p = 0.0009), hypertension (p < 0.0001), and smoking (p < 0.0001) were jointly related to B-mode score. An interaction between the diagnosis group and history of smoking was found to be of marginal significance (p = 0.0165). Neither the patient's race nor any other interaction were related to the B-mode score after control for these factors (p > 0.05). For each 1-year increase in age, there was an estimated 0.27 mm increase in B-mode score. Patients with a history of diabetes were found to have higher B-mode scores (2.2 mm), as were patients with a history of hypertension (2.0 mm). There was no evidence that the magnitude of these differences changed with group membership or smoking status.

After adjustment to the mean age of all patients (59.05 years) and the average rate of hypertension (51.9%) and diabetes (14.9%), smoking increased mean B-mode in all groups, although the magnitude of this effect ranged from only 0.2 mm in the HC group to 4.9 mm in the TIA group (Figure 3). For both smokers and nonsmokers, ANOVA of the adjusted mean B-mode score clearly indicated differences between the groups (p < 0.0001). For smokers, pairwise comparison of groups after Bonferroni adjustment indicated that the HC patients had significantly lower scores than the other three groups (p < 0.0006), but there were no significant differences...
between any of the other pairs (p>0.05). For nonsmokers, pairwise comparison of groups after Bonferroni adjustment for multiple testing indicated that only two pairs of groups differed significantly, HC from CAD (p=0.0036) and HC from TIA+CAD (p=0.0006).

Because of the interaction between smoking status and group membership, implying that the difference between smokers and nonsmokers varies depending on group membership, the comparison between the smokers and nonsmokers must be made within groups. While there was a significant difference in B-mode scores between smokers and nonsmokers for the CAD and TIA groups (p≤0.0007), no such difference existed between smokers and nonsmokers in either the HC or the TIA+CAD group (p>0.1520).

Discussion

Our results indicate that TIA patients had significantly more carotid atherosclerosis than did patients who were free of cerebrovascular symptoms, regardless of their coronary status. To our knowledge, this is the first in vivo documentation that TIA patients have more extensive carotid atherosclerosis than do asymptomatic patients. That patients with TIA have more atherosclerotic involvement appears reasonable, since symptomatic cerebrovascular events frequently arise from atherosclerotic plaques in the extracranial system. This conclusion is consistent with the autopsy reports of Solberg and McGarry, who demonstrated increased carotid atherosclerosis in patients with symptomatic cerebrovascular disease.

As previously reported, neurologically asymptomatic individuals with CAD had more extensive carotid atherosclerosis than did patients with angiographically normal coronary arteries. This result is consistent with previous reports that have demonstrated a clear association between a clinical history of ischemic heart disease (IHD) and increased atherosclerotic involvement of surface area in the carotid system. Moreover, some association might be expected, since cerebrovascular and coronary disease have many common risk factors (e.g., age, hypertension, diabetes, hyperlipidemia, and smoking). Our results support the current practice of many physicians who routinely examine patients for carotid atherosclerosis before performing coronary surgery.

In contrast, the extent of extracranial carotid atherosclerosis in those TIA patients who were symptomatic (TIA+CAD) did not differ significantly from those who were asymptomatic (TIA). The relatively small sample size of the TIA+CAD group (n=39) and our reliance on historical information to assess coronary atherosclerosis in TIA patients almost certainly reduced the power of this comparison.

Perhaps most interestingly, our results suggest that much of the difference in the extent of carotid atherosclerosis between the CAD and the TIA groups is explained by a difference in age. TIA patients were approximately...
10 years older than the CAD patients. It is our impression that cardiologists and cardiovascular surgeons already have a low threshold for evaluation of the neck in patients scheduled for bypass surgery and in patients with neurovascular symptoms. The current data suggest that even patients who lack neurovascular symptoms but have coronary disease are likely to also have extracranial carotid disease. We are currently following up the patients with coronary disease described in this report for progression of carotid atherosclerosis and development of cerebrovascular symptoms. Over a short follow-up period (4 years), approximately 7% of the patients have experienced a cerebrovascular event, and 4% have undergone endarterectomy (unpublished observations).

In addition, at present several clinical trials are evaluating the effects of various anticoagulants, lipid-lowering agents, and antihypertensive agents for their effects on retardation of the progression of carotid atherosclerosis. Since extensive natural history data are not yet available, we believe it would be premature to suggest specific treatment regimens for neurologically asymptomatic patients with extensive carotid atherosclerosis. Our data suggest, however, that these patients should be followed up with a vigilance equal to that afforded patients with TIA and extensive carotid atherosclerosis.

That we could detect no difference in the extent of carotid atherosclerosis among the CAD, TIA, and TIA+CAD groups does not, of course, imply that no difference exists. Given a large enough sample size, we would be virtually assured of detecting some difference among these groups. However, we feel that the sample size in this report is quite respectable ($n_{	ext{CAD}}=382$, $n_{	ext{TIA}}=107$, $n_{	ext{TIA+CAD}}=39$) and that whatever differences may exist are likely to be small.

To assure that real differences between our patient groups have not been masked by differences in risk factor profiles, we also report a comparison after adjustment for significant risk factors. The risk factors we identified (age, smoking, hypertension, diabetes) have been previously discussed. In addition, Duncan has reported that systolic and diastolic blood pressures, total cholesterol, triglycerides, and peripheral vascular disease history differed between patients with carotid disease and patients admitted for aortic and mitral valve replacement surgery. Holme et al. also found that elevated blood pressure and elevated serum cholesterol were important risk factors for carotid atherosclerosis in an autopsy population; however, they failed to find any association between carotid atherosclerosis and several other variables, including smoking and diabetes. Unlike Bauer et al., who found significantly greater extracranial atherosclerosis among Caucasians, or McGarry et al. and Solberg and McGarry, who found larger lesions in autopsied vessels of blacks, we did not find race to be a risk factor for carotid atherosclerosis in this study.

Multivariable adjustment for these risk factors did not change our conclusion that the age-adjusted differences among the CAD, TIA, and CAD+TIA groups were small. This analysis did, however, emphasize the importance of smoking as a risk factor for carotid atherosclerosis. In the TIA group, smoking was associated with a 4.9 mm increase in the mean adjusted B-mode score, and in all three groups, the impact of smoking on carotid atherosclerosis was larger than the effect of either hypertension or diabetes. In contrast, however, smoking had almost no effect on carotid atherosclerosis among hospital controls. Risk factor adjustment did not account for differences in the extent of carotid atherosclerosis between HC and other groups. This suggests that patients free of atherosclerosis in both the coronary and carotid systems differ from CAD and TIA patients either in some risk factor not included in our model (e.g., blood pressure, lipids) or in genetic factors. The results from ongoing population-based investigations, such as the Atherosclerosis Risk in Communities study, should provide unique insights into the natural history of atherosclerosis in persons who are free of cardiovascular symptoms.

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References


Index Terms: cerebrovascular disease • carotid atherosclerosis • transient ischemic attacks • risk factors
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