Carotid Plaque Ultrasonic Heterogeneity and Severity of Stenosis

Ali F. AbuRahma, MD; John T. Wulu, Jr, PhD; Brad Crotty

Background and Purpose—Several studies have reported on the correlation of ultrasonic carotid plaque morphology, cerebrovascular symptoms, and intraplaque hemorrhage. This study correlates ultrasonic carotid plaque morphology with the degree of carotid stenosis.

Methods—Carotid arteries (n=2460) were examined by using color duplex ultrasound during a 1-year period. Carotid stenoses were classified into <50%, 50% to <60%, 60% to <70%, and >70% to 99%. Ultrasonic plaque morphology was characterized as either heterogeneous (mixed hyperechoic, hypoechoic, and isoechoic) or homogeneous.

Results—Heterogeneous plaques were noted in 138 of 794 arteries with <50% stenosis, in 191 of 564 arteries with 50% to <60% stenosis, in 301 of 487 arteries with 60% to <70% stenosis, and in 496 of 615 arteries with 70% to 99% stenosis. The higher the degree of stenosis, the more likely it is to be associated with heterogeneous plaques. Heterogeneous plaques were present in 59% of the arteries with ≥50% stenoses versus 17% of the arteries with <50% stenoses, in 72% of the arteries with ≥60% stenoses versus 24% of the arteries with <60% stenosis, and in 80% of the arteries with >70% stenoses versus 34% of the arteries with <70% stenoses (P<0.0001 and odds ratios of 6.9, 8.1, and 8.0, respectively). Heterogeneous plaques were associated with an incidence of symptoms that was higher than that for homogeneous plaques for all grades of stenoses; percentages were, respectively, as follows: 68% versus 16% for <50% stenosis; 76% versus 21% for 50% to <60% stenosis; 79% versus 23% for 60% to <70% stenosis, and 86% versus 31% for ≥70% to 99% stenosis (P<0.0001 and odds ratios of 8.9, 11.9, 12.6, and 13.7, respectively). Heterogeneity of plaques was more positively correlated with symptoms than with any degree of stenosis (regardless of plaque structure).

Eighty percent of all heterogeneous plaques were symptomatic versus 58% for all stenoses ≥50%, 68% for all stenoses ≥60%, and 75% for all stenoses ≥70% (P<0.0001, P<0.0001, and P=0.02, respectively).

Conclusions—The higher the degree of carotid stenosis, the more likely it is to be associated with ultrasonic heterogeneous plaque and cerebrovascular symptoms. Heterogeneity of the plaque was more positively correlated with symptoms than with any degree of stenosis. These findings suggest that plaque heterogeneity should be considered in selecting patients for carotid endarterectomy. (Stroke. 2002;33:1772-1775.)

Key Words: carotid stenosis

Several large randomized multicenter trials, such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), concluded that compared with medical therapy, the combination of carotid endarterectomy (CEA) and best medical therapy significantly reduces the risk of stroke only for patients with significant carotid artery stenosis.1,2 Similarly, the Asymptomatic Carotid Atherosclerosis Study (ACAS) confirmed the benefits of CEA over medical therapy for patients with ≥60% asymptomatic carotid stenosis.3 In spite of these trials, many clinicians are still reluctant to recommend CEA for patients with moderate (50% stenosis) symptomatic carotid artery stenosis and for patients with asymptomatic carotid stenoses ≥60%.4–6

Several studies have reported on the correlation of ultrasonic carotid plaque morphology, cerebrovascular symptoms, and intraplaque hemorrhage.7–11 These studies have suggested that ultrasonic carotid plaque morphology can be critical in producing cerebrovascular ischemic events and may be helpful in patient selection for carotid endarterectomy. No study to date has examined the correlation of ultrasonic carotid plaque heterogeneity and the severity of carotid stenosis. Therefore, the present study correlates ultrasonic carotid plaque morphology and the degree of carotid stenosis.

Subjects and Methods

The present study includes 2460 carotid arteries from subjects that underwent color duplex ultrasound using the HDI 5000 SonosCT System (Advanced Technology Laboratory) during a 1-year period (July 1, 2000, through June 30, 2001). The study pool was derived from a total of 5409 carotid arteries examined in our noninvasive vascular laboratory during this time. The following were excluded...
from analysis: arteries that were normal or had minimal stenosis with only intimal thickening; arteries with high peak systolic velocities secondary to tortuosity, kinking, or any other elevated peak systolic velocities with no apparent underlying plaque, as identified on ultrasonography or immediate postoperative carotid duplex ultrasound studies; and total carotid artery occlusions. Hemispheric transient ischemic attack (TIA) symptoms and stroke were considered if the symptoms were referable to the territory appropriate to the affected carotid artery.

Longitudinal and cross-sectional ultrasound images were taken throughout the common extracranial portion of the internal carotid and the external carotid arteries bilaterally. The severity of stenosis was classified as <50%, ≥50%, ≥60%, ≥70% to 99%, and total occlusion, on the basis of our previously described criteria. The morphology of the plaque was classified into homogeneous or heterogeneous. Heterogeneous plaque is composed of a mixture of hypoechoic, isoechoic, and hyperechoic lesions; homogeneous plaques consist of only 1 of these 3 types of plaque. An isoechoic plaque, and a hypoechoic plaque was not as bright as an isoechoic plaque, and a hyperechoic plaque was brighter than an isoechoic plaque.

**Statistical Analysis**

The differences between various variables were calculated by using a χ2 test, with a value of P<0.05 considered statistically significant. The odds ratio and the 95% CI were also calculated.

**Results**

Table 1 summarizes the correlation between stenosis classification, plaque morphology, and neurological events (TIA/stroke). Heterogeneous plaques were noted in 138 of 794 arteries with 50% stenosis, 191 of 564 arteries with 50% to 60% stenosis, 301 of 487 arteries with 60% to 70% stenosis, and 496 of 615 arteries with 70% to 99% stenosis. The higher the degree of stenosis, the more likely it is to be associated with heterogeneous plaque.

Table 2 summarizes the correlation of plaque heterogeneity with the severity of stenosis. Heterogeneous plaques were present in 59% of stenoses ≥50% versus 17% of stenoses ≤50% (P<0.001 with an odds ratio of 6.9), in 72% of stenoses ≥60% versus 24% of stenoses <60% (P<0.001 and an odds ratio of 8.2), and in 80% of stenoses ≥70% versus 34% of stenoses <70% (P<0.0001 and an odds ratio of 8.0).

Table 3 summarizes the correlation of cerebrovascular symptoms with the heterogeneity of plaque and degree of stenosis. Heterogeneity of the plaques was more positively correlated with symptoms than with any degree of stenosis (regardless of plaque structure). Eighty percent of all heterogeneous plaques were symptomatic versus 58% for all stenoses ≥50%, 68% for all stenoses ≥60%, and 75% for all stenoses ≥70% (P<0.0001, P<0.001, and P=0.02, respectively, and an odds ratio of 0.3, 0.5, and 0.8, respectively).

**Discussion**

Several randomized prospective multicenter trials have concluded that compared with medical therapy alone, the combination of CEA and best medical therapy significantly reduces the risk of stroke in patients with ≥70% symptomatic carotid artery stenosis and also in patients with ≥60% asymptomatic carotid stenosis. Despite these landmark studies, some physicians are still reluctant to recommend CEA for patients with ≥60 asymptomatic carotid stenosis and for some patients with symptomatic moderate (50%) carotid stenosis, particularly women. A significant number of patients with severe carotid artery disease may actually

**TABLE 1.** Stenosis Classification/Plaque Morphology/Neurological Events

<table>
<thead>
<tr>
<th>Stenosis Classification (N)</th>
<th>Homogeneous Plaques, n (%)</th>
<th>Heterogeneous Plaques, n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50% (794)</td>
<td>127 (16)</td>
<td>94 (68)</td>
<td>8.9 (5.8–13.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥50%&lt;60% (564)</td>
<td>78 (21)</td>
<td>145 (76)</td>
<td>11.9 (7.7–18.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥60%&lt;70% (487)</td>
<td>43 (23)</td>
<td>238 (79)</td>
<td>12.6 (7.9–20.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥70%–99% (615)</td>
<td>37 (31)</td>
<td>427 (86)</td>
<td>13.7 (8.4–22.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total (2460)</td>
<td>285</td>
<td>904</td>
<td>14 (9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P values are for symptomatic homogeneous vs heterogeneous plaques within stenosis classification.

**TABLE 2.** Plaque Heterogeneity vs Severity of Stenosis

<table>
<thead>
<tr>
<th>Stenosis Classification (N)</th>
<th>Homogeneous, n (%)</th>
<th>Heterogeneous, n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% stenosis (N=1666)</td>
<td>678 (41)</td>
<td>988 (59)</td>
<td>6.9 (5.6–8.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;50% stenosis (N=794)</td>
<td>656 (83)</td>
<td>138 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60% stenosis (N=1102)</td>
<td>305 (28)</td>
<td>797 (72)</td>
<td>8.2 (6.8–9.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;60% stenosis (N=1358)</td>
<td>1029 (76)</td>
<td>329 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70% stenosis (N=615)</td>
<td>119 (20)</td>
<td>496 (80)</td>
<td>8.0 (6.4–10.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;70% stenosis (N=1845)</td>
<td>1215 (66)</td>
<td>630 (34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P values are for heterogeneous values within stenosis groups.*
TABLE 3. Correlation of Cerebrovascular Symptoms vs Heterogeneity of Plaque and Degree of Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic, n (%)</th>
<th>Asymptomatic, n (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All heterogeneous* (N = 1126)</td>
<td>904 (80)$\dagger$</td>
<td>222 (20)</td>
<td></td>
</tr>
<tr>
<td>All $\geq$50% stenosis† (N = 1666)</td>
<td>968 (58)</td>
<td>698 (42)</td>
<td>0.3 (0.3–0.4)</td>
</tr>
<tr>
<td>All $\geq$60% stenosis (N = 1102)</td>
<td>745 (68)</td>
<td>357 (32)</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>All $\geq$70% stenosis (N = 615)</td>
<td>464 (75)</td>
<td>151 (25)</td>
<td>0.8 (0.6–1.0)</td>
</tr>
</tbody>
</table>

*Includes all stenoses (including $<50\%$ stenosis).
†Includes heterogeneous and homogeneous plaques.
$\dagger P<0.0001$ vs all $\geq50\%$ stenosis and all $\geq60\%$ stenosis for symptomatic groups.
$\ddagger P<0.02$ vs all $\geq70\%$ stenosis for symptomatic groups.

Remain asymptomatic, which emphasizes the fact that factors other than stenosis may be critical in the production of cerebrovascular symptoms. It is believed that carotid plaques can produce cerebrovascular ischemic symptoms either by blood flow reduction secondary to carotid stenosis or by embolization secondary to plaque disruption. The widespread use of duplex technology of the carotid artery has further emphasized the presence of severe carotid artery disease in asymptomatic patients and mild to moderate stenoses in symptomatic patients; ie, factors other than the degree of stenosis may be responsible for determining the incidence of cerebrovascular symptoms.

Several investigators have studied the correlation of carotid plaque morphology and cerebrovascular symptoms. It has been suggested that ultrasonic carotid plaque morphology may be as critical as severe stenosis in producing cerebrovascular symptoms and, therefore, can be important in selecting patients for CEA. Several investigators have concluded that hypoechoic plaques and echolucent plaques are associated with an incidence of cerebrovascular symptoms that is higher than that for hyperechoic plaques. Biasi et al. concluded that a significant number of brain infarcts are seen in patients with echolucent or hypoechoic carotid plaques. Tegos et al. reported that retinal symptoms are mainly associated with hypoechoic plaques, whereas cerebrovascular events are associated with intermediate echoic plaques, and asymptomatic plaques are mainly hyperechoic.

Reilly et al. reported that plaques could be characterized as homogeneous or heterogeneous, with the latter being described as a combination of hyperechoic, isoechoic, and hypoechoic plaques. The homogeneous plaques consisted of uniformly high to medium level echoes, whereas the heterogeneous plaques consisted of mixed high-level, medium-level, and low-level echoes. They also concluded that homogeneous plaques were correlated with a fibrous lesion on pathological examination and that the heterogeneous plaques were correlated with the presence of intraplaque hemorrhage, ulceration, and loose stroma containing lipids, cholesterol, and proteinaceous deposits. In a previous study, we reported that heterogeneous plaques were more likely to result in plaque hemorrhage and adverse neurological events. Other investigators classified plaques into 4 major subtypes: echolucent (type 1), echolucent with small echogenic areas (type 2), echogenic with small echolucent areas (type 3), and echogenic (type 4). Cerebrovascular events were mainly present in type 1 and type 2 lesions, whereas, type 3 and type 4 lesions were mainly asymptomatic. They also reported that type 1 and type 2 lesions were associated more frequently with intraplaque hemorrhage or ulceration.

Our present study specifically examined the correlation between plaque morphology, ie, heterogeneity versus homogeneity, and the degree of carotid artery stenosis. The higher the degree of stenosis, the more likely it was associated with heterogeneous plaques. Heterogeneous plaques were also associated with an incidence of cerebrovascular symptoms (TIA/stroke) that was higher than that in homogeneous plaques for all grades of stenoses. Heterogeneity of the plaques was found to be more positively correlated with symptoms than with any degree of stenosis, regardless of the plaque structure. Eighty percent of all heterogeneous plaques were symptomatic versus $58\%$ of all stenoses $\geq50\%$, $68\%$ of all stenoses $\geq60\%$, and $75\%$ of all stenoses $\geq70\%$ ($P<0.0001$).

Recently, other investigators have attempted to define plaque morphology by introducing objective criteria with the use of computerized image analysis of the plaque echo texture. El-Barghouty et al. analyzed carotid plaques by using computerized image analysis and attempted to quantify the degree of plaque heterogeneity by quantifying the gray scale median (GSM) of the plaque. They described the value of the plaque echogenicity from a range of 0, which is totally black (soft areas), to 255, which corresponds to white (dense, fibrotic, or calcified) areas on the plaque. In a later study from the same institution, they defined points of reference that allow standardization of plaque analysis in such a way that the density of the plaque was compared with the density of blood and adventitia within the same lesion. They also correlated the GSM of the plaque with the incidence of cerebral infarction as seen on CT imaging; plaques with GMSms of $>50$ were associated with a 9% incidence of cerebral infarction, as opposed to those with a GSM of $<50$, which had a 40% incidence of cerebral infarction. Similar findings were reported by Biasi et al.

One of the limitations of ultrasonic characterization of plaque morphology is reproducibility. Ultrasonography is usually a technologist-dependent study, with variation also occurring from machine to machine. DeBray et al. suggested that echo-density measurement should be used to reflect the overall brightness of the plaque, with the term hyperechoic referring to echogenic plaque and the term hypoechoic referring to echolucent plaque. The terms homogeneous and heterogeneous should be used for plaque of uniform and nonuniform consistency, respectively, thus, expressing their ultrasonic texture. DeBray et al. also used a reference point to which plaque echo density should be compared: the stenomeidomastoid muscle for isoechoic plaque, the blood for hypoechoic plaque, and the bone of the cervical vertebrae for hyperechoic plaque. Sabetai et al. also proposed computer-assisted plaque characterization with B-mode image normalization by means of digital image processing, which was found to be a reliable method for quantitative assessment of carotid plaque morphology.
In a multicenter natural history study, the Asymptomatic Carotid Stenoses and Risks of Stroke (ACRS) study, to identify patients with asymptomatic internal carotid stenosis at high risk of stroke, Nicolaides et al. set up a method of standardization of echogenic images obtained through the computer. This method reiterates the gray shadows of the entire image, according to fixed values given to known components of the images, such as the blood and adventitia, which are always present and at the same depth as the carotid plaque. Plaque characterization was expressed as a number of means of the GSM. However, it should be noted that computerized analysis of echo density is not presently available in commercially used duplex ultrasound systems in the United States.

Other investigators have attempted to characterize plaque morphology by using helical CT scanning and MRI. Estes et al. have shown that helical CT scanning can differentiate between plaque containing calcium, lipid in the stroma, and fibrous tissue, as seen by histological examination.

With the rapid advances in duplex technology, such as the development of 3D ultrasound, which allows a more comprehensive evaluation of the carotid plaque, duplex technology may become more critical in selecting a subset of patients who may develop carotid symptoms and benefit from CEA.

In conclusion, the present study confirmed that the higher the degree of carotid stenosis, the more likely it is to be associated with ultrasonic heterogeneous plaque and cerebrovascular symptoms. Heterogeneity of the plaque was more closely related to symptoms than the degree of stenosis. These findings suggest that plaque ultrasonic heterogeneity should be considered in selecting patients for CEA, particularly in asymptomatic carotid disease.

References
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