The Symptomatic Carotid Plaque

Jonathan Golledge, MChir; Roger M. Greenhalgh, MD; Alun H. Davies, DM

Background—The natural histories of equally severe symptomatic and asymptomatic carotid stenoses are very different, which suggests dichotomy in plaque behavior. The vascular biology of the symptomatic carotid plaque is presented in this review.

Summary of Review—Histology studies comparing asymptomatic and symptomatic plaques were identified from MEDLINE. Reports in which stenosis severity was not stated or not similar for symptomatic and asymptomatic patients were excluded. In vitro studies and reports from the coronary circulation were reviewed with regard to the vascular biology of the plaque. Histology studies comparing carotid plaques removed from symptomatic and asymptomatic patients reveal characteristic features of unstable plaques: surface ulceration and plaque rupture (48% of symptomatic compared with 31% of asymptomatic, P<0.001), thinning of the fibrous cap, and infiltration of the cap by greater numbers of macrophages and T cells. In vitro studies suggest that macrophages and T cells release cytokines and proteinase, which stimulate breakdown of cap collagen and smooth muscle cell apoptosis and thereby promote plaque rupture.

Conclusions—Infiltration of inflammatory cells to the surface of carotid plaques may be a critical step in promoting plaque rupture and resultant embolization or carotid occlusion. Further understanding of cell recruitment and behavior in carotid atherosclerosis may allow better detection of unstable plaques and therapeutic methods of plaque stabilization. (Stroke. 2000;31:774-781.)

Key Words: atherosclerosis □ carotid artery diseases □ leukocytes

Stroke is the second most common cause of death worldwide, with an incidence in the United Kingdom of approximately 400/100 000.1 The neurological deficits that follow stroke have been used to classify the stroke and provide some information about the prognosis and pathophysiology.2-4 The frequency of related carotid artery disease varies with the type of stroke4 (Table 1).

Mechanism of Stroke in Carotid Artery Disease: Embolization Versus Ischemia

While it is likely that some strokes associated with carotid artery disease result from hypoperfusion,6 the majority of such strokes appear to result from embolization from an atherosclerotic plaque or acute occlusion of the carotid artery and propagation of thrombus distally. In support of embolization as the etiology of most strokes, few infarcts are in watershed areas,7 microemboli can be detected in the middle cerebral artery,8,9 and stenosis or restenosis of similar hemodynamic severity are much less likely to be associated with stroke when asymptomatic10-14 (Figure 1). The frequency of embolization on transcranial Doppler (TCD) is greater in patients with recent symptoms such as transient ischemic attack (TIA) compared with patients with similarly severe asymptomatic disease.8,9 A high frequency of microemboli (≥2 per hour) correlates with risk of subsequent ipsilateral ischemic symptoms, although no relationship has been demonstrated between microemboli and subsequent stroke alone.15 Because many of the microemboli are asymptomatic, other factors, such as the size of emboli and the collateral blood supply, must be important in determining the effect of any one emboli.

Relationship Between Presenting Symptom and Stroke

While there are many risk factors for ischemic stroke,16, transient ischemic events in patients with significant carotid stenosis are powerful predictors of subsequent stroke.11,12 Figure 1 compares the incidence of stroke ipsilateral to a severely stenosed carotid artery in patients with and without recent transient ischemic symptoms, using data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Asymptomatic Carotid Atherosclerosis Study (ACAS).11-14 Clearly, the stroke risk associated with a symptomatic stenosis is much greater. Table 2 illustrates the stroke rates from the 3 trials related to the severity of stenosis.11-14,17 For symptomatic stenoses there is a clearly increasing stroke risk with severity of stenosis. Interestingly, in ACAS there was no association between the stroke rate and the severity of stenosis, although the number of patients with 80% to 99%
steno-

cis was only 88. The low risk of stroke associated with
asymptomatic severe carotid stenosis has been confirmed by
other studies. Therefore, these data, therefore, suggest 2 types of
carotid artery disease: one form stable and unlikely to
produce symptomatic embolization or carotid occlusion and a
second form, while not necessarily being any more stenotic,
unstable and at high risk of producing symptomatic emboliz-
ation or carotid occlusion.

**Methods**

To investigate the biology underlying the differences in
plaque behavior, we have assessed studies that compare the
histology of plaques removed from symptomatic and asympto-
tomatic patients. Using PUBMED, MEDLINE, and hand-
searching of journals, we identified 21 studies that compared
carotid plaque histology and assessment of plaque, in addition to differences in method of
analysis have been used, while Table 4 includes the 3 plaque
features for which disparate methods of analysis have been
made. There is some variation in the findings of different studies,
possibly related to variation in time between onset in symptoms
and assessment of plaque, in addition to differences in method of
plaque removal and analysis. Unfortunately, little information is
given on the reproducibility of the different plaque assessments.

The summation analysis demonstrates that plaque rupture
or ulceration is much more common in symptomatic patients
(48% versus 31%, P < 0.001), but lumen thrombus (40% versus
35%) and intraplaque hemorrhage (48% versus 50%) are equally common in symptomatic and asymptomatic pa-
tients (Table 3). Although the methods of assessment have
been different, most studies have shown that the fibrous cap
is thinner and inflammation is
more common, with greater number of macrophage and T
cells detected in the cap of symptomatic plaques (Table 4). The core of the plaques would appear to be similar in
symptomatic and asymptomatic patients, with no significant
difference in frequency or size of necrotic core in most
studies in which similarly severe stenoses have been com-
pared. Therefore, studies that did not state severity of
carotid stenosis or in which the degree of stenosis was not
comparable were excluded. Reports that stated only macro-
scopic findings or did not compare symptomatic and asympto-
tomatic patients were also not included. Most studies did not
state whether plaque histology was analyzed in a blinded
fashion. A total of 11 studies were thereby excluded. In
addition, basic science reports describing the vascular biology
of the unstable atherosclerotic plaque were also studied.

**The Vascular Biology of the Unstable Plaque**

**Studies From the Carotid Circulation**

**The Atherosclerotic Plaque**

The atherosclerotic plaque at the carotid bifurcation is an
example of the advanced fibrous plaque found at sites of
predilection throughout the arterial system. It is composed of
a dense cap of connective tissue embedded with smooth
muscle cells, overlying a core of lipid and necrotic debris (Figure 2). The plaque contains monocyte-derived macrophages, smooth muscle cells, and T lymphocytes (Figure 2). Interaction between these cells types and the connective
tissue appears to determine the development of the plaque,
including important complications, such as plaque rupture.

**Comparison of Carotid Plaque Histology From Symptomatic and Asymptomatic Patients**

A large number of studies have compared carotid plaques
removed from symptomatic and asymptomatic patients in an
attempt to understand the mechanisms underlying plaque "acti-
vation." Comparisons have been principally restricted to
plaques taken from patients with any focal symptoms, such as
TIA, amaurosis fugax, or stroke with minimal disability, and
from those with no symptoms. No studies have isolated plaque
features peculiar to patients with 1 symptom type. The studies
comparing plaque histology in asymptomatic and symptomatic
patients with similar stenosis severity are summarized in Tables
3 and 4. Table 3 includes the 3 plaque features for which
summary analysis is possible, because common methods of
assessment have been used, while Table 4 includes the 3 plaque
features for which disparate methods of analysis have been
made. There is some variation in the findings of different studies,
possibly related to variation in time between onset in symptoms
and assessment of plaque, in addition to differences in method of
plaque removal and analysis. Unfortunately, little information is
given on the reproducibility of the different plaque assessments.

**TABLE 1. Classification of Stroke Related to Outcome and Incidence of Carotid Artery Disease**

| Stroke Type* | Neurological Deficit               | Frequency† | 30-Day Mortality† | 1-Year Mortality† | 1 Year Alive and Independent† | 1-Year Mortality† | 1-Year Mortality† | 1-Year Mortality† | 1-Year Mortality† | 1-Year Mortality† | 1-Year Mortality† | 1-Year Mortality† | Occlusion†† | Occlusion†† |
|-------------|-----------------------------------|------------|------------------|------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|-----------|-----------|
| TACI        | (1) Higher cortical loss           | 19%        | 39%              | 60%              | 4%                | 11%              | 29%              |                  |                  |                  |                  |                  |                  |           |           |
|             | (2) Hemisensory/motor loss         |            |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |           |           |
|             | (3) Homonymous hemianopia          |            |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |           |           |
| PACI        | Only 2 of TACI deficits            | 35%        | 4%               | 16%              | 55%               | 27%              | 14%              |                  |                  |                  |                  |                  |           |           |
| POCI        | Cranial nerve: hemisensory/motor loss, or bilateral hemisensory/motor loss, or cerebellar deficit, or isolated homonymous hemianopia | 26% | 7% | 19% | 62% | 8% | 3% | | | | | | | | |
| Lacunar     | Pure motor, or pure sensory, or ataxia | 20% | 2% | 11% | 60% | 11% | 0 | | | | | | | | |
| Total       |                                   | 10%        | 23%              | 49%              | 16%               | 14%              |                  |                  |                  |                  |                  |                  |           |           |

*TACI indicates total anterior circulation infarcts; PACI, partial anterior circulation infarcts; and POCI, posterior circulation infarcts.
†Based on data from the Oxfordshire Community Stroke Project. 3
‡Frequency of disease in related carotid bifurcation, based on data from Mead et al. 4
atherosclerotic plaque removed from symptomatic patients. In symptomatic patients the necrotic core is placed nearer to the fibrous cap and the minimum cap thickness is less (Table 3, Figure 2). Thus, while the volume of fibrous cap and lipid core may be similar in symptomatic and asymptomatic plaques, the position of the core and local thinning of the cap may predispose to rupture. An interesting study by Sitzer and colleagues relates plaque histology to frequency of embolization on TCD. The authors discovered an association between plaque ulceration, lumen thrombus, and the frequency of TCD microemboli, which suggests the importance of plaque rupture in the pathogenesis of stroke.

**Studies From the Coronary Circulation and Experimental Models**

**Plaque Features and Risk of Rupture**

To date, more detailed studies have been performed in atherosclerotic plaques removed from patients with unstable plaques, the position of the core and local thinning of the cap may predispose to rupture. An interesting study by Sitzer and colleagues relates plaque histology to frequency of embolization on TCD. The authors discovered an association between plaque ulceration, lumen thrombus, and the frequency of TCD microemboli, which suggests the importance of plaque rupture in the pathogenesis of stroke.

### TABLE 2. Relationship Between Severity of Stenosis and Stroke Rate

<table>
<thead>
<tr>
<th>Stenosis Severity*</th>
<th>Patient Stroke Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NASCET (2-Year)¹¹</td>
</tr>
<tr>
<td>60%–69%</td>
<td>428†  13%</td>
</tr>
<tr>
<td>70%–79%</td>
<td>43    21%</td>
</tr>
<tr>
<td>80%–89%</td>
<td>33    27%</td>
</tr>
<tr>
<td>90%–99%</td>
<td>24    35%</td>
</tr>
<tr>
<td>80%–99%</td>
<td>57    31%</td>
</tr>
</tbody>
</table>

Values given are the ipsilateral stroke rates at the time points stated. NS indicates not stated.

*Definition of stenosis varied.
†For patients with 50%–69% stenosis.
angina in comparison to those with symptomatic carotid artery disease. 43– 49 Because the hemodynamic environment of the coronary circulation is very different from that of the carotid arteries, care should be taken in relating findings from one vascular bed to another. Postmortem and atherectomy studies have demonstrated that plaques removed from patients with unstable coronary symptoms have larger lipid-filled cores and thinner fibrous caps, which contain larger numbers of activated macrophages and T lymphocytes but smaller numbers of smooth muscle cells and less collagen content than plaques from patients with stable angina. 43– 47 The likelihood of plaque rupture is a balance between the tensile strength of the plaque and the stress exerted on it. The plaque features demonstrated in patients with unstable angina have been shown in vitro to confer low tensile strength. 48 Interestingly, decreasing fibrous cap thickness drastically increases the circumferential stress on the plaque, whereas increasing stenosis severity actually decreases circumferential stress. 49

**Cellular Biology of the Plaque and Rupture**

In vitro studies have suggested the pathogenic mechanisms underlying the unstable plaque. Smooth muscle cells lay down collagen, the principal connective tissue component of the fibrous cap. Collagen breakdown is dependent on the

![Collagen breakdown](image)

**Figure 3.** Vascular biology of the unstable plaque. T lymphocytes, by stimulating macrophages and inducing apoptosis of smooth muscle cells, may be central to plaque destabilization. Release of MMPs from macrophages promotes collagen breakdown.

**Table 3. Histological Comparison of Plaques Removed From Symptomatic and Asymptomatic Patients: Summary Analysis**

<table>
<thead>
<tr>
<th>Plaque Feature/Reference</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulceration/plaque rupture</td>
<td>Bassiouny et al 32 18/31 6/14 NS</td>
<td>Seeger et al 40 15/27 2/12 P = 0.02</td>
<td>Carr et al 36 14/19 8/25 P = 0.004</td>
</tr>
<tr>
<td></td>
<td>Bassiouny et al 37 19/59 8/40 NS</td>
<td>Total 76/157 (48%) 35/113 (31%) P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Lumen thrombus</td>
<td>Bassiouny et al 32 17/31 5/14 NS</td>
<td>Sitzer et al 8 20/27 5/12 P = 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carr et al 36 12/19 20/25 NS</td>
<td>Total 54/136 (40%) 32/91 (35%) NS</td>
<td></td>
</tr>
<tr>
<td>Intraplaque hemorrhage</td>
<td>Bassiouny et al 32 12/31 12/14 NS</td>
<td>Sitzer et al 8 6/27 2/12 NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carr et al 36 16/19 14/25 P = 0.06</td>
<td>Bassiouny et al 37 11/59 7/40 NS</td>
<td></td>
</tr>
<tr>
<td>Total 103/216 (48%)</td>
<td>72/144 (50%) NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistical comparison by χ² test.

**Cellular Recruitment to the Plaque**

Leukocyte recruitment is dependent on the expression of adhesion molecules on the intimal surface, plus the release of soluble factors favoring leukocyte attraction and activation. In vitro studies have demonstrated that leukocyte adhesion and transmigration is an orderly process requiring initially rolling along the endothelium promoted by interaction between endothelial selectins and leukocyte ligands. Further leukocyte infiltration is promoted by attractants such as monocyte chemotactic protein (MCP-1), while firm adhesion requires binding of leukocyte CD18 and endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1). Expression of these adhesion molecules has been studied in coronary plaques, and increased expression of P-selectin, E-selectin, ICAM-1, and VCAM-1 has been correlated with high density of macrophages and T lymphocytes in the fibrous cap (Table 5). 56,58 One study has demonstrated increased ICAM-1 expression in the stenotic region of symptomatic plaques (Table 4). It is uncertain by which route leukocytes enter the plaque. Three possibilities exist: first, via the intima lining the lumen; second, via the vasa vasorum; and third, via the new vessels often demonstrated within the intima of complex plaques (neovasculature). 59 O’Brien et al. 58 in studying coronary plaques, have demonstrated that the
expression of E-selectin, ICAM-1, and VCAM-1 was twice as common in the neovasculature of the plaque as the arterial lumen and correlated this with density of macrophages and T cells. The authors suggest that these immature vessels may be the most important source of the inflammatory focus.

**Plaque Thrombogenicity**

On plaque rupture, exposure of the necrotic core to the circulation promotes thrombosis. This appears to be an important mechanism of plaque progression, in addition to embolization. Postmortem studies\(^5\) suggest that plaque rupture is often asymptomatic. Clearly, symptoms are more likely to develop if the developing thrombus is larger. Increased expression of tissue factor, the most important stimulant of the clotting cascade, has been demonstrated in plaques from patients with unstable angina or myocardial infarction.\(^6\) Interestingly, in an animal model, plaque rupture is associated with increased tissue factor production from circulating monocytes, which is reduced by treatment with a nitric oxide precursor.\(^6\) As yet, no data have been published on the thrombogenicity of the symptomatic carotid plaque.

**Triggers to Plaque Rupture**

Because plaque rupture depends on a balance between the tensile strength of the plaque and stress exerted on it, rupture is likely triggered by a sudden increase in stress on the plaque or, less likely, by a sudden reduction in plaque strength. Possible causes include sudden increases in blood pressure or pulse rate (eg, during exercise or sympathetic system stimulation),\(^6\) vaso- spasms forcing plaque contents through a weakened plaque cap,\(^6\) and hemorrhage into the plaque.\(^6\) There are presently no data to support triggers of plaque rupture in the carotid circulation.

**Potential Therapeutic Measures to Stabilize the Unstable Carotid Plaque**

**Statins**

There is now good evidence that treatment with statins lowers stroke risk by approximately 30%.\(^6\) This effect is likely to be multifactorial. Lowering cholesterol will reduce ischemic heart disease as well as carotid and intracerebral atherosclerosis. Thus, some of the benefit from statins likely result from decreased incidence of cardiac embolization. Interestingly, as in the coronary circulation, the reduction in carotid intimal

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### Table 4. Histological Comparison of Plaques Removed From Symptomatic and Asymptomatic Patients

<table>
<thead>
<tr>
<th>Plaque Feature</th>
<th>Reference</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous cap: fibrous tissue (% of plaque)</td>
<td>Feeley et al(^{34})</td>
<td>66±8%</td>
<td>88±14%</td>
<td>*P&lt;0.05</td>
</tr>
<tr>
<td>Collagen (mg/mg dry weight)</td>
<td>Seeger et al(^{35})</td>
<td>0.17±0.01</td>
<td>0.20±0.01</td>
<td>*P=0.08</td>
</tr>
<tr>
<td>Cap thinning</td>
<td>Carr et al(^{36})</td>
<td>18/19</td>
<td>12/25</td>
<td><em>P=0.003</em>**</td>
</tr>
<tr>
<td>Minimum cap thickness</td>
<td>Bassiouny et al(^{37})</td>
<td>0.2±0.2 mm</td>
<td>0.4±0.4 mm</td>
<td>*P&lt;0.006</td>
</tr>
<tr>
<td>Median cap volume</td>
<td>Hatsuaki et al(^{38})</td>
<td>170 mm(^3)</td>
<td>230 mm(^3)</td>
<td>NS***</td>
</tr>
<tr>
<td>Cap inflammation: foam cells</td>
<td>Carr et al(^{38})</td>
<td>16/19</td>
<td>11/25</td>
<td><em>P=0.006</em>**</td>
</tr>
<tr>
<td>Macrophages (mean±SD)</td>
<td>Bassiouny et al(^{37})</td>
<td>1144±1104</td>
<td>385±622</td>
<td>*P&lt;0.01††</td>
</tr>
<tr>
<td>Macrophage rich areas (area mean±SD)</td>
<td>Jander et al(^{39})</td>
<td>18±10%</td>
<td>11±4%</td>
<td>*P=0.005††</td>
</tr>
<tr>
<td>T cells (number/mm(^3))</td>
<td>Jander et al(^{39})</td>
<td>71±34</td>
<td>41±31</td>
<td>*P=0.005††</td>
</tr>
<tr>
<td>ICAM-1 (mean area±SEM)</td>
<td>De Graba et al(^{40})</td>
<td>29.5±2.4%</td>
<td>15.7±2.7%</td>
<td><em>P=0.002</em>*</td>
</tr>
<tr>
<td>Plaque core: necrotic core</td>
<td>Bassiouny et al(^{42})</td>
<td>19/31</td>
<td>7/14</td>
<td>NS***</td>
</tr>
<tr>
<td>Extractable lipid (mg/mg dry weight)</td>
<td>Seeger et al(^{35})</td>
<td>0.37±0.14</td>
<td>0.29±0.01</td>
<td><em>P&lt;0.001</em></td>
</tr>
<tr>
<td>Cholesterol (mg/mg dry weight)</td>
<td>Seeger et al(^{35})</td>
<td>0.09±0.01</td>
<td>0.06±0.01</td>
<td><em>P&lt;0.005</em></td>
</tr>
<tr>
<td>Necrotic core</td>
<td>Carr et al(^{36})</td>
<td>18/25</td>
<td>16/19</td>
<td>NS***</td>
</tr>
<tr>
<td>Mean % necrotic core</td>
<td>Bassiouny et al(^{37})</td>
<td>22±16%</td>
<td>26±18%</td>
<td>NS††</td>
</tr>
<tr>
<td>Median volume of lipid core</td>
<td>Hatsuaki et al(^{38})</td>
<td>60 mm(^3)</td>
<td>10 mm(^3)</td>
<td>NS***</td>
</tr>
<tr>
<td>Median volume of necrotic core</td>
<td>Hatsuaki et al(^{38})</td>
<td>60 mm(^3)</td>
<td>60 mm(^3)</td>
<td>NS***</td>
</tr>
</tbody>
</table>

*Wilcoxon rank sum and Fisher’s exact tests; **ANOVA; ***Chi-squared; ****Box-Whisper plots; †Mann-Whitney; ††Student t-test.

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### Table 5. Studies of Adhesion Molecules in Atherosclerosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Samples</th>
<th>Control</th>
<th>Findings</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Wal et al(^{35})</td>
<td>PM coronary and aorta</td>
<td>Pulmonary artery of infants</td>
<td>ICAM-1, E-selectin abundant</td>
<td>Related to TLO and MO</td>
</tr>
<tr>
<td>Johnson-Tidey et al(^{56})</td>
<td>PM coronary and carotid</td>
<td>Nonatherosclerotic regions</td>
<td>Selective binding of MO to plaque</td>
<td>Inhibited by antibody to adhesion molecules</td>
</tr>
<tr>
<td>Poston et al(^{37})</td>
<td>CEA</td>
<td>PM arteries</td>
<td>E-selectin, ICAM-1</td>
<td>Related to TLO and MO</td>
</tr>
<tr>
<td>O’Brien et al(^{38})</td>
<td>Coronary plaques</td>
<td>Nonatherosclerotic coronary segments</td>
<td>E-selectin, ICAM-1 and VCAM-1 neovasculature</td>
<td>Related to TLO and MO</td>
</tr>
<tr>
<td>DeGraba et al(^{40})</td>
<td>CEA</td>
<td>Asymptomatic plaques</td>
<td>ICAM-1 in stenotic region of symptomatic</td>
<td></td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy; PM, postmortem; TLO, T-lymphocytes; and MO, macrophages.
thickening is very small as a result of statin therapy, and therefore the important effect of therapy is likely to be plaque stabilization. Experimental studies in a rabbit model of atherosclerosis have demonstrated that lowering cholesterol leads to stabilization of atherosclerotic plaques over a period of 8 to 16 months. There is increased collagen and decreased inflammatory cells, MMPs, and proteolytic activity in the fibrous cap. Statins also have a range of other potential benefits, including improved endothelial function, reduction in hypercoagulability, and beneficial modulation of immune function, which likely contributes to their effect in stroke reduction.

**β-Blockers**
These drugs have been shown to reduce reinfarction and sudden death following myocardial infarction and therefore have been suggested to have a role in plaque stabilization or blunting of triggers to plaque rupture.

**Anticoagulants and Antiplatelet Agents**
The principal effect of these agents is to reduce the complication of plaque rupture rather than stabilize plaques, although the anti-inflammatory effect of aspirin might have a stabilizing effect.

**Tetracyclines**
In animal models of aortic aneurysms, doxycycline reduces aneurysm growth by inhibiting MMP activity. The similar effect of tetracyclines in carotid plaques may reduce the risk of plaque rupture.

**Identification of the Unstable Carotid Plaque**

**Ultrasound**
Ultrasound studies have demonstrated an association between echolucent plaques, surface ulceration, and symptoms. Echolucent plaques are lipid rich and have also been shown to herald an increased risk of subsequent development of TIA or stroke; unfortunately, clear prediction of stroke without warning has not been demonstrated. Improved determination of plaque morphology with computer-guided assessment of gray-scale median may better predict stroke risk.

**Angiography**
Although ulceration demonstrated on angiography has been associated with increased risk of stroke, in general it does not appear possible to detect unstable plaques from angiography.

**Thermography**
Studies on carotid endarterectomy samples have related increased temperature to inflammatory cell density and demonstrated cellular areas through infrared thermography.

**Radiolabeled Imaging**
Radiolabeled antibodies to macrophages or adhesion molecules could potentially identify unstable plaques.

**Conclusions and Further Research**
Comparisons of plaques from symptomatic and asymptomatic patients have revealed characteristic features of unstable carotid plaques. These studies, along with in vitro work, suggest that infiltration of inflammatory cells into the fibrous cap of a carotid plaque is a key step. Subsequent release of collagen-digesting enzymes and cytokines that promote smooth muscle cell apoptosis can weaken the surface of the plaque, thus promoting thrombosis, embolization, and arterial occlusion. Future studies investigating the recruitment of inflammatory cells and release of mediators may lead to strategies of plaque stabilization. Uniformity in reporting and analyzing carotid plaques will be an important consideration in these studies.

**Acknowledgment**
The BUPA Foundation provided financial support for this work.

**References**


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Stroke. 2000;31:774-781
doi: 10.1161/01.STR.31.3.774

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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