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 stroke\(^4\) (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 asymptomatic\(^10-14\) (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%
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 debris41 (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.41

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 asymptomatic patients. Using PUBMED, MEDLINE, and hand-searching of journals, we identified 21 studies that compared carotid plaque histology.8,21–40 Carotid plaque characteristics, such as surface ulceration, intraplaque hemorrhage, and lumen thrombosis, have been shown to vary with stenosis severity.25,32 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 macroscopic findings or did not compare symptomatic and asymptomatic 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.21–31 In addition, basic science reports describing the vascular biology of the unstable atherosclerotic plaque were also studied.

The Vascular Biology of the Unstable Plaque

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 “activation.”8,21–40 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 4.8,32–40 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.

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 patients (Table 3). Although the methods of assessment have been different, most studies have shown that the fibrous cap of symptomatic plaques is thinner44–38 and inflammation is more common, with greater number of macrophage and T cells detected in the cap of symptomatic plaques36,37,39 (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 compared.8,32–38 (Table 4). The quantity of extractable lipid has been found to be greater in symptomatic plaques in 1 study.35 This histology finding equates with results from ultrasound studies that demonstrate echolucent, lipid-rich plaques are more often associated with symptoms.52

Detailed histological examinations have demonstrated there are subtle differences in the characteristics of the

<table>
<thead>
<tr>
<th>Stroke Type*</th>
<th>Neurological Deficit</th>
<th>Frequency†</th>
<th>30-Day Mortality†</th>
<th>1-Year Mortality†</th>
<th>1 Year Alive and Independent†</th>
<th>50%–99% Stenosis††</th>
<th>Occlusion††</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI</td>
<td>(1) Higher cortical loss</td>
<td>19%</td>
<td>39%</td>
<td>60%</td>
<td>4%</td>
<td>11%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>(2) Hemisensory/motor loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Homonymous hemianopia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACI</td>
<td>Only 2 of TACI deficits</td>
<td>35%</td>
<td>4%</td>
<td>16%</td>
<td>55%</td>
<td>27%</td>
<td>14%</td>
</tr>
<tr>
<td>POCI</td>
<td>Cranial nerve: hemisensory/motor loss, or bilateral hemisensory/motor loss, or cerebellar deficit, or isolated homonymous hemianopia</td>
<td>26%</td>
<td>7%</td>
<td>19%</td>
<td>62%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Lacunar</td>
<td>Pure motor, or pure sensory, or ataxia</td>
<td>20%</td>
<td>2%</td>
<td>11%</td>
<td>60%</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>10%</td>
<td>23%</td>
<td>49%</td>
<td>16%</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

*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

*Definition of stenosis varied.
†For patients with 50%-69% stenosis.
Angina in comparison to those with symptomatic carotid artery disease. 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. 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. Interestingly, decreasing fibrous cap thickness drastically increases the circumferential stress on the plaque, whereas increasing stenosis severity actually decreases circumferential stress.

Cellular Biology of the Plaque and Rupture

Invitro 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 balance between the proteolytic enzymes metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinase (TIMPs). High levels of MMPs have been demonstrated at the site of the inflammatory infiltrate in the fibrous cap. While smooth muscle cell apoptosis has also been demonstrated in unstable plaques, studies in cultured cells suggest that the T lymphocytes may be central to plaque instability. T cells can induce macrophages to secrete MMPs via stimulation of CD40, and in addition, through production of interleukin-1, can promote SMC apoptosis (Figure 3). Accumulation of T cells and macrophages in the fibrous cap has been correlated with plaque ulceration, lumen thrombosis, TCD emboli frequency, and cortical symptoms in the carotid circulation.

Leukocyte 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). 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 (neovascularature). O'Brien et al, 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 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. 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. 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), vaso-spasm forcing plaque contents through a weakened plaque cap, and hemorrhage into the plaque. 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%. 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 thickness</td>
<td>Carr et al 36</td>
<td>18/19</td>
<td>12/25</td>
<td>P=0.003***</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>Hatsukami et al 37</td>
<td>170 mm³</td>
<td>230 mm³</td>
<td>NS***</td>
</tr>
<tr>
<td>Cap inflammation: foam cells</td>
<td>Carr et al 36</td>
<td>16/19</td>
<td>11/25</td>
<td>P=0.006***</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/mm²)</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>P=0.002**</td>
</tr>
<tr>
<td>Plaque core: necrotic core</td>
<td>Bassiouny et al 32</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>P&lt;0.001*</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>P&lt;0.005*</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>Hatsukami et al 38</td>
<td>60 mm³</td>
<td>10 mm³</td>
<td>NS***</td>
</tr>
<tr>
<td>Median volume of necrotic core</td>
<td>Hatsukami et al 38</td>
<td>60 mm³</td>
<td>60 mm³</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 M0</td>
</tr>
<tr>
<td>Johnson-Tidey et al 36</td>
<td>PM coronary and carotid</td>
<td>Nonatherosclerotic regions</td>
<td>Selective binding of M0 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, and VCAM-1 neovascular</td>
<td>Related to TLO and M0</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 neovascular</td>
<td>Related to TLO and M0</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 M0, macrophages.
thickening is very small as a result of statin therapy, and therefore the experimental 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 contribute 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**

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eruption of atheromatous plaque caused by coronary artery spasm. 


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