Pathogenesis of Carotid Thrombosis

A. Torvik, MD, A. Svidland, MD, and C.F. Lindboe, MD

We histologically examined specimens from 11 patients with recent occluding thrombi at the carotid bifurcation to study local factors in the vessel wall that precipitated the thrombi. The area of stenosis of the vessel lumen was determined morphometrically. Severe atherosclerotic stenosis was frequent but was not a prerequisite for thrombus formation since specimens from almost one half of the patients had only moderate narrowing of the lumen (<60% stenosis). Specimens from three patients showed ulcerations, those from one showed intraplaque hemorrhage, and those from one massive plaque rupture, all of which were thought to be important in thrombogenesis. All such types of plaque complications may thus precipitate thrombi but no single complication was particularly predominant, and specimens from one half of the patients showed no complications at all. Screening of the carotid arteries for stenosis can therefore detect only one half of the individuals who ultimately will develop thrombosis, and the risk caused by plaque complications seems to be moderate in unselected materials. (Stroke 1989;20:1477–1483)

Modern noninvasive ultrasound techniques have greatly improved the possibilities for detailed diagnosis of carotid stenosis and atherosclerotic complications, such as intraplaque hemorrhages and plaque ulcerations.1–5 Such information may be of crucial importance if the prognostic significance of each complication is known. Most clinical investigators have found an increasing risk of thrombosis with an increasing degree of stenosis,6–11 but observations concerning plaque ulcerations12–16 and intraplaque hemorrhages17–23 have been more uncertain and controversial.

In postmortem studies, several authors have maintained that thrombi in the coronary24–34 and intracranial35 vessels are preceded by rupture of atherosclerotic plaques. This mechanism has also been implicated in a case of carotid occlusion.36 Other authors have found intraplaque hemorrhage to be the main underlying lesion in both coronary37,38 and intracranial39,40 vessels. In some studies, it may have been difficult to determine whether the intraplaque hemorrhages resulted in ruptures or vice versa.

In a recent study of the carotid bifurcation in elderly asymptomatic individuals, we found that one half had >50% stenosis and one third had >60% stenosis.41 Nearly all individuals in the latter group had recent or old intraplaque hemorrhages, and one half of them had ulcerations and/or recent mural thrombi. In addition, numerous healed ulcerations and endothelialized mural thrombi were seen. We concluded that all types of atherosclerotic complications are frequent in asymptomatic individuals but that the complications apparently have a great tendency for self-healing without deleterious effects on the cerebral circulation. Furthermore, we pointed out that all types of complications were correlated and that the clinical significance of each complication would therefore probably be difficult to elucidate.

To study the pathogenesis of carotid thrombi more directly, we examined serial sections from 11 patients with recent thrombi. As will be described, atherosclerotic stenosis was clearly an important factor, but one half of the cases had only moderate narrowing. One half of the thrombi were precipitated by plaque complications, but no single complication was of particular importance.

Subjects and Methods

We collected 17 cases with suspected recent thrombi in the region of the carotid bifurcation in 1985 and 1986. We inspected the carotid bifurcation from all patients with a clinical history suggesting recent infarction in the territory of the middle cerebral artery, and we included all vessels showing local hyperemia in the region of the bifurcation. In our experience, local hyperemia of this type is strongly suggestive but is not a definite sign of recent thrombosis.

The removed specimens were fixed unopened in 10% formaldehyde. When necessary, they were
Figure 1. Schematic drawing of carotid bifurcation showing segments studied histologically. Each segment was 5 mm thick. IC, internal carotid artery; EC, external carotid artery; CCA, common carotid artery.

also decalcified in formic acid. Care was taken not to crush the arteries during dissection and further handling. After fixation and decalcification, the specimens were cut transversely into 5-mm-thick segments and studied using a dissection microscope. Five segments from each specimen were then embedded in paraffin (Figure 1) and sectioned serially. Every 30th section was mounted, and the thrombi could thus be studied throughout their entire longitudinal extent. Hematoxylin and eosin was used as a routine stain. Additional sections were stained with the Lendrum method.

We calculated the degree of stenosis (reduction in lumen area) from histologic sections from all segments by means of an instrument for image analysis (mini-MOP) as described elsewhere.41 The areas of the original and the residual lumen at the margin of the occluding thrombus were digitized, and the degree of stenosis was calculated from these figures. The area of the lumen of the most distal section of segment V was also determined. This section showed little or no atherosclerosis. When determining the area of the original lumen, the foldings of the internal elastic lamina were not taken into account since this seems to reflect the in vivo situation better than the total length of the lamina.42

We discarded specimens from five patients because the lumen was completely occluded by organized material in one segment, even though recent thrombus material was usually present proximal or distal to this segment. The specimen from one patient had no thrombus at all. Specimens from the remaining 11 patients with recent thrombi were analyzed for pathogenetic factors that precipitated the thrombi. Five patients were men and six were women (Table 1), and their mean age was 73 (range 53–87) years.

Results

The main findings are summarized in Table 1. All thrombi started locally at the bifurcation, and all patients had more or less severe atherosclerosis at the site of the occlusion. There was no indication that other general diseases, such as coagulopathies, had contributed to the thrombosis. Nor was there any suspicion that any occlusion was embolic.

The duration of the patients' symptoms varied from 3 to 30 days. Clinical information was too limited to determine how many patients had minor symptoms, such as transient ischemic attacks, before the major attack. Most patients obviously had had an acute and severe course. Two patients (Cases 9 and 11) initially had transitory symptoms, and one of these (Case 9) had an ulceration with an old mural thrombus that could have caused emboli. In the other patient with transitory symptoms, no morphologic explanation was found for the initial attack. All patients had appropriate infarcts in the territory of the occluded artery.

The degree of stenosis in the various segments is shown in Table 2. Specimens from four patients showed >80% and specimens from seven showed >60% stenosis at the site of the occlusion (Figure 2A). It is remarkable that nearly one half of the patients had slight to moderate stenosis (Figure 2B).

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of symptoms (days)</th>
<th>Maximum stenosis (%)</th>
<th>Plaque ulceration</th>
<th>Intraplaque hemorrhage</th>
<th>Plaque rupture</th>
</tr>
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<tbody>
<tr>
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<td>82</td>
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<td>29</td>
<td>97</td>
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<tr>
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<td>81</td>
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<tr>
<td>8</td>
<td>78</td>
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<td>6</td>
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It should be noted that the proximal part of the internal carotid artery, the carotid sinus, is normally considerably wider than the distal part of this artery. In our specimens, the mean area of the sinus was 75% greater than that distally. A considerable narrowing of the proximal part of the internal carotid artery can therefore take place before the proximal lumen equals the distal lumen. When the area of maximum stenosis was compared with the area of the lumen in the most distal section of segment V, only three patients showed >50% area reduction, whereas four had slight narrowing and four cases had no narrowing at all (Table 2, right-hand column).

Table 2 also indicates the segment containing the origin of the thrombi, defined as the oldest mural part of the thrombus. Specimens from only two patients (Cases 8 and 9) showed mural thrombi that were definitely older than the acute clinical history. Both cases had quite large ulcerations, and the oldest part of the thrombus covered the bottom of the ulcers (Figure 3). In 10 of the 11 patients, the

**TABLE 2. Percent Stenosis in Segments From 11 Patients With Carotid Thrombosis Arranged by Decreasing Degree of Stenosis**

<table>
<thead>
<tr>
<th>Case</th>
<th>Segment</th>
<th>Area of maximum stenosis (% of distal ICA area)</th>
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<tr>
<td></td>
<td>I</td>
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<tr>
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<td>14</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>35</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery.

*Origin of thrombus.

**Figure 2. Photomicrographs of thrombi in specimens from patients with severe (A, Case 5) and slight (B, Case 4) stenosis. A: Lendrum stain, ×15; B: hematoxylin and eosin stain, ×15.**
thrombi originated in segments III or IV (Figure 1). The thrombi originated at the point of most severe stenosis in six patients, slightly distal to it in three, and slightly proximal to it in two.

Ulcerations were present at the origin of the thrombus in three patients (Table 1, Figure 4). Intraplaque hemorrhage, which narrowed the lumen markedly and may have been important for thrombus formation, was seen in only one patient (Table 1, Figure 5A). However, proximally there was no fibrous covering separating the plaque and the thrombus, and small traces of plaque material were seen in the base of the thrombus (Figure 5B). Although a primary intraplaque hemorrhage is the most likely explanation in this instance, a secondary hemorrhage entering the plaque from the vascular lumen cannot be entirely excluded. Numerous small intraplaque hemorrhages and ulcerations were seen in segments without thrombi, as observed previously in many asymptomatic individuals.41

Plaque rupture, with large amounts of atherosclerotic material in the thrombus, was seen in only one case (Table 1, Figure 6). One additional case (Case 1) showed a break in the membranous lining of a small atheromatous plaque (Figure 7), but there was no atheromatous material in the thrombus and it is uncertain whether this break was important in formation of the thrombus. The maximum stenosis in this patient was only 56%.

Discussion

As expected, the degree of atherosclerosis among our cases was more severe than that in a comparable series of asymptomatic individuals.41 No other common pathogenetic factor for the precipitation of thrombi could be demonstrated.

It should be emphasized that specimens from only one patient showed a major plaque rupture (Table 1). This observation is in contrast to the findings in coronary24-34 and intracranial35 occlusions, where plaque ruptures have been found to be the main underlying lesion for thrombi. It is possible that the amount of fibrous tissue in atherosclerotic plaques differs, and this may explain the different mechanisms of vascular occlusions.

Similarly, a significant intraplaque hemorrhage was found in only one patient (Table 1). The results of previous investigations have been controversial in this respect. Several authors have maintained that intraplaque hemorrhages are the most important precipitating factor in carotid,17-22 coronary,37,38 and intracranial39,40 occlusions, whereas other authors have been unable to verify these findings.23-35 Our observations suggest that small intraplaque hemorrhages are very frequent inciden-
Plaque ulcerations, which probably contributed to the formation of the thrombi, were found in specimens from three patients (Table 1). Previous reports concerning the pathogenetic role of ulcerations have been controversial.\textsuperscript{12-16} Our observations show that ulcerations may be important, but since healed and open ulcerations are frequently found in asymptomatic individuals,\textsuperscript{41} the increased risk that ulcerations carry is not clear.

Altogether, our study shows that all types of atherosclerotic complications are important, but we...
found no single predominant mechanism, as has been claimed for other vessels. Although our series contains few persons, the marked differences from previous observations on the coronary and intracranial arteries suggest that there may be true differences in the pathogenesis of thrombi in different vessels.

Even severe stenosis was not a prerequisite for carotid thrombosis (Table 1). It is noteworthy that nearly one half of the patients had only moderate stenosis (<60%) at the site of occlusion. This moderate narrowing becomes even less impressive when the area of the lumen at the site of the occlusion is compared with that at distal levels, where the lumen normally is narrower than at the sinus (Table 2).

Thus, occluding thrombi frequently developed in carotid vessels where no hemodynamic factors that disturbed blood flow could be demonstrated.

Atherosclerotic stenosis (with or without ulcerations, ruptures, or hemorrhages) obviously remains the greatest risk factor for thrombosis. However, carotid stenosis is also frequent in asymptomatic elderly individuals, and almost one half of the thrombi in our series occurred in patients without significant stenosis. Screening of the carotid arteries for stenosis can therefore detect only one half of the persons who will ultimately develop thrombosis, and the risk caused by plaque hemorrhages and ulcerations seems to be moderate in unselected materials.

References

27. Bouch DC, Mongomery GL: Cardiac lesions in fatal cases of recent myocardial ischemia from a coronary care unit. Br Heart J 1970;32:795-803
34. Falk E: Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coro-

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