Extracranial Thrombotically Active Carotid Plaque as a Risk Factor for Ischemic Stroke

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Patients with substantial carotid artery narrowing are at increased risk for major stroke,1-6 but the pathogenic mechanisms linking carotid atherosclerosis and ischemic brain injury still need to be fully clarified. Clinical trials designed to evaluate the beneficial effects of endarterectomy in symptomatic and asymptomatic patients have focused on carotid stenosis severity and plaque ulceration as risk factors for cerebrovascular events. The results of the European Carotid Surgery Trial2,3 and the North American Symptomatic Carotid Endarterectomy Trial (NASCET)4,5 suggest that surgery is indicated for stroke prevention when stenosis is more than 70%. The NASCET study showed that among asymptomatic patients with high-grade carotid stenosis (>70%) not treated by surgery, the 2-year rate of any ipsilateral stroke was 26.0% for major stroke and 13.1% for fatal stroke.7 The

Asymptomatic Carotid Atherosclerosis Study7 suggested that indications for carotid endarterectomy could be broadened to include asymptomatic patients with carotid stenosis of more than 60% and that the aggregate risk over 5 years for ipsilateral stroke and any periprocedural stroke was estimated at 11.0% for asymptomatic patients treated medically.

Context Recent studies suggest that factors other than the degree of carotid stenosis are involved in ischemic stroke pathogenesis, especially modifications of plaque composition and related complications.

Objective To examine the role of carotid plaque rupture and thrombosis in ischemic stroke pathogenesis in patients undergoing carotid endarterectomy, excluding those with possible cardiac embolization or with severe stenosis of the circle of Willis.

Design, Setting, and Patients A total of 269 carotid plaques selected from an Interinstitutional Carotid Tissue Bank were studied by histology after surgical endarterectomy between January 1995 and December 2002. A total of 96 plaques were from patients with ipsilateral major stroke, 91 plaques from patients with transient ischemic attack (TIA), and 82 plaques from patients without symptoms.

Main Outcome Measures Differences in the frequency of thrombosis, cap rupture, cap erosion, inflammatory infiltrate, and major cardiovascular risk factors between study groups.

Results A thrombotically active carotid plaque associated with high inflammatory infiltrate was observed in 71 (74.0%) of 96 patients with ipsilateral major stroke (and in all 32 plaques from patients operated within 2 months of symptom onset) compared with 32 (35.2%) of 91 patients with TIA (P < .001) or 12 (14.6%) of 82 patients who were without symptoms (P < .001). In addition, a fresh thrombus was observed in 53.8% of patients with stroke operated 13 to 24 months after the cerebrovascular event. An acute thrombus was associated with cap rupture in 64 (90.1%) of 71 thrombosed plaques from patients with stroke and with cap erosion in the remaining 7 cases (9.9%). Ruptured plaques of patients affected by stroke were characterized by the presence of a more severe inflammatory infiltrate, constituted by monocytes, macrophages, and T lymphocyte cells compared with that observed in the TIA and asymptomatic groups (P < .001). There was no significant difference between groups in major cardiovascular risk factors.

Conclusion These results demonstrate a major role of carotid thrombosis and inflammation in ischemic stroke in patients affected by carotid atherosclerotic disease.

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The potential for accurately predicting ipsilateral stroke risk only on the basis of carotid stenosis severity remains uncertain. Inzitari et al found that patients with a total occlusion of a carotid artery have a reduction in 5-year risk for ipsilateral stroke in comparison with patients with severe stenosis. Moreover, the NASCET study showed that the presence of an angiographically evident carotid plaque ulceration in symptomatic patients with a high degree of stenosis increases the relative risk for stroke. In addition, conclusive data are still lacking regarding the possible benefit of carotid endarterectomy in symptomatic patients with ulcerated lesions and a less severe degree of stenosis.

The severity of carotid stenosis is no longer sufficient to identify patients at high risk to develop an acute cerebrovascular event. Identification of other factors may improve risk stratification and help to decrease the likelihood of disabling stroke in the carotid territory of the brain. A major future challenge is to identify high risk before the clinical event develops.

Plaque structure could be an independent risk factor for ischemic stroke. Atherosclerotic plaque composition and related complications may represent an important determinant of increased stroke risk as suggested by different pathologic studies, although the reported results are contradictory. This study examines the role of carotid plaque rupture and thrombosis in the pathogenesis of acute cerebrovascular events.

**METHODS**

**The Interinstitutional Carotid Tissue Bank**

The Interinstitutional Carotid Tissue Bank (ICTB) was created to collect carotid specimens from patients affected by disabling ischemic stroke and from patients with transient ischemic attack (TIA) and patients who were asymptomatic who underwent carotid endarterectomy at the Mayo Clinic and Mayo Foundation, Rochester, Minn, and the University of Rome Tor Vergata, Rome, Italy. The ICTB is located at the University of Rome Tor Vergata, while the database is available for both institutions. The electronic database was created to collect all patients undergoing surgical endarterectomy at both institutions and records all clinical variables, risk factors profile, pharmacological treatment, assessment of cardiovascular pathology, and Duplex scan examination of epiaortic vessels. This database also includes the results of brain computed tomographic scan examination and the result of selective carotid and cerebral angiography.

**Selection of Cases**

The database included 351 patients who underwent carotid endarterectomy between January 1995 and December 2002. A total of 4 plaques, removed by surgeons in various fragments, were excluded to avoid gross artifacts at the histomorphometric examination. Seventy-eight patients did not match the inclusion criteria for the study and were excluded. Thus, a total of 269 cases formed the study population (187 collected at Mayo Clinic and 82 at the University of Rome) (TABLE 1). Plaques were divided into 3 groups: 96 from patients with ipsilateral major stroke, 91 from patients with TIA, and 82 from patients without symptoms (control), who underwent carotid endarterectomy for asymptomatic high-grade stenosis. None of the patients enrolled underwent bilateral endarterectomy. The data of 43 plaques from 91 patients from the second group have been reported in a previous article. Major stroke was defined as a clinical syndrome characterized by rapidly developing focal or at times global symptoms without significant clinical improvement within 7 days in the distribution of symptomatic carotid artery, not hemorrhagic and with no cause other than vascular origin, assessed by brain computed tomographic study as a cortical or deep white matter or basal ganglia lesion of more than 1 cm. Transient ischemic attack was defined as recent (<120 days before surgery) occurrence of any sudden focal neurologic deficit that cleared completely within 24 hours, without previous stroke. Asymptomatic patients never developed neurological symptoms or cerebral lesions assessed by computed tomography. Angiographic carotid stenosis was measured in both institutions using the method from the NASCET trial by 2 independent physicians; interobserver and intraobserver reliability was more than 95%.

Patients undergoing carotid endarterectomy at both institutions were excluded from the ICTB if they had a probable cardiac embolization source (rhythm disorders, mitral valve stenosis, prolapse or calcification, mechanical cardiac valves, recent myocardial infarction, left ventricular thrombus, atrial myxoma, endocarditis, dilated cardiomyopathy, patent foramen ovale), because the cerebrovascular event might then be caused from cardiac and not carotid emboli; symptoms that could be attributed to nonatherosclerotic disease (aneurysm, fibromuscular dysplasia); or stenosis of more than 50% of the circle of Willis.

The study was approved by the institutional review boards of the Mayo Clinic and Mayo Foundation and the University of Rome Tor Vergata; all patients gave oral consent to be entered in the ICTB database.

**Assessment of Risk Factors**

To rule out the influence of major cardiovascular risk factors on plaque histomorphological characteristics, the risk factor profile of patients was assessed. Hypertension was determined by a case history of antihypertensive drug treatment. Patients affected by either insulin-dependent diabetes mellitus or treated with diet, oral hypoglycemic agents, or both were included in the diabetic group. Patients who smoked at least 20 cigarettes per day during the past 2 years were classified as current smokers. Patients with a total serum cholesterol level of more than 200 mg/dL (>5.18 mmol/L) or who were treated in the past 12 months with a lipid-lowering drug were considered hypercholesterolemic. Hypertriglyceridemia was docu-
mented either on the basis of the case history or when the serum triglyceride level exceeded 150 mg/dL (>1.70 mmol/L). History of coronary artery disease and obstructive peripheral vascular disease, previous coronary artery bypass graft surgery, and preoperative use of aspirin and statins were assessed from the clinical history.

**Histological Sampling and Light Microscopy**

Intraoperative carotid plaques were removed en bloc to preserve plaque structure. Samples were fixed immediately on removal in 10% buffered formalin for 24 hours. The sampling method has been previously reported. Briefly, after decalcification, if necessary, specimens were cut transversely every 5 mm, embedded in paraffin, and stained with hematoxylin-eosin and Movat pentachrome stains. Each segment was removed and numbered sequentially to reconstruct the entire plaque length by sequential slices. For each plaque, 3 to 10 sections were examined according to the extension of the plaque (mean, 5 sections per artery). The entire plaque was evaluated for the presence of an acute or organized thrombosis, plaque rupture or erosion, extension of necrotic core, calcification, and intraplaque hemorrhage.

A thrombotically active plaque (TAP) was defined by the presence of an acute thrombus constituted of platelets or fibrin on the plaque surface and characterized by laminar flow with or without interspersed red and white blood cells. Thrombosis was divided into 2 categories: thrombosis associated with plaque rupture or superficial erosion. Plaque rupture was defined as a complete disruption of the fibrous cap over a lipid core with contact of an acute thrombus with the lipid pool. Superficial erosion was defined as plaque denuding, associated with the presence of an acute thrombus in direct contact with the subepithelial tissue of the cap without any contact with the lipid pool demonstrated in serial sections. Organized thrombus was characterized by fibrous tissue, sometimes stratified, associated with a typical angiomatosis, with a network of large thin-walled vascular channels and a variable number of macrophagic cells loaded with hemosiderin, visible as scattered brown refractive pigments. Two pathologists (A.M., S.F.), who were blinded to the patients’ clinical findings, evaluated all histocytological components of the plaques; intraobserver and interobserver reliability was more than 98%.

**Immunohistochemical Studies**

The immunohistochemical study was used to characterize and quantitate the inflammatory cells present in the cap of ruptured plaques, using the CD68 (antihuman macrophages, Dakopatts, Denmark) and CD3 (antihuman T cell, Dakopatts) monoclonal antibodies. Cell counting was performed at a magnification of ×400 using a test grid with an area of 0.22 mm². An average of 10 fields per section (until the SEM was <5%) were counted. In 30 randomly selected plaques, 10 for each group, we evaluated the expression of interleukin 6 (IL-6) antibody (RD System, Minneapolis, Minn).

**Statistical Analysis**

Data were analyzed using SPSS version 11.0 (SPSS Inc, Chicago, Ill) soft-
The Pearson χ² test was used to assess the differences in the frequency of thrombosis, cap rupture, and cap erosion, and risk factors between the groups. The t test for unpaired samples was used to evaluate differences in age, degree of angiographic stenosis, and degree of inflammatory infiltrate between the groups. Partial correlation co-

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<th>Table 2. Thrombotically Active Plaques, Cap Rupture, and Cap Erosion by Study Group</th>
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<td><strong>No. of Plaques (%)</strong></td>
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<td><strong>Patients With Major Ipsilateral Stroke (n = 96)</strong></td>
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Abbreviation: TIA, transient ischemic attack.

**Figure 1.** Histopathology Micrographs From Symptomatic and Asymptomatic Patients Who Underwent Carotid Endarterectomy

A. Ruptured Carotid Plaque (Patient With Ipsilateral Major Stroke)

B. Carotid Plaque With Acute Thrombus (Patient With Transient Ischemic Attack)

C. Carotid Plaque Without Associated Thrombus (Asymptomatic Patient)

D. Ruptured Carotid Plaque (Patient With Ipsilateral Major Stroke)

All micrographs contain Movat pentachromic stain. A. A carotid plaque from a patient affected by ipsilateral major stroke who underwent carotid endarterectomy within 2 months of symptom onset. Fibrous cap plaque rupture with intraluminal thrombus is evident (magnification ×2). B. Carotid plaque from patient with transient ischemic attack, characterized by the presence of an acute thrombus associated with a superficial erosion (arrowheads) (magnification ×10). C. Carotid plaque from an asymptomatic patient, characterized by a large lipid core and a thin fibrous cap, without the presence of acute or organized thrombus within the lumen (magnification ×2). D. An organized thrombus characterized by stratified fibrous tissue, associated with typical angiomatosis, with a network of large thin-walled vascular channels (arrowheads) and a variable number of macrophagic cells loaded with hemosiderin, in a ruptured carotid plaque of a patient affected by ipsilateral major stroke operated within 12 months of symptom onset (magnification ×2).
RESULTS
Clinical Data
Asymptomatic patients and patients affected by major stroke were older than those affected by TIA (Table 1). There was no significant difference in the degree of angiographic stenosis observed between groups either in the ipsilateral or contralateral carotid. In particular, the mean (SEM) ipsilateral carotid stenosis values were 86.1% (1.0%) in patients with stroke, 79.5% (3.0%) in patients with TIA, and 84.6% (1.1%) in asymptomatic patients, whereas the mean (SEM) contralateral carotid stenosis values were 60.9% (2.7%), 64.2% (5.6%), and 57.5% (3.4%), respectively. Forty-three percent of patients were treated with statins with no statistically significant differences between the 3 groups. All patients with symptoms (both stroke and TIA) were taking aspirin at the time of intervention. The time interval between symptom onset and carotid endarterectomy was 1 to 30 months for patients with stroke and 3 to 22 months for patients with TIA.

Morphological Data
A TAP was observed in 71 (74.0%) of 96 plaques from patients with ipsilateral major stroke. This prevalence was significantly higher compared with plaques from patients with TIA (32 [35.2%] of 91 cases, P<.001) or asymptomatic patients (12 [14.6%] of 82 cases, P<.001) (Table 2). An acute thrombus was associated with cap rupture in 64 (90.1%) of 71 thrombosed plaques from patients with stroke (Figure 1A) and with cap erosion in the remaining 7 cases (9.9%). A thrombotic occlusion of the vascular lumen, documented by angiographic stenosis of more than 95%, was observed in 29 cases (40.8% of cases with a TAP). In the TIA group, the prevalence of erosion was approximatively twice that of patients with stroke, being present in 11 of 32 plaques with TAP (Figure 1B). In asymptomatic patients (Figure 1C), cap erosion was uncommon (1.2%); in this group, the presence of a TAP was also less common than in the other 2 groups, although 14.6% of these patients had pathological evidence of a TAP.

Table 3 shows the prevalence of TAP in relation to the time interval between the acute cerebral event and carotid endarterectomy in patients with stroke. In these cases, all 32 plaques from patients who had endarterectomy within 2 months of symptom onset showed a TAP associated with rupture of the fibrous cap (Figure 1A). The presence of TAP decreased in parallel with the increase of the time interval from symptom onset to surgery, although it was still present in 53.8% of the plaques from patients who had endarterectomy 13 to 24 months after symptom onset. Along with a reduced presence of TAP, organization of the thrombus was observed in patients who had endarterectomy later than 2 months after symptom onset (Figure 1D). In a small percentage of cases, fibrin was present inside the organized thrombus mass. In addition to TAP, an associated organized thrombus was also observed in 3 of 13 plaques of patients with stroke who underwent carotid endarterectomy 3 to 6 months after symptom onset. A similar finding was observed in 18 plaques of patients who had endarterectomy at least 7 months after symptoms. Only 2 of 96 cases of stroke had neither acute thrombus nor organized thrombus present at the histological examination.

Cap Inflammation
The immunohistochemical study demonstrated that the cap of ruptured plaques in patients affected by stroke was characterized by many inflammatory cells, principally monocytes and macrophages (CD68) and T lymphocytes (CD3) (Figure 2A) compared with those cells observed in ruptured plaques from patients with TIA and patients without symptoms. Ruptured plaques in patients with stroke had inflammation in the cap almost twice as dense as that in patients with TIA (P=.001) and patients without symptoms (P=.001) (mean [SEM], 49.2 [3.5] vs 29.9 [4.4] vs 29.1 [3.8] inflammatory cells×mm², respectively). No significant differences were observed in inflammation between patients with TIA and patients without symptoms (P=.89). A high expression of IL-6 was observed in the macrophagic cells present in the plaques cap of patients with stroke (Figure 2B).

Relationship Between Risk Factors, Thrombosis, and Plaque Rupture
By univariate analysis, there was no significant difference in the distribution of the various risk factors between the 3 study groups (Table 1). This may be due to the fact that only patients who underwent carotid endarterectomy and who presented with a high degree of carotid stenosis and a large atherosclerotic plaque burden were selected. The correlation between stroke and mural thrombosis remained highly signifi-
cant (P=.001), after adjustment for age and major cardiovascular risk factors.

COMMENT

Our study is the first to our knowledge to describe a large clinicopathologic series of carotid endarterectomy specimens demonstrating that thrombosis associated with plaque rupture is one of the major determinants of ischemic stroke in patients affected by carotid atherosclerotic disease. In addition, our study showed the presence of a fresh thrombus several months after the first cerebrovascular event, suggesting that a continuous vulnerable status of the plaque, if not removed, may trigger continuous release of embolic material, which in turn may be related to subsequent cerebrovascular events.

Plaque histopathologic examination showed the presence of a fresh endoluminal thrombus, localized at the rupture site of the fibrous cap in all cases submitted to carotid endarterectomy within 2 months of symptom onset. This finding suggests that thrombosis plays a crucial role in the pathogenesis of stroke and supports the notion that neurological symptoms are probably caused by emboli arising from thrombotic lesions, as demonstrated by 24-hour transcranial Doppler examinations.11,12

Considering the different types of circulation, it can be assumed that major stroke has a pathogenetic mechanism due to rupture and thrombosis of a moderately stenotic plaque, similar to that observed in myocardial infarction.21 Nevertheless, it has been suggested that patients with high-grade stenosis and poor collateral flow in the circle of Willis, and therefore secondary decreased intracranial flow, are probably more susceptible to embolic events than patients with emboli into normally perfused cerebral bed.22

The fundamental role of cap rupture and thrombosis in major cerebrovascular events is confirmed by the fact that we have excluded cases in which the cerebrovascular event could have been related either to cardiac embolic disease or to stenosis or malformation in the circle of Willis. Furthermore, the absence of high-grade stenosis or imaging suggestive of thrombosis at the angiographic examination of the contralateral carotid artery suggests that the ischemic stroke was related to the lesion in the ipsilateral carotid artery. In addition, our study demonstrated that the carotid plaque remains thrombotically active after the initial clinical event, thus possibly predisposing patients to a continuous release of emboli in the intracranial vascular bed. These observations suggest that after an acute cerebrovascular event the carotid plaque remains chronically unstable if triggering factors, such as a high inflammatory infiltration of the plaque and an increase in shear stress due to luminal narrowing progression, are not removed. This vulnerable state may cause new cap rupture, erosion, or both, together with thrombus formation, and may be responsible for cases of “stroke in evolution” or “delayed stroke” as demonstrated by observations showing release of embolic debris from carotid occlusion up to 22 months after a major stroke.23 The presence of TAP observed in plaques removed several months after symptom onset may help to explain the recurrence of a second ipsilateral stroke, which affected 12 of 96 patients in the stroke group in our study. Therefore, these observations favor the consideration of early percutaneous/surgical intervention in association with aggressive medical treatment to reduce the risk of subsequent events.
The role of carotid ulceration and thrombosis has been previously evaluated in various clinicopathological studies with contradictory results.14,17 These discordant findings may be related to different patient groups enrolled in some studies (ie, symptomatic patients included only a limited number of cases of stroke), and thus published data on patients with symptoms are representative of TIA rather than stroke. In particular, a significant difference in the prevalence of carotid thrombosis in patients with and without symptoms (29% vs 12%, respectively) was observed by Van Damme and Vivario.27 In that series, the low prevalence of thrombosis in patients with symptoms was most likely because only 20 of 121 cases included were affected by stroke. A higher prevalence of plaque thrombosis has been also demonstrated in a morphologic study by Sitzer et al11 (74% of the symptomatic population), although in this study the total number of patients affected by stroke was not reported. Conversely, no significant differences were observed in rates of carotid thrombosis in patients with and without symptoms in 2 different clinical studies,14,15 although the number of patients affected by stroke was low in both studies.

In addition to plaque rupture and thrombosis, other factors may increase the risk of stroke. Our results showed that the severity of clinical event is significantly correlated with cap inflammation in ruptured plaques, suggesting that diffuse plaque inflammation may be related to the severity of cerebrovascular events influencing embolic size and composition as well as brain vessels and/or tissue responsiveness.24,25 Increasing evidence suggests that posts ischemic inflammation contributes to the extension of ischemic brain injury.25,26 Cerebral ischemia is accompanied by a marked inflammatory reaction that is initiated by ischemia-induced expression of cytokines, adhesion molecules, and other inflammatory mediators.27,28 Furthermore, therapeutic strategies aimed at reducing inflammation have decreased progression of brain damage.29,30 These studies together with our data suggest the hypothesis that inflammatory cells infiltrating the ruptured carotid plaques may release vasoactive substances promoting severe cerebral ischemia. Moreover, carotid inflammatory cells could release some cytokines, such as IL-6, a key regulator of inflammatory mechanism in stroke pathophysiology,31 directly in the intracerebral vascular circle.

The major limitation of our study is that we did not include all patients who had a carotid stroke, but limited our analysis only to patients who underwent carotid endarterectomy at different time intervals from the acute event. In the future, sophisticated imaging technique with tissue characterization may give similar morphologic information without the need of tissue sample analysis. Another limitation is that C-reactive protein and cytokine levels were not available in the database for all patients enrolled in our study.

Our study may have several important clinical implications. The findings suggest that major stroke is significantly associated with an acute thrombosis which in turn complicates a vulnerable plaque characterized by a diffuse inflammatory infiltrate. Conversely, patients affected by TIA and patients without symptoms were characterized by more stable plaques at the histologic examination. These data, therefore, suggest 2 types of carotid artery disease: one form that is stable and unlikely to produce symptomatic embolization or carotid occlusion and another form that is not necessarily stenotic but unstable and at high risk of producing symptomatic embolization or complete occlusion of a carotid artery.

The present study demonstrates that the grade of stenosis is not sufficient to identify patients at high risk to develop an acute cerebrovascular event, and it is of great importance to identify other factors for correct risk stratification of ischemic disabling events in patients affected by atherosclerotic carotid disease. Besides imaging techniques, such as pixel analysis at ultrasonography, magnetic resonance, and local temperature probes that could help in identifying vulnerable plaques.32,33 High sensitive inflammatory circulating markers, such as C-reactive protein, pregnancy-associated plasma protein A, cytokines (eg, IL-6), are possible candidates for active plaque detection.31,34,36 In the Physicians’ Health Study,38 high baseline C-reactive protein levels were associated with increased risk of stroke, independent of smoking and other risk factors. In addition, we previously demonstrated that patients with hyperfibrinogenemia were characterized by a greater inflammatory infiltrate and thinner atherosclerotic plaque cap and also had increased risk of thrombosis and rupture compared with patients with lower fibrinogen levels, independent of other risk factors.39 Moreover, individual major histocompatibility complex haplotypes may determine the specific inflammatory patterns, the type of immune response to exogenous antigens, and the induction of autoimmune reactions in the plaque. Therefore, polymorphisms in genes coding for metabolic proteins (cytokines, proteolytic enzymes) involved in the processes related to plaque destabilization might represent useful markers to stratify the population at high risk for vascular atherosclerotic diseases.

The present study has implications for the natural history and management of acute cerebrovascular disease. Our results showed the presence of TAP up to 2 years after the onset of a cerebrovascular event. Only 46.2% of cases had stabilized plaques associated with an organized thrombus. Further studies are necessary to establish whether, immediately after an ischemic event, initiating aggressive medical therapy designed to stabilize plaque and decrease the inflammatory infiltrate will reduce the risk of stroke progression and whether early carotid endarterectomy procedure that completely removes the atherosclerotic plaque will decrease the risk of subsequent ischemic events.

Author Contributions: Dr Spagnoli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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