The importance of carotid artery atherosclerosis in the pathogenesis of cerebral ischemia and infarction has been recognized for many years. As early as 1856, Savory pointed out this relationship, and in 1904 Chiari suggested the possibility of cerebral emboli originating from the cervical portion of the carotid artery. The concept was further popularized by Fisher’s clinicopathologic reports of symptomatic carotid artery disease, and in 1954 the first paper describing a feasible technique for the surgical reconstruction of the carotid artery appeared in the literature.

The pathogenic role of carotid atherosclerotic plaques in the development of stroke is thought to reflect their embolic properties, hemodynamic significance, or, more realistically, a combination of both. Considered in this context, the problem of assessing the effectiveness of various modes of therapy in patients with carotid artery disease has been in part the assumption that all individuals with a “carotid plaque” have an equivalent risk of suffering a stroke. It is now believed that this population is more heterogeneous than originally thought, and attention has shifted to the study of the various types of carotid artery lesions encountered in clinical practice. The focus of this shift has been the search for subgroups of patients who share certain specific types of carotid plaques and the investigation of the association between plaque morphology and the risk of ipsilateral brain infarction. The morphologic variables that have been considered may be grouped into several categories: 1) size of the plaque (and degree of stenosis caused), 2) plaque surface configuration (smooth, rough, or ulcerated), and 3) plaque histologic composition (fat, fibrous tissue, calcium, intramural hemorrhage).

This review will discuss the significance of plaque histologic composition, intramural hemorrhage, and ulceration in relation to high-degree stenosis as independent or aggregate risk factors for the occurrence of ipsilateral stroke; current concepts about the technologies which allow identification of these morphologic characteristics; the ultrastructural composition of carotid plaques and their relation to the atherosclerotic process elsewhere in the human body, particularly the coronary arteries; and, finally, the implications for management decisions while awaiting more definitive data.

Plaque Size: High-Grade Versus Low-Grade Stenosis

The degree of carotid stenosis is one of the most commonly cited criteria for classification of patients at high risk for stroke. Imparato et al reported the pathologic and preoperative diagnostic data in 69 carotid specimens from 50 symptomatic patients. In this series approximately 77% of the arteries examined were found to have more than 70% stenosis. Of these, only 20% were caused by simple fibrous thickening while the rest showed pathologic evidence of other histologic composition, including intraplaque hemorrhage. Interestingly, the percentage of plaques with greater than 70% stenosis was similar in the group of patients with focal (82%, ipsilateral side) and nonfocal symptoms (90%), even though there were four times as many plaques in the former group. In contrast, only 53% of patients with focal symptoms had stenoses greater than 70% in their contralateral asymptomatic side.

In 1986 Fisher and Ojemann reported the pathologic characteristics of plaques removed from 108 patients who had experienced transient ischemic attacks (TIA), transient monocular blindness (TMB), or prolonged neurologic deficits and from 33 asymptomatic individuals. Since the measurements were done on pathologic specimens, the degree of stenosis was not reported as a percentage but rather as total millimeters of residual lumen. In this study all patients with hemispheric TIA had residual lumens of less than 2 mm, and 90% of those with TMB had lumens of less than 1 mm. The great majority (94%) of patients with fixed neurologic deficits had severe stenosis or occlusion, as demonstrated angiographically and/or pathologically. In contrast, only 15% of the asymptomatic group had residual lumens of less than 1 mm.

More recently, O’Holleran et al reported a long-term follow-up of asymptomatic, untreated individuals who had ultrasonic carotid studies. Over a 5-year period the cumulative stroke and TIA rate was 60%
in patients with greater than 75% stenosis and only 12.7% in those with less than 75% stenosis (p<0.0001). The cumulative risks for stroke alone were 16% in the first group and 3% in the second (p<0.001). Also using ultrasonographic data, Sterpetti et al found that hemispheric symptoms were almost four times as frequent in patients with greater than 50% stenosis, while only one sixth of all asymptomatic patients had more than 50% stenosis. In addition, as the degree of stenosis increased beyond 70%, the incidence of new symptoms also showed a sharp increase.

Cumulative evidence suggests that carotid atherosclerotic plaques are not static lesions but rather that they undergo dynamic changes in their histology and size. Some of these changes seem to be associated with increased risk for stroke. Weinberger et al reported that the development of symptoms in patients whose plaques progressed was more frequent (25%) than in those whose plaques regressed or had not changed (8%, p<0.001). In addition, plaques that became obstructive and disrupted flow were associated with a higher frequency of symptoms (40%) than those that did not (13%, p<0.001). Although suggested in other series, a relation between plaque progression and symptom formation has not been observed by all investigators.

### Plaque Surface: Ulceration

Ulcers or craters which modify the intraluminal surface of the plaque have also been postulated as important factors in the development of emboli. Exposure of the vessel wall's media is believed to trigger the development of mural thrombi and embolic material. The first study in which the issue of ulceration of carotid plaques was discussed was that of Julian et al. Seventeen cases of ulcerative carotid lesions were found among 231 symptomatic patients who had undergone endarterectomy, and thrombi were found lying in the ulcer crater in all of the cases. The authors suggested that this pattern of lesion was associated with increased risk for cerebral embolization. They also suggested that ulcerated lesions might be more prevalent than previously suspected since no characteristic clinical or radiographic pattern allowed this differentiation from other lesions. Years later, Imparato et al found in their series that 33% of all lesions showed signs of ulceration regardless of whether they produced symptoms. Only 25% of the ulcerated plaques were accompanied by mural thrombus, all in symptomatic patients. On the other hand, there were an equal number of nonulcerated plaques showing mural thrombus. Similarly, in their follow-up series plaque ulceration was the most frequently observed morphologic change (46%) although its significance in symptom formation was unclear.

More recently, the relationship between ulceration of carotid plaques and the occurrence of TIA or TMB has been shown to be less clear than previously suspected. In one study patients with TMB had a greater percentage of ulcerated plaques (57%) than those with TIA (24%) or those who were asymptomatic (27%). In a clinicangiographic study, Thiele et al found a correlation between transient ischemic symptoms and ulceration, particularly in plaques which caused greater than 50% stenosis. In general, however, the majority of recent studies have failed to show a consistent pattern of increased risk for stroke in patients with ulcerated plaques.

### Plaque Composition: Histology and Intraplaque Hemorrhage

The most common histologic classification of carotid plaques is based on their content of fatty, fibrous, and calcific material. This classification allows ultrasonic characterization into soft, dense, or calcified plaques, respectively, based on their echogenic properties. In O'Holleran's study individuals with less organized plaques (soft or dense) had a higher risk of TIA and stroke even if the degree of stenosis was less than 75%. Similarly, the presence of heterogeneous carotid plaques in Sterpetti's series correlated statistically with the development of new deficits. In a very recent report, Langfeld et al graded lesions according to their echogenicity and found that soft or heterogeneous plaques occurred more commonly in symptomatic patients. Intramural hemorrhage is one of the plaque characteristics most extensively studied, not only because of its importance as a marker for higher risk of cerebral embolism, but also because of its implications for pathogenesis and preventive management. The concept of intraplaque hemorrhage was originally brought into perspective by Imparato et al. In 1979 these investigators showed that 80% of significant stenoses found in symptomatic patients were not due to simple fibrous thickening but rather to a number of other factors, predominantly intraplaque hemorrhage. Later, in a follow-up series which included 376 patients, they showed that intraplaque hemorrhage was the only factor significantly more common in symptomatic patients and in patients with focal symptoms as well as in plaques with a high degree of stenosis (p<0.001).

Other authors have studied the significance of plaque hemorrhage with rather consistent results. In 1982 Lusby et al found that 49 of 53 plaques (92.5%) obtained from symptomatic individuals contained acute or recent hemorrhages while only 7 of 26 plaques (27%) from asymptomatic patients did. In addition, 43 of 46 symptomatic patients whose plaques caused greater than 50% stenosis also showed multiple intramural hemorrhages. Persson et al studied 57 carotid artery plaques from 54 patients. Of these, 34 patients were symptomatic, and in 33 of them carotid plaques showed intramural hemorrhages with connections between the hemorrhage and the lumen in 28. In contrast, only 11 of the 21 asymptomatic patients had intraplaque hemorrhages, and only one had a plaque-lumen connection. In Fisher and Ojemann's review, the incidence of hemorrhage inside carotid plaques was 39% in patients...
with TIA and 65% in those with TMB in contrast to 19% in asymptomatic individuals.7

The interest in intraplaque hemorrhage as a potential risk factor for cerebrovascular events has also focused on intraplaque neovascularization. Both deep and superficial new vessels have been described as having a complex angiomatous appearance and relatively thin walls.18 These small, fragile vessels could represent the underlying anatomic and pathologic changes leading to intramural hemorrhages. Further study of intraplaque neovascularization using immunohistochemical staining techniques has begun to uncover some of the more specific characteristics of these new vessels (Gomez CR et al; unpublished data). Although a relatively new concept in the context of cerebrovascular disease, the potential significance of neovascularization has been previously recognized in relation to the atherosclerotic process affecting coronary arteries.19-21

Clinical Evaluation of Plaque Morphology

When considering the various morphologic characteristics described above, it is also important to review the methods capable of allowing the differentiation and classification of plaques in vivo. Although angiography has traditionally been considered the "gold standard" for diagnosis, its limitations for studying plaque morphology are several. Angiography displays the appearance of an intraluminal column of iodinated contrast. The degree of stenosis can be adequately assessed and measured with this technique,22,23 but the evaluation of plaque surface ulceration is subject to a high degree of interobserver variability, probably because of the blanplan characteristics of the images.24 This observation is particularly true for small ulcers.22 Plaque histology and intraplaque hemorrhage are outside the scope of angiography. Furthermore, although considered to be unequivocal in the documentation of completely occluded carotid arteries, instances of false-positives have been reported.25

Carotid duplex ultrasound is complementary to angiography.26 This technique provides information which adds another dimension to carotid plaque examination. Current instrumentation allows histologic characterization and classification of the plaque,27,28 including the identification of ulcers and intraplaque hemorrhages.29,30 The effect of plaques on flow (degree of turbulence) also assists in the determination of the degree of stenosis.26 The main limitation of carotid duplex ultrasound is its inability to differentiate between complete and subtotal occlusion, a so-called "string sign." However, newer instruments which use color flow Doppler imaging promise to overcome this limitation.31

Other methods with some potential value in the evaluation of carotid plaques and their embolicogenic potential include computerized assisted tomography32 and indium-111 platelet scintigraphy.33

Summary and Future Perspective

The subject of carotid plaque morphology is more complex than originally thought, particularly with respect to morphologic determinants of stroke risk. Individuals who appear to be at a higher risk for stroke are those who have soft-dense (heterogeneous) plaques or plaques with hemorrhage within them, especially if the plaque narrows the vessel's lumen by more than 70 to 75%. Plaque ulceration, on the other hand, does not appear to be a reliable predictor of stroke risk. It is more likely that ulceration is only a marker of plaque instability and that other factors contributing to this instability represent a higher risk for cerebral infarction.

The characterization of plaque morphology in the clinical setting is probably best accomplished by a combination of ultrasonic and angiographic data. These tests should be used in a complementary fashion to obtain the largest amount of information possible about the plaque. Finally, considering the growing importance of intraplaque hemorrhage as a risk for stroke, potential uses of ultrasound may include the identification of neovascularity, which may require color flow Doppler imaging because of the small size of these new vessels. The ability to detect neovascularization before intraplaque hemorrhage occurs may change the rationale for choosing a stroke prevention program. If a subgroup of patients is identified in which antiplatelet or anticoagulant agents increase the risk for stroke by precipitating intraplaque hemorrhage, then these patients may be candidates for surgical intervention or other therapies. However, the decision to treat medically or surgically cannot be inferred from existing data and will have to await the results of ongoing studies.

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