Comments, Opinions, and Reviews

The Unstable Carotid Plaque

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"A long dispute means both parties are wrong." (Voltaire)

Stroke is one of the leading causes of morbidity and mortality in Western countries.[1] In 1951 Fisher stated that ". . . thrombosis of the internal carotid artery . . . may well prove to be one of the major causes of apoplexy."[2] The importance of the extracranial vasculature in the production of cerebral ischemia was emphasised in the Framingham Study of 1970, in which Kannel et al[3] documented the high incidence of embolic stroke of noncardiac origin. Atherosclerotic plaque of the carotid bifurcation apparently produced symptoms, but the mechanism that triggers an asymptomatic carotid plaque to become symptomatic remains a mystery.

Atheromatous plaques have been a subject of interest since the midnineteenth century,[4] but the true nature of atherosclerosis in humans is still debatable.[5-7] The two important and persuasive theories that have emerged are the lipid theory[5] and the response to injury hypothesis.[6] The former emphasizes the crucial role of lipids, particularly cholesterol esters, in catalyzing atheroma formation; the latter stresses the importance of damage to the arterial endothelium that triggers a proliferative response of myointimal cells from the arterial media.

Carotid plaques occur preferentially at the carotid sinus and on the outer and lateral walls where shear stress is high.[8] However, some argue that atherosclerotic plaques develop more readily where shear stress is low, allowing flow-dependent lipids to accumulate.[9] Motomiya and Karino[10] also observed a recirculation zone in the carotid sinus, where particles such as platelets and lipoprotein molecules sweep sluggishly along, adhere to, and infiltrate the vascular wall.

Progression of atherosclerosis is well documented by serial angiography of the systemic, coronary, and extracranial circulations.[11-14] Progression of carotid stenosis and even spontaneous regression of arterial plaque was observed and established by clinical, angiographic, and ultrasound data and from animal experimentation.[15-19] In the Toronto Asymptomatic Carotid Bruit Study, lesions progressed in 28% and regressed in 4% of 496 arteries over 2 years with serial monitoring by continuous-wave Doppler.[20] Transient ischemic attack (TIA) and stroke were much commoner in patients with progressing stenosis than in those with stationary lesions ($p<0.0001$).[21]

Of several putative risk factors, the presence of ischemic heart disease or peripheral vascular disease and the severity of the stenosis were related to progression, but age, sex, hypertension, diabetes mellitus, smoking, and cholesterol concentration were not.[22] Therefore, although systemic factors may play a major role in the early stages of plaque formation, they seem to exert little or no influence when the plaques are large, causing at least >50% stenosis. However, neurologic outcome correlated highly with acute local changes in large, severely stenosing, unstable plaques, and a correlation also exists with progression or regression, possibly reflecting plaque instability. However, once the artery occludes, the threat of stroke seems to drop precipitously.

To explore this idea, we followed 40 patients with unilateral carotid occlusion by serial clinical and Doppler evaluation over 6 years. Timing of events to occlusion was facilitated by performing Doppler examinations at 6-month intervals and by ensuring that when an ischemic cerebral event occurred, a further Doppler study was performed as soon as possible. In 19 patients the carotid artery was already occluded upon entering the study, and in 21 patients carotid stenosis progressed to occlusion during the study. More ischemic cerebral events occurred in the patients with carotid stenosis progressing to occlusion than in those whose arteries were already occluded. In the already-occluded group there were four TIAs, no strokes, and two vascular deaths over a mean follow-up of 48 months; in the 21 patients observed to have carotid stenosis progressing to occlusion, there were nine TIAs, three strokes, and four vascular deaths over a mean

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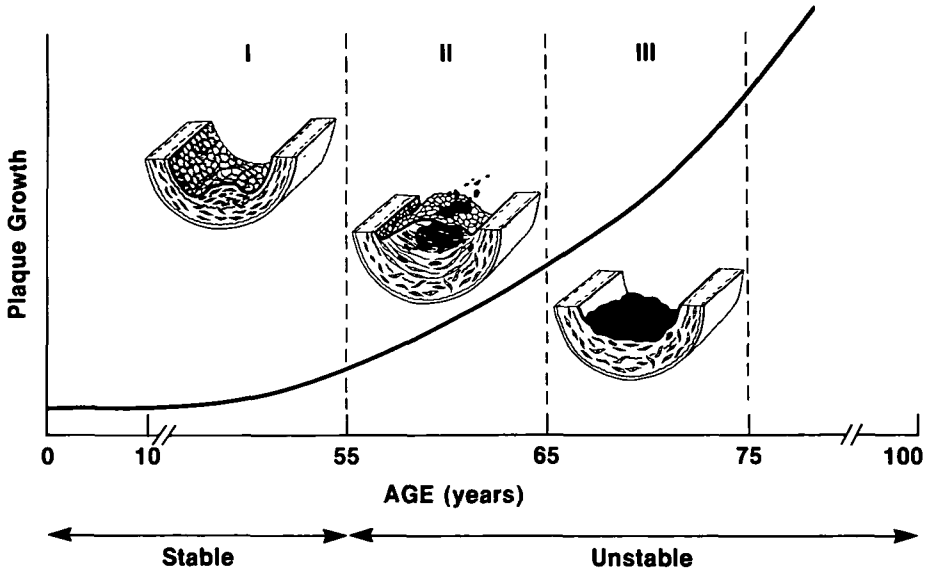

FIGURE 1. *Schematic representation of evolution of carotid plaque from stable to unstable condition.*

follow-up of 30 months.[23] The risk of ipsilateral stroke in our patients was maximal at or just prior to the moment of occlusion, and no strokes occurred after the arteries occluded. Thus, it seems that as the stenosis becomes tighter, the plaque become unstable and produces symptoms but becomes stable once the artery occludes (Figure 1).

However, the main question that still remains is what local changes cause this plaque instability. There is conflicting evidence concerning the role of intraplaque hemorrhage and surface clot in the pathogenesis of carotid artery stroke.[24-31] In our own prospective clinicopathologic study in Toronto, of 71 consecutive carotid endarterectomy specimens, plaque hemorrhages did not appear to relate to the timing of symptoms but did correlate with plaque size and with the severity of the stenosis.[32] The relation of neovascularization to acute plaque pathology, to both the instability of plaque in the severely stenosed artery as well as to the genesis of deep, destructive hemorrhage, is also uncertain.[29] Our data indicate that hemorrhages were mainly located deep within the area of high-density neovascularization. Thus hemorrhages may contribute to the acute progression of carotid stenosis that compromises the blood flow until hemodynamic insufficiency occurs. This is in agreement with the findings of Fisher and Ojemann[33] that events relate to the time of arterial occlusion.

Carotid artery disease is of unquestioned importance in the pathogenesis of cerebral ischemia, but the responsible event or mechanism still remains uncertain. The causes of plaque becoming unstable and symptomatic are clearly multifactorial, and symptoms are produced either by restriction of blood flow or by embolism. A better understanding of the factors responsible for plaque instability may lead to more specific and effective management than is currently possible. The potential hazards of anticoagulants and antiplatelet drugs in encouraging further plaque hemorrhage are but one aspect of immediate, practical relevance. Data from most published clinicopathologic studies are of limited value since they are retrospective and are usually restricted to symptomatic patients. Only a prospective, carefully designed and executed study with cooperation between pathologists and clinicians investigating intact plaques from both symptomatic and asymptomatic patients will answer these questions.

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