Comments, Opinions, and Reviews

Progression and Regression of Carotid Stenosis

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RELENTLESS PROGRESSION of atherosclerosis over the years is well-documented by serial angiography of the systemic, coronary and extracranial cerebral circulations.1-4 Spontaneous regression of arterial plaques is almost as well-established by data from clinical angiography and ultrasound,5,6 and from animal experimentation.5 Understanding the factors which influence the waxing and waning of atherosclerotic lesions could have fundamental implications for therapeutic management.

Whether the fatty streaks found in infants' arteries progress to the advanced, ulcerated, thrombotic or hemorrhagic, stenosing lesions seen in patients with cerebrovascular disease is controversial.7,8 There is good evidence that arteries do not just slowly corrode like rusty pipes but that plaques may enlarge or contract dynamically in response to local or systemic stimuli. According to the "response-to-injury" hypothesis, increased shear stress related to the anatomical angle of the arterial origin, to hypertension and to other local mechanical factors, desquamates the vessel endothelium and exposes underlying connective tissue to platelet and lipoprotein infiltration. Focal proliferation of smooth-muscle cells which migrate from the media to the intima helps to form the early mound of the embryo plaque, with subsequent deposition of lipids within these cells. If the "injury" continues the damage progresses, but if it is interrupted and the endothelial barrier is restored, the arterial lesion may regress. The injury need not be mechanical; a variety of systemic and metabolic factors, such as chronic hypercholesterolemia, can have the same effect.7 Shear stress also relates to blood viscosity: the higher the viscosity, the greater the "drag" between the laminae of blood flow and the vessel wall.9

Carotid plaques occur preferentially at the carotid sinus and on the outer and lateral walls where, extrapolating from animal experiments, shear stress is highest.10 Some argue that atherosclerotic lesions develop more readily where shear stress is low, and flow-dependent lipids accumulate.11 Using an ingenious technique which makes human arteries transparent, Moto-miya and Karino observed the eddies and turbulence produced when suspensions of microspheres are flushed along the vessel. They found a "recirculation zone" in the carotid sinus, where particles such as platelets and lipoprotein molecules are swept along the vascular wall, to adhere and infiltrate.12

Restenosis after carotid endarterectomy is histologically distinct from atherosclerosis, relates more to intimal proliferation of fibrous tissue, and is probably unaffected by putative risk factors.13,14

Once a plaque starts growing, it alters the local dynamics and disturbs laminar flow, increasing shear stress at the constriction and causing turbulence downstream.9 This may produce ulceration by directly eroding the smooth lipid-bearing plaque or, the sudden decrease in pressure distal to the stenosis may cause advanced atheroma to collapse, disintegrate and ulcerate.15 The wide spectrum of pathological changes occurring in severely stenosing plaques differs from that of the fatty or fibrous plaque which evolves over many years. These "complex" plaques16 are more liable to sudden alterations such as intraplaque hemorrhage, acute ulceration, and thrombosis. Ultramicroscopy of even apparently smooth plaques may show multiple shallow ulcerations of the endothelium which are a suitable substrate for thrombosis.17 Such acute changes occurring in unstable severely stenotic plaques may account for the rapid progression or regression seen on serial angiographic17 or ultrasound examinations (fig. 1).

Clinical documentation of the progression of atherosclerosis has serious methodological limitations. Angiography is usually considered the "gold-standard" of evaluation, but identifies only major changes in calibre. Also, arterial stenosis cannot be equated with atheroma, and operative exploration of acute carotid plaques reveals intraplaque hemorrhage more frequently than the anticipated thrombus.16,17 Anecdotes of popliteal stenosis noted on serial angiography to resolve following cessation of smoking and "dietary treatment"19 add little substance.

Javid and colleagues calculated the annual rate of change of carotid stenosis in 86 patients subjected to serial angiography over 1 to 9 years (mean 3 years); 59% of patients showed progression while the lesions appeared stationary in the remainder.3 Roederer and colleagues,20 using duplex scanning, grouped patients with asymptomatic carotid bruits into six categories of severity of carotid stenosis, and found that progression occurred in 17-38% (depending on the length of observation), and regression occurred in 2-3%. Progressive stenosis correlated with subsequent occlusion, and with development of symptoms, and was related to smoking, diabetes, and age less than 65 years. Observing minor atheromatous changes with serial real-time imaging of carotid arteries, Hennerici and colleagues noted progression in 30% of 31 patients and regression in 19%. Intraplaque hemorrhage was rare, since it occurs mainly in severe stenosis, and all these lesions were minimally stenosing (<30%).8 Improvements in B-mode scanning techniques may help unravel the pathological basis of these progressive changes.21
They have facilitated identification of different plaque morphologies, varying from “flat” plaque to “complex” plaques with and without echodense material. However, appearances are sometimes deceptive and cannot yet be relied upon without pathological correlation (fig. 2).

In the Toronto Asymptomatic Cervical Bruit Study, lesions progressed in 28% and regressed in 4% of 496 arteries over two years’ serial monitoring by continuous-wave Doppler. TIAs and stroke were much commoner in patients with progressing stenosis, compared to those with stationary lesions ($p < 0.0001$) (fig. 3). Of putative risk factors, presence of ischemic heart disease or peripheral vascular disease, and severity of stenosis were related to progression; age, sex, hypertension, diabetes mellitus, smoking, and cholesterol were not. Severity of stenosis also related to development of symptoms ($p < 0.001$) (table I). Although severe stenosis relates to development of symptoms, the risk for TIA or stroke becomes negligible once the artery occludes: fewer than half of patients (8/17) with arteries progressing to occlusion over two years’ observation became symptomatic. Only one of these had an ischemic stroke, the remainder having only TIAS.

Local factors seem more important than systemic factors in the changing pathology of the complex, severely stenosing plaque and therefore are more important in the genesis of symptoms. Reviewing carotid plaques removed at surgery, Imparato and colleagues emphasized the frequency of intraplaque hemorrhage and its relevance to subsequent ulceration and symptoms. In a prospective study of carotid endarterectomy specimens, Lusby and colleagues found acute intraplaque hemorrhage in 92% of symptomatic patients compared to 27% of asymptomatic patients, and related symptoms to “intimal disruption” by hemorrhage into the plaque.

Patients may remain asymptomatic as long as the plaque remains smooth and the endothelium intact, however tight the stenosis. For reasons which remain unclear, as the stenosis becomes tighter, the plaque becomes “unstable” and erodes, probably from sudden microhemorrhage. Well-developed atheromatous plaque then may bulge into the lumen to produce acute hemorrhage.
stenosis or, a fragile thrombus may form on the endothelium which is stretched tautly over the suddenly enlarged plaque. Neovascularization, the proliferation within the plaque of a dense plexus of microvessels, is probably the source of the intraplaque hemorrhage. Eruption of such hemorrhagic blebs, with embolism of probably the source of the intraplaque hemorrhage. Eruption of such hemorrhagic blebs, with embolism of probably the source of the intraplaque hemorrhage. Eruption of such hemorrhagic blebs, with embolism of probably the source of the intraplaque hemorrhage.27

Thrombus which forms over the residual, raw ulcer may separate to cause thromboembolic stroke. This occurs more readily in deep craters than in shallow ulcers which sometimes re-endothelialize without producing any symptoms.28 Serial Doppler examinations of asymptomatic patients who become symptomatic may fortuitously detect such acute progressing and regressing stenosis of the arterial lumen.

The causes of plaque becoming “unstable” and symptomatic are multifactorial, so it is unlikely that a single therapeutic strategy will prove sufficient. Regarding the enlargement of a smooth, “stable” plaque by changing local flow, or by reducing plasma lipoprotein levels or viscosity may prove more effective than reducing platelet aggregation after a plaque has erupted or eroded. Aspirin therapy for threatened stroke is rational when symptoms result from thromboembolism, but hypothetically is dangerous if it increases the chance of hemorrhage into the plaque. A better understanding of the factors producing progression and regression of arterial stenosis may lead to more specific and effective management than is currently possible.

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References


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