Clinical Assessment of Atherosclerotic Lesions
Emerging From Angiographic Shadows

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In the mid to late 1800s, the light microscopic features of atherosclerosis were discovered as Virchow and others used techniques that were novel at the time for paraffin embedding, sectioning, and staining of tissues. From then until the past few years, detailed characterization of atherosclerotic lesions has been limited to autopsied or excised tissues, which display only a single time point per specimen. Today, the goal of visualizing and characterizing the diseased arterial wall in living patients has become a reality with the use of several techniques. In this issue of Circulation, Cai and colleagues demonstrate that magnetic resonance can provide a living “biopsy” of carotid atherosclerotic plaques. Preoperative MRIs correlated well with paraffin section histology of endarterectomy specimens, classified by criteria of the Committee on Vascular Lesions of the Arteriosclerosis Council.

Because the clinician has such difficulty defining atherosclerosis in living patients, this ubiquitous disease must be managed indirectly. Downstream effects on end-organ ischemia and infarction are measured. An offending plaque may be bypassed or it may be cracked at the edge and displaced by stretching of the underlying tissue. The antecedents to atherosclerosis, termed risk factors, are treated mostly in terms of their relation to end-organ events. Clinical trials have taught us how changing certain risk factors can affect those events. All of this happens with scant knowledge of atherosclerotic lesion progression in the angiographic shadows.

The obscurity of atherosclerosis to the clinician has led to a largely dichotomized approach. If ischemia or infarction has not yet occurred, then the job of the clinician is to identify the risk factors and treat them where evidence for efficacy is strong. If ischemia or infarction has occurred, the first task is often to assess and remedy the impaired coronary flow, with a heightened program of risk factor modification coming next.

The approach may change as new technology brings atherosclerosis out of the shadows and into the light. MRI is the most elegant and perhaps ultimately the most useful of several techniques for characterizing lesions. Carotid B-mode ultrasound can provide intima-media thickness measurements predictive of both cerebral and coronary vascular events. Coronary intravascular ultrasound has shown that patients with normal or minimally abnormal angiograms may have extensive nonstenosing coronary atherosclerosis. The ankle-brachial index, a venerable measure of iliofemoral atherosclerosis, predicts cardiovascular and all-cause mortality.

The determination of coronary calcium deposits by enhanced computed tomography of the heart is entering clinical practice faster than many would like. Coronary calcium scoring provides a reasonably good estimate of the total burden of coronary atherosclerosis. The ability of coronary calcium scoring to predict clinical coronary events has been found to be equal to estimation on the basis of the number of coronary arteries with >50% angiographic stenosis and either equal to or better than the Framingham logistical estimate on the basis of multiple risk factors. Key questions not yet answered by prospective data are whether year-to-year changes in the calcium score may be responsive to treatment and/or predictive of events.

The ruptured or ulcerated atherosclerotic plaque is the most dangerous lesion, but evidence indicates that plaque rupture is frequently silent, unaccompanied by clinical symptoms. Recently, MRI of the myocardium with gadolinium contrast has demonstrated that microinfarcts can be visualized in patients with advanced coronary atherosclerosis with or without coronary intervention. If microinfarcts are caused by fibrin-platelet emboli from ulcerated plaques, clinical treatments that stabilize plaques might be validated by demonstrating the cessation of new microinfarct formation.

The National Institutes of Health–funded Multi-Ethnic Study of Atherosclerosis (MESA) multi-center trial is studying the progression of human atherosclerosis as examined by many of these techniques, including ankle-brachial index, carotid B-mode ultrasound, computed tomography of coronary arteries, and MRI of the heart, as well as by stimulated vasodilation of the brachial artery. The population-based, longitudinal data supplied by this and other studies will provide an essential foundation for treatment studies and, ultimately, changes in clinical practice.

Current clinical paradigms, as indicated earlier, focus on the antecedent risk factors and the sequelae of end-organ ischemia/infarction, largely omitting the intermediary role of the atherosclerotic lesion in the pathophysiological sequence. The future clinical paradigms will increasingly include atherosclerosis in the middle—that is, risk factors leading to definable, quantifiable atherosclerosis, which in turn lead to myocardial and brain ischemia/infarction.

Nonetheless, evidence-based medicine reminds us that what really counts is morbidity and mortality. Will we want

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to treat a patient merely because her carotid plaque has excessive lipid content and a thin fibrous cap? Will that qualify as a surrogate or a biomarker for clinical events? Today we treat abnormal glucose, low-density lipoprotein cholesterol, and blood pressure partly or largely for the purpose of reducing excess risk of the atherosclerotic events predicted by these parameters. It makes sense that we will someday apply metabolic and pharmaceutical treatment to high-risk plaques for the same reason. Much remains to be done in assigning clinical risk estimates to lesion characteristics and also to time- and treatment-dependent changes in lesion characteristics as quantified by the new techniques.

Advances in diagnosis prosper when they march hand-in-hand with advances in treatment. We stand at the threshold of accurate noninvasive assessment of atherosclerosis. Is there a corresponding ability to treat atherosclerosis effectively by metabolic or pharmacological means? The answer is yes. In the context of noninvasive lesion assessment, statins have been shown to reduce the progression of carotid intima-media thickness defined by ultrasound, and high-dose atorvastatin achieved regression in patients with familial hypercholesterolemia.

Corti et al reported in an earlier issue of Circulation a longitudinal, uncontrolled study of the effect of simvastatin on atherosclerotic plaque dimensions by use of MRI. After 12 months of simvastatin treatment, vessel wall thickness and area were significantly reduced in the aorta and carotid arteries without a change in vessel lumen area. In another remarkable study, Zhao et al examined carotid plaque composition quantitatively by MRI in 8 patients with combined hyperlipidemia who had been treated intensively with lovastatin, niacin, and colestipol for 10 years. An untreated, nonrandomized control group was composed of 8 patients matched for age and baseline lipoproteins. In the untreated group, the atherosclerotic lipid core comprised 17% of carotid intima-media cross-sectional area. In the treated group, only 1% of the cross-sectional area belonged to the lipid core (P=0.01 for the comparison). Thus, the lipid core seemed to be almost eliminated from the lesions by metabolic/pharmacological treatment. The 8 treated patients were randomly chosen from a larger group of 60 patients treated intensively, and the larger group experienced only 3 major coronary events (cardiac death or myocardial infarction) over 10 years, or 0.5% per year.

If randomized clinical trials confirm these results, a paradigm shift in atherosclerosis treatment will begin. Most risk factors presumably influence atherothrombotic events via their effects on lesions, although this hypothesis will require rigorous testing. If this is proven, the risk factors may be viewed as 2 steps removed from clinical events, with lesions just 1 step away. Ultimately, one can foresee a new clinical paradigm that includes the assessment of atherosclerotic lesions in addition to risk factors fitted to an evidence-based model of end-organ and clinical risk reduction.

References


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