Editorial

In Vivo Assessment of the Risk Profile of Evolving Individual Coronary Plaques
A Step Closer

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The natural history of coronary plaques within an individual patient with coronary disease is highly heterogeneous. Over time, each plaque may exhibit a different temporal pattern of progression, quiescence, or regression, as well as a variable rate of change. The trajectory of the natural history of a particular plaque depends on the level of systemic risk factors and patient-specific genetics, as well as local phenomena, such as the detailed local blood flow patterns, arterial wall characteristics, including plaque size and shape, and arterial remodeling characteristics. Local endothelial shear stress (ESS) is one of the most fundamental factors influencing endothelial structure and function, and it is the central factor responsible for the localization of coronary atherosclerotic plaque formation and progression. Recent methodological innovations allow detailed in vivo characterization of local ESS and remodeling behavior of the artery based on biplane angiography, intravascular ultrasound (IVUS), reconstruction of the artery in 3-dimensional space, and computational fluid dynamics calculations. Analysis of the radiofrequency patterns from the IVUS signal has also been used to estimate plaque composition. These methodologies not only allow detailed characterization of plaque at a single point in time but, if studied in a serial manner, now allow prognostic insight into how plaques change over time and what antecedent features predict the future behavior of that plaque.

Animal models have been extremely helpful in identifying the anatomic natural history of coronary plaque because in vivo serial studies can be performed over time and histological validation of the in vivo IVUS studies can be performed at the end of an animal’s course of study. Such investigations have demonstrated that the formation of plaque and the remodeling response of the arterial wall to that plaque are highly variable and change dramatically over time. Focal areas of low ESS, located at the inner surface of curved sections of the epicardial coronary arteries, at bifurcations and branch points, and downstream from an existing luminal obstruction, consistently lead to increased expression of proatherogenic and proinflammatory genes, which result in the formation and progression of focal plaque, culminating in highly inflamed atheroma with intense accumulation of lipids and activated inflammatory cells, augmented expression and activity of matrix-degrading enzymes, and disruption of supporting matrix, associated with subsequent excessive expansive remodeling and thinning of the fibrous cap overlying the plaque. Areas of moderate or physiological shear stress are generally vasculoprotective, with increased expression of atheroprotective molecules, such as nitric oxide and decreased expression of degrading enzymes. Areas of high ESS may be associated with atrophy of smooth muscle cells, increased macrophages, matrix degradation, increased thrombogenicity, and high mechanical strain.

Pilot serial studies of the anatomic natural history of coronary disease in humans using small numbers of patients have confirmed that areas of low ESS are indeed associated with an increase in plaque size over time and associated expansive or constrictive remodeling responses. These studies are limited by very small sample size (<15 patients), brief follow-up (typically 6 to 8 months), the presence of only minor luminal obstructions at baseline, characterization of the artery based only on gray-scale IVUS without tissue characterization, and an inadequate sample size for investigating the clinical natural history consequences of the anatomic natural history.

The study by Samady et al in the current issue of Circulation provides important new data concerning the in vivo serial assessment of coronary plaque in humans, identifying both the change in plaque characteristics and the antecedent features associated with the different natural histories. They studied the left anterior descending coronary artery in 20 patients with stable, nonobstructive coronary artery disease with coronary angiography, gray-scale IVUS, and radiofrequency IVUS (VH-IVUS) at baseline and again after 6 months of follow-up. They reconstructed the coronary arteries in 3-dimensional space, performed computational fluid dynamics to calculate local ESS, and correlated the local ESS patterns at baseline to the VH-IVUS and remodeling characteristics at follow-up. They observed that areas with low ESS developed progression of plaque area and necrotic core, as well as constrictive remodeling, compared with other shear stress environments, whereas areas of high ESS were associated with progression of necrotic core and dense calcium, regression of fibrous and fibrofatty tissue, and excessive expansive arterial remodeling compared with other shear stress environments. Although they could not measure fibrous
cap thickness, they concluded that low ESS leads to plaque progression but that high ESS leads to transformation of the plaque to a more vulnerable phenotype. It remains unclear whether the presumed more vulnerable phenotype that may lead to a new clinical event originates from an area of low ESS and intense focal inflammation or from an area of high ESS.

The authors have done a valuable job of refining the concept of in vivo assessment of the evolving risk of individual coronary plaques. Although the in vivo assessment of detailed local intravascular hemodynamics and arterial remodeling behavior is established and reliable, the in vivo assessment of plaque composition by analysis of the radiofrequency signal is potentially less accurate and reliable, as acknowledged by Samady et al. Radiofrequency IVUS assessment appears to be a good approximation of arterial wall characteristics, but there are important limitations and caveats to this methodology. Some of the reported inconsistencies between VH-IVUS and true histology such as the presence and size of the necrotic core within an atheroma may reflect differences in the underlying pathobiology of human plaque (used in the validation of VH-IVUS) and porcine plaque (used in the analysis identifying poor correlation) and inconsistencies of alignment of VH-IVUS with histology images. Improvement in radiofrequency assessment and/or new methodologies such as optical coherence tomography or near-infrared spectroscopy imaging may allow enhancement of tissue characterization. As indicated by Samady et al, it will be essential not only to characterize the individual plaque at a single point in time but also to characterize driving pathobiological mechanisms such as local ESS to understand the likely composition and behavior of that plaque in the future to determine whether it will remain quiescent, will progress to additional high-risk characteristics likely to lead to rupture, or will progress to a more stable flow-limiting fibrotic plaque.

The most important prognostic feature to identify in terms of risk status of an individual coronary plaque, however, is not the anatomic evolution of the plaque per se but whether the plaque will cause a new clinical event such as a new acute coronary syndrome resulting from plaque rupture or plaque erosion or an accelerated progression of a more fixed, flow-limiting lesion that will cause worsening ischemia. The fundamental limitation of most animal models in terms of applicability to humans is that, although the anatomic progression of coronary disease is almost indistinguishable from that in humans, spontaneous plaque rupture and clinical events are extremely rare in animal models of coronary atherosclerosis. Furthermore, the majority of thin cap fibroatheromas by VH-IVUS may heal spontaneously. Consequently, the clinical manifestations of the anatomic natural history of coronary plaque can be studied meaningfully only by clinical trials in humans. The study by Samady et al is indeed be enhanced by measurement of ESS at the baseline evaluation. The full report of that study is awaited with interest. The payback from this ultimate prognostic understanding is enormous, if it can be sufficiently sensitive and specific, because early stages of high-risk plaque leading to new clinical events may enable the development of preemptive therapeutic strategies, either mechanical or pharmacological, to prevent adverse coronary events. The benefits from these preemptive strategies may be invaluable for patient care and medical economics. We are getting closer, but we are not there yet.

Disclosures

Dr Stone and Dr Feldman are supported by a research grant from Boston Scientific Company, Inc.

References


**KEY WORDS:** Editorials, atherosclerosis, cardiac imaging techniques, ultrasonics, plaque, atherosclerotic
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Circulation. 2011;124:763-765
doi: 10.1161/CIRCULATIONAHA.111.042788
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/7/763

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