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EDITORIAL COMMENT

Asymmetric Longitudinal Lesion Geometry

Expanding Clinical Applications of Biomechanics*

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Initial in vivo investigations to characterize coronary plaques at high risk to rupture and cause new clinical events focused on assessment of the anatomic aspects of plaque size and composition by intravascular imaging modalities (1). In part because of the low positive predictive value of predicting plaque rupture on the basis of plaque anatomy alone (2), attention has expanded to include more sophisticated interactions between the biomechanics of the plaque itself, along with its local hemodynamic environment, and the vascular biology of atherosclerosis.

The biomechanical investigations of plaque initially focused on endothelial shear stress (ESS), the very small magnitude stresses that are intensely proinflammatory and proatherogenic. These stresses result from alterations in the local blood flow pattern in the vascular microenvironment associated with curves, bifurcations, and luminal obstructions and are pathobiologic not by causing a mechanical disruption due to the physical stress per se but by inducing phenotypic switching of the endothelium, culminating in the broad constellation of atherosclerotic phenotypic features (3–6).

More recently, in vivo use of biomechanics to understand plaque behavior is expanding to include broader applications of the mechanical properties of the plaque and the mechanical forces affecting that plaque. Recent methodologies, for example, have been able to analyze detailed plaque constituents along the longitudinal course of the lesion by intravascular ultrasound–virtual histology, incorporate the empiric data of the constituent mechanical properties of the plaque, and calculate the plaque structural stress along the course of the plaque (7). These stress-strain insights on the basis of the composite mechanical properties of plaque constituents may add important insight concerning the likelihood of a plaque to rupture (8).

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Another complementary, important biomechanical approach has been to characterize the regional distribution of hemodynamic stress due to the external arterial pressures from the lumen along the longitudinal course of the plaque as it encroaches into the lumen, axial plaque stress (APS), which is often asymmetrical related to the detailed geometry of where plaque forms. In this issue of *iJACC*, Lee et al. (9) extend their previous pioneering work investigating the geometric contour of the plaque along its long axis (10) and now apply their conceptual approach of APS to identify the location of plaque rupture and the implications for clinical presentation. They studied 125 patients with documented plaque rupture and related the location of the rupture to the longitudinal lesion asymmetry assessed by the luminal radius change along the segment length (i.e., whether the steeper curve of the luminal encroachment was on the upstream or the downstream portion of the plaque).

They observed that plaque rupture most frequently occurred upstream from the minimal lumen area (MLA) and more frequently presented with a clinical pattern of acute myocardial infarction (ST-segment elevation myocardial infarction or non–ST-segment elevation myocardial infarction) and TIMI (Thrombolysis In Myocardial Infarction) flow grade <3 (66%), while plaque rupture occurring downstream from the MLA more frequently presented with unstable angina or nonacute coronary syndrome. The radius gradient ratio (i.e., upstream vs. downstream steeper slope of the lesion) was an independent predictor of upstream rupture. Plaque burden and lesion length were also independent predictors of TIMI flow

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grade <3, but no other intravascular ultrasound characteristics were associated with the location of plaque rupture.

There are a number of provocative implications from these observations. Most important, identification of the lesion asymmetry may be prognostically useful to help predict the location and clinical consequences of plaque rupture. There are additional implications for a more fundamental understanding of the vascular biology of plaque instability and rupture. The vast majority of plaque ruptures observed in this study occurred either upstream (56%) or downstream (28%) from the MLA, and very few occurred at the MLA itself (16%). APS was highest at either the upstream or downstream locations, where the respective plaque rupture occurred, which are the same plaque regions where the proinflammatory and proatherogenic low-ESS environment is also localized (11). There may be an important colocalization of adverse regional environments in these upstream and downstream portions of the plaque related to both the plaque's internal instability, due to plaque-degrading proteases from the intense local inflammation due to low ESS (4,5), as well as from the increased luminal APS forces affecting that plaque. The observation that plaque rupture infrequently occurs at the MLA, where wall shear stress is highest and where abnormalities of fractional flow reserve originate, but instead occurs primarily in the upstream or downstream regions may also call into question the direct mechanistic link between the severity of the MLA and the development of new cardiac events. The mechanistic consequences of a narrow MLA (and positive fractional flow reserve) may not be limited to the throat of the obstruction per se but to the upstream and downstream consequences of the obstruction where the lumen-derived stresses (APS) are high and where plaque vulnerability is most precarious from the low ESS.

There are a few perspectives concerning this important study that warrant consideration as well. The investigators excluded coronary lesions that were diffuse in terms of luminal obstruction, but recent observations suggest that many lesions, especially longer lesions, are in fact very heterogeneous along their longitudinal course, more like a complex "mountain range" than a single mountain peak, with multiple peaks as well as valleys that are each associated with their own heterogeneous local composition and mechanical stresses (7,12). Enhanced anatomic precision for reconstruction on the basis of optical coherence tomography along the course of an artery may also provide more accurate insights to inform a detailed biomechanical understanding compared with the less precise intravascular ultrasound imaging. Last, it must be acknowledged that plaque disruption and new clinical events may develop from intraplaque hemorrhage from leaky vasa vasorum within the plaque, associated with focal fibrosis and scarring (13) without disruption of the thin fibrous cap, as well as from plaque erosion without the presence of an inflamed fibroatheroma with a thin fibrous cap (6).

The ongoing advances applying biomechanics methods to the in vivo study of plaque vascular biology and its clinical consequences are enormously valuable both for prognostication and for understanding the fundamental nature of atherosclerosis. Pathobiologic manifestations of atherosclerosis are protean and are likely changing as therapies and risk factors evolve (6). We clearly need to learn more about how mechanical stresses result from, and contribute to, the phenotypic manifestations of coronary disease.

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