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EDITORIAL COMMENT

Conceptual New Biomechanical Approaches to Identify Coronary Plaques at Risk of Disruption*

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The goal of identifying high-risk plaques before they become disrupted (i.e., plaque rupture or intraplaque hemorrhage) leading to plaque progression and/or a new clinical event has preoccupied cardiologists for many years, with its promise that early and accurate identification of high-risk plaques would enable the development of pre-emptive therapeutic strategies to avert cardiac morbidity and mortality. The plaque morphology that underlies the majority of plaque disruption is the highly inflamed thin cap fibroatheroma (TCFA). Plaque disruption is a very complicated pathobiological and biomechanical process that is dependent on the nature and constituents of the plaque itself (1), as well as the external mechanical forces affecting that plaque. Rupture of the TCFA's fibrous cap occurs when plaque stress exceeds plaque strength, leading to abrupt superimposed intraplaque/intraluminal thrombus and a clinical acute coronary syndrome. In contrast, intraplaque hemorrhage, associated with subsequent plaque fibrosis and abrupt worsening of luminal encroachment and stable angina, is probably related to intraplaque hemorrhage either from immature vasa vasorum that are created as the plaque enlarges and its core becomes hypoxic or from subclinical plaque cap rupture (1).

Recent progress in invasive in vivo intravascular imaging has identified many features of the predominant precursor TCFA phenotype with variable success using combinations of coronary angiography, intravascular ultrasound (IVUS), backscatter radiofrequency analysis of IVUS images, optical coherence tomography, near-infrared spectroscopy, and, more recently, molecular imaging (2,3). Sophisticated analytic approaches combining anatomic features, such as necrotic core thickness, plaque cap thickness, and arterial remodeling index, enhance the assessment of individual plaque instability and likelihood of rupture (4). A critical limitation of a prognostic strategy focusing on anatomic characterization alone, however, is that plaques, even advanced plaques, exhibit a very heterogeneous natural history (5), and only a small minority of these ostensibly high-risk plaques actually cause a new cardiac event (6). The majority of presumably high-risk plaques become quiescent and a single anatomic snapshot may not provide sufficient clinical prognostic insight concerning that plaque's future natural history.

Combined multimodality imaging assessments focusing on features of the plaque beyond anatomy alone, such as ongoing pathobiological stimuli that may exacerbate local plaque progression and inflammation, also appear to provide incremental prognostication of high-risk plaques. Local low wall or endothelial shear stress (ESS), for example, is responsible for plaque development/TCFA formation and also serves as an ongoing pro-inflammatory stimulus (7). Indeed, when an assessment of plaque clinical risk based on an anatomy metric (plaque burden) is combined with a metric representing ongoing inflammation/atherogenesis (local low ESS), the positive predictive value to identify plaques that progress to cause clinical events increases from approximately 20% (6,8) to 41% (8). Innovative imaging approaches to identify and characterize the mechanistic determinants of plaque inflammation and degradation, such as near-infrared fluorescent imaging of molecules associated with inflammation (3) also provide enormous promise to enhance prediction of plaques likely to rupture beyond risk assessment based on plaque anatomy alone.

To add to these multimodality approaches to the risk assessment of individual plaques, Choi et al. (9)

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in this issue of *iJACC* provide first insights into a new conceptual approach to plaque risk assessment based on a calculation of the external mechanical forces acting on individual plaques. They used coronary computed tomographic angiography (CTA) images, segmented the lumen borders, and performed computation fluid dynamics calculations to determine the local coronary blood flow patterns, pressure field, and local ESS along the course of the artery. The shape of the coronary luminal obstruction was determined from the luminal radius change along the length of the plaque (radius gradient). Obstructing plaques were divided into those where the steepest radius change was in the more proximal (upstream) portion of the plaque and those in the more distal (downstream) portion of the plaque. They then calculated the axial plaque stress (APS), which characterizes the distribution of mechanical stress in the axial (i.e., longitudinal) direction of the artery centerline.

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The investigators observed that the magnitude of stenosis severity, pressure change, and fractional flow reserve (FFR) was similar in each type of plaque geometry, and the pressure gradient, FFR_{CT}, and ESS were consistently higher in upstream segments in all obstructions. However, APS was distinctly different in upstream- versus downstream-dominant lesions: APS was higher in the upstream segment of the upstream-dominant obstructions and higher in the downstream segment of the downstream-dominant obstructions. There was a significant negative correlation between APS and obstruction length. The authors suggest that measurement of plaque-specific APS will provide additive information to detect high-risk plaques and to predict the potential rupture location and its subsequent clinical significance.

This provocative study provides another conceptual approach to understanding the high-risk plaque by focusing on the external mechanical forces acting on the plaque and shows how differences in the longitudinal location of the most severe obstruction importantly influences the nature and magnitude of the biomechanical forces acting on the plaque.

There are limitations of the study that are important to acknowledge. Accurate segmentation of the lumen borders by CTA, the foundation of the entire assessment in this study, is often problematic due to suboptimal resolution and imprecise definition of vascular boundaries (2). Many of the subtleties of plaque geometry over the 9 to 11 mm length of a typical plaque may not be reliably assessed by the relatively low resolution CTA methodology. It would be valuable to repeat this kind of study using the higher resolution definition of lumen borders available from optical coherence tomography or IVUS imaging. There are also important caveats concerning the biomechanics of the metrics proposed in the study. The APS metric assumes that the critical plaque stress is in the longitudinal direction, but there may be multiple patterns of low and/or disturbed flow that may exert major plaque destabilizing influences in multiple directions.

It also must be emphasized that differences in the absolute magnitude of the mechanical stresses imposed on the artery and plaque constituents, such as the values of APS being approximately 40-fold higher than the values of ESS, may not be germane to an understanding of the respective mechanisms by which these different stresses contribute to the processes of plaque disruption. Although the high absolute values of APS may lead to mechanical rupture of plaque structures if the structures (e.g., TCFA's thin fibrous cap) become sufficiently weak, the low absolute values of ESS exert their pathobiological effect by causing local phenotypic changes within endothelial cells that promote local atherogenesis/inflammation, degrading the plaque (10) and increasing its proclivity to rupture from external mechanical forces.

As we focus on the complex external mechanical forces affecting plaque, it will, of course, be critical to incorporate into our risk assessment the complex and evolving nature of the plaque itself. Future risk assessments may be able to efficiently perform sophisticated biomechanical evaluations from multimodality imaging methods that simultaneously acquire images of the coronary lumen for computation fluid dynamics analyses, the arterial wall in its full thickness to assess plaque constituents, including plaque burden and cap thickness, as well as the molecular constituents of the plaque and their pathobiological activity. The journey to a clinically relevant in vivo understanding of the multifaceted risk of an individual plaque has been long and arduous. As our imaging modalities and our analytic approaches become more comprehensive we will hopefully soon be able to identify the highest risk plaque early in its natural history and be able to perform pre-emptive strategies to avert adverse cardiac events. Although realization of that goal is still in the distance, we are clearly getting closer, and the ultimate benefit for patients with coronary disease certainly justifies the journey.

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