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EDITORIAL COMMENT

The Ongoing Quest to Predict Plaque Rupture*

Habib Samady, MD, David S. Molony, PhD

Acute coronary syndrome (ACS) results from a culmination of ongoing systemic cardiovascular risk factors, inflammation, oxidative stress, and an underlying plaque susceptible to abrupt luminal obstruction. Although plaque erosion, calcified nodule, and spontaneous coronary dissection can all be pathologic substrates for ACS, the most common underlying plaque phenotype in ACS is a ruptured thin cap fibroatheromas (TCFA) (1). These vulnerable plaques predominantly develop in proximal and bifurcation coronary segments where flow is disturbed promoting abnormal wall shear stress (WSS). Current methodologies attempting to detect these vulnerable plaques include intravascular ultrasound (IVUS) and optical coherence tomography (OCT). The use of these imaging tools to predict vulnerability focuses on morphology alone and critically ignore the underlying biomechanics of plaque rupture.

At its most simple definition, plaque rupture is a mechanical event that occurs when plaque stress exceeds the mechanical strength of the overlying fibrous cap. Calculating plaque structural stress (PSS) can be achieved by a computational technique called finite element analysis (FEA). To quantify the stress within an object, accurate inputs for the load (blood pressure), material properties, and geometry are necessary. Early studies using FEA in human autopsies demonstrated that a fibrous cap overlying a soft lipid pool is associated with elevated cap stress (2). Histologic specimens have indicated that a threshold of 300 kPa is associated with plaque rupture (3). More recent studies combining IVUS and FEA techniques allow for in vivo assessment of PSS. In one such study, PSS has been shown to be higher in culprit lesions of patients with ACS than in those with stable coronary syndromes (4), suggesting that such contemporary in vivo analysis can corroborate our prevailing assumptions of the importance of biomechanics in the pathophysiology of ACS.

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In this issue of *iJACC,* Costopoulos et al. (5) present an interesting study in which PSS was compared between fibroatheromas with plaque rupture in ACS patients to fibroatheromas from a non-ACS control cohort without plaque rupture. They make numerous important observations. First, investigating the relationship between plaque morphology and PSS, they find that higher PSS has a positive correlation with lumen area and a negative correlation with plaque burden (i.e., that PSS is higher in smaller plaques). They also find that PSS is increased in regions with necrotic core area ≥10% and reduced when dense calcium area was ≥10%.

Second, the authors demonstrate that both PSS and the variation of PSS over the cardiac cycle are higher in ruptured fibroatheromas than nonruptured fibroatheromas. This finding poses an interesting question as to whether the cyclic loading, perhaps from fatigue, or maximum load plays a greater role in plaque rupture. The authors find that PSS in virtual histology fibroatheromas was predictive of ruptured plaque with an area under the curve (AUC) of 0.70. Furthermore, PSS in virtual histology fibroatheromas + plaque burden ≥70% was even more predictive of plaque rupture, with an area under the curve of 0.84. These findings suggest that, although higher PSS tends to reside in smaller plaques, when it is observed in fibroatheromas with

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From the Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia. Dr. Samady has received institutional research funding from Volcano Corporation, St. Jude Medical, Medtronic Inc., and Abbott Vascular; and has received honoraria for being on steering committees of studies funded by Volcano Corporation and St. Jude Medical. Dr. Molony has reported that he has no relationships relevant to the contents of this paper to disclose.

larger plaque burden, rupture likelihood is increased. Finally, they found that in high-risk regions, a PSS value >135 kPa distinguished ruptured from non-ruptured plaques. Taken together, these data describe the complex interaction of plaque burden, cap thickness, plaque composition, and vascular remodeling that determine PSS, which likely play important roles in plaque rupture.

Several limitations are important to acknowledge. First, IVUS frames showing rupture were reconstituted with necrotic core to simulate their status before rupture. Clearly, this assumption is necessary as it is unlikely to image a plaque immediately prior to rupture. However, the underlying reconstituted plaque composition is somewhat speculative and yet a critical component of the computed PSS. Second, microcalcifications that have been found to act as a significant stress amplifier could not be considered in the current study because IVUS does not have the resolution to directly image them (6). Third, with a resolution of 100 μm, IVUS is not capable of resolving the <65-μm fibrous cap thickness of histologically defined TCFAs. The term "VH-TCFA" refers to a fibroatheroma without a visible fibrous cap by IVUS imaging, implying that the cap can range in thickness up to 100 μm. Not knowing the exact fibrous cap thickness, the investigators empirically ascribed a cap thickness of 65 μm to VH-TCFAs for their computational modeling. Yet, fibrous cap thickness has been shown to be one of the most important criteria in determining PSS. A study of idealized plaques found a large variation in cap stress at a resolution below 100 μm (7), emphasizing the importance of accurate measurement of fibrous cap thickness. An intriguing future study investigating PSS could aim to combine IVUS for whole plaque characterization and OCT for fibrous cap assessment. A recently developed method has simplified the challenge of coregistering these intravascular imaging modalities (8).

Even if multimodality intravascular imaging with PSS measurement tools could accurately and reproducibly predict plaque rupture in high risk patients, would it be of clinical value? Would such high-risk plaque in vulnerable patients result in intensification of systemic treatment or perhaps application of local therapies? At present, there is no evidence that such therapies are either efficacious or cost-effective. This paradigm is further complicated by the observation that plaque rupture could be clinically silent, yet at other times could lead to an ACS. Another challenge to the potential clinical utility of high PSS is that its highest predictive value for rupture is in the presence of plaque burden >70% that may result in revascularization regardless of PSS value in a relevant clinical context. Nevertheless, detection of other biomechanical parameters may be important in smaller plaque. Indeed, WSS, which is the frictional force of blood acting on the vessel wall, has been shown to be an important factor both in the early and more advanced stages of plaque progression. Endothelial cells on the lumen surface sense shear stress and atherosclerotic changes are brought about through signal mechanotransduction. One proposed concept of plaque evolution is that plaques exposed to low WSS slowly progress, and those exposed to high WSS transform toward a more vulnerable phenotype characterized by increased necrotic core, regression of fibrous plaque, thinning of fibrous cap, and positive remodeling (9,10). This vulnerable plaque has increased PSS and will eventually rupture once this stress exceeds the strength of the fibrous cap. The time course of these dynamic stages as well as factors regulating them need further investigation.

A growing body of evidence suggests that biomechanics plays an important role in determining which plaques evolve toward a vulnerable phenotype and rupture. Going forward, studies identifying detailed mechanistic pathways as well as larger natural history studies combining PSS and WSS (fluid-solid interaction) will shed light on the prognostic value of imaging and biomechanics. For now, Costopoulos et al. (5) have ignited a debate as to whether PSS is unraveling the complexity of plaque vulnerability.

ADDRESS FOR CORRESPONDENCE: Dr. Habib Samady, Division of Cardiology, Department of Medicine, Emory University School of Medicine, 1364 Clifton Road F622, Atlanta, Georgia 30322. E-mail: hsamady@emory.edu.

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