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Editorial

The stenotic vulnerable plaque: Identifying the substrate of acute coronary syndromes

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In this issue of *Atherosclerosis*, Varshney et al. [1] compared the spatial distribution of local biomechanical and anatomical high-risk features in coronary plaques with large *vs* non-large lipid cores. The progression of coronary artery disease entails a complex interplay of biomechanical forces acting on local mechanoreceptors incited by vascular and patient–specific risk factors. Anatomically predisposed vascular areas, exposed to low and oscillatory endothelial shear stress (ESS), develop endothelial dysfunction, early atherosclerosis, and expansive remodeling, especially in the presence of severe systemic risk factors, such as diabetes, hyperlipidemia and, smoking (Fig. 1) [2,3]. These anatomical changes in the coronary vasculature sustain a very low ESS microenvironment that leads to intense inflammation, lipid pool enlargement, further plaque progression, and ultimately development of non-stenotic thin cap fibroatheromas (Fig. 1) [4,5]. In this milieu of low ESS and ongoing inflammation, a fraction of these non-stenotic plaques encroach further into the lumen and evolve into stenotic thin cap fibroatheromas (so called vulnerable plaques) that demonstrate a wider heterogeneity in ESS values with low ESS in the upstream segments, high ESS at the neck of the plaque, and oscillatory ESS in the downstream region (Fig. 1). Some of these atherosclerotic plaques may become latent, while others are at risk to rupture leading to acute coronary syndromes (ACS). Indeed, vascular biology studies have shown that both low and high ESS play a pivotal role in high-risk plaque transformation by stimulating endothelial cells to produce plasmin and transforming growth factors, which subsequently stimulate macrophages to release metalloproteins. The latter degrade collagen and matrix and induce smooth muscle cell apoptosis, increasing the necrotic core burden and decreasing the stability of the fibrous cap [6–8]. Consequently, recognizing the spatial proximity of low and high shear stress zones with other anatomical and morphological predictors of ACS using computation imaging may be helpful to improve our understanding of vulnerable plaque substrates, identify high–risk patients and ultimately develop targeted cardiac interventions.

Pathology reports suggest that atherosclerotic plaques with a thin fibrous cap, large necrotic core, and/or speckled pattern of calcification are associated with vulnerability to rupture [9]. Intracoronary imaging, utilizing optical coherence tomography (OCT) or intravascular ultrasound (IVUS) combined with virtual-histology or near-infrared spectroscopy (NIRS) can help detect these high-risk plaque features, including thin-cap fibroatheroma, greater plaque burden (PB), larger necrotic core, lower minimal lumen area (MLA), and large lipid core plaques (LRP) that are associated with higher risk of future ACS [10,11]. In the current study, Varshney et al. [1] investigated the spatial proximity of local biomechanical plaque modifiers (i.e., ESS magnitude) in relation to anatomical (i.e., PB, MLA) and morphological (i.e., lipid core size) markers of plaque vulnerability. The authors calculated ESS on n = 60 arteries (from n = 49 patients) by co–registering coronary angiograms and IVUS images. Minimum ESS (minESS), maximum ESS (maxESS), maximum plaque burden (maxPB), and MLA were calculated in 3 mm coronary artery segments. The authors observed that maxESS was located frequently at the site of MLA (28/57, 49.1%) or 3 mm proximal to the site of MLA (16/57, 28%). Maximum PB co-localized frequently at the site of MLA (47%). In contrast, minESS was located either proximal (18/39, 46%) or distal to the site of MLA (21/39, 54%) but was not observed at the site of MLA. Maximum lipid core burden index in a 4 mm segment (maxLCBI4mm) detected by NIRS was found proximal to (14/37, 37.8%), distal to (11/37, 29.7%), or at the site of (12/37, 32.4%) MLA in similar proportions.

It is worthwhile to recognize the investigators' efforts to derive minESS and maxESS values. This technique is used to mitigate extremely high or low ESS values that might result from inherent errors in calculating boundary flow conditions and teases out more biologically relevant maximum and minimum ESS values for each coronary segment as opposed to absolute cut-offs. Using this approach, the authors found that minESS, maxESS, maxPB, and maxLCBI4mm were discordantly distributed in both high risk (LRP) and non-high risk (non-LRP) plaques. In addition, the locations of MLA, minESS and maxESS were spatially discordant from the maxLCBI4mm in most arteries. Interestingly, when the data were divided into low ESS (<1.0 Pa) and high ESS (>3.5Pa) using absolute cut-off values, arteries with large lipid core plaques demonstrated significantly greater areas of high ESS when compared to non-large LRP arteries. Yet, the percentage of arterial area

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demonstrating low ESS was similar between both large and non-large LRP coronary arteries.

Recently, a *post hoc* analysis of the FAME II (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) study reported that higher ESS is associated with a greater risk of vessel related myocardial infarction (MI) and had an incremental prognostic value over fractional flow reserve (FFR) [8]. The MLA often resides in the middle segments of coronary lesions and is therefore associated with higher ESS, due to inherent geometric calculations. However, patients who had relatively higher ESS in the proximal segments of the lesions were found to be at the greatest risk of MI. Taken together, the spatial heterogeneity between biomechanical, anatomical, and histological markers of plaque vulnerability suggests a complex interplay that needs further investigation as a determinant of future risk of ACS. In addition, the current study reports that arteries with large LRP demonstrated lower minESS and higher maxESS compared with non-large LRP arteries. Whether these observations hint that a greater difference in ESS (delta ESS) is a major variable in the development of a vulnerable plaque remains to be explored using more advanced imaging modalities with better spatial resolution.

The study by Varshney et al. [1] has some limitations that need to be considered. It is observational in nature and fails to capture the impact of a constantly changing hemodynamic milieu on plaque progression and vulnerability due to a lack of longitudinal data. In addition, coronary lesions vary in length, and therefore the exact spatial proximity of low or high ESS segments (calculated in 3 mm absolute segments) with maximum PB, and large lipid cores (calculated in 4 mm absolute segments) was difficult to be identified with precision. Furthermore, atherosclerotic plaques that are more eccentric demonstrate higher ESS on the shoulders and lower ESS downstream to the lesion promoting greater plaque vulnerability and propagation. Hence, future studies characterizing plaque eccentricity could help us discern the spatial relationship between MLA, maximum PB, maxLCBI4mm, and ESS better. Moreover, identifying additional high-risk morphological markers such as thin fibrous cap and large necrotic core could further aid in identifying the true spatial proximity of local biomechanical forces with morphological features of vulnerable plaque. Lastly, the lack of follow-up clinical data renders this study hypothesis-generating in nature but hard to derive clinical value.

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (The Bypass Angioplasty Revascularization Investigation 2 Diabetes) trials failed to demonstrate the benefits of revascularization among patients with chest pain randomized based on a combined strategy of >70% diameter stenosis by angiogram and a positive cardiac stress test [12,13]. Recently, the ISCHEMIA trial demonstrated no additional benefits of coronary revascularization over medical management in patients with moderate to severe ischemia identified by non-invasive cardiac stress tests and coronary narrowing on coronary computed tomography (CT) angiography [14]. While many observers were quick to denounce the utility of coronary revascularization, these negative trials indicate that our current diagnostic strategies select patients at greater risk of angina due to reduced myocardial blood flow arising from luminal stenosis rather than identifying those at greater risk of ACS from vulnerable atherosclerotic plaques. In addition, the use of OCT or IVUS to identify high risk plaque features has failed to gain widespread acceptance in the cardiology community due to lack of awareness, technical challenges, and additional cost with relatively modest positive predictive values in detecting ACS. Finally, the constantly changing hemodynamic and morphological features of coronary plaques necessitates a more dynamic approach combining multiple prognostic markers to identify high risk lesions. Recent observations have hinted that computational hemodynamic indices (CT-fractional flow reserve, CT-endothelial shear stress, CT-axial plaque stress), when combined with diameter stenosis and other adverse plaque characteristics such as positive remodeling, low attenuation plaque, napkin ring sign or spotty calcification by cardiac CT, can aid in identifying patients and lesions vulnerable to future ACS [15]. However, further research is required to refine image resolution, improve segmentation time and decrease artifacts arising from blooming and cardiac motion, before large clinic trials could be planned to study the utility of cardiac CT as a single non-invasive diagnostic platform that can truly identify patients who would benefit from precise interventions directed towards the vulnerable plaque. In this regard, additional pragmatic investigations similar to the current study should be encouraged.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Kumar is on the scientific advisory board for Kiniska. Dr. Giannopoulos reports a research grant from the Iten-Kohaut-Foundation. Dr Chatzizisis has received speaker honoraria, consultation fees and research grant from Boston Scientific, and research grant from Medtronic.

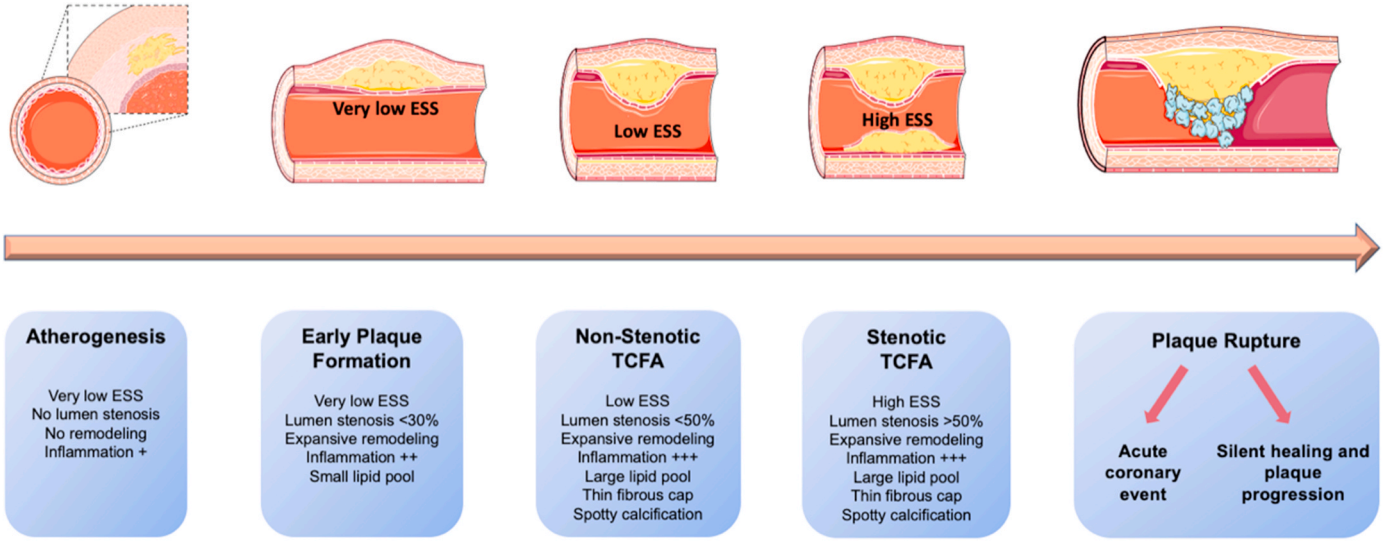

Fig. 1. Development of the stenotic vulnerable plaque.ES, endothelial shear stress; TCF, thin-cap fiberoatheroma.

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