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SHEAR STRESS: THE DARK ENERGY OF ATHEROSCLEROTIC PLAQUES.

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SHEAR STRESS: THE DARK ENERGY OF ATHEROSCLEROTIC PLAQUES.

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Myocardial infarction, a leading cause of death, occurs when an atherosclerotic plaque within the coronary arterial wall becomes unstable causing thrombosis, vessel occlusion and infarction. In the majority of cases, this process results from rupture of the plaque to expose thrombogenic material; but plaque instability can also result from endothelial denudation (plaque erosion). The two processes differ in lesion morphology and composition, associated type of thrombus, as well as epidemiology, indicating different pathophysiological mechanisms.[1] The 'holy grail' in interventional cardiology is the identification of plaques at a high risk of destabilisation since accurate *a priori* prediction will allow pre-emptive treatment, avoiding acute coronary syndrome ultimately leading to improved patient outcomes. However, the predictive value of imaging of plaque components has remained poor leading several groups to investigate whether prediction of plaque destabilisation can be enhanced by mapping of blood flow patterns, which have profound effects of vascular physiology[2].

Plaques develop at predilection sites (bends and bifurcations) that are exposed to disturbed patterns of blood flow. Flowing blood generates a mechanical force called shear stress (sometimes called endothelial shear stress; ESS) at the vessel lumen that potently governs endothelial physiology, function and viability[2]. Flow disturbances over plaques, further create complex ESS with regions exposed to shear stress that is lower than physiological (herein low ESS) and other regions exposed to high ESS. To complicate matters further, disturbed blood flow also creates alterations in flow direction including oscillations in direction (oscillatory shear index; OSI) and shear stress gradients over the endothelium (ESSG). A considerable debate is currently underway over which ESS metrics matter the most, with a focus on which are the most important 'drivers' of atherosclerosis progression and thus clinical outcomes. The PREDICTION and PROSPECT studies showed that low baseline ESS is associated with accelerated plaque growth and remodelling[3] and associated with more major adverse cardiac events[4]. Studies of patients with stable angina also found that low baseline ESS is a predictor of plaque growth, whereas low and oscillatory ESS or high ESS associate with a change to a more vulnerable plaque phenotype with a regression of plaques size[5, 6]. It is difficult to develop a unified model of plaque responses to ESS from these studies due to both differences in methodology (e.g. imaging modalities, analysis methods) and patient demographics[7]. This prompted Hoogendoorn et al. to use a porcine model of coronary artery atherosclerosis which had the advantage of carefully-controlled experimental conditions, to show that low ESS or multidirectional ESS are associated with plaque growth and disease progression[8]. Thus, the hypothesis that perturbation of ESS magnitude or direction can drive plaque progression has become even more intriguing.

These observations provide the context for the study from Thondapu and colleagues who report the first comparison of the hemodynamic environment in ruptured versus eroded plaques in this issue of *Cardiovascular Research*[9]. This study analysed local blood flow dynamics in 37 patients with acute plaque rupture or erosion using intravascular optical coherence tomography (OCT). Three shear stress parameters were analysed (ESS magnitude, OSI and ESSG). Since these shear stress features can spatially overlap, the authors used multivariate statistical analysis to identify the specific shear stress factors that independently correlate with rupture or erosion. They find that plaque rupture is associated with elevated ESSG, whereas plaque erosion independently associates with high ESS, high ESSG and high OSI (Figure). Comparison of ruptured versus eroded plaques showed that ESSG was higher in ruptured plaques, while OSI was higher in eroded plaques. In addition to identifying the shear stress profiles of ruptured versus eroded plaques, the authors found that spatial differences in the composition of ruptured plaques (lipid-rich versus layered structures) were also associated with specific shear stress signatures. Collectively, the inference from these data is that quantitation of ESSG and OSI may predict vessel regions that are at risk of plaque rupture or erosion thereby opening the possibility for tailored management and treatment strategies. Looking forward, a prospective longitudinal study of plaques before and after erosion would provide accurate plaque geometries and complement the current study. Moreover, even though Thondapu et al[9], and other groups, have described the shear stress conditions at atherosclerotic plaques, there is still a lack of proof of causality.

Over recent years, clinical outcome studies have demonstrated the clear benefits of invasive haemodynamic assessment beyond anatomical assessment with angiography. In parallel, image-based computational fluid dynamics modeling has been developed to characterize and predict intracoronary haemodynamics[10]. When combined with OCT, the modern interventional cardiologist can not only 'see' plaque morphology and composition in remarkable detail, they can also measure its functional significance, and predict the benefit of intervention. Whilst helpful, thus far, these models have focused mainly on predicting ischaemia in the context of chronic coronary syndromes. Several groups have progressed this field by attempting to use haemodynamics information to predict plaque growth and progression towards instability[3-6], however the interpretation of such studies is limited by a lack of understanding of the biological effects of shear stress on the vasculature. Taking an analogy from astrophysics, we view shear stress as the 'dark energy' of the vasculature since it is ubiquitous and vitally important but its effects are largely unknown. Hence, plaque mechanobiology research is needed to understand the mechanisms that vascular endothelial cells use to sense various shear stress parameters (ESS, OSI, ESSG) through mechanoreceptors and how this mechanical information is transduced via signaling pathways and executed by RNA metabolism pathways into cellular actions and behaviours. Defining the mechanisms of ESS mechanosensing will provide a step change in our understanding of plaque biology may inform the identification of lesions at high risk of conversion to acute coronary syndromes, which could potentially be a major step forward in clinical cardiology. Plaque mechanobiology also has the exciting prospect of leading to the discovery of a new class of cardiovascular treatments that slow atheroprogression by targeting mechanosensitive pathways to reduce adverse cardiac events.

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