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EDITORIAL COMMENT

Linking Physiology and Biology in Plaque Erosion

A Gordian Knot

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Developments in invasive and noninvasive imaging have enabled in vivo characterization of plaque phenotypes and allowed more accurate stratification of cardiovascular risk. Cumulative data have shown that lesions with specific morphologic characteristics (ie, with active inflammation and a large plaque burden with an increased necrotic core that is covered by a thin fibrous cap) that are exposed to an unfavorable hemodynamic milieu are likely to rupture and cause events. However, one-third of these cardiovascular events are caused by lesions with a nonvulnerable phenotype that have an intact fibrous cap, and these events have been attributed to plaque erosion (PE).

Several studies over recent years have investigated the pathobiological mechanisms involved in endothelial denudation and examined the implications of flow patterns on endothelial cell death.[1] In vivo computational fluid dynamic studies in patients with cardiovascular events have demonstrated increased endothelial shear stress (ESS) and ESS gradient (ESSG) in eroded plaques compared with disease-free segments or stable lesions, and a recent report that compared flow patterns in patients with plaque rupture (PR) and PE has shown higher ESSG in PR and increased oscillatory ESS in PE.[2-4] Although experimental studies have attempted to investigate the association between flow patterns and local vascular inflammation and immune response in PE, no study had examined in humans the interplay between coronary physiology and biology in this setting.[5]

The study by Ahmed et al[6] in this issue of *JACC: Basic to Translational Science* is the first to explore in vivo the effects of the local hemodynamic forces on the proinflammatory pathways involved in PE. The authors analyzed data of the OPTICO-ACS (Optical Coherence Tomography in Acute Coronary Syndrome) study, which examined the local immune response in patients with PR and PE, and involved assessment of the culprit vessel with the use of optical coherence tomography (OCT) and blood sample collection at the culprit lesion site and the peripheral circulation.[7] The authors segmented the OCT data from the patients with PE, fused the annotated lumen borders with the coronary angiography to reconstruct vessel anatomy, and performed blood flow simulation. The ESS and ESSG computed at the culprit lesion site were associated with the proinflammatory mediators and immune phenotypes assessed at the culprit lesion and peripheral circulation. The authors found an inverse correlation between minimum ESS at the lesion site and T lymphocytes, which could contribute to endothelial cell death. The maximum ESS at the lesion site was correlated with macrophage inflammatory protein (MIP)-1β levels and with the ratio of interleukin (IL)-6 levels at the culprit lesion site and peripheral circulation; both cytokines promote T-cell and monocyte adhesion and activation. Finally, increased ESSGs at the lesion site were positively correlated with natural killer cells, which promote plaque vulnerability, MIP-1β, and hyaluronic acid, which activates Toll-like receptor 2, a mediator of PE, and

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were inversely related to IL-4, which has anti-inflammatory properties.

The findings of this analysis are interesting and thought provoking. The authors should be congratulated for this work because they demonstrated for the first time a link between the local hemodynamic forces and immune pathways involved in the pathogenesis of PE. This unique analysis is expected to attract attention and stimulate further research in the field and the design of prospective studies that will combine 3-dimensional modeling and computational fluid dynamic analysis with blood sampling to measure biomolecule release from plaques and explore the links of flow patterns and proinflammatory pathways involved in vulnerable plaque formation and destabilization.

However, apart from its originality, it has significant limitations that should be acknowledged. First, coronary reconstruction did not include side branches, which critically determine ESS distribution.[8,9] This is especially important in eroded plaques, which are often located near the origin of side branches—in the OPTICO-ACS study, there was a side branch within 3 mm in 61.3% of the eroded plaques[7]—where flow perturbations are often noted that can trigger a local inflammatory response and T-lymphocyte adhesion, leading to PE.

Second, blood flow simulation was performed using a steady flow profile. This assumption did not allow computation of the multidirectional ESS indices and especially of the oscillatory shear index, which appears to be involved in the pathogenesis of PE.[4]

Third, a control group of patients with stable angina was not included. This limitation is a consequence of the design of the OPTICO-ACS study and is acknowledged by the authors. It would have been helpful however, to compare the associations between proinflammatory mediators and flow patterns in patients with PE and PR that were also recruited in the OPTICO-ACS. This analysis should be considered in the future because the inclusion of both groups would enrich our understanding about the proinflammatory implications of the same biomechanical stimuli in these 2 different clinical scenarios.[4]

The differences in the time interval between coronary events and blood sample collection also is a limitation of the analysis that is recognized by the authors and is likely to have affected the reported results. For most of the proinflammatory mediators included in this study there was no difference between their levels at the lesion site and the systemic circulation and therefore it is unclear whether these were produced indeed by the culprit plaque. The concentrations of only 7 biomarkers were higher at the lesion site (IL-8, IL-10, interferon-γ, interferon-γ-induced protein-10, MIP-1α, granzyme A, and matrix metalloproteinase-9 activity), and none of them were correlated with the distribution of the local hemodynamic forces. Conversely, the levels of MIP-1β and hyaluronic acid, which have been associated with the ESS patterns, were lower at the culprit lesion compared with the peripheral circulation; therefore, it is unclear whether these molecules were produced by the culprit lesion.

Finally, local blood samples were collected across the entire lesion and not in locations with different ESS distribution—ie, upslope, throat, and downslope of the lesion. This may have prevented detection of differences in immune activity across the lesion and co-localization of the ESS with the triggered pro-proinflammatory pathways. Recently a dedicated catheter device that allows unstirred blood sample collection from different plaque locations has been designed, and its use is expected to resolve these uncertainties and allow accurate assessment of the link between flow patterns and local inflammatory activity.[10]

Despite the above limitations this study is important in the field as it sets a new paradigm for examining in vivo the interplay of plaque biology and physiology. It may not have untangled the Gordian knot, but it provides an alternative pathway for loosening it.

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