Structural Stress of Coronary Plaques to Predict Risk for Clinical Events

New Biomechanical Modeling Frontiers Derived From Plaque Anatomy

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Plaque disruption generally occurs in the setting of a thin cap fibroatheroma morphology, characterized by a large necrotic lipid core, intense macrophage infiltration, microcalcifications, and a thin fibrous cap, but it has recently become clear that characterization of plaque risk based on anatomy alone is necessary but not sufficient to predict those high-risk plaques likely to destabilize and cause a new clinical event. Using the baseline anatomic plaque characteristics of large plaque burden, small minimal lumen area, and thin cap fibroatheroma morphology, the major long-term natural history follow-up studies have generally demonstrated a major adverse cardiac event (MACE) rate ≤20% over 1 to 3 years of follow-up. The low positive predictive accuracy of these ostensibly high-risk plaques for subsequent adverse clinical events based on plaque anatomy alone is likely related to inadequate assessment of the true vulnerability of an individual plaque by current imaging modalities utilizing intravascular ultrasound (IVUS), optical coherence tomography, or near-infrared spectroscopy and the fact that the majority of high-risk plaques continue to evolve over time and become quiescent, so that an imaging snapshot at a single point in time does not adequately represent the natural history path of that particular plaque.

See Article by Brown et al

A variety of innovative in vivo approaches are being actively pursued to go beyond assessment of plaque anatomy alone to identify which apparent high-risk plaques based on anatomy will actually progress to cause a new MACE in follow-up. Candidate in vivo approaches include assessment of active inflammation within plaques by identifying ongoing local proinflammatory low endothelial shear stress and by near-infrared fluorescence imaging of targeted inflammatory molecules or processes. Other innovative approaches have been to assess adverse biomechanical stresses affecting the plaque from the lumen such as axial plaque stress using coronary computed tomographic angiography and assessment of the plaque mechanical properties by simple plaque deformability (palpography) or more sophisticated finite element analysis of the entire plaque that incorporates the detailed mechanical properties of the plaque constituents.

Plaque rupture is ultimately a mechanical process and it occurs when the plaque structural stress exceeds the material strength of the tissue. In this issue of Circulation: Cardiovascular Imaging, Brown et al provide a comprehensive assessment of plaque characteristics of 170 patients who underwent 3-vessel VH-IVUS assessment and were then followed up for 3 years. A 2-dimensional finite element simulation for plaque structural stress (PSS) was performed for 44 nonculprit lesions (NCLs; 22 MACE and 22 non-MACE) composed of arterial wall, fibrous tissue, necrotic core, and dense calcium, as determined from IVUS categorization of end-diastolic images. Mechanical properties of plaque components were derived from experimental data for dense calcium and for the other components from explanted carotid arteries. Simulated stress values were presented as PSS. The maximum PSS within the 200 µm of the lumen border were then explored as a potential predictor of MACE.

The investigators found that MACE NCLs exhibited smaller lumen and increased plaque burden and plaque volume compared with non-MACE NCLs, but plaque composition, defined by VH-IVUS, was not significantly different between MACE NCLs and non-MACE NCLs. In contrast, however, PSS was highly variable along the longitudinal course of individual plaques, especially MACE NCL. PSS was significantly increased in MACE NCLs at specific high-risk regions of plaques (ie, regions with plaque burden ≥70% and in VH-thin cap fibroatheroma) compared with non–high-risk regions of the same plaques, as well as non-MACE NCLs. PSS was similar at minimal lumen area sites in both types of lesions or within other non–high-risk regions of the plaque. Using receiver operating characteristic curve analyses to determine cutoff points for PSS to predict MACE, they observed that PSS markedly increased the ability of VH-IVUS to predict MACE in plaques with plaque burden of ≥70% and minimal lumen area of ≤4 mm², but less significant for plaques classified as VH-thin cap fibroatheroma. The presence of superficial dense calcium invasions was also associated with increased risk of MACE.

The sophisticated, multidimensional, validated approach presented by Brown et al is extremely valuable to understand the constituents and vascular biology of coronary plaque, and also to predict which specific plaques will be most likely to rupture. Previous efforts to risk-assess plaque mechanical...
deformation using palpography were not generally successful because of imprecision of the methods, but the current study provides an important new dimension and sophistication for in vivo plaque assessment. The study also underscores the marked heterogeneity of plaque structures and properties along the longitudinal course of the plaque. If it were possible to calculate PSS in a routine and time-efficient manner in the catheterization laboratory, then this information could be enormously useful to identify the most high-risk plaques and inform management decisions.

There are many concerns and limitations about this approach, but the investigators have been diligent to address many of them: the accuracy of tissue characterization by VH-IVUS has been questioned, but these investigators have shown reasonable correlation in PSS estimation for plaque composition based on images of VH-IVUS and images of histology of the same sections. Moreover, mechanical properties of plaque constituents were derived by a detailed analysis of ex vivo carotid artery samples, which should reduce some of the concerns. Only a small number of plaques underwent biomechanical analysis and PSS assessment relative to all plaques available in the present study, and certainly a broader array of plaques will need to be studied in the future with these techniques. Time and resources necessary to accomplish PSS assessment may be a major limitation of broader application of the methodology.

We also need to be cognizant that in the current era, most clinical events related to ostensibly high-risk coronary plaques are not acute coronary syndromes, which are primarily related to plaque rupture, but instead worsening of stable angina or progressive angina. It is unlikely that the factors that lead to worsening of plaque and luminal obstruction are the same factors that are responsible for an abrupt acute coronary syndrome. Although it is certainly possible that subclinical plaque rupture and progressive layering of superimposed thrombus is responsible for worsening of lumen obstruction, it is also possible that intraplaque hemorrhage from leaky, immature vasa vasa-rum related to an enlarging plaque with intraplaque hypoxia and initiation of local angiogenesis inside the plaque leads to intense intraplaque inflammation and fibrosis without plaque cap rupture. Plaque erosion without disruption of the fibrous cap overlying the plaque may also be responsible for a substantial number of new cardiac events. It is unclear whether PSS assessment will necessarily predict which plaques are at risk for these vascular outcomes not related to rupture of a thin fibrous cap.

The field of risk-stratification of individual coronary plaques appropriately focused for many years on in vivo anatomic characterization of the high-risk plaque. That process has been successful, but it has become clear that anatomic characterization by traditional intracoronary imaging is not sufficient to identify the small numerator of high-risk plaques that cause a new clinical event from the large denominator of ostensibly high-risk plaques. The in vivo PSS study by Brown et al has brought us a major step forward in understanding the detailed mechanical aspects of coronary plaque and, most importantly, how we can apply that information to predict the future course of individual plaques. The field of accurate plaque prognostication is again becoming invigorated by these more sophisticated analyses beyond plaque anatomy. We are making major progress to identify true high-risk lesions and getting closer to our ultimate goal of sufficiently accurate prognostication to enable consideration of pre-emptive strategies to avert major cardiac events.

Disclosures
None.

References


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