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EDITORIAL COMMENT

Imaging Biomechanical Endothelial Forces With Coronary Computed Tomography

A Positive Step, but Not Yet the Jewel in the Crown in the Quest for Vulnerable Plaque Prediction*

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Approximately 735,000 Americans sustain a myocardial infarction annually, of which 525,000 are the first presentation of acute coronary syndrome (ACS) and 210,000 are a repeat occurrence (1). Consequentially, there is significant interest in the early detection of atherosclerosis and reliable identification of so-called "vulnerable plaque" that is more prone to rupture and precipitate ACS.

Coronary computed tomographic angiography (CTA) has emerged as an accurate imaging modality to detect atherosclerosis and define plaque morphology. Coronary CTA studies have highlighted plaque features associated with the development of ACS (2,3) including positive remodeling (PR), low attenuation plaque (LAP), spotty calcification, and the napkin-ring sign. However, the presence of these features represents only 1 facet of plaque vulnerability. Motoyama et al. (3) showed that patients with PR and LAP were more likely to develop ACS; however, the presence of PR or LAP was associated with ACS in only 22% of patients at 2 years, and 15% at just under 4 years follow-up. This shows the importance of adverse plaque characteristics (APCs), but also that morphological classification alone is insufficient.

This is not surprising given the complex processes that govern atherogenesis. Atherosclerotic lesions within the coronary tree form at specific sites of pulsatile hemodynamic stress even though the entire vasculature tree is exposed to genetic, environmental, and lifestyle factors. Perhaps the most well-known of these is endothelial wall shear stress (WSS). This represents the tangential frictional force caused by blood flow against the endothelium and is proportional to blood velocity and viscosity. Low WSS attenuates nitric oxide (NO)–dependent atheroprotection, increases low-density lipoprotein uptake, promotes oxidative stress and inflammation, and results in vascular smooth muscle cell migration and plaque thrombogenicity. It is also implicated in plaque progression and the development of APC (4). WSS may therefore provide some explanation as to the discordance between high-risk plaque features and future acute coronary events. Initial studies measured WSS by invasive angiography and intravascular ultrasound (4); however, newer alternative techniques using computational fluid dynamics (CFD) on coronary CTA datasets have also begun to emerge (5).

Although conceptually appealing, WSS represents only 1 facet of the hemodynamic forces present at the endothelial surface. Blood flow within the coronary arteries also results in 2 other forces known as axial and circumferential stress. Axial stress relates to the longitudinal stretching of vessels exposed to blood flow and cardiac motion, whereas circumferential stress results from hydrostatic pressure exerting an outward radial force (6). These additional "stressors" on the endothelial surface have, until recently, not been easy to measure in vivo; however, with the advent of advanced biomedical engineering techniques, our understanding of these additional hemodynamic forces is now increasing.

Biomedical engineering is the application of engineering principles to the fields of biology and health

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care. Although seen by many as new technology, examples can be traced back to ancient Egypt. In the 20th century biomedical engineering underpinned technologies such as the stethoscope, pacemakers, and imaging methods including magnetic resonance, computed tomography, and ultrasound. In recent years, driven by simultaneous advancements in science, technology, and computing, new electrical and mechanical engineering concepts, including CFD have emerged, and are becoming increasingly accessible and relevant to clinicians, who can now apply these novel tools to longstanding issues to further improve patient care.

The introduction of fractional flow reserve by coronary computed tomography (FFR_{CT}) in 2011 (7) heralded a new era of biomedical engineering application to coronary CTA. Initially this was met with skepticism, likely related to the introduction of the new and unfamiliar concepts of CFD and precisely how FFR_{CT} was derived. It was not widely appreciated that FFR_{CT} was based upon technology that had been in existence in other industries for more than 50 years. The major limitation of CFD had been computer processing power that had to evolve before it could meaningfully transition into clinical applications. As data emerged supporting the validity of the scientific principles of CFD and its clinical validation, clinical acceptance and recommendation for its use has become more established within multiple health care systems (8). In the EMERALD (Exploring the Mechanism of Plaque Rupture in Acute Coronary Syndrome Using Coronary CT Angiography and Computational Fluid Dynamic) study by Lee et al. (9) in this issue, additional biomechanical CFD indices are assessed to determine whether they better predict those patients likely to develop ACS. Using a case-control study design, the authors identified 72 patients with ACS who had undergone coronary CTA 1 month to 2 years before their event. The coronary CTA scans were evaluated in a blinded fashion for diameter stenosis, APC, FFR_{CT}, $\Delta FFR_{CT,}$ axial plaque stress (APS), and WSS.

There are several important findings from this study. The first is that diameter stenosis and APCs were related to ACS with a c-index of 0.747. Second, although the addition of hemodynamic indices improved the prediction of plaques subsequently resulting in ACS, the incremental value of these to the c-index was small (+FFR_{CT}: 0.028, +APS: 0.018, WSS: 0.025). Indeed, the greatest improvement in the c-index was 0.040 by the incorporation of ΔFFR_{CT}. Given these relatively modest results, it remains unclear whether these indices provide clear additional clinical value to diameter stenosis and APC in isolation.

A notable limitation of the current study is the small cohort that included only 72 patients with ACS. This requires the prediction models to be validated statistically in a much larger study. Furthermore, this study used an isolated coronary CTA dataset at any point from 1 month to 2 years before the acute coronary event. This introduces a significant assumption that the hemodynamic indices derived from an isolated time point were representative of the entire intervening period. This methodology does not account for the dynamic and pulsatile nature of intracoronary forces or the prescription of antianginal or primary preventative therapies that may have altered these forces, and the resultant FFR_{CT} values, after the scan had been acquired. With the derivation of FFR_{CT} itself requiring sublingual nitroglycerin (GTN) to be administered to introduce maximal hyperemia, it is also unclear whether also measuring WSS and APS under this condition is valid and whether sufficient enough in vivo validation exists. The current study also introduces ΔFFR_{CT} as a new feature that might be important in predicting plaque rupture. The validation of this measure is undescribed. Existing studies of FFR_{CT} largely relied on a single measure of invasive FFR distal to a stenosis and did not include manual pull back with simultaneous invasive FFR measurements across the entirety of a vessel and across patients with serial stenoses.

As biomedical engineering gains an increasing prominence within cardiology, the derivation of newer hemodynamic indices by CFD is likely to increase our understanding of plaque biology and pathophysiology. This study signals further potential utility to measuring additional noninvasive hemodynamic forces alongside conventional descriptors of stenosis severity and plaque morphology. It also indicates that further work is required before a meaningful clinical application can be harnessed from these derived measurements to support value-based imaging and reduce the incidence of ACS.

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