JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 16, 2018

PUBLISHED BY ELSEVIER

High Coronary Shear Stress in Patients With Coronary Artery Disease Predicts Myocardial Infarction

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ABSTRACT

BACKGROUND Coronary lesions with low fractional flow reserve (FFR) that are treated medically are associated with higher revascularization rates. High wall shear stress (WSS) has been linked with increased plaque vulnerability.

OBJECTIVES This study investigated the prognostic value of WSS measured in the proximal segments of lesions (WSS_{prox}) to predict myocardial infarction (MI) in patients with stable coronary artery disease (CAD) and hemodynamically significant lesions. The authors hypothesized that in patients with low FFR and stable CAD, higher WSS_{prox} would predict MI.

METHODS Among 441 patients in the FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II) trial with FFR ≤0.80 who were randomized to medical therapy alone, 34 (8%) had subsequent MI within 3 years. Patients with vessel-related MI and adequate angiograms for 3-dimensional reconstruction (n = 29) were propensity matched to a control group with no MI (n = 29) by using demographic and clinical variables. Coronary lesions were divided into proximal, middle, and distal, along with 5-mm upstream and downstream segments. WSS was calculated for each segment.

RESULTS Median age was 62 years, and 46 (79%) were male. In the marginal Cox model, whereas lower FFR showed a trend (hazard ratio: 0.084; p = 0.064), higher WSS_{prox} (hazard ratio: 1.234; p = 0.002, C-index = 0.65) predicted MI. Adding WSS_{prox} to FFR resulted in a significant increase in global chi-square for predicting MI (p = 0.045), a net reclassification improvement of 0.69 (p = 0.005), and an integrated discrimination index of 0.11 (p = 0.010).

CONCLUSIONS In patients with stable CAD and hemodynamically significant lesions, higher WSS in the proximal segments of atherosclerotic lesions is predictive of MI and has incremental prognostic value over FFR.
(J Am Coll Cardiol 2018;72:1926–35) © 2018 by the American College of Cardiology Foundation.

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Manuscript received April 6, 2018; revised manuscript received July 10, 2018, accepted July 16, 2018.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.07.075

Fractional flow reserve (FFR) has emerged as an important invasive physiological index of epicardial lesion severity (1). Compared with patients with preserved FFR, those with low FFR (≤0.80) treated with medical therapy alone have higher rates of subsequent major adverse cardiac events (2). The major adverse cardiac events in patients with low FFR are largely driven by subsequent target vessel revascularization and not myocardial infarction (MI) (2,3). Although FFR incorporates the aggregate hemodynamic effect of an epicardial lesion on the subtended myocardium, regional plaque hemodynamics likely contributes to subsequent acute coronary syndromes. Indeed, a hemodynamically significant coronary lesion will demonstrate a spectrum of fluid dynamic forces upstream from the lesion, within the lesion, and distal to the lesion. One important regional force, wall shear stress (WSS), is the tangential force produced by viscous blood on the adjacent endothelium (4). Physiological WSS has been associated with atheroprotective signaling pathways, low WSS with inflammation and proatherogenic pathways, and high WSS with activation of matrix metalloproteinases in the shoulders of plaques with phenotypic transformation toward features of plaque vulnerability (5–8). These features of plaque vulnerability associated with high WSS include progression of plaque necrotic core and calcium, regression of fibrous tissue and fibrofatty tissue, and a greater expansive remodeling, as well as the development of increased plaque strain over time (5,9,10). In addition, high-risk plaque features such as thin-cap fibroatheromas tend to co-localize within regions of high WSS in the proximal segments of lesions (11). In line with these observations, studies have shown that plaque rupture often occurs in the proximal segments of stenoses, a finding suggesting a role for local hemodynamic forces in the pathobiology of acute coronary syndromes (12–14).

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Accordingly, we hypothesized that, in patients with stable coronary artery disease (CAD) and hemodynamically significant lesions treated medically, 1) high WSS in the proximal segments of coronary lesions predicts MI, and 2) proximal lesion WSS has an incremental prognostic value over FFR in predicting MI.

METHODS

STUDY GROUP AND STUDY DESIGN. The design of the FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II) trial (15) and its 3-year results (3) have been previously published. Briefly, in the FAME II trial, 1,220 patients from 28 sites in Europe and North America with stable angina and angiographically documented CAD involving up to 3 vessels were randomized and assigned, when at least 1 vessel had FFR ≤0.80, to receive medical therapy only (n = 441) or to undergo FFR-guided percutaneous coronary intervention in addition to medical therapy (n = 447). Patients with FFR >0.80 across all lesions were not randomized, and 50% of these patients were followed in a registry. For this post hoc analysis, only the medical therapy group was used (n = 441).

OUTCOMES. The primary outcome of this study was vessel-related myocardial infarction (VR-MI). Follow-up was censored at 3 years. All events and culprit vessels were adjudicated by an independent clinical event committee, blinded to FFR values, which went through the detailed narrative of each event and lesion assigned as VR-MI. In patients with >1 designated culprit vessel, the vessel with lower FFR was studied.

ANGIOGRAPHIC RECONSTRUCTION OF TARGET VESSELS. All baseline angiographic reconstruction, computational fluid dynamics (CFD), and WSS computations were done at the Emory University Cardiovascular Imaging and Biomechanical core laboratory in Atlanta, Georgia by independent analysts who were blinded to baseline FFR values, clinical data, and patients' outcomes. QAngio XA 3D RE (Medis Medical Imaging Systems, Leiden, the Netherlands) was used to create 3-dimensional (3D) geometric reconstructions of each patient's target vessel by using end-diastolic angiographic projections at least 25° apart. All visible branching vessels were added as cylindrical extensions perpendicular to the vessel centerline with the branch location, diameter, and orientation determined from the angiograms (Online Appendix). Validity and interobserver and intraobserver variability of 3D quantitative coronary angiography by QAngio XA 3D RE has been previously reported (16–18). The resulting 3D vessel point cloud was wrapped to form a triangulated surface (Geomagic Studio 12, Geomagic, Research Triangle Park, North Carolina). Extensions were added to each inlet (2 diameters) and outlet (8 diameters) to ensure a smooth transition of flow at the boundaries. The geometry was then meshed using ICEM CFD (Ansys ICEM, Ansys 17, Ansys, Canonsburg, Pennsylvania).

BOUNDARY CONDITIONS AND COMPUTATIONAL FLUID DYNAMICS. Patient-specific velocities were

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CFD = computational fluid dynamics

CI = confidence interval

DS% = 3-dimensional angiographic percentage diameter stenosis

FFR = fractional flow reserve

MI = myocardial infarction

3D = 3-dimensional

WSS = wall shear stress

WSS_{prox} = wall shear stress measured in proximal segments of lesions