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Combination of plaque burden, wall shear stress, and plaque phenotype has incremental value for prediction of coronary atherosclerotic plaque progression and vulnerability

Michel T. Corban [a,1], Parham Eshtehardi [a,1], Jin Suo [b], Michael C. McDaniel [a], Lucas H. Timmins [a,b], Emad Rassoul-Arzrumly [a], Charles Maynard [c], Girum Mekonnen [a], Spencer King 3rd [d], Arshed A. Quyyumi [a], Don P. Giddens [b], Habib Samady [a,*]

[a] Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA
[b] Wallace H Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA
[c] Department of Health Services, University of Washington, Seattle, WA, USA
[d] Saint Joseph's Hospital, Atlanta, GA, USA

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ABSTRACT

Aims: Large plaque burden, certain phenotypes, and low wall shear stress (WSS) are associated with adverse outcomes and high WSS with development of plaque vulnerability. We aimed to investigate the incremental value of the combination of plaque burden, WSS and plaque phenotype for prediction of coronary atherosclerotic plaque progression and vulnerability.

Methods: Twenty patients with CAD underwent baseline and 6-month follow-up coronary virtual histology-intravascular ultrasound (VH-IVUS) and computational fluid dynamics modeling for calculation of WSS. Low WSS was defined as <10 dynes/cm^2 and high WSS as ≥ 25 dynes/cm^2. Baseline plaque characteristics and WSS were related to plaque progression and vulnerability.

Results: In 2249 VH-IVUS frames analyzed, coronary segments with both plaque burden >40% and low WSS had significantly greater change in plaque area at follow-up ($+0.68 \pm 1.05$ mm^2), compared to segments with plaque burden >40% without low WSS (-0.28 ± 1.32 mm^2) or segments with low WSS and plaque burden $\leq$40% ($+0.05 \pm 0.71$ mm^2) ($p = 0.047$). Among plaque phenotypes, pathologic intimal thickening (PIT) had the greatest increase in necrotic core (NC) area ($p = 0.06$) and greatest decrease in fibro-fatty (FF) area ($p < 0.0001$). At follow-up, compared to segments with either plaque burden >60%, PIT, or high WSS, those with a combination of plaque burden >60%, PIT, and high WSS developed greater increase in NC area ($p = 0.002$), greater decrease in FF ($p = 0.004$) and fibrous areas ($p < 0.0001$), and higher frequency of expansive remodeling ($p = 0.019$).

Conclusion: Combination of plaque burden, WSS, and plaque phenotype has incremental value for prediction of coronary plaque progression and increased plaque vulnerability in patients with non-obstructive CAD.

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1. Background

Landmark natural history studies have described an association between intravascular ultrasound (IVUS)-derived plaque burden and characteristics with progression of atherosclerosis and major adverse cardiovascular events (MACE) [1,2].The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial demonstrated an association between large plaque burden, minimal lumen area, thin-cap fibroatheroma (TCFA) morphology and MACE in patients with acute coronary syndrome who underwent percutaneous coronary intervention of culprit lesion [1].

Abbreviations: CAD, Coronary Artery Disease; CFD, Computational Fluid Dynamics; DC, Dense Calcium; EEM, External Elastic Membrane; FA, Fibroatheroma; FF, Fibro-fatty Tissue; FI, Fibrous Tissue; NC, Necrotic Core; PIT, Pathological Intimal Thickening; VH-IVUS, Virtual Histology-Intravascular Ultrasound; WSS, Wall Shear Stress.

* Corresponding author. Division of Cardiology, Department of Medicine, Emory University School of Medicine, 1365, Clifton Road, Suite F606, Atlanta, GA 30322, USA. Tel.: +1 (404) 778 12 37; fax: +1 (404) 712 56 22.
E-mail address: hsamady@emory.edu (H. Samady).

[1] Drs. Corban and Eshtehardi contributed equally to this manuscript.

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It has been recognized however that the evolution of human coronary atherosclerosis is complex and multifactorial, involving the interplay of systemic cardiovascular risk factors, regional plaque morphology, and local hemodynamic forces including wall shear stress (WSS). Indeed, recent clinical data corroborate experimental findings linking low WSS to atherosclerosis and have shown that coronary segments with low WSS develop greater plaque progression [2–4], constrictive vascular remodeling [3], and major adverse cardiac events (MACE) [2]. We have also demonstrated an association between high WSS and IVUS-defined features of plaque vulnerability, namely plaque regression driven by large reductions in fibrous and fibro-fatty tissue, increase necrotic core and dense calcium, and expansive vascular remodeling [3].

Because plaque burden, plaque phenotype, and WSS have each been associated with adverse clinical outcomes, we hypothesized that in patients with coronary artery disease (CAD), a combination of large plaque burden and low WSS is associated with greater plaque progression than large plaque burden or low WSS alone, and that a combination of large plaque burden, certain plaque phenotypes and high WSS is associated with development of increased plaque vulnerability.

2. Methods

2.1. Patient population and imaging protocol

Twenty patients presenting to the cardiac catheterization laboratory at Emory University Hospital with an abnormal non-invasive stress test or stable anginal syndromes and found to have a non-obstructive lesion requiring invasive physiologic evaluation were enrolled. Different analyses of this comprehensive vascular profiling dataset have been previously published [3,5]. All patients underwent baseline and 6-month follow-up biplane coronary angiography and virtual histology-IVUS (VH-IVUS) using a phased-array 20 MHz Eagle Eye® Gold Catheter and s5™ Imaging System (Volcano Corporation, Rancho Cordova, California). VH-IVUS imaging was performed by locating the IVUS catheter as distal as possible in the left anterior descending coronary artery using a fiduciary side branch as the starting point and using an automated continuous pullback at a rate of 0.5 mm/s (R-100 Imaging Catheter Pullback Device, Volcano Corporation, Rancho Cordova, California) after administration of systemic heparin and 200 μg of intracoronary nitroglycerine. Patient-specific baseline pressures and velocities were recorded in the proximal and distal parts of the index vessel (ComboWire®, Volcano Corporation, Rancho Cordova, California) and computational fluid dynamics (CFD) modeling techniques were utilized to calculate WSS at baseline as previously described [3,6]. All patients received optimal medical therapy for cardiovascular risk factors including 80 mg atorvastatin and aspirin daily for the duration of the study.

2.2. IVUS analysis and definitions

IVUS measurements of external elastic membrane (EEM), plaque (plaque and media: EEM − lumen), and lumen cross-sectional areas were performed for every recorded VH-IVUS frame (0.5 mm thickness), defined as an IVUS segment in the current analysis. Plaque burden was calculated as plaque area divided by EEM area × 1007. In order to assess plaque composition, absolute and relative (percentage) area of VH-IVUS parameters (fibro-fatty [FF] tissue, fibrous [FI] tissue, necrotic core [NC], and dense calcium [DC]) were measured for each IVUS segment [7–10]. To assess plaque phenotype, coronary plaques were classified qualitatively based on atheroma composition [8,11]. Based on established criteria, pathological intimal thickening (PIT) was defined as plaque primarily consisting of FI and FF tissue with ≥15% FF, <10% confluent NC, and <10% confluent DC. Fibrotic plaque was defined as predominantly FI tissue with <15% FF tissue, <10% confluent NC, and <10% confluent DC. Fibroatheroma was defined as a plaque with ≥10% confluent NC, and TCFA as fibroatheroma with necrotic core in direct contact with the lumen in at least 3 consecutive VH-IVUS frames [8,11].

Baseline and follow-up IVUS images were reviewed side by side on a display and were co-registered. The distal end of the target segment was determined by the presence of a reproducible index side branch. Change in areas of EEM, lumen, plaque, and four components of plaque (NC, DC, FI tissue, and FF tissue), as well as plaque burden were calculated as follow-up minus baseline values for each IVUS segment by a single experienced investigator. Intra-observer analysis demonstrated excellent reproducibility for plaque and NC areas [3].

Serial remodeling index of each VH-IVUS frame was calculated as ΔEEM area (EEM area at follow-up − EEM area at baseline) with excessive expansive remodeling defined as ΔEEM area/Δplaque area (plaque area at follow-up − plaque area at baseline) > 1 according to the ACC/ESC clinical expert consensus documents on standards for acquisition, measurement and reporting of IVUS studies [12,13]. Increased plaque vulnerability was considered when a VH-IVUS frame develops all three of the following at follow-up: increase in NC area, decrease in FI or FF tissue area, and development of expansive remodeling [14,15].

Based on previous investigations [1,6,8,11], we selected a plaque burden cut-off of 40% as defining a lesion and to investigate with the prognostic value of low WSS. To identify the plaque burden cut-off that may be associated with development of plaque vulnerability, we investigated the relationship between baseline plaque burden and change in plaque components at follow-up. We found that compared to all other cut-offs of plaque burden (including >40%, >50% and >70%), segments with plaque burden >60% demonstrated greater decrease in plaque area, FI and FF areas ($p < 0.0001$), increase in DC area ($p < 0.0001$), increase in NC area and higher frequency of expansive remodeling (albeit non-significant). We therefore selected a plaque burden >60% to be combined with plaque phenotype and high WSS for our investigation of plaque vulnerability.

2.3. WSS analysis and definitions

As previously described [3,6], the three-dimensional (3D) path of the IVUS catheter during pullback was determined by using corresponding biplane angiographic projections acquired prior to pullback. Biplane images were spatially co-registered with a custom designed platform beneath the patient that contained markers enabling definition of precise geometric locations in 3D space. The 3D reconstructed catheter core served as the stem to rebuild the geometry, and the 3D position of each ECG-gated IVUS frame was determined from speed of catheter pullback. Following frame adjustment due to catheter rotation, each frame was aligned perpendicular to the catheter core. Arterial branches were added based on information from angiography and IVUS images and oriented perpendicular to the catheter core. Spline curves connected frame lumen boundary points, which was subsequently meshed (CFD-GEOM, CFD Research Corporation, Huntsville, Alabama) and imported into the CFD solver (CFD-ACE, CFD Research Corporation, Huntsville, Alabama).

Pulsatile inlet and outlet boundary conditions were specified as a series of velocity profiles derived from acquired Doppler data. Transient inlet velocity profiles were assumed to plug flows with magnitudes equal to 80% of the peak velocity registered in the Doppler ultrasound sample volume (corresponding to peak values

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