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WALL SHEAR STRESS TOPOLOGICAL SKELETON VARIABILITY PREDICTS ATHEROSCLEROTIC PLAQUE GROWTH IN HUMAN CORONARY ARTERIES

Giuseppe De Nisco (1), Eline Hartman (2), Valentina Mazzi (1), Diego Gallo (1), Claudio Chiastra (1), Joost Daemen (2), Jolanda Wentzel (2), Umberto Morbiducci (1)

(1) Polito^{BIO}Med Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy
(2) Department of Cardiology, Biomedical Engineering, Erasmus MC, Rotterdam, Netherlands

INTRODUCTION

Although low wall shear stress (WSS) has become the consensus hemodynamic mechanism for coronary atherosclerosis, the exact biomechanical stimulus affecting atherosclerosis evolution is still undetermined [1]. In this regard, recently there is a marked in the topological skeleton analysis applied to the WSS vector field [2,3]. The WSS topological skeleton consists of fixed points, where the WSS vector vanishes, and manifolds, namely the regions connecting them, where the WSS vector field contracts or expands. The interest in such an analysis is dictated by its ability to (1) identify flow features usually classified as "disturbed flow", linked to atherosclerosis onset and development, and (2) quantify the contraction/expansion action exerted by the WSS on the endothelium. Very recent findings have demonstrated a link between the WSS topological skeleton features and adverse vascular response [4-7], showing its capability to concur to the identification of the complex biomechanical stimulus affecting atherosclerosis evolution [6,7].

Based on these pieces of evidences this study tests the ability of WSS topological skeleton features to predict the temporal evolution of coronary artery plaque burden (PB), a hallmark of atherosclerosis development, in 49 patient-specific computational models of human coronary arteries. The final aim is to probe whether hemodynamic quantities giving a direct measure of the variability of the contraction/expansion action exerted by the blood flow on endothelial cells are capable to predict longitudinal local PB changes.

METHODS

Patient population. An overview of the methods is provided in Figure 1. Forty-eight hemodynamically stable patients from the IMPACT study data set [8] were used in the analysis. The IMPACT study enrolled patients with acute coronary syndrome and with at least one non-stented non-culprit coronary segment accessible for intracoronary imaging. The presence of previous coronary artery bypass graft surgery, 3-vessel disease, renal insufficiency (creatinine clearing < 50 ml/min), left ventricular ejection fraction < 30%, and atrial fibrillation, were considered as exclusion criteria. All patients underwent percutaneous coronary intervention of the culprit coronary vessel. After successful treatment, a non-culprit coronary segment (right - RCA, left anterior descending - LAD, or left circumflex - LCX coronary artery) was imaged by coronary computed tomography (CCTA) angiography and intravascular ultrasound (IVUS) at the time of the intervention (T1) and at 1 year follow-up (T2).

Computational hemodynamics. The lumen geometry of 49 imaged coronary arteries (18 RCA, 18 LAD, and 13 LCX,) was reconstructed at T1 [8]. IVUS images were segmented into lumen contours and stacked upon the 3D CCTA centerline. Luminal regions proximal and distal to the IVUS segment were added using lumen segmentations from the CCTA images. Transient computational fluid dynamics simulations were performed by using the finite volume method (Fluent, Ansys Inc.). Blood was modelled as non-Newtonian Carreau fluid. Patient-specific inflow and outflow boundary conditions were derived from ComboWire Doppler flow velocity measurements. If velocity-based flow measurements were inaccurate or not available, a generalized flow rate [9] was prescribed as inflow BC, while a proper diameter-based scaling law [9] was applied to estimate the flow ratio at the outflow sections.

Wall shear stress-based descriptors. The most widely adopted descriptors of WSS magnitude, multidirectionality and topological skeleton features were tested. In detail, three canonical WSS-based descriptors of "disturbed flow", i.e., TAWSS, OSI, and RRT, were computed. Additionally, the transverse WSS (transWSS), representing the average WSS component acting orthogonal to the time-average

WSS vector direction, was considered [10]. Moreover, the contraction/expansion action exerted by hemodynamic shear forces on the endothelium was quantified according to a Eulerian-based method for the analysis of the WSS topological skeleton based on the divergence of the WSS unit vector field (DIV_{WSS}) [2]. Negative (positive) DIV_{WSS} values at the luminal surface identify WSS contraction (expansion) regions. Here the quantity Topological Shear Variation Index (TSVI) was used as a measure of the variability of the local contraction/expansion action exerted by the WSS along the cardiac cycle. Technically, the TSVI is defined as [4,5]:

$$TSVI = \left\{\frac{1}{T}\int_0^T [DIV_{WSS} - \overline{DIV_{WSS}}]^2 dt\right\}^{1/2} \quad (1)$$

where T is the cardiac cycle duration.

Statistical analysis. The analysis was focused at the IVUS imaged arterial segments. Each IVUS segment was divided into 3mm/45° sectors [8]. In all IVUS frames at T1 and T2, lumen and external elastic membrane contours were semi-automatically segmented, and PB was assessed as the ratio between plaque area and total vessel area, multiplied by 100. The mean values of the difference between PB measurements at T2 and T1 was evaluated for each sector and used for the analysis (PB growth). Hemodynamic descriptors were averaged over each 3mm/45° sector and divided into artery-specific low, mid and high tertiles to perform a statistical difference analysis on the associated PB growth measurements. Significance was assumed for $p < 0.05$.

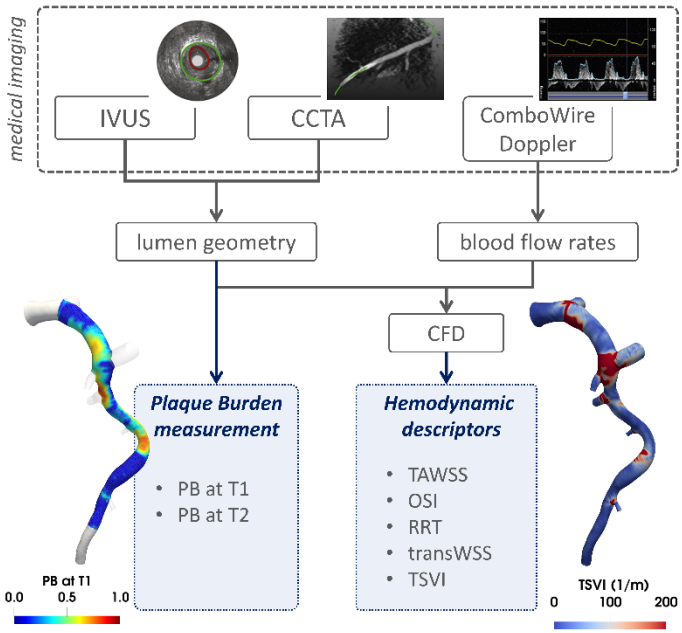

Figure 1: Overview of study methods.

RESULTS

Figure 2 reports the (mean ± sem) PB growth values associated to low, mid, or high values of each hemodynamic descriptor. It clearly emerged that sector exposed to high TSVI values at T1 exhibited significantly higher PB growth in the T2-T1 time interval, compared to the exposure to low or mid TSVI at T1. As expected, a significant association emerged also for the exposure to low TAWSS at T1 and PB growth. Finally, an association between PB growth in the T2-T1 time interval and WSS multidirectionality at T1, quantified in terms of OSI and transWSS, emerged. However, the scarce multidirectional action of the WSS in the investigated coronary arteries (with OSI <0.01 and transWSS <0.15 Pa), suggests a secondary role for WSS multidirectionality in promoting aggravating biological events.

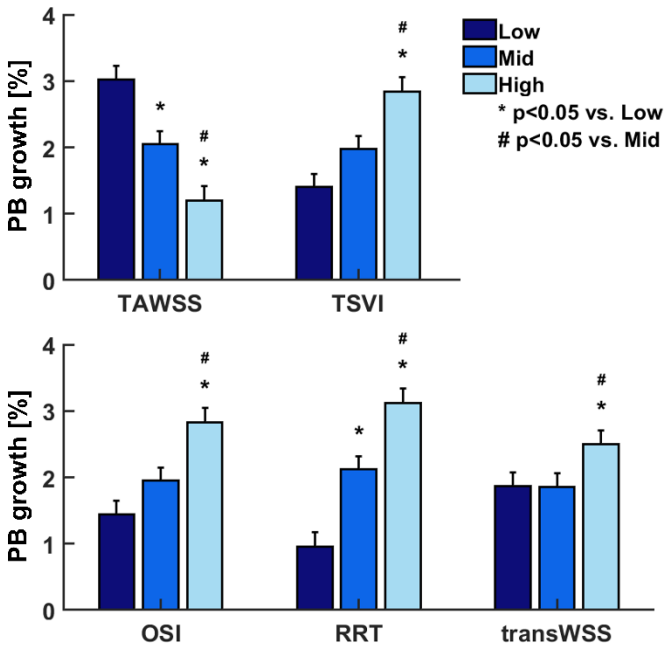

Figure 2: Hemodynamic descriptors vs. estimated PB growth.

DISCUSSION

This study tested the capability of CFD-derived WSS topological skeleton features and canonical WSS-based descriptors of disturbed flow to predict local plaque burden temporal changes in human coronary arteries. The main results can be summarized as follows: (1) as confirmation, luminal sectors characterized by low TAWSS values at T1 exhibited significant plaque growth; (2) luminal exposure to high variability in the WSS contraction/expansion action was associated with significant PB growth. Physically, TSVI describes the variability of the contraction/expansion action exerted by WSS on the endothelium. Thus, it describes different features of the WSS vector field with respect to TAWSS and it represents a different hemodynamic stimulus to the endothelium. Translating this into mechanistic implications, the variability in the contraction/expansion action exerted by shear forces on endothelial cells reflects on intra- and inter-cellular tension variability that could lead to aggravating biological events. Recent results on a large dataset of 188 atherosclerotic coronary arteries confirm the effectiveness of TSVI as biomechanical biomarker able to identify intermediate coronary lesion site of subsequent myocardial infarction at 5-year follow-up [7].

In conclusion, high TSVI is a strong predictor of PB growth in the analyzed population, encouraging further clinical trials to enforce the presented results and translate this concept into clinical practice.

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