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Review

Shear stress and advanced atherosclerosis in human coronary arteries

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ABSTRACT

The role of low and oscillating shear stress as a key factor for localizing early atherosclerotic plaques is generally accepted. Once more advanced plaques protrude into the lumen, the shear stress they are exposed to changes. The influence of shear stress on plaque composition in advanced atherosclerosis is not fully understood.

In this review, we discuss our recent studies on the relationship between shear stress and plaque composition and the location of plaque rupture in human coronary arteries. We have shown that elevated shear stress levels can be found over plaques inducing only mild luminal narrowing and are not subjected to treatment. Regional exposure of certain plaque regions to high shear stress is therefore a condition that will pertain for a prolonged period of time. We have also shown that in more advanced atherosclerosis the necrotic core experiences higher shear stress. Low shear stress plaque regions can be found downstream of the plaque and are stiffer. High shear stress plaque regions can be found either at the upstream, shoulder or cap region of the plaque and are softer. The plaque regions with the highest strain levels are the regions that are exposed to the highest shear stress. The high shear stress plaque regions are the only plaque regions that get softer over time. Finally, high shear stress is also associated with the location of plaque rupture in non-culprit lesion in human coronary arteries.

Combining our findings with data from literature, we can conclude that advanced coronary plaques grow in the distal regions. The distal plaque regions are exposed to low shear stress, are stiffer and have a stable plaque phenotype. The regions exposed to high shear stress are softer, and are associated with vulnerable plaque features.

1. Introduction

Blood flow induced shear stress is the normalized frictional force that the flowing blood exerts on the arterial wall. Shear stress represents only a small part of the total mechanical load the arterial wall is exposed to, and it is generally accepted that shear stress is sensed by the endothelium only (Malek et al., 1999). This inner lining of the arterial wall is very sensitive to shear stress: in healthy arteries, alterations in average flow lead to changes in luminal dimensions to keep shear stress within narrow limits (Kamiya and Togawa, 1980; Zarins et al., 1987). It is also generally accepted that, in the presence of systemic risk factors, shear stress plays a key role in early atherosclerosis. Low and/or oscillating shear stress leads to endothelial dysfunction inducing a pro-atherogenic environment. Shear stress is therefore regarded as one factors leading to the focal distribution of atherosclerotic plaques (VanderLaan et al., 2004). The processes that relate shear stress to the early phase of atherosclerosis were reviewed extensively (Cecchi et al., 2011; Chatzizisis et al., 2007; Slager et al., 2005a).

During early stages of plaque development, the arterial wall remodels outward (Glagov et al., 1987). This compensatory remodeling response, presumable mediated by the endothelium covering the healthy part of the arterial wall (Wentzel et al., 2003), leads to a preservation of the lumen geometry. The fact the lumen geometry largely remains unchanged implies that, providing that the average flow does not change appreciably over time, the shear stress patterns the endothelium is exposed to remain largely unchanged during early plaque build-up .

The remodeling process cannot compensate for plaque build-up in the more advanced stages of atherosclerosis. The plaque will then protrude into the lumen and the shear stress distribution over the plaque will change (Slager et al., 2005b; Wentzel et al., 2012, Accepted for publication). The influence of shear stress on plaque composition in advanced atherosclerosis is not fully understood and of great interest from a clinical perspective (Wentzel et al., 2012).

In this manuscript, we will review our most important studies on the in vivo assessment of shear stress in human coronaries, and how shear stress relates to plaque composition and the location of plaque rupture. A brief description of the main findings from these studies will be followed by a discussion, in which our results will be compared to other in vivo data that relate shear stress to markers of advanced atherosclerosis in human coronary arteries.

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2. Shear stress versus plaque composition

To investigate the effect of shear stress in the more advanced stages of atherosclerosis, imaging plaque composition is crucial. This is especially challenging in human coronary arteries: Not only are coronary plaques small, they also move considerably. The currently available non-invasive technologies are not capable of imaging coronary plaques. Although multi-slice detector computer tomography (MSCT) is a promising and rapidly evolving technique (Rybicki et al., 2008), it cannot provide the required contrast to detect relevant plaque components (van der Giessen et al., 2010c).

We therefore have to rely on invasive technologies for coronary plaque imaging. One of the most widely used imaging modalities to investigate the composition of human coronary plaques in vivo is based on intravascular ultrasound (IVUS). Virtual histology (IVUS-VH) uses the spectral information in the radio-frequency (RF) ultrasound signal reflected by the region of interest in the vessel wall (Nair et al., 2002). This region of interest is approximately 0.5 mm deep along the ultrasound beam and spans approximately 20 degrees in the circumferential direction. The resolution along the ultrasound beam is reduced to approximately 0.2 mm during post-processing . Using a classification tree, which was developed using ex vivo experiments on human coronaries, IVUS-VH classifies the region of interest as fibrous, fibro-fatty, calcified or necrotic tissue. Although the predicative accuracy of IVUS-VH to detect necrotic tissue is only approximately 75%, it is used in many clinical trials to study e.g., the efficacy of new pharmaceutical agents (Serruys et al., 2008) and in natural history studies to investigate the development of atherosclerotic plaques (Diletti et al., 2011; Stone et al., 2011).

We combined plaque composition from IVUS-VH with a 3D reconstruction method for human coronary arteries. This reconstruction technique is called ANGUS and relies on the combination of bi-plane angiography and IVUS (Slager et al., 1998). The IVUS images are superimposed on the 3D catheter path, determined from biplane angiography. The lumen of the artery is extracted from the IVUS images and the 3D lumen information is fed into a mesh generator. The resulting finite element mesh is combined with patient specific flow measurement to solve the Navier–Stokes equations. Within the generally applied limits – rigid wall, no vessel wall movement, stress-free outlet boundary conditions – we can apply computational fluid dynamics (CFD) to determine the velocity and shear stress distribution in the coronary artery using standard numerical techniques. Using this approach, we can relate the computed shear stress distribution along the lumen to the local plaque composition determined from IVUS-VH (Fig. 1A).

This combination of imaging techniques and CFD was applied in 10 patients with coronary artery disease (Wentzel et al., Accepted for publication). For each cross-section obtained from the IVUS images, we determined wall thickness, plaque burden (defined as plaque area over vessel area), median shear stress and the location of the largest necrotic core and necrotic core in contact with the lumen. A necrotic core in contact with the lumen is assumed to have a fibrous cap thinner than 0.2 mm, the resolution of IVUS-VH . First, we determined whether wall thickness in a cross-section was larger than 0.5 mm, the threshold value for the presence of a plaque. If plaque was present in a cross-section, plaque burden was determined and used to classify the cross section. We used plaque burden of 40% (Glagov et al., 1987) to separate cross section with early plaques from cross sections with advanced plaques. In the cross sections containing a plaque, we determined the average shear stress that the location of the major necrotic core was exposed to. If the average shear stress the necrotic core was exposed to was lower than the median value, it was defined as low shear stress and above that value as high shear stress. The same procedure was followed for the necrotic core in contact with the lumen (Fig. 1B). We found that for *early* plaques, the major necrotic core was exposed to low shear stress in 61% of the cross section and to high shear stress in 39% of the cross sections. For the *advanced* plaques, this relationship changed: In 40% of the cross sections, the major necrotic core was exposed to low shear stress while in 60% of the cross sections, the major necrotic core was exposed to high shear stress ($p < 0.05$, Fig. 1C). For the necrotic core in contact with the lumen, we observed a similar relationship: In 61% of the cross sections containing advanced plaques, the necrotic core in contact with the lumen was exposed to high shear stress.

From this study, we can conclude that in early disease, the necrotic core can mainly be found in low shear stress regions, while in more advanced atherosclerosis, the plaque protrudes into the lumen, with the necrotic core exposed to higher shear stress levels.

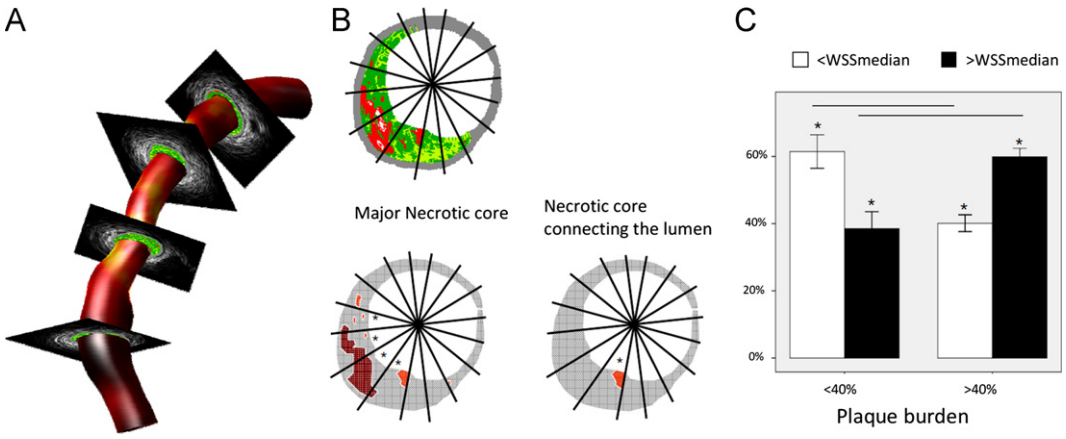

Fig. 1. (A) 3D reconstruction of lumen and wall of a coronary artery combined with IVUS-VH. The shear stress is color coded on the lumen of the 3D reconstruction. (B) Cross section with virtual histology; red indicates the location of the major necrotic core. The lower panels explain which sectors (*) are studied to explore the relationship between shear stress and the major necrotic core and the necrotic core in contact with the lumen. (C) The percentage of cross sections for which necrotic core is located at low shear stress (< WSSmedian, white bars) or high shear stress (> WSSmedian, black bars) for early disease (< 40% plaqueburden) and advanced disease (> 40% plaque burden). Adapted from Wentzel et al., 2012, Accepted for publication and reprinted with permission from Eurointervention. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)