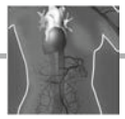
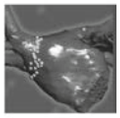


Wall shear stress and evolution of coronary atherosclerosis: an emerging intravascular imaging modality

"We have recently demonstrated that in patients with coronary artery disease treated with high-dose statins, coronary segments with low wall shear stress indeed develop greater plaque progression and constrictive vascular remodeling compared with segments with physiologic or high wall shear stress."

KEYWORDS: atherosclerosis ■ plaque progression ■ plaque vulnerability ■ wall shear stress

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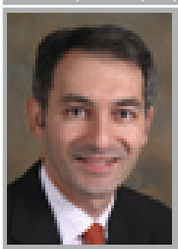

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Atherosclerosis is a diffuse systemic process associated with traditional cardiovascular risk factors leading to systemic inflammation, oxidative stress and endothelial dysfunction. However, the pathophysiology and prognosis of individual coronary plaques may be markedly different between two patients with identical systemic risk profiles, implying an important role for genetic predisposition, as well as local factors in the natural history of atherosclerosis.

Human autopsy studies have demonstrated that the vast majority of thin-cap fibroatheromas and ruptured plaques occur in the proximal third of the major coronary arteries [1]. Similarly, clinical studies have demonstrated that culprit lesions in patients with ST-elevation myocardial infarction are frequently located in proximal coronary arteries, immediately distal to bifurcations, and in proximity to major curvatures [2]. This focal distribution of clinically important coronary plaques in segments known to have disturbed blood flow infers an important role for regional wall shear stress (WSS) in the pathogenesis of clinically manifest coronary artery disease (CAD).

Abnormal WSS in geometrically susceptible coronary segments is thought to promote the development of atherosclerosis. Indeed, low WSS has been implicated in a number of pathologic mechanisms including increased VCAM-1 expression [3], sustained activation of sterol regulatory element-binding proteins, which are key transcription factors that upregulate the expression of genes that encode the low-density lipoprotein receptor and fatty acid synthase [4,5], increased production of reactive oxygen species [6] and a proatherogenic endothelial cell phenotype [7]. Furthermore, experimental studies in ApoE-knockout mice and porcine models of atherosclerosis have demonstrated that vascular segments with low and oscillatory WSS result in proatherogenic flow-mediated inflammatory responses and development of regional atherosclerosis [8–10]. Pilot clinical data have suggested that these experimental observations linking low WSS to plaque progression may hold true in the human coronary vasculature [11]. We have recently demonstrated that in patients with CAD treated with high-dose statins, coronary segments with low WSS indeed develop greater plaque progression and constrictive vascular remodeling compared with segments with physiologic or high WSS [12].

"Our recent study in patients with coronary artery disease treated with high-dose statins also demonstrated an association between high wall shear stress segments and intravascular ultrasound features of plaque vulnerability..."

Early plaque progression within a low WSS segment could result in gradual luminal narrowing that eventually results in an increase in WSS into the physiologic range. Whether a small plaque with physiologic WSS remains quiescent or progresses further, may depend on continued exposure to atherogenic risk factors, inflammation and/or endothelial dysfunction. As a plaque continues to encroach into the lumen, WSS is thought to increase into the high range. The ensuing high WSS has been shown to induce apoptosis of smooth-muscle cells [3,13], increase matrix metalloproteinases and TGF-β [6], which induce thinning of the plaque fibrous cap making it more vulnerable to fissuring or rupture [7].

Future Medicine part of fsg

Clinical evidence supporting the association of high WSS with features of plaque vulnerability can be found in a study by Fukumoto *et al.* who demonstrated localization of high WSS with plaque rupture in patients with acute coronary syndromes [14]. Our recent study in patients with CAD treated with high-dose statins also demonstrated an association between high WSS segments and intravascular ultrasound (IVUS) features of plaque vulnerability, namely plaque regression (driven by large reductions in fibrous and fibro-fatty plaque), increased necrotic core and dense calcium, and expansive vascular remodeling [12].

> "*Translating the mechanistic link between wall shear stress and atherogenesis adds a novel dimension beyond plaque morphology to the prediction of focal plaque progression and vulnerability in high-risk patients with coronary artery disease.*"

Despite the clinical observations indicating that low WSS is associated with plaque progression and constrictive remodeling, and that high WSS is associated with increased plaque vulnerability and expansive remodeling, the precise interplay between WSS, vascular remodeling and further plaque development has not been fully elucidated. A large-scale natural history study (506 patients with 1-year follow-up), PREDICTION, evaluating the role of coronary WSS in patients with CAD has recently been completed. Preliminary results of the PREDICTION study are largely in keeping with our findings and show that low WSS is an independent predictor of worsening lumen narrowing, the need for percutaneous coronary intervention and is indicitaive of major adverse cardiac events at follow-up [15,16].

Technical challenges persist in developing a clinically useful intravascular WSS assessment tool that can be used in stratifying individual lesions in patients with CAD. These include the invasive nature of measurements required to derive WSS calculations (intracoronary velocity measurement, IVUS and biplane coronary angiography) and the significant postprocessing resources required for computational fluid dynamic models. Efforts are underway to streamline this process [17] both in terms of data acquisition and postprocessing, in order to enhance the potential clinical utility of WSS assessment as an adjunct to existing intravascular imaging tools such as IVUS, optical coherence tomography and near infrared spectroscopy [18]. Translating the mechanistic link between WSS and atherogenesis adds a novel dimension beyond plaque morphology to the prediction of focal plaque progression and vulnerability in high-risk patients with CAD. As such, WSS assessment may have significant value in developing diagnostic strategies that may identify high-risk coronary plaques that could undergo more intensive local or systemic therapies to reduce adverse coronary events.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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