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To cite this article: Yiannis S Chatzizisis & George D Giannoglou (2010) Shear stress and inflammation: are we getting closer to the prediction of vulnerable plaque?, Expert Review of Cardiovascular Therapy, 8:10, 1351-1353, DOI: [10.1586/erc.10.126](https://doi.org/10.1586/erc.10.126)

To link to this article: <https://doi.org/10.1586/erc.10.126>



Published online: 10 Jan 2014.



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# Shear stress and inflammation: are we getting closer to the prediction of vulnerable plaque?

*Expert Rev. Cardiovasc. Ther.* 8(10), 1351–1353 (2010)



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**“...the critical question is why only few among many individual local plaques evolve to atheromata with thin fibrous cap, rupture and lead to acute coronary syndrome.”**

Despite the systemic nature of atherosclerosis, its distribution is multifocal and heterogeneous, such that multiple atherosclerotic lesions at different stages of progression coexist in the same individual and in the same artery at a single point in time [1]. A portion of atherosclerotic lesions are atheromata with a thin fibrous cap (so-called ‘vulnerable plaques’) prone to acute disruption, and consequent acute coronary syndrome [2]. These lesions are currently neither identified nor treated before plaque rupture. Even though we know that atherosclerotic lesions preferentially develop in regions of low endothelial shear stress (ESS), the critical question is why only few among many individual local plaques evolve to atheromata with thin fibrous cap, rupture and lead to acute coronary syndrome. The magnitude of low ESS is likely to be a critical determinant of the individual natural history of atherosclerotic lesions [3–5].

In arterial regions with disturbed flow, low ESS reduces the bioavailability of nitric oxide, thereby inducing endothelial dysfunction and exposing the endothelium to the atherogenic effect of local and systemic risk factors [1,6,7]. Low ESS also promotes LDL-cholesterol (LDL-C) uptake and synthesis by the endothelium, leading to subendothelial accumulation of LDL-C [8]. The increased mitotic and apoptotic activity of endothelial cells induced by the local low ESS, as well as the conformational changes of endothelial cells from fusiform

to polygonal shape, promote the widening of the junctions between endothelial cells, thereby accentuating the subendothelial deposition of LDL-C [1]. Within the intima, LDL-C undergoes oxidative modification by reactive oxygen species [8]. Low ESS mediates the production of reactive oxygen species within the intima by enhancing gene expression and post-transcriptional activity of the major oxidative enzymes at endothelial cell membranes [1]. The minimal intimal accumulation of oxidized LDL-C constitute the earliest histopathologic stage of atherosclerosis, so-called fatty streaks [2].

Low ESS upregulates the expression of several adhesion molecules, chemoattractant chemokines and proinflammatory cytokines [1,9]. Adhesion molecules are expressed by endothelial cells and mediate the rolling and adhesion of circulating leukocytes on the endothelial surface, whereas chemoattractant chemokines promote transmigration of leukocytes into the intima. Once monocytes infiltrate beneath the endothelium they differentiate to macrophages, phagocytose the oxidized LDL-C and transform into foam cells. Foam cells produce cytokines, growth factors, reactive oxygen species and matrix-degrading enzymes, sustaining atherosclerosis progression. The intensity of oxidized LDL-C accumulation in the subendothelial space is a major stimulus for the ongoing inflammatory process [8].

**KEYWORDS:** coronary atherosclerosis • inflammation • shear stress • vascular biology • vascular remodeling

The accumulation of lipid-laden foam cells constitute the intermediate lesions or pathologic intimal thickening, which evolve through several stages of progression [2].

**“*In vivo* invasive technologies for the assessment of plaque inflammation now exist, with thermography and optical coherence tomography being quite promising.”**

A portion of intermediate lesions, at some point during their natural history, acquire a fibrous cap and evolve to early fibroatheromas. Although the pathophysiologic events occurring during the transition of intermediate lesions to early fibroatheromas are not well understood, it appears that the regional disruption of the internal elastic lamina constitutes the key event [4,10]. Histopathology studies in a diabetic, hyperlipidemic swine model of native atherosclerosis have shown that in the setting of very low levels of local ESS, and subsequently intense accumulation of inflammatory cells within the intima, the internal elastic lamina undergoes local fragmentation by the elastolytic metalloproteinases-2 and -9, and cathepsins (K, L and S), especially at the shoulders of the plaque where dynamically changing mechanical forces occur [4]. These internal elastic lamina breaks constitute the gateway for vascular smooth muscle cells, which are originally located in the media, to enter the intima. Within the intima the vascular smooth muscle cells elaborate extracellular matrix proteins (i.e., collagen and elastin), proliferate and promote plaque progression. Furthermore, vascular smooth muscle cells encompass the core of the lipid-laden foam cells (lipid core), produce extracellular matrix and create the fibrous cap, separating the thrombogenic lipid material from the circulating platelets and other prothrombotic factors. The fibrous cap along with the underlying lipid core forms an early fibroatheroma [2].

Following their formation the early fibroatheromas progress along an individualized natural history, which is critically dependent on the balance of two competing processes: inflammation with concomitant matrix degradation versus fibroproliferation with matrix synthesis [1]. A portion of early fibroatheromas evolve into thin capped atheromata, whereas others remain quiescent or evolve into fibrous stenotic plaques. The magnitude of low ESS appears to be a key regulator of the balance between inflammation/matrix degradation and fibroproliferation/matrix synthesis, such that the lower the ESS the more severe the inflammation and elastolytic enzyme activity. Augmented elastase activity promotes severe internal elastic lamina fragmentation and extension of the inflammatory cells to the media, where they alter the stiffness of the arterial wall [11] and promote expansive, and sometimes excessively expansive, vascular remodeling, thereby sustaining the initial low ESS stimulus and consequently increasing the likelihood of an early fibroatheroma to evolve to a thin-capped atheroma [4,12,13].

*In vivo* invasive technologies for the assessment of plaque inflammation now exist, with thermography and optical coherence tomography being quite promising [14]. Further to invasive technologies, as a potential aid for the direct assessment of the severity of plaque inflammation, new molecular imaging nanotechnologies have been

developed within the last few years [15,16]. Molecular imaging of inflammation in atherosclerosis is an emerging field that is based on the strategy that certain molecular imaging agents (tracking agents) carry an affinity ligand (e.g., peptide, engineered antibody or other small molecule), which binds specific molecular mediators of inflammation within the plaque (e.g., VCAM-1 and macrophages). Using appropriate, preferably noninvasive, molecular imaging systems, such as MRI, computed tomography, ultrasound, nuclear imaging or optical imaging, the tracking agents are detected and the signal intensity, and indirectly the severity of inflammation, is assessed.

Therefore, the major characteristics of individual atherosclerotic plaques contributing to the ongoing process of the respective natural history trajectories include:

- The magnitude of ESS, which constitutes the stimulus for ongoing inflammation and plaque progression;
- The severity of inflammation that a plaque acquires over its development and progression;
- The nature of vascular remodeling response to the presence of the plaque;
- The stiffness of the arterial wall [10,11,17].

The magnitude of inflammation, vascular remodeling response and wall stiffness are directly determined by the local ESS environment [1,11]. Measurement of local ESS, complemented by the assessment of the severity of inflammation and the nature of vascular remodeling and stiffness at early stages of the natural history of a given minimally stenotic lesion, would allow for detailed risk stratification of that lesion to evolve into a thin-capped atheroma based on the following conceptual scheme:

- High-risk plaque with very low ESS, intense inflammation, excessive expansive remodeling and reduced vascular stiffness;
- Medium-risk plaque with low/moderate ESS, moderate inflammation, less excessive expansive remodeling and normal vascular stiffness;
- Low-risk plaque with physiologic ESS, limited inflammation, compensatory expansive remodeling and normal or increased vascular stiffness.

**“Measurement of local endothelial shear stress, complemented by the assessment of the severity of inflammation and the nature of vascular remodeling and stiffness at early stages of the natural history of a given minimally stenotic lesion, would allow for detailed risk stratification of that lesion to evolve into a thin-capped atheroma...”**

Risk stratification of early atherosclerotic lesions and identification of their subsequent natural history may permit the development of novel lesion-specific therapeutic strategies. Identification of a high-risk plaque at its early stages of development would potentially justify highly selective, prophylactic local interventions, such as implantation of stents or targeted delivery of

anti-inflammatory drugs, supplemented by an intensive systemic pharmacologic approach to limit the severity of inflammation, stabilize the plaque and therefore avert a future acute coronary event. Application of less aggressive strategies, such as moderate antiatherosclerotic therapies combined with regular follow-up, could be justified for low- or moderate-risk lesions. The clinical and economic benefits of identifying and treating high-risk individual coronary lesions before an adverse cardiac event can occur are anticipated to be enormous.

#### 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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