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REVIEW

Endothelial shear stress in the evolution of coronary atherosclerotic plaque and vascular remodelling: current understanding and remaining questions

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Abstract The heterogeneity of plaque formation, the vascular remodelling response to plaque formation, and the consequent phenotype of plaque instability attest to the extraordinarily complex pathobiology of plaque development and progression, culminating in different clinical coronary syndromes. Atherosclerotic plaques predominantly form in regions of low endothelial shear stress (ESS), whereas regions of moderate/physiological and high ESS are generally protected. Low ESS-induced compensatory expansive remodelling plays an important role in preserving lumen dimensions during plaque progression, but when the expansive remodelling becomes excessive promotes continued influx of lipids into the vessel wall, vulnerable plaque formation and potential precipitation of an acute coronary syndrome. Advanced plaques which start to encroach into the lumen experience high ESS at their most stenotic region, which appears to promote plaque destabilization. This review describes the role of ESS from early atherogenesis to early plaque formation, plaque progression to advanced high-risk stenotic or non-stenotic plaque, and plaque destabilization. The critical implication of the vascular remodelling response to plaque growth is also discussed. Current developments in technology to characterize local ESS and vascular remodelling *in vivo* may provide a rationale for innovative diagnostic and therapeutic strategies for coronary patients that aim to prevent clinical coronary syndromes.

Keywords Shear stress • High-risk plaque • Inflammation • Vascular remodelling

1. Introduction

Atherosclerotic plaques are regions in the arterial system characterized by intimal thickening with excessive build-up of oxidized low-density lipoprotein cholesterol accompanied by inflammatory cell infiltration, smooth muscle proliferation, and extracellular matrix accumulation.[1] Plaques prone to rupture (so-called vulnerable plaques) are further characterized by the presence of a large necrotic core covered by an inflamed thin fibrous cap.[2] Rupture of a vulnerable coronary atherosclerotic plaque is responsible for the majority of acute coronary events,[3] which are the leading cause of morbidity and mortality in the Western world.

Although the risk factors for atherosclerotic plaque formation, including high cholesterol, diabetes, and high blood pressure, are systemic in nature, plaques are located at specific sites in the arterial system. These sites include side-branches, the outer waist of bifurcations, or the inner curve of arteries, where disturbed flow and low endothelial shear stress (ESS) occur.[4–7] In contrast, arterial regions exposed to moderate/physiological ESS are protected from atherosclerosis.

Early observations on the relationship between ESS and plaque localization were based mainly on autopsy material,[8,9] and consequently did not allow investigation of the influence of ESS on atherosclerosis. The advent of three-dimensional (3D) reconstruction techniques for coronary arteries *in vivo*,[10–13] based on biplane angiography and

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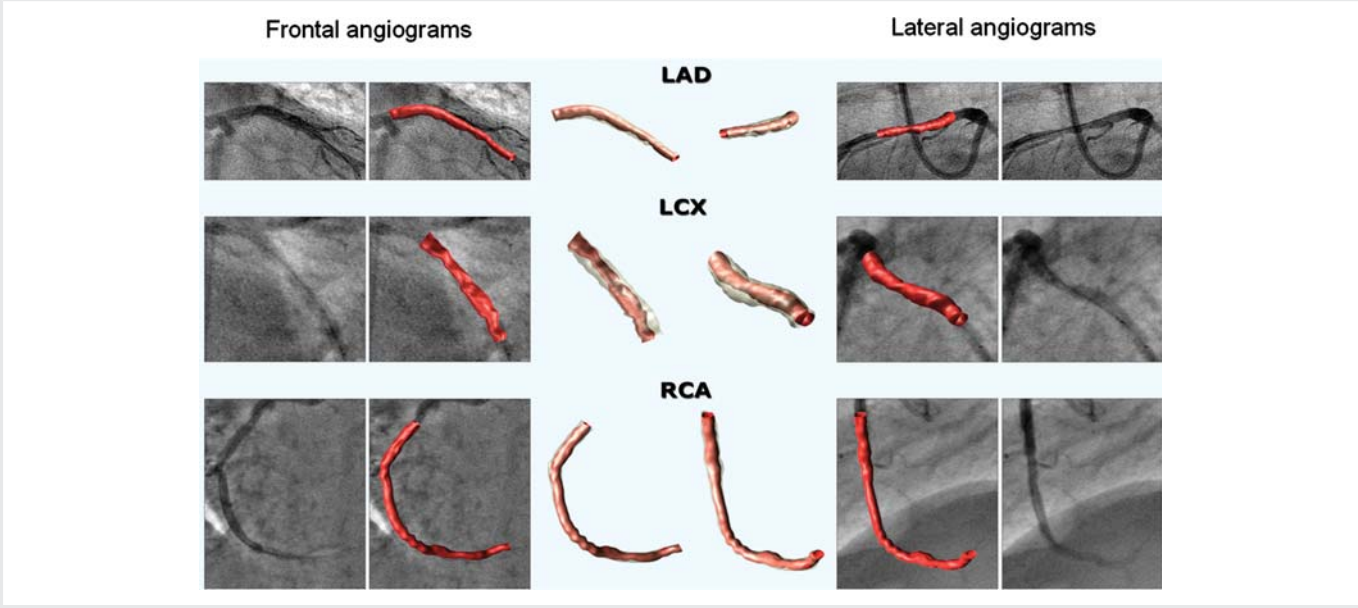

Figure 1 Three-dimensional (3D) reconstruction of human coronary arteries based on fusion of biplane angiography and intravascular ultrasound[10,11] Central panels show 3D reconstruction of left anterior descending artery (LAD), right coronary artery (RCA), and left circumflex (LCX) depicted in the same orientation as the frontal and lateral biplane angiograms. Left and right panels show the frontal and lateral biplane angiograms of the coronary arteries, respectively.

intravascular ultrasound, opened new avenues in the investigation of the role of ESS in the natural history of atherosclerosis (*Figure 1*). These 3D reconstruction techniques have been validated *in vivo*[10,14–16] and applied at different centres around the world.[17–20] By using these techniques, co-localization was found between low ESS regions and *de novo* atherosclerotic plaque[18,21–23] and in-stent restenosis[24–27] in coronary arteries of patients and laboratory animals.[28,29] Moreover, using serial measurements, low ESS was also shown to play a role in plaque progression[18,23,28] and the evolution of plaques into a phenotype that is prone to rupture.[28–30] Another observation was that advanced plaques which start to encroach into the lumen are exposed to high ESS, which appears to be involved in acute plaque disruption.[31]

The pathophysiological mechanisms responsible for the evolution of early lesions to either advanced high-risk plaques with lumen preservation/expansion or to high-risk plaques with lumen narrowing have not been well investigated. The dynamic interplay between local ESS environment, vascular remodelling and vascular biology appears to play a key role in the natural history of atherosclerosis. The purpose of this review is to present the complex dynamic interplay of local ESS (ranging from low to moderate/physiological and to high ESS), coronary atherosclerosis, vascular remodelling, and plaque destabilization throughout the natural history of atherosclerosis. The pathophysiological mechanisms that are responsible for plaque heterogeneity and transition through different stages of plaque evolution are discussed.

2. Definition of ESS and blood flow patterns

Endothelial shear stress is the tangential stress due to the friction of the flowing blood on the endothelial surface of the arterial wall

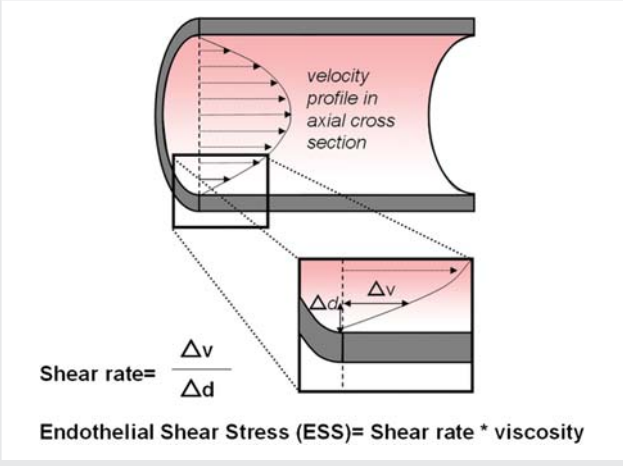

Figure 2 Endothelial shear stress (ESS) exerted by the blood flow is determined by the shear rate (i.e. velocity gradient) at the wall multiplied by viscosity. Adapted from Slager *et al.*[33]

(*Figure 2*).[32,33] It is expressed in units of force per unit area (Newtons per square metre or Pascals or dynes per square centimetre; 1 $N/m^2 = 1$ Pa $= 10$ dyn/cm^2). In human coronary arteries, it can be assessed using computational fluid dynamics in 3D reconstructions of the arteries, applying patient-specific flow measurements.

The different blood flow types determine the ESS patterns, which are characterized by direction and magnitude.[34] Blood flow may be either undisturbed laminar, referring to smooth streamlined flow, or disturbed laminar flow, characterized by areas of flow reversal (i.e. flow separation, recirculation, and reattachment to forward flow; *Figure 3A*).

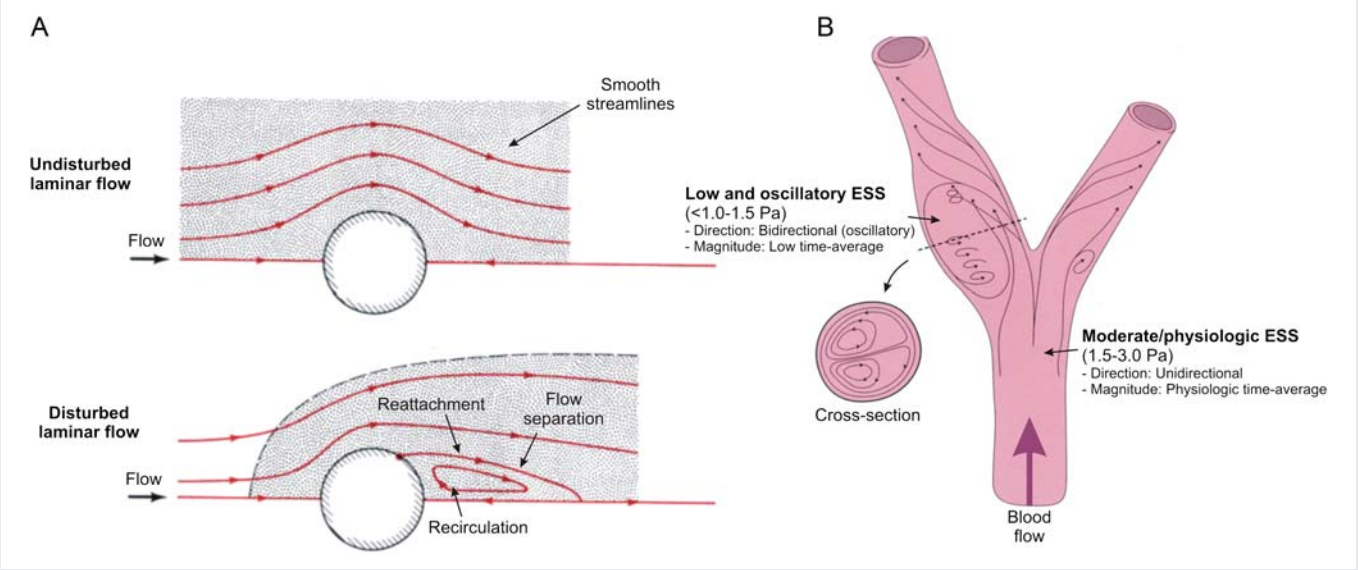

Figure 3 (*A*) Types of blood flow. (*B*) Types of ESS. Adapted from Chatzizisis *et al.*[34]

In relatively straight arterial segments, ESS is pulsatile and unidirectional, with a magnitude that varies approximately between 1.5 and 3.0 Pa (moderate, physiological ESS) over the cardiac cycle and yields a positive time average (*Figure 3B*). In contrast, in geometrically irregular regions, where disturbed laminar flow occurs, pulsatile flow generates low and/or oscillatory ESS. Low ESS is unidirectional, with periodically varying magnitude that results in a significantly low time average (approximately $<1.0-1.5$ Pa; *Figure 3B*). Of note, the absolute cut-off point for low ESS appears to be dependent on concomitant conditions as presented below (Section 3). Low ESS typically occurs at the inner areas of curvatures and potentially at the upstream shoulders of a stenosis. Low oscillatory ESS is bidirectional, with a fluctuating magnitude between systole and diastole, resulting in a low time average (approximately $<1.0-1.5$ Pa; *Figure 3B*). Low oscillatory ESS occurs primarily downstream of stenoses, at the lateral walls of bifurcations and at the ostia of branches. High ESS is characterized by a significantly high time average (approximately >3.0 Pa) and occurs at the upstream and most stenotic site of the plaque.

3. Dynamic nature of local ESS

ESS is a dynamic factor that changes in direction and magnitude with plaque formation and vascular remodelling.[35] As a continuous variable, ESS covers a wide spectrum of values, from low ESS to moderate/physiological ESS and to high ESS. The cut-off points defining low, moderate/physiological, and high ESS may vary among species, and among vascular beds (e.g. femoral, carotid, and coronary arteries) in the same species.[36] Even in the same vascular location, ESS changes over time in response to several systemic and local factors. The severity of systemic risk factors (e.g. hypercholesterolaemia) certainly influences the effect of the local haemodynamic environment. Furthermore, the stage of atherosclerosis development, the remodelling response of the wall to plaque formation, as well as regional structural and stiffness characteristics critically determine the local ESS environment and the subsequent natural history of individual atherosclerotic lesions.[33,35,37]

4. Role of ESS in atherogenesis and early plaque formation

In straight arterial regions with non-disturbed flow, where ESS varies within a moderate/physiological range, endothelial cells express various atheroprotective genes, and decrease several pro-atherogenic ones, leading to stability and quiescence.[34] The role of high ESS in early atherosclerosis is not well investigated, but it appears to be atheroprotective. In contrast, in regions with low and disturbed flow where low ESS occurs, the atheroprotective genes are suppressed, while the pro-atherogenic genes are over-expressed, thereby promoting atherogenesis. Endothelial cells sense the local low ESS stimuli through several mechanoreceptors located on their surface.[32,34,38] These mechanoreceptors in turn trigger a network of intracellular cascades, which culminate in the activation of transcription factors that transmigrate into the nucleus and shift gene and subsequently phenotypic endothelial cell expression to an atherosclerotic state.[32,33,39–42]

The largest body of evidence regarding the role of ESS in atherosclerosis is derived from *in vitro* and *in vivo* animal studies. Although these studies utilized fairly heterogeneous ESS patterns both in direction and magnitude, which do not always resemble the real human blood flow conditions, they provided the foundation and advanced our understanding concerning the role of ESS in atherosclerosis. *Figure 4* shows the implication of low ESS in the pathophysiology of early atherosclerosis.[32,34] ESS induces endothelial dysfunction by reducing nitric oxide and increasing endothelin-1,[43] provokes endothelial cell apoptosis[44] and conformational changes of endothelial cells from fusiform to polygonal shape,[45] induces subendothelial accumulation of low-density lipoprotein cholesterol,[46] and modulates the oxidative transformation of low-density lipoprotein cholesterol by stimulating the production of reactive oxygen species.[47] Through

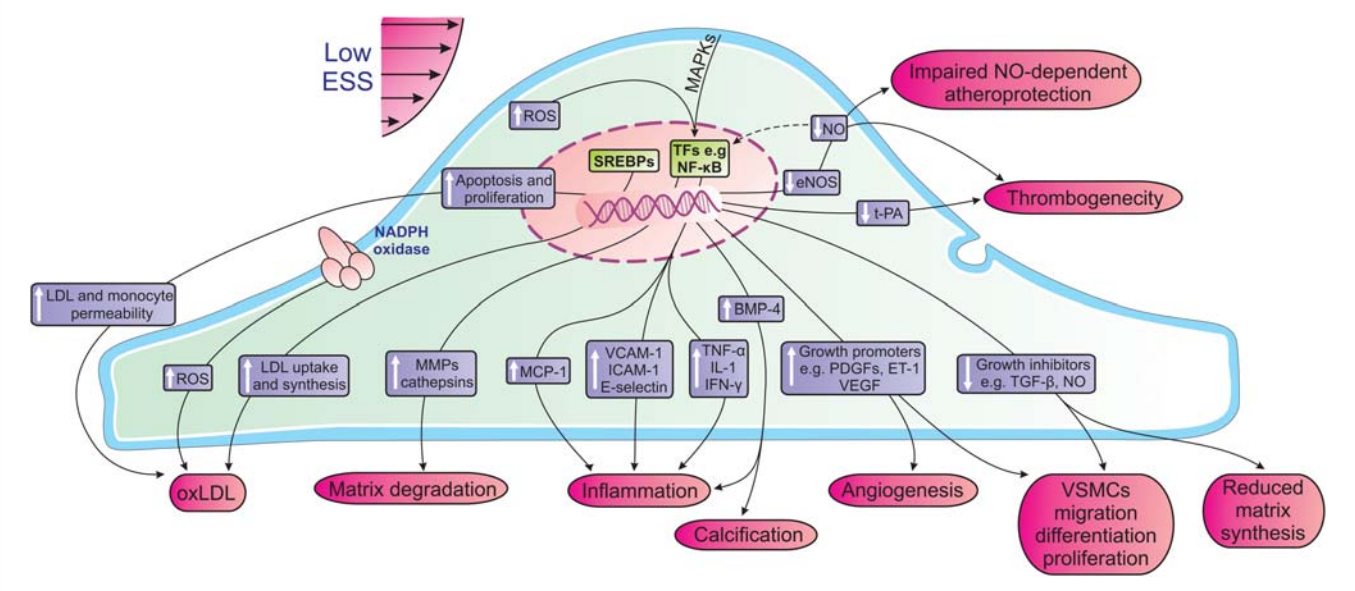

Figure 4 Molecular and cellular mechanisms through which low ESS promotes atherosclerosis. Data are derived from *in vitro* and animal *in vivo* experiments by applying a great variety of ESS patterns, both in direction and in magnitude. BMP, bone morphogenic protein; eNOS, endothelial nitric oxide syntase; ET, endothelin; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-γ; IL, interleukin; LDL, low-density lipoprotein cholesterol; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NO, nitric oxide; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; SREBP, sterol regulatory elements binding protein; TF, transcription factor; TGF-β, transforming growth factor β; TNF-α, tumour necrosis factor-α; t-PA, tissue plasminogen activator; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell. Adapted from Chatzizisis *et al.*[34]

activation of nuclear factor-κB, low ESS also up-regulates the expression of several adhesion molecules, chemoattractant chemokines, and pro-inflammatory cytokines,[48,49] thereby promoting transmigration of circulating monocytes into the intima. Once monocytes infiltrate beneath the endothelium, they differentiate to macrophages and ultimately evolve to foam cells, which sustain the atherosclerosis progression.[50] Over-expression and increased activity of metalloproteinases (MMPs), particularly MMP-2 and −9, and cathepsins (e.g. cathepsins K, L, and S), which are the major proteases associated with extracellular matrix degradation, is also mediated by low ESS, probably through nuclear factor-κB-dependent pathways.[29,30,51–53] The accumulation of lipid-laden foam cells constitutes the early atherosclerotic lesions, which evolve through several stages of progression.[54]

5. ESS and evolution of early plaque to high-risk plaque

A proportion of early atherosclerotic plaques evolve to high-risk rupture-prone plaques, which are widely considered to be precursors of ruptured plaques.[55] Histopathology, angiographic, and intravascular ultrasound studies have shown that 60–70% of acute coronary syndromes are attributed to ruptured thin-capped fibroatheromas, whereas the remaining 30–40% of acute coronary syndromes are attributed to plaque erosions or calcified nodules.[55] Although the great majority of thin-capped fibroatheromas obstruct the coronary lumen by less than 50% prior to rupture, show expansive remodelling, and do not limit coronary flow or produce angina, a substantial portion of rupture-prone plaques are obstructive.[3]

5.1 High-risk plaques with lumen preservation due to compensatory or excessive expansive remodelling

The natural history of coronary vulnerable plaques has recently been investigated in a serial study, using hyperlipidaemic, diabetic pigs, demonstrating the remarkable heterogeneity of the evolution patterns.[35] In these pigs, the majority of plaques with high-risk features developed in areas characterized by persistently low ESS (<1.0 Pa) with enhanced inflammation (*Figure 5*).[29,32–34] In the setting of severe inflammation, the underlying internal elastic lamina can also undergo severe fragmentation. The media becomes severely inflamed and acquires the enzymatic products that shift the extracellular matrix balance towards accelerated degradation, thereby promoting compensatory or even excessive wall expansion and accommodation of the enlarging plaque (*Figure 5*).[28,30,35,56] Excessive expansive remodelling may lead to exacerbation of the local low ESS environment, consequently fostering continued lipid accumulation and inflammation, which lead to additional matrix protease expression, intensive matrix degradation within the inflamed vascular wall and the fibrous cap shoulders, and ultimately, acquisition of characteristics of vulnerability.

5.2. High-risk plaques with lumen narrowing

Lumen-narrowing plaques can be either stable fibrotic or unstable high-risk plaques. The majority of plaques with lumen narrowing are stable lesions with constrictive remodelling. Histologically, these plaques are typically fibroproliferative and calcified lesions with limited inflammation, characterized morphologically by a relatively

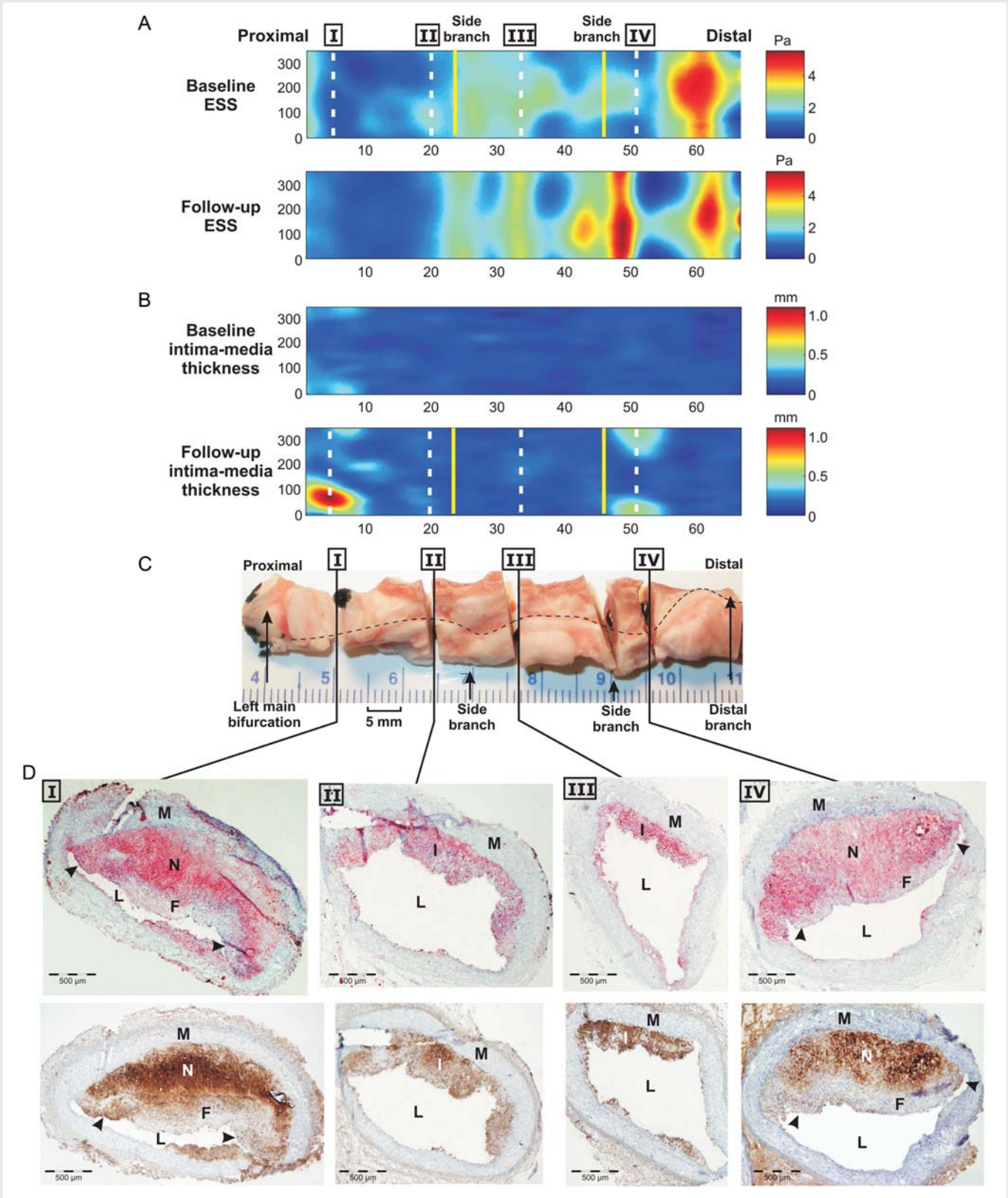

Figure 5 A three-dimensionally reconstructed swine left circumflex artery at baseline and follow-up. (*A*) ESS at baseline and follow-up. (*B*) Intima–media thickness at baseline and follow-up. (*C*) The harvested coronary artery at follow-up dissected in the sections I–IV indicated with dashed white lines in *A* and *B*. (D) Oil red O and CD45 staining of sections I–IV. Sections I and IV revealed thin-capped fibroatheromas (black arrowheads denote thin cap) with large lipid core originating from arterial regions with low ESS at baseline. F, fibrous cap; I, intima; L, lumen; M, media; and N, necrotic core). Adapted from Chatzizisis *et al.*[30]

thick, collagen-rich fibrous cap, which overlies a small, deep lipid core.[55,57] Most of these fibrotic plaques undergo constrictive remodelling, leading to lumen obstruction and subsequent development of clinical syndromes, such as chronic stable angina and provokable ischaemia. Stenotic lesions with a thick fibrous cap and constrictive vascular remodelling may evolve from a variety of preceding vascular and haemodynamic conditions, although the specific mechanisms responsible for these evolving patterns have not been well characterized.

In contrast to stable stenotic plaques, high-risk stenotic plaques may develop directly as a phenotypically independent stage in the natural history of atherosclerosis[22,58] or, more likely, indirectly as an end-stage in the evolution of non-obstructive high-risk plaques to obstructive ones. Several mechanisms are likely to be responsible for that transition of non-obstructive high-risk plaques to obstructive, as follows.

(i) Histopathology data in humans and animals have shown that clinically silent repetitive fibrous cap micro-ruptures may lead to the evolution of stenotic high-risk plaques through wound-healing processes, with subsequent fibrosis and vascular constriction.[59]
(ii) Fibroproliferative response with vascular constriction and luminal stenosis may also occur from intraplaque haemorrhage as a result of fibrous cap rupture and subsequent accumulation of luminal blood or as a result of rupture of neovessels within the plaque. The latter process leads to expansion of the necrotic core,[60] and influx of large amounts of red bloods cells that contain phospholipids and free cholesterol in the plaque, which trigger a fibrotic and constrictive response.[61]
(iii) Obstructive plaque may also develop when the growing plaque exceeds the ability of outer vessel wall to expand.[22,58,62] Loss of functional endothelium at the site of the plaque[63] may explain the evolution of early lesions to stenotic plaques, because dysfunctional endothelium might hamper the compensatory remodelling response. One could hypothesize that as eccentric plaques grow in a circumferential manner,[64] expansive vascular remodelling would stop if the full circumference is occupied by plaque.
(iv) Loss of the ability of the vessel wall to expand as a result of the ensuing vascular stiffness from progressive plaque growth and calcification may also lead to gradual plaque encroachment into the lumen.[37]
(v) Genetic characteristics also influence the nature of the vascular remodelling response to changes in local ESS, even in the absence of atherosclerosis.[65]

6. ESS and plaque destabilization

6.1. ESS and destabilization of high-risk plaques with lumen preservation

The extracellular matrix is regulated by the balance between macromolecule synthesis and enzymatic breakdown. Among other factors, low ESS plays an important role in regulating this balance. *In vitro* studies have shown that low ESS increases the expression of MMPs and cathepsins. Animal studies have also demonstrated that low ESS induces the elastolytic activity of elastases (MMP-2, −9, −12, and cathepsins K, L, and S) and collagenases (MMP-1, −8, and −13) relative to their endogenous inhibitors.[30] Collagenases degrade interstitial collagen mostly in the fibrous cap, thereby promoting fibrous cap thinning, whereas elastases break down elastin fibres in the internal elastic lamina, facilitating the migration of macrophages from the intima to media, thereby promoting wall expansion, as well as the migration of smooth muscle cells from the media to intima, thereby promoting plaque growth.[32] Furthermore, low ESS has been shown to induce smooth muscle cell apoptosis and de-differentiation in the fibrous cap, leading to reduced production of extracellular matrix in the cap.[66]

These *in vivo* investigations clearly demonstrated that low ESS-induced extracellular matrix degradation and reduced production promotes matrix remodelling, internal elastic lamina degradation, and thinning of the fibrous cap, all of which are critical steps in the development of a high-risk rupture-prone plaque. Clinical natural history studies are needed to elucidate the pathophysiological basis of high-risk plaque rupture further in the setting of plaques with a preserved lumen.

6.2. ESS and destabilization of high-risk plaques with lumen narrowing

As mentioned above, as plaques are growing the local ESS changes in magnitude, directionality, and spatial distribution.[35,67,68] Thus, a developing plaque itself can modify the local ESS milieu in specific parts of, and adjacent to, the lesion. Depending on the shape of the plaque, lumen narrowing due to a stenotic lesion results in a heterogeneous ESS distribution, with potentially relative low ESS occurring in the upstream shoulder of the plaque, high ESS at the most stenotic site of the plaque, and low oscillatory ESS at the downstream shoulder.[67–69]

6.2.1 Effects of low ESS in the vicinity of plaque

As a result of the haemodynamic heterogeneity associated with the formation of advanced stenotic plaque, the composition of the plaque along its length is also fairly heterogeneous. The downstream plaque region exposed to low and oscillatory ESS contains significantly more smooth muscle cells and less inflammation, while the upstream shoulder region potentially exposed to low ESS appears more inflamed, containing a high number of macrophages,[70,71] and expressing higher gelatinolytic activity.[70] This is in line with observations in carotid and coronary arteries that ruptured sites occur predominantly at upstream locations[71–75], whereas the downstream parts are prone to plaque growth.[76]

6.2.2 Effects of high ESS in the most stenotic plaque region

In contrast to low ESS-mediated effects at the upstream shoulder and downstream plaque regions, high ESS at the neck of the plaque may also trigger the pathobiological processes that weaken the fibrous cap, thus promoting plaque rupture.[77,78] Computational fluid dynamic studies in human carotid arteries[31] and coronary arteries[17] showed that plaque disruption coincides with high ESS. A study in human coronary arteries showed that in high ESS regions of stenotic plaques the strain is high, indicating a more vulnerable plaque phenotype, while at the low ESS regions the strain is lower (*Figure 6*).[68] Six month follow-up data acquired at the high ESS regions of these plaques showed a significant increase in strain, suggesting that high ESS may induce pathobiological responses in plaques with lumen narrowing that lead to plaque fragility.[67,79,80] Corroborative data have come from another prospective natural history clinical study, which showed that high ESS is associated with regression of fibrous and

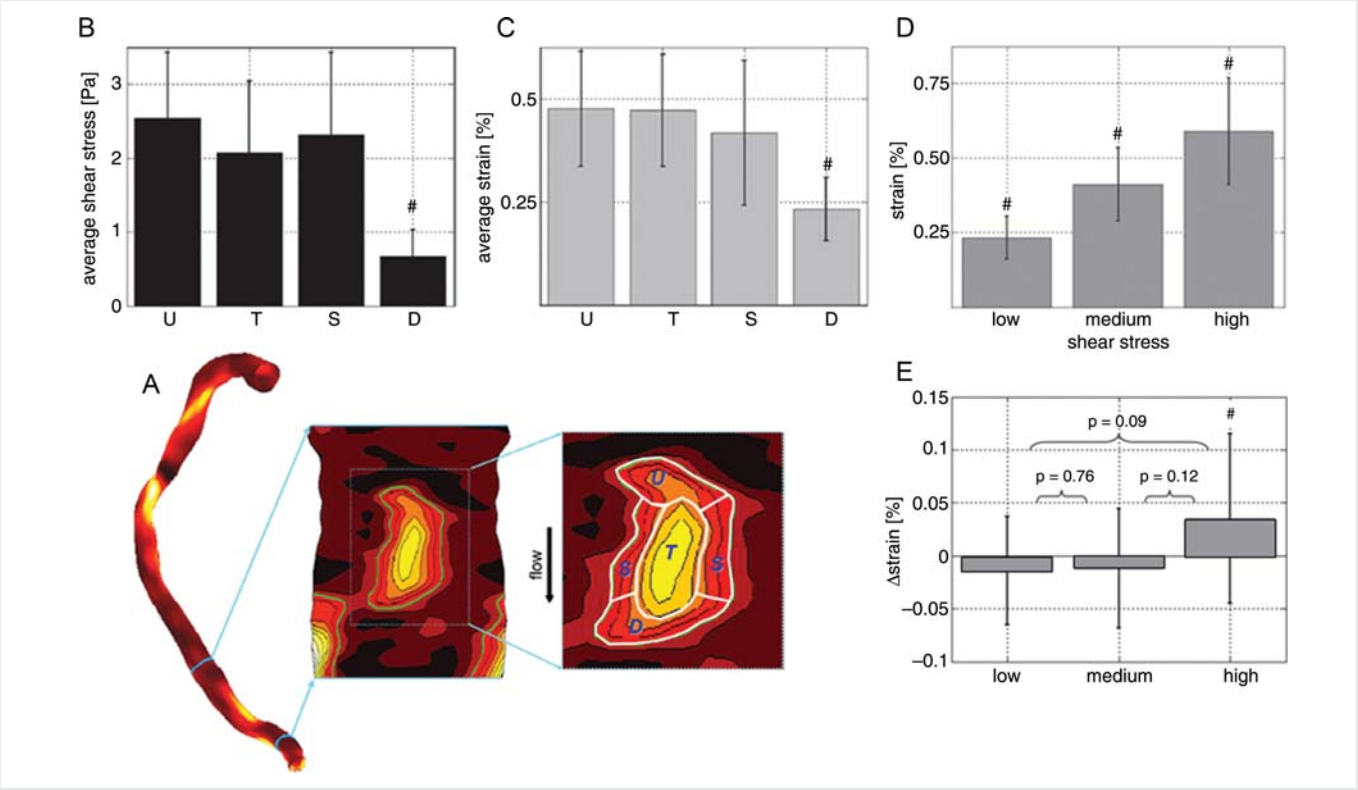

Figure 6 *(A)* The results of the three-dimensional reconstruction of a right coronary artery with intravascular ultrasound-derived wall thickness data colour-coded. A wall-thickness map was used to identify plaques and divide those plaques into regions, as follows: the upstream (U), most stenotic throat region (T), shoulder (S), and downstream region (D). Shear stress and strain were averaged in those regions. (*B* and *C*) ESS and strain are significantly lower in the downstream region. After pooling all the regions, the regions with the highest shear stress levels showed the highest strain (*D*), indicating that those were the weakest plaque regions.[68] A subset of the patients was imaged at six-month follow-up, showing that plaque regions exposed to the highest shear stress levels increased in strain, indicating that these regions became weaker over time (*E*), adapted from Gijsen *et al.*[67,68]

fibrofatty tissues in stenotic plaques, shifting these plaques to a rupture-prone phenotype.[81]

Several mechanisms responsible for the high ESS-induced fibrous cap destabilization have been proposed, but are mostly based on *in vitro* experiments, which applied fairly heterogeneous ESS patterns in direction and magnitude that did not always resemble the real human blood flow conditions.[78] The mechanisms described below therefore need to be confirmed *in vivo* with specimens obtained from autopsy or animal experiments. High ESS-induced nitric oxide may increase expression of MMPs by macrophages.[82] Also, plasmin, which is produced by the endothelium in response to high ESS,[83] is a strong activator of proteolytic MMPs (i.e. MMP-1, −3, −9, −10, and −13).[84] Increased production of reactive oxygen species in the setting of high ESS further stimulates the increased expression and activity of MMPs.[85–87] In addition, high ESS increases endothelial cell production of transforming growth factor-β and nitric oxide, which further suppress smooth muscle cell proliferation and induce apoptosis of smooth muscle cells.[68,88,89] These changes lead to reduced extracellular matrix production and excessive matrix degradation in the fibrous cap, thereby promoting cap thinning and plaque rupture. Following acute plaque disruption at the most stenotic site, the local high ESS environment promotes plaque thrombogenicity,[34,90,91] which may contribute to abrupt thrombus formation and, therefore, the clinical manifestation of an acute coronary syndrome. Histopathology studies have shown that erosion of stenotic plaques is considered to be responsible for 20–40% of acute coronary syndromes.[55]

7. Clinical importance of *in vivo* assessment of local ESS

As plaque rupture accounts for the great majority of acute coronary syndromes, understanding of the mechanisms responsible for the formation of high-risk plaques is likely to have considerable clinical impact.[32,78] The studies described in the previous subsections highlight the influence of ESS at different stages of atherosclerotic plaque growth and thus the importance of assessing not only plaque morphology characteristics, but also ESS characteristics for optimal risk stratification. Early identification of local ESS patterns, local plaque morphology, and local remodelling responses will probably enable identification of the early stages of plaques that will evolve into a high-risk, rupture-prone lesion.[92] Early identification of these lesions may provide the framework and justification for pre-emptive strategies to interrupt the natural history of these high-risk plaques.

To date, the methodologies to characterize local ESS distribution have been used for research purposes only, because no tools are available to provide ESS profiling in combination with plaque

morphology in a routine manner. The time needed for ESS profiling depends on the time needed to obtain the 3D reconstruction, to segment the coronary artery wall components, and to perform the computational fluid dynamics. Attempts are underway to speed up the patient-specific 3D reconstruction technique by improving the 3D reconstruction techniques[93–95] or using biplane angiography solely for coronary 3D reconstruction.[96–99] Non-invasive imaging modalities, such as computed tomography or magnetic resonance imaging, may also be invaluable tools for obtaining the 3D geometry of the lumen of coronary arteries, and allow application of computational fluid dynamics to these geometries to characterize local ESS and subsequent vascular wall behaviour.[100–102]

8. Conclusions

Endothelial shear stress influences the vessel dimensions and wall composition in different ways during the progression of atherosclerotic plaque development. In the presence of risk factors, low ESS promotes the formation of early atherosclerotic lesions, which evolve through several stages of progression. At these early stages of atherosclerosis, physiological and high ESS are atheroprotective. Some early atherosclerotic plaques may evolve either to non-stenotic high-risk rupture-prone plaques, which develop in areas characterized by persistently low ESS and excessive expansive remodelling, or to stenotic high-risk plaques. The formation of obstructive high-risk plaques may be related to the following factors: (i) subclinical rupture of a thin fibrous cap, leading to a fibro-proliferative and constrictive healing process; (ii) intraplaque haemorrhage; and (iii) excessive plaque growth that exceeds the remodelling capacity of the arterial wall. Intriguingly, the development of obstructive high-risk plaques alters the initially low local haemodynamic environment by creating high ESS conditions in the neck of the plaque and low ESS in downstream plaque regions and potentially in the upstream shoulder, suggesting the dynamic interplay between local ESS, plaque development, and vascular remodelling.

The sustained low ESS environment is a key mediator of the destabilization of non-obstructive high-risk, rupture-prone plaque by promoting excessive inflammation and matrix degradation, thereby leading to plaque fragility and rupture. In contrast, obstructive high-risk plaques can be destabilized at the most stenotic site under the influence of high ESS conditions, triggering molecular pathways that weaken the plaque, or at the upstream shoulder and downstream parts exposed to low ESS environments.

Serial vascular imaging studies of local plaque morphology and local remodelling patterns, in combination with ESS profiling, will be invaluable to understand the pathophysiological mechanisms during the natural history of individual coronary plaques. Risk stratification of individual coronary lesions may enable optimal selection of appropriate treatment strategies for patients with high-risk coronary artery disease. Long-term natural history studies in humans will be essential to clarify the natural history of coronary atherosclerosis in the current era of cholesterol-lowering, anti-inflammatory, and anti-platelet therapies. Such a study (the PREDICTION trial) is now underway and is anticipated to shed light into the role of ESS in the natural history of atherosclerosis.[103]

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