The role of low endothelial shear stress in the conversion of atherosclerotic lesions from stable to unstable plaque

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Current Opinion in Cardiology 2009, 24:580–590

Purpose of review

Local hemodynamic factors are major determinants of the natural history of individual atherosclerotic plaque progression in coronary arteries. The purpose of this review is to summarize the role of low endothelial shear stress (ESS) in the transition of early, stable plaques to high-risk atherosclerotic lesions.

Recent findings

Low ESS regulates multiple pathways within the atherosclerotic lesion, resulting in intense vascular inflammation, progressive lipid accumulation, and formation and expansion of a necrotic core. Upregulation of matrix-degrading proteases promotes thinning of the fibrous cap, severe internal elastic lamina fragmentation, and extracellular matrix remodeling. In the setting of plaque-induced changes of the local ESS, coronary regions persistently exposed to very low ESS develop excessive expansive remodeling, which further exacerbates the proinflammatory low ESS stimulus. Recent studies suggest that the effect of recognized cardioprotective medications may be mediated by attenuation of the proinflammatory effect of the low ESS environment in which a plaque develops.

Summary

Low ESS determines the severity of vascular inflammation, the status of the extracellular matrix, and the nature of wall remodeling, all of which synergistically promote the transition of stable lesions to thin cap fibroatheromata that may rupture with subsequent formation of an occlusive thrombus and result in an acute coronary syndrome.

Keywords

coronary atherosclerosis, extracellular matrix-degrading enzymes, inflammation, remodeling, shear stress, unstable plaque

Curr Opin Cardiol 24:580–590

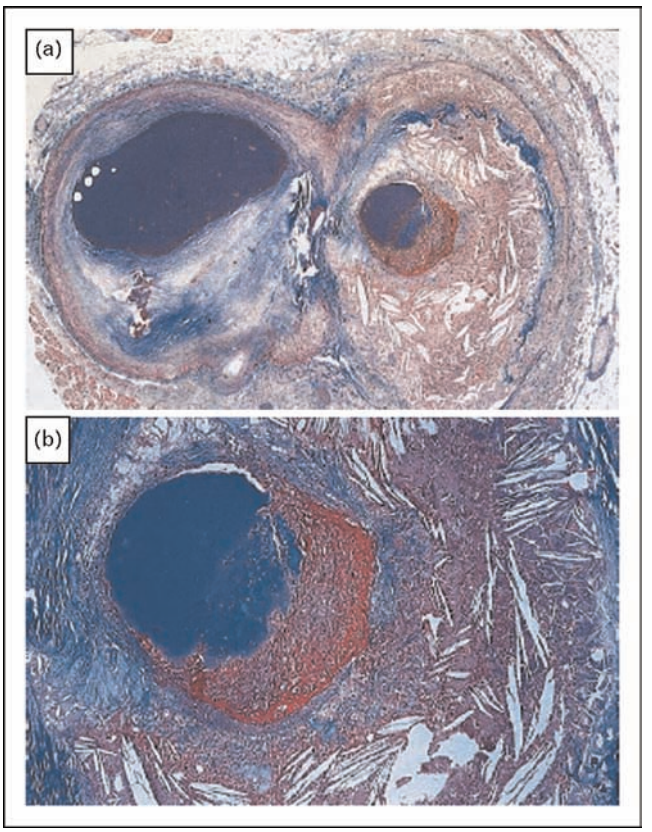
0268-4705

Introduction

Atherosclerosis is a systemic disease with heterogeneous manifestations. Lesions with various morphologies typically coexist in the coronary arteries of affected individuals (Fig. 1) [1]. Early lesions may remain quiescent for long periods, evolve toward flow-limiting, fibrocalcific plaques that become clinically evident as stable angina or develop a more inflamed phenotype. Only few among the many inflamed plaques develop a particularly unstable phenotype that renders them prone to rupture and consequently trigger an acute coronary event [2]. Fibrocalcific stable plaques may also evolve from subclinical plaque rupture and subsequent healing and fibrosis [3]. Increasing interest has focused on the mechanisms by which a subpopulation of early lesions transition to vulnerable, rupture-prone plaques. Early in-vivo identification of plaques destined to become vulnerable would be of enormous clinical value, as it would provide the rationale for intensive systemic pharmacological treatment and possibly selective, prophylactic local interventions to avert future coronary events.

Despite the exposure of the entire coronary artery system to identical systemic risk factors, the distribution of atherosclerotic plaques [4], and particularly of high-risk plaques [5•,6•], is highly focal. Local hemodynamic factors related to disturbed flow patterns are responsible for the nonrandom susceptibility to atherosclerosis. Local flow properties exhibit remarkable heterogeneity over short distances, even in adjacent arterial regions, corresponding to the heterogeneity in the spatial distribution of atherosclerotic plaque [7,8]. Endothelial shear stress (ESS) is the tangential force per unit area exerted on the endothelial surface of the arterial wall by flowing blood. Local low ESS, in particular, determines proatherogenic endothelial cell morphologic and functional characteristics that induce local plaque formation [9]. Spatial

Figure 1 Atherosclerotic plaque heterogeneity within a human coronary artery



(a). Cross section of a human coronary artery just distal to a bifurcation. The atherosclerotic plaque to the left (circumflex branch) is fibrotic and partly calcified, whereas the plaque to the right (marginal branch) is lipid-rich with a nonoccluding thrombus superimposed. (b) Higher magnification of the plaque–thrombus interface reveals that the fibrous cap over the lipid-rich core is extremely thin, inflamed, and ruptured with a real defect in the cap. Trichrome stain, staining collagen blue and thrombus red. Reproduced with permission from [1].

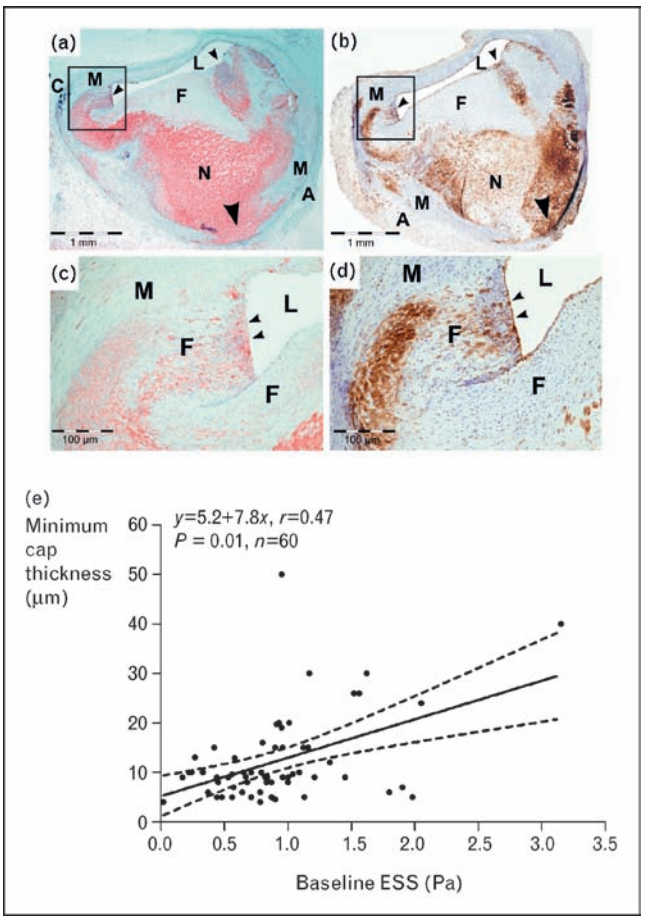
gradients of ESS in geometrically irregular regions, as well as temporal shear stress gradients, have also been implicated in atherogenesis. Arterial regions of naturally occurring low ESS, such as branch points, bifurcations, and inner surfaces of curvatures, are the regions primarily involved in atherogenesis and plaque progression [7,10–12]. Accumulating evidence now suggests that low ESS is a critical determinant not only of plaque formation and growth, but also of the transition of a developing plaque to a rupture-prone phenotype [13••].

The purpose of this review is to summarize the mechanisms linking low ESS with the transition of developing plaques to unstable, rupture-prone atheromata.

Morphologic features of unstable plaques

Plaque rupture with superimposed thrombosis is the predominant cause of acute coronary syndromes (ACSs) and sudden coronary death and may contribute to the progression of stable, fibrocalcific plaque. The thin-cap fibroatheroma (TCFA) is the typical precursor lesion of rupture-mediated thrombosis, accounting for about two-thirds of ACS. The remaining coronary events are attributed to plaque erosion or calcified nodules [14]. TCFAs are characterized by a thin fibrous cap, measuring less than 65 μm, overlying a large necrotic core. The fibrous cap is intensely inflamed particularly at its shoulders (Fig. 2a–d). TCFAs contain less collagen and fewer vascular smooth muscle cells (VSMCs) and are more often located within expansively remodeled

Figure 2 Role of low endothelial shear stress in fibrous cap attenuation and the formation of thin cap fibroatheromata



Digital photomicrographs of oil red O-stained (a and c) and CD45-stained (b and d) fibroatheroma from a porcine coronary artery, with a thin fibrous cap inflamed at its shoulders (small black arrowheads). (c and d) Magnifications of the black box in a and b, respectively. The necrotic core is extended into the media through the disrupted IEL (a and b; large black arrowheads). (e) Association of minimum cap thickness with the magnitude of baseline ESS; dashed lines represent 95% CI for the regression line. The arteries were snap frozen and not pressure-fixed immediately after harvesting; the actual lumen dimensions can therefore not be accurately assessed because of tissue shrinkage at −80°C. A, adventitia; C, calcification; ESS, endothelial shear stress; F, fibrous cap; IEL, internal elastic lamina; L, lumen; M, media; N, necrotic core. Reproduced with permission from [13••].

arterial segments, compared with lesions with a stable phenotype [14].

Endothelial shear stress as a determinant of plaque formation and localization

Extensive in-vitro work has elucidated the molecular basis of the flow-dependent, region-specific susceptibility to atherosclerosis. Shear stress is sensed by endothelial cell mechanoreceptors [15]. A complex system of mechanotransduction activates signaling pathways that modulate gene expression profiles [16] and ultimately evokes distinct endothelial cell phenotypes [17]. The transcription factor Krupell-like factor-2 (KLF-2) orchestrates multiple shear-responsive atheroprotective genes under favorable flow conditions [18,19]. Atheroprotective flow also upregulates NF-E2-related factor-2 (Nrf2)-dependent antioxidant genes [20]. The mitogen-activated protein kinase phosphatase (MKP)-1, a negative regulator of p38 and c-Jun NH(2)-terminal kinase (JNK), is a critical mediator of the anti-inflammatory effects of physiologic values of ESS [21•]. In contrast, low ESS mutes the effect of KLF-2 and induces the transcriptional regulator nuclear factor-kappa B (NF-κB), which promotes proinflammatory gene and protein expression [22,23••]. Overall, the low ESS-induced endothelial cell changes convert biomechanical forces to biochemical responses, enhancing the formation of an early atherosclerotic lesion.

Role of low endothelial shear stress in the destabilization of progressing plaques

The extent of the maladaptive local inflammatory response to the subendothelial accumulation of apolipoprotein B-containing lipoproteins critically influences the subsequent differentiation of an early lesion. In the setting of local low ESS, the predominance of inflammation, cell death, and extracellular matrix (ECM) degradation over ECM synthesis and fibroproliferation largely determines the transition of a subpopulation of early lesions to rupture-prone plaques.

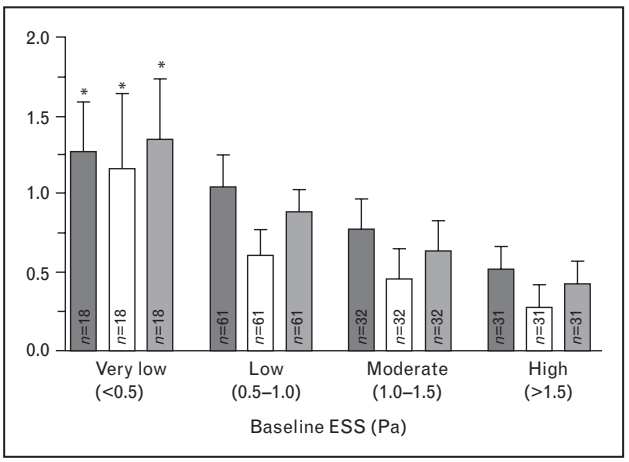
Upregulation of local vascular inflammation

Low ESS exerts a key role in the ongoing recruitment of circulating inflammatory cells into the vessel wall, where they differentiate to potent sources of proinflammatory mediators [24]. NF-κb induces the expression of adhesion molecules [intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, E-selectin], chemoattractant chemokines, such as monocyte chemoattractant protein (MCP)-1, and proinflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1, and interferon (IFN)-γ] [7,22,25]. Adhesion molecules facilitate the adhesion of circulating leukocytes to the endothelial surface, whereas MCP-1 promotes their transmigration into the intima. In-vivo experimental studies have confirmed that low ESS indeed fosters an inflamed plaque phenotype, consistent with the abundance of in-vitro evidence. In a mouse carotid artery model of induced flow pattern variations, regions exposed to low ESS developed vulnerable lesions, with increased expression of VCAM-1, ICAM-1, IL-6 [26], and chemokines, predominantly fraktalkine [27]. Our group recently demonstrated that the extent of inflammatory cell infiltration is related in a dose-dependent manner to the magnitude of the preceding low ESS, utilizing a well established diabetic hyperlipidemic swine model of atherosclerosis (Fig. 3) [13••]. This natural history study clearly indicated that highly inflamed TCFAs exclusively develop in sites of preceding low ESS.

Subendothelial lipid retention and expansion of the necrotic core

Necrotic core expansion is a key factor of lesion destabilization [14]. Plaque progression rate is determined by the dose-responsive, synergistic effect of systemic hyperlipidemia and local low ESS [28••]. Low ESS colocalizes with elevated luminal surface low-density lipoprotein (LDL) cholesterol concentration, thereby locally exposing the endothelium to maximal lipoprotein levels [29•]. Increased permeability of endothelial cells to lipoproteins [30], widening of intercellular junctions [7,31], and the upregulation of LDL receptors [32] potentiate intracellular lipid influx in fibroatheromata developing in a low ESS milieu. Furthermore, low ESS-induced proin-

Figure 3 Association of the magnitude of low endothelial shear stress with the severity of high-risk plaque characteristics



Association of ESS magnitude at baseline (week 23) with the severity of high-risk plaque characteristics at follow-up (week 30), in a serial study utilizing a diabetic, hyperlipidemic model of atherosclerosis. ESS, endothelial shear stress; ■, intima-to-media ratio; □, lipid content; ▒, inflammation. $^{*}P < 0.05$ for each characteristic in very low ESS vs. the respective characteristic in moderate or high ESS; $P = 0.13$ for inflammation in very low ESS vs. low ESS. Reproduced with permission from [13••].

flammatory cytokines, oxidative stress, and activation of the Fas ligand promote macrophage apoptosis. When inflammation prevails in the intima, the apoptotic process is not properly coupled with phagocytic clearance (efferocytosis); as a result, accumulating necrotic debris contributes to the expansion of the necrotic core [33••]. Intimal neovascularization is also critical in promoting plaque progression and instability [34••]. Neovessels may serve as conduits for the extravasation of inflammatory cells and erythrocyte membrane-derived cholesterol and proinflammatory interleukins into the core [35•,36•]. Low ESS may contribute to plaque neovascularization by promoting intimal thickening with resulting local hypoxia, a potent angiogenic stimulus [37], and by upregulating the expression of the angiogenic factor vascular endothelial growth factor (VEGF) [26].

Extracellular matrix degradation

The status of the ECM is regulated by the balance between macromolecule synthesis and enzymatic breakdown. Collagenases degrade the major plaque-stabilizing structural protein, that is, interstitial collagen. Elastases break down elastin fibers, facilitating the migration of macrophages and VSMCs and promoting arterial remodeling [38]. Recent work has shown that the activation of JNK, a regulator of flow-responsive inflammatory gene expression, is modulated by ECM remodeling [39•], suggesting a positive feedback pathway by which inflammation-driven matrix remodeling further augments the endothelium-dependent vascular inflammation. In-vitro studies have associated low ESS with the upregulation of matrix metalloproteinases (MMPs) [40] and cathepsins [41]. Mohler *et al.* [42••] determined time-dependent patterns in the expression of genes implicated in porcine coronary plaque progression and found that MMP-9 was remarkably upregulated at advanced stages of plaque evolution. Our group further showed a lesion-specific, ESS-related variability in the expression of ECM catabolizing enzymes. Exposure to very low ESS induced the activity of MMP-2, 9, 12 and cathepsins K, L, S relative to their endogenous inhibitors, ultimately resulting in the formation of TCFAs [43••]. Minimum cap thickness in these TCFAs was related to the magnitude of baseline ESS (Fig. 2e). These in-vivo investigations clearly demonstrated that low ESS-induced ECM degradation promotes matrix remodeling and thinning of the fibrous cap, both critical steps in rendering a plaque rupture-prone.

Heparan sulfate proteoglycans

Recent evidence suggests a role of low ESS in the enzymatic regulation of matrix glycosaminoglycans. Proteoglycans can alter subendothelial lipid deposition and retention. Although proteoglycans with predominantly chondroitin and dermatan sulfate chains display increased affinity to atherogenic lipoproteins [44], heparan sulfate proteoglycans are considered antiatherogenic due to their potential to inhibit LDL binding [45] and monocyte adhesion [46]. Heparanase-mediated removal of heparan sulfate chains from ECM proteins facilitates proteolytic digestion by MMPs [47]. We recently found that heparanase was upregulated in coronary segments that were exposed to low ESS and evolved to TCFAs; notably, heparanase colocalized with inflammatory cells, lipid deposition, and MMP expression (Fig. 4) [48••]. Overall, heparanase may be a powerful regulator of plaque progression and may act in concert with MMPs in the degradation of the ECM under low ESS conditions.

Smooth muscle cell migration and apoptosis

Inflammatory mediators including IFN-γ, FasL, TNF-α, and reactive oxygen species can activate caspases and elicit mitochondrial dysfunction and apoptosis of VSMCs [49], resulting in a likely decrease in the number of smooth muscle cells (SMCs) in TCFAs [14]. Low ESS promotes VSMC migration from the media to the intima through upregulation of the SMC mitogens platelet-derived growth factor (PDGF)-A and PDGF-B [50], endothelin-1 [51], and VEGF [26]. However, low ESS also induces VSMC apoptosis, mediated by the downregulation of protein-Rho-GDP dissociation inhibitor alpha (Rho-GDIa), a modulator of Rho family signal transduction [52••]. The apoptotic death of this major cellular source for the renewal of the fibrous cap's collagen may represent a further mechanism of plaque destabilization. Furthermore, VSMCs exert an antiapoptotic effect on macrophages and monocytes [53], such that VSMC apoptosis may indirectly facilitate apoptosis of inflammatory cells and thus cause an increase in the size of the necrotic core.

Effect of low endothelial shear stress on arterial remodeling

The arterial wall dynamically responds to plaque formation. The nature of the wall's remodeling, regulated by systemic, genetic, and local hemodynamic factors, can range from constrictive to compensatory expansive to excessive expansive [54]. Expansively remodeled coronary plaques are associated with increased inflammation [55] and unstable clinical presentation [56]. Interestingly, Okura *et al.* [57••] reported that the remodeling pattern of ACS culprit lesions might be a better predictor of long-term (3-year) clinical outcome than the presence of plaque rupture. A dynamic interplay between the local ESS and the vascular remodeling is a critical determinant of the natural history of an individual lesion [2]. We recently showed that regions culminating in high-risk excessive expansive remodeling had been exposed to very low ESS throughout their natural history, utilizing serial, in-vivo vascular profiling of porcine coronary

Figure 4 Colocalization of heparanase with lipids and inflammatory cells in a coronary region of low endothelial shear stress

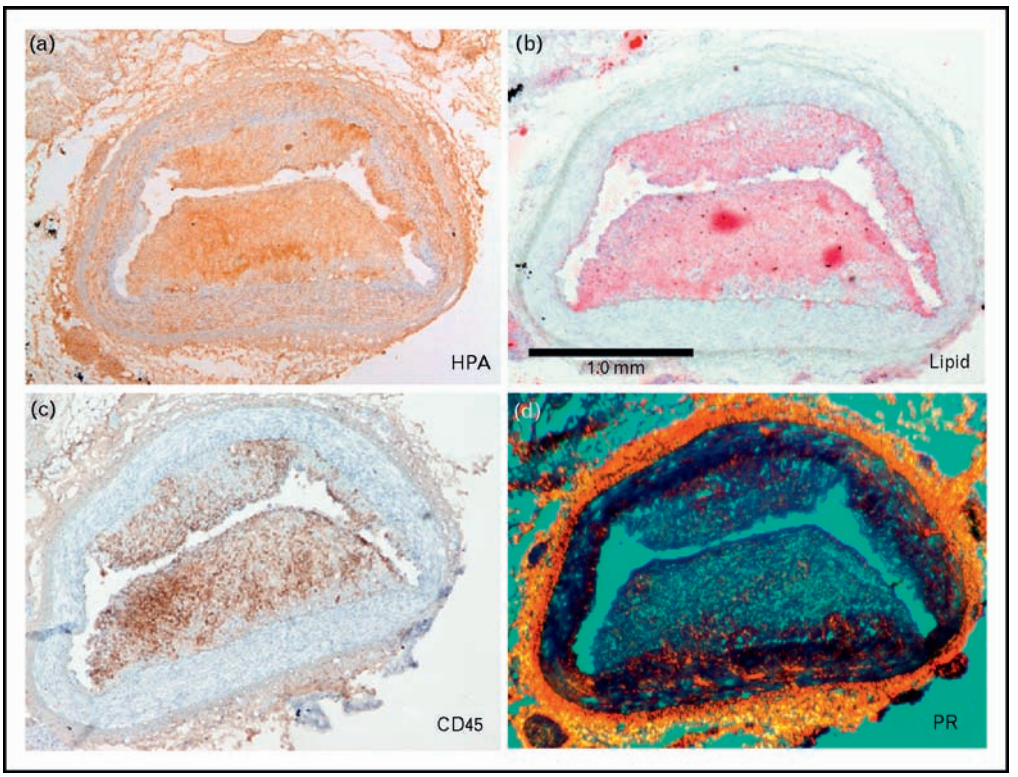


Figure from a porcine coronary artery section, showing a thin cap fibroatheroma that developed in a coronary region of preceding low ESS. Note that immunostaining for heparanase (HPA, a) colocalizes with staining oil-red-O (lipids, b), and immunostaining with CD45 (inflammatory cells, c). Staining with picrosirius red (PR, d) indicates collagen and reveals the thin fibrous cap overlying the necrotic core.

arteries at five consecutive time points [58••] (Fig. 5). In the setting of plaque-induced changes of the local geometry and thereby of local flow waveforms, only a small subpopulation of developing atheromata is located in a persistently low ESS milieu, related to the magnitude of low ESS and, consequently, the magnitude of intense inflammation. The elaboration of matrix-degrading proteases, with subsequent elastolysis in the internal elastic laminae and the media beneath the plaque, is critical in promoting aneurysm-like expansion of the highly inflamed wall and turning the ostensibly protective function of compensatory remodeling into a detrimental local environment [13••]. Local excessive expansive remodeling contributes to further lowering of the low ESS, thus reinforcing the vicious cycle of the intense proinflammatory stimulus and ultimately promoting the evolution of an early atheroma to a TCFA.

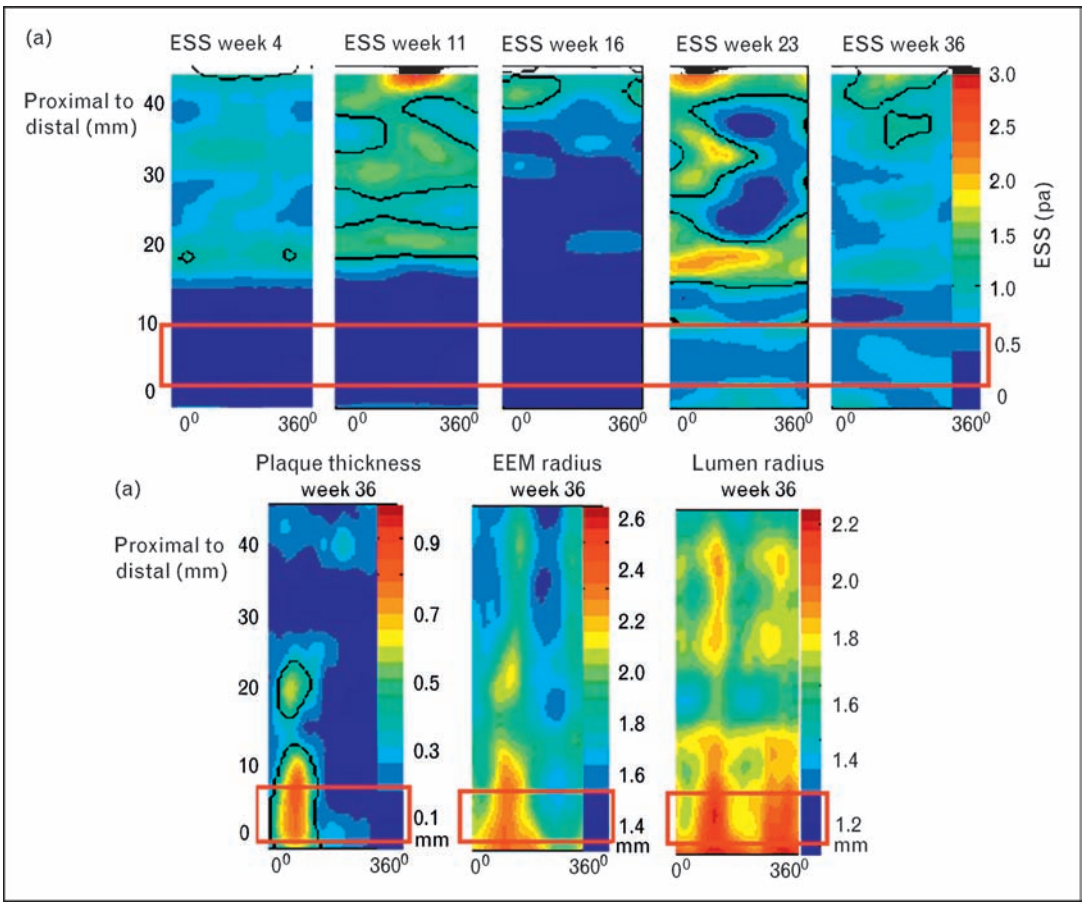
Thrombogenicity of the necrotic core

Low ESS augments the thrombogenicity of the necrotic core and thus the extent of thrombosis in the event of acute plaque disruption. Low ESS-induced macrophage accumulation and SMC apoptosis are sources of tissue factor, a potent procoagulant factor [59]. Although atheroprotective flow-activated KLF-2 induces thrombomodulin and endothelial nitric oxide synthase expression and reduces plasminogen activator inhibitor-1 and tissue factor expression, muting of KLF-2 shifts the balance toward a prothrombotic state [60].

Plaque-induced changes of local endothelial shear stress

The magnitude, directionality, and spatial distribution of local shear stress all change in response to the changes of local arterial geometry induced by a growing plaque. Thus, a developing plaque itself can modify the local ESS milieu in specific parts of and adjacent to the lesion. Lumen narrowing because of a stenotic plaque results in increased flow velocity at the throat of the plaque, low ESS in the upstream region, and disturbed flow in the form of directionally oscillatory ESS in the downstream shoulder of the plaque [61]. The composition of an individual plaque displays considerable spatial heterogeneity. The downstream region contains significantly more smooth muscle cells, whereas the upstream portion is more inflamed, containing a high number of macrophages [62] and expressing higher gelatinolytic activity [63]. Cheng *et al.* [26] showed in a mouse model that

Figure 5 Effect of persistently low endothelial shear stress in the formation of expansively remodeled atherosclerotic plaque

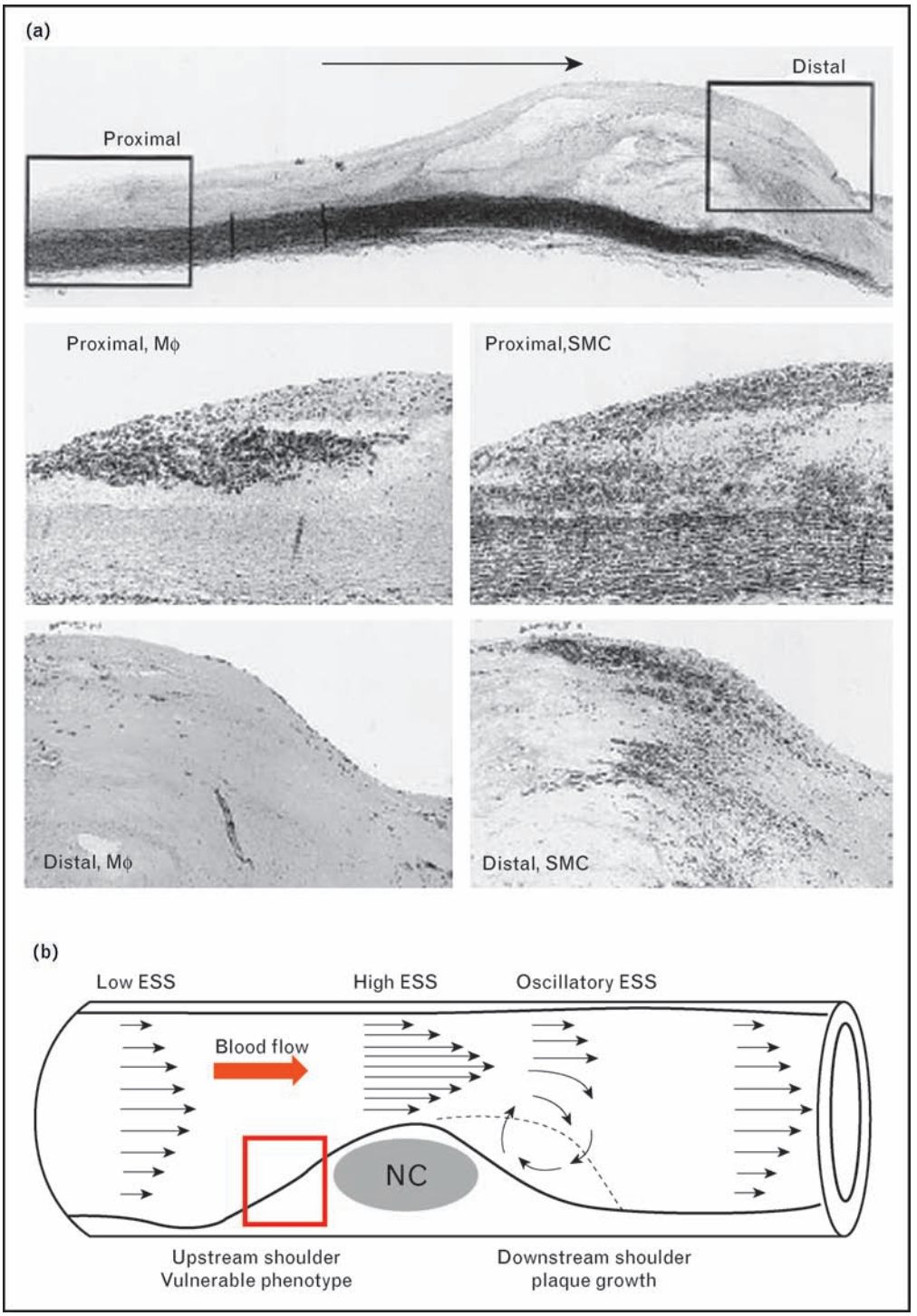


Representative example of a serially profiled porcine coronary artery. (a) Two-dimensional maps show the ESS distribution along the artery length at five consecutive time points of in-vivo vascular profiling at weeks 4, 11, 16, 23, and 36 after the induction of diabetes and hyperlipidemia. In each map, the horizontal axis represents the artery circumference (°) and the vertical axis the artery length (mm). The red rectangle includes a proximal segment which is peristently exposed to low ESS, throughout its natural history. (b) Two-dimensional maps showing the plaque thickness, external elastic lamina radius, and lumen radius distribution along the artery length at final week 36; in each map, the horizontal axis denotes the artery circumference (°) and the vertical axis the artery length (mm). Red rectangles include the same proximal segment, as in subpart a. This arterial segment displays maximal plaque thickness and also significant expansion of the vessel wall, as indicated by the orange–red color in the corresponding maps. Note that even the lumen exhibits maximal expansion, despite the formation of significant plaque, indicating excessive expansive remodeling, that is, an exaggerated, aneurysm-like form of arterial remodeling that not only preserves normal lumen dimensions, but also actually causes lumen increase under the effect of sufficiently low ESS. ESS, endothelial shear stress.

regions exposed to low ESS upstream of a perivascular shear stress modifier exhibited the most profound development of highly inflamed, vulnerable carotid plaques, whereas stable lesions formed in the downstream vortices of lowered/oscillatory ESS. Overall, the plaque-induced changes of local ESS seem to exert a differential effect in distinct portions of a stenotic lesion and critically affect the longitudinal distribution of plaque morphology; a self-perpetuating local environment conducive to further plaque growth is established downstream of the lesion, whereas a vulnerable, rupture-prone phenotype develops in the low-ESS upstream shoulder (Fig. 6).

Plaque rupture represents the most devastating complication of atherosclerotic disease. Frank plaque rupture may be related to low ESS-mediated inflammation and matrix degradation culminating in severe plaque fragility and severe proclivity to rupture from simple daily hemodynamic stresses [64]. It has also been postulated that localized high shear stress may actually trigger fibrous cap rupture [65–67]. Because the values of wall shear stress are markedly lower than the values of blood pressure-induced tensile stress in the plaque cap, it is unlikely that high wall shear stress contributes significantly to the direct mechanical failure of the cap. However, high ESS may induce pathobiologic responses within the plaque that also exacerbate plaque fragility, as suggested by the reported association of regions with high ESS with high strain, a presumed surrogate marker of vulnerable plaque composition [68,69]. Further, high ESS may be implicated in local endothelial erosion, increased platelet adhesion, and induction of acute coronary thrombosis [7].

Figure 6 Association between longitudinal atherosclerotic plaque morphology and spatial distribution of local endothelial shear stress



(a) Top: histologic appearance of a human carotid artery plaque stained with Elastic–van Gieson. Horizontal arrow indicates the direction of blood flow. Box on the left indicates proximal (upstream) shoulder of plaque; box on the right represents the distal (downstream) shoulder. Middle: boxed area of proximal shoulder stained with anti-CD68 (macrophages; MΦ) and anti-a-actin (smooth muscle cell, SMC). Bottom: boxed area of distal shoulder stained with anti-CD68 (macrophages; MΦ) and anti-a-actin (smooth muscle cell, SMC). Note the abundance of macrophages in the upstream shoulder and of smooth muscle cells in the downstream shoulder, respectively. Modified from [62]. (b) Differential spatial distribution of ESS along a lumen-protruding plaque. Arrows represent velocity vectors. The upstream shoulder is exposed to low ESS. Local ESS is elevated in the throat, and low/oscillatory in the downstream shoulder of the developing plaque. These local ESS conditions promote the formation of a vulnerable, rupture-prone plaque phenotype, indicated by the red rectangle, upstream of the lesion, and additional growth, indicated by the dashed line, downstream of the plaque. ESS, endothelial shear stress; NC, necrotic core.

Effect of antiatherosclerotic medications on the proinflammatory effect of low endothelial shear stress

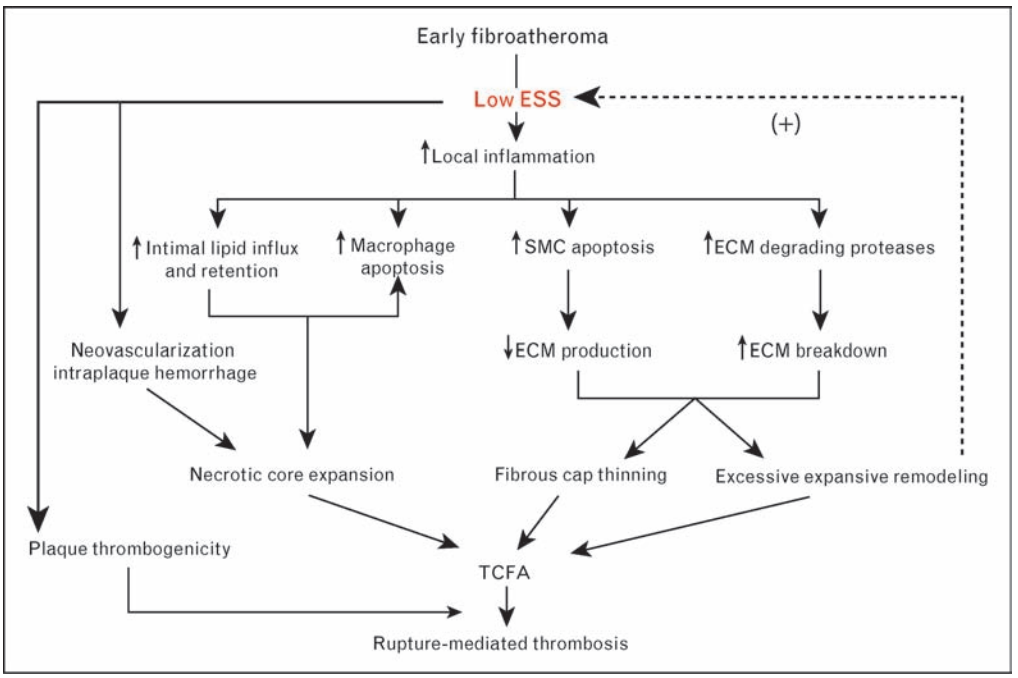
The plaque-stabilizing effect of recognized antiatherosclerotic drugs may, at least in part, be mediated by the attenuation of the proinflammatory low-ESS environment of high-risk plaques, indirectly emphasizing the critical role of low ESS in plaque destabilization. We have shown that lifetime administration of valsartan in a diabetic, hyperlipidemic swine model, alone or in combination with simvastatin, attenuated the proinflammatory effect of local low ESS. These medications reduced the expression of MMP-9, which is actively involved in the ECM degradation, as well as the MMP/tissue inhibitor of metalloproteinases (TIMP) ratio, thereby shifting the ECM balance toward less degradation and limiting the severity of expansive remodeling. The beneficial effect of valsartan and simvastatin in reducing the severity of inflammation and stabilizing high-risk plaque characteristics in regions of low ESS was independent of a blood pressure-lowering and lipid-lowering effect [70••]. Statins, in particular, are potent promoters of the atheroprotective regulator KLF-2 and up-regulate several of its downstream transcriptional targets [71]. Statins may thereby exert their well described nonlipid-lowering vasculoprotective effects by counterbalancing the proatherogenic effect of low ESS on the KLF-2-regulated genes cassette.

Clinical perspectives of the in-vivo assessment of endothelial shear stress

As discussed above, low ESS is a major determinant of vascular disorder and clearly plays a critical role in rendering a subpopulation of developing atheromata prone to rupture. A sophisticated computational model by Ohayon *et al.* [72••] recently showed that the proclivity for acute plaque disruption is not determined by fibrous cap thickness alone, but rather by a combination of cap thinning, necrotic core thickness, and expansive arterial remodeling. These high-risk morphologic features are all exacerbated in plaques that progress in a low-ESS setting (Fig. 7).

Despite major advances in prevention and treatment, the thrombotic complications of atherosclerotic disease remain a major cause of mortality. Residual cardiovascular morbidity is observed despite the aggressive pharmacological treatment in high-risk patients [73] and despite the addition of coronary interventions to optimal medical therapy [74]. Major cardiac events occur in nontarget lesions following successful interventions [75], clearly indicating the inadequacy of currently applied methodologies to predict and adequately target plaques that eventually culminate in acute coronary events. Coronary interventions are currently employed either to treat ACS culprit lesions or to restore flow in

Figure 7 Role of low endothelial shear stress in the formation of rupture-prone plaque



Schematic presentation of the mechanisms whereby low local ESS promotes the conversion of an early fibroatheroma to a thin cap fibroatheroma, major precursor lesion of rupture-mediated thrombosis. ECM, extracellular matrix; ESS, endothelial shear stress; SMC, smooth muscle cell; TCFA, thin-cap fibroatheroma.

obstructive, flow-limiting plaques, thereby ignoring a large proportion of minimally stenotic TCFAs, potential precursors of ACS. Although several imaging techniques have been proposed to assess morphologic or functional characteristics of rupture-prone plaques before they rupture, no widely accepted diagnostic method to prospectively identify such high-risk plaques is available at present.

Knowledge of local flow patterns and identification of arterial regions with naturally occurring low ESS cannot currently prompt interventions in native anatomy to prevent atherosclerosis or atherosclerotic sequelae. However, in-vivo identification of coronary regions of low ESS and expansive remodeling, utilizing catheterization-based [10] or noninvasive techniques of vascular profiling [76••], may be predictive of future high-risk plaque formation and can be used to risk-stratify individual lesions that have, or are likely to acquire, characteristics of vulnerability [77••]. The early characterization of a coronary region most likely to progress to a rupture-prone phenotype may enable primary prevention at the level of individual atherosclerotic plaque and thereby provide the rationale for focused systemic or local treatments to avert future coronary events. Established systemic approaches and novel therapeutic targets may be employed to impede or even reverse the progression towards vulnerable plaques and stabilize high-risk plaque characteristics. Furthermore, regional therapy of high-risk plaque in the form of highly selective, prophylactic coronary interventions may be justified to 'eradicate' plaques destined to become vulnerable. The association of drug-eluting stents [78••,79••], drug-coated balloon catheters [80••], and, more recently, bioabsorbable everolimus-eluting stents [81] with a lower risk of coronary in-stent restenosis or stent thrombosis may render preemptive stenting of high-risk plaques plausible. A large-scale clinical natural history study (the PREDICTION trial) is currently underway to investigate whether coronary segments with low ESS and expansive remodeling are the regions that result in rapid progression of atherosclerosis and eventually in plaque rupture. This study may validate the predictive value of vascular profiling for the accurate risk stratification of early coronary plaques and thereby potentially change the paradigm for management of patients with coronary artery disease.

Conclusion

Low ESS regulates multiple pathways that synergistically induce plaque destabilization. Low ESS upregulates local inflammation, promotes reduced synthesis and increased catabolism of ECM macromolecules, and elicits excessive expansive wall remodeling, a high-risk remodeling pattern that further exacerbates the adverse low-ESS stimulus. Early lesions persistently exposed to low ESS may thereby progress towards highly inflamed TCFAs. The in-vivo measurement of ESS may be used for the early identification of lesions that are likely to acquire a rupture-prone phenotype and trigger coronary thrombosis. Early identification of high-risk plaques before they become vulnerable may set the stage for focused systemic treatments or prophylactic local interventions to avert future coronary events.

Acknowledgements

This work was supported by grants from Boston Scientific, Inc., the Novartis Pharmaceuticals, Inc., the George D. Behrakis Research Fellowship, the Onassis Foundation, the Hellenic Harvard Foundation, the Hellenic Atherosclerosis Society, the AG Leventis Foundation, the Propondis Foundation, and the National Institutes of Health R01 GM 49039 (to E.R.E.).

The authors thank Prof. George D. Giannoglou for his encouragement and support.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 620).

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