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**STATE-OF-THE-ART PAPER**

# Role of Endothelial Shear Stress in the Natural History of Coronary Atherosclerosis and Vascular Remodeling

## Molecular, Cellular, and Vascular Behavior

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**Although the entire coronary tree is exposed to the atherogenic effect of the systemic risk factors, atherosclerotic lesions form at specific arterial regions, where low and oscillatory endothelial shear stress (ESS) occur. Low ESS modulates endothelial gene expression through complex mechanoreception and mechanotransduction processes, inducing an atherogenic endothelial phenotype and formation of an early atherosclerotic plaque. Each early plaque exhibits an individual natural history of progression, regression, or stabilization, which is dependent not only on the formation and progression of atherosclerosis but also on the vascular remodeling response. Although the pathophysiologic mechanisms involved in the remodeling of the atherosclerotic wall are incompletely understood, the dynamic interplay between local hemodynamic milieu, low ESS in particular, and the biology of the wall is likely to be important. In this review, we explore the molecular, cellular, and vascular processes supporting the role of low ESS in the natural history of coronary atherosclerosis and vascular remodeling and indicate likely mechanisms concerning the different natural history trajectories of individual coronary lesions. Atherosclerotic plaques associated with excessive expansive remodeling evolve to high-risk plaques, because low ESS conditions persist, thereby promoting continued local lipid accumulation, inflammation, oxidative stress, matrix breakdown, and eventually further plaque progression and excessive expansive remodeling. An enhanced understanding of the pathobiologic processes responsible for atherosclerosis and vascular remodeling might allow for early identification of a high-risk coronary plaque and thereby provide a rationale for innovative diagnostic and/or therapeutic strategies for the management of coronary patients and prevention of acute coronary syndromes. (J Am Coll Cardiol 2007;49:2379–93) © 2007 by the American College of Cardiology Foundation**

Atherosclerosis is a chronic, inflammatory, fibroproliferative disease primarily of large- and medium-sized conduit arteries (1,2). Although the entire vasculature is exposed to the atherogenic effects of the systemic risk factors (e.g., hyperlipidemia, cigarette smoking, hypertension, diabetes mellitus, chronic infections, and genetic predisposition), atherosclerotic lesions form at specific regions of the arterial tree, such as in the vicinity of branch points, the outer wall of bifurcations, and the inner wall of curvatures, where disturbed flow occurs (3). Local factors, such as hemodynamic forces, play a major role in the regional localization of atherosclerosis (4–7). These local hemodynamic forces include flow-generated endothelial shear stress (ESS) and blood pressure-derived tensile stress, with ESS playing the most fundamental role in atherosclerosis.

The first evidence implicating ESS in the localization of atherosclerosis was described over 40 years ago by Caro et al. (8). Later, sophisticated computational fluid dynamic simulations in autopsy-based models of coronary arteries (9), carotid bifurcations (10), and distal abdominal aortas (11) showed that areas with low ESS correlated to the localization of atherosclerosis found at autopsy. Further support of the atherogenic role of low ESS was also derived from in vivo experiments in animal models (12–14). In vivo investigations in humans, using a combination of intravascular ultrasound (IVUS) or magnetic resonance imaging and computational fluid

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**Abbreviations and Acronyms**

**EC** = endothelial cell
**ECM** = extracellular matrix
**eNOS** = endothelial nitric oxide synthase
**ESS** = endothelial shear stress
**IEL** = internal elastic lamina
**IL** = interleukin
**LDL** = low-density lipoprotein cholesterol
**MAPK** = mitogen-activated protein kinase
**MMP** = matrix metalloproteinase
**NF-κB** = nuclear factor-kappa B
**NO** = nitric oxide
**ROS** = reactive oxygen species
**SREBP** = sterol regulatory elements binding protein
**TCFA** = thin cap fibroatheroma
**TF** = transcription factor
**VSMC** = vascular smooth muscle cell

dynamics confirmed the mechanistic role of low ESS in the development and progression of atherosclerosis (15–17). More recent molecular and cellular studies have begun to clarify the detailed pathways by which low ESS leads to atherosclerosis as well as the development of thin cap fibroatheromas, presumed or suspected "vulnerable plaques," responsible for acute coronary syndromes (18–22).

In addition to the processes of atherosclerosis development and progression, the local remodeling characteristics of the arterial wall in response to plaque growth constitute crucial determinants of the natural history and clinical manifestations of an individual atherosclerotic lesion. Local factors undoubtedly play an important role in the nature of the remodeling response as well (5,15,22–25).

The purposes of this review are to explore the molecular, cellular, and vascular biologic processes supporting the role of low ESS in the natural history of coronary atherosclerosis and vascular remodeling and indicate likely mechanisms concerning the different natural history trajectories of individual coronary lesions. An enhanced understanding of the pathobiologic processes responsible for atherosclerosis and vascular remodeling might allow for early identification of a high-risk coronary plaque and thereby provide a rationale for innovative diagnostic and/or therapeutic strategies for the management of coronary patients and prevention of acute coronary syndromes.

## Definitions of ESS and Blood Flow Patterns

Endothelial shear stress is the tangential stress derived from the friction of the flowing blood on the endothelial surface of the arterial wall and is expressed in units of force / unit area ($N/m^2$ or Pascal [Pa] or $dyne/cm^2$; 1 $N/m^2$ = 1 Pa = 10 $dyne/cm^2$) (26,27) (Table 1). Endothelial shear stress is proportional to the product of the blood viscosity ($\mu$) and the spatial gradient of blood velocity at the wall (ESS = $\mu \times dv/dy$) (Fig. 1).

The nature of fluid flow through a tube is dependent on the velocity of flow and the presence of geometric irregularities or obstructions. Fluid flow might be either laminar or turbulent (26,28) (Fig. 2). Laminar flow refers to a

**Table 1 Terminology of Arterial Hemodynamics**

| Term | Definition |
|---|---|
| Endothelial shear stress (ESS) | The tangential force derived by the friction of the flowing blood on the endothelial surface. It is the product of the shear rate at the wall and the blood viscosity ($\mu$). |
| Shear rate | The spatial gradient of blood velocity, which describes how fast the blood velocity increases from areas at the arterial wall toward areas at the center of the lumen (i.e., dv/dy, where dv is change in flow velocity unit and dy is change in unit of radial distance from the wall). Physiologically, the shear rate decreases at the center of the lumen and gradually increases toward the wall. |
| Blood viscosity | A principal property of blood related to its internal friction that causes blood to resist flow. Hematocrit is the major determinant of blood viscosity. |
| Newtonian blood behavior | Constant blood viscosity independent of shear rate. In large-sized arteries (e.g., aorta) blood behaves largely in a Newtonian fashion. |
| Non-Newtonian blood behavior | Non-constant blood viscosity inversely related to shear rate. Blood has non-Newtonian properties, especially in veins, small-sized arteries, and in the microcirculation. |
| Laminar flow | Smooth, streamlined blood flow where viscous forces prevail against inertial forces. |
| Undisturbed laminar blood flow | Smooth streamlined flow characterized by concentric layers of blood moving in parallel along the course of the artery. The highest velocity is found at the centre of the lumen, whereas the lowest velocity occurs along the wall. Uniform laminar blood flow primarily occurs in relatively straight arterial segments. |
| Disturbed laminar blood flow | Disturbed laminar flow characterized by reversed flow (i.e., flow separation, recirculation, and reattachment to forward flow). Disturbed laminar blood flow occurs in arterial segments with geometric irregularities (e.g., curvatures, branches, bifurcations), or upstream and downstream of stenoses. |
| Turbulent blood flow | Flow in which the blood velocity at any given point varies continuously over time, even though the overall flow is steady. In turbulent flow the inertial forces are more significant than viscous forces. Turbulent blood flow rarely occurs but has been described in human aorta at peak systole, during heavy exercise in much of the central arterial system, distal to severe stenoses (>75%), and in aneurysms. |
| Reynolds number (Re) | The ratio of blood inertial forces to viscous forces. For a given geometry, whether the flow will be laminar or turbulent is determined by its Reynolds number. For low Re values blood flow is laminar, whereas for high Re values (typically, above 2,000) blood flow is turbulent. |

*Continued on next page*

**Table 1 Continued**

| Term | Definition |
|---|---|
| Steady blood flow | Blood flow in which velocity does not vary with time. This type of flow does not occur in vivo; however, it has been largely used in computational fluid dynamic studies. |
| Pulsatile (unsteady) blood flow | Blood flow with periodically changing velocity during the cardiac cycle. |
| Steady ESS | ESS that does not vary with time (i.e., constant direction and magnitude). |
| Pulsatile ESS | Unidirectional ESS with a magnitude varying, typically, within a range of 15 to 70 dyne/cm$^2$ over the cardiac cycle, yielding a positive time-average. |
| Low ESS | Unidirectional ESS with a periodically varying magnitude over the cardiac cycle, yielding a significantly low time-average (<10 to 12 dyne/cm$^2$). |
| Oscillatory ESS | Bidirectional ESS with a periodically varying magnitude over the cardiac cycle, yielding a very low time-average, usually close to 0. |
| ESS spatial gradient | ESS variations over short distances. High ESS spatial gradients occur primarily in geometrically irregular arterial regions. |

streamlined flow and can be further divided into undisturbed laminar flow, characterized by smooth streamlines (Fig. 2A), and disturbed laminar flow, characterized by areas with reversed flow (i.e., flow separation, recirculation, and reattachment to forward flow) or circumferential swirling (26,29) (Fig. 2B). In turbulent flow the velocity at any given point varies continuously over time, even though the overall flow is steady (Fig. 2C). For a given geometry, whether the flow will be laminar or turbulent is determined by its Reynolds number (Re); for low Re values, flow is laminar, whereas for high Re values (typically, above 2,000), flow is turbulent (7,26,30).

The pulsatile (unsteady) nature of the arterial blood flow in combination with the complex geometric configuration of the coronaries determines the ESS patterns, which are characterized by direction and magnitude (10,31,32). In relatively straight arterial segments, ESS is pulsatile and unidirectional with a magnitude that varies within a range of 15 to 70 dyne/cm$^2$ over the cardiac cycle and yields a positive time-average (4–6) (Fig. 3). In contrast, in geometrically irregular regions, where disturbed laminar flow occurs, pulsatile flow generates low and/or oscillatory ESS.

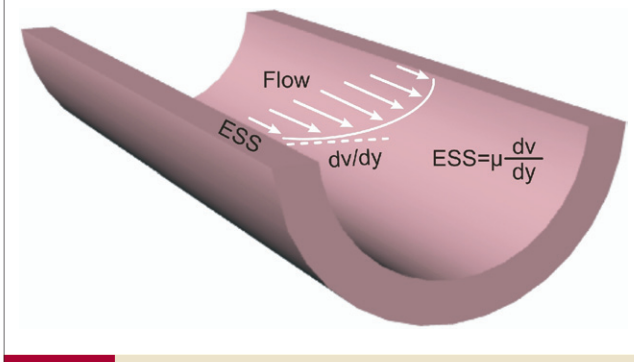


**Figure 1 Definition of ESS**

Endothelial shear stress (ESS) is proportional to the product of the blood viscosity ($\mu$) and the spatial gradient of blood velocity at the wall (dv/dy).

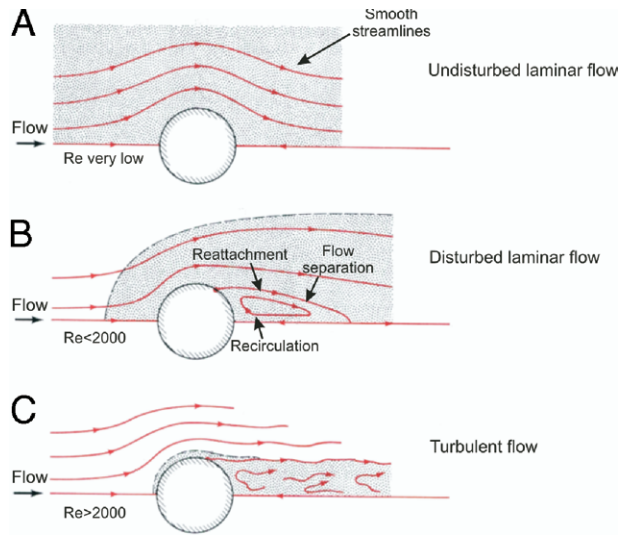


**Figure 2 Characteristics of Flow Patterns**

Schematic figure illustrating the characteristics of flow patterns. **(A)** Undisturbed laminar flow is a smooth streamlined flow chacterized by concentric layers of blood moving in parallel along the course of the artery; **(B)** disturbed laminar flow is characterized by reversed flow (i.e., flow separation, recirculation, and reattachment to forward flow); **(C)** in turbulent flow the blood velocity at any given point varies continuously over time, even though the overall flow is steady. Adapted from Munson et al. (28). Re = Reynolds number.

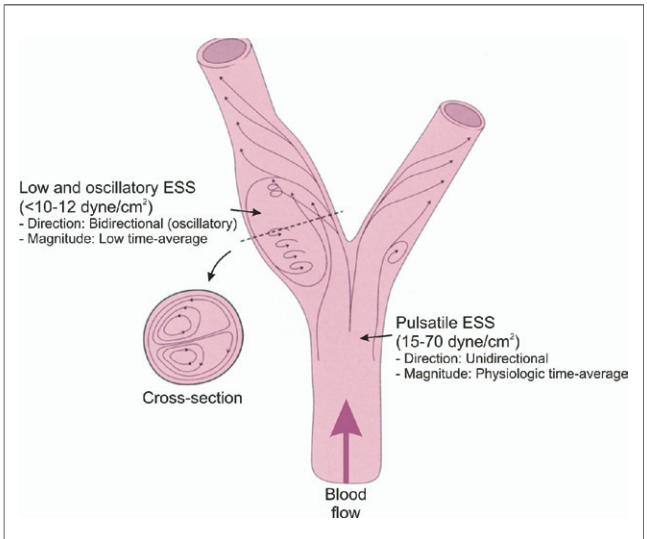


**Figure 3 Definition and Example of Pulsatile, Low, and Oscillatory ESS**

Definition of pulsatile, low, and oscillatory endothelial shear stress (ESS). Adapted from Ku et al. (10).

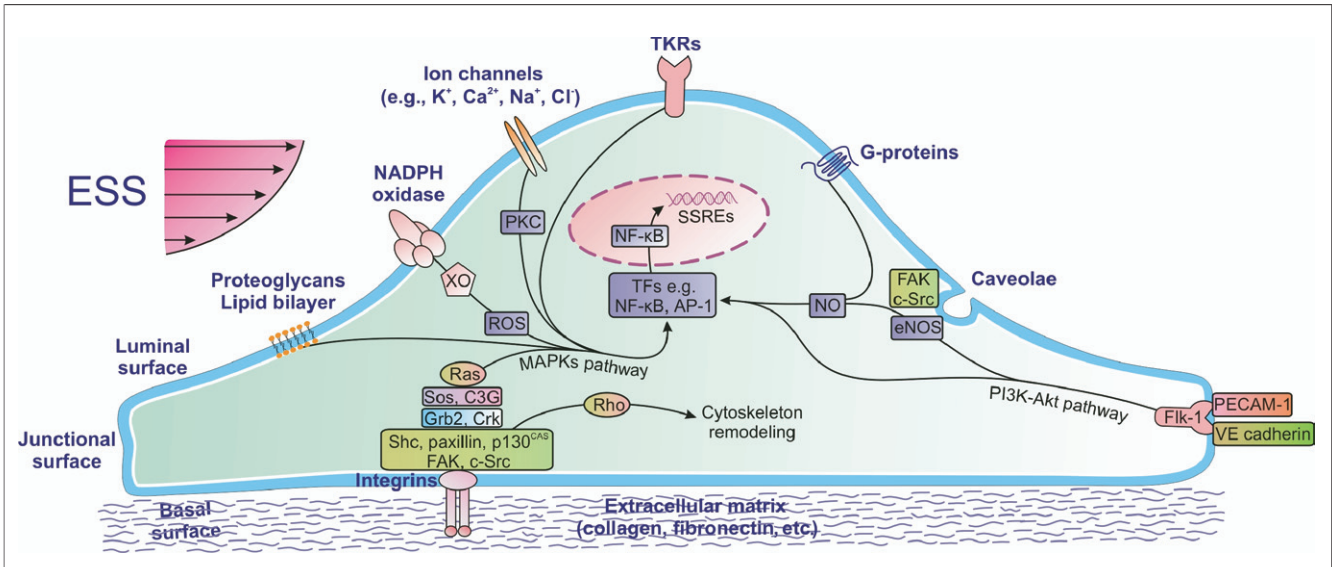


**Figure 4** **Endothelial Mechanotransduction of ESS**

Local endothelial shear stress (ESS) is sensed by luminal endothelial mechanoreceptors, such as ion channels ($K^+$, $Ca^{2+}$, $Na^+$, $Cl^-$), G-proteins, caveolae, tyrosine kinase receptors (TKRs), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase (XO), plasma membrane lipid bilayer, and heparan sulfate proteoglycans. Also, ESS signals are transmitted through the cytoskeleton to the basal or junctional endothelial surface, where certain integrins or a mechanosensory complex consisting of platelet endothelial cell adhesion molecule-1 (PECAM-1) and Flk-1 are activated, respectively, and initiate a downstream signaling cascade. Activated integrins phosphorylate and activate a multiple complex of non-receptor tyrosine kinases (FAK, c-Src, Shc, paxillin, and $p130^{CAS}$), adaptor proteins (Grb2, Crk), and guanine nucleotide exchange factors (Sos, C3G), thereby activating Ras family GTPase. Active Ras plays a pivotal role in intracellular transduction of ESS signals as it triggers various parallel downstream cascades of serine kinases; each of these kinases phosphorylates and hence activates the next one downstream, ultimately activating mitogen-activated protein kinases (MAPKs). Besides integrin-mediated mechanotransduction, ESS activates a number of other downstream signaling pathways initiated by luminal or junctional mechanoreceptors. These pathways include the production of reactive oxygen species (ROS) from NADPH oxidase and XO, activation of protein kinase C (PKC), activation of Rho family small GTPases (which mediate the remodeling cytoskeleton resulting in temporary or permanent structural changes of ECs), release of endothelial nitric oxide synthase (eNOS) and other signaling molecules from caveolae, and activation of phosphoinositide-3 kinase (PI3K)-Akt cascade. Ultimately, all of these signaling pathways lead to phosphorylation of several transcription factors (TFs), such as nuclear factor-kappa $\beta$ (NF-κB) and activator protein-1 (AP-1). These TF proteins bind positive or negative shear stress responsive elements (SSREs) at promoters of mechanosensitive genes inducing or suppressing their expression, thereby modulating cellular function and morphology.

Low ESS refers to ESS that is unidirectional at any given point but has a periodically fluctuating magnitude that results in a significantly low time-average (approximately <10 to 12 dyne/cm$^2$) (4,6,15) (Fig. 3). However, the absolute threshold effect of low ESS is likely dependent on concomitant conditions, such as systemic factors, or interspecies differences (33). Low ESS typically occurs at the inner areas of curvatures as well as upstream of stenoses (34). Oscillatory ESS is characterized by significant changes in both direction (bidirectional) and magnitude between systole and diastole, resulting in a very low time-average, usually close to 0 (4–6) (Fig. 3). Oscillatory ESS occurs primarily downstream of stenoses, at the lateral walls of bifurcations, and in the vicinity of branch points (6,10,34,35). Beside the temporal oscillations, ESS experiences significant spatial oscillations over short distances, especially in geometrically irregular regions, resulting in high spatial gradients, which are also involved in atherosclerosis (14,35–37).

Although low ESS and oscillatory ESS are closely associated with atherogenesis, the relative importance of these different ESS patterns is unclear. In a mouse carotid artery in vivo model, both low ESS and oscillatory ESS led to atherosclerotic plaque formation, but only low, nonoscillatory ESS was associated with inflammatory changes and proclivity to rupture (21). Different vascular territories (e.g., femoral, carotid, and coronary arteries) might also respond differently to various ESS stimuli (33). The magnitude of local low ESS is critically associated with the severity of atherosclerotic plaque characteristics (19).

## ESS Mechanoreception, Signal Transduction, and Mechanosensitive Gene Expression

Endothelial cell (EC) surfaces (luminal, junctional, and basal) are equipped with numerous mechanoreceptors capable of detecting and responding to ESS stimuli (38–40) (Fig. 4). After activation of mechanoreceptors, a complex network of several intracellular pathways is triggered, a process known as mechanotransduction (38,39,41–45) (Fig. 4). These pathways are activated simultaneously and cross-talk with each other; the great majority of them converge into the mitogen-activated protein kinase (MAPKs) cascade at various levels, suggesting the key role of MAPKs in ESS mechanotransduction (39). Cytoskeleton constitutes a central mediator in ESS signaling by providing

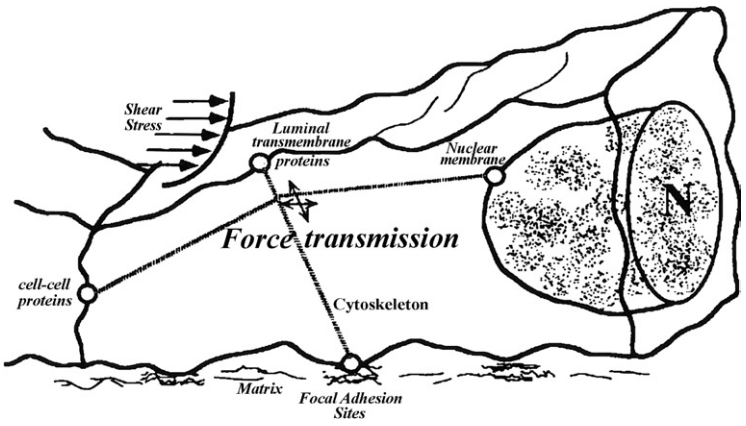


**Figure 5** **Role of Cytoskeleton in ESS Mechanotransduction**

The endothelial cytoskeleton transmits the shear forces to the focal adhesions located at the basal endothelial surface, where a downstream intracellular signaling cascade starts. The shear forces can also be transmitted to mechanoreceptors at the cell–cell junctions, luminal surface, and nucleus (N). Adapted from Davies et al. (45). ESS = endothelial shear stress.

a scaffold for the formation or translocation of various signaling molecules, serving as a bond between the luminal surface, where ESS is imposed, and several luminal, basal, or junctional formations, where the signaling pathways initiate (45) (Fig. 5). These pathways lead to phosphorylation of several transcription factors (TFs), which bind positive or negative shear stress responsive elements (SSREs) at promoters of mechanosensitive genes, inducing or suppressing their expression and, ultimately, modulating cellular function and morphology (4,6,46–48). In arterial regions with non-disturbed flow, where ESS varies within a physiologic range, the ECs express various atheroprotective genes and suppress several pro-atherogenic ones, leading eventually to stability and quiescence in that region (6,48). In contrast, in regions with low and disturbed flow where low ESS occurs, the atheroprotective genes are suppressed, whereas the pro-atherogenic genes are upregulated, thereby promoting the atherosclerotic process (6,48).

## Role of Low ESS in Atherosclerosis

**Low ESS attenuates nitric oxide (NO)-dependent atheroprotection.** Nitric oxide, a key component of normal vascular tone, also possesses strong anti-inflammatory, anti-apoptotic, anti-mitogenic, and anti-thrombotic properties (49) (Table 2). Physiologic pulsatile ESS constitutes the most potent stimulus for continuous NO production by the endothelium, an effect that is regulated at either transcriptional level through upregulation of endothelial nitric oxide synthase (eNOS) gene expression (50) or at post-transcriptional level by eNOS protein phosphorylation and activation (51). In arterial regions with disturbed flow, low ESS reduces the bioavailability of NO by decreasing eNOS messenger ribonucleic acid (mRNA) and protein expression, thereby exposing the endothelium to the atherogenic effect of local and systemic risk factors (12,13,49,52,53) (Fig. 6). In addition, low ESS downregulates prostacyclin, another endothelial vasodilatory substance (4,53), while upregulating endothelin-1 (ET-1) (4,52,53), a potent vasoconstrictive and mitogenic molecule, thereby precipitating atherosclerosis.

**Low ESS promotes low-density lipoprotein cholesterol (LDL) uptake, synthesis, and permeability.** Low ESS causes a sustained endothelial activation of sterol regulatory elements binding proteins (SREBPs), a family of endoplasmic reticulum-bound TFs that upregulate the expression of genes encoding LDL receptor, cholesterol synthase, and fatty acid synthase (54) (Fig. 6). In the context of systemic hyperlipidemia, this effect results in an increased engagement and synthesis of LDL by the ECs, ultimately promoting the subendothelial accumulation of LDL (55). Activated SREBPs also appear to induce interleukin (IL)-8 and, concomitantly, monocyte accumulation into the intima, suggesting an additional role of these TFs in the local inflammatory processes (56).

In addition to active SREBPs-dependent LDL uptake and synthesis, disturbed flow increases the permeability of the endothelial surface to LDL (14,38,57) (Fig. 6). The regulation of cell cycle and survival by shear forces might play an important role in increasing LDL permeability. Highly mitotic and apoptotic activity of ECs was found in regions susceptible to atherosclerosis, where low and oscillatory ESS occur (58,59). The accentuated ECs mitosis and apoptosis as well as the conformational changes of ECs from fusiform to polygonal shape associated with low ESS might be responsible for the widening of the junctions between ECs (4,55,60). These small "gaps" between ECs, in combination with flow stagnation and the subsequent prolongation of the residence time of circulating LDL, facilitate the infiltration of LDL underneath the endothelium (6,29).

**Table 2** Endothelial Genes and Vascular Functions Regulated by Low ESS in Atherosclerosis

| | Effect of Low ESS |
|---|---|
| Impaired flow-dependent vasodilation | |
| Vasodilators | |
| eNOS/NO | Downregulated (4,12,13,52,53) |
| Prostacyclin | Downregulated (4,53) |
| Vasoconstrictors | |
| ET-1 | Upregulated (4,52,53) |
| Subendothelial accumulation of LDL | |
| Endothelial LDL uptake and synthesis | Increased (54) |
| Endothelial LDL permeability | Increased (14,57) |
| Blood stagnation—accumulation of LDL close to the wall | Increased (6,29) |
| ECs proliferation and apoptosis | Increased (58,59) |
| Oxidative stress | |
| Oxidative enzymes | |
| NADPH oxidase | Upregulated (61) |
| Xanthine oxidase | Upregulated (62) |
| Antioxidative enzymes | |
| Mn SOD | Downregulated (47) |
| Glutathione | Downregulated (63) |
| Inflammation | |
| Chemoattractants (MCP-1) | Upregulated (46,47,66) |
| Adhesion molecules (VCAM-1, ICAM-1, E-selectin) | Upregulated (21,46,47,65-68) |
| Cytokines (TNF-$\alpha$, IL-1, IFN-$\gamma$) | Upregulated (46,47) |
| BMP-4 | Upregulated (7,101) |
| Leukocyte pseudopod projection | Increased (69) |
| Blood stagnation—accumulation of monocytes close to the wall | Increased (6,29,68) |
| VSMCs migration, differentiation, and proliferation | |
| Growth promoters | |
| PDGF-A, PDGF-B | Upregulated (4,70) |
| ET-1 | Upregulated |
| VEGF | Upregulated (21,71) |
| bFGF | Unclear (4,73) |
| ACE | Unclear (4,38) |
| Angiotensin II | Unclear (38,73) |
| Growth inhibitors | |
| eNOS/NO | Downregulated |
| TGF-$\beta$ | Downregulated (4,74,75) |
| PAI-1 | Downregulated (22,72) |
| Regulation of extracellular matrix content and composition | |
| Increased matrix degradation | |
| MMP-2, MMP-9 | Upregulated (21,22,80-82) |
| Cathepsin L | Upregulated (93) |
| Reduced matrix synthesis | |
| IFN-$\gamma$ | Upregulated |
| VSMCs apoptosis | Increased |
| eNOS/NO | Downregulated |
| TGF-$\beta$ | Downregulated |
| Neovascularization | |
| VEGF | Upregulated |
| Other angiogenic factors (e.g., angiopoietin-2) | Upregulated (46) |
| Plaque calcification | |
| BMP-4 | Upregulated |
| Plaque thrombogenecity | |
| eNOS/NO | Downregulated |
| Prostacyclin | Downregulated |
| Thrombomodulin | No effect (38,104) |
| t-PA | Downregulated (38,105) |
| Blood stagnation— accumulation of blood thrombogenic factors close to the wall | Increased (6,29) |

ACE = angiotensin-converting enzyme; bFGF = basic fibroblast growth factor; BMP = bone morphogenic protein; EC = endothelial cell; eNOS/NO = endothelial nitric oxide synthase/nitric oxide; ESS = endothelial shear stress; ET = endothelin; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; LDL = low-density lipoprotein cholesterol; MCP = monocyte chemoattractant protein; MMP = matrix metalloproteinase; Mn SOD = manganese-dependant superoxide dismutase; NADPH = nicotinamide adenine dinucleotide phosphate; PAI = plasminogen activator inhibitor; PDGF = platelet derived growth factor; TGF = transforming growth factor; TNF = tumor necrosis factor; t-PA = tissue plasminogen activator; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor; VSMC = vascular smooth muscle cell.

**Low ESS promotes oxidative stress.** Once LDL particles are engulfed in the subendothelial layer, they are associated with intimal proteoglycans, become entrapped, and undergo oxidative modification (1,2). Low ESS promotes production of reactive oxygen species (ROS) into the intima and, eventually, oxidation of LDL, by enhancing gene expression and post-transcriptional activity of the major oxidative enzymes (nicotinamide adenine dinucleotide phosphate [NADPH] oxidase and xanthine oxidase) at EC membranes (49,61,62) (Fig. 6). Low ESS appears also to downregulate the intracellular ROS scavengers, such as manganese superoxide dismutase and glutathione, further augmenting local oxidative stress (47,63). Generated ROS degrade NO and its co-factors (e.g., tetrahydrobiopterin), reducing the bioavailability of atheroprotective NO and further enhancing the production of ROS (e.g., superoxide [$O_2^-$] or peroxynitrite [$ONOO^-$]) (49).

**Low ESS promotes inflammation.** The recruitment of circulating inflammatory cells (monocytes, T-lymphocytes, mast cells, eosinophils, dendritic cells) into the intima to scavenge oxidized LDL constitutes a major pathogenetic component in the atherosclerotic process (64). Low ESS plays a key role in the localized attachment and infiltration of these cells into the arterial wall through activation of certain TFs, notably nuclear factor-kappa $\beta$ (NF-$\kappa$B), and subsequent translocation to the nucleus (36,65–67) (Fig. 6). Activation of NF-$\kappa$B is further promoted by low shear-induced oxidative stress (61). In addition, a negative feedback mechanism occurs between NF-$\kappa$B and NO, in that reduced eNOS expression and subsequent NO production occurring in low ESS regions increases the activity of NF-$\kappa$B (67).

Various endothelial genes are upregulated downstream to low shear-induced NF-$\kappa$B activation. These include genes that encode several adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1; intercellular

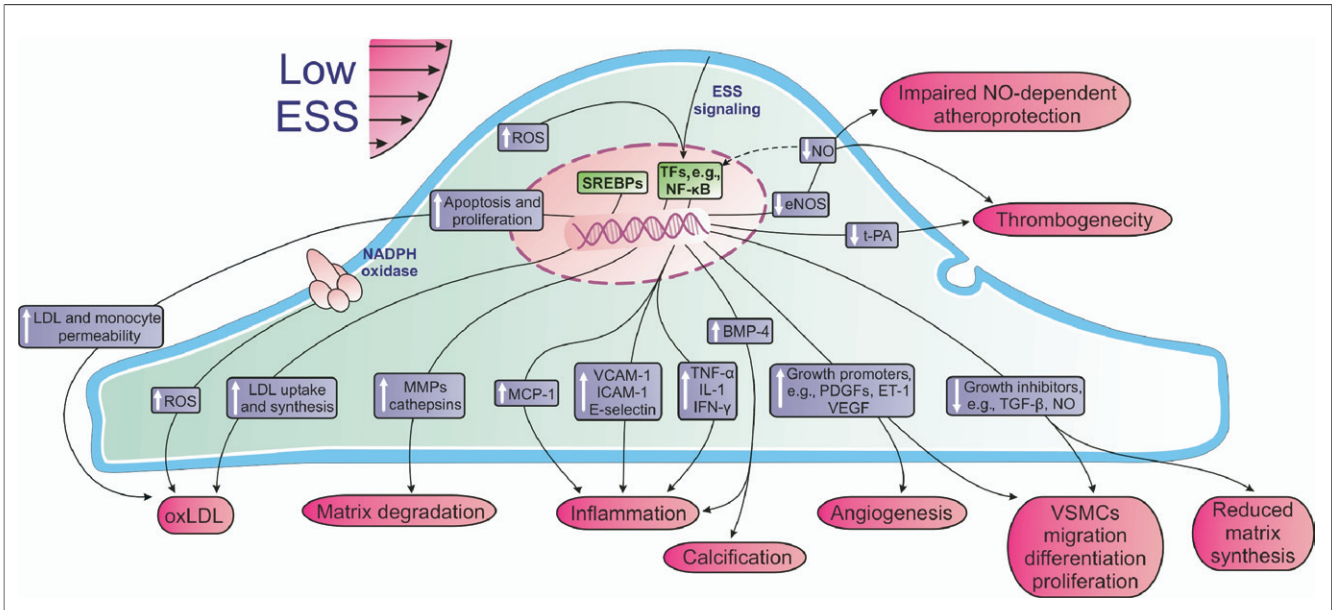


**Figure 6** **Role of Low ESS in Atherosclerosis**

In arterial regions with disturbed laminar flow, low endothelial shear stress (ESS) shifts the endothelial function and structure toward an atherosclerotic phenotype, thereby promoting atherogenesis, atherosclerotic plaque formation and progression, and vascular remodeling. BMP = bone morphogenic protein; ET = endothelin; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; LDL = low-density lipoprotein cholesterol; MCP = monocyte chemoattractant protein; MMP = matrix metalloproteinase; NO = nitric oxide; PDGF = platelet-derived growth factor; SREBP = sterol regulatory elements binding protein; TF = transcription factor; TGF = transforming growth factor; TNF = tumor necrosis factor; t-PA = tissue plasminogen activator; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor; VSMC = vascular smooth muscle cell; other abbreviations as in Figure 4.

adhesion molecule (ICAM)-1 and E-selectin; chemoattractant chemokines, such as monocyte chemoattractant protein (MCP)-1; and pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)-1, and interferon (IFN)-$\gamma$ (21,46,47,65–68). Adhesion molecules are expressed on EC surface and mediate the rolling and adhesion of circulating leukocytes on the endothelial surface, whereas MCP-1 promotes transmigration of leukocytes, particularly monocytes, into the intima. The intimal infiltration of inflammatory cells appears also to be mechanistically facilitated by blood flow stagnation and endothelial junction widening, primarily occurring in areas with disturbed flow (6,29,68) (Fig. 6). Low ESS might also provoke pseudopod projection through mechanotransduction processes and binding of leukocytes on the endothelium (69). Once monocytes infiltrate underneath the endothelium they undergo structural and functional alterations and differentiate to macrophages, which sustain the inflammation, oxidative stress, and dynamic matrix remodeling, thereby promoting atherosclerosis progression (1,2,64).

**Low ESS promotes vascular smooth muscle cell (VSMC) migration, differentiation, and proliferation.** Low ESS promotes endothelial gene and protein expression of potent VSMC mitogens, such as platelet-derived growth factor (PDGF)-A and -B isoforms (4,70), ET-1 (4,52,53), and vascular endothelial growth factor (VEGF) (21,71) (Fig. 6). Low ESS-induced formation of ROS and pro-inflammatory cytokines also promote the expression of these growth factors (1). Also, low and disturbed flow decreases the endothelial expression of plasminogen activator inhibitor (PAI)-1, an inhibitor of VSMC migration (22,72). Although the effect of low ESS on basic fibroblast growth factor (bFGF), angiotensin converting enzyme (ACE), and angiotensin II is yet unclear (4,38,73), potent suppressors of cell growth and migration, such as NO (52) and transforming growth factor (TGF)-$\beta$ (4,74,75) are downregulated in areas with low and disturbed flow (Fig. 6). Ultimately, low ESS-mediated over-expression of growth promoters and under-expression of growth inhibitors by the ECs stimulate VSMCs to migrate from media to intima through a regionally disrupted internal elastic lamina (IEL) (76,77). Within the intima VSMCs acquire a "synthetic" phenotype, producing collagen and other extracellular matrix (ECM) proteins, and proliferate (1). Over time, VSMCs along with the fibroblasts create a fibrous cap around the lipid core isolating the thrombogenic lipid material from the circulating platelets. The fibrous cap along with the lipid core constitute the so-called early atherosclerotic plaque (fibrous cap atheroma; American Heart Association type IV lesion) (78,79).

**Low ESS promotes ECM degradation in vascular wall and plaque fibrous cap.** The ECM of vascular wall and fibrous cap is composed of a complex mixture of collagen and elastin fibers within a ground substance of proteoglycans and glycosaminoglycans. In vitro and in vivo animal

experiments have demonstrated that low ESS upregulates gene expression and activity of matrix metalloproteinases (MMPs), particularly MMP-2 (or gelatinase-A) and −9 (or gelatinase-B) (21,22,80–82), which are the major proteases associated with ECM degradation in the atherosclerotic plaques (83–86) (Fig. 6). Pro-inflammatory cytokines (TNF-$\alpha$, IL-1, IFN-$\gamma$) comprise the major stimuli for the release of MMPs from their key cellular sources (ECs, macrophages, VSMCs, T-lymphocytes, and mast cells) via the MAPKs pathway and subsequent activation of TFs (e.g., NF-$\kappa$B and activator protein [AP]-1) (86–88). Low ESS increases MMPs expression by ECs through activation of these TFs. Moreover, low ESS enhances the accumulation of macrophages and VSMCs within the plaque, where the upregulated pro-inflammatory cytokines stimulate them to secrete MMPs. Reactive oxygen species, which are central effectors in low ESS signaling, also enhance the expression and activity of MMPs (86).

Whereas MMPs are the matrix degrading endopeptidases that have been most extensively investigated, several other proteases have been shown to play a key role in matrix breakdown, including cysteine proteases (e.g., cathepsins S, K, L) (89–92), serine proteases (e.g., tissue plasminogen activator [t-PA], urokinase-plasminogen activator [u-PA], plasmin) (87), and mast cells-derived chymase and tryptase (64,87). Low ESS upregulates the expression of cathepsin L by ECs, macrophages, and VSMCs, probably through an NF-$\kappa$B–dependent and cytokine-dependent pathway similar to that of MMPs (93) (Fig. 6).

**Low ESS attenuates ECM synthesis in vascular wall and plaque fibrous cap.** In addition to intensive ECM degradation, low and disturbed flow attenuates ECM synthesis. Interferon-$\gamma$, a pro-inflammatory cytokine derived by the activated T-lymphocytes in response to low ESS, constitutes a potent inhibitor of collagen synthesis by VSMCs (94,95) and simultaneously promotes Fas-related VSMC apoptosis (96). Vascular smooth muscle cell apoptosis can be also induced by low shear-generated oxidative stress through activation of Fas signaling pathways (97). Next to their role in VSMC turnover, TGF-$\beta$ and NO constitute potent inducers of collagen synthesis by VSMCs as well as anti-inflammatory molecules (49,74). Downregulated endothelial expression of TGF-$\beta$ and eNOS genes due to low ESS might contribute to increased inflammation and reduced matrix synthesis (98) (Fig. 6).

**Potential role of low ESS in plaque neovascularization.** Neovascularization (angiogenesis) constitutes a key factor in the progression and vulnerability of atherosclerotic plaques by supplying them with lipoproteins, inflammatory cells, matrix proteases, and ROS (99). Low ESS indirectly promotes intimal neovascularization by inducing intimal thickening and thus ischemia, upregulating the expression of VEGF (21,71) and other angiogenic factors (e.g., angiopoietin-2) (46), enhancing local inflammation, oxidative stress, and expression of matrix degrading enzymes and accentuating EC and VSMC migration and proliferation (100) (Fig. 6).

**Potential role of low ESS in plaque calcification.** Bone morphogenic protein (BMP)-4, a member of the TGF-$\beta$ superfamily of cytokines (74), has recently been shown to be upregulated in ECs exposed to low and oscillatory ESS (7,101) (Fig. 6). The BMP-4 stimulates the expression and activity of NADPH oxidase, thereby leading to ROS production, NF-$\kappa$B activation, pro-inflammatory cytokine expression, and subsequent increased monocyte adhesivity of ECs. In addition, BMP-4 participates in plaque calcification, suggesting a potential role of low ESS in the formation of spotty deposits of calcium at the base of the plaque, close to the IEL, surrounded by inflammatory cells (19,102,103).

**Low ESS increases plaque thrombogenecity.** Low ESS increases plaque thrombogenecity by downregulating the expression of eNOS and prostacyclin, well known for their anti-thrombotic properties (52,53) (Fig. 6). Furthermore, low ESS exerts no effect on thrombomodulin, a major anticoagulant of endothelial surface, which is physiologically upregulated by laminar flow (38,104), whereas it decreases the expression of t-PA, thereby promoting thrombosis (38,105) (Fig. 6). Blood stagnation occurring at areas with disturbed flow might also facilitate the accumulation of blood thrombogenic factors (e.g., platelets) close to the wall (29). All these thrombogenic actions might be detrimental in the setting of an acute fibrous cap disruption, contributing to abrupt thrombus formation and, therefore, manifestation of an acute coronary syndrome.

## Role of Low ESS in Atherosclerotic Wall Remodeling

The nature and clinical significance of an atherosclerotic plaque is dependent not only on the formation and progression of atherosclerosis but also on the vascular remodeling response to that atherosclerosis (106,107). A controlled and self-limited physiologic process of matrix protein synthesis and breakdown maintains the integrity of the arterial wall. The key mediators of this balance are the matrix-producing cells, primarily VSMCs and fibroblasts, and the matrix-degrading proteases, primarily MMPs and cathepsins (86,91). The function of VSMCs is regulated by a dynamic equilibrium between growth-promoting (e.g., PDGF, ET-1, VEGF, angiotensin II) and growth-inhibiting molecules (e.g., TGF-$\beta$, NO, IFN-$\gamma$). Similarly, the activity of MMPs and cathepsins is regulated by a balance between their synthesis and post-transcriptional activation and inhibition by their inhibitors (e.g., tissue inhibitors of matrix metalloproteinases [TIMPs], cystatin C for cathepsins) (86,91). Although the pathophysiologic mechanisms involved in the remodeling of the atherosclerotic wall are incompletely understood, the dynamic interplay between local hemodynamic milieu and the biology of the wall is likely to be important (23,86).

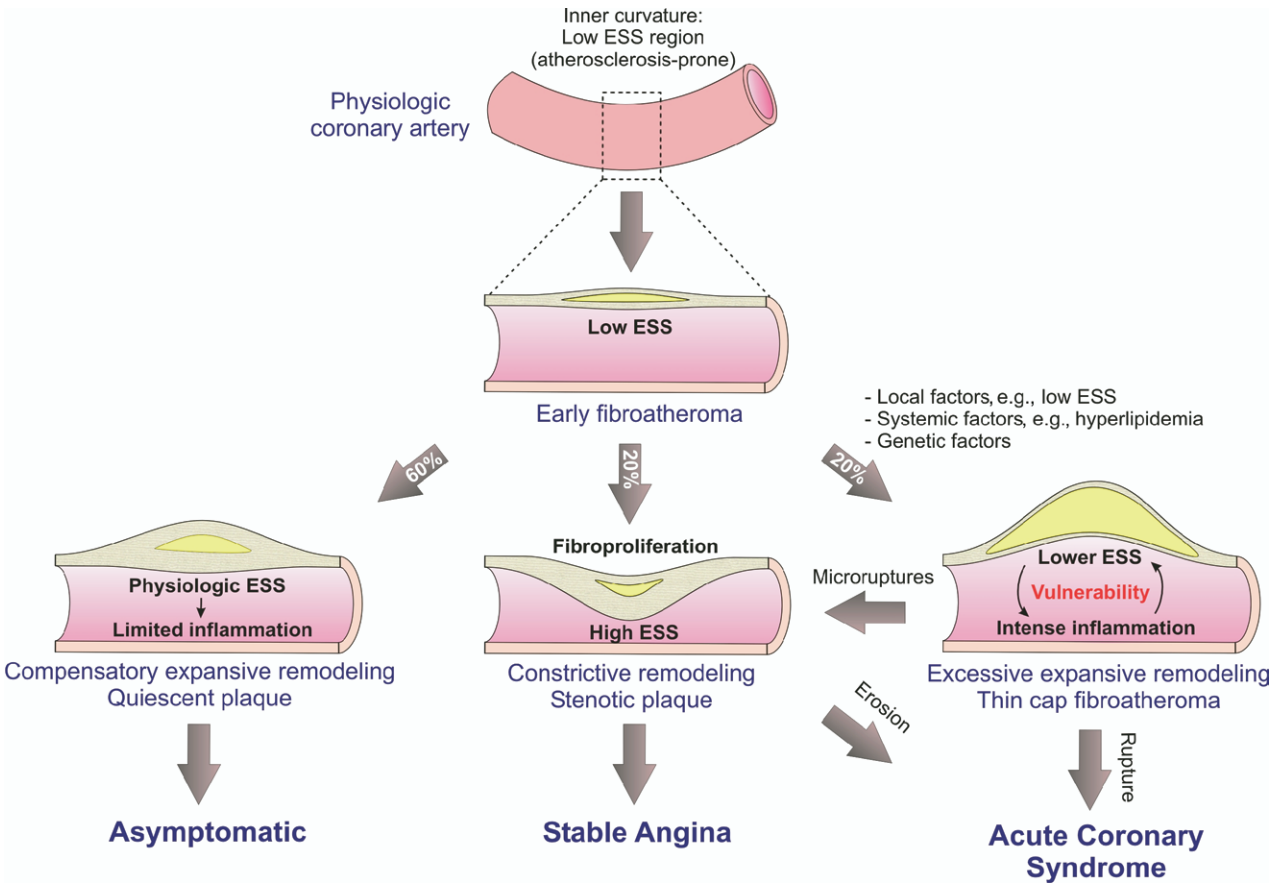


**Figure 7** **Proposed Natural History of Coronary Atherosclerosis**

The initiating process of atherosclerosis in an atherosclerosis-prone host is a low endothelial shear stress (ESS) environment, leading to the formation of an early fibroatheroma, which might be diffuse. The vascular response to that early fibroatheroma likely determines the nature of the subsequent natural history of that plaque. If there is local compensatory expansive remodeling, then the local ESS is normalized, the hemodynamic stimulus for further plaque progression is resolved, and the early lesion evolves to a quiescent plaque with limited inflammation. However, in the presence of certain local, systemic, and genetic factors, the local vascular wall might undergo excessive expansive remodeling. In this context the local low ESS environment persists, promoting further plaque progression and vessel expansion. A self-perpetuating vicious cycle is established among local low ESS, excessive expansive remodeling, and plaque inflammation, transforming the early fibroatheroma to a thin cap fibroatheroma. The stenotic plaques might either evolve with a phenotype promoting fibroproliferation consistently throughout their natural history course or represent an end-stage of scarring in the setting of prior inflamed thin cap fibroatheroma through repetitive microruptures and healing. Also, the stenotic plaques might infrequently undergo local erosion or develop calcified nodules and lead to local thrombus formation and manifestation of an acute coronary syndrome. The percentages reported in the figure are based on intravascular ultrasound studies (23,110,111).

**Expansive remodeling.** Expansive (or outward) remodeling, the process of arterial enlargement in response to local atherosclerotic plaque formation or hemodynamic disturbance, was initially described in primates (108). Glagov et al. (109) was the first to demonstrate in human coronary arteries that the presence of atherosclerotic plaque within the arterial wall leads to vessel enlargement so that the lumen remains preserved (i.e., compensatory expansive remodeling). More recent studies indicated that although approximately 60% of atherosclerotic coronary arteries with minor luminal stenosis exhibit compensatory expansive remodeling, approximately 20% exhibit excessive expansive remodeling, such that both vessel and lumen are actually larger than the neighboring, non-involved areas (23,110,111) (Fig. 7).

Although in normal arteries, low ESS elicits an adaptive response of the arterial wall leading to constrictive remodeling and, consequently, an increase in ESS to physiologic levels, in atherosclerotic arteries the response to low ESS is very complex (15,21,23,24,112). Low ESS leads to the development of focal plaque and, in the setting of a continued low ESS environment, the wall beneath the plaque becomes inflamed and acquires the enzymatic products that shift the ECM balance toward degradation. Within such an environment IEL undergoes severe fragmentation, and the atherosclerotic process extends into the media degrading the collagen and elastin fibers, thereby promoting arterial expansion and accommodation of the enlarging plaque (20–22,86,113) (Fig. 7).

It is currently unknown what factors determine whether the expansive remodeling response to atherosclerosis becomes either compensatory or excessive. Recent observations, however, indicate that low ESS leads to excessive expansive remodeling and, furthermore, that the severity of IEL degradation and excessive expansive remodeling is significantly associated with the magnitude of low ESS (20). In the setting of very low ESS, local lipid accumulation, inflammation, and oxidative stress are enhanced, thereby promoting intensive ECM degradation, culminating in excessive vascular wall expansion, which perpetuates or exacerbates the local low ESS environment (19,20) (Fig. 7). Systemic factors (e.g., magnitude of hyperlipidemia, hyperglycemia, hypertension) and genetic factors might also interplay with the low ESS microenvironment and modulate the excessive expansion of the arterial wall (19,20).

**Constrictive remodeling.** When fibroproliferative processes predominate against inflammation and subsequent matrix breakdown, the atherosclerotic wall undergoes constrictive or inward remodeling, leading to luminal narrowing (114). Approximately 20% of even minimally diseased human coronary arteries exhibit constrictive remodeling, suggesting that vascular constriction might occur as a direct response to plaque growth (23,110,115,116) (Fig. 7). Histopathology data showed that constrictive remodeling might also occur as a stage in the evolution of high-risk plaques through processes of wound healing in response to repetitive plaque microruptures (117,118) (Fig. 7). Studies indicate also that lipid-lowering treatment with statins enhances fibroproliferative processes leading to constrictive remodeling (119). Low ESS does not appear to play a direct role in the pathobiology of constrictive remodeling.

## Role of Low ESS in the Differential Development of Early Fibroatheroma Into High-Risk, Quiescent, or Stenotic Atherosclerotic Plaque

The classification of individual atherosclerotic lesions has been an issue of substantial and ongoing debate concerning histologic characteristics and functional correlates. The first systematic classification was reported by Stary et al. (78) and later modified by Virmani et al. (79). In this review we use a simplified classification scheme of atherosclerotic plaques based on discrete histomorphologic, functional, and clinical characteristics (i.e., histopathology, progression rate, associated vascular remodeling pattern, degree of vulnerability, and related clinical outcome): 1) high-risk plaques; 2) quiescent plaques; and 3) stenotic plaques (Table 3). High-risk plaques are typically thin cap fibroatheromas (TCFAs) in 60% to 70% of cases, characterized by a thin, inflamed fibrous cap and a large necrotic lipid core, rich in neovessels (79,120,121) (Fig. 7). These high-risk plaques are usually minimally stenotic lesions associated with expansive vascular remodeling and an increased risk of sudden rupture and precipitation of an acute coronary syndrome (106,107,122–125). Quiescent plaques are non-stenotic or minimally stenotic lesions with a thick fibrous cap and a small lipid core (Fig. 7). These plaques remain biologically quiescent and thus cause no symptoms (30). Finally, stenotic plaques are stable fibroproliferative lesions with modest inflammation, characterized morphologically by a relatively thick, collagen-rich fibrous cap, overlying a small lipid core (79,124,126) (Fig. 7). These lesions are associated with constrictive vascular remodeling and over time might become occlusive, resulting in chronic stable angina (106,107,115,122).

Although atherosclerosis is a systemic and diffuse disease, its manifestations are multi-focal, given that plaques of each of the aforementioned types co-exist in the same patient, indeed even in the same artery, at a single point in time (127,128). Local factors, such as low ESS and local remodeling response, are likely critical determinants of the subsequent natural history of each individual atherosclerotic plaque (15,18,129).

**Development of high-risk plaques (TCFAs).** There have been very limited serial investigations of the progression of early atherosclerotic plaque to determine the natural history of each plaque and the determinants responsible for the course of that natural history. A recent study using serial IVUS and immunohistochemical analyses in a diabetic atherosclerotic pig model found that low ESS was an independent predictor of plaque location, development, and progression to a high-risk plaque with intensive lipid accumulation, inflammation, thin fibrous cap, IEL fragmentation, media thinning, and excessive expansive remodeling (18–20) (Fig. 7). Furthermore, the magnitude of low ESS at baseline was significantly associated with the severity of high-risk plaque characteristics in follow-up. Intriguingly, in areas of low ESS where high-risk plaque developed, excessive expansive remodeling occurred, associated with persistence of a low ESS environment despite continued plaque growth, thereby fostering a vicious cycle among low ESS, excessive expansive remodeling, and high-risk plaque characteristics (19,20) (Fig. 7).

**Development of quiescent plaques.** The hemodynamic or morphologic characteristics promoting plaque quiescence are not well understood. A recent serial IVUS and histopathology natural history study demonstrated that those local coronary arterial subsegments that developed only minimal or intermediate atherosclerotic plaque after prolonged follow-up were those areas with either physiologic or slightly low ESS at baseline (18–20). These areas primarily developed compensatory and not excessive, expansive remodeling and did not acquire the high-risk characteristics of plaque progression, lipid accumulation, inflammation, and IEL degradation compared with areas with lower ESS at baseline (Fig. 7). Furthermore, the ESS after long-term follow-up in these areas with only minimal or intermediate plaque was virtually the same as at baseline, suggesting there was little ongoing stimulus for exacerbation of plaque progression and arterial expansion (20). However, the long-term stability or quiescence of these plaques is unknown. If local vascular conditions later change, such that a low ESS microenvironment is recreated or the systemic atherosclerotic stimulus is enhanced, then the process of

**Table 3** Classification Scheme for the Natural History of Early Atherosclerotic Plaques (Early Fibroatheromas)

| Plaque Trajectory | Histopathology | Progression Rate | Vascular Remodeling | Proclivity to Rupture | Clinical Manifestation |
|---|---|---|---|---|---|
| Quiescent plaque | Small lipid core<br>Thick fibrous cap | Minimal | Compensatory expansive remodeling | Low | Asymptomatic |
| Stenotic plaque | Small lipid core<br>Very thick fibrous cap | Gradual | Constrictive remodeling | Low | Stable angina |
| High-risk plaque | Large lipid core<br>Thin and inflamed fibrous cap | Increased | Excessive expansive remodeling | High | Acute coronary syndrome |

progressive atherosclerosis, inflammation, and vascular remodeling might again re-emerge.

**Development of stenotic (fibrous) plaques.** Stenotic lesions either evolve with a phenotype promoting fibroproliferation consistently throughout its natural history course (115) or represent an end-stage of scarring in the setting of prior repetitive microruptures of an inflamed TCFA (117) (Fig. 7). The local hemodynamic or morphologic factors responsible for an early plaque to evolve into a fibrous plaque are unknown. The magnitude of local ESS stimuli for cellular proliferation/fibrosis versus inflammation might play a decisive role in determining whether the balance between ECM degradation and synthesis favors less inflammation and more ECM synthesis (i.e., development of stenotic plaque) or favors ECM degradation (i.e., development of TCFA) (130) (Fig. 7).

Stenotic plaques infrequently undergo local erosion or develop calcified nodules, which might lead to local thrombus formation and manifestation of an acute coronary syndrome (20% to 40% of cases) (79). Low ESS does not appear to play a role in the pathophysiology of plaque erosion. However, high ESS, which occurs at the neck of highly stenotic plaques, might be responsible for the local endothelial erosion and induction of acute coronary thrombosis (31) (Fig. 7).

## Clinical Implications of Assessing ESS

Because ruptured TCFAs account for the great majority of the acute coronary syndromes, early understanding of the degree of risk associated with an individual plaque and the identification of plaques at risk to evolve to TCFAs is anticipated to have considerable clinical impact. Although systemic therapy is the foundation to reduce risk in patients with coronary disease, systemic strategies alone might be insufficient to adequately address the high-risk patient or the high-risk coronary lesion. The PROVE-IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22) trial, for example, indicated that although very aggressive systemic therapy (i.e., atorvastatin 80 mg q.d.) reduced the primary end point of death or a major cardiovascular event by 16% compared with standard statin therapy (i.e., pravastatin 40 mg q.d.) after a mean follow up of 24 months, a primary end point event nevertheless still occurred in 22.4% of the intensive treatment group (131). Clearly an incremental approach beyond systemic therapy would be of value in the management of these high-risk patients. A focused strategy of identification of an early stage of a high-risk lesion might be complementary to systemic therapy by enabling a highly selective local intervention to avert a future acute coronary event (103).

Several in vivo technologies for the assessment of the functional and morphologic characteristics of a particular plaque now exist, including multislice computed tomography, magnetic resonance imaging, position emission tomography, IVUS-based virtual histology and palpography, thermography, optical coherence tomography, near-infrared spectroscopy, intravascular magnetic resonance imaging, and angioscopy (103). Although these modalities might be useful to characterize a particular plaque, they might be insufficient to optimally predict future risk, because they provide a snapshot of the plaque at only a single point in time. Thus, these modalities are most useful to identify only the ends of the spectrum between a stenotic plaque and a high-risk plaque, but they cannot address the stimuli responsible for the subsequent natural history of that plaque. Incorporation of an in vivo assessment of local ESS stimuli and local remodeling behavior of a particular plaque might substantially enhance the prognostic significance of these imaging modalities, because one can then have insight both into the existing nature and the future natural history of that plaque (15,23,25).

The most comprehensive technique for investigating the relationship between ESS and vascular pathobiology is a methodology known as "vascular profiling," which uses routine IVUS and coronary angiography to create an accurate 3-dimensional representation of the coronary artery, and this forms the basis of identifying both local ESS and vascular remodeling behavior (5,15) (Fig. 8). Vascular profiling is accurate (132–134) and highly reproducible (135) and can be used to track changes in lumen, wall thickness, and ESS in periods as short as 6 to 9 months in human (15,23) or in experimental animals (18,19). Future technologies might be able to non-invasively assess local ESS and remodeling behavior with multi-slice computed tomography, magnetic resonance imaging, or other imaging approaches (17). A natural history clinical study of atherosclerotic plaques using vascular profiling techniques in patients with coronary artery disease is now underway (PREDICTION [Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology] trial) to determine the incremental value of characterizing the local

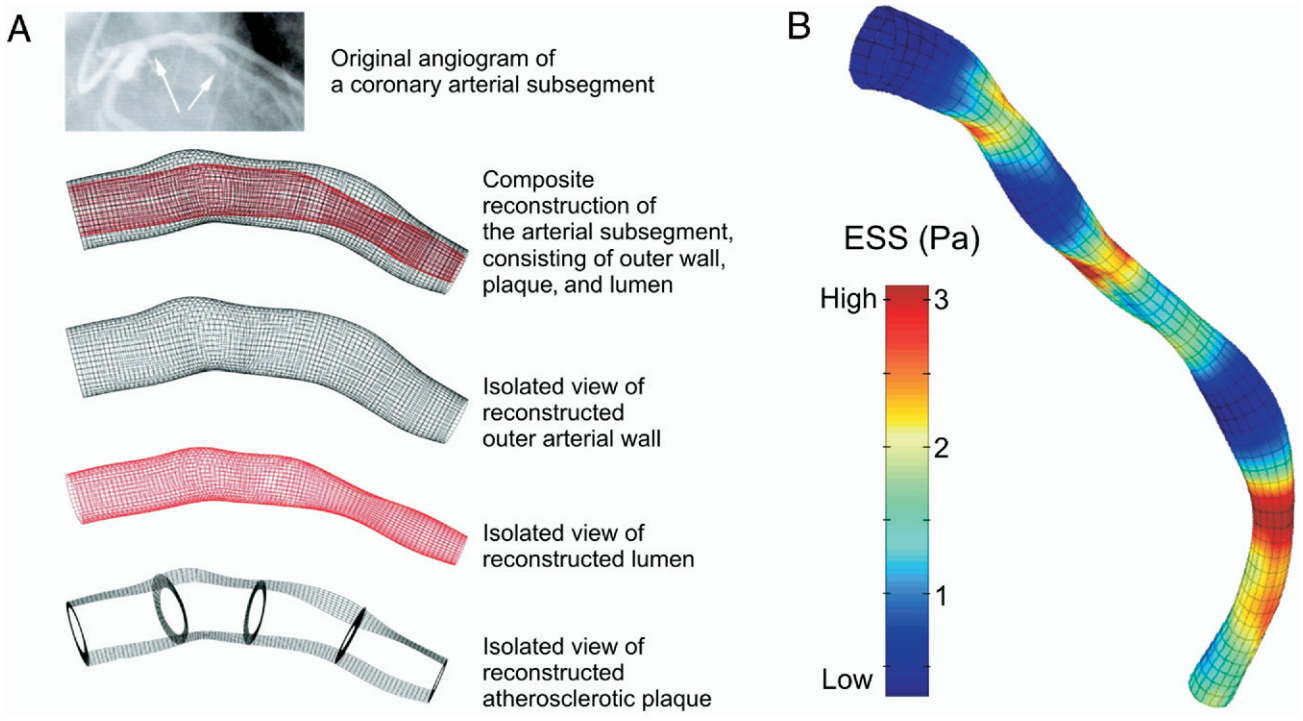


**Figure 8** Example of Vascular Profiling With Reconstructed Human Coronary and Profile of ESS Along Length of Coronary Artery

**(A)** Example of a 3-dimensional (3D) reconstructed coronary arterial segment. **(B)** Example of endothelial shear stress (ESS) profiling along a 3D reconstructed left anterior descending artery. **Panel A** was adapted from Stone et al. (15). Pa = Pascal.

ESS and remodeling environment to predict the development of new acute cardiac events.

In vivo understanding of the local hemodynamic environment responsible for individual plaque behavior and natural history, in combination with molecular imaging and the information provided by systemic biomarkers of vulnerability, might allow for detailed risk stratification of individual early coronary plaques (5,19,103). Identification of a high-risk plaque in its early stages of development might provide a rationale for highly selective, prophylactic local coronary interventions (e.g., implantation of stents), supplemented by an intensive systemic pharmacologic approach, to avert a future acute coronary event (15,103,136). The clinical and economic implications of identifying and treating individual high-risk coronary lesions are anticipated to be enormous.

## Conclusions

Low ESS is a powerful local stimulus for atherogenesis, formation, and progression of an early atherosclerotic plaque and differentiation to high-risk plaque. Variations in the local intravascular hemodynamic environment over time lead to dynamic interactions with the arterial wall that might either exacerbate or ameliorate the progression of an early plaque. An in vivo understanding of plaque characteristics, local ESS, and vascular remodeling response might lead to an enhanced understanding of the pathobiology of coronary artery disease and provide opportunities for highly selective pre-emptive local interventions.

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