Shear stress and plaque development

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Abstract

Although traditional cardiovascular risk factors 'prime the soil' for atherogenesis systemically, atherosclerosis primarily occurs in a site-specific manner with a predilection towards the inner

wall of curvatures and outer wall of bifurcations with sparing of flow-dividers. Wall shear stress is a frictional force exerted parallel to the vessel wall that leads to alteration of the endothelial phenotype, endothelial cell signaling, gene and protein expression leading to a proinflammatory phenotype, reduced nitric oxide availability and disruption of the extracellular matrix, which in turn leads to plaque development. Clinical and experimental data are emerging that suggest the pathobiology associated with abnormal wall shear stress results in atherosclerotic plaque development and progression.

Keywords

atherosclerosis; endothelium; inflammation; nitric oxide; oxidative stress; plaque; wall shear stress

Although cardiovascular risk factors such as age, hypertension, diabetes, hyperlipidemia and smoking are associated with systemic atherogenesis, atherosclerosis primarily affects large and medium-sized elastic and muscular arteries in a site-specific manner, with a predilection towards the inner wall of curvatures and outer wall of bifurcations with sparing of flow-dividers, with the exception of the pulmonary circulation, which is devoid of atherosclerosis [1,2]. Local hemodynamic forces have been proposed to regulate the site-specific predilection of atherosclerosis and are primarily of two types. One is an outward deforming force that is exerted perpendicular to the vessel wall by the blood pressure and is called 'tensile stress'. The other is a frictional force that is exerted parallel to the vessel wall by virtue of the viscosity of blood and is called 'wall shear stress' (WSS) [3]. It should be noted that the tensile stress is several orders of magnitude larger than the WSS.

Mechanical stress is defined as force per unit area ($1\ Pa = 1\ N/m^2 = 10\ dynes/cm^2$). WSS is defined as the tangential stress on the endothelial surface of the arterial wall derived from the friction of the flowing blood [4]. WSS (τ) is directly proportional to the velocity of blood flow, and inversely proportional to the cube of the arterial radius (R), where flow rate is Q and fluid viscosity is μ: $\tau = 4\ \mu\ Q/R^3$. Shear rate at the arterial wall is the spatial gradient of blood flow velocity (dv/dy). Blood viscosity is a factor of internal friction that causes blood to resist flow and primarily depends on hematocrit and fibrinogen content. WSS (τ) can also be calculated as the product of blood viscosity (μ) and shear rate: $\tau = \mu\ (dv/dy)$ [4,5]. Fluid mechanics models have shown that WSS values of ± 4 Pa are seen in areas susceptible to atherogenesis and are greater than 1.2 Pa in areas protected from atherogenesis. While the 0.5–1.2 Pa range is considered physiological WSS, values below and above this range are considered low and high WSS, respectively [6].

Two contradicting explanations were advanced in the 1960s to explain the effects of WSS in influencing atherogenesis. The first hypothesis was that high shear stress induced endothelial injury and increased permeability to lipids that favored atherogenesis [7,8]. The second hypo thesis was that low shear stress promoted modification of mass transport of atherogenic substances between the lumen and the vessel wall to cause atherosclerosis [9]. Over the years, low WSS has been shown to be predictive of plaque development.

Fluid dynamics & WSS

The nature of the flow of a fluid through a tube is dependent on the velocity of flow and the geometry of the tube. Flow is described as laminar if viscous forces prevail over inertial forces, resulting in the fluid flowing in concentric laminae parallel to the course of the artery, with the highest flow velocity in the center of the tube and the lowest in the periphery. Disturbed laminar flow is characterized by departure of flow from the streamline pattern such that there is formation of flow separation, recirculation and reattachment to forward flow of the laminae. Laminar flow occurs in relatively straight arterial segments and disturbed laminar flow in arterial segments with geometric irregularities, such as curvatures, branches, bifurcations and upstream or downstream from stenoses (FIGURE 1). Laminar flow occurs up to a certain velocity, called the 'critical velocity', above which turbulence occurs because inertial forces dominate over viscous forces. Turbulence is governed by the Reynold's number (Re), which is proportional to the density of fluid (ρ), the diameter of the tube (D) under consideration and the flow velocity (V) while being inversely proportional to the viscosity (μ): $Re = \rho DV/\mu$. The higher the value of Re, the greater the probability of turbulence, such that flow is not turbulent if Re is less than 2000 and definitely turbulent if Re is greater than 3000 [4,10].

The varying geometry of blood vessels and pulsatility of blood flow adds complexity to the patterns of blood flow and, as a result, the WSS vector in different areas of the body. In relatively straight arterial segments where laminar flow occurs, WSS is pulsatile and unidirectional, yielding a positive time-average, varying within the range of 1.5–7.0 Pa over the cardiac cycle [11,12]. In geometrically irregular sections, such as inner curves of vessels and upstream from stenoses, WSS maintains its predominantly unidirectional direction, but flow yields a relatively low positive time-average of less than 1.0–1.2 Pa [11,12]. In outer walls of bifurcations and downstream from stenoses, cyclic departure of the WSS vector from the predominant axial alignment occurs bi directionally during systole, accounting for oscillations in blood flow, and thereby creating oscillatory shear stress that yields a very low time-average (zero or even negative) [11,12].

Mechanisms relating WSS to atherosclerosis development

Effects on endothelial phenotype

The direct effects of WSS on endothelial cells have been elucidated primarily by *in vitro* experiments that investigated the effects of different types of shear flow on cultured endothelial cells lining the flow channel. One of the earliest observations was that sustained laminar flow and consequently physiological WSS induced an ellipsoidal endothelial cell morphology and alignment in the axial direction of flow in a time-dependent manner, whereas low WSS induced polygonal endothelial cell morphology and loss of alignment, findings that were subsequently confirmed *in vivo* [13–15]. Furthermore, laminar WSS was found to arrest endothelial cells in G_0 or G_1 phase of the cell cycle, preventing cell turnover, whereas low WSS accelerated cell turnover that subsequently leads to increases in lipid uptake in regions of disturbed flow through widening of gap junctions between polygonal endothelial cells [16–18].

Effects on endothelial cell signaling

Endothelial cells sense WSS on their luminal side through primary cilia that function as sensors and signal amplifiers of hydrodynamic forces [19]. Integrins, VEGFR-2, ion channels, G-protein-coupled receptors and trimeric G proteins, adhesion molecules (e.g., platelet endothelial cell adhesion molecule-1), gap junctions and membrane lipids have been found to modulate sensing of WSS by endothelial cells [20]. In addition to different mechano-sensing mechanisms interacting with one another to carry out cell signaling, the endothelial cyto skeleton has been found to play a central role in mediating mechano-transduction through conformational change [21,22]. The activation of these mechanosensors leads to triggering of phosphorylation cascades of signaling molecules and subsequent expression of proatherosclerotic genes, such as procoagulant, proapoptotic and proinflammatory genes that promote the atherosclerotic process [23,24].

Effects on low-density lipoprotein uptake

Sterol regulatory element-binding proteins (SREBPs) are key transcription factors that upregulate the expression of genes that encode the low-density lipoprotein (LDL) receptor and fatty acid synthase [25]. Laminar flow results in transient activation of SREBP, whereas disturbed flow results in sustained activation of SREBP [26], which results in subendothelial accumulation of LDL by enhanced permeability through endothelial junctions and LDL receptor-ediated endocytosis [27,28]. This LDL is subsequently oxidized to produce oxidized LDL, which is proatherogenic.

Effects on redox state

Reactive oxygen species (ROS) are a family of molecules including molecular oxygen and its derivatives, such as superoxide anion (O_2^-), hydroxyl radical (HO^-) and lipid radicals. The three main sources of ROS are xanthine oxidase, NADH/NADPH oxidase and nitric oxide (NO) synthase [29].

Although, laminar WSS initially activates NADPH oxidase, the major source of O^{2-} in vascular cells, this effects wanes after 24 h [30]. Laminar WSS also stimulates production of copper zinc-containing superoxide dismutase (SOD) [31] and vascular extracellular SOD [32], responsible for O_2^- scavenging, as well as glutathione (GSH) peroxidase, which is responsible for H_2O_2 scavenging [33], thereby having a predominant antioxidant effect.

Low and oscillatory WSS increases production of ROS and enhances gene expression of major oxidative enzymes, such as NADPH and xanthine oxidases at endothelial cell membranes, thereby stimulating not only sustained but also higher production of O_2^- [34], without an effect on Cu/Zn SOD [30]. Low and oscillatory WSS also decouple endothelial NO synthase (eNOS), which results in the production of ROS [34]. Therefore, low and oscillatory WSS have a discrete pro-oxidant effect, resulting in the induction of oxidative stress that refers to the excessive production of ROS such they overwhelm the endogenous antioxidant defense mechanisms to oxidize biological macromolecules (e.g., DNA, proteins and lipids), subsequently leading to altered endothelial function.

Effects on endothelial NO production & eNOS expression

The endothelium releases NO, which plays a central role in vascular homeostasis, not only by modulating vasomotor tone but also by inhibiting the expression of monocyte chemotactic protein-1 and VCAM-1, preventing propagation of lipid oxidation, inhibiting smooth muscle proliferation and decreasing platelet aggregation, all of which represent the earliest steps in atherosclerosis [35].

Laminar WSS affects endothelial function, which is measured *in vitro* by NO production primarily by two mechanisms. The first mechanism is acute and occurs within seconds of induction of laminar WSS, which induces an acute increase in intracellular calcium that enhances the binding of calmodulin to eNOS to increase eNOS activity and subsequent production of NO [36]. The second mechanism is chronic and occurs after several hours of laminar WSS, which stimulates an increase in eNOS mRNA transcription via the MAPK pathway, and sustained stability of this mRNA via tyrosine kinases. Impaired endothelial function in regions of low WSS has been recently been confirmed by our group in a mouse model (FIGURES 2C & 2D) [37].

Low and oscillatory WSS also induce NO production and eNOS expression [38], but through a different pathway and in addition, decouple eNOS to induce production of ROS such as O_2^- and H_2O_2, which are proinflammatory [34]. *In vivo* human studies using brachial artery reactivity have confirmed the direct relationship between WSS and endothelial function [39,40].

Effects on proinflammatory pathways

Laminar WSS produces anti-inflammatory effects through regulation of endothelial gene expression by transcription factors such as NF-κB and Krüppel-like factor (KLF)-2, thereby controlling inflammation, thrombosis/hemostasis, vascular tone and blood vessel development to effect atheroprotection [41–44].

By contrast, low WSS induces expression of inflammatory molecules such as VCAM-1 and ICAM-1, C-reactive protein, VEGF, IL-6 and upregulation of several broad-acting inflammatory cytokines and receptors, consistent with a proinflammatory phenotype (FIGURE 3) [45–77].

Effects on vascular smooth muscle cells & extracellular matrix

Low WSS can stimulate vascular smooth muscle cell migration from the media to the intima, followed by proliferation that results in formation of a fibrous cap, neointimal formation and arterial wall thickening [48,49]. High WSS produces the opposite effect [50–54].

The extracellular matrix (ECM) consists of collagen and elastin fibers within a ground substance composed of proteoglycans and glycosaminoglycans. The ECM surrounds endothelial cells and provides scaffolding for the vascular wall and fibroatheroma. Matrix metalloproteinases (MMPs) are enzymes that degrade the ECM. Low WSS induces production of MMPs through upregulation of gene expression and stimulation by proinflammatory cytokine release from endothelial cells, macrophages and vascular smooth

muscle cells that results in ECM degradation, and subsequent loss of this support outside the vascular wall to effect vascular remodeling [55–57].

High WSS can also stimulate production of MMPs in endothelial and smooth muscle cells that can degrade the internal elastic lamina of vessel and produce arterial enlargement. In addition, high WSS also stimulates endothelial cells to produce plasmin that dissolves the proteoglycan matrix [58,59] as well as NO and TGF-β that might suppress matrix production by smooth-muscle cells and induce apoptosis of smooth-muscle cells [60,61]. It is thought that if these molecular events occur after the formation of thin cap fibroatheromas in an area of low WSS, thinning of the fibrous cap can occur that makes plaque more vulnerable to fissuring and rupture [62].

Experimental models of WSS & atherosclerosis development

The cause–effect relationship between altered WSS patterns and plaque development was first studied in the carotid arteries of ApoE-knockout mice that were fed a high-fat diet. A conical perivascular shear stress modifier was applied around the carotid artery to create regions of low WSS, high WSS and oscillatory WSS, while maintaining undisturbed flow in the contralateral carotid artery that served as the control arm. Atherosclerotic lesions developed in the regions with low WSS and oscillatory WSS, whereas regions with high WSS were protected. The low WSS regions developed larger atherosclerotic lesions with greater lipid content, fewer smooth muscle cells, lesser collagen and greater outward remodeling compared with their counterparts in the oscillatory WSS region. In addition, regions with low WSS had higher expression of proatherogenic inflammatory mediators (e.g., VCAM-1, ICAM-1, C-reactive protein, VEGF and IL-6, as well as higher MMP activity) and intraplaque hemorrhages. In conclusion, the study showed that low WSS produced larger lesions that were of vulnerable phenotype, whereas oscillatory WSS produced smaller lesions that were of stable phenotype [63].

We have also observed a colocalization of proinflammatory adhesion molecules such as VCAM-1 and ICAM-1 with low WSS in with the inner curvature of the ApoE mouse (FIGURE 2A) [46]. In a subsequent study in ApoE-knockout mice using a novel partial carotid ligation model, we demonstrated that in zones of low WSS, the intimal RNA developed upregulation of pro atherogenic genes (such as those governing VCAM-1 and ICAM-1 expression), as well as downregulation of antiatherogenic genes (e.g., those governing eNOS and KLF-2 expression) (FIGURE 2B) [37]. In addition, the low WSS regions exhibited endothelial dysfunction and developed rapidly progressive atherosclerosis to advanced lesions within 4 weeks (FIGURES 2C & D). This model was unique in that it allows the study of atherosclerosis development and progression in a considerably shorter duration of time and allows for intimal RNA isolation in order to study alterations in genes induced by atherosclerosis-promoting environments.

In a swine diabetic model of atherosclerosis, Chatzizis *et al.*demonstrated that low WSS promoted plaque development and progression to high-risk atherosclerotic plaques that were characterized by a large lipid core, inflammation, thin fibrous cap, severe internal elastic lamina degradation and excessive expansive remodeling [64].

Clinical studies of WSS & atherosclerosis development

WSS & early atheroma development

The role of WSS in plaque development was first suggested in *ex vivo* studies in human aortic specimens where fatty streaks and atheromatous plaque were found to be distributed in regions of low WSS [9,65]. Subsequent studies confirmed these findings in human carotid bifurcations using laser Doppler velocimetry [6,11], coronary vasculature using cinemicrographic techniques [66] and abdominal aorta using MRI velocimetry [67]. These studies described oscillations in the WSS vector during systole and formation of slow recirculatory secondary flows within areas of low WSS as promoters of atherogenesis and exercise as its inhibitor [6,11,66,67].

Cross-sectional studies of the carotid tree in humans using Doppler ultrasound demonstrated that, in patients with unilateral carotid plaques, the common carotid artery with plaque had a lower mean peak WSS compared with the contralateral side devoid of plaque [68]. Similar carotid ultrasonic studies demonstrated that patients with diabetes [69], hypertension [70] and left ventricular hypertrophy [71] had lower WSS compared with controls, and that accumulation of traditional cardiovascular risk factors, such as age and BMI, hypertension, hyperlipidemia, diabetes and smoking, was associated with lower WSS independent of carotid intima-media thickness [72]. In addition, studies using MRI have shown an inverse correlation between wall thickness and WSS [73].

In the coronary circulation, studies using quantitative coronary angiography have shown that low WSS correlates with atherosclerosis progression (FIGURE 4) [74]. Higher resolution evaluation of coronary WSS can be performed using intravascular ultrasound (IVUS), biplane angiography, Doppler flow velocity measurement and computational fluid dynamic models. These more detailed evaluations have shown that vessel wall thickness (an index of atherosclerosis) is inversely correlated with WSS [75]. Subsequently, prospective studies using these techniques demonstrated that low WSS is associated with development of atherosclerosis and outward remodeling [12], as well as neointimal thickness after stent implantation [76].

WSS & vascular remodeling

Vascular remodeling was first described in human autopsy studies as a compensatory change in vessel size as a result of increasing plaque burden and changes in local WSS in an effort to preserve the cross-sectional luminal area. Indeed, it was found that the development of luminal stenoses was delayed until the coronary plaque began to occupy 40% of the internal elastic lamina area [77]. This was later corroborated *in vivo* using IVUS and correlated with clinical presentations such that positive (outward) remodeling and larger plaque areas were associated with an unstable clinical presentation, and negative remodeling with a stable clinical presentation [78].

Positively remodeled vessels often contain eccentric plaque, resulting in a portion of the cross-sectional area of the vessel covered with plaque (the plaque-rich wall) and the remaining portion free of plaque (the plaque-free wall). Two explanations for positive remodeling have evolved. The first suggests that the plaque-free wall expands in response to

increased WSS, resulting in positive remodeling and expansion of the lumen, thereby maintaining a low WSS environment on the plaque-rich wall, further facilitating plaque development [77,79,80]. The second explanation is that an increase in vascular inflammation and MMP production results in fragmentation of the internal elastic lamina, extension of inflammation into the underlying media that causes atrophy of the media and digestion of the surrounding ECM, resulting in positive remodeling [77,81]. Evidence in favor of the former explanation includes studies that have shown that vessels with smaller the plaque-free circumferential wall area have lesser compensatory enlargement [82,83]. Interestingly, progression of coronary atherosclerosis can also be accompanied by an over-compensatory increase in luminal cross-sectional area; on the other hand, regression may be associated with no change in luminal cross-sectional area [84].

Negative (inward) remodeling refers to a local shrinkage of vessel size and, consequently, reduction in luminal area beyond that is explained by increasing plaque burden [78]. As eccentric plaques grow in size and encroach into the plaque-free wall, the ability of the vessel to undergo compensatory enlargement decreases and the plaque assumes a more concentric shape. Such plaques can rupture and heal by fibrosis, further constricting the vessel, resulting in negative remodeling [85,86].

WSS & plaque vulnerability & rupture

The term 'vulnerable plaque' is used to describe plaques that are prone to thrombosis and those that can undergo rapid progression and thus have a high probability of precipitating an acute coronary event. Several cardiovascular pathology studies have helped to characterize such plaques to create major and minor criteria for defining vulnerable plaques, as well as a histopathological classification system. Major criteria include the presence of active inflammation (monocyte, macrophage or T-cell infiltration), a thin cap (<65 μm) with a large lipid core (>40% of the total volume of the plaque), the presence of endothelial denudation with superficial platelet aggregation, fissuring of the surface of the plaque to promote platelet aggregation and the presence of hemodynamically significant stenosis (>90%). Minor criteria include the presence of superficial calcified nodules, intraplaque hemorrhage, endothelial dysfunction and expansive remodeling [87,88].

Current *in vivo* imaging techniques, such as IVUS and optical coherence tomography, allow us to clinically define coronary plaques with vulnerable features and prospectively evaluate their prognostic value. One such study is Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), which investigated 3-year clinical outcomes in patients with acute coronary syndromes who underwent three vessel radiofrequency backscatter or 'virtual histology' (VH)-IVUS to assess plaque burden and content. The preliminary results of PROSPECT suggest that nonculprit lesions with high-risk IVUS features (plaque burden at least 70%, large necrotic core without a visible cap and minimum luminal area up to 4 mm^2) are far more likely to be associated with future major cardiac events compared with nonculprit lesions without these high-risk IVUS features (17 vs 2%; $p < 0.05$) [89]. Experimental studies suggest that low WSS produces plaque with a vulnerable phenotype, whereas oscillatory WSS results in the development of a more stable phenotype [90]. In human carotid arteries, endarterectomy specimens have demonstrated

higher macrophage and lipid concentrations in areas of low and oscillatory WSS [91]. Coronary circulation studies using VH-IVUS have shown that the plaque necrotic core content is higher in segments with low WSS [92,93]. It is possible, however, that a stable plaque phenotype in humans is produced in low WSS coronary segments by recurrent subclinical rupture vulnerable-type plaques progressively resulting in fibrotic lesions [94]. At some point in this process, the WSS increases into the physiologic range. Exactly what drives further plaque formation in segments with physiologic WSS is not known and may involve systemic risk factors, inflammation and endothelial dysfunction. However, as plaque continues to encroach into the lumen, the WSS becomes supraphysiologic or high due to the acceleration of blood flow through the constricted vessel. The ensuing high WSS is thought to induce several biological changes within the fibrous cap that can weaken it and make the plaque more vulnerable to fissuring or rupture [95–97]. As in early-stage vulnerable plaques, the fibrous cap of the more advanced plaque can rupture and heal by fibrosis, causing increasing luminal constriction, or develop overlying thrombus, occluding the vessel and manifesting as an acute coronary syndrome (FIGURE 5) [47,98]. Recent *in vivo* human studies have demonstrated plaque ulceration in areas of high WSS by IVUS of the human coronary arteries and MRI of human carotid arteries, respectively [95–97]. Furthermore, IVUS-derived palpography, a measure of plaque strain in human coronary arteries, has been associated with regions of high WSS [99]. Prospective studies are underway to evaluate the predictive value of WSS on regional plaque progression in human coronary atherosclerosis.

Expert commentary

Atherosclerosis begins with fatty streak formation in an atherogenic milieu that is created by the interplay of systemic cardiovascular risk factors and local hemodynamic forces, such as a low WSS. The precise interplay between WSS, vascular remodeling and further plaque development is not entirely clear and is currently under active investigation. However, it is thought that coronary segments that are geometrically susceptible to low WSS (i.e., outer hips of bifurcations, inner curvatures of vessels, immediately distal to bifurcations and distal to existing plaque) develop atherosclerosis. Within low-WSS segments, the developing plaque could take one of two courses: evolve into a vulnerable phenotype, such as a thin-cap fibroatheroma; or progress into a more stable phenotype, with gradual luminal narrowing that eventually results in an increase in WSS into the physiologic range. It can be speculated that the antiatherogenic effects of physiologic WSS might inhibit further plaque formation in some cases; however, continued exposure to atherogenic risk factors, inflammation and/or endothelial dysfunction can result in plaque progression despite physiologic WSS. However, as plaque continues to encroach into the lumen, the WSS becomes high due to acceleration of blood flow. The ensuing high WSS is thought to facilitate biological changes within the fibrous cap and the plaque itself, making it more vulnerable to fissuring or rupture. The plaque rupture can either heal by fibrosis, causing gradual luminal constriction, or be associated with thrombus, resulting in vessel occlusion and an acute coronary syndrome. Nevertheless, it should be emphasized that the pathobiology of human plaque progression and its translation into clinical events are still uncertain and remain to be fully elucidated by ongoing mechanistic and natural history studies.

Five-year view

With increased understanding of systemic and local factors governing plaque development and the advent of novel imaging techniques, such as optical coherence tomography, endothelial function testing and WSS measurement, the identification of coronary segments that are vulnerable to rapid progression or rupture can be anticipated. Very high-risk segments likely identified with such multimodality imaging could be preemptively treated to prevent acute coronary syndromes and improve clinical outcomes. A combination of focal therapy for targeted vulnerable coronary segments and systemic therapy would represent a paradigm shift in our treatment of chronic coronary artery disease, which is currently focused on relieving symptoms of ischemia but not improving outcomes.

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Key issues

- Although cardiovascular risk factors such as age, hypertension, diabetes, hyperlipidemia and smoking 'prime the soil' for atherogenesis systemically, atherosclerosis primarily affects large and medium-sized elastic and muscular arteries in a site-specific manner, with a predilection towards the inner wall of curvatures and outer wall of bifurcations, with sparing of flow dividers.

- Wall shear stress (WSS) is thought to determine the site-specific predilection of atherosclerosis.

- At the cellular level, low WSS leads to alteration of the endothelial phenotype, endothelial cell signaling, and gene and protein expression, leading to a proinflammatory phenotype, reduced nitric oxide availability and disruption of the extracellular matrix leading to plaque development.

- These concepts have also been shown in experimental models of atherosclerosis. The cause–effect relationship between altered WSS patterns and plaque development has been demonstrated in a number of experimental models of atherosclerosis.

- The relationship between altered WSS and plaque development in human coronary atherosclerosis is not fully understood. However, it is thought that low WSS promotes early plaque development. Blood accelerates with luminal narrowing, thereby initially increasing WSS into the physiologic range. What governs further plaque development in the physiologic WSS environment is unknown, but probably involves systemic risk factors and inflammation. With further luminal encroachment, WSS approaches the supraphysiologic or high range. The ensuing high-WSS environment is associated with certain biological processes that promote plaque vulnerability and destabilization.

- Natural history studies are required to fully elucidate the relationship between WSS, plaque progression and plaque rupture, as well as their translation into clinical events.
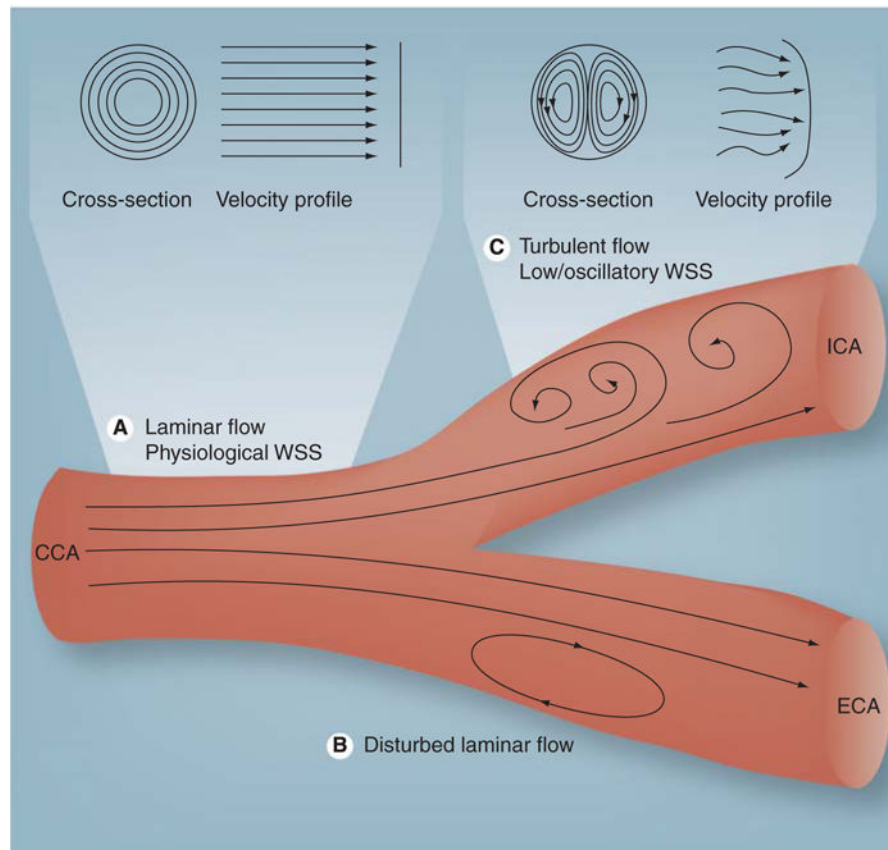
Figure 1. Schematic diagram of the carotid bifurcation demonstrating different types of flow
(A) Laminar flow in which the layers of fluid move in a streamlined and concentric fashion to produce a conical velocity profile. **(B)** Disturbed laminar flow in which layers of fluid separate, flow in the reverse direction and then reattach to maintain forward flow. **(C)** Turbulent flow in which velocity of fluid varies continually, but the overall flow is in the forward direction albeit with a flatter velocity profile.
CCA: Common carotid artery; ECA: External carotid artery; ICA: Internal carotid artery; WSS: Wall shear stress.
Adapted from [100].
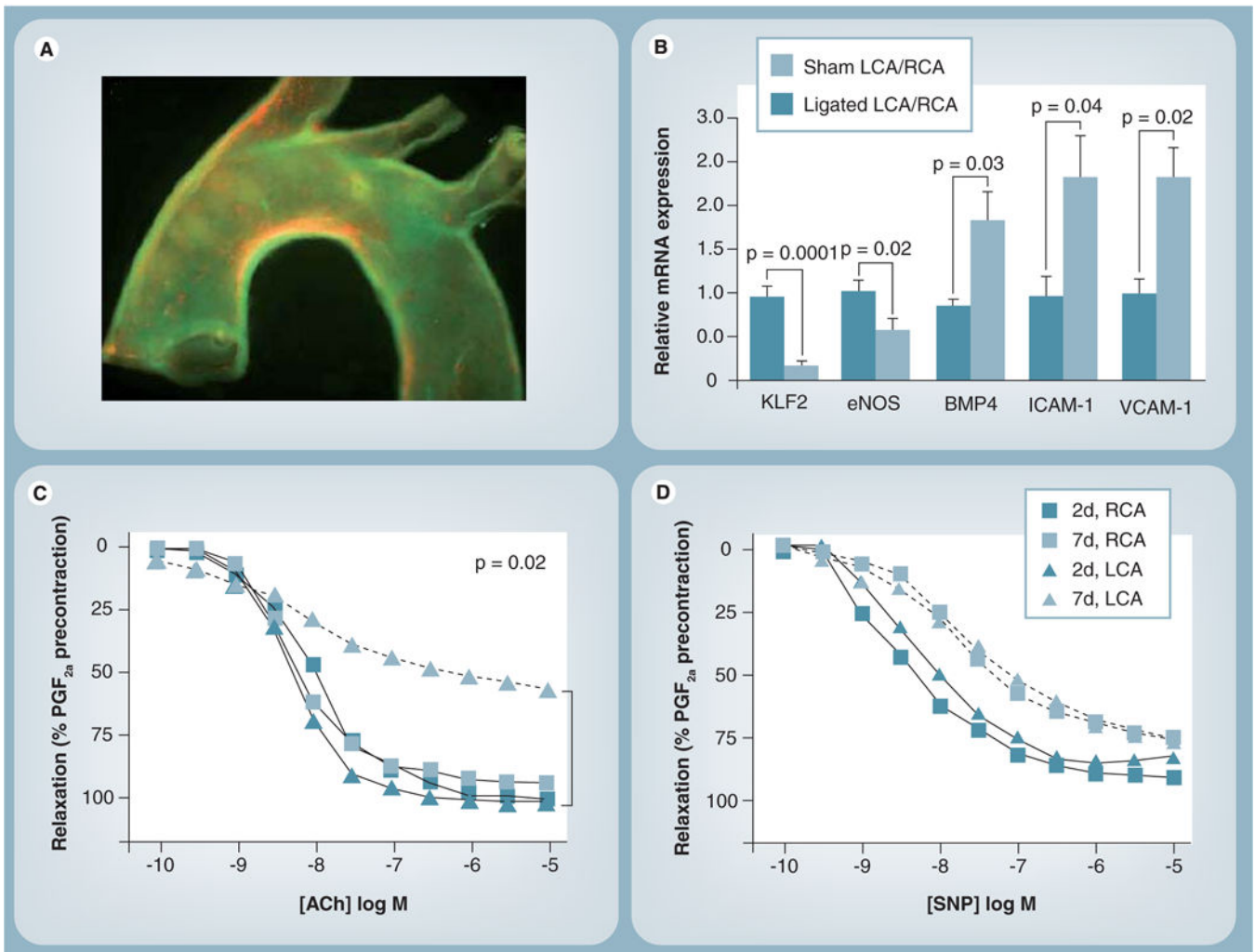
Figure 2. Effects of wall shear stress on inflammation and endothelial function
(A) Epifluorescence image of a whole mouse aortic mount showing the expression of
ICAM-1 and VCAM-1 along the inner curvature of the arch and in the orifices of the arch
vessels, areas that correspond to relatively lower values of mean wall shear stress (WSS).
(B) Bar graphs depicting that partial ligation results in decreases in KLF-2 and eNOS, while
increasing BMP4, ICAM-1 and VCAM-1 expression. **(C)** Impaired endothelium-dependent
vasodilation as evident by lack of acetycholine-induced relaxation of arterial rings obtained
from the left carotid artery of ApoE-knockout mice that underwent partial ligation and were
fed a high-fat diet. **(D)** No impairment of endothelium-independent vasodilation as evident
by complete relaxation induced by sodium nitroprusside.
ACh: Acetylcholine; BMP: Bone morphogenic protein; eNOS: Endothelial nitric oxide
synthase; KLF: Krüppel-like factor; LCA: Left carotid artery; PGF: Prostaglandin F; RCA:
Right carotid artery; SNP: Sodium nitroprusside.
Adapted from [37,46].
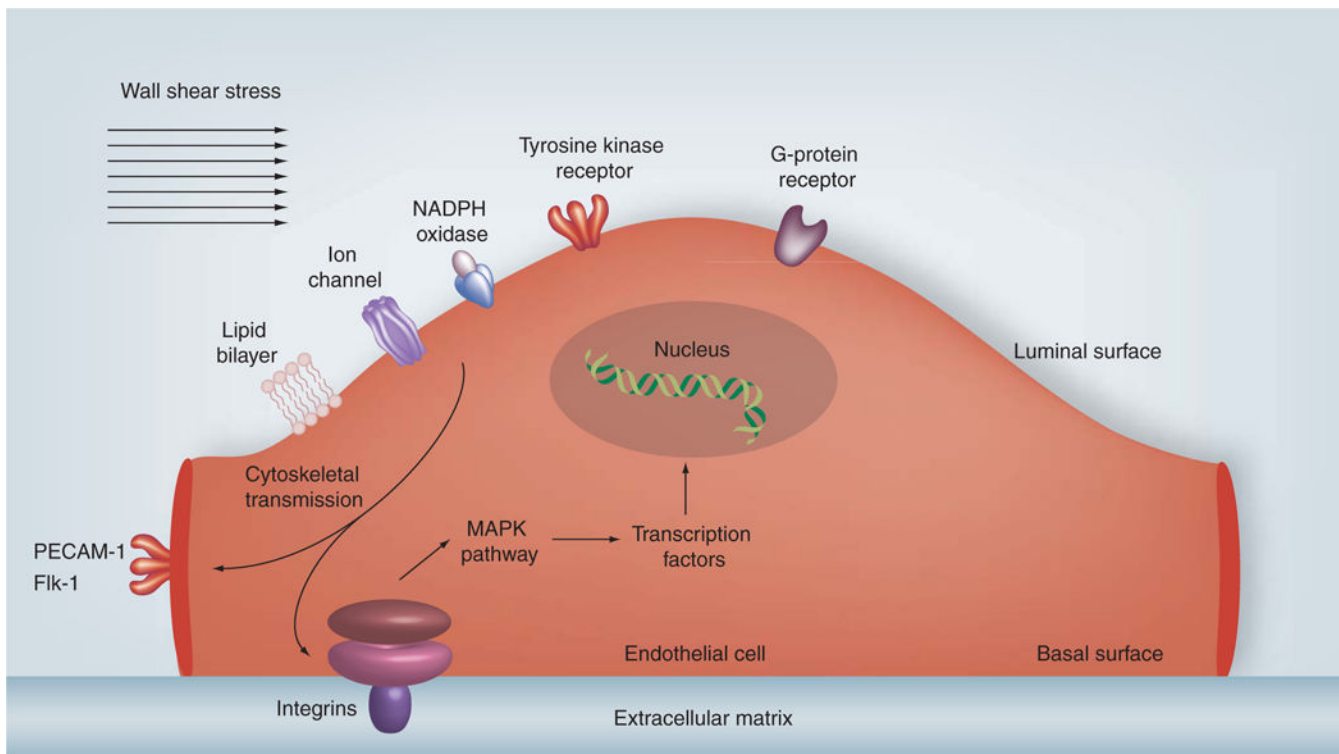
Figure 3. Schematic diagram broadly showing the regulation of transcription in the endothelial cells by wall shear stress

Wall shear stress is sensed on the luminal surface of endothelial cells by ionic channels, lipid layer, tyrosine kinase, G protein, NADPH oxidase and xanthine oxidase receptors that activate integrins on the basal surface of the endothelial cell or PECAM-1 and Flk-1 on the endothelial cell junctional surface via cytoskeletal transmission of shear forces. This initiates a downstream signaling cascade that activate MAPKs and other pathways to phosphorylate transcription factors, such as NF-κB and Krüppel-like factor 2, which regulate expression of atherogenic or atheroprotective genes.

PECAM-1: Platelet endothelial cell adhesion molecule-1.

Adapted from [47,98].
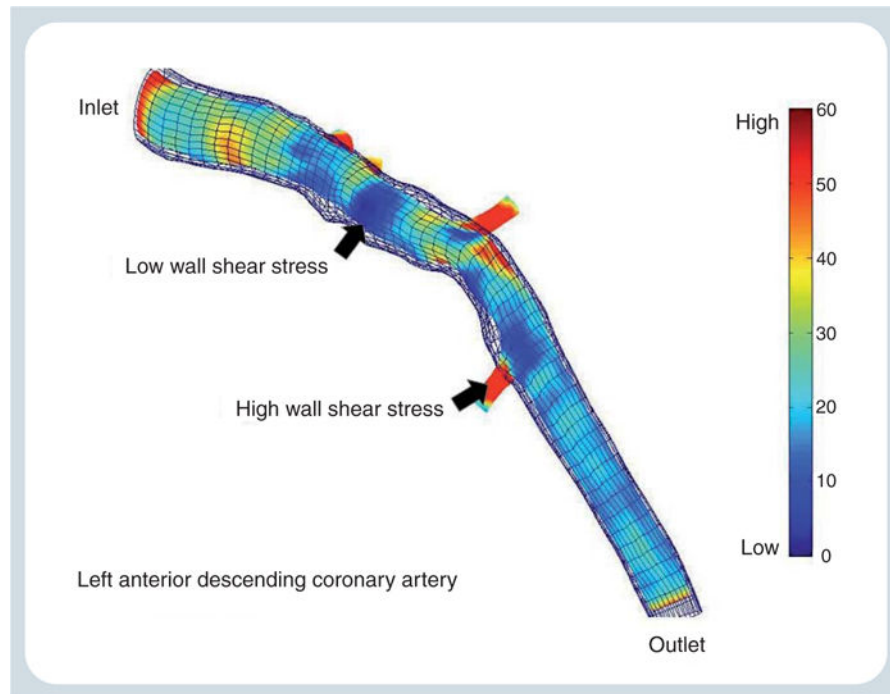
Figure 4.
Wall shear stress profile of the left anterior descending coronary artery from a patient with nonobstructive coronary artery disease performed in our laboratory, outlining areas of low and high wall shear stress.
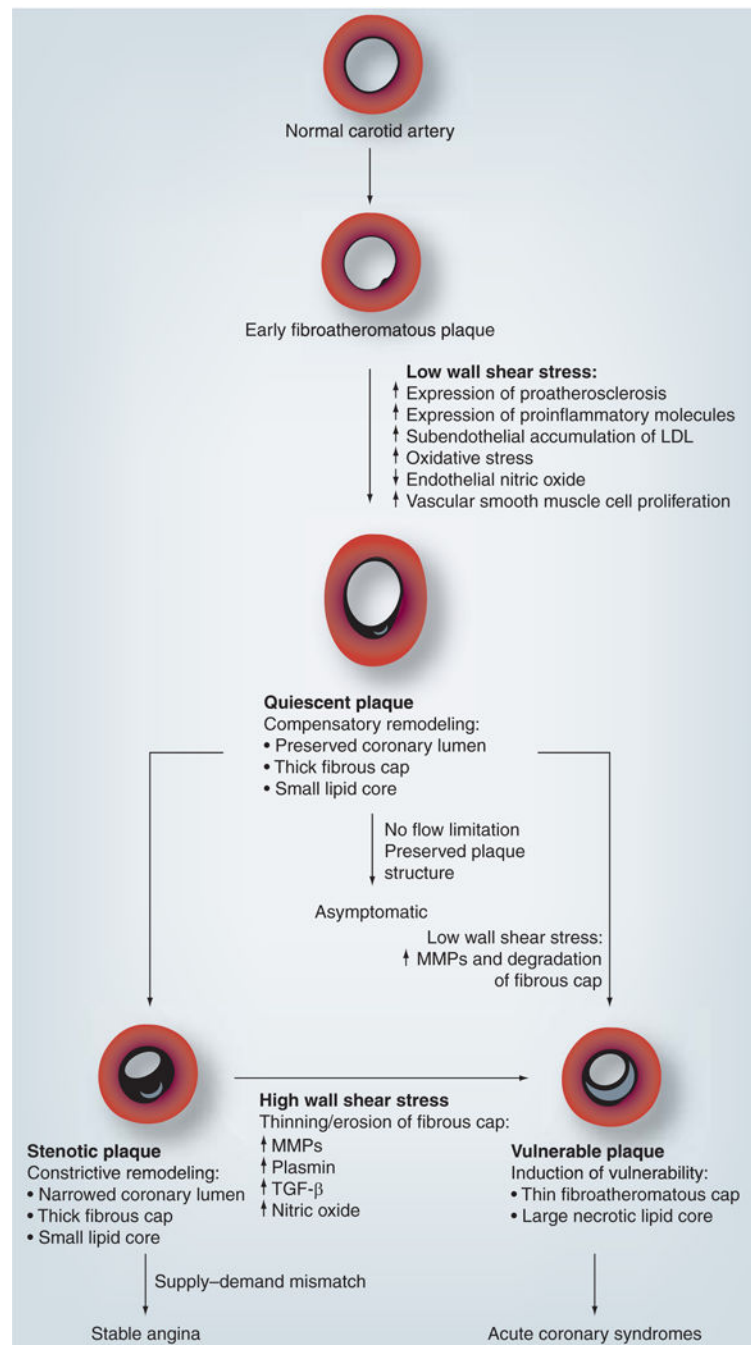
Figure 5. Development of atherosclerotic plaque and the role of wall shear stress in influencing plaque differentiation into quiescent, stenotic and vulnerable phenotypes

LDL: Low-density lipoprotein; MMP: Matrix metalloproteinase.

Adapted from [47,98].