Hemodynamic Shear Stress and Its Role in Atherosclerosis

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Atherosclerosis, the leading cause of death in the developed world and nearly the leading cause in the developing world, is associated with systemic risk factors including hypertension, smoking, hyperlipidemia, and diabetes mellitus, among others. Nonetheless, atherosclerosis remains a geometrically focal disease, preferentially affecting the outer edges of vessel bifurcations. In these predisposed areas, hemodynamic shear stress, the frictional force acting on the endothelial cell surface as a result of blood flow, is weaker than in protected regions. Studies have identified hemodynamic shear stress as an important determinant of endothelial function and phenotype. Arterial-level shear stress (>15 dyne/cm²) induces endothelial quiescence and an atheroprotective gene expression profile, while low shear stress (<4 dyne/cm²), which is prevalent at atherosclerosis-prone sites, stimulates an atherogenic phenotype. The functional regulation of the endothelium by local hemodynamic shear stress provides a model for understanding the focal propensity of atherosclerosis in the setting of systemic factors and may help guide future therapeutic strategies.

JAMA. 1999;282:2035-2042 www.jama.com

FOR MORE THAN A CENTURY, HEmodynamic forces have been proposed as factors regulating blood vessel structure[1,2] and influencing development of vascular pathology such as atherosclerosis,[3-5] aneurysms,[6] poststenotic dilatations,[7] and arteriovenous malformations.[8] The flow of blood, by virtue of viscosity, engenders on the luminal vessel wall and endothelial surface a frictional force per unit area known as hemodynamic shear stress.[9-11] Shear stress has not only been shown to be a critical determinant of vessel caliber,[2,11,12] but has also been implicated in vascular remodeling[13,14] and pathobiology.[5]

Atherosclerosis, which remains the leading cause of death in the developed world, is associated with genetic predisposition and multiple risk factors such as hypertension,[15] smoking,[16] hyperlipidemia,[17] diabetes mellitus,[18] social stress,[19] sedentary lifestyle,[18] viral infection,[20] and possibly chlamydial infection.[21] Despite the systemic nature of its associated risk factors, atherosclerosis is a geometrically focal disease that has a propensity to involve the outer edges of blood vessel bifurcations.[5,22,23] In these susceptible areas, blood flow is slow and changes direction with the cardiac cycle, resulting in a weak net hemodynamic shear stress. In contrast, vessel regions that are exposed to steady blood flow and a higher magnitude of shear stress remain comparatively disease-free.[4,5,22-25]

Recent animal, molecular, and cellular studies of the endothelium's response to hemodynamic shear stress have provided new insights into its possible contribution to the pathogenesis of atherosclerosis.[10,26-30] In this article, we review the recent advances made in understanding the regulation of endothelial cell function and gene expression by shear stress. The modulation of endothelial phenotype by local hemodynamic shear stress is postulated to contribute to the focal geometric progression of atherogenesis in the setting of local and systemic risk factors that enhance the thrombotic, proliferative, and inflammatory components of this pathological process.

THE VESSEL WALL AND HEMODYNAMIC FORCES

The luminal surface of the blood vessel and its endothelial surface are constantly exposed to hemodynamic shear stress.[9,10] The magnitude of the shear stress can be estimated in most of the vasculature by Poiseuille's law[9] (FIGURE 1, A), which states that shear stress is proportional to blood flow viscosity, and inversely proportional to the third power of the internal radius.[11,12,31,32] Measurements using different modalities show that shear stress ranges from 1 to 6 dyne/cm² in the venous system and between 10 and 70 dyne/cm² in the arterial vascular network (Figure 1, B). In numerous experiments, shear stress has been shown to actively influence vessel wall remodeling.[1,2,33] Specifically, chronic increases in blood flow, and consequently shear stress, such as seen in the radial artery of dialysis patients proximal to their arteriovenous fis-

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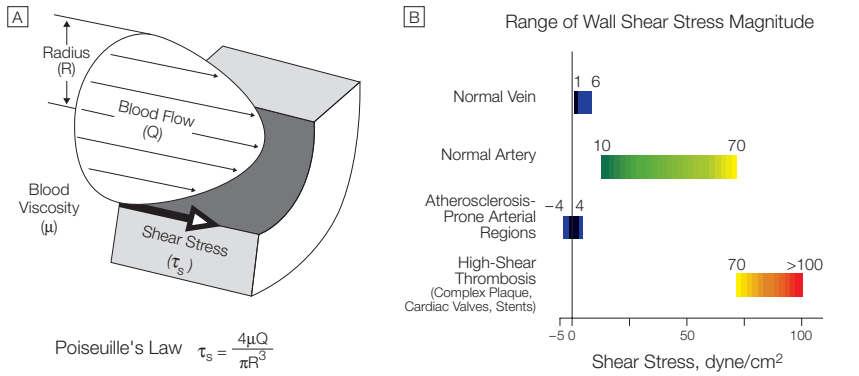
Figure 1. Hemodynamic Shear Stress



A, Cross-sectional schematic diagram of a blood vessel illustrating hemodynamic shear stress, τ_s, the frictional force per unit area acting on the inner vessel wall and on the luminal surface of the endothelium as a result of the flow of viscous blood. B,Tabular diagram illustrating the range of shear stress magnitudes encountered in veins, arteries, and in low-shear and high-shear pathologic states.

tula,[34] or in feeder arteries supplying cerebral arteriovenous malformations,[8] lead to expansion of the luminal radius such that mean shear stress is returned to its baseline level.[1,34] Conversely, decreased shear stress resulting from lower flow or blood viscosity[35] induces a decrease in internal vessel radius.[2] The net effect of these endothelial-mediated compensatory responses is the maintenance of mean arterial hemodynamic shear stress magnitude at approximately 15 to 20 dyne/cm^2.[11,34] This shear stress–stabilizing process is dependent on intact endothelial function and is abolished by prior selective destruction of the endothelial monolayer.[2]

SHEAR STRESS AND THE LOCALIZATION OF ATHEROSCLEROTIC PLAQUES

Atherosclerotic lesions long have been known to occur near vascular branching points.[36] Two contradictory hypotheses were advanced in the 1970s to explain this distribution of lesions. The first implicated high shear stress (400 dyne/cm^2)[3] via direct endothelial injury and denudation, as suggested by experimental exposure of endothelium to supraphysiological shear stress (400 dyne/cm^2). The second, proposed by Caro et al,[4] invoked low shear stress. Subsequent observations and studies made in the last 3 decades have validated the low-shear hypothesis of atherosclerosis.[5,22,24,25] An explanatory mechanism for this association has recently begun to evolve[10,26,28-30] that can serve to explain the focal nature of the inflammatory and proliferative responses to injury that likely underlie atherogenesis.[37]

Atherogenesis preferentially involves the outer walls of vessel bifurcations and points of blood flow recirculation and stasis (FIGURE 2, A and B). In these geometrically predisposed locations, fluid shear stress on the vessel wall is significantly lower in magnitude and exhibits directional changes and flow separation, features absent from regions of the vascular tree generally spared from atherosclerosis. Direct measurements and fluid mechanical models of these susceptible regions have revealed shear values on the order of ±4 dyne/cm^2 compared with greater than 12 dyne/cm^2 in the protected areas.[5,38] This association suggests that physiological or elevated levels of shear stress might shield against atherosclerosis via effects on the endothelium, a hypothesis since confirmed in cholesterol-fed miniature swine.[39]

Atherosclerotic lesions co-localize with regions of low shear stress throughout the arterial tree, from the carotid artery bifurcation[5,23,24] to the coronary,[22,40] infrarenal, and femoral artery vasculatures.[41] High-speed cinematography and microparticle flow analysis in postmortem coronary arterial trees have correlated subintimal thickening with the low wall shear stress of bifurcations[22]; in contrast, pathologic lesions were absent from the flow-dividers and inner wall where shear is higher. The local rates of atherosclerosis progression in patients with coronary artery disease were found by serial quantitative coronary angiography to correlate inversely with shear stress magnitude, even when controlled for systemic risk factors such as circulating levels of lipoproteins.[42]

Flow analysis and corresponding carotid endarterectomy pathological sections showed greatest plaque thickness in the outer wall of the carotid sinus where flow shows stasis and shear is low in magnitude and exhibits direction reversal[13] (Figure 2). Gnasso et al[23] found that plaque-affected human carotid arteries exhibited significantly lower wall shear stress than did disease-free controls. The co-localization of atherosclerosis to low-shear areas has also been confirmed in the only location in the human body where 2 arteries join to form a vascular confluence, at the apex of the intracranial vertebrobasilar junction.[43]

The localization of atherosclerosis to low shear regions has been further established in human abdominal aortas both at autopsy[41] and with noninvasive magnetic resonance phase velocity mapping.[44,45] The same pattern of early plaque localization is observed in young trauma patients,[46] regardless of ethnic origin[47] or dietary habits.[48] En-face examination of endothelial surfaces in human thoracic aortas reveals leukocyte adhesion, accumulation of subendothelial macrophages and lymphocytes, irregular endothelial morphology with denuded regions covered with platelets, and dilated intercellular clefts in the outer walls but not in the inner walls or flow divider of bifurcations.[49] Measurements of wall shear stress using echo-Doppler ultrasound in healthy young patients (aged 28-38 years) revealed a statistically significant inverse relationship between intima-media thickness in the carotid artery and local wall shear stress.[50] Similar localization of atherosclerotic lesions has been reproduced in prospective experimental animal studies in the aorta[51,52] and

carotid arteries.[53] These data together establish a clear correlation between low wall shear stress and subintimal thickening and atherosclerosis initiation. They are consistent with the hypothesis that low wall shear stress contributes importantly to conditions that favor atherogenic transformation.

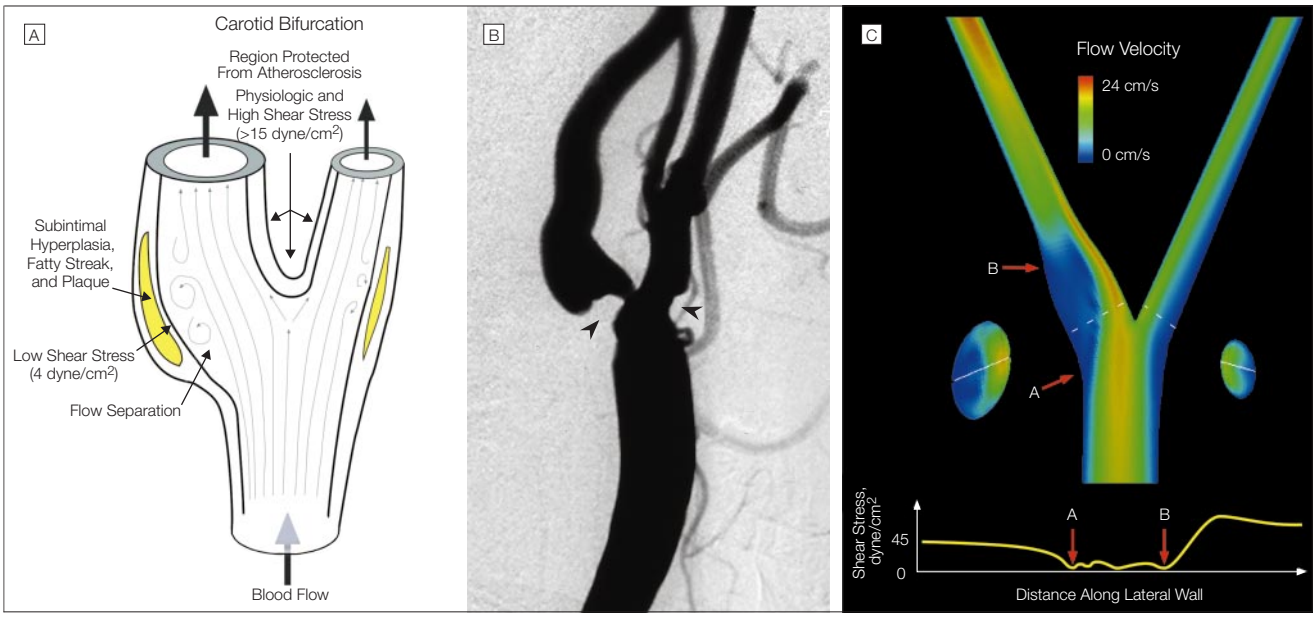
BIOLOGICAL RESPONSE OF THE ENDOTHELIUM TO SHEAR STRESS

In Vivo Responses to Surgically Induced Alterations in Shear Stress

Additional insight into the importance of the endothelial response to hemodynamics has also been gained from animal experiments in which shear stress has been acutely or chronically altered. Increasing shear stress in the rat by surgical construction of an aortocaval shunt results in increased cyclic guanosine 3′5′-monophosphate (presumably as a result of increased nitric oxide release),[54] and elevated shear increased endothelial nitric oxide synthase (eNOS) messenger RNA (mRNA), protein, and activity in high-shear stressed aortas compared with sham-operated controls.[55] These increases were followed by vessel structural expansion[54] similar to that seen in the canine model.[1] This structural increase in vascular lumen to normalize shear was prevented in the rat model by inhibition of nitric oxide synthase (NOS) with N-ω-nitro-l-arginine-methyl ester.[56] The central role of eNOS in shear-mediated structural remodeling was confirmed by Rudic et al[57] when, in wild-type mice, the common carotid artery responded to surgically induced decrease in flow by reducing caliber to normalize shear stress to its preoperative level, whereas it failed to do so in mutant mice that lacked the gene for eNOS.[57] In a baboon polytetrafluoroethylene graft fistula model, elevated shear stress was associated with increased expression of eNOS, a lower degree of neointimal and smooth muscle proliferation, and even induced regression of previously established neointima.[58] In contrast with their high-shear counterparts, low-shear grafts exhibited greater smooth muscle cell proliferation and higher levels of platelet-derived growth factor–A protein and mRNA.[59] The connection between high shear stress and low intimal proliferation has been further clarified in rodent experiments showing that focal increases in shear stress in the aorta resulted in corresponding decreases in angiotensin-converting enzyme activity.[60]

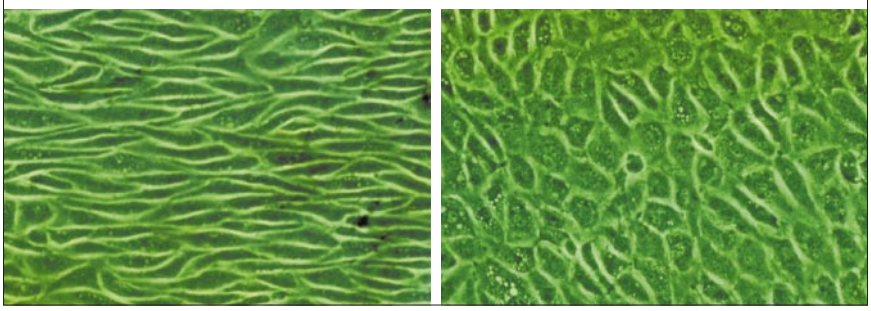
Shear stress has also been associated with the endothelial proliferative state in animal studies. Endothelial cell proliferation increased 18-fold within 48 hours of reduction in shear stress.[61] Decreasing shear stress was followed by endothelial cell loss and desquamation, altered morphology with decreased elongation, decrease in actin stress fibers, greater monocyte attachment to and migration across the endothelial layer,[62] and increased endothelial surface expression of vascular cell adhesion molecule 1.[63] The increased endothelial cell loss in response to decreased shear has re-

Figure 2. Localization of Atherosclerosis Lesions



A, Schematic illustration of the focal nature of atherosclerosis and its tendency to involve the outer walls of vascular bifurcations such as the carotid, coronary, renal, and iliac artery flow dividers. B, Left lateral cervical carotid arteriogram in a 75-year-old man who experienced an embolic stroke in the left temporal lobe. Focal narrowing is seen at the outer walls of the common carotid artery bifurcation in both the internal carotid artery (arrowhead) and the external carotid artery (arrowhead). C, Velocity map of the carotid bifurcation at end-systole using computational fluid dynamic modeling illustrates the lower velocities seen at the outer lateral edges (blue).[38] The computed wall shear stress (bottom) shows the focal low shear magnitude at the outer walls that correspond exactly to the atherosclerosis-prone areas of the carotid bifurcation (compare with B) and is in contrast with the less susceptible inner regions of the bifurcation where flow velocity and, consequently, hemodynamic shear stress at the vessel wall is higher (yellow and green). (Courtesy of Drs David Saloner and Liang-Der Jou, University of California, Berkeley).

Figure 3. Transformation of Endothelial Cell Morphology by Fluid Shear Stress



Bovine aortic endothelial cells exposed to physiologic shear stress (>15 dyne/cm^2, left panel) for 24 hours align in the direction of blood flow while those exposed to low shear stress (right panel) do not (phase contrast; original magnification ×125). See "Biological Response of the Endothelium to Shear Stress" section.

Table. Endothelial Response to Hemodynamic Shear Stress*

	Hemodynamic Shear Stress	
	Physiologic Arterial Magnitude (τ_S>15 dyne/cm^2)	Low Arterial Magnitude (τ_S~ ± 0-4 dyne/cm^2)
Endothelial cell morphology	Fusiform aligned	Polygonal unaligned
Endothelial cell function		
Vasoactive agents		
Vasoconstrictors		
ET-1[102]/ECE[86]	Low	High
ACE[60]	Low	High
Vasodilators		
NO/NO syntase[67-69,81-83]	High	Low
PGI_2/PGI_2 synthase[66-84]	High	Low
CNP[86]	High	Low
Adrenomedullin[87]	High	Low
Antioxidant enzymes		
COX-1, 2[85]	High	Low
Mn SOD[85]	High	Low
Cu/Zn SOD[93]	High	Low
Growth regulators		
Growth factor		
PDGF-B[78,97]	Low	High
PDGF-A[59]	Low	High
Growth inhibitor		
TGF-β[88]	High	Low
Inflammatory mediators		
MCP-1[101]	Low	High
Adhesion molecules		
VCAM-1[100,101,103]	Low	High
Thrombosis/fibrinolysis		
tPA[89,90]	High	Low
TM[89]	Low	High
Endothelial proliferation[78]	Low	High
Endothelial apoptosis[79]	Low	High

*ET-1 indicates endothelin 1; ECE, endothelin-converting enzyme; ACE, angiotensin-converting enzyme; NO, nitric oxide; PGI_2, prostacyclin; CNP, C-type natriuretic peptide; COX, cyclooxygenase; Mn SOD, manganese-containing superoxide dismutase; Cu/Zn SOD, copper/zinc-containing superoxide dismutase; PDGF-A, B, platelet-derived growth factor A-chain, B-chain; TGF-β, transforming growth factor beta; MCP-1, monocyte chemotactic peptide 1; VCAM-1, vascular cell adhesion molecule 1; tPA, tissue-type plasminogen activator; and TM, thrombomodulin.

cently been suggested to be the result of apoptosis, which remains unabated until the shear normalization has been restored.[64] These in vivo experiments obtained in various species using different methods to alter hemodynamics help establish a framework to understand the propensity for intimal hyperplasia and atherosclerosis initiation in areas of low shear stress and the protective effect of elevated shear stress in sheltered regions of the vasculature.

The correlations between hemodynamic factors and intimal hyperplasia in humans and animal models[5,22,1,7,7] have led to intensive study of the in vitro endothelial response to fluid shear stress in the past decade.[10,26-30,65]

Short-term Effects of Shear Stress on Endothelial Function

Hemodynamic shear stress resulting from second-to-minute time-scale variation in flow increases secretion of prostacyclin[66] and nitric oxide,[67,68] both of which hinder platelet activation,[69,70] attenuate smooth muscle proliferation,[71] and inhibit neointima formation following experimental balloon injury in animals.[72,73] Physiological shear stress (>15 dyne/cm^2) decreases in vitro endothelial cell turnover by decreasing both the basal rate of proliferation [74,75] and the rate of apoptosis from growth factor depletion, tumor necrosis factor α or hydrogen peroxide exposure [74,76,77] via activation of Akt, and attenuated caspase-mediated killing.[76]

Control of Endothelial Gene Expression and Phenotype Switching by Shear Stress

Fluid shear stress transforms polygonal, cobblestone-shaped endothelial cells of random orientation into fusiform endothelial cells aligned in the direction of flow (FIGURE 3). Shear stress of physiological and elevated magnitudes decreases endothelial turnover by decreasing both proliferation[78] and apoptosis,[79,80] increasing the production of vasodilators,[81-87] paracrine growth inhibitors,[88] fibronolytics,[89-92] and antioxidants,[93,94] and suppressing production of vasoconstrictors,[95,96] paracrine growth promot-

ers,[78,97,98] inflammatory mediators,[99] and adhesion molecules.[100,101] These responses contribute to functional switching of endothelial phenotype by shear stress from a quiescent atheroprotective phenotype under physiological and elevated levels of shear stress (>15 dyne/cm^2) to an atherogenic phenotype at low shear stress (0-4 dyne/cm^2) with high endothelial turnover. Shear stress thus regulates the endothelial phenotype on a time scale of hours to days by controlling the expression of all its known major functional product classes (TABLE).

Detrimental Effects of Oscillatory and Turbulent Shear Stress

Oscillatory shear stress, unlike steady shear stress, can fail to induce $[Ca^{2+}]_i$ transients[103] or suppress endothelin 1 mRNA.[102] In vitro oscillatory shear stress of low magnitude (±5 dyne/cm^2) increases endothelial levels of superoxide anion (O_2^-) via activation of its biosynthetic enzyme, nicotinamide adenine dinucleotide (reduced form) oxidase,[94] and enhances monocyte adhesion.[104] Oscillatory shear stress is a weaker inducer of eNOS than steady shear stress,[105] and creates greater endothelial cell proliferation.[75,77] Similarly, turbulent shear stress, in contrast to steady laminar shear stress, induces in vitro endothelial cell turnover[106] and fails to stimulate in vitro mRNA expression of eNOS, Mn^2 + superoxide dismutase, and COX-2 genes.[85]

Although extrapolation from in vitro data to the living organism may be difficult, these findings suggest that elevated arterial-level shear stress (>15 dyne/cm^2) induces a quiescent, antiproliferative, antioxidant, and antithrombotic phenotype,[10,28,78] while time- and direction-varying low shear stress magnitude (<4 dyne/cm^2), as seen in regions prone to atherosclerosis,[5,22] results in an aggressive and proliferative phenotype.

A Model of Atherogenesis Based on the Endothelial Response to Shear Stress

Investigations of the cellular mechanisms of atherosclerosis initiation and progression have contributed to a con-

Figure 4. Model of Atherogenesis

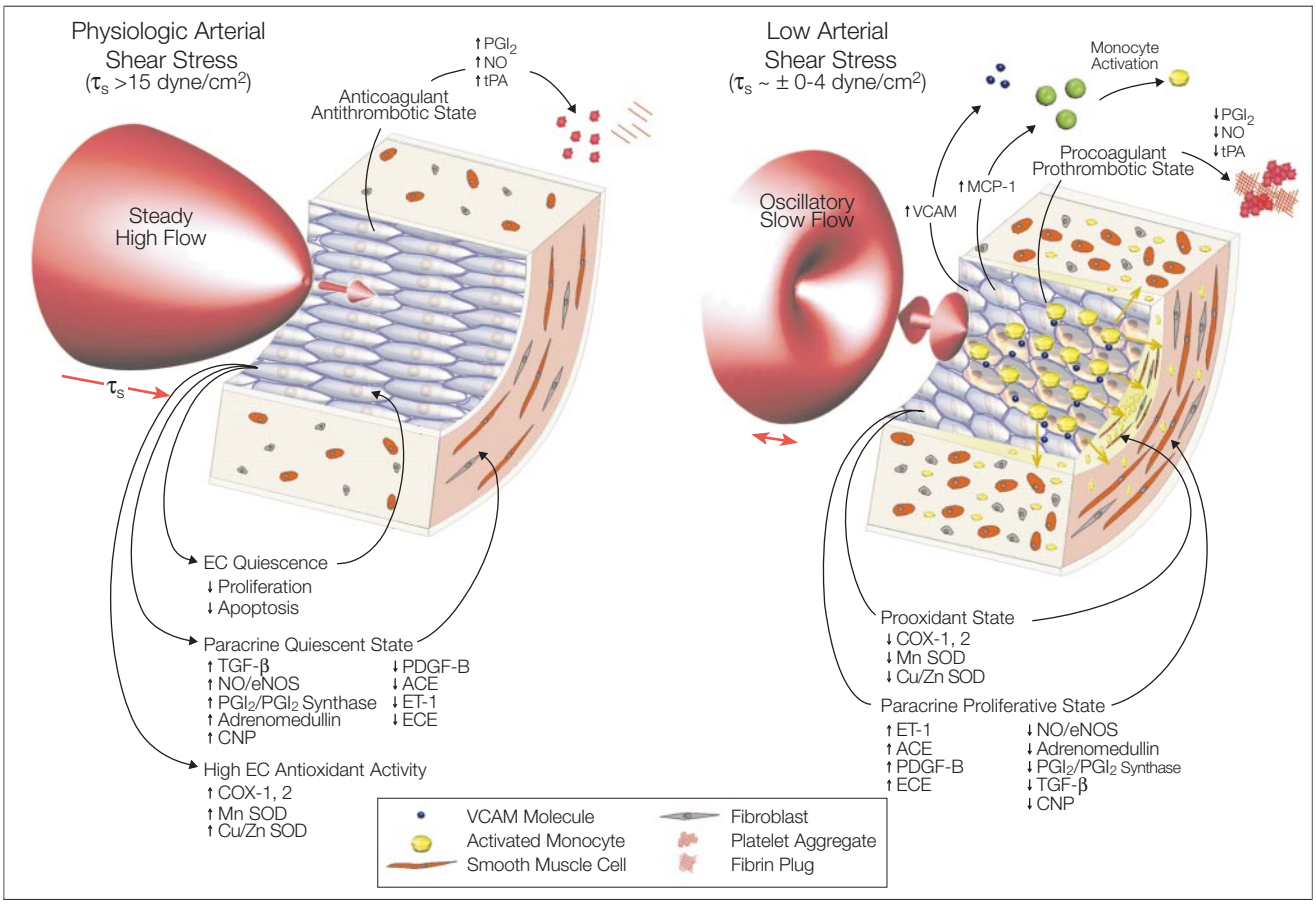


Illustration of the arterial endothelial phenotypic switch from atheroprotective (left panel) to atherogenic (right panel) induced by the local low-magnitude shear stress (<4 dyne/cm^2) conditions found in atherosclerosis-prone regions of vascular bifurcations.[5,22,24] The atherogenic endothelial phenotype resulting from weak local hemodynamic shear stress at the vessel wall includes the low shear-mediated recruitment and activation of monocytes, increased platelet activation, increased vasoconstriction and paracrine growth stimulation of vessel wall constituents, increased oxidant state, and increased apoptosis and cellular turnover (right panel). τ_s Indicates shear stress; NO, nitric oxide; EC, endothelial cell; and NOS, endothelial nitric oxide sythase. For other abbreviations, see footnote to Table.

sistent model involving immune and inflammatory responses perpetuated by a self-reinforcing cycle of monocyte recruitment, lipid accumulation by macrophages, increased smooth muscle cell proliferation, increased oxidant activity, and eventual plaque rupture and thromboembolic complications.[37,107] The paradigm of endothelial functional regulation by shear stress can explain the focal propensity of the atherosclerotic response to intimal injury (FIGURES 2 and 4 and Table).

The shear-controlled gene expression of endothelial cells likely has evolved to maintain global vascular structural and functional homeostasis through local control by transduction of hemodynamic shear. Shear stress of physiological arterial magnitudes (>15 dyne/cm^2) appears to produce an atheroprotective endothelial phenotype (Figures 3 and 4) that consists of decreased expression of vasoconstrictors, paracrine growth factors, inflammatory mediators, adhesion molecules, oxidants, and elevated production of vasodilators, growth inhibitors, fibrinolytics, antiplatelet factors, and antioxidants. The atheroprotective phenotype is imparted by physiological and elevated shear and renders endothelium less susceptible to pathogenic stimuli of injury, cell adhesion, cell proliferation, and lipid uptake (Figure 4).

In contrast, the outer walls of vessel bifurcations are characterized by low and oscillatory shear stress due to vascular network architectural constraints (0±4 dyne/cm^2) and are prone to atherosclerosis. These focal areas manifest greater endothelial cell cycling and vulnerability to systemic apoptogenic stimuli such as oxidized low-density lipoprotein and tumor necrosis factor (TNF) α. Endothelial cells under the hemodynamic conditions described in Figure 4 might preferentially activate circulating monocytes and encourage local adhesion and diapedesis. Persistently low antioxidant levels likely act in synergy with reduced production of nitric oxide to potentiate the steady paracrine mitogenic stimulation of vessel wall constituents. High endothelial production of vasoconstrictor and mitogenic substances such as endothelin 1, angiotensin II, and platelet-derived growth factor B acts to perpetuate underlying smooth muscle and fibroblast proliferation. In addition, reduced production of fibrinolytic tissue-type plasminogen activator, coupled with low production of nitric oxide and prostacyclin, may foster focal platelet aggregation and fibrin deposition, accelerating plaque formation and increasing the risk of thromboembolic events. This hypothesis is compatible with systemic effects of hyperlipidemia on blood viscosity,[108] and with possible effects of low blood flow on increased platelet aggregation[109] and thrombosis.[110]

This model does not preclude the important contributions of known systemic cardiovascular risk factors. These deleterious systemic factors, such as smoking, hyperlipidemia, hypertension, or infectious agents, although thought to act on all regions of the vasculature, may be particularly potent in accentuating the local atherogenic phenotype of the endothelial cell in regions of low shear stress. Similarly, the systemic benefits of exercise, such as the observed increase in human NOS activity with cycle training,[111] may induce local elevations of atheroprotective shear stress at otherwise atherosclerosis-prone low-flow regions at bifurcations. Sufficient activity-related elevation of local shear stress might then shift endothelial phenotype along the continuum from atherogenic toward atheroprotective, thus attenuating (and potentially reversing) this chronic disease process.

CONCLUSION

Shear stress studies have altered our concept of the endothelium from that of a passive, nonthrombogenic surface to that of a dynamically responsive vascular element producing autocrine and paracrine factors under the functional regulation of local hemodynamic forces.[10,26-30,65] These findings have underlined the importance of studying endothelial cell function under flow conditions and have renewed efforts to identify novel and known gene products that may be regulated by shear stress.[85,112] The molecular phenotypic switching of endothelium by shear stress offers an integrated model to explain the focal nature of atherosclerosis. Future work will address therapeutic approaches to thwart the local atherogenic phenotype of the endothelial cell in lesion-prone low-shear regions, without interfering with its ability to maintain global vascular homeostasis, and should include studies of interactions of this regulation by clinically established cardiovascular risk factors.

Funding/Support: Dr Malek was supported by a National Institutes of Health (NIH) Medical Scientist Training Program grant, the Whitaker Foundation, and the Boston Neurosurgical Foundation. Dr Alper is supported by NIH grant HL15175 and by a grant-in-aid from the American Heart Association. Drs Izumo and Alper were Established Investigators of the American Heart Association during the course of this research.
Acknowledgment: We apologize to those colleagues whose work was not cited due to space limitations.

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