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RESEARCH REVIEW

Mechanopathobiology of Atherogenesis: A Review

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Cardiovascular disease is the number one cause of mortality in the United States. Atherosclerosis, the primary etiology of cardiovascular disease is hypothesized to be a time-dependent response to arterial injury. Although risk factors for atherosclerosis are systemic in nature, certain arteries (e.g., coronary arteries) are more susceptible to plaque formation than others. The heterogeneous distribution of atherosclerosis in the vasculature is thought to be related to biomechanical factors. A review of the relevant pathological features of atherogenesis and how physiologically-consistent mechanical stimuli can impact those processes supports this notion. However, specific investigations geared toward finding the mechanistic link between mechanical stimuli and early atherogenic processes are required to differentiate those stimuli that facilitate and those that inhibit atherogenesis. Such knowledge is required for intelligent direction in the search for potential targets for clinical intervention.

Key Words: **atherosclerosis; vascular biomechanics; mechanobiology; cardiovascular disease; coronary; arterial dynamics.**

INTRODUCTION

In the United States cardiovascular disease (CVD) currently afflicts over 70 million people and claims almost a million lives each year [1]. The most prominent cardiovascular diseases, heart disease and stroke, account for almost 40% of all deaths and an estimated economic burden of 394 billion dollars in 2005 [2]. Atherosclerosis, the primary etiology of CVD, is characterized by intimal plaques that form as a time-dependent response to chronic arterial injury [3]. The mechanism of the vessel response to this insult is not well characterized but it is clear that the result is an atherosclerotic plaque with the potential to rupture, thrombose, and occlude the injured artery, leading to the loss of blood flow to vital organs such as the heart and brain [4]. Current therapies for CVD are directed at the revascularization of occluded blood supplies or the reduction of risk factors associated with atherosclerosis (e.g., dyslipidemia, hypertension, diabetes, and smoking). These approaches have led to modest reductions in mortality for coronary heart disease [5]. Unfortunately, this trend is leveling off, demonstrating a lack of understanding of the true pathogenic mechanisms of the disease [6]. That is, known risk factors do not completely determine the probability of disease, and revascularization merely slows the inevitable. Similar therapies have not been as successful in the management of stroke, as indicated by the little change in mortality rate over the same time period, further demonstrating the need to better understand the pathogenesis of atherosclerosis [6]. With the aging population, the prevalence of CVD will continue to increase unless a more basic understanding of the primary causes and pathogenesis of atherosclerosis is reached. Such an understanding would certainly lead to new therapies directed at prevention of those primary causes and halting the pathogenic process.

Possible contributors to the development of atherosclerosis can be categorized as biochemical (e.g., lipids) or biomechanical (e.g., hypertension). The most noteworthy biochemical agent associated with atherosclerosis is low-density lipoprotein (LDL) [7, 8]. However, LDL, like other documented risk factors, provides a systemic

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type stimulus while atherosclerosis is a highly localized, heterogeneous disease predominately affecting the coronary arteries, infrarenal abdominal aorta, and carotid bifurcation, while sparing the thoracic aorta and arteries of the upper extremities [9]. On the other hand, biomechanical forces are not necessarily systemic and vary greatly with anatomical location. The complex biomechanical milieu of the vasculature is an area of intense research. There is a preponderance of data to suggest that these complex biomechanical stimuli play a pivotal role in the location-specific development of atherosclerosis. In other words, biomechanical forces (depending on their magnitude, frequency, direction, etc.) either facilitate or protect against the systemic insults provided by the above mentioned risk factors. This paper extends previous reviews of the mechanopathobiology of atherosclerosis by going beyond the observational correlations between local hemodynamics and atherosclerotic lesion localization. This review will articulate how vasculature-specific mechanical stimuli can affect known atherogenic processes. Furthermore, we will demonstrate the need for more rigorous mechanistic studies that provide a framework for mapping a biomechanical stimulus to a well-defined spectrum spanning atheroprotective to atherogenic. First, it is prudent to summarize the relevant, known pathobiological features of atherosclerosis.

RELEVANT PATHOLOGICAL FEATURES OF ATHEROGENESIS

The development of atherosclerotic plaques has been hypothesized to be a "response to injury" to the vessel wall [10]. This injury is usually a chronic low level insult to the endothelial or smooth muscle cells of the arterial wall manifesting itself in endothelial dysfunction [11]. This leads to, among other things, lipid accumulation [12] and leukocyte adhesion and infiltration [13–17] (Fig. 1). Therefore, any investigation of the potential mitigating effects of biomechanics in atherogenesis should be made with respect to these pathobiologic mechanisms.

Endothelial Dysfunction

The endothelium has three important functions that are particularly relevant to atherogenesis: (1) maintenance of a selectively permeable barrier between the intravascular space and the tissue space, (2) ability to modify and transport lipoproteins into the vessel wall, and (3) provision of a nonadherent surface for leukocytes [18]. In accordance with the response to injury hypothesis, loss of these functions can be the most preliminary event in atherogenesis [11]. Injurious agents lead to inflammatory responses that ultimately cause endothelial cell (EC) death through apoptosis [19]. Russell Ross postulated that if the injury is chronic, the remaining viable ECs in the vessel wall will proliferate (to heal the wound) until they reach senescence, at which time the wound will not heal properly resulting in increased convection of macromolecules (e.g., LDL) from the circulation to the vessel wall [11] (Fig. 1).

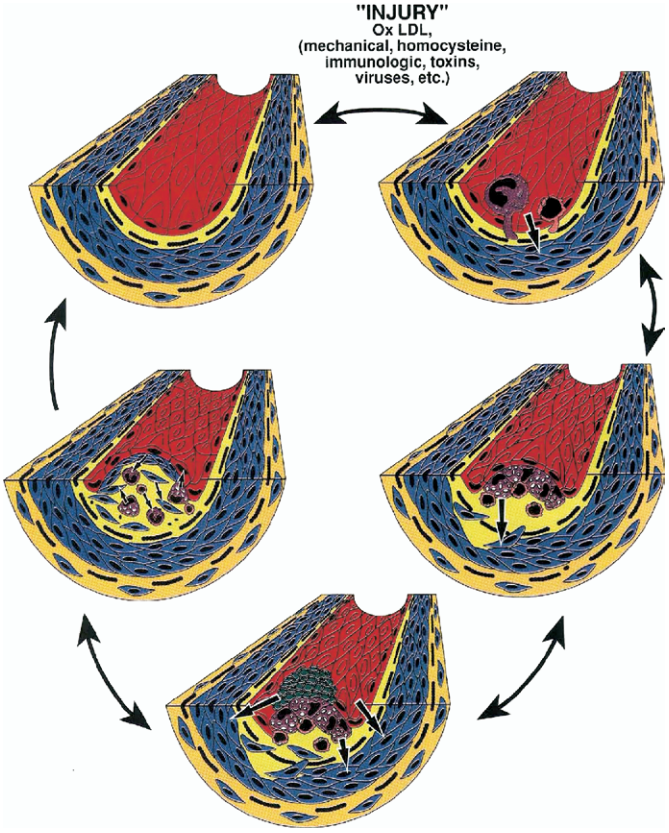

FIG. 1. The response-to-injury hypothesis of atherosclerosis. Several different sources of injury to the endothelium (e.g., oxLDL, mechanical, homocysteine, immunological, toxins, virus, etc.) can lead to endothelial cell dysfunction. One of the parameters associated with endothelial cell dysfunction is increased adherence of monocytes/macrophages and T lymphocytes (top right). These cells then migrate between the endothelium and localize subendothelially. The macrophages become large foam cells because of lipid accumulation and, with the T cells and smooth muscle, form a fatty streak (middle right). As the lesions accumulate more cells, and the macrophages scavenge the lipid, some of the lipid-laden macrophages may emigrate back into the bloodstream by pushing apart the endothelial cells. On doing so, those sites where blood flow is irregular (e.g., branches and bifurcations) with eddy currents and back currents, may become thrombogenic sites that lead to formation of platelet mural thrombi (bottom). Ultimately, the formation and release of numerous growth-regulatory molecules and cytokines from a network established between cells in the lesion consisting of activated macrophages, smooth muscle, T cells, platelets, and endothelium lead to progression to a fibrous plaque or advanced, complicated lesion (middle left). Each of the stages of lesion formation is potentially reversible if the injurious agents are removed or when protective factors intervene to reverse the inflammatory and fibroproliferative processes. Cell color coding: smooth muscle (blue), endothelium (red), macrophage (violet), T cell (pink), and platelet (green). Figure reproduced with permission from Macmillan Publishers Ltd [11].

Indeed, endothelial cells of vascular lesions have been shown to have shortened telomeres indicating a senescent phenotype [20].

Lipid Accumulation

Lipid accumulation is a major manifestation of the vascular response to injury, and there are three means by which this occurs. First, dysfunctional ECs lose their selective barrier function. Illustrating this is the observation that convection of horseradish peroxidase from the plasma to the intima is increased in rats with spontaneous hypertension (a well-known chronic arterial insult and risk factor for atherosclerosis) [21]. Since the permeability of the internal elastic lamina remains relatively unchanged with hypertension, macromolecules accumulate in the intima [21]. An intact endothelium minimizes this effect, while a chronically injured endothelium amplifies it [21]. In addition, confluent monolayers of endothelial cells exposed to atherogenic levels of LDL show a dose-dependent increase in macromolecular permeability [22]. The effect is even more pronounced when the lipids are oxidized, as demonstrated by Rong *et al.* [23]. They showed that injection of cholesterol oxidation products in rabbits resulted in accumulation of those products in the aortic wall and increased vascular permeability and accumulation of lipids and macromolecules even under normocholesterolemic conditions [23]. Similar results have been seen for endothelial dysfunction induced by nicotine and streptozotocin induced diabetes [24, 25].

Second, EC dysfunction leads to altered expression of lipoprotein receptors used to internalize and modify various lipoproteins. Certain lipoproteins, specifically oxidized LDL, perpetuate the insult by activating ECs and trigging the inflammatory cascade [26]. Sawamura *et al.* identified the lectin-like low-density lipoprotein receptor-1 (LOX-1) specific for oxidized LDL (ox-LDL) [27]. The modification of native LDL to ox-LDL is a result of oxidative stress (a common manifestation of chronic insult) on ECs and macrophages [28]. Binding and internalization of ox-LDL by LOX-1 on ECs can stimulate the production of monocyte chemotactic protein-1 (MCP-1) and increase monocyte adhesion [29] as well as trigger the apoptotic cascade [30]. LOX-1 mRNA is positively regulated by its injurious ligand ox-LDL in a concentration-dependent manner [31, 32], illustrating the role of EC dysfunction in the binding and internalization of ox-LDL. The results of several other studies also support this notion. For example, lysophosphatidylcholine, a major component of ox-LDL that has been implicated in atherogenesis [33–35], induces mRNA and protein expression of LOX-1 in cultured ECs [31]. Similarly, tumor necrosis factor-alpha, which has been shown to be increased in atherosclerosis [36, 37], induces a concentration dependent increase in LOX-1 expression [38]. There is also a

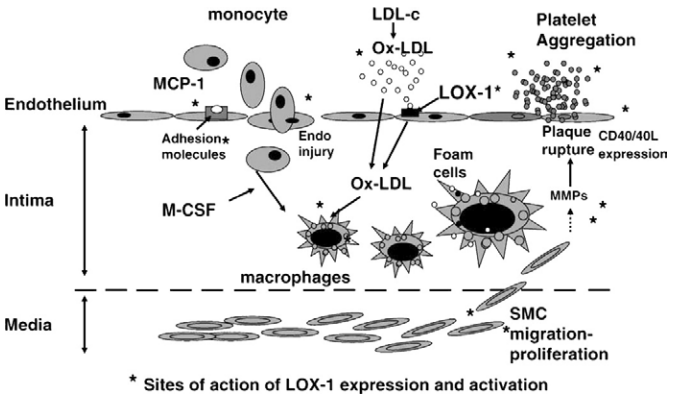

FIG. 2. LOX-1 expression and activation has been demonstrated from the beginning of atherosclerosis (such as endothelial activation and apoptosis) to the culmination into an acute event (such as plaque rupture). Figure reproduced with permission from European Society of Cardiology [26].

complicated crosstalk between angiotensin II, which is known to cause EC dysfunction [30, 39], and LOX-1. That is, angiotensin II induces LOX-1 mRNA and protein expression [30] and ox-LDL up-regulates angiotensin II receptors [40]. Although originally discovered as an endothelial scavenger receptor, LOX-1 has also been shown to be expressed by macrophages and smooth muscle cells (SMCs) where it contributes to foam cell formation [41]. In vivo studies demonstrating LOX-1 expression in balloon injury [42] and vein graft [43] models of atherosclerosis lend even greater validity to the role ox-LDL accumulation via LOX-1 in atherosclerotic processes. Figure 2 illustrates the multifaceted role of LOX-1 in atherosclerosis [44].

A third means by which lipid accumulation may occur in response to vessel injury is that once lipids have been transported into the subintimal space, they are retained there by SMCs and macrophages that ingest lipoproteins (e.g., ox-LDL) via scavenger receptors [45, 46]. Since these receptors are not down-regulated by increasing intracellular concentrations of cholesterol, these cells continue to accumulate lipid and become foam cells [47, 48]. In addition, SMCs in atherosclerotic lesions undergo a phenotypic modulation from a contractile to a synthetic phenotype [49, 50]. Synthetic SMCs have a decreased cholesteryl esterase activity compared with contractile SMCs and therefore cannot metabolize cholesterol which leads to even more lipid accumulation [51].

Inflammatory Cell Infiltrate

Atherosclerosis has been described as an inflammatory process [3] in that a major manifestation of the "response to injury" is leukocyte adhesion and infiltration. Mononuclear leukocytes have been identified in lesions in various stages of atherosclerosis [10, 52, 53]. Davies *et al.* demonstrated this infiltration process in

human coronary arteries with known atherosclerosis via scanning electron microscopy [13]. Monocytes and T lymphocytes adhere to the luminal surface of an artery where the endothelial layer is altered. Once there, they spread, migrate along the surface, and then extravasate through the endothelium into the subendothelial intimal space. This process is mediated through a variety of chemokines that allow these inflammatory cells to "home" to regions of insult or injury [54] and adhesion molecules that provide the necessary contacts for the cells to attach and migrate from the vascular lumen into the vessel wall [55].

Chemokines

The role of chemokines in inflammatory reactions is to become immobilized to the endoluminal surface of arteries, where they are presumed to enhance integrin adhesiveness and mediate leukocyte arrest and firm adhesion [56, 57]. In addition, they have been shown to promote transendothelial migration of leukocytes [58, 59]. The inflammatory component of atherosclerosis is demonstrated by the observation that MCP-1 is expressed on the luminal surface of human atherosclerotic lesions [60], and by ECs and SMCs in early and advanced atherosclerotic lesions [60–63]. Also, atherogenic agents such as minimally modified LDL [64], and lysophosphotidylcholine [65] can induce the transcription of MCP-1 mRNA in ECs. IL-8 is another chemokine with an established role in atherosclerosis [66]. It has been shown to arrest monocyte rolling and induce firm adhesion in a dose-dependent manner on EC monolayers under flow conditions [67, 68].

Adhesion Molecules

Adhesion molecules related to the inflammatory process of atherosclerosis can be grouped into two categories, namely the selectins and the immunoglobulin adhesion molecules. Selectins are adhesion molecules that provide a loose attachment for leukocytes that allow them to roll along the luminal surface [69] (Fig. 3), and include P-selectin, E-selectin, and L-selectin. L-selectin is constitutively expressed in leukocytes [55]. E-selectin is expressed in activated ECs but its role in atherosclerosis has not been well established [55]. P-selectin is not constitutively expressed by ECs but is expressed in ECs overlying active atherosclerotic plaques [70]. In addition, P-selectin is focally expressed in lesion prone areas of rabbit aortas after one week of an atherogenic diet [71, 72]. This expression preceded macrophage infiltration, indicating P-selectin's role in monocyte recruitment [55, 71, 73].

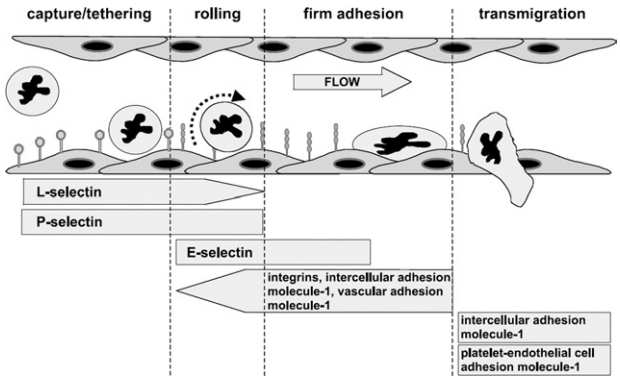

FIG. 3. Schematic representation of leukocyte rolling, adhesion, and transmigration across the endothelium and the cellular adhesion molecules involved in these processes. Figure reproduced with permission of Blackwell Publishing [210].

Immunoglobulin adhesion molecules allow leukocytes to firmly adhere to the endothelium and extravasate into the vessel wall (Fig. 3) and include intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). ICAM-1 is detected on ECs of atherosclerotic lesions and is increased by injury [74], whereas normal ECs show little expression [70, 75]. VCAM-1 is expressed in ECs overlying lipid containing human atherosclerotic lesions [76]. Like P-selectin, VCAM-1's involvement in monocyte recruitment has been demonstrated by the fact that its expression was seen in lesion prone areas, 1 wk after the onset of atherogenic diet in rabbits and prior to macrophage appearance [55, 71, 73]. Furthermore, expression of VCAM-1 is modulated by lipid-based injury; LDL can induce its expression in human coronary artery ECs [77]. The more atherogenic lipoprotein, ox-LDL, up-regulates ICAM-1 [78], and enhances tumor necrosis factor-alpha induced expression of VCAM-1 and ICAM-1 in human arterial ECs [79].

ROLE OF BIOMECHANICS IN ATHEROSCLEROSIS

Established risk factors for atherogenesis (e.g., hypertension and dyslipidemia) are systemic in nature and therefore cannot account for the fact that certain arteries such as the coronary arteries, carotid bifurcation, and infrarenal abdominal aorta are more susceptible to atherosclerosis than others [9]. Furthermore, the spatial distribution of atherosclerosis within the highly susceptible coronary arterial tree is heterogenous [80–84]. Evidence suggests that biomechanical forces could account for this heterogeneity [81, 85–87] by providing a facilitating or protective effect for the various systemic risk factors. This section will examine the current understanding of the relationship between biomechanical stimuli and atherogenesis with respect to the pathobiological processes discussed above. First, a brief description of the vascular biomechanical environment is provided.

Biomechanical Environment of the Vasculature

The cells (i.e., EC and SMC) of the vasculature live in a dynamic mechanical environment due the hemody-

namics of blood flow as well as the movement of the surrounding tissue beds. Mechanical stimuli seen by cells of a blood vessel include shear force due to contact with blood flow, strain due to pressure distension of the diameter of the vessel, and strain due to mural deformation of a vessel by its tethering to a surrounding tissue bed. Physiological arterial shear stress magnitude ranges from 0 to 30 dyne/cm^2 during a cardiac cycle [88, 89]. In addition the direction of the shear changes due to blood flow reversal leading to oscillatory shear stress. The time average mean shear stress and amplitude of the oscillation are dependent upon anatomical location. Circumferential strain due to pressure distention ranges from 5 to 20% depending on arterial size and location [90]. While every major artery in the body experiences these two mechanical stimuli, several other arteries also experience extraneous mechanical deformations due to their tethering to surrounding tissue beds. The coronary arteries are by far the most well-known example of this as described in the following section. Although less well studied, there are other examples of arteries that undergo tissue bed-induced deformations. The renal arteries have been shown to have cyclic changes in curvature due to kidney movement caused by respiration [91]. Bending in the femoral arteries has been shown to induce spiral secondary flows indicating the interrelated nature of the solid and fluid mechanics [92]. Just recently, Cinthio *et al.* quantified the degree of longitudinal motion of several arteries (i.e., aorta, carotid, popliteal, and brachial arteries). They showed significant variation in the pattern of longitudinal motion over the cardiac cycle among different anatomical locations as well as subjects. Furthermore, they demonstrated that the intimal/medial portion of the arteries had a different longitudinal motion pattern than the adventitial portion, suggesting massive shear strains between the media and adventitia. This work provides another anatomically heterogeneous mechanical stimulus that could mitigate the development of atherosclerosis.

Coronary Biomechanical Environment

The mechanical environment of a coronary artery is complex and spatially variable. Using flow visualization and high-speed cinemicrographic techniques, Asakura and Karino showed that the flow patterns in the left and right coronary circulation are complicated with distinct regions of disturbed flow, recirculation, and secondary flows [80]. Velocity and wall shear stress can vary greatly with both longitudinal and circumferential position in the coronary arteries [80, 93–96]. In general, arterial geometry has been shown to be a key component in the distribution of shear stress in the coronary vasculature (Fig. 4) [97].

The effect of geometry on arterial biomechanics is further complicated by the fact that it is dynamic. That

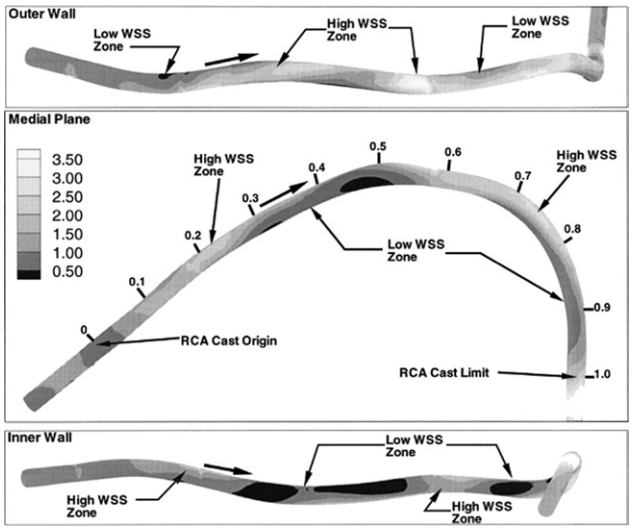

FIG. 4. Contour plot of normalized wall shear stress (WSS) magnitude in a right coronary artery model for steady flow with a Poiseuille inlet velocity profile. Note the alternating regions of high and low WSS on the model walls. WSS values are normalized by the inlet Poiseuille value. Figure reproduced with kind permission of Springer Science and Business Media [97].

is, the geometry of a given coronary artery changes in time due to its firm attachment to the epicardial surface of a beating heart (Table 1) [98–101]. Gross *et al.* showed that curvature (inverse of the radius of curvature) in coronary arteries ranged from 0.25 to 1.8 cm^{-1} [100]. The degree of twisting and the rate of change of curvature were also shown to be highly position-specific [101]. In addition, coronary vessels undergo 4 to 6% cyclic longitudinal stretch during each cardiac cycle [98, 99]. These cyclic motions of bending, stretching, and twisting as well as translational displacement can alter blood flow and, therefore, shear stress [102, 103]. Those dynamic motions can also lead to complex mural deformations and stress patterns in the arterial wall. These studies demonstrate the highly variable and complex biomechanical environment of the coronary arteries, which is depicted schematically in Fig. 5. This environment is sufficiently complex to provide both atherogenic and atheroprotective stimuli, which could account for the heterogeneous distribution of atherosclerotic lesion in the coronary vasculature despite systemic risk factors. We now summarize some key studies that suggest that biomechanical stimuli play a role in the location-specific pathogenic processes of atherogenesis.

Effects of Biomechanics on Atherogenic Response of Vascular Cells and Tissue

Mechanical forces and deformations are an important component of the vascular environment. These forces are sensed and communicated to the interior of vascular cells via several different signaling pathways.

TABLE 1

Dynamic Coronary Artery Geometry*

Motion parameter	Explanation	Mean value for RCA†	Mean value for LAD‡
Displacement (cm)	3D displacement of a material point	6.00 ± 2.59	2.91 ± 0.74
Strain	Relative length change of a point	0.054 ± 0.020	0.040 ± 0.018
Curvature (C) (cm^{-1})	Inverse of the radius of curvature	0.39 ± 0.10	0.48 ± 0.17
Bending (cm^{-1})	Rate of change of curvature	0.95 ± 0.35§	1.16 ± 0.44
Pulse curvature (cm^{-1})	$C_{max} - C_{min}$ over cardiac cycle	0.33 ± 0.14	0.39 ± 0.12
Torsion (T) (cm^{-1})	Shear strain caused by a torque	1.50 ± 0.60	2.69 ± 0.79
Twisting (cm^{-1})	Rate of change of torsion	12.13 ± 5.50§	26.35 ± 14.60
Pulse torsion (cm^{-1})	$T_{max} - T_{min}$ over cardiac cycle	4.45 ± 2.59	8.65 ± 5.08

* Table adapted with kind permission of Springer Science and Business Media [99].
† Mean values for four patients' right coronary arteries (RCA).
‡ Mean values for eight patients' left anterior descending arteries (LAD).
§ Values for bending and twisting represent total bending and twisting rather than instantaneous rates of change, which would have units of ($cm^{-1}s^{-1}$).

The mechanism of mechanotransduction is an area of intense research and could provide numerous chemotherapeutic targets. A detailed discussion of the various mechanosignaling pathways is beyond the scope of this review. Regardless, changes in mechanical forces alter cell signaling, which in turn can potentially lead to endothelial activation and/or dysfunction leading to lipid accumulation and inflammatory activation. The mechanosensitivity of each of these pathogenic processes and their associated molecules (described in detail above) is described below and summarized in Table 2.

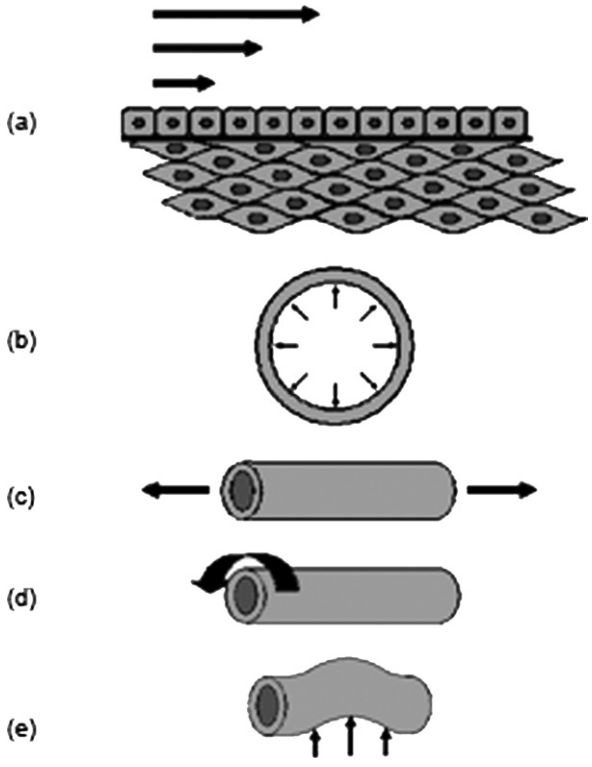

FIG. 5. Schematic of vascular mechanical stimuli including: (A) flow-induced shear stress, (B) pressure-induced circumferential distention and the tissue bed-induced deformations of (C) longitudinal stretching, (D) twisting, and (E) bending.

Endothelial Dysfunction

Mechanical forces have been shown to lead to EC dysfunction characterized by EC proliferation, apoptosis, and increased permeability. One of the most studied mechanical forces with respect to EC dysfunction is shear stress. Permeability of the vessel wall is increased by cyclic changes in shear stress [104–106] and high spatial shear stress gradients [107], but decreased by increasing levels of shear [105]. The increase in EC permeability in response to shear forces is potentially mediated through changes in endothelial cell-cell contacts [108, 109]. That is, increasing magnitude and duration of shear stress on ECs leads to enhanced expression of proteins associated with both tight and adherens junctions [109], while exposure to low shear stress causes tight junctions to become discontinuous (i.e., leaky) [108]. This suggests that low or oscillating shear levels facilitate systemic atherogenic factors (e.g., LDL). This is also supported by the observation that low shear stress impairs endothelial wound healing while high shear stress enhances wound repair through increased cell spreading and migration [110]. Shear stress can also alter EC proliferation [106, 110–115] and apoptosis [116–120], depending on the magnitude and spatial and time variation of the shear stress. For instance, ECs exposed to 10 to 15 dynes/cm^2 of shear stress and laminar flow conditions have little or no proliferation or apoptosis [106, 118, 119, 121–123]. On the other hand, low shear stress can cause increased proliferation and apoptosis, hence increased EC turnover [14, 114, 115, 124, 125].

Based on the above data relating shear stress to endothelial dysfunction, a hypothetical mapping of

TABLE 2

Summary of Atherogenic Processes and Their Mechanosensitivities

Pathogenic process	Role in atherogenesis	Mechanosensitivity
Proliferation	Initial response to endothelial injury (i.e., wound healing)	Abrupt ↓* SS** can ↑# EC## proliferation [115]; ↑ SS ↓ DNA synthesis [204]; Turbulent flow ↑ EC turnover [106, 112]; ↑ SS ↓ EC proliferation [114]; ↑ CS ↑ EC proliferation [132, 205];
Apoptosis	Cause of endothelial dysfunction; found in atherosclerotic lesions	Physiologic SS and CS suppress apoptosis in ECs [118, 119, 121–123, 135]; ↓ SS induces EC apoptosis [125]; ↑ CS ↑ EC apoptosis [134]; Turbulent flow ↑ EC turnover [112]
Permeability	Allows macromolecular (e.g., lipids) uptake into vessel wall	↑ CS ↑ permeability [134]; ↑ SS ↓ permeability [105]; ↑ SS gradient ↑ permeability [107]; Cyclic Δ's† SS ↑ permeability [104–106]; ↑ Transmural pressure ↑ permeability [107, 137, 151, 206]
LDL uptake	Can cause endothelial injury, lipid accumulation, and inflammatory activation	↓SS can ↑ cholesterol permeability [108, 109, 207]; Δ's pulse pressure and flow alter cholesterol uptake [153]; ↑ Pressure alters LDL permeability [151]; ↑ SS ↑ Binding, internalization and uptake of LDL [145–147]
LOX-1 expression	Cellular receptor for ox-LDL uptake	↑ SS ↑ LOX-1 mRNA and protein [144]
Cholesteryl esterase	Allows macrophages and SMCs to digest cholesterol Dysfunction or loss of expression can lead to cholesterol accumulation and foam cell formation	SMC phenotypic modulation, which is mechanosensitive (see text), can cause ↓ in cholesteryl esterase activity [155–159]
MCP-1	Leukocyte chemoattractant	↑ SS ↓ MCP-1 expression [165]; ↑ CS ↑ MCP-1 expression [167–169]
IL-8	Leukocyte chemoattractant; facilitates TEM	↑ SS ↓ IL-8 expression [161, 162, 208]
P-selectin	Leukocyte rolling	A threshold level of is shear required for P-selectin rolling function [172]
ICAM-1	Leukocyte arrest and activation	↑ SS ↑ ICAM-1 expression [174–176, 179, 209]
VCAM-1	Leukocyte arrest and activation	↑ SS ↓ VCAM-1 expression [177, 178, 209]

* ↓ denotes decrease or downregulation.
† Δ's denotes changes in.
# ↑ denotes increase or upregulation.
** SS denotes shear stress.
CS denotes cyclic stretch.

shear stress onto an atherogenicity spectrum can be seen in Fig. 6. Of course, this scheme must be evaluated with caution since the majority of these studies have been performed in two dimensional monoculture conditions. SMC/EC coculture has been shown to dramatically alter the proliferative response of ECs to various stimuli including shear stress [126, 127]. The response is also dependent upon the culture media [128], substrate [128], and type of cells used (venous *versus* arterial) [129]. A more accurate description of the mitigating effects of shear stress on atherogenesis requires continued research using more physiological model systems such as three-dimensional EC/SMC coculture [126, 127], *ex vivo* experimental preparations [130, 131], and *in vivo* trials. This type of paradigm could be extended to all combinations of mechanical stimuli and atherogenic processes as discussed below. Such a description could provide intelligent direction in the search for therapeutic targets.

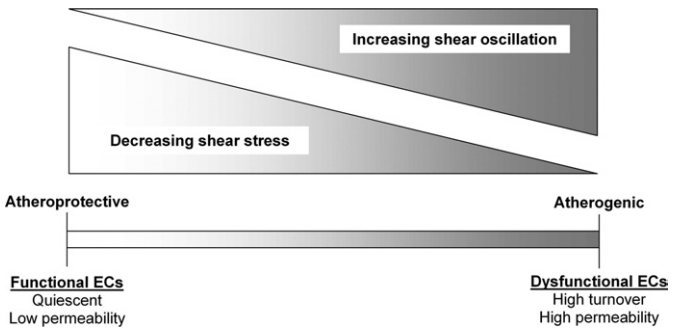

FIG. 6. Pictorial representation of how the biomechanical stimulus shear stress maps to a continuum between atheroprotection and atherogenicity. If the atherogenicity of shear stress can be characterized by the level endothelial cell dysfunction a map can be drawn relating a given type of shear stress (e.g., low magnitude, high oscillation) to its potential to facilitate atherogenesis. Further research is required to provide quantification to this representation. Such information could help to determine thresholds for atherogenesis or atheroprotection.

Other mechanical stimuli that can potentiate or inhibit EC dysfunction manifested by proliferation, apoptosis, and increased permeability are cyclic stretch and hydrostatic pressure. More specifically, physiological levels of cyclic stretch can increase EC proliferation [90, 132, 133], suppress apoptosis [122], and provide an atheroprotective effect for the endothelium [134]. Although the increased proliferation is a contra-

dictory response for atheroprotection, there does seem to be an analogous effect of moderate levels of cyclic stretch to the protective effect of moderate levels (10 to 15 dyne/cm^2) of shear stress [118, 119, 121–123, 135, 136]. On the other hand, supraphysiological levels of cyclic stretch can cause increased permeability and apoptosis [134]. That hydrostatic or transmural pressure is also an important determinant of endothelial dysfunction is suggested from the well-known fact that hypertension is a risk factor for atherosclerosis. Indeed, increased pressure has been implicated in mass transport of material (e.g., lipids) from the lumen to the vessel wall [137], as well as alterations in EC proliferation and apoptosis [138].

Lipid Accumulation

Accumulation of lipids in atherogenesis is also modulated by mechanical forces. For instance, lipids accumulate at the luminal surface in areas where blood flow velocity and wall shear stress are low [109, 139] and where particle residence times and the permeability of the endothelial layer are enhanced (a known manifestation of EC dysfunction as detailed above) [139–143]. Lipid accumulation is also mediated by shear-sensitive receptors. The expression of LOX-1, a key modulator of LDL-induced endothelial insult and lipid accumulation (recall Fig. 2), has been shown to be regulated by physiological levels of shear stress [144]. Also, the binding, internalization, and degradation of unmodified LDL by the vessel wall is highly dependent on shear stress [145–147]. Cyclic strain and pressure also effect lipid accumulation. For example, cyclic stretch causes an increase in reactive oxygen species [148] and oxidative stress [149] in ECs, which increase the oxidation of LDL and increase EC permeability and uptake of ox-LDL. Hypertension (i.e., increased intraluminal pressure) has been predicted to increase convective pressures or the driving force for the transport of material (e.g., LDL) from the lumen to the vessel wall [150–152]. This is substantiated by data showing that increased transmural pressure leads to increased filtration velocity [139] and uptake of cholesterol [153]. Cytoskeletal rearrangement has been implicated as a factor in both shear and stretch mediated LDL accumulation [154].

Loss of expression of cholesteryl esterase by SMCs that have been phenotypically altered from a contractile to a synthetic phenotype (a common event in atherogenesis, see above) is another means by which lipids are accumulated in the vessel wall. The phenotypic state of SMCs is regulated at least in part by mechanical forces, as demonstrated by the observation that cyclic stretch creates a substrate-dependent modulation of proliferation and h-caldesmon expression *in vitro* [155]. In vivo studies have also shown the importance of mechanical injury in the phenotype of vascular SMCs. For example, balloon inflation injury to the media was shown to promote extracellular matrix synthesis and decrease α-actin content in SMCs [156]. Zhang *et al.* showed that neointimal smooth muscle cells of external jugular veins transposed to the carotid artery position display a more primitive synthetic phenotype [157], supporting the notion that the change from the venous to the arterial biomechanical milieu triggers phenotypic alteration. Further evidence comes from *ex vivo* organ culture studies wherein cyclic stretch was found to be necessary to maintain the contractile function of SMCs in cultured rat portal veins [158]. Goldman *et al.* exposed rat vena cava to arterial pressures [159], leading to a large increase in medial circumferential strain and a concomitant reduction in the SMC filamentous actin coverage. Taken together, these previous studies demonstrate that mechanical forces are important modulators of lipid accumulation, another important event in atherogenesis.

Inflammatory Cell Recruitment and Adhesion

Shear forces in conjunction with apical chemokines promote the migration of leukocytes across the endothelium [58, 59]. Both chemokines described above (IL-8 and MCP-1) have been shown to be responsive to mechanical stimuli. For example, human umbilical vein endothelial cells showed increased production of IL-8 mRNA and protein under low flow as compared to those exposed to high flow [160–163]. IL-8 is also upregulated in response to cyclic stretch [164]. Similarly for MCP-1, steady shear (ramp flow and the steady component of step flow) diminishes protein [165] and mRNA [166] expression, while cyclic strain induces protein and mRNA expression [164, 167–169].

The adhesion molecules are also mechanosensitive in that oscillatory flow induces up-regulation of adhesion molecules and cytokines that mediate monocyte/EC interactions [170, 171]. More specifically, those adhesion molecules described above (i.e., P-selectin, ICAM-1, and VCAM-1) have very specific responses to biomechanical forces. Fluid shear above 0.5 dyne/cm^2 significantly enhances HL-60 myelocyte rolling on P-selectin at site densities of 200/μm^2 and below [172]. Shear stress can also modulate expression of VCAM-1 and ICAM-1 [170, 173]. Laminar flow generated shear stress (>2.5 dyne/cm^2) directly and selectively upregulates ICAM-1 expression on the surface of endothelial cells and promotes leukocyte adhesion in a dose-independent fashion [174–176]. VCAM-1, on the other hand, is down-regulated by shear stress in a dose-dependent manner [177, 178]. While we are not aware of any studies specifically relating mural stresses or cyclic strains with the expression of adhesion molecules, veins subjected to arterial flow show increases in ICAM-1 expression [179], which is abolished by stretch

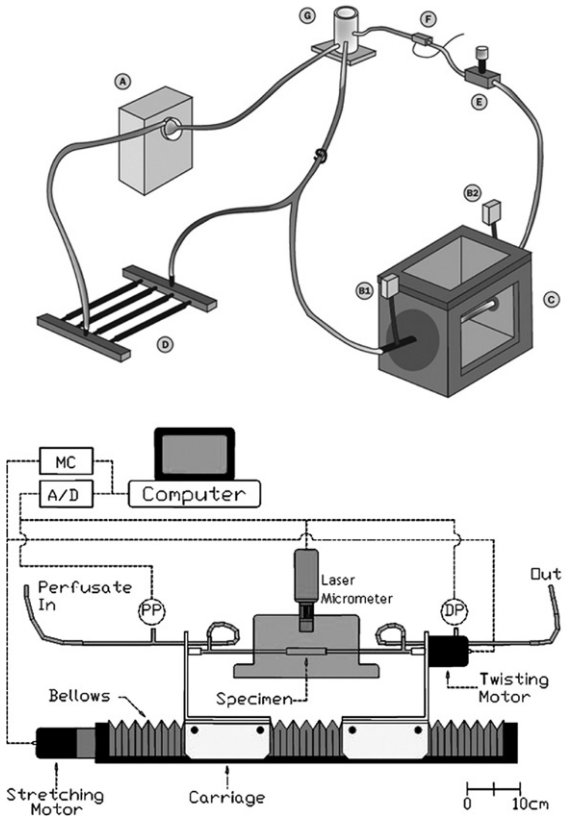

FIG. 7. Schematic of closed-loop perfusion/organ culture system (top). The loop is composed of a Biomedicus centrifugal pump that provides pulsatile pressure and flow (A), a heat exchanger (D), a tissue-housing chamber (C), proximal (B1) and distal (B2) pressure transducers, a variable resistance valve (E), flow probe (F), collection reservoir (G), and vessel bypass (H). To provide realistic tissue bed-induced deformations the tissue housing chamber is with custom built mechanical stimulation system (bottom). A motion control program systematically operates two stepper motors. The Stretching Motor rotates a precision-threaded lead screw transmitting longitudinal motion to the two carriages. The Twisting Motor is fixed to a perfusion tee which rotates an amount specified by the motion control program. Bottom panel adapted and used with permission of The American Physiological Society [183].

activated cation channel blockers [180], suggesting the role of cyclic stretch in the expression ICAM-1. This data demonstrates that the expression of mediators of the inflammatory cell recruitment component of atherogenesis is sensitive to mechanical stimulation.

Correlations Between Biomechanics and Lesion Localization

Prior to our more detailed understanding of the mechanobiology of vascular cells, several groups began to find correlations between physiological biomechanical forces or deformations and the location of atherosclerotic lesions in attempts to find the mitigating factor that accounted for the heterogeneous distribution of atherosclerosis [83, 84, 131, 181–183]. These studies can be grouped into the ones that examine shear stress and the ones that examine mural stress. In addition, several groups have investigated correlations between biomechanics and vein graft stenosis by intimal hyperplasia (an accelerated form of atherogenesis). This work has demonstrated that anastomosis angle, graft diameter, and graft compliance are all important mechanical factors in determining the likelihood of intimal hyperplasia and subsequent graft failure [184]. Our laboratory has determined that the flow condition in the host artery should also be considered in evaluating the biomechanical status and failure potential of a vein graft [185]. Although this work is germane to the topic of cardiovascular mechanopathobiology, the details of these and other similar studies and their implications could form the basis for a separate review article and are beyond the scope of this paper.

Shear Stress

Areas of low or oscillating shear stress within the arterial tree have been correlated with atherogenesis in a variety of models including the carotid bifurcation [186–189], abdominal aorta [190, 191], and coronary vasculature [80, 85, 192, 193]. The lower wall shear rate near the carotid artery bifurcation is associated with larger intimal/medial thickness than at a more proximal site, suggesting accelerated atherosclerotic lesion formation for the bifurcation region [187]. The suprarenal abdominal aorta, which tends to have a lower incidence of plaque formation, has an uncomplicated, laminar flow pattern while the more atherosclerosis-prone infrarenal abdominal aorta has a more complicated flow pattern characterized by flow separation, vortices, and flow reversal [194]. In the coronary circulation, lesion location also depends on geometric factors such as curvature, bifurcation angle, and position of the ostia of branches [94, 96, 195–197], all of which can affect shear stress. Furthermore, the rate of progression of atherosclerosis, which is highly variable among lesions in the same patient, has been related to variations in shear stress [198]. Clearly, shear stress has been shown to be an important contributor to atherogenesis both in correlative and mechanistic type studies.

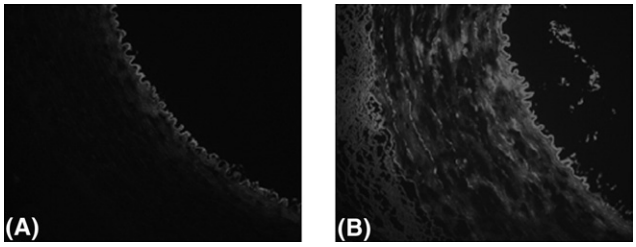

FIG. 8. Cross-sections of porcine arterial segments perfused with Evan's blue dye-labeled albumin at arterial hemodynamic conditions *ex vivo* with (B) or without (A) cyclic longitudinal stretching of 7% over *in vivo* length. Note the increased albumin concentration in stretched arterial segment.

Mural Stress

Much attention has been given to the correlations between shear stress and atherogenesis. However, this neglects an extremely important component of the vascular biomechanical milieu, namely, mural stress. The previous discussion has demonstrated that cyclic stretch and hydrostatic pressure have the capacity to potentiate or inhibit pathogenic features of atherosclerosis. Furthermore, we are just beginning to understand the degree to which tissue-beds induce vascular deformations and therefore mural stresses. Nowhere is this clearer than in the coronary arteries, which seem to be exquisitely susceptible to atherosclerosis [199]. Given the effects of mural stress on vascular cells, the effects of shear stress alone cannot account for the high susceptibility of coronary arteries to atherosclerosis. Indeed, *in vivo* studies of mural deformations have demonstrated that regions of coronary arteries that undergo increased levels of cyclic flexion exhibit a greater degree of atherosclerotic lesion formation [181, 182]. On the contrary, the intramyocardial coronary arteries, which experience cyclic radial compression due to contraction of the surrounding myocardial muscle, have a low occurrence of atherosclerosis, indicating a protective effect of mechanical compression [83, 84]. A similar phenomenon has been seen in the vertebral arteries, where the portions of the vessel that are surrounded by bone tend to be free of lesions while the intervertebral portions are more prone to atherogenesis [84, 200].

The protective effect provided by external radial support as seen in the intramyocardial arteries and the vertebral arteries presents an ideal situation that may be an excellent avenue for clinical intervention. Indeed, Thubrikar *et al.* used rigid casts to reduce circumferential wall distension in rabbit arteries, which resulted in a reduction in atherosclerotic lesion development [201]. On the other hand, nonconstrictive (those that do not impede circumferential distension) perivascular supports have been shown to induce intimal growth in arteries and are a common method for experimental induction of arterial injury and atherosclerosis [202]. There clearly is a need for further work to investigate this particular mechanical phenomenon to develop safe clinical interventions.

Our laboratory has been investigating the effects of mural stress on vascular mechanopathobiology using our unique *ex vivo* dynamic organ culture device (Fig. 7) [131, 183]. We have shown that arterial segments perfused with arterial hemodynamics and cyclic axial stretching (7% beyond *in vivo* length) had an increase in macromolecular permeability over segments perfused without stretching (Fig. 8) [203]. Furthermore, cyclic stretch led to an increase in apoptotic cells on the lumenal surface of the arterial segments [203]. These preliminary studies, demonstrating a potential correlation between mural stress and atherogenesis, require follow-up investigation to provide further evidence for the mechanistic link between biomechanics and EC dysfunction, lipid accumulation, and inflammatory cell recruitment and infiltration.

CONCLUSIONS

The biomechanical environment of the vasculature is extremely complex including temporal and spatial variations as well as fluid and solid stresses. This com-

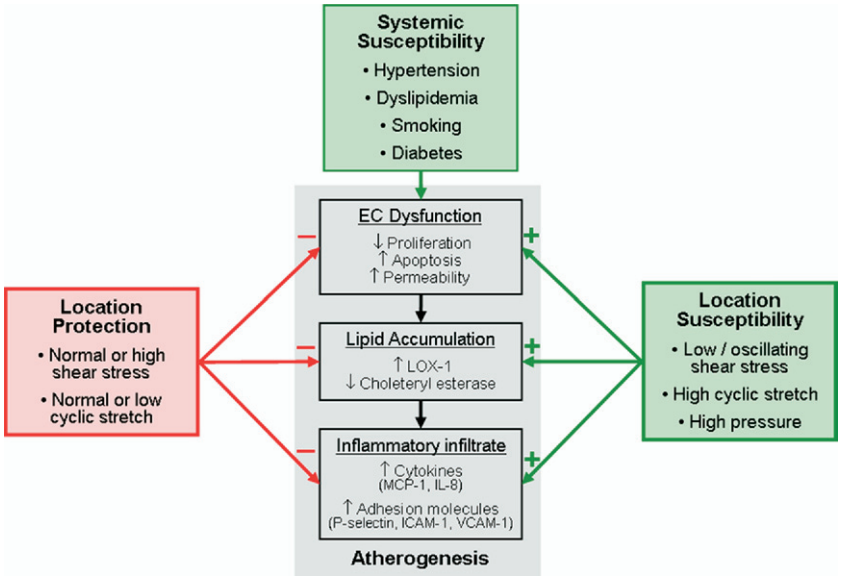

FIG. 9. Summary schematic demonstrating how established risk factors provide a systemic preponderance toward atherogenesis while location-specific biomechanical factors may influence lesion localization by stimulating (red) or inhibiting (green) atherogenic processes.

plex pattern of biomechanical stimuli provides a mechanism by which systemic insults such as diabetes mellitus, smoking, and dyslipidemia can result in a highly localized heterogeneous distribution of disease such as atherosclerosis (Fig. 9). Biomechanical forces can either facilitate vascular insult/injury or protect against it. The next major innovation in the prevention and treatment of CVD must come from the basic understanding of the complex biomechanical milieu of the vasculature and the mechanism by which this environment affects the pathological processes of atherogenesis.

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