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Vascular Mechanobiology: Homeostasis, Adaptation, and Disease

Jay D. Humphrey[1] and Martin A. Schwartz[1,2]

[1]Department of Biomedical Engineering, Yale University, New Haven, Connecticut 06520, USA; email: jay.humphrey@yale.edu

[2]Department of Cell Biology, Department of Internal Medicine (Cardiology), and Cardiovascular Research Center, Yale University, New Haven, Connecticut 06520, USA

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Abstract

Cells of the vascular wall are exquisitely sensitive to changes in their mechanical environment. In healthy vessels, mechanical forces regulate signaling and gene expression to direct the remodeling needed for the vessel wall to maintain optimal function. Major diseases of arteries involve maladaptive remodeling with compromised or lost homeostatic mechanisms. Whereas homeostasis invokes negative feedback loops at multiple scales to mediate mechanobiological stability, disease progression often occurs via positive feedback that generates mechanobiological instabilities. In this review, we focus on the cell biology, wall mechanics, and regulatory pathways associated with arterial health and how changes in these processes lead to disease. We discuss how positive feedback loops arise via biomechanical and biochemical means. We conclude that inflammation plays a central role in overriding homeostatic pathways and suggest future directions for addressing therapeutic needs.

Contents

1. INTRODUCTION

The essential function of the vascular system, transport of oxygen and nutrients to and transport of waste from the tissues, is aided by its remarkable ability to adapt to changing conditions. Examples abound. Sustained increases in cardiac output cause central arteries to enlarge, which reduces the resistance to flow and thus reduces workload on the heart (1). Normal tissue growth or locally increased metabolic activity triggers angiogenesis, which increases local supplies of blood to match demand (2). In these and many similar examples, one recognizes that transporting blood throughout the body is fundamentally a mechanical process. Consequently, to maintain the integrity of the vasculature and to enable the appropriate adaptations, cells of the vascular wall sense and respond to diverse mechanical stimuli. Endothelial cells (ECs) of the intima appear to mainly sense wall shear stresses resulting from blood flow, while smooth muscle cells (SMCs) of the media and fibroblasts (FBs) of the adventitia mainly sense changes in intramural stress that result from local changes in blood pressure or axial loading. Mechanical stimuli thus guide vascular remodeling processes that mediate homeostasis.

Vessels vary in composition, structure, and function along the vascular tree, which determines both the forces that they experience and how they grow (change mass) and remodel (change structure). The largest arteries are highly elastic, which enables them to distend and then recoil to augment pulsatile blood flow while resisting the highest pressures within the vasculature. Medium-sized arteries are muscular, which enables them to control regional flow via vasoactive changes in caliber. The smallest arteries (arterioles) exhibit strong vasoactive potential and are under the control of both the endothelium and sympathetic nervous system; by constricting or dilating, they control blood flow to end organs and tissues and set the mean arterial pressure experienced by proximal vessels. Capillaries, the smallest blood vessels, where gas and nutrient exchange occurs, are thin walled and minimally vasoactive. The venous system similarly consists

of small veins (venules), medium-sized veins, and large veins, which return blood to the heart to circulate again. This review focuses primarily on large arteries, which are sites of vascular diseases such as aneurysms and atherosclerosis.

We first introduce basic concepts in arterial mechanics and mechanobiology and then briefly review components of the arterial tree—different cell types and extracellular matrix (ECM) as well as differences in structure and function by region—and how they form an integrated system. We then focus on local mechanobiological functions that are driven by feedback control mechanisms, particularly those contributing to homeostasis versus pathogenesis. Whereas homeostasis is driven by negative feedback, disease generally involves insidious positive feedback loops that drive aberrant remodeling (3). We conclude by discussing opportunities for better understanding the mechanobiology by using multiscale approaches, both experimental and computational. We approach this problem by borrowing ideas of equilibrium and stability from mechanics as a conceptual framework for understanding both homeostasis and its failure in disease.

2. BASIC ARTERIAL MECHANICS AND MECHANOBIOLOGY

The large arteries form a curved, tapering, branching network (**Figure 1**). Blood flow within these central arteries is pulsatile due to the cardiac cycle, with pressure pulsations amplified along the human aorta due to its spatially varying geometry and properties. This pulsatility dampens in the muscular arteries and especially in the arterioles, resulting in steady flow within the capillaries and veins (4). Notwithstanding the importance of pulsatility, mean values of flow-induced wall shear stress τ_w and pressure-induced circumferential (θ) intramural stress σ_θ provide considerable insight. These components of the Cauchy stress are often computed as (5)

$$\tau_w = \frac{4\mu Q}{\pi a^3}, \qquad 1.$$

$$\sigma_\theta = \frac{Pa}{h}, \qquad 2.$$

where Q is the flow, P the distending pressure, a the luminal radius, h the thickness of the wall, and μ the viscosity of the blood (often assumed to be Newtonian, as appropriate at high shear rates in large vessels). Copious experimental findings have shown that the mean values of these two hemodynamically induced stresses tend to be maintained near normal (i.e., homeostatic) set points in response to modest perturbations in blood flow and pressure (1, 6). In particular, if ε denotes a fold change in mean flow and γ a fold change in mean pressure, restoring mean wall shear stress and circumferential stress toward normal requires that (7)

$$a \to \varepsilon^{1/3} a_o, \qquad 3.$$

$$h \to \gamma \varepsilon^{1/3} h_o, \qquad 4.$$

where the subscript o denotes an original homeostatic value. Consequently, wall shear stress can be efficiently controlled via changes in luminal radius, including rapid vasoactive regulation or more permanent remodeling over longer periods. Intramural stress can similarly be controlled by changes in wall thickness, although influenced by radius. A vessel is considered locally mechanoadapted if changes in luminal radius and wall thickness restore the mean values of these two components of stress toward normal; the vessel is otherwise mechanically maladapted. Less is known about the control of mean axial (z) wall stress, $\sigma_z = f/\pi h\,(2a + h)$, where f is axial force, yet

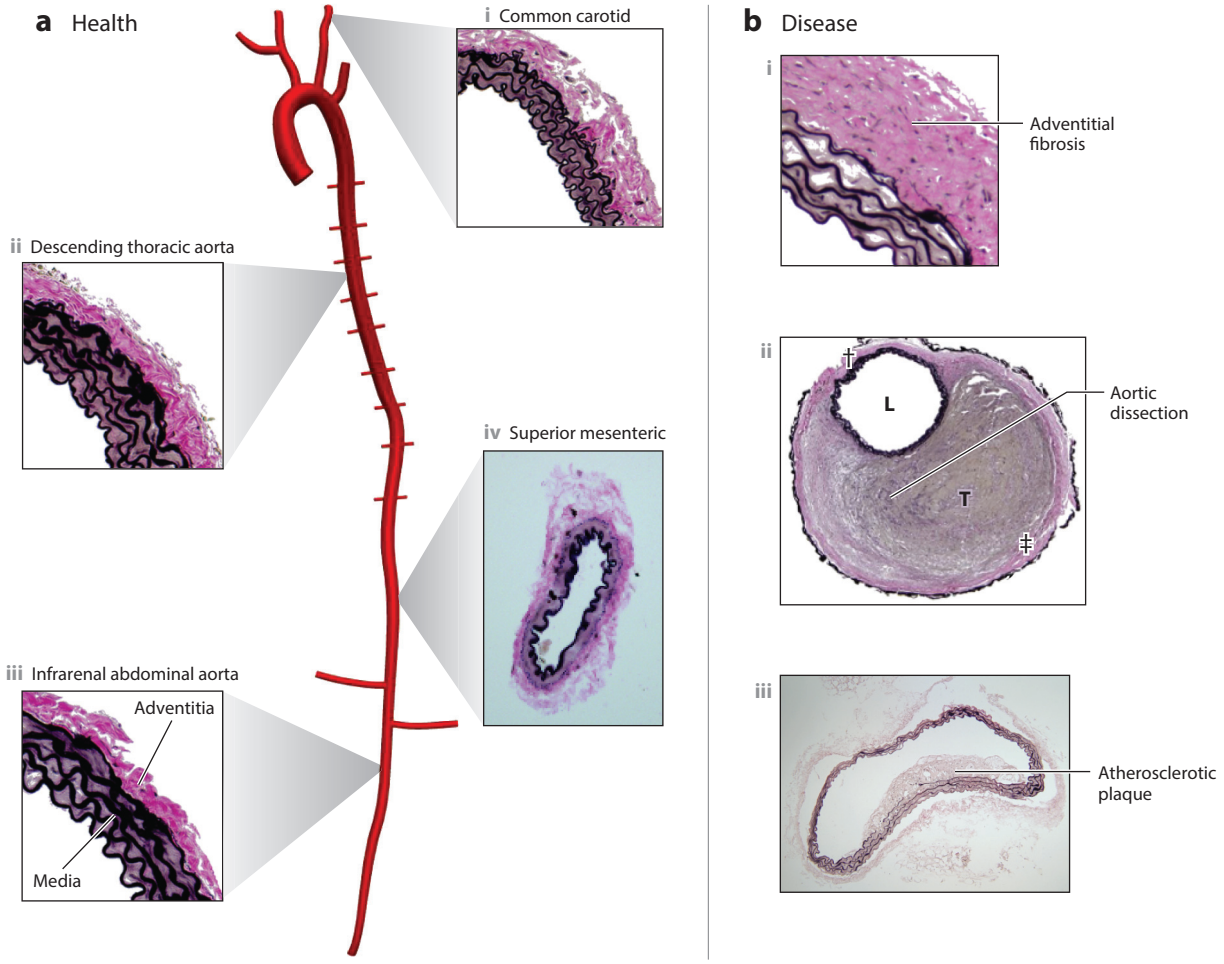

Figure 1

(*a*) Overview of central arteries of a healthy mouse vasculature reconstructed from a micro–computed tomography image, showing the aortic, brachiocephalic, common carotid, subclavian, intercostal, and renal arteries, with representative histological images of portions of (*i*) a healthy common carotid artery (elastic), (*ii*) the descending thoracic aorta (elastic), (*iii*) the infrarenal abdominal aorta (elastic), and (*iv*) the superior mesenteric artery (muscular). Note the nearly concentric elastic lamellar structures in the media of the elastic arteries (elastin shown in *black*), in contrast to the smooth muscle–rich media of the muscular artery. Note, too, the abundant collagen (*pink*) in the adventitia of both types of arteries. Arterial microstructure arises during development and is maintained in health via a slow but continual replacement of cells that die and matrix that degrades; such replacement is accomplished via homeostatic processes driven by negative feedback. Resident macrophages can participate in the homeostatic removal of dead cells, debris, and damaged matrix. (*b*) Cross sections of mouse arteries for pathologies that affect large arteries: (*i*) hypertension-induced adventitial fibrosis, (*ii*) contained rupture with a thrombus-filled false lumen (L denotes the true lumen, T the thrombus, and daggers the adventitia), and (*iii*) an early atherosclerotic lesion in the intima of the abdominal aorta. Such maladaptive remodeling or catastrophic events are driven and/or preceded by compromised or lost homeostasis, typically via positive feedback.

associated changes in axial stretch tend to be among the fastest adaptations in many cases (8). Although these simple relations provide considerable insight, details of the nonlinear mechanics are often needed to understand general cases of homeostasis and pathogenesis. Further details on the mechanics of the vascular wall, both normal and diseased, can be found elsewhere (5, 9).

Table 1 Shear stress–driven endothelial cell signaling and associated vascular responses

	Reduced shear stress[a]	Physiological shear stress[b]	Elevated shear stress[c]
Signals	Smad2/3 NF-κB ET-1	Smad1/5 eNOS/NO	NF-κB eNOS/NO
Outcome	Inward remodeling	Homeostasis	Outward remodeling

Abbreviations: eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; NO, nitric oxide.
[a]Flow-induced shear stress below physiological levels promotes inward remodeling in association with high activation and signaling by Smad2/3, NF-κB, and ET-1, with low eNOS/NO.
[b]Physiological levels of shear stress promote arterial stabilization in association with low NF-κB and low expression of inflammatory mediators, high activation of Smad1/5, and moderate activation of eNOS and production of NO, with low cell proliferation.
[c]Shear stress above physiological levels promotes outward remodeling in association with high NF-κB, higher eNOS/NO, cell proliferation, and suppression of stabilization pathways.

3. COMPONENTS OF THE ARTERIAL WALL

3.1. Endothelial Cells

ECs line the inner surfaces of all blood vessels and form a selective permeability barrier between the blood and tissues (10); they modulate and guide inflammation by controlling the transmigration of immune cells from the bloodstream to tissues (11); and they are the main sensors of flow-induced wall shear stress, which allows them to influence SMC contractility and thus luminal caliber. Many excellent reviews are available on EC mechanobiology and mechanisms of flow sensing and consequences thereof (12, 13).

EC responses to flow vary with magnitude and pattern, as befits a physiological regulator (**Table 1**). Flows at magnitudes near the physiological target stabilize the vasculature, inducing EC alignment in the direction of flow and suppressing EC cycle progression as well as inflammatory and remodeling pathways (14–16). Modest changes in flow drive resultant adaptive remodeling (inward for lower flow, outward for higher flow) that restores shear stress to proper levels (Equation 3), which terminates the remodeling via homeostatic control. Flow-regulated remodeling processes often involve activation of inflammatory pathways such as NF-κB (**Figure 2*a***), leading to the expression of leukocyte recruitment genes (17–19). These effects are consistent with remodeling processes that require the participation of inflammatory cells, often monocytes and macrophages (20, 21). Additionally, lower-than-normal shear stress typically leads to reduced production of the vasodilator nitric oxide (NO) and increased production of the vasoconstrictor endothelin-1 (ET-1) to induce vasoconstriction, whereas higher-than-normal shear stress leads to upregulation of NO and downregulation of ET-1 to induce vasodilation (22, 23). ECs also respond to cyclic circumferential wall strain, but the literature is sparse and the effects less dramatic than those for flow. Finally, flows in branching or highly curved regions of the arterial tree can result in regions of low and multidirectional flow, often simply termed disturbed flow (24). Such flows induce mild but chronic activation of inflammatory pathways that may represent a state of futile flow-dependent remodeling (25). In the absence of other risk factors, this state appears to be neutrally stable but predisposed to pathological remodeling, as discussed below.

3.2. Smooth Muscle Cells

SMCs were long thought to exhibit either a mature/contractile phenotype that mediates vasoconstriction or an embryonic/synthetic phenotype, whereby they proliferate, migrate, and elaborate

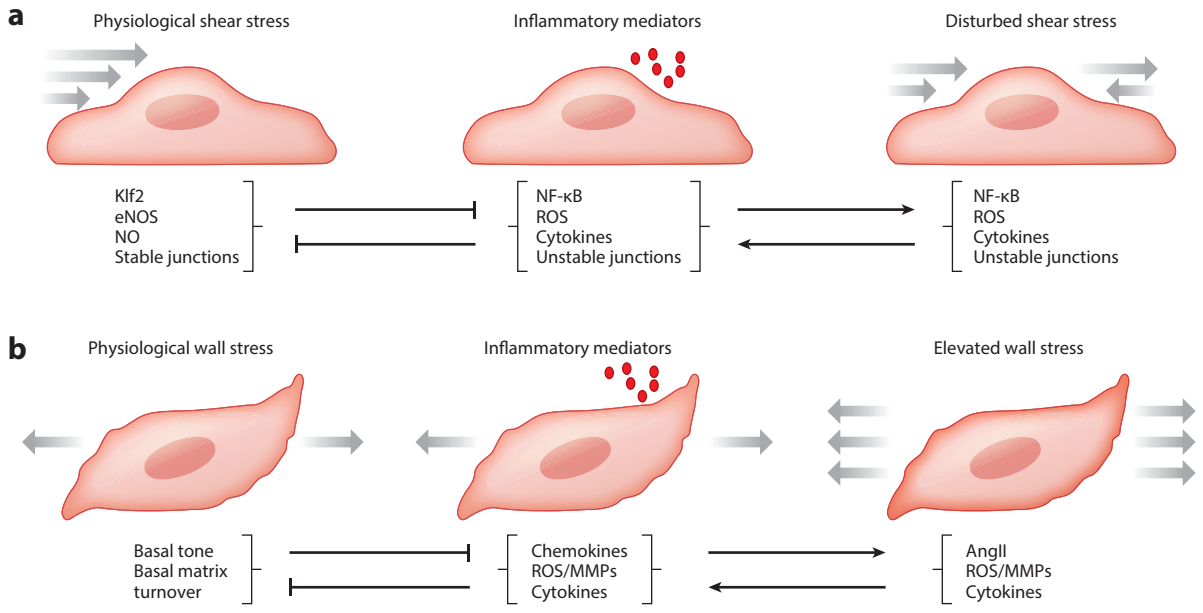

Figure 2

(*a*) Schema of ECs subjected to mechanical and/or inflammatory stimuli. Physiological wall shear stress from blood flow activates multiple pathways that oppose inflammation and remodeling, most prominently Klf2, which mediates expression of anti-inflammatory, antithrombotic, and antioxidative genes. One important downstream gene codes for eNOS, which catalyzes the synthesis of NO. NO promotes junctional stability, suppresses SMC contraction and proliferation, and suppresses activation of leukocytes and platelets. In contrast, disturbed flow or inflammatory mediators activate the transcription factor NF-κB and downstream genes, inducing ROS production and destabilizing junctions. NF-κB reduces Klf2 expression, and ROS react with NO to generate peroxynitrite. High levels of inflammatory mediators over long periods alter endothelial phenotype, reducing expression of flow sensors such as PECAM and VE-cadherin, which inhibit flow responses. Disturbed flow also sensitizes ECs to inflammatory factors, amplifying these responses. (*b*) Schema of SMCs subjected to mechanical and/or inflammatory stimuli. Physiological levels of intramural stresses arising largely from blood pressure stimulate the continual turnover of cells and matrix to maintain the structure and function of the arterial wall despite inevitable cell death and matrix degradation over long periods in maturity. Both elevated wall stress, as in hypertension, and inflammatory cell infiltration can disrupt normal processes and lead to maladaptive remodeling or diverse disease states (as in **Figure 1**). Such outcomes are driven via the increased production or presence of chemokines (such as MCP-1), cytokines (such as TGFβ, IL-6, IL-17a, and TNF-α), and MMPs (such as MMP-1, -2, -9, and -12). Abbreviations: AngII, angiotensin II; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; IL, interleukin; Klf2, Krüppel-like factor 2; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; NO, nitric oxide; PECAM, platelet endothelial cell adhesion molecule; ROS, reactive oxygen species; SMC, smooth muscle cell; TGFβ, transforming growth factor beta; TNF-α, tumor necrosis factor-alpha.

ECM constituents of the developing arterial wall. More recent work, however, shows that SMCs adopt a wider range of phenotypes depending on artery type and disease. For SMCs in elastic arteries, contractile proteins appear to play a minor role in setting the caliber but instead enable the SMCs to mechanically probe the physical state of the ECM and to mediate matrix synthesis and assembly within the mechanically stressed artery wall. This matrix phenotype enables the primary function of an elastic artery: to store elastic energy during systole and to use this energy during diastole to recoil the vessel and augment antegrade and retrograde flow while maintaining the appropriate stiffness and strength. In muscular arteries, SMCs appear to respond primarily to changes in endothelium-derived vasoactive molecules, including wall shear stress–regulated NO and ET-1, thus allowing appropriate vasoregulation of flow. Importantly, wall shear stress tends to be regulated best in muscular arteries, with actomyosin-induced contractility driving luminal caliber to control flow. In arterioles, SMCs respond strongly to changes in both sympathetic signaling

and endothelium-derived vasoactive molecules, thereby allowing central nervous system control of peripheral resistance and thus mean blood pressure, as required in orthostatic changes, control of body temperature, and fight-or-flight situations. Smooth muscle contractility in arterioles is also subject to a unique mechanosensitive (myogenic) response whereby the cells contract against increasing pressure-induced intramural stress. Hence, even the contractile phenotype exhibited by SMCs in muscular arteries and arterioles differs by degree. Additional details on vascular SMCs and their roles in arterial development, aging, and disease can be found elsewhere (26–28).

Importantly, perturbation of hemodynamic loads in healthy vessels modulates the SMC phenotype to promote homeostasis; in contrast, such phenotypic changes are ill controlled in disease and can lead to maladaptations (**Figure 2*b***). In either case, SMCs are highly sensitive to changes in applied loads, which activate a wide range of cytoplasmic signals and gene expression events (29–31) to modulate SMC structure and phenotype. Integrin-mediated adhesions appear to be major transducers in this setting, although N-cadherin, which links SMCs to each other in the vessel wall, can also experience changes in mechanical loads and contribute to mechanically guided regulation (32). In general, cyclic strains (or stresses) at magnitudes that mimic physiological values (~5–10% for circumferential strains) promote physiological SMC phenotypes. Conversely, higher-than-normal values of cyclic strain (or stress) typically activate inflammatory pathways (33, 34). Such responses presumably occur in adaptive remodeling but are central in pathological settings. Hypertension, for example, initially increases wall stress and strain; such an increase results in thickening of the wall via SMC hypertrophy or hyperplasia and ECM deposition to restore the strain/stress toward normal values (Equation 4).

3.3. Fibroblasts

Despite the paucity of information on adventitial FBs, there is nonetheless increasing recognition of the importance of these cells in arterial homeostasis and disease (35–37), and considerable information is available for FBs from other tissues (38, 39). Briefly, vascular FBs establish and maintain the adventitia, which consists primarily of fibrillar collagen I plus accessory proteins and proteoglycans, including decorin and biglycan. These proteoglycans are critical in collagen fibrillogenesis, and loss of biglycan renders large arteries susceptible to aneurysm and dissection (40, 41). FBs are highly sensitive to both stretch and ECM stiffness, with multiple changes in gene expression, including increased synthesis of fibrillar collagens and other matrix proteins (42–44). FBs from most tissue sources also integrate signals from mechanical loading and soluble factors such as transforming growth factor beta (TGFβ), angiotensin II (AngII), and interleukin 17a (IL-17a) to determine rates of collagen synthesis, secretion, and turnover (45, 46).

3.4. Extracellular Matrix

Arterial ECM consists of myriad proteins, glycoproteins, and glycosaminoglycans that collectively endow the wall with site-specific functionality (47). Whereas all blood vessels have an intimal layer with ECs adhered to an underlying basement membrane consisting primarily of laminin and type IV collagen, the medial and adventitial layers differ by artery type. The medial layer of elastic arteries consists of alternating layers of elastic laminae that delimit monolayers of SMCs embedded within a matrix consisting largely of collagens (primarily types III and V) and glycosaminoglycans (primarily versican); the number of such elastic laminae decreases with luminal caliber and thus with distance from the heart. The adventitial layer of elastic arteries consists primarily of undulated collagen I, with small amounts of admixed elastic fibers, proteoglycans, and (in thick vessels) a vasa vasorum (a network of small blood vessels that perfuse the tissue). In contrast, the

medial layer of muscular arteries consists primarily of many layers of contractile SMCs embedded within sparse collagens and glycosaminoglycans and delimited by a prominent internal elastic layer and an external elastic layer (except in intracranial arteries). Again, the adventitial layer consists primarily of type I collagen. Thus, elastic arteries consist of abundant elastic lamellae to store elastic energy. Interestingly, elastic fibers (consisting of ~90% elastin as a core and ~10% associated glycoproteins such as fibrillins and fibulins) emerged evolutionarily with the appearance of a high-pressure, pulsatile circulatory system (47). In contrast, muscular arteries contain abundant SMCs that contract and relax to regulate local blood flow. Elastic energy storage and smooth muscle contractility represent two primary arterial functions that dominate in different parts of the arterial tree.

The ECM also serves instructional roles. Binding of cells to ECM proteins through integrins regulates a vast array of intracellular signals and functions (48). Different matrix proteins such as fibronectin (which preferentially binds $\alpha_5\beta_1$) and collagen (which preferentially binds $\alpha_2\beta_1$ or $\alpha_1\beta_1$) can drive phenotypic changes, with fibronectin generally promoting a proinflammatory phenotype and intact collagen an anti-inflammatory phenotype (49). The ECM also serves as a rich repository for growth factors, cytokines, and proteases, enabling diverse regulatory roles (50). Importantly, cytokines such as TGFβ and proteases such as the matrix metalloproteinases (MMPs) are secreted in matrix-bound latent forms. Activation of latent TGFβ bound within the matrix can be controlled by both matrix composition and matrix mechanics, with the former enabling cells to actively pull on the latency complex to liberate the active TGFβ dimer and the latter allowing a similar mechanical opening of the latency complex (51). Matrix degradation products can also drive phenotypic changes, often stimulating an inflammatory/degradative cell phenotype (28, 52, 53). Degradation of ECM by specific proteinases (e.g., MMP-1 for collagen, MMP-2 and MMP-9 for denatured collagen, and MMP-12 for elastin) can expose cryptic sites that bind distinct receptors (54, 55) or can liberate fragments having cryptic sites that can then bind cell receptors and modulate cell phenotypes (56, 57). Degradation of collagens and other ECM proteins can influence the function of ECs, as, for example, in regulating angiogenesis. Clearly, active cell mechanics, passive matrix mechanics, and biochemical mechanisms all contribute to ECM regulation of biological processes.

4. MECHANICAL HOMEOSTASIS

The physiologist Walter Cannon (58) introduced the concept of homeostasis in the 1920s as an extension of the notion of a stable internal environment (milieu intérieur) introduced by Claude Bernard in the 1870s. Homeostasis is the process by which cells, tissues, and organs maintain key variables within defined ranges (alternatively, near target values or set points). Classical examples include maintenance of core body temperature and pH in interstitial fluids. Homeostasis exists at all scales in the vasculature, from subcellular to cellular to tissue levels, as reflected by regulated values of stress at both focal adhesions and the entire wall (59). The aforementioned responses of healthy arteries to sustained modest changes in blood flow and pressure, reflected in Equations 3 and 4, are manifestations of tissue-level mechanical homeostasis.

Mechanical homeostasis requires an input (mechanical stimulus) and an output (biological response) that is ultimately resolved via negative feedback by a system that consists of a collection of functional cells and ECM (**Figure 3*a***). For arteries, mechanical inputs include the hemodynamic and axial loads that act on the vessel. Combining standard equations of vascular mechanics with knowledge of the geometry and material properties allows for calculation of the mechanical state in terms of continuum metrics such as stress, strain, stiffness, and energy. Although the equations of mechanics dictate the values of these mechanical quantities, comparisons to set points require

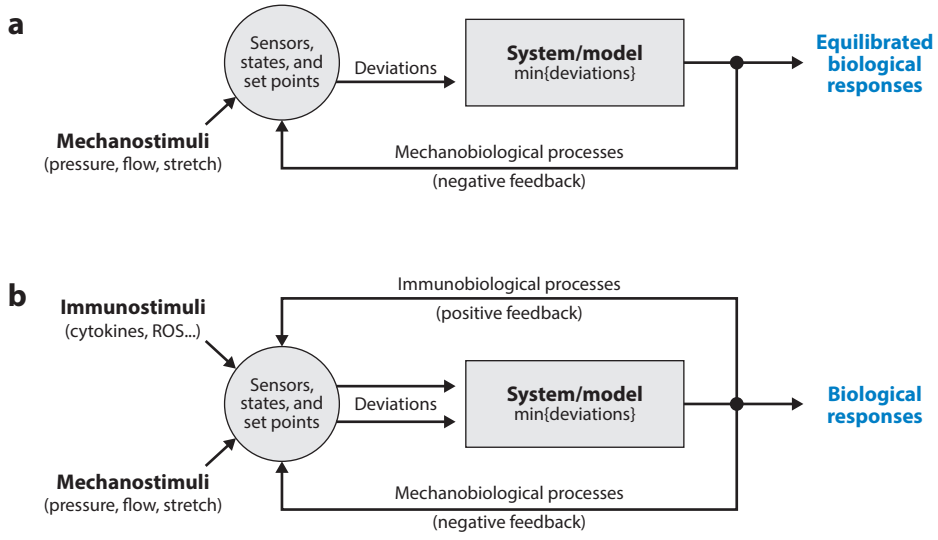

Figure 3

(*a*) Schema of key components of mechanical homeostasis in arteries. Mechanical stimuli (pressure, flow, and axial force) combine with local geometry and properties to define the mechanical state, which can be calculated using equations of continuum biomechanics. Cells must sense this state and compare perceived values against homeostatic targets, or set points. Any deviation in mechanical state from the set point stimulates the effector cells to modify their phenotype and/or the extracellular matrix (collectively the system to be modeled) to minimize the deviation (denoted as min{deviations}). Various computational models, both phenomenological and mechanistic and both single scale and multiscale, can be used to quantify the associated biological response, which can affect the geometry and material properties and hence the mechanical state. Continued negative feedback can maintain or restore the homeostatic state. (*b*) Although (para)inflammation can contribute to the negative feedback and subsequent remodeling, chronic inflammation often drives positive feedback that exacerbates perturbations and promotes disease progression. Various cell types can contribute to this disease-promoting inflammation, including monocytes, macrophages, and T cells, as well as endothelial cells, smooth muscle cells, and fibroblasts that undergo a phenotypic modulation toward an inflammatory (or degradative) phenotype.

that the cells sense these values, which may or may not reflect the actual state. That is, whereas the actual mechanical state alone dictates the outcome in mechanics, for example, rupture of the arterial wall when stress exceeds strength, in mechanobiology it is not the mechanical state but rather what the cell perceives that state to be that determines outcome on the basis of comparisons to the desired set points. Hence, states, sensors, and set points are equally important in determining possible deviations from homeostatic targets that dictate subsequent cellular responses. Such responses reflect the underlying cellular phenotype, which often changes, and typically lead to reorganization or turnover of the ECM. Upon designation of the effector cells and ECM herein as a system, it can be modeled at various levels, from gene regulatory networks to cell signaling to phenomenological models of tissue growth and remodeling (G&R). Multiscale models that capture both mechanisms and manifestations are especially useful.

As noted above, sustained increases or decreases in blood pressure tend to drive thickening or thinning of the arterial wall to actively return intramural stress toward a target value (7, 60, 61). Yet, such mechanoadaptations exhibit considerable regional differences that illustrate differences in mechanism and disease susceptibility. Elastic arteries tend to increase in caliber, in part due to their elastic response to increased pressure in the absence of a strongly opposing vasoactive response, which reflects the matrix SMC phenotype that primarily supports mechanosensing

and mechanoregulation of the ECM. Muscular arteries tend to maintain their caliber due to the contractile SMC phenotype. Arterioles, in contrast, tend to decrease in caliber in hypertension (62, 63) due to exuberant (myogenic) vasoconstriction in the absence of a strong elastic response, reflecting their specialized contractile SMC phenotype. This distinctive myogenic constriction to increased pressure is thought to protect against end-organ microcirculatory damage by reducing the ability of the pulse pressure wave to propagate into the organ.

A central principle is that long periods of vasoconstriction or vasodilation [on a timescale of usually days to weeks (1), although in some cases only 4 h (64)] enable remodeling to alter the baseline vessel geometry and properties. This process is often referred to as entrenchment. Remodeling of both the cytoskeleton and ECM contributes to this process, the latter often via cross-linking through tissue transglutaminase during the vasoactive period. Similar entrenchment has been observed ex vivo in tissue equivalents, with associated changes in cross-linked ECM generating what is sometimes referred to as residual matrix tension (65, 66) during which cells attempt to promote a tensional homeostasis (66, 67). Further support for the coupled roles of vascular tone and matrix turnover in remodeling derives from studies in mice wherein deletion of endothelial nitric oxide synthase, an enzyme catalyzing the production of NO, blocks long-term flow-dependent vessel remodeling (68).

Although the mechanics and physiological principles behind mechanoregulation of wall thickness are relatively well understood, how constituent cells sense intramural stress is emphatically not. It is notable that the mean wall shear stress in the human aorta is on the order of 1.5 Pa, whereas the mean circumferential intramural stress is on the order of 150 kPa—five orders of magnitude higher. Intramural stresses on the order of 150 kPa can be generated by fully contractile SMCs within muscular arteries and perhaps by arterioles, but probably not by SMCs involved in sensing and regulating the ECM. Thus, SMCs in large arteries are apparently stress shielded, with the ECM bearing most of the load. It has long been thought that elastic fibers bear most of the intramural stress at normal blood pressures while collagen fibers bear more at higher pressures (69). This distribution is thought to maximize energy storage at physiological loads, consistent with a recent bilayered stress analysis (70). Only in cases of acute supraphysiological increases in blood pressure, such as in weight lifting and fight-or-flight responses, does the collagen of the adventitia likely engage and carry the higher loads to protect the more vulnerable underlying SMCs and elastic fibers. Dramatic sustained elevation in blood pressure can engage the adventitia, however, resulting in an increased deposition of collagen that is sometimes adaptive, sometimes fibrotic. Hence, ECs, SMCs, and FBs seem to have different homeostatic set points that can vary with region, and these different values seem to enable the different cell types to work together to promote a robust, integrated vessel and vascular network. As noted above, it is not understood exactly how the intramural cells sense their local mechanical environment. The intramural cells—SMCs of the media and FBs of the adventitia—may sense mechanical loading through their own cyclic deformations due to intramural strain. Alternatively, they may sense forces indirectly via integrins and changes in the mean or cyclic stress within the elastic and collagen fibers, which necessarily balance much of the applied force.

5. AN INTEGRATED FRAMEWORK WITH NEGATIVE FEEDBACK

Whereas mechanical homeostasis in healthy arteries is characterized by negative feedback that restores the preferred state following a perturbation, risk factors such as hypertension and vascular aging, as well as major diseases of arteries, including aneurysms and atherosclerosis, are often associated with either compromised homeostasis or positive feedback loops that promote pathological processes (71). A constrained mixture model for soft tissue G&R reveals three key classes of

constitutive relations that are needed to model mechanical homeostasis and its biomechanical consequences in the vasculature (72): (*a*) the rates at which new structural constituents are produced and incorporated within an extant cell or tissue (denoted as $m^\alpha > 0$, where $\alpha = 1, 2, \ldots, N$ denotes N individual families of structurally significant constituents); (*b*) the rates at which these structural constituents are removed (denoted as $r^\alpha > 0$), often via cell death or matrix degradation; and (*c*) the typically nonlinear and anisotropic mechanical properties of each constituent (often captured by a stored energy function $W^\alpha > 0$). Contained within the stored energy function are additional modulators of homeostasis, including the effective values of prestretch (or prestress) at which new structural constituents are incorporated within the extant matrix, as well as their orientations and cross-link density. If one uses a heredity integral approach rather than a rate-based approach (73), one can alternatively prescribe a survival function q^α rather than a removal function. In this case, the three requisite constitutive functions are $m^\alpha(\tau)$, $q^\alpha(s,\tau)$, and $W^\alpha(\tau)$, where $q^\alpha(s,\tau) \in [0,1]$ accounts for the finite half-life of each constituent that is produced at G&R time $\tau \in [0,s]$ and survives to current time s. The normal half-life of vascular collagen is on the order of 70 days, although it can be as low as 7 days in hypertension (74). Remarkably, the normal half-life of vascular elastin is on the order of 50 years (47), although loss of elastic fiber integrity is accelerated in diseases such as aneurysms and atherosclerosis. Genetic diseases that affect elastic fibers—including Marfan syndrome, which results from mutations to the *FBN1* gene—also reduce the half-life of elastin. These very different constituent- and state-specific half-lives suggest the utility of mixture models. Reorganization of the cytoskeleton or ECM as part of remodeling in the absence of mass turnover can also be captured via such functions, since remodeled constituents are effectively newly produced from removed ones.

A fundamental relation from mass balance for a constrained mixture defines changes in wall composition via evolving constituent-specific apparent mass densities (72); specifically,

$$\rho^\alpha(s) = \rho^\alpha(0)Q^\alpha(s) + \int_0^s m^\alpha(\tau)q^\alpha(s,\tau)\mathrm{d}\tau, \qquad 5.$$

where total mass density $\rho(s) = \sum \rho^\alpha(s)$. Note that $Q^\alpha(s) = q^\alpha(s,0)$, with $Q^\alpha(0) = 1$. As a simple illustrative example, consider the following functional forms for rates of production and subsequent survival,

$$m^\alpha(\tau) = m^\alpha_\mathrm{o}(1 + K^\alpha \Delta\sigma), \qquad 6.$$

$$q^\alpha(s,\tau) = \exp\left(-\int_\tau^s k^\alpha_\mathrm{o}(1 + \Delta\sigma^2)\mathrm{d}t\right), \qquad 7.$$

where $m^\alpha_\mathrm{o} > 0$ is an original homeostatic rate of production (mass per volume per time) and $k^\alpha_\mathrm{o} > 0$ is an original homeostatic rate of removal (units of inverse time in this first-order-type kinetic decay), both constant in health in maturity and defined individually for each structurally significant constituent. It can be shown that $m^\alpha_\mathrm{o} = \rho^\alpha(0)k^\alpha_\mathrm{o}$ to ensure balanced turnover within homeostatic states. Importantly, the basal rates can be modulated by deviations in the mechanical state from the homeostatic target, here illustrated for deviations Δ in a scalar measure of intramural stress σ (e.g., first invariant or magnitude) from its set point σ_o, with $K^\alpha > 0$ constituent-specific gain-type parameters. For example, given the advantages of normalizing these deviations to focus on nondimensional values, let $\Delta\sigma = [(1-\delta)\sigma - \sigma_\mathrm{o}]/\sigma_\mathrm{o}$, where the parameter $\delta \in [0,1]$ accounts for the ability of the effector cell to sense the mechanical state: $\delta = 0$ if the cell can sense the actual stress σ and $\delta = 1$ if the cell can no longer sense the stress. Intermediate values of δ capture degrees to which mechanosensing is compromised. In summary, in the context of **Figure 3*a***, the state is

determined by solving linear momentum balance to find the stress σ, the sensor incorporates the factor δ, and the set point is given by σ_o.

In this formulation, tissue maintenance is captured by balanced rates of production and removal in a normal, unchanging mechanical state (i.e., $\Delta\sigma = 0$). Equations 6 and 7 further show that when the stress σ deviates from its homeostatic value (i.e., $\Delta\sigma \neq 0$), the rates of production and removal change in an attempt to hasten restoration of the stress back toward the homeostatic target (i.e., within a particular tolerance), with the effective rates returning toward the original values once the stress relaxes to its homeostatic value. Hence, this system demonstrates negative feedback regulation; in the context of **Figure 3*a***, Equations 6 and 7 are part of the model that defines the responsive system. The necessity of negative feedback in mechanical homeostasis in the vasculature was recognized early on by Taber (75) and has been enforced in all such models since. Taber and others used a finite kinematic growth model rather than the constrained mixture model noted above, which means that growth laws were prescribed in terms of deformations, not mass turnover (76), yet enforcement of negative feedback remains a common feature. Moreover, different metrics (stress, strain, stiffness, energy, and so forth) can be used to drive the feedback loops, although again the precise set-point variables remain unknown in many cases. Nonetheless, mean intramural stress is a convenient metric because it requires knowledge of only the current geometry and applied loads (Equation 1), and not the past configurations that are needed to compute strain or strain energy. Wall shear stress also appears to be a particularly good candidate in endothelial mechanobiology (15); values of wall shear stress can be easily computed from hemodynamic simulations, whereas computing microscale endothelial deformations, stiffness, or energy storage is difficult.

When the illustrative constitutive relation above for mass production is augmented with a similar negative feedback term for flow-induced wall shear stress, as in, for example,

$$m^\alpha(\tau) = m^\alpha_o(1 + K^\alpha_\sigma \Delta\sigma - K^\alpha_\tau \Delta\tau_w), \qquad 8.$$

the associated computational models recover ideal mechanoadaptations, as defined by Equations 3 and 4 (72), as well as salient features of many disease conditions. Here, $K^\alpha_\tau > 0$ are gain-type parameters that modulate the effects of deviations in wall shear stress from homeostatic values, where $\Delta\tau_w = (\tau_w - \tau^o_w)/\tau^o_w$ and the index o again denotes the original homeostatic target or set point. The negative sign associated with this shear term accounts for the observation that NO (which is upregulated in ECs in increased flows when $\Delta\tau_w > 0$) decreases matrix production by SMCs and FBs, whereas ET-1 (which is upregulated in ECs in decreased flows when $\Delta\tau_w < 0$) increases matrix production by SMCs and FBs (77, 78). The relative magnitudes of the stress differences ($\Delta\sigma$ and $\Delta\tau_w$) and associated gains (K^α_σ and K^α_τ) dictate the differential effects of altered intramural and wall shear stress, both regionally and in different conditions.

6. POSITIVE FEEDBACK LOOPS IN VASCULAR DISEASE

6.1. Local-Global Effects

Central artery stiffening, a key risk factor for many cardiovascular diseases (79), introduces positive feedback via effects on global hemodynamics, specifically pulse wave velocity (PWV). Whereas decreased arteriolar radii increase peripheral resistance and thereby increase mean arterial pressure, including in hypertension, increased structural stiffness of the central (elastic) arteries increases central pulse pressures and the propagation of the pulse wave (via the PWV) into the microcirculation of end organs (63). Although limited theoretically (80), the following relation provides

considerable intuition:

$$\mathrm{PWV} = \sqrt{Eh/2\rho_f a}. \qquad 9.$$

Here, E denotes a linearized material stiffness of the wall, ρ_f is the mass density of the fluid (blood), and a and h are luminal radius and wall thickness, respectively. This Moens-Korteweg equation reveals that the structural stiffness of the wall, Eh, and luminal radius a are the main factors in determining the speed at which the pressure pulse propagates within central arteries. Recall from above that if blood pressure increases in a central artery γ-fold without a change in blood flow ($\varepsilon = 1$), then restoration of the local mean intramural stress requires a γ-fold increase in wall thickness without a change in luminal radius. According to the Moens-Korteweg equation, however, this increase in wall thickness will also increase PWV unless material stiffness decreases via reverse wall remodeling, which tends either not to occur or to be insufficient. Without such remodeling or a compensatory change in luminal radius (which will alter local shear stress regulation if $\varepsilon = 1$), this local mechanoadaptation will increase PWV, which in turn will cause the reflected pressure wave to return to the central vasculature earlier in the cardiac cycle, thus augmenting the central pulse pressure (4). That is, an insidious positive feedback loop can arise wherein local adaptations via mechanical responses to increased pressure cause global changes in hemodynamics that increase the pressure that drives the local attempt of mechanoadaptation (81). In addition, an increase in proximal blood pressures can elicit baroreceptor resetting (82), effectively reducing baroreceptor sensitivity. A structurally stiffer wall will also distend less with each cardiac cycle, thus reducing a possible cyclic strain mechanostimulus; such a reduction can affect SMC phenotype and possibly even EC phenotype. Endothelial dysfunction, that is, reduced availability of the vasodilator and inflammation inhibitor NO, is common in large arteries in hypertension and aging (83–85). Hence, locally adaptive thickening of the arterial wall in hypertension can have negative consequences that shift the control toward positive feedback and loss of mechanical homeostasis.

6.2. Inflammation

It is increasingly realized that inflammation plays key roles in vascular conditions and diseases (86–88), including aging, abdominal aortic aneurysms (AAAs), and atherosclerosis (**Figure 3*b***). For example, very low wall shear stress can upregulate leukocyte adhesion molecule expression by ECs and promote local inflammation (89, 90). The recruited inflammatory cells secrete chemokines and cytokines that contribute to inflammatory activation of ECs and SMCs and further recruitment of inflammatory cells, often leading to a positive feedback loop and a pathological neointima (**Figure 1*b***), as in atherosclerosis (86). Activated inflammatory cells can similarly populate the adventitia, sometimes leading to adventitial fibrosis (**Figure 1*b***) and thus overall structural stiffening (91, 92), as seen in aortic aging and hypertension (45, 93). The media tends to be immunoprotected (94) until the internal and/or external elastic laminae are compromised, at which time the media can become inflamed, as in some aneurysms, particularly those of the abdominal aorta (95). Although resident macrophages participate in this process, many inflammatory cells, including neutrophils, monocytes, and T cells, reach target arteries by transport via the lumen or the vasa vasorum and similarly via the lymphatic system, including that within perivascular fat (96, 97).

Inflammation plays key roles in diverse remodeling processes, not just in infections and tissue injury (98, 99). Cells of the monocyte and macrophage lineage in particular are essential for many aspects of arterial remodeling, including homeostatic removal of dead cells and cellular debris or partially degraded and damaged ECM (21, 22). The term parainflammation has been used to

delineate the homeostatic function of inflammation (99). Yet because the immune system developed to fight infections, it often takes priority over other biological processes whose contribution to survival is less acute. Inflammation can thus dramatically modify other biological processes. In particular, inflammatory signals, typically chemokines and cytokines but also proteases, can significantly alter the gain and rate parameters and set points (see Equation 8) inherent in homeostatic processes, including mechanical processes (99). Altered gain and rate parameters can accelerate responses to stimuli, thus facilitating the needed response; altered homeostatic targets can similarly promote an opportune response, as in adaptations (100). The term adaptive homeostasis has been used to describe the beneficial changes that facilitate such adaptations (101).

The close relationship between vascular function and immunity is often critical in other ways. Tissue inflammation leads to the production of cytokines that act on the endothelium to recruit leukocytes to fight infection or repair damaged tissue (102, 103). The endothelium is thus an essential participant in immune function by directing leukocyte traffic. Inflammation also acts on the endothelium to increase permeability to plasma proteins, such as complement and antibodies, that participate in immunity (10, 11). Many inflammatory signals affect vascular permeability. Inflammatory signals also affect NO production and/or availability to control vessel tone and local blood flow (104). One pernicious mechanism involves reactive oxygen species generated during inflammation that combine with NO to produce peroxynitrite (**Figure 2*a***); this process thus replaces a vasodilator and inflammatory suppressor with a vasoconstrictor and inflammatory activator (105). Inflammation therefore modulates vascular function in ways that override normal homeostatic functions.

The proposal that homeostatic systems with greater potential for adaptability can also have greater disease susceptibility (99) underscores the potential for inflammation in vascular disease progression as well. Set-point changes induced by inflammation may lead, for example, to a vicious positive feedback cycle that promotes chronic inflammation (**Figure 3*b***). Indeed, the seemingly irreversible effects of hypertension on central artery structure and properties may result, in part, from such a process. Recent studies using a mouse model of induced hypertension suggest that changes in thoracic aorta structure, properties, and stresses are slightly reversed but largely persist after the hypertensive stimulus (i.e., exogenous AngII) is removed, apparently due to persistent low-level inflammation (92, 106). Therefore, the renin-angiotensin system is a central node in blood pressure control. Chronic infusion of AngII is, accordingly, a common method of inducing hypertension in rodents. This peptide is a potent vasoconstrictor, first thought primarily to increase total peripheral resistance via arteriolar constriction. Yet exogenous AngII has myriad effects on the vasculature, including stimulation of a proinflammatory state in large arteries (107–109). For example, exogenous angiotensin promotes FB-macrophage interactions that involve the proinflammatory cytokine IL-6, which then promotes adventitial fibrosis (110). In the case of the illustrative constitutive relations noted above for the production and removal of constituents α (Equations 6 and 7), inflammation can be captured by adding another stimulus to the mass production term, namely

$$m^{\alpha}(\tau) = m^{\alpha}_{\mathrm{h}}(1 + K^{\alpha}_{\sigma}\Delta\sigma - K^{\alpha}_{\tau}\Delta\tau_{\mathrm{w}} + K^{\alpha}_{\rho}\Delta\rho_{\varphi}), \qquad 10.$$

mainly in the adventitia where inflammatory cells infiltrate, but also in the media (note that the subscript h denotes a potentially new homeostatic value, in contrast to the subscript o in Equation 8 that denotes the original homeostatic value). Here, $\Delta\rho_{\varphi} \in [0, 1]$ is a normalized measure of inflammatory cell burden, typically $CD4^{+}$ T cells in the adventitia of angiotensin models of hypertension, but $CD68^{+}$ macrophages and other cell types as well. If the inflammation resolves, $\Delta\rho_{\varphi} \to 0$, the stimulus reverts back to a mechanobiological one alone; if inflammation persists ($\Delta\rho_{\varphi} > 0$), the rate of production is permanently altered even if mechanical stresses return to normal.

We recently found that description of extreme adventitial fibrosis in an angiotensin-infusion mouse model (92) required that the gain parameter for mass production become a function of inflammation, namely $K_\sigma^\alpha = \hat{K}_\sigma^\alpha(\Delta\rho_\varphi)$, and similarly that the rate of mass removal parameter become a function of inflammation, namely $k_b^\alpha = \hat{k}_b^\alpha(\Delta\rho_\varphi)$. Indeed, the intramural stress set point also changed; $\sigma_\mathrm{h} = \hat{\sigma}_\mathrm{h}(\Delta\rho_\varphi)$, with subscript h again denoting a new homeostatic state. Each of these changes is consistent with inflammation overriding a homeostatic process (99). Importantly, none of these model changes were needed to capture the observed mechanoadaptation of the minimally inflamed infrarenal abdominal aorta. Why such dramatic regional differences—fibrosis in the thoracic aorta and adaptation in the infrarenal aorta—arise in the same animal model is not clear, but regional variations in AngII receptors [greater in the distal than the proximal aorta (111)], adrenoceptors (112), and SMC phenotype may play roles. Other differences, including local hemodynamics (113) and perivascular tissue, particularly fat, may also contribute.

Not surprisingly, inflammation is also involved in the in vivo progression of tissue-engineered vascular grafts that are implanted as biodegradable polymeric constructs (114). The presence of the polymer elicits a strong inflammatory response, which drives early neotissue formation as the polymer degrades. Thereafter, neotissue formation is presumed to be driven largely by the mechanobiology, which enables good computational model descriptions and predictions of the evolving geometry, composition, and properties of the neovessel (115). There is a need, however, to determine whether long-term persistent inflammation may also play a role, particularly given that the neotissue is not equivalent to normal vessels (116). In multiple systems, ECM arising during injury responses or pathological situations contains altered proteins or other factors [perhaps antigens, given the roles of T cells in adventitial fibrosis (45)] that stimulate fibrosis. That is, inflammatory cells can stimulate the production of aberrant ECM by otherwise normal synthetic cells such as FBs, while aberrant ECM can also stimulate normal cells to produce additional aberrant ECM in the absence of inflammatory cells (117), thus establishing another type of positive feedback loop. Conversely, FBs from fibrotic tissue can be returned to a nonfibrotic phenotype by exposing them to normal matrix (118). There is clearly a pressing need to better understand how pathological changes in ECM promote positive or negative feedback.

6.3. Cellular Phenotypic Transitions

Different cell types or states show substantial differences in mechanosensing parameters and outputs. ECs align perpendicular to, and muscle cell types align parallel to, the direction of stretch (119). Similar variability is observed in stiffness sensing. In general, less contractile cell types such as immune cells have a lower stiffness threshold, spreading and organizing their cytoskeleton on compliant substrates, whereas more contractile cells remain round until stiffness reaches higher levels (120). Cell type also determines the signaling and gene expression pathways that depend on stiffness (121). In the case of flow-induced shear stress, ECs of different types (vascular versus lymphatic) have different set points (15), which likely extends to different subtypes of vessels (arterial, venous, capillary) or different tissues. Vascular ECs and lymphatic ECs exhibit drastically different responses to oscillatory flow, which is proinflammatory in arterial blood ECs but triggers valve morphogenesis in lymphatic ECs (122).

There is now strong evidence that both ECs and SMCs undergo phenotypic transitions in diseased arteries. Immunohistochemistry, fate mapping, and bulk RNA sequencing (RNA-seq) show that ECs in diseased vessels undergo graded transitions to mesenchymal phenotypes [endothelial-to-mesenchymal transition (endo-MT)] (123). Involving downregulation of EC-specific receptors such as PECAM-1, VE-cadherin, and VEGFR2 that are involved in shear stress mechanotransduction, this process may inhibit or alter homeostasis. More recent single-cell RNA-seq of plaque

ECs revealed clusters of cells with inflammatory or mesenchymal gene expression signatures and decreased expression of EC-specific genes involved in flow sensing (124). One cell cluster also exhibited a progenitor signature that is suggestive of cell fate transitions. EC deletion of TGFβ receptors reduced the prevalence of these populations, supporting a role for endo-MT. This type of altered EC phenotype is also likely a component of normal morphogenesis and remodeling. For example, sprouting of angiogenic ECs to form new blood vessels involves limited and transient endo-MT (123). In pathological settings, however, these transitions are never resolved and can progress to more extreme phenotypes.

SMCs in diseased arteries have long been known to transition from a contractile phenotype with high expression of smooth muscle myosin, actin, and other lineage-specific cytoskeletal proteins to a synthetic phenotype characterized by increased proliferation, motility, and ECM production (53). Subsequent studies expanded this repertoire, demonstrating that a fraction of neointimal SMCs developed into macrophage-like cells with reduced expression of SMC-specific genes and upregulation of a subset of macrophage markers (125). Analyses of single-cell RNA-seq in both human and mouse arteries revealed SMC-derived progenitor clusters that likely give rise to multiple fates, including chondrogenic and osteogenic phenotypes (126). In all cases, SMC-specific genes were downregulated. These events are again predicted to reflect or result in altered or defective mechanosensing.

6.4. Aneurysms and Atherosclerosis

Aneurysms are focal dilatations of the arterial wall. Aneurysms in all locations exhibit fragmented or degraded elastic fibers, SMC apoptosis, and fibrosis with concomitant stiffening; they also share aging and hypertension as major risk factors (127, 128). AAAs correlate with atherosclerosis and have a strong inflammatory component (129); they also frequently develop an intraluminal thrombus that exacerbates inflammation, thus creating a positive feedback loop whereby increased dilatation can drive increased thrombosis. Disturbed flows and altered EC mechanobiology can contribute to the early inflammatory phenotype via the recruitment of leukocytes, with subsequent changes in SMC phenotype. In intracranial aneurysms, regions of low flow correlate with regions of maximal enlargement (130). Aneurysm enlargement increases the proinflammatory reverse and transverse components of wall shear stress, accelerating disease. In contrast, thoracic aortic aneurysms (TAAs) are more strongly linked with genetic mutations than with inflammation, with mutations in genes for cytoskeletal proteins (e.g., smooth muscle α-actin and smooth muscle myosin heavy chain) and ECM proteins (e.g., fibrillin-1, a glycoprotein that associates with elastin to form elastic fibers and connects SMCs to elastic fibers). These causative mutations suggest that TAAs may arise, in part, from dysfunctional mechanosensing or mechanoregulation of ECM by SMCs (131, 132). In the equation $\Delta\sigma = [(1-\delta)\sigma - \sigma_o]/\sigma_o$, the parameter $\delta < 1$ can model reduced mechanosensing. In particular, if a cell perceives the stress to be lower than the homeostatic value, it may promote proteolytic degradation in an attempt to raise the (perceived) stress toward its target value, thus increasing the vulnerability of the wall to dissection or rupture. Progressive fibrosis of the vessel may protect against rupture but may also interfere with mechanosensing, thus contributing to further pathological remodeling. Both cases therefore involve positive feedback mechanisms. The SMC phenotypic transitions seen in aneurysms, including reduced expression of SMC-specific cytoskeletal genes (133, 134), also likely interfere with sensing of mechanical forces and thus with homeostasis.

Atherosclerosis is an inflammatory/metabolic disease of muscular and elastic arteries (135, 136), with intimal lesions characterized by accumulations of lipids, necrotic debris, calcification, and remodeled matrix. Disturbed flow at bends and branches within the arterial tree is a local risk

factor (137, 138) due to activation of EC inflammatory pathways (10, 102). Leukocyte recruitment, increased junctional permeability that facilitates entry of lipoproteins into the vessel wall, and oxidative stress establish positive feedback loops that increase inflammatory status and promote disease progression (**Figure 2*a***). Encroachment of lesions into the lumen exacerbates abnormal flows, with high shear at the region of luminal narrowing and very low/disturbed shear on the downstream side. Luminal narrowing is, however, a relatively late event in plaque progression. Plaques at early stages trigger outward remodeling to preserve lumen diameter, so-called Glagov compensatory enlargement, driven in part by stress shielding of SMCs and consequent local medial atrophy as well as by conventional physiological remodeling, in which high wall shear stress increases lumen diameter. Yet at later stages, Glagov enlargement fails, and the lumen continues to narrow. It has been speculated that the failure of continued outward remodeling may be because of stiffening of the adventitia or resistance due to the surrounding tissue, but the existence of aneurysms would seem to argue against this view. An alternative model is based on endo-MT-driven decreases in VE-cadherin and PECAM in the ECs of atherosclerotic plaques. Loss of these receptors that mediate flow sensing (139) likely explains the compromised flow-dependent outward remodeling that, in the face of lesion growth, contributes to vessel narrowing.

7. FROM MECHANICS TO MODELING THE MECHANOBIOLOGY

7.1. Vascular Mechanics

As noted above, quantifying the mechanical state of arteries is essential for understanding both health and disease. Advances in vascular mechanics over the past few decades (5, 9) have underscored the concepts of mechanical equilibrium and stability. For example, analysis of the nonlinear biomechanics of a saccular aneurysm in the brain (140) reveals that these lesions do not exhibit a limit point instability upon quasi-static inflation (i.e., the quasi-equilibrated states are mechanically stable) and moreover that they do not exhibit resonant instabilities during pulsatile loading (i.e., they are dynamically stable). Eliminating the possibility of unstable mechanical behaviors focuses attention on more relevant aspects of lesion enlargement, including matrix turnover that drives the enlargement of an aneurysm through a sequence of mechanically equilibrated states, primarily via collagen degradation and deposition. We recently suggested the applicability of these concepts to the mechanobiologically controlled dynamic enlargement of aneurysms (141) and to vascular mechanobiology in general (73, 142).

Consider another example of the importance of understanding mechanics in mechanobiology. Arteries are residually stressed; that is, there exists a self-equilibrating state of stress in the absence of external loading, which can be revealed by introducing a radial cut into an excised cylindrical segment. This residual stress field includes compressive circumferential and axial stresses in the inner portion of the wall and complementary tensile circumferential and axial stresses in the outer wall. Although values of these residual stresses are low (on the order of 3 kPa), they have a tremendous effect on the calculated transmural distribution of intramural stress under in vivo (axially stretched and pressurized) conditions, where biaxial stresses can be on the order of 150 kPa or more (5). Indeed, when the two predominant structural layers of an elastic artery—the media and adventitia—are separately accounted for, a nonlinear analysis of intramural stress reveals two key findings (70). First, the transmural distribution of stress is nearly homogeneous in both the media and adventitia. Second, these stresses are naturally higher in the media than in the adventitia in an elastic artery under physiological loads. In other words, nonlinear analyses that account for the presence of residual stress reveal what appear to be separate homeostatic target values of stress in the media (sensed by SMCs) and adventitia (sensed by FBs), with these stresses

tending to be uniform within each layer rather than decreasing monotonically with radial location (as expected in an inflated cylindrical tube). In hindsight, the existence of higher stresses in the media of an elastic artery should have been expected; these deformation-dependent stresses promote the fundamental function—to store elastic energy during systole—because the abundant elastic fibers of the media are the primary constituents that store energy when deformed. Importantly, however, this bilayered analysis of the wall also suggests that large acute increases in blood pressure result in a greater increase in intramural stress in the adventitia than in the media, thus allowing the stiffer and stronger collagen of the adventitia to engage and stress-shield the more vulnerable SMCs and elastic fibers of the media, revealing another important structure-function relationship of these vessels. In summary, the multilayered structure reflects the complex functionality of an elastic artery: to store and use elastic energy while withstanding the highest pressures in the vasculature. Toward this end, it is also important to recognize the different homeostatic target stresses for the different cell types (in the mouse aorta): ~6.5 Pa wall shear stress for ECs, ~300 kPa circumferential stress for SMCs, and ~100 kPa circumferential stress for FBs. The axial stress experienced by SMCs and FBs, ~200 kPa, appears to be closer in magnitude, reminding us that the intramural cells are subject to biaxial stresses.

7.2. Modeling the Mechanobiology

There are advantages to couching the concept of mechanical homeostasis in terms of continuum mechanics and dynamical systems, wherein one can exploit a large body of mathematical tools. Simply put, mechanical equilibrium requires that the sum of all forces be zero, typically resulting in a body that is static; mechanical stability implies that the body will return to this, or at least a nearby, equilibrium configuration following a mechanical perturbation. By analogy, one can postulate that mechanobiological equilibrium requires that the sum of mass production and mass removal be zero ($m^\alpha - r^\alpha = 0$). Mechanobiological stability further requires that the system be stable against perturbations (73, 143). The simplest visual illustration of stable, neutrally stable, and unstable equilibria is, of course, that of a rigid sphere placed within a valley, on a flat plane, or on a hill (**Figure 4**). In each case, the equilibrium state is the same (i.e., the reaction force is equal and opposite to the weight of the sphere), yet the mechanical situations are very different: The sphere in the valley will return to its original equilibrium position when perturbed (asymptotically stable), the sphere on the flat plane will move to a new nearby equilibrium position (neutrally stable), and the sphere on the hill will move to another state far from the original one (unstable). Asymptotically stable responses can represent homeostatic responses; neutrally stable responses, adaptive homeostasis; and unstable responses, cases of disease progression by positive feedback. Because of the need to evaluate responses to small perturbations, both asymptotic expansions and the theory of small deformations superimposed onto large deformations are appropriate frameworks for study. Such analyses have promise to describe and predict diverse vascular responses, including those that are homeostatic, adaptive, or maladaptive (**Figure 4**).

Comparison of two recent constrained mixture-based G&R approaches for assessing mechanobiological stability reveals that the types of (in)stabilities that are admitted depend on the representation of the mechanobiological system. First, if one defines a system in terms of rate equations for position (mechanically) and mass production (mechanobiologically), then the system admits either a neutral stability or an instability (142). On the basis of this approach, progressive AAA enlargement may represent a mechanobiological instability despite remaining mechanically stable. That this simulation suggests neutral stability implies, in turn, that such an aneurysmal enlargement may represent an attempted adaptation to an initiating insult, that is, a new stable mechanobiological state. Multiple factors were found that could stabilize AAA

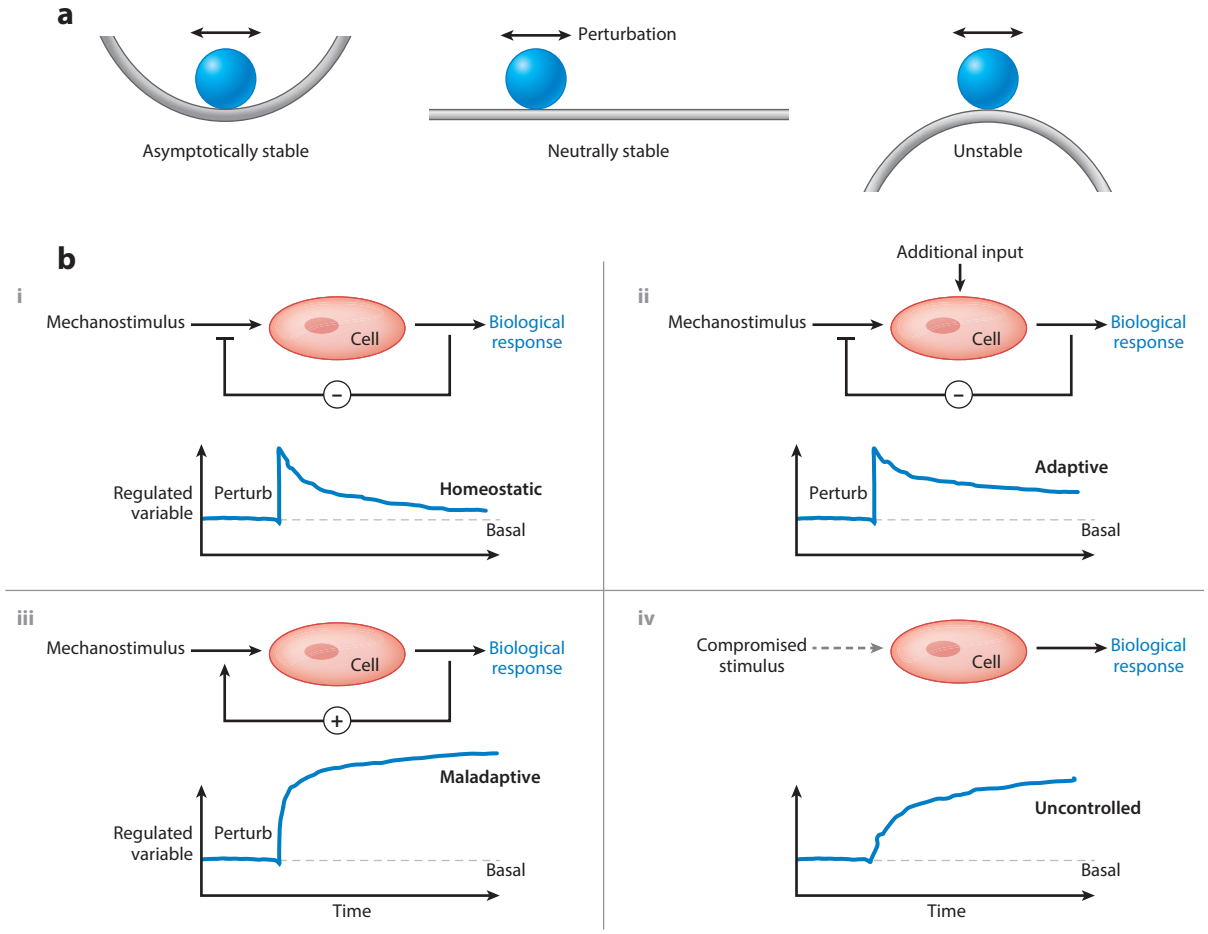

Figure 4

(*a*) Conceptual representation of three common types of (in)stabilities: asymptotically stable, neutrally stable, and unstable. Imagine that a perturbation in loading causes the rigid sphere to move, returning to its original location on the left, finding a new nearby location in the middle, and falling far from its original position on the right. Neutral stability allows for not only adaptivity in biology but also increased vulnerability to instabilities that manifest as diseases. (*b*) Possible control systems relevant to arterial health and disease. (*i*,*ii*) Negative feedback (*minus sign*) is restorative, as in cases of acute or modest sustained changes in hemodynamics (*i*), but can be overridden by additional stimuli, such as inflammation (*ii*). (*iii*) In contrast, positive feedback (*plus sign*), as in adventitial fibrosis (**Figure 1**), is typically maladaptive, moving the controlled variable from its basal value (*horizontal dashed line*). (*iv*) Finally, systems that rely on appropriate input can become maladaptive when the input signal is compromised or lost, as in dysfunctional mechanotransduction. Overall, negative feedback promotes asymptotic mechanobiological stability, negative feedback with additional nonmechanical stimuli represents neutral stability, and cases of positive feedback or compromised mechano-input represent instabilities.

enlargement, including increased rates of collagen production, which was predicted computationally (144) and confirmed experimentally using an antago-*miR29b* treatment (143). The low rate of rupture of intracranial saccular aneurysms, less than 0.1% per year (127), is also consistent with the concept of aneurysmal stability or adaptivity. Yet second hits, such as intraluminal thrombosis in AAAs or dissections in TAAs, would compromise any attempted adaptation. Although adaptive homeostasis (98, 101) can be highly beneficial biologically, it can also expose a vulnerability to

maladaptations characteristic of disease, which may explain the continued enlargement of certain aneurysms until rupture.

Second, if one chooses rate equations on the basis of mass density and biaxial stresses for an elastic artery subjected to altered loading, asymptotic stability is possible in addition to neutral stability and instability (73). In particular, such a numerical artery can respond to a transient perturbation and return to its original state, or it can respond to a sustained perturbation via geometric and compositional adaptations that restore the stresses toward normal. Many different parameters affect the stability; these include the intrinsic material stiffness as well as magnitudes of the gain parameters that control ECM production and the rate parameters that control its degradation. Similar findings were reported for a stability analysis based on rate equations for total potential energy (145), which again suggested that increased rates of production, decreased rates of degradation, or increased material stiffness can stabilize responses. Similar mechanobiological stability analyses can also be examined using the theory of kinematic growth (146).

8. FUTURE PERSPECTIVES

Hypertension and vascular aging are key risk factors for diverse cardiovascular, renovascular, and neurovascular diseases. Atherosclerosis and aneurysms are but two examples of chronic diseases that involve pathological remodeling of the vessel wall, often over decades. As we have seen, these diseases arise through complex regulatory loops in which homeostatic control is corrupted or overcome by the appearance of positive feedback mechanisms. While physiological regulation is dominated by negative feedback that promotes stability in the face of perturbations, positive feedback often results in instabilities that promote continual pathological remodeling, that is, disease progression.

Past and many current efforts in vascular disease research have focused largely on inhibiting obvious steps in the disease etiology. For example, hypertension is widely treated using diuretics to reduce blood volume or inhibitors of the renin-angiotensin pathway or voltage-gated calcium channels to limit vasoconstriction. Statins, which inhibit cholesterol synthesis, are by far the most widely used medical treatment for atherosclerosis. Importantly, the clinical success of these inhibitors now appears to depend heavily on unintended consequences. Statins, 20 years after their clinical introduction, were found to induce expression of the anti-inflammatory transcription factor Klf2 (Krüppel-like factor 2), a major contributor to drug efficacy (147, 148). Similarly, inhibitors of the angiotensin pathway have anti-inflammatory benefits that substantially diminish disease progression independently of direct effects on SMC relaxation and pressure reduction (149). These fortuitous successes were accompanied, however, by a vastly larger number of drugs that failed in preclinical studies or clinical trials, many due to unanticipated harmful effects (150, 151). These results point toward the importance of achieving a more complete, systems-oriented understanding of the relevant homeostatic and disease processes and associated consequences of different classes of drugs.

A long-term goal for investigators of vascular biomechanics, cell signaling, immunobiology, matrix biology, and mechanobiology should be integrative quantitative models that are sufficiently rich to identify therapeutic targets for blocking disease processes without substantially impeding homeostatic processes. Progress over the past 20 years leads us to believe that reasonably detailed and accurate mechanobiological models are within reach. It may be optimistic, but a cell biological model that includes regulation of the principal signaling and gene expression pathways in ECs, SMCs, FBs, and immune cells that govern homeostasis seems achievable. Considerable advances have been realized in allied fields, including cardiac mechanics and mechanobiology, wherein logic-based cell signaling models describe myriad empirical findings and thus promise

to provide predictive capability (152). Such models, when extended across multiple interacting cell types having diverse phenotypes, should enable much better prediction of remodeling under conditions of interest as well as expected outcomes for potential therapeutic intervention.

Nonetheless, one further step is needed to solve the bigger problem: to synthesize knowledge across scales within a single modeling framework that includes gene regulation, cell signaling, and cell- and tissue-level mechanical consequences. Such an achievement may require integrating different modeling approaches (e.g., cell signaling, agent based, differential equation based) so that the combined effects of forces on cell signaling and the effects of cells on force generation and matrix synthesis and assembly can be assessed. While the precise path to integration remains to be determined, a comprehensive approach of this general type is the basic requirement for understanding the multiscale physical and regulatory interactions that govern vascular homeostasis, adaptation, and disease. The benefit to both basic science and clinical research would be considerable.

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