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Mechanisms of Arterial Remodeling in Hypertension: Coupled Roles of Wall Shear and Intramural Stress

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Abstract

Hypertension causes and is caused by significant changes in the structure and function of arteries. Diverse data collected over the past four decades reveal that many of these changes result from a mechanical stress or strain mediated reorganization and turnover of cells and extracellular matrix in vasoaltered states that promotes a “mechanical homeostasis.” This paper reviews diverse data on the mechanobiological behaviors of vascular cells (endothelial, smooth muscle, and fibroblasts) and associated changes that manifest at the tissue level. Although experimental design is often motivated by the thought that altered flow largely affects arterial caliber and altered pressure largely affects wall thickness, all three primary descriptors of vessel geometry (radius, thickness, length) are coupled strongly to all three primary measures of stress (wall shear, circumferential, axial). Hence, mechanobiological responses by resident cells should likewise be expected to be sensitive to all three primary stresses. It also appears that cellular production of vasoactive molecules, growth factors, cytokines, matrix proteins, and proteases depends nonlinearly, often sigmoidally, on changes in stress. This suggests that there is a need to quantify coupled, nonlinear “mechanical dose response curves” that correlate altered stresses with cellular activity; moreover, mathematical models can help integrate such information across multiple length scales (from molecule to cell and tissue) and time scales (from minutes to days and months). For example, quantification of stress mediated synthesis and cross-linking of collagen organization within the hypertensive arterial wall, and associated signaling pathways, may suggest new therapeutic strategies based on targeted levels of inhibition.

Keywords

collagen turnover; elastin damage; smooth muscle phenotype; nitric oxide; endothelin; growth factors

Diverse data collected over the past four decades suggest the existence of a mechanical homeostasis across multiple length and time scales in the vasculature. For example[1], stress fibers within endothelial and vascular smooth muscle cells appear to disassemble and then reassemble in a mechanically preferred manner when perturbed from a normal value of mechanical stress or strain; focal adhesions in smooth muscle cells and fibroblasts tend to increase in area in response to local increases in mechanical loading so as to maintain the stress constant at a preferred value; fibroblasts tend to increase the tractions they exert on extracellular matrix when external loads are decreased from a preferred value, thus suggesting an attempt to enforce a “tensional homeostasis”; vascular smooth muscle cells tend to re-lengthen to their normal, preferred values when an arteriole is forced into a vasoconstricted state for an extended period; and arteries tend to decrease in caliber in response to sustained decreases in flow-induced wall shear stress, to increase in thickness in response to sustained increases in pressure-

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induced circumferential stress, and to lengthen in response to extension-induced increases in axial stress. Whereas changes in the cytoskeleton and integrins occur within minutes, changes at the cell-cell and cell-matrix level occur over hours and those at the vessel level occur over days to weeks or months. Hence, despite marked differences in length scales (dimensions from nm to cm) and time scales (durations from minutes to months), mechanobiological control mechanisms in the vasculature tend to restore values of stress or strain toward preferred (homeostatic) values in response to diverse perturbations from normal[2–5]. Biomechanics and mechanobiology thus play key roles in vascular development, tissue maintenance in maturity, normal adaptations, aging, disease progression, and responses to injury or clinical interventions.

A current challenge in hypertension research is to understand how mechanobiological mechanisms at molecular and cellular levels (e.g., altered turnover of collagen) manifest at tissue and organ levels and, conversely, how mechanical loads at tissue and organ levels (e.g., increased pulse pressure) are sensed by molecular structures and result in altered gene expression. To gain increased understanding, we can exploit lessons learned from all areas of vascular research for it appears that the same fundamental cell-mediated mechanisms govern diverse cases of vascular growth (i.e., change in mass) and remodeling (i.e., change in structure) via the reorganization and/or turnover of cells and extracellular matrix in evolving biomechanical states[1].

Biomechanical Consequences of Perturbed Flow and Pressure

Notwithstanding complexities of in vivo mechanics due to pulsatile blood flow and nonlinear anisotropic wall properties[4], the normal artery is subjected to three primary mechanical stresses: a blood flow induced wall shear stress τ_w, a blood pressure induced circumferential wall stress σ_θ, and an axial wall stress σ_z that appears to arise during development and to persist into maturity due to the long half-life of elastin[6]. Mean values of these three components of stress (i.e., forces acting over oriented areas) can be calculated as[4]

$$\tau_w=\frac{4\mu Q}{\pi a^3},\quad \sigma_\theta=\frac{Pa}{h},\quad \sigma_z=\frac{f}{\pi h(2a+h)}, \tag{1}$$

where μ is the blood viscosity, Q the mean volumetric flow rate, a and h the luminal radius and wall thickness in any pressurized configuration, P the transmural pressure (with low perivascular pressure), and f the axial force that maintains the axial "prestretch" (which is appreciated via the axial retraction of a transected artery). The second equation reveals the importance of the thickness:lumen ratio (h/a), noting that h is total, not intimal-medial, thickness, and the third equation shows the importance of wall cross-sectional area, which is often reported with regard to "eutrophic" vs. "hypertropic" remodeling. Although the importance of axial stress and stretch in hypertension was recognized years ago7, it has received little attention because of the inability to infer values in vivo.

Large arteries appear to maintain these stresses near homeostatic values (e.g., on the order of 1.5 Pa for τ_w and 100 kPa for both σ_θ and σ_z in specific arteries[2–4], where 1 kiloPascal (kPa) equals 7.5 mmHg). Hence, it is instructive to consider how clinically measurable changes in flow or pressure might lead to tissue level changes in geometry (in addition to changes in structure and function). Let perturbed values of flow Q and pressure P be related to original values via $Q = \varepsilon Q_o$ and $P = \gamma P_o$, where a subscript or superscript o denotes original and ε,γ denote sustained percent changes from original (e.g., $\gamma = 1.3$ if P increases 30% from original). Equation 1 reveals that *if* mean wall shear stress and then mean circumferential stress are

restored via growth and remodeling processes, *then* specific morphological changes to large arteries should be:

$$\text{If } \tau_w=\frac{4\mu(\varepsilon Q_o)}{\pi a^3}\text{(perturbed) and } \tau_w^o=\frac{4\mu Q_o}{\pi a_o^3}\text{(original),}\quad \text{then } \tau_w=\tau_w^o \text{ requires } \frac{4\mu(\varepsilon Q_o)}{\pi a^3}=\frac{4\mu Q_o}{\pi a_o^3},\ \text{or } a=\varepsilon^{1/3}a_o; \tag{2}$$

$$\text{If } \sigma_\theta=\frac{(\gamma P_o)(\varepsilon^{1/3}a_o)}{h}\text{(perturbed) and } \sigma_\theta^o=\frac{P_o a_o}{h_o}\text{(original),}\quad \text{then } \sigma_\theta=\sigma_\theta^o \text{ requires } \frac{(\gamma P_o)(\varepsilon^{1/3}a_o)}{h}=\frac{P_o a_o}{h_o},\ \text{or } h=\varepsilon^{1/3}\gamma h_o. \tag{3}$$

For example, a 30% sustained increase in flow alone should cause a 9% increase in both caliber and wall thickness (i.e., if $\varepsilon = 1.3$, then $(1.3^{1/3})\ 1 = .09$ with $\gamma = 1.0$); in contrast, a 30% sustained increase in pressure alone should cause a 30% increase in thickness but no change in caliber (i.e., $\gamma = 1.3$ with $\varepsilon = 1.0$). In other words, a mean stress-mediated growth and remodeling response would require coordinated changes in luminal radius *a* and wall thickness *h* based directly on percent perturbations in hemodynamics from original. Such changes are commonly observed clinically and in animal studies[3,4,8,9], hence supporting this general hypothesis. Note, too, that *if* luminal radius and wall thickness are dictated by flow and pressure, *then* restoring σ_z (equation 1) to its original value requires a change in axial force *f*, which typically would cause a change in length (e.g., possible tortuosity). That responses to all stresses must be considered together is reinforced by observed, coupled effects of pressure (e.g., cyclic circumferential stress or strain) and flow (wall shear stress) induced changes at cellularand tissue levels[10–12].

Before considering cellular mechanisms by which arteries can achieve gross changes in geometry, structure, and function, note three subtle points. First, the above (equilibrium) equations for σ_θ and σ_z are deceptively simple because nonlinear dependencies of pressure on radius (traditional pressure-diameter data) and axial force on length (common uniaxial data) are not denoted explicitly, nor are observations that pressure-diameter relations differ at different axial stretches and axial force-length relations differ at different pressures[4]. There is a need, therefore, to account for changes in wall composition, that is, material properties. Second, equations 1–3 do not account for changes in perivascular tethering or the pulsatility of flow and pressure, which can play important roles in arterial growth and remodeling. There is a need, therefore, for more research on the associated mechanobiology. Third, changes in arterial geometry in response to altered loads depend on coupled elastic deformations (i.e., nonlinear wall properties), acute and chronic changes in vascular tone (i.e., smooth muscle contraction or relaxation), and reorganization or turnover of cells and matrix in potentially evolving biomechanical states (i.e., growth and remodeling). Hence, even in a simple case of a single sustained change of flow or pressure, the means by which and the durations over which radius tends toward $\varepsilon^{1/3}a_o$ and thickness tends toward $\varepsilon^{1/3}\gamma h_o$ can be complex and depend on both short-term and long-term cellular responses, including altered proliferation, migration, differentiation, apoptosis, synthesis and degradation of matrix, cross-linking of matrix, integrin binding that governs cell-matrix interactions, and cadherin activity that governs cell-cell interactions.

Vascular Mechanobiology

The first reports of mechanobiological responses by vascular cells appeared in the mid-1970s[1–5]. Since then, it has been shown that many different non-structurally significant molecules (e.g., vasoactive, growth factors, cytokines, proteinases, coagulation factors, an so

forth) and structurally significant constituents (e.g., fibronectin, elastin, collagens, proteoglycans) are produced by fibroblasts, smooth muscle, and endothelial cells in response to altered mechanical loads[2,3,13–15]. Although associated mechanisms of mechanotransduction are not understood fully, G-proteins, ion channels, receptors for growth factors and vasoactive molecules, and the cytoskeletal–integrin–extracellular matrix axis play fundamental roles. For example, changes in tissue-level loads can cause rapid reorganization or remodeling of integrins and associated intracellular proteins so as to promote mechanical homeostasis[1]. Integrins play diverse roles, from influencing cell migration, proliferation, and apoptosis to enabling cells to survey their local mechanical environment or to alter myogenic responses[16,17]. Recall, however, that σ_θ is often on the order of 100 kPa in arteries. Although some investigators suggest that intramural cells necessarily "feel" this level of stress, the aforementioned findings that some cells attempt to maintain stress on the order of 3 to 10 kPa at focal adhesions suggests that the full load supported by the extracellular matrix need not be felt by resident cells, with the possible exception of contractile smooth muscle cells. Rather, cells can be "stress shielded" by matrix and may merely survey their local environment to determine appropriate mechanobiological responses[1,18]. There is a need for more research on this important aspect of mechanotransduction, which will be essential for linking molecular level responses and tissue level stimuli.

Even after molecular mechanisms of mechanotransduction are understood fully, tissue level responses (e.g., increasing wall thickness in response to increased pressure, due to increases in collagen) should continue to be correlated with changes in the continuum metrics of stress or strain[19] for this level of understanding is fundamental to clinical care (e.g., prognosis, surgical planning, medical device design)[20]. That said, such correlations must capture underlying complexity; altered gene expression often relates nonlinearly to mechanical stimuli, thus cellular responses must be measured at multiple levels of stress or strain. For example, consistent with observed tissue level changes in caliber, data reveal an increasing sigmoidal relationship between increased τ_w and eNOS mRNA[21] and a decreasing sigmoidal relationship between increased τ_w and ET-1 mRNA[22]. Ultimately, however, we must know the amounts of nitric oxide (NO) and endothelin-1 (ET-1) produced, not just changes in mRNA expression. Li et al.[23] reported data sufficient to quantify collagen synthesis in terms of smooth muscle cell stretch, again suggesting an increasing sigmoidal relationship. Unfortunately, data from most reports are not sufficient to construct appropriate nonlinear relationships since the objective is often to show statistical differences between an unloaded and one or two loaded cases. There is a need, therefore, for data sufficient to quantify "mechanical dose response curves," which is to say that we must quantify better the responses at multiple levels of loading.

There are two issues related to such quantification. First, cellular production of a particular molecule often depends on changes in multiple types of loads. For example, whereas endothelial production of ET-1 decreases with increasing wall shear stress[22] (e.g., 3.5 fold due to an increase in shear from 0 to 2.0 Pa), it increases with increasing cyclic stretch[24] (e.g., 1.7 fold due to a 10% stretch relative to no stretch). Similarly, whereas endothelial production of eNOS increases with increasing wall shear stress[21] (e.g., 2.5 fold due to an increase in shear from 0 to 1.5 Pa), it also increases with increases in cyclic strain[25] (~1.9 fold at 6% and 3.1 fold at 10% stretch relative to no stretch). Wall shear stress and cyclic circumferential stretch can change simultaneously in vivo, hence mechanical dose response curves (actually surfaces) must account for complex responses to multiple stimuli. Second, there is a need to quantify changes in terms of all known pathways even for phenomenological modeling. For example, cyclic stretch (or stress) mediated production of collagen by smooth muscle cells likely occurs via multiple processes[23]: mechanical stress appears to increase both angiotensin-II (ANG-II) production and AT_1 receptor sensitivity, which in turn can stimulate the production of latent transforming growth factor-beta (TGF-β), which can be activated by mechanical stress and thereby cause an increased production of collagen. Hence, although collagen production can

be correlated directly to changes in cyclic stretch (or stress), it can also be correlated with mechano-controlled ANG-II activity and subsequent production and activation of TGF-β[26,27]. Knowing that blood flow also alters TGF-β activity[28], we again see the need for quantification in terms of multiple stimuli to appreciate potential overlaps in cases of altered wall shear stress and intramural stress (or stretch). Indeed, cyclic stretch correlates with smooth muscle cell proliferation in culture, with stretch upregulating PDGF. The importance of stress-mediated changes in TGF-β and PDGF, as well as other growth factors and cytokines, has been confirmed in numerous in vivo studies of hypertension[8,29,30]. There is a need, however, to quantify time-dependent intramural changes in molar concentrations of growth factors produced as a function of multiple simultaneously applied stresses or stretches and to determine, probably in cell culture, whether such effects are competitive or synergistic. Finally, although most attention in arterial biology and mechanics has been focused on endothelial and smooth muscle cells, there is increasing evidence that adventitial fibroblasts play important roles in vascular homeostasis as well as in disease progression and injury responses[31–32]. Thus, there is a need for similar data on mechano-control of fibroblast activity.

Complementary Roles of Vasoactivity and Matrix Remodeling

Briefly, there are two primary roles of altered vasoactivity relative to growth and remodeling. First, altered smooth muscle tone changes the biochemomechanical state in which cell and matrix reorganization and turnover occurs and, second, vasoactive molecules play important roles in modulating the rates of cell and matrix turnover within the vasoaltered states.

Vasoaltered States

In response to a local increase in blood flow above normal, which increases τ_w, the endothelium upregulates eNOS and increases its production of NO, which causes the wall the dilate and return shear stress toward original. If the flow returns to normal soon thereafter, NO production likewise returns toward normal and the vessel maintains its original caliber. This is the normal vasoactive response. If the local increase in flow is sustained, however, as, for example, in an arterio-venous fistula or vigorous exercise, the increased production of NO enables cell and matrix reorganization or turnover to occur in the dilated state (noting that an increased radius a and isochorically decreased thickness h increaseσ_θ but not necessarilyσ_z). Hence, combined wall shear and intramural stress mediated growth and remodeling in a vasodilated state allows the wall to become entrenched at a larger radius and wall thickness. NO production may then return to normal if τ_w is normalized, which may "reset" control with regard to increased flow.

Similarly, consider the case of a sustained increase in pressure. Because large arteries are nearly elastic, and thus distensible, an initial local increase in pressure tends to increase the luminal radius and isochorically decrease thickness. Again, these changes serve to increase σ_θ, which sets into motion smooth muscle and possibly endothelial and fibroblast mediated growth and remodeling. Yet, the initial pressure-induced increase in caliber would also decrease τ_w, which in turn would tend to decrease endothelial production of NO and increase production of ET-1 to restore shear toward normal. Thickening thus occurs in an initially constricted state at the original caliber via increases in smooth muscle (hyperplasia and/or hypertrophy driven by stress-mediated increases in PDGF, TGF-β, etc.) and extracellular matrix (particularly fibrillar collagens driven by increases in TGF-β, connective tissue growth factor (CTGF), etc.) mass[3,5,14,15,23]. Hence, the wall again becomes entrenched within a vasoaltered state, with multiple stresses simultaneously playing important roles. Once the wall has thickened sufficiently to restore σ_θ toward original (i.e., increased the ability of the wall to withstand the increased pressure), at a preserved caliber and thus τ_w, it would seem that the endothelium could return to its normal production of NO. It appears, however, that NO production may not normalize in hypertension, a situation often referred to as "endothelial dysfunction". Whether the endothelium is actually impaired in its ability to produce NO or if there is a resetting of its

mechano-regulatory target, an increased competition for L-arginine (e.g., by arginase[33]), or a competitive upregulation of other vasoactive molecules (e.g., ANG-II) is not clear, however. Finally, although usually not discussed, the overall increase in thickness at the same radius necessarily increases cross-sectional area and thereby decreasesσ_z unless the axial force decreases proportionately. The latter may occur due to a net increase in the collagen:elastin ratio that unloads the prestretched elastin[6], which may be related to the aforementioned observation that axial prestretch decreases in hypertension[7]. Potential implications of this to overall (biaxial) mechanical homeostasis remain unknown, however.

Altered Rates of Turnover

Another important aspect of wall shear stress regulated changes in vasodilator/vasoconstrictor production is that NO is an inhibitor of smooth muscle cell proliferation and synthesis of collagen whereas ET-1 is a promoter of smooth muscle proliferation and synthesis of collagen. For example, NO has been shown to decrease collagen production by cultured vascular smooth muscle cells by 30–40% in a dose-dependent (perhaps sigmoidal) manner depending on NO donor concentration[34]. Conversely, collagen I production has been shown to depend non-monotonically on ET-1 concentration[35], peaking at an ~5 fold increase at 10^{-8} M. Effects due to ET-1, which are fundamental in hypertension[36], can be augmented by those of other vasoconstrictors, particularly ANG-II. Recall, therefore, that cyclic mechanical stretch increases collagen production via an ANG-II/TGF-β pathway[23], apparently involving an increase in AT_1 receptor synthesis or sensitivity[37].

Although ANG-II tends to have a stronger effect than ET-1 on SMC proliferation (125% increase versus 25% increase, both at 10^{-8} M), both can affect collagen production by inducing growth factors. For example, ET-1 induces an increased production of CTGF; ANG-II induces an increased production of both CTGF and TGF-β (which stimulates CTGF production further) [37,38]. Noting that TGF-β acts through a Smad signaling pathway, ANG-II/TGF-β control of collagen synthesis is complicated further by the ability of ANG-II to directly activate Smad signaling[38]. Because of the key role played by ANG-II, it is not surprising that ACE inhibitors and AT_1 receptor antagonists (e.g., losartan) have been effective in reducing ANG-II stimulated collagen production. Nevertheless, quantitative relationships between mechanically induced changes in intramural concentrations of NO, ET-1 and ANG-II, and their combined effects on the growth factor production or activation that modulate collagen synthesis, would increase our overall understanding.

In addition to altered collagen production (e.g., mass fraction), its undulation, orientation, cross-linking, and interactions with other matrix proteins or proteoglycans are fundamental to defining the stiffness of the arterial wall. There is a need, for example, for information on the “prestretch” at which new fibers are incorporated within extant matrix and similarly what mechanical cues dictate the orientation of collagen fibers that are deposited by smooth muscle cells or fibroblasts[20]. With regard to cross-linking, both lysyl oxidase and tissue transglutaminase activity (tTG) can play important roles in cross-linking matrix proteins within vasoconstricted states and thereby entrenching a vessel at a different caliber[39]. For example, reduced τ_w decreases endothelial production of NO, which is an inhibitor of tTG activity. Conversely, tTG activity appears to be increased by increased intracellular calcium associated with increased smooth muscle contractility as occurs in cases of reduced τ_w. There is a need to identify possible mechano-regulation of tTG availability and activity, particularly because tTG associates with β-integrins and integrin clustering is sensitive to changes in mechanical loading.

MMP Activity

The structural integrity of the extracellular matrix depends on a delicate balance between synthesis and degradation, and its contribution to arterial stiffness is increasingly recognized

as an important determinant of vascular health or disease[40,41]. Matrix metalloproteinases (MMPs) represent an important class of enzymes capable of degrading matrix constituents[42,43]; they are produced by endothelial cells, smooth muscle cells, fibroblasts, and infiltrating inflammatory cells. MMP expression is controlled transcriptionally by inflammatory mediators, growth factors, cell-cell and cell-matrix interactions, and mechanical stress or strain. By degrading matrix, MMPs not only affect wall stiffness, they also impact cell migration, proliferation, apoptosis, and differentiation and thereby play an important role in vascular remodeling in hypertension[44] as well as other vascular diseases, particularly atherosclerosis and aneurysms[4,20]. There are 22+ members of the MMP family, but MMP-2 and MMP-9 (gelatinases), MMP-1 (interstitial collagenase), MT1-MMP (membrane type MMP), and MMP-12 (macrophage metalloelastase) have tended to attract considerable attention in vascular research. For example, it has been shown that 5% static and 10% cyclic uniaxial stretch upregulate the production of MMP-2 and MMP-9 (2 to 5 fold) by vascular smooth muscle cells in culture[45] and 2.5, 5, and 10% cyclic uniaxial stretches similarly increase MMP-2 production (2 to 10 fold) by endothelial cells in a dose dependent manner[46].

Whereas MMPs are secreted primarily as inactive pro-forms, they are activated by serine proteases, reactive oxygen species, other MMPs, and even multiple types of mechanical stress. Indeed, stress can affect the kinetics of MMP-matrix interactions and thus rates of collagen degradation. The activity of MMPs is regulated further by tissue inhibitors of MMPS, or TIMPs, but there has been little attention to possible mechano-regulation of TIMPs. Despite significant information on the role of MMPs, and associated intracellular signaling pathways, in vascular development, adaptation, disease progression, and response to injury, there has been little attempt to quantify MMP/TIMP production or activation as a function of multiple levels of mechanical stimuli, including the biaxial loading as exists in vivo, which as noted above is essential for determining mechanical dose response curves and achieving predictive capability. There is also a need to understand better the time-course of MMP activity, which appears to increase soon after any mechanical perturbation or injury and then return slowly toward baseline values[47].

Mechanical Damage

Although considerable attention has appropriately been directed towards the turnover of vascular collagen[29], the important roles of elastin cannot be ignored[48,49]. Vascular elastin, with its associated fibrillins and fibulins, appears to be produced primarily during development and early post-natal periods. Hence, in contrast to vascular collagen, which is produced continuously and has a normal half-life of ~70 days, structurally significant vascular elastin appears to be produced early in life and have a half-life on the order of decades[4]. It is thus degradation or mechanical damage of elastin, not frank turnover, that is of most importance in vascular disease and injury, particularly in aneurysms, atherosclerosis, hypertension, restenosis following angioplasty/stenting, and aging. Elastin is likely susceptible to mechanical fatigue damage (i.e., gradual weakening due to repetitive cycling, noting that arteries can experience 30 million loading cycles per year), which could be more problematic in cases of increased pulse pressure[48]. There is, of course, increasing evidence that increased pulse pressure in hypertension may be a more important mechanical stimulus for growth and remodeling in large arteries than increased mean pressure[40,50]. Much can be learned about load-induced fragmentation of elastin in hypertension from the literature on arterial aging[48,49]. Similarly, Marfan syndrome, due to a mutation in the fibrillin-1 gene, appears to represent a type of “accelerated aging”, particularly in the aorta, and thus may provide insight into general aspects of mechanically induced damage to elastin. Of course, in addition to its important structural role, elastin plays important biological roles, as, for example, by influencing smooth muscle cell migration, proliferation, and differentiation status. There is a need, therefore, to understand

better the mechanical basis of rates of degradation or damage of elastin in hypertension and associated effects on wall remodeling.

Need for Integrative Mathematical Models

The 1998 Bioengineering Consortium (BECON) Report of the U.S. National Institutes of Health stated,

> "The success of reductionist and molecular approaches in modern medical science has led to an explosion of information, but progress in integrating information has lagged … Mathematical models provide a rational approach for integrating this ocean of data, as well as providing deep insight into biological processes."

Whereas the need remains to develop more robust mathematical models at all scales (e.g., macro, micro, and nano), there is also a need to develop approaches that integrate models across diverse scales. That is, "multiscale modeling" promises to be an important contributor to integrating information on molecular and cellular mechanisms with understanding at the tissue level. Note, for example, that significant progress is being realized in modeling the kinetics of basal NO release by the endothelium[51], diffusion of NO within the arterial wall[52], and kinetics of NO activation of soluble guanylate cyclase within smooth muscle cells[53]. Similar effort must be directed toward modeling the kinetics, diffusion, and activity of ET-1 and ANG-II as well as key cytokines, growth factors, and MMPs. Moreover, progress is being made in developing tissue level mathematical models that account for mechano-regulated deposition and degradation of individual structurally important constituents within the arterial wall, their contributions to overall structural integrity, and associated reaction-diffusion models for the non-structurally significant substances that influence cell and matrix turnover[1,20], which can exploit the increased understanding at the molecular level. Much remains to be accomplished, however, before such models can provide reliable descriptive and predictive capability, thus there is a need for increased effort in this direction.

Perspective

Since the mid-1970s, myriad experiments have demonstrated a mechanical homeostasis across multiple length and time scales in the vasculature and similarly the ubiquitous role of cell mediated mechano-regulation of structure and function in nearly all aspects of vascular health and disease. Nevertheless, there is a need for additional experiments that provide data sufficient to quantify mechanical dose response curves and that explore potentially competitive or synergistic effects by multiple cell types exposed simultaneously to changes in multiple components of stress or strain; there is also a need for mathematical models that can help integrate information from molecular, cellular, and tissue level studies. For example, understanding better the molecular mechanisms of stress-mediated regulation of collagen synthesis and degradation in vasoaltered states promises to suggest new pharmacological interventions to control the altered wall stiffness that causes and is caused by hypertension.

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