Role of Mechanotransduction in Vascular Biology
Focus on Thoracic Aortic Aneurysms and Dissections
Jay D. Humphrey, Martin A. Schwartz, George Tellides, Dianna M. Milewicz

Abstract: Thoracic aortic diseases that involve progressive enlargement, acute dissection, or rupture are influenced by the hemodynamic loads and mechanical properties of the wall. We have only limited understanding, however, of the mechanobiological processes that lead to these potentially lethal conditions. Homeostasis requires that intramural cells sense their local chemomechanical environment and establish, maintain, remodel, or repair the extracellular matrix to provide suitable compliance and yet sufficient strength. Proper sensing, in turn, necessitates both receptors that connect the extracellular matrix to intracellular actomyosin filaments and signaling molecules that transmit the related information to the nucleus. Thoracic aortic aneurysms and dissections are associated with poorly controlled hypertension and mutations in genes for extracellular matrix constituents, membrane receptors, contractile proteins, and associated signaling molecules. This grouping of factors suggests that these thoracic diseases result, in part, from dysfunctional mechanosensing and mechanoregulation of the extracellular matrix by the intramural cells, which leads to a compromised structural integrity of the wall. Thus, improved understanding of the mechanobiology of aortic cells could lead to new therapeutic strategies for thoracic aortic aneurysms and dissections. (Circ Res. 2015;116:1448-1461. DOI: 10.1161/CIRCRESAHA.114.304936.)

Key Words: actomyosin ■ elastic fibers ■ focal adhesion ■ Marfan syndrome

Thoracic aortic aneurysms and dissections (TAADs) are responsible for significant morbidity and mortality in the young and old alike.1,2 Advances over the past 15 years in medical imaging and genetics have increased the number of diagnosed TAADs,3,4 which has raised the need to better understand the natural history of these potentially lethal conditions. Progressive dilatation, acute dissection, and rupture of the thoracic aorta are fundamentally biomechanical processes; in particular, dissection and rupture are extreme cases of tissue-level failures that occur when local wall stress exceeds strength. There is a need, therefore, to quantify stresses (ie, the mechanics) within the aortic wall and to understand how the intramural cells respond to these stresses (ie, the mechanobiology) by producing, organizing, or degrading the extracellular matrix (ECM) that endows the wall with its structural integrity.

We focus on cell–matrix interactions in TAADs and suggest that the vulnerability of the thoracic aorta to aneurysm, dissection, and ultimately rupture results, in large part, from dysfunctional mechanical homeostasis, that is, a compromised ability of intramural cells to sense their mechanical environment and to regulate the ECM to respond to that environment.1,5 We
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further suggest that actomyosin contractility, independent of tissue-level vasoactivity, is central to both sensing and regulating the mechanical state of the matrix. This interpretation leads naturally to a hypothesis that genetic mutations that affect the mechanostimulus (eg, stresses conveyed to cells through the ECM), mechanosensing (eg, via membrane receptors or actomyosin functionality), or resultant mechanosignaling (eg, second messengers) can lead to TAADs. To support this hypothesis, we first review aortic wall composition, vessel-level mechanics and mechanoadaptations, and mechanobiological processes and then discuss how mutant genes predisposing to TAADs can disrupt mechanical homeostasis.

Aortic Wall Composition

The thoracic aorta is a composite tube consisting of 3 layers: an intima comprising endothelial cells on a basement membrane, an elastin- and smooth muscle–rich media, and a collagen- and fibroblast-rich adventitia (Figure 1). The aorta is continually subjected to complex cyclic mechanical loads from pulsatile blood pressure and flow and, in the case of the ascending aorta, the beating heart itself. Most of the structural integrity of the aortic wall derives from myriad ECM proteins, glycoproteins, and glycosaminoglycans. Of the structural constituents, elastic fibers and fibrillar collagens represent ≈60% of the normal wall by dry weight and dominate its elasticity (ie, ability to distend and recoil without dissipating energy), tensile stiffness (changes in stress associated with changes in strain), and strength (maximum stress sustained without failure). Glycosaminoglycans constitute only ≈3% to 5% of the normal wall, but contribute to the compressive stiffness. Most of the remaining ≈35% of the wall consists of smooth muscle cells (SMCs). Vessel-level vasomotion induced by SMCs can contribute to mechanoadaptations by elastic arteries, such as common carotids, and perhaps the aorta in some circumstances. Nevertheless, the primary role for aortic SMCs is to govern the mechanical properties by regulating ECM in the media. Fibroblasts similarly regulate matrix in the adventitia. Elastic fibers consist of a core of elastin (90%) surrounded by microfibrils composed primarily of fibrillins, but also fibulins and other glycoproteins. These fibers are organized within the media primarily as concentric laminae, each separated by a layer of SMCs and associated collagens and glycosaminoglycans (Figure 1). The elastin is unique in that, under normal conditions, it is deposited, organized, and cross-linked before adulthood, and its half-life is ≈50 years in humans. Consequently, elastic fibers become prestressed because of somatic growth and typically withstand millions of cycles of loading imposed by the heart (≈34 million cycles/year in humans). The elastic fibers are linked structurally to the SMCs through oblique extensions from the elastic lamellae. These extensions attach at the cell membrane to dense plaques, or focal adhesions, that connect to intracellular contractile filaments that project across the cell at the same oblique orientation as the elastic extensions (Figure 1). This configuration forms a contractile-elastic unit, which is a tension-bearing or -sensing structure in SMCs. The oblique orientation of this structural unit reverses direction in adjacent elastic lamellae, thus contributing to a uniform distribution of stress across the normal wall.

Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>Ang-II</td>
<td>angiotensin-II</td>
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<tr>
<td>ECM</td>
<td>extracellular matrix</td>
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<tr>
<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
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<tr>
<td>SMC</td>
<td>smooth muscle cell</td>
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<td>TAAD</td>
<td>thoracic aortic aneurysm and dissection</td>
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<td>TGF-β</td>
<td>transforming growth factor-β</td>
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Figure 1. Thoracic aortic aneurysms and dissections (TAADs) manifest clinically at the macro (tissue)-level but result from mechanisms at the micro (molecular)-level. Shown are aortic structure and relevant mechanical stresses (see text) that result from hemodynamic loading. The stressed wall consists of 3 layers (intima, media, and adventitia) populated, respectively, by 3 cell types (endothelial, smooth muscle, and fibroblasts). Medial lamellar units consist of paired concentric delaminating elastic laminae (elastin plus microfibrils), with associated smooth muscle cells, collagens, and glycosaminoglycans. A unique contractile-elastic unit consists of colinear extracellular microfibrils connecting through heterodimeric transmembrane complexes (integrins) with intracellular actomyosin filaments to create load-bearing or sensing functions. Linker proteins within the focal adhesion have structural or signaling roles. ECM indicates extracellular matrix.
It seems that fibrillins contribute to the long-term stability of elastic fibers; this stability may result from connections to SMCs at dense plaques that suppress protease activity, but the precise mechanisms remain unknown. Long-term stability also seems to result from desmosine and isodesmosine crosslinks, with fibrulins promoting effective lysyl oxidase-mediated cross-linking during elastogenesis. Regardless, competent elastic fibers contribute most to aortic compliance (ie, distensibility) and resilience (ie, the ability to store energy during systole and to use that energy during diastole to augment blood flow). Damage to (eg, via mechanical fatigue, a loss of strength because of repeated loading) or degradation of (eg, loss of mass via proteolysis) elastic fibers causes irreversible changes in wall structure and function.

In contrast, collagen fibers contribute primarily to overall stiffness and strength. The 2 primary types of collagen within the aortic wall are I (≈70%) and III (≈30%); the former is found primarily in the adventitia and the latter in the media where it mainly associates with elastic fibers. Both collagens exist as fibers; hence, their structural contributions depend on intra- and intermolecular cross-links, as well as overall fiber diameters, orientations, and interactions with other constituents. Indeed, normal fibrillogenesis requires interactions with fibronectin, other collagens (eg, type V), and proteoglycans (eg, biglycan); hence, defects in these allied constituents can compromise collagen stiffness or strength and predispose to TAADs. Mutant genes encoding the procollagens for types I and III also lead to TAADs, particularly for type III in vascular Ehlers–Danlos syndrome. It is important that some collagen fibrils run parallel to the aforementioned contractile-elastic units in the media.

Under normal conditions, the larger collagen fibers tend to undulate slightly and orient in a symmetrical-diagonal manner with respect to the long axis of the aorta. This organization seems to complement the elastic fiber–dependent distensibility that is favorable during systole. Loss of elastic fiber integrity can decrease the undulation of collagen fibers, which manifests at the vessel level as a loss of distensibility/extensibility (ie, increased stiffness). Loss of elastic fibers and increased stiffness are characteristic of aortic aging and thoracic aortic disease. Unlike elastic fibers, collagen fibers in the aorta seem to have a short half-life (perhaps months) and are not affected by mechanical fatigue. Rather, appropriate turnover of collagen (deposition and degradation) is critical for aortic homeostasis, including adaptations to altered hemodynamics or responses to disease or injury. Beyond its contribution to wall properties during normal cyclic changes in pressure, adventitial collagen plays a special role as a protective sheath—it bears an increasing portion of wall stress during acute increases in pressure, thus shielding medial SMCs from excessive stresses. Not surprisingly, sustained increases in blood pressure can induce significant increases in adventitial collagen, which is mediated in part by increases in local angiotensin-II (Ang-II) signaling.

Loss of elastic fiber integrity not only affects the cell biology, it also reduces aortic resilience, which allows the wall to dilate either uniformly, as in aging when the loss is diffuse or, locally, as in aneurysms when the loss is focal. In contrast, loss of collagen fiber integrity decreases strength, which can render the aortic wall vulnerable to rupture. Glycosaminoglycans accumulate with aging and as part of the pathology in TAADs with localized pooling potentially contributing to the risk of dissection. In addition to these and other structural roles, many ECM constituents have instructive roles. Functional elastic fibers contribute to an SMC phenotype that is contractile and quiescent, thus not migratory, proliferative, or highly synthetic. Microfibrils sequester latent transforming growth factor-beta (TGF-β), a cytokine important to many aspects of cellular activity, including SMC differentiation and matrix turnover. Other growth factors and proteases are similarly sequestered by the ECM. Finally, both mechanically damaged and proteolytically degraded matrix can alter the phenotype of resident cells or lead to an infiltration of inflammatory cells. A compromised ECM thus has mechanical and biological consequences.

In summary, medial SMCs and adventitial fibroblasts are the primary cell types responsible for establishing, maintaining, or restoring the structural integrity, and hence much of the functionality, of the normal thoracic aortic wall (Figure 1). Because the function of the aorta is largely mechanical, it is not surprising that these cells are sensitive to changes in their mechanical environment. Therefore, mechanics is important both for understanding the aorta as a load-bearing structure (eg, normal distension versus dilatation, dissection, or rupture) and for identifying mechanical stimuli that drive cellular responses (eg, homeostatic adaptations versus maladaptations or disease progression).

**Wall Mechanics and Mechanoadaptations**

A useful concept in biomechanics is mechanical stress, a force intensity having units of force per area (eg, N/m²). Two particularly important components of aortic stress are (Figure 1) circumferential stress σθ (caused by the distending blood pressure changing the circumference cyclically) and axial stress σz (caused by forces in the direction of the long axis, including those arising from somatic growth). Other components include the radial stress σr (due directly to blood pressure and perivascular constraints) and wall shear stress τw (caused by frictional interactions between the endothelium and flowing blood). Quantifying stresses as a function of position and time requires solving nonlinear differential equations, but mean values can be estimated easily in straight segments: 

\[ \sigma_r = \frac{P h}{2}, \quad \sigma_z = \frac{Q}{\pi a^2}, \quad \tau_w = \frac{4 \mu Q}{\pi a^2} \]

where P is the transmural pressure, a the inner radius, h the thickness of the wall, f the axial force, Q the mean volumetric blood flow, and μ the viscosity of the blood. Of these 4 stresses, σr and σz are the largest in the aorta: ≈150 kPa under normal conditions, where 1 Pa = 1 N/m² and 1 kPa = 7.5 mm Hg. Abdominal aortic aneurysms may rupture when the larger of these 2 stresses exceeds 450 kPa; comparable values of in vivo failure stresses have yet to be suggested for thoracic aneurysms but are likely similar. There are, however, accumulating in vitro data for the human thoracic aorta on biaxial mechanical and failure properties. Finally, the mean radial stress is only ≈6 kPa (compressive) and wall shear stress ≈1.5 Pa (5 orders of magnitude smaller than σr and σz). Although typically neglected in analyses of wall mechanics, σr may be important in cases of increased glycosaminoglycans. Regardless of magnitude, all components of stress...
affect the mechanobiology, with endothelial cells sensitive to changes in $\tau_\theta$ and SMCs and fibroblasts sensitive to changes in $\sigma_r$ and $\sigma_\theta.$

The seminal paper by Wolinsky and Glagov\textsuperscript{12} revealed that the average tension per lamellar unit of [descending thoracic] aortic media was remarkably independent of species and nearly constant at a mean value of $T=2$ N/m. Hence, the normal number of elastic laminae is fixed for each species, including ≈5 in murine to over 60 in human aorta. Because tension $T=P/v$ and stress $\sigma_\theta=TVh$, the ≈15 μm thickness of a lamellar unit yields an average circumferential stress per lamellar unit of ≈133 kPa, close to the mean value for the wall. Importantly, this finding suggests that intramural cells deposit and organize ECM during development to establish a preferred mechanical state (via morphogenesis), which they subsequently seek to maintain under normal conditions (via homeostasis). Complementary studies further suggest that these cells seek to restore this state when blood pressure or flow increase from normal.\textsuperscript{52,53} Such mechanoadaptations reveal that the mature aorta retains some of its developmental ability to respond to changes in hemodynamics. Developmental adaptations include differential changes in the ascending aorta and pulmonary trunk after closure of the ductus arteriosus, whereby these 2 vessels adapt to their different pressures and flows,\textsuperscript{54} and differential changes in the descending thoracic aorta and infrarenal aorta after birth, when increased renal and gastrointestinal flows change the hemodynamics within the infrarenal segment.\textsuperscript{55} The most conspicuous aortic mechanoadaptation in maturity is thickening of the wall to restore intramural stresses in hypertension.\textsuperscript{57,52}

Maintenance of arterial caliber in response to increased blood pressure (to restore wall shear stress toward normal) tends to involve vessel-level changes in vasoactivity,\textsuperscript{30} which are greater in muscular arteries than elastic arteries. Although there is little information on possible basal tone in the human aorta, the murine aorta exhibits vessel-level vasoactivity (ie, contractility) similar to that of carotids and other elastic arteries.\textsuperscript{56} SMC contractility is diminished in the thoracic aorta of mice having mutations in genes that predispose to TAADs\textsuperscript{57–60}; hence, contributions of shear stress mediation should be considered in these mouse models, particularly given that the ascending aorta is relatively thin, having ≈8 medial lamellar units. The mechanoadaptive role of shear stress is less clear in human aortas because the thick media consists of 60+ layers of elastic laminae and SMCs, which increases the diffusive pathway.

The human aorta may adapt to changes in pressure and flow like other elastic arteries, yet it exhibits a distinct behavior in extreme exercise.\textsuperscript{61} Marked increases in caliber manifest in the subclavian artery in the dominant arm of professional tennis players and in iliac arteries of professional cyclists, whereas the thoracic and abdominal aorta change modestly.\textsuperscript{62} It may be that the extreme compliance (inverse of stiffness) of the normal aorta accommodates dramatic pressure-induced changes in flow without entrenching changes in caliber. Consistent with this idea, the aorta is responsible for ≈65% of total arterial compliance;\textsuperscript{63} values of distensibility are ≈6-fold greater in the proximal aorta than in common carotids in young healthy individuals and 2-fold greater than in the descending thoracic and abdominal aorta.\textsuperscript{64} Yet, the ascending aorta may stiffen more and earlier during normal aging than either the common carotids or descending thoracic aorta\textsuperscript{64,65} and it exhibits earlier and more dramatic lengthening during aging.\textsuperscript{66} These changes may result from the unique biaxial loading experienced by the ascending aorta—it alone experiences cyclic circumferential stresses because of the distending pressure and cyclic axial stresses from the downward motion of the contracting heart. The ascending aorta also has the highest percentage of elastin, which, of all structural constituents in an artery, is uniquely susceptible to mechanical fatigue because of the inability to repair the elastic fibers.\textsuperscript{9}

The unique structural and mechanical features of the ascending aorta may contribute to its vulnerability to TAADs, but this is complicated by global versus local effects. For example, thickening of the wall could restore mean values of wall stress toward normal in hypertension, but defects within individual medial lamellar units (eg, accumulated glycosaminoglycans) could still increase stress locally and initiate a delamination.\textsuperscript{30} Loss of functional elastin, whether by mechanical fatigue or proteolytic degradation, would be expected to affect mechanosensing\textsuperscript{9} as well as to contribute to arterial dilatation and lengthening,\textsuperscript{25} with extreme cases of the latter leading to tortuosity.\textsuperscript{24,36} Although decreases in the in vivo axial stretch of an artery tends to off-load the vessel axially and beneficially decrease both the axial and circumferential stress (because of biaxial coupling),\textsuperscript{67} extreme cases leading to tortuosity are maladaptive. Tortuosity of other arteries, including vertebrals, may also be indicators of thoracic aortic disease risk.\textsuperscript{68} That is, although the most dramatic effects may manifest in the thoracic aorta, other vessels can be affected.\textsuperscript{69}

In summary, aortic cells typically seek to establish, maintain, and restore a homeostatic mechanical state, which can be accomplished via matrix turnover within elastically deformed or vasoaltered states. Such a process requires intramural cells to assess the mechanical state of the ECM, then either to entrench remodeled matrix or to prestress new matrix as it is deposited. Importantly, both of these processes require actomyosin contractility separate from vessel-level vasoactivity, as discussed later. Finally, the ascending aorta seems to have a unique structure and properties consistent with its unique mechanical loading, which may render it particularly vulnerable to fatigue-induced damage of elastic fibers that, in turn, could adversely affect mechanosensing and mechanoregulation of matrix.

Mechanobiology

A seminal finding that cells respond to mechanical stimuli was the observation that SMCs change their production of ECM, including fibrillar collagens and glycosaminoglycans, in response to cyclic mechanical loading.\textsuperscript{70} Later studies showed that this SMC mechanobiological response occurred because of increased Ang-II signaling,\textsuperscript{71} increased sensitivity to Ang-II through its primary receptor, angiotensin-II type I receptor,\textsuperscript{72} and increased production of a downstream effector molecule, TGF-β.\textsuperscript{73} These findings were supported, respectively, by an attenuated load-induced production of matrix after treatment with an angiotensin-converting enzyme inhibitor, an angiotensin-II type I receptor antagonist, or a TGF-β neutralizing
antibody. Another load-induced response by SMCs is altered production of matrix metalloproteinases,\textsuperscript{73} the potency of which can depend on mechanical loading.\textsuperscript{74} Hence, cyclic loading of SMCs affects both matrix production and degradation. Such mechanobiological effects are complicated by related effects. For example, Ang-II increases interleukin-6 and monocyte chemoattractant protein-1, which in vivo facilitates recruitment of monocytes/macrophages that produce cytokines and proteases that contribute to matrix turnover, particularly in adventitial fibrosis.\textsuperscript{75} Nevertheless, cyclic loading also alters SMC expression of platelet-derived growth factor\textsuperscript{76} and cationic channels involved in cell contractility.\textsuperscript{77} Figure 2 summarizes some key responses of SMCs to cyclic loading, where \( \sigma(\lambda(t)) \) represents the stress \( \sigma \) that depends constitutively on the stretch \( \lambda \) that varies with time \( t \) during loading. Such findings clearly link the mechanics and mechanobiology.

Similar observations hold for fibroblasts,\textsuperscript{46} which are fundamental to adventitial integrity. Fibroblasts can additionally use mechanical stresses (generated via actomyosin contractility) to activate latent TGF-\( \beta \) sequestered within matrix.\textsuperscript{79} Although long ignored, adventitial fibroblasts are significant contributors to aortic wall homeostasis,\textsuperscript{79} particularly in depositing, organizing, and degrading the collagen fibers that are essential for maintaining overall wall strength and preventing rupture.\textsuperscript{80} Both mechanical stress and TGF-\( \beta \) are required for fibroblasts to differentiate into myofibroblasts,\textsuperscript{79} which are also increasingly recognized as important in aortic mechanobiology, particularly aneurysmal enlargement in the absence of functional SMCs.\textsuperscript{81}

Mechanical stimuli affect multiple signaling pathways (Figure 3), including the mitogen-activated protein kinase (MAPK) pathway downstream of Ang-II\textsuperscript{83} and the SMAD (Sma in \textit{C elegans} and Mad in \textit{Drosophila}) pathway downstream of TGF-\( \beta \).\textsuperscript{84} There is also crosstalk between TGF-\( \beta \) and MAPK signaling and between Ang-II and SMAD signaling.\textsuperscript{85} Further complicating such signaling are the following observations: influences of Ang-II on TGF-\( \beta \) can be mediated by epidermal growth factor and its MAPK signaling;\textsuperscript{86} elevated mechanical stress can increase local Ang-II\textsuperscript{87} and activate latent TGF-\( \beta \),\textsuperscript{88} both of which affect matrix metalloproteinase promoter activity;\textsuperscript{89} Ang-II can also activate latent matrix metalloproteinase-2, whereas matrix metalloproteinase-2 can activate latent TGF-\( \beta \);\textsuperscript{90} and SMCs exposed to Ang-II increase their expression of TGF-\( \beta \).\textsuperscript{91}

Therefore, ECM, integrins, and growth factor/cytokine signaling are highly interconnected and responsive to mechanical loading.\textsuperscript{91}

Notwithstanding the already complex local wall mechanics and cellular mechanosensing and mechanoregulation of ECM in thoracic aortic disease, aging and hypertension are the major risk factors for TAADs.\textsuperscript{89,92} Interestingly, Ang-II and TGF-\( \beta \) are also important in aging\textsuperscript{92} and hypertension,\textsuperscript{93} wherein a switching of SMC phenotype toward synthetic\textsuperscript{94} can increase the production of matrix that thickens and stiffens the wall. Although thickening of the wall can favorably decrease mean wall stress locally,\textsuperscript{90,95} a global increase in structural stiffness can lead to increased pulse wave velocities and central pulse pressures\textsuperscript{92,94} that adversely increase proximal aortic loading. Because different vascular disorders manifest in different regions (eg, Marfan syndrome in the aortic root and vascular Ehlers–Danlos more diffusely), altered hemodynamics caused by aortic stiffening need not increase stress on vulnerable regions uniformly, and attempts to reduce central pressures could have differential effects. Finally, changes in stress-mediated matrix production that thickens the wall can also potentially diminish structural integrity locally (eg, via accumulated glycosaminoglycans)\textsuperscript{37,38}. In summary, given the effects of stress on Ang-II and TGF-\( \beta \) production,\textsuperscript{71,72} the complex interactions among many related signaling pathways,\textsuperscript{83–90} and the differential effects of these biomolecules on different cell types,\textsuperscript{75,76} it should not be surprising that the roles of Ang-II and TGF-\( \beta \) in TAADs remain controversial\textsuperscript{41,95}—their roles in the basic mechanobiology and mechanics are similarly complex.

**Mechanical Homeostasis Across Scales**

Experiments focusing on responses of tissue equivalents, isolated cells, and subcellular structures to mechanical stimuli suggest that homeostatic targets also exist at these levels of organization.\textsuperscript{96,97} For example, fibroblasts seeded within initially stress-free but mechanically constrained collagen gels generate an endogenous stress of \( \approx 3,2 \) kPa that reaches steady-state within hours.\textsuperscript{98} The term tensional homeostasis was coined to describe this process.\textsuperscript{99} Indeed, if this stress is manually increased or decreased relative to the endogenous level, the cells quickly begin to return the stress toward the level they established originally. Not surprisingly, these cell-mediated processes depend on actomyosin contractility and appropriate integrins attaching to the ECM\textsuperscript{78,90} and are regulated through

![Figure 2. Some of the many smooth muscle cell responses to an applied stress (\( \sigma \)) or stretch (\( \lambda \)). Angiotensin II (Ang-II) is a potent vasoconstrictor that also regulates both the production of intracellular contractile and extracellular matrix (ECM) proteins (partly through transforming growth factor-beta [TGF-\( \beta \)] and connective tissue growth factor [CTGF]) and the removal of ECM (partly through monocyte chemoattractant protein-1 [MCP-1] and thus monocytes/macrophages [Mφ]). Matrix metalloproteinases (MMPs) contribute further to matrix removal, whereas platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF) contribute to cell proliferation. Finally, stress/stretch-activated ionic channels also play important roles in contraction.](http://circres.ahajournals.org/)

\[ \text{Contractile Proteins / Integrins} \quad \text{ECM Sensing & Regulation} \]

\[ \text{Ang-II} \quad \text{ECM Production} \]

\[ \text{MCP-1 / Mφ} \quad \text{MMPs} \]

\[ \text{PDGF / EGF / IGF} \quad \text{Proliferation} \]

\[ \text{Matrix Degradation} \]

\[ \text{CELL PHENOTYPE} \]

\[ \text{Cell} \]

\[ \text{Mechano-Stimulus} \]

\[ \text{Stretch Activated Channels} \]

\[ \text{Contractile Proteins / Integrins} \quad \text{ECM Sensing & Regulation} \]

\[ \text{ECM Degradation} \]

\[ \text{TGF-\( \beta \)} \]

\[ \text{CTGF} \]

\[ \text{MCP-1} \]

\[ \text{Mφ} \]

\[ \text{MMPs} \]

\[ \text{PDGF} \]

\[ \text{EGF} \]

\[ \text{IGF} \]

\[ \text{Proliferation} \]

\[ \text{Matrix Degradation} \]

\[ \text{CELL PHENOTYPE} \]
RhoA/RhoKinase and MAPK signaling pathways, among others. Recalling that smooth muscle contractility can contribute to vessel-level adaptations to altered hemodynamics, we see similar signaling (RhoA/RhoKinase, calcium/calmodulin, and MAPK) involved in both low (≈3–5 kPa) and high (≈100 kPa) contractile stress-mediated ECM remodeling.

Similar to findings at the tissue level, fibroblasts decrease or increase their stiffness (which reflects changing cytoskeletal stress because of the nonlinear stress–strain behavior) in response to increases or decreases, respectively, in cell stretch. Such findings suggest that fibroblasts also seek a tensional homeostasis, a concept that was confirmed for equibiaxially stretched SMCs, suggesting that a rapid disassembly/reassembly of cytoskeletal proteins (ie, dynamic equilibrium) allows cells to return intracellular stiffness, and hence stress, toward a preferred value after perturbations from endogenous levels. These findings are consistent with reports that individual cells generate stresses ≤5 kPa within initially unloaded 3D hydrogels, with stress localized at focal adhesions. Such observations suggest that cells not only modify the matrix to establish a preferred microenvironment in which to reside, they also maintain their own stress at a target level (recall Newton’s third law of motion, for every action there is an equal and opposite reaction).

Nearly linear relationships have been observed between cell-induced forces at focal adhesions and focal adhesion area in fibroblasts and SMCs, which suggests a target value of stress around 3 to 6 nN/μm² (ie, 3–6 kPa). Slightly higher values (≈10–12 kPa) were found for myofibroblasts that exhibit supervenature focal adhesions and increased actomyosin contractility relative to synthetic SMCs and fibroblasts. Nevertheless, these findings collectively suggest the existence of target values of stress. Of course, stresses at focal adhesions relate directly to stresses in the cytoskeleton, including prestresses. Indeed, it was appropriately noted that RhoA-dependent “preexisting cytoskeletal tension affects the actomyosin apparatus, which in turn coordinates the ability of the cell to adapt to the externally applied stress.”

In summary, whether at organ (vessel mechanoadaptations), tissue (collagen gels and hydrogels), cellular (isolated nonconfluent and embedded within matrix), or subcellular (focal adhesions and cytoskeleton) scales, a mechanical homeostasis seems to exist whereby intramural cells try to establish, maintain, or restore a preferred mechanical state. Whether this state is defined locally by stress, strain, stiffness, or another metric is not clear, but stress correlates well with many observations (stress and strain are related via constitutive relations, thus, one can be written in terms of the other; stress and stiffness are related linearly for materials, such as the aorta that exhibit an exponential stress–strain relation). Interestingly, studies at tissue, cell, and subcellular levels all reveal a preferred level of stress ≈5 kPa.

These findings, coupled with the existence of target stresses within the aortic wall of ≈150 kPa, suggest that 2 distinct classes of SMCs (or their behaviors) contribute to arterial mechanics. First, fully contractile SMCs that generate stresses of ≈100 kPa can contribute directly to overall load bearing, including control of caliber (recall that, at least in the mouse,
tissue-level aortic contractility is similar to that in other elastic arteries. Second, synthetic SMCs, fibroblasts, and myofibroblasts that seem to seek a target stress of ≈5 to 10 kPa cannot contribute directly to overall load bearing, but instead contribute indirectly by regulating the load-bearing ECM. That is, synthetic cells seem to take stress by the ECM, although yet being able to sense and thereby respond to these loads. Stress shielding is consistent with the dynamic nature of mechanosensing, namely, turnover of focal adhesion and cytoskeletal proteins within minutes. That is, although true load-bearing must be sustained, mechanosensing can be intermittent, particularly given that adjustments via matrix turnover occur over periods of hours, days, or weeks.

**Mechanosensing of Matrix**

The ability of medial SMCs and adventitial fibroblasts/myofibroblasts to respond to changes in mechanical stimuli requires that they interact directly with the ECM. Their primary mechanosensors are heterodimeric transmembrane complexes called integrins (Figure 1), which are denoted αβ and cluster to form dense plaques/focal adhesions. Vascular SMCs, fibroblasts, and myofibroblasts use a repertoire of integrins, including αβ, αβ, αβ, αβ, αβ, and αβ by SMCs and αβ, αβ, αβ, αβ, αβ, and αβ by (myo)fibroblasts. These integrins mediate binding to specific constituents of the matrix (eg, αβ for fibronectin and αβ for laminin), with some overlap in specificity (eg, αβ, αβ, and αβ bind fibronectin). Although there is redundancy in genes encoding integrins, deficiency in either α or β leads to a vascular phenotype, including reduced mechanoadaptivity. Particular matrix constituents can influence cell phenotype and thus responses to chemo- or mechanostimulation. For example, fibronectin tends to promote a synthetic smooth muscle phenotype, whereas laminin tends to promote a contractile phenotype. Importantly, microfibrils consisting primarily of fibrillin-1 connect aortic SMCs to the elastic laminae primarily via αβ and αβ integrins. That these microfibrils tend to align coaxially with actomyosin fibers within the cell suggests an efficient transferal of loads from cytoskeleton to integrin to matrix and vice versa. Loss of such connections would be expected to alter SMC signaling and phenotype.

In summary, integrin engagement and actomyosin contractile activity are fundamental to mechanosensing and mechanoregulation of matrix and thus mechanical homeostasis. Findings at tissue, cellular, and subcellular levels of actomyosin-generated stresses of ≈5 kPa are consistent with mechanosensing, not gross load-bearing. Although such active stresses are much lower than those involved in vasoactive changes of vessel diameter, the intracellular structures and signaling pathways are similar. Thus, pathways fundamental to SMC mechanobiological changes in general and mechanosensing in particular overlap considerably with those in vasoactivity. Similar considerations apply to fibroblasts and myofibroblasts.

Finally, mechanostimulation of cells involves receptor tyrosine kinases (eg, receptors for epidermal and platelet-derived growth factors), serine–threonine receptors (eg, TGF-β type I and II receptors), G-protein coupled receptors (eg, angiotensin-II type I and endothelin-I type A receptors), and stretch-activated cationic (eg, Ca2+) channels. These pathways may involve ligand-independent, mechanical activation of the receptors, load-induced secretion of ligand, opening of channels, or release of active ligand. For example, mechanical activation of latent TGF-β can be achieved via actomyosin activity and integrins that bind the latency complex (eg, αβ and αβ), which could affect adventitial remodeling. Interestingly, cell-generated stresses needed to activate TGF-β are ≈5 to 9 kPa, similar to typical stresses at focal adhesions, in cells placed within otherwise unloaded matrix and endogenous levels established in collagen gels by cells. It may be that mechanosensing and the mechanoregulation of cytokines, proteases and their action, or cross-linkers, such as transglutaminases that are stored within the ECM, are highly complementary, again involving the same intracellular structures and signaling pathways. Finally, transmembrane polycystins seem to contribute to mechanosensing in vascular cells; they often colocalize with stretch-activated calcium channels and modulate their activity. Polycystin-1,2 play important roles in mechanosensing both individually (via filamin-A-related interactions with cytoskeletal actin) and in cooperation with focal adhesions.

**Mechanoregulation of Matrix**

Theoretical studies of soft tissue growth and remodeling suggest that, under normal conditions, cells deposit new structural constituents within extant matrix at a homeostatic stress or stretch. This conjecture is appreciated easily in tissue maintenance: if stressed matrix is removed during normal turnover, the only way to maintain the same properties and geometry under a similar load is to replace this matrix with the same constituents having the same stresses. Such mechanoregulated deposition is supported computationally and experimentally. Computations of arterial mechanoadaptations show that ongoing replacement of stressed matrix with either unstressed or less stressed matrix causes a numeric artery to dilate under a constant pressure, which violates tissue maintenance. Experiments reveal that SMCs and fibroblasts mediate collagen assembly via integrins (eg, αβ) and RhoA activity, which implicate an active process of organization. Indeed, embryonic fibroblasts can produce procollagen independent of actin, but they cannot organize and align collagen fibers without functional actin, thus implying an actomyosin-based mechanoregulation of the fibers via integrins.

Interestingly, TGF-β influences both αβ integrin and SMC α-actin levels in cells that remodel collagen gels in vitro and focal adhesion kinase is increased in SMCs concomitant with the synthesis of proteins in response to exogenous Ang-II and its associated MAPK signaling. Fibronectin is also necessary for proper collagen assembly and fibronectin assembly is mechanoregulated via integrins (αβ) and actomyosin activity. Elastic fiber assembly is similarly mediated by cell-generated mechanical loads. Clearly, matrix deposition and organization are mediated by active cell processes that involve force generation.
Cells also actively remodel extant matrix into mechanically preferred states. For example, fibroblasts build-in a residual matrix tension (likely ≈5 kPa) in mechanically constrained collagen gels that persists even if subsequent actomyosin activity is blocked. In other words, residual matrix tension preserves some cell-mediated changes in matrix organization without requiring continued actomyosin activity, which would be energetically favorable. Transglutaminases may play a role in such entrenchment just as in tissue-level arterial remodeling, noting that matrix bound transglutaminases can be activated by mechanical stress.

In summary, cells seem to modulate their ECM to match the forces encountered. Diverse findings suggest that when organizing either newly produced or extant matrix, cells seek to establish, maintain, or restore a preferred (homeostatic) mechanical state that correlates well with a target stress or stiffness. Fundamental to such mechanoregulation of matrix is the ability of the cells first to sense the mechanical state, which requires integrin expression and actomyosin activity. Among its many effects, TGF-β can increase the expression and organization of contractile proteins within SMCs and fibroblasts, which correlates with increased integrin clustering. It seems, therefore, that this cytokine known primarily for increasing the production of matrix simultaneously enables cells to actively organize and sense the deposited matrix through focal adhesions and actomyosin complexes. Establishing and maintaining matrix at a preferred state is fundamental to the overall structural integrity of tissues and the health of the cell. In extreme cases, however, loss of contact with matrix causes cells to undergo a special form of apoptosis called anoikis. Clearly then, if dysfunctional mechanosensing leads cells to misinterpret a normal or high stress environment as a low stress environment, they may inadvertently apoptosis or elicit an atrophic remodeling response, both of which could compromise overall structural integrity.

Genes Predisposing to Thoracic Aortic Disease

Since the discovery in 1991 that mutations in FBN1 predispose individuals with Marfan syndrome to TAADs, mutations in many other genes have similarly been identified. In addition, common single base pair variants and genomic copy number variants in some of these same genes increase the risk for TAADs in the general population. These genes can be categorized based on their effects on mechanosensing and mechanoregulation of matrix by medial SMCs, particularly through disruption of the contractile-elastic unit.

Numerous mutated genes predisposing to TAADs alter proteins in the microfibril sheath that encapsulates elastin (Figure 1). FBN1 encodes fibrillin-1, the major protein in the microfibrils that connect elastic fibers to dense plaques in SMCs. Fibroblasts explanted from patients with Marfan syndrome consistently exhibit decreased deposition of fibrillin-1 into the ECM, thus suggesting that FBN1 mutations compromise connections between SMCs and elastic fibers. Mutations in fibrillin-1-associated glycoprotein 2 (encoded by MFAP5), another component of microfibrils, also predispose to TAAD. Other mutant genes that lead to thoracic aortic disease affect proteins that normally contribute to the structural integrity of the wall (eg, fibulin-4 and collagen III), which also connect structurally to the SMCs and could alter the mechanical stimuli sensed by these cells as the wall experiences either the same or increased cyclic loads.

Other genes predisposing to TAADs encode proteins that contribute to the structure or function of the SMC contractile unit, as well as cytoskeletal components linking these units to the dense plaques. The 2 major proteins in the contractile unit are the SMC-specific isoform of actin, α-actin, and SM-myosin heavy chain, which form thin and thick filaments, respectively. Mutations in the corresponding genes, ACTA2 and MYH11, predispose to thoracic aortic disease. Preliminary data suggest that mutations in these genes disrupt the ability of monomers of α-actin and myosin heavy chain to form functional filaments. SMCs also have a dedicated kinase, myosin light chain kinase (MYLK), that phosphorylates the regulatory light chain to initiate SMC contraction. MYLK loss of function, predicted to decrease activation of the regulatory light chain, also predisposes to TAADs. Type I cyclic guanosine monophosphate (cGMP)-dependent protein kinase (PRKG1) controls regulatory light chain dephosphorylation to relax SMCs. A gain of function mutation in PRKG1 that increases dephosphorylation of the regulatory light chain also predisposes to thoracic aortic disease. Finally, mutations in filamin-A, a cytoplasmic protein that links actin filaments and is strongly implicated in mechanotransduction, predispose to TAADs. All of these mutations in SMC contractile, structural, and signaling genes are predicted to decrease the cells’ ability to generate the force needed to appropriately sense and regulate the mechanical state of the matrix.

Genetic alterations in mouse models have identified additional genes involved in ECM integrity or mechanosensing that predispose to TAADs. These genes encode other proteins and proteoglycans in the matrix (eg, collagen V, biglycan, and lysyl oxidase), transmembrane structures (eg, polycystin-1,2), intracellular signaling molecules (eg, integrin linked kinase), and calcium-binding proteins. Interestingly, increased S100A12 (a calcium-binding protein) resulted in reduced vinculin, SM-myosin heavy chain, and SM-α-actin, each of which can contribute to effective sensing and regulation of ECM. Increased S100A12 also increased IL-6 production and activation of TGF-β pathways. Finally, TGF-β signaling in Loey’s–Dietz syndrome has been suggested to be Ang-II-dependent and thoracic aortic disease in the Fbn1−/−Smad model depends on intramural increases in Ang-II production.

Genome-wide association studies in patients who do not have Marfan syndrome show that common SNPs in FBN1 still associate with thoracic aortic disease. Although altered or diminished fibrillin-1 can contribute to premature mechanical fatigue or elastolysis, consistent with compromised wall properties expected during aneurysmal dilatation and altered mechanosensing, fibrillin-1 plays additional roles—it sequesters latent TGF-β in the ECM. It has been proposed that mutations in FBN1 can lead to inappropriate release of active TGF-β from the matrix and that excessive TGF-β signaling can cause the increased SMAD and MAPK signaling in aortas of Marfan mouse models. Aortic tissue from patients undergoing
surgical repair of familial TAADs also exhibit increased TGF-β signaling based on immunostaining of phosphorylated SMAD2. It is thus surprising that loss of function mutations in genes encoding proteins critical for TGF-β signaling also predispose to TAADs, including those involving genes that encode type 1 and 2 transforming growth factor receptors (TGFBR1 and TGFBR2), one of the 3 isoforms of TGF-β (TGFβ2), and related signaling molecules, SMAD3 (SMAD3) and SMAD4 (SMAD4). Thus, the paradox of mutations decreasing TGF-β signaling, despite evidence of increased TGF-β in end-stage aortic tissues, raises questions as to the precise role(s) played by TGF-β signaling in thoracic aortic disease. Studies in mice demonstrate that TGF-β signaling is critical for proper development of the aorta. Loss of TGF-β signaling disrupts the differentiation of neural crest–derived SMCs that populate the ascending aorta and the secondary heart field epithelial-to-mesenchymal transition involved in forming SMCs in the aortic root during development. The importance of TGF-β in the differentiation of aortic SMCs is illustrated by the finding that ascending aortas in Tgfb2−/− mice are small and thin-walled, and mice with the Tgfb2 gene conditionally deleted in vascular SMCs display arterial dilation and dissection. These studies showed that TGF-β gene mutations do not disrupt cardiovascular development; migration or homing of cells to the aorta during development was normal. Rather, decreased TGF-β signaling predisposes to slowly progressing, primarily adult-onset vascular diseases initially involving the aortic root and ascending aorta. TGF-β may be required for full differentiation of aortic SMCs during development and specifically the development of a full complement of contractile-elastic units to withstand life-long mechanical loading of the aorta. Supporting this hypothesis, SMCs explanted from patients with TGFBR2 mutations show reduced expression of proteins in the SMC contractile unit when compared with control SMCs, and they differentiate to a lesser degree than control SMCs in response to TGF-β. Thus, failure to build the contractile-elastic units to withstand life-long mechanical loading of the aorta—engaged as a protective sheath—is defective (Figure 4). Consequently, if any one of these 3 essential links—matrix stiffness, transmembrane structures, or cytoskeletal structures, including the actomyosin apparatus, and proper signaling to express and assemble these links—is defective (Figure 4), mechanosensing and mechanoregulation will be compromised. That is, mechanical homeostasis will be dysfunctional, and the aorta will become vulnerable to structural failure.

Given the apparent importance of TGF-β and possibly Ang-II in TAADs, their mechanobiological roles must be considered. To this end, in vitro and in vivo studies reveal direct relationships between mechanical stimuli on SMCs and both Ang-II and TGF-β activity. These results are consistent with the influence these biomolecules have on matrix production/degradation and the actomyosin-integrin structures that are needed to organize a matrix capable of supporting hemodynamically induced loads. Indeed, Ang-II and TGF-β play similarly important roles in hypertension and aging wherein the wall can thicken to counteract increased pressure-induced wall stress, though not all matrix production need be structurally protective. Interestingly, a transcriptional analysis of vascular aging identified altered cell–matrix interactions as particularly important. Mechanical stress and TGF-β signaling are also complementary partners in the differentiation of fibroblasts to myofibroblasts, which enables increased synthesis and organization of matrix. These processes may play important roles in adventitial remodeling in severe cases of increased mechanical stress, which, when the media degenerates in TAADs, is engaged as a protective sheath.

Unifying Hypothesis
An emerging concept is that altered cell–matrix connections, especially via the contractile-elastic unit, play important roles in TAADs. Given that such connections are fundamental determinants of cell phenotype and cell survival, this hypothesis is intuitive. Based on our review of the mechanics and mechanobiology, both computational and experimental, we submit further that many of the identified genetic mutations in TAADs implicate 2 specific, complementary aspects of cell–matrix interactions that directly affect the structural integrity of the aortic wall. Functional connections must exist between SMCs and surrounding ECM to enable these cells (i) to actively assess their mechanical environment and express appropriate mechanosensitive genes and (ii) to actively remodel extant matrix or prestress newly produced matrix as it is incorporated within the wall. Both of these cell-mediated functions are necessary for establishing, maintaining, or restoring structural integrity in response to altered biomechanical loads. Moreover, cell-level actomyosin contractile activity is fundamental to such mechanosensing and mechanoregulating of the matrix, as suggested by the convergence of TAAD-related signaling pathways with mechanisms of cell sensing and regulation of matrix (Figure 3). Consequently, if any one of these 3 essential links—matrix stiffness, transmembrane structures, or cytoskeletal structures, including the actomyosin apparatus, and proper signaling to express and assemble these links—is defective (Figure 4), mechanosensing and mechanoregulation will be compromised. That is, mechanical homeostasis will be dysfunctional, and the aorta will become vulnerable to structural failure.

Figure 4. Confluence of some of the gene mutations that predispose to thoracic aortic aneurysms and dissections and affect the mechanostimulus (eg, transferal of stress from the matrix to the cell), the mechanosensing of this stimulus, or the associated mechanosensitive signaling pathways. See text for information on the affected genes and related references. ECM indicates extracellular matrix; and TAADs, thoracic aortic aneurysms and dissections.
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Closure

The normal thoracic aorta can maintain its geometry, structure, and function over decades and adapt well to modest sustained changes in hemodynamics. Such maintenance and adaptivity are achieved, in large part, by intramural cells properly sensing their chemomechanical environment and actively regulating the ECM to ensure appropriate compliance and structural integrity. However, aging results in diffusely diminished smooth muscle function, lost elastic fiber integrity, remodeled collagen, increased glycosaminoglycans, and increased intramural Ang-II and TGF-β. These changes can manifest clinically as decreased arterial distensibility, increased pulse wave velocity, and increased central systolic and pulse pressure, all of which feedback to increase the hemodynamic loads. Many of these same changes are found at tissue, cellular, and molecular levels in some individuals having TAADs. In some cases, therefore, TAADs may represent an accelerated, exaggerated localized aging of the aorta. In other cases, mutations (eg, inaccelerated, exaggerated localized aging of the aorta. In syndrome.175 Elucidation of these pathways may identify new mechanisms regulating the ECM to ensure appropriate compliance and structural integrity, remodeled collagen, increased glycosaminoglycans, and increased intramural Ang-II and TGF-β.2,172 These changes can manifest clinically as decreased arterial distensibility, increased pulse wave velocity, and increased central systolic and pulse pressure, all of which feedback to increase the hemodynamic loads.2,172 Many of these same changes are found at tissue, cellular, and molecular levels in some individuals having TAADs.143,173 In some cases, therefore, TAADs may represent an accelerated, exaggerated localized aging of the aorta. In other cases, mutations (eg, in TGFBR1/2) likely compromise the developing matrix and differentiation of SMCs, which affects subsequent function and structural integrity, including arterial tortuosity at young ages.2 Thus, ineffective cell–matrix interactions likely render the wall vulnerable to increases in hemodynamic loading, even during development. The aortic wall will fail as a structure, namely dissect or rupture, if and only if local mechanical stresses exceed mechanical strength. There is a pressing need, therefore, to focus on local, not global, mechanics.174 In contrast, mechanobiological responses by aortic cells need not depend on the actual mechanical environment—responses depend on what the cell can perceive (ie, sense) and achieve (eg, genes that can be expressed). Based on the diverse findings collected together herein, we submit that TAADs arise, in large part, because of an inappropriate mechanosensing and mechanoregulation of ECM by medial SMCs that renders the aortic wall vulnerable to dilatation and dissection. An associated or subsequent inability of adventitial fibroblasts to maintain or restore a sufficiently strong adventitia can further lead to rupture. Future research should thus focus on local, not global, mechanics; mechanisms by which cells sense changes in local mechanical stimuli; and associated signaling and gene expression pathways that govern the structural integrity of the aortic wall. Some guidance forward is found in the recent elucidation of abnormal mechanosignaling in the heart in Marfan syndrome.175 Elucidation of these pathways may identify new therapeutic targets to decrease destructive (low-stress) or enhance constructive (high-stress) mechanosensitive remodeling of matrix. On this foundation, translational efforts to prevent TAAD may be successful in preventing aneurysms and dissections of the thoracic aorta.

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Disclosures

None.

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