Published in final edited form as:

Curr Opin Biomed Eng. 2018 March ; 5: 50–57. doi:10.1016/j.cobme.2018.01.002.

Bio-chemo-mechanics of thoracic aortic aneurysms

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Abstract

Most thoracic aortic aneurysms (TAAs) occur in the ascending aorta. This review focuses on the unique bio-chemo-mechanical environment that makes the ascending aorta susceptible to TAA. The environment includes solid mechanics, fluid mechanics, cell phenotype, and extracellular matrix composition. Advances in solid mechanics include quantification of biaxial deformation and complex failure behavior of the TAA wall. Advances in fluid mechanics include imaging and modeling of hemodynamics that may lead to TAA formation. For cell phenotype, studies demonstrate changes in cell contractility that may serve to sense mechanical changes and transduce chemical signals. Studies on matrix defects highlight the multi-factorial nature of the disease. We conclude that future work should integrate the effects of bio-chemo-mechanical factors for improved TAA treatment.

Graphical Abstract

Introduction

Thoracic aortic aneurysm (TAA) is characterized by a dilated aorta that may eventually dissect or rupture. About 60% of TAAs occur in the ascending aorta (AA) between the aortic valve and the innominate artery. TAAs have an incidence of approximately 1 per 10,000 people [1]. TAA is associated with traditional cardiovascular risk factors such as smoking, hypertension, and aging. TAA is also associated with bicuspid aortic valve (BAV), which is the most common congenital heart abnormality. Up to half of all patients with BAV may

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Conflict of Interest

The author declares no conflict of interest.

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develop TAA. There is a significant genetic component to TAA, with up to 29 TAA-associated genes identified to date. Most of the identified genes encode SMC contractile proteins, extracellular matrix proteins, or signaling molecules in the TGF- β pathway [2]. One of the first TAA-associated genes identified was fibrillin-1 (*FBNI*), a matrix protein that also interacts with TGF- β . Mutations in *FBNI* cause Marfan Syndrome (MFS), which is characterized by changes in the skeletal, ocular, and cardiovascular system, including an increased incidence of TAA. Recommendations for the management of TAA depend on whether it is associated with degenerative etiology (i.e. hypertension or aging) or with a congenital disorder (i.e. BAV or MFS). Despite different etiology, TAA is associated with a common histopathology including disruption and loss of elastic fibers, changes in cell amount or phenotype, and infiltration of inflammatory cells in the aortic wall [3].

This review focuses on the unique bio-chemo-mechanical environment of the AA that makes this vascular region particularly susceptible to TAA. The environment includes solid mechanics, fluid mechanics, cell phenotype, chemical signaling, and matrix composition. Examples of each environmental consideration are given in Table 1. The AA experiences biaxial loading and high, pulsatile flows because it is connected directly to the aortic valve in the heart. TAA incidence in the AA is increased with BAV, which alters the fluid flow patterns and may cause endothelial cell (EC) responses to altered shear stress [4]. The AA contains boundaries delineating smooth muscle cells (SMCs) from various embryonic origins that may respond differently to mechanical and chemical cues [5]. The AA has the highest elastin content of any artery, so genetic defects affecting the elastic fibers may significantly alter AA structure and function. Because 20% of TAAs are linked to mutations in genes encoding SMC contractile proteins, matrix proteins, or mechanosensitive signaling molecules, it has been hypothesized that TAA progression may be caused by defective mechanosensing between SMCs and the matrix [6]. This review will summarize recent advances toward determining and synthesizing the effects of changes in the AA bio-chemo-mechanical environment on TAA development, progression, and failure.

Solid mechanics

The AA experiences cyclic biaxial loading during the cardiac cycle. Axial strain in the human AA is 7.5%, while circumferential strain is 13.5% from diastole to systole. Strain values are 10 – 20% higher in women than in men [7], which may be important for evaluating sex-linked differences in TAA susceptibility and outcomes. Strain values over the cardiac cycle in various animal models are in the same range. Physiologic strain values calculated from the unloaded state for mouse AA range from 1.1 – 1.7 for axial stretch ratios and 1.4 – 1.8 for circumferential stretch ratios. The large range of axial stretch values is a result of different methods of calculation. Values in the range of 1.1 – 1.2 are determined from calculating marker displacement along the AA before and after dissection [8], while values in the range of 1.7 – 1.8 are determined by assuming that the in vivo axial stretch is the value at which the force is constant during in vitro pressurization from 10 – 140 mmHg [9]. As axial stretch significantly affects the biaxial mechanical behavior and correlates with AA dilation in mouse models of TAA [9], in vivo axial stretch is a critical consideration for modeling mechanical stresses in human TAA [10].

Increased aortic stiffness correlates with an increased risk of adverse cardiovascular outcomes [11]. Hence, aortic stiffness has been investigated as a metric for predicting outcomes in TAA. In patients with connective tissue disorders (CTDs) like MFS that lead to TAA, AA stiffness is increased and correlates with higher rates of aortic dilation and surgical aortic root replacement [12]. Clinical stiffness measurements are typically structural measurements that depend on the AA material properties, geometry, and applied blood pressures. In vitro experiments allow the separation of material and geometric changes and control over the applied loads, although they neglect the role of supportive tissues and organs surrounding the aorta. Azadani et al. [13] found that the material stiffness of human TAA samples positively correlates with dilation. Bellini et al. [9] found that the AA material stiffness, but not the structural stiffness, positively correlates with dilation in 10 different mouse models of TAA. While TAA is generally associated with an increase in aortic stiffness, Lee et al. [14] found that the TAA medial layer in a mouse MFS model had a lower material stiffness than control samples when measured locally by atomic force microscopy. These contrasting results highlight the difference between global and local measures of aortic stiffness and tissue remodeling in TAA. While global increases in aortic material stiffness are important for determining the wall stresses and predicting failure, local changes in material stiffness are important for SMC and EC mechanosensing and related chemical signaling that may also contribute to wall failure.

Energy loss has been proposed as a biomechanical parameter that may predict TAA outcomes. Chung et al. [15] found a higher energy loss during cyclic loading for human TAAs with diameters larger than 5.5 cm. A normal human AA has a diameter of 2.5 cm. Prophylactic surgery is recommended when the TAA reaches 5.5 cm if the patient is asymptomatic and has no additional risk factors for rupture or dissection [3]. A common histological finding in TAA is fragmented or absent elastic fibers. As elastic fibers provide energy storage capacity in the large arteries, it is reasonable that energy loss increases when they are fragmented or absent. In three different mouse models with severe defects in elastic fiber structure, increased energy loss was the most striking AA mechanical phenotype [16]. Mouse AA completely lacking elastin has a smaller diameter than control and develops stenosis, while mouse AAs missing fibulin-4 or lysyl oxidase (necessary for assembly and crosslinking of elastic fibers, respectively) have larger diameters than control and develop TAA. These differences show that defective elastic fibers and increased energy loss alone are not causative for TAA, but may be one of many changes in the bio-chemo-mechanical environment that contributes toward its progression.

TAAs can fail due to rupture or dissection. Rupture occurs when the wall stresses exceed the failure strength of the wall. Dissection occurs when a small tear forms at the intima that is propagated into the media allowing blood to pool and form a false lumen. While previous studies have investigated failure stresses of human TAA samples under uniaxial loading, recent studies have focused on more relevant loading conditions for TAA failure such as biaxial rupture [17], ultimate shear [18], radial shear [19], and crack propagation [20]. Duprey et al. [17] show that biaxial rupture risk correlates with material stiffness of the human TAA, extending studies that correlate material stiffness with TAA dilation [13]. Sommer et al. [18] show that human TAA tissue has anisotropic failure behavior and that dissected tissue has much lower failure stress than undissected tissue. Witzenburg et al. [19]

show that porcine aorta has low strength in radial shear, which may contribute to dissection risk. Shamansouri et al. [20] show no correlation between toughness (resistance to crack propagation) and material stiffness, indicating that material stiffness may not predict dissection probability, but could still predict rupture probability [17]. Shamansouri et al. [20] and Davis et al. [21] also explored regional heterogeneity of biaxial mechanics in human TAA tissue, which will be important for modeling of regional wall stresses to predict failure [22].

Fluid mechanics

The AA experiences complex hemodynamics. Quantifying the hemodynamic characteristics and comparing them across TAA states is challenging. Von Spiczak et al. [23] used 4D phase contrast MRI to visualize flow in the AA and proposed two and three dimensional metrics for objective quantification of vortex flows. They found that the strength, elongation, and radial expansion of the vortex flows peaked at systole and reached minimum values at diastole. Alterations in vortex flow parameters appeared to correlate with the degree of dilation in TAA patients. Hemodynamics can become even more complicated if the TAA dissects and forms a false lumen [24]. Altered hemodynamics due to changes in valve geometry may contribute to TAA formation in BAV. Cao et al. [25] used fluid-structure interaction (FSI) models to determine flow characteristics of normal tricuspid aortic valve (TAV) and different morphotypes of BAV. They used a constant aortic geometry and only changed aortic valve geometry in their models to eliminate other geometric effects on the hemodynamics. They found that all BAV morphotypes alter the helicity, skewness, and displacement of the flow profile, while oscillatory wall shear stress was highly dependent on BAV morphotype and appeared to correlate with regions known to dilate. Youssefi et al. [26] imaged patients with a variety of valve morphotypes and used computational fluid dynamics (CFD) to calculate flow eccentricity, helicity, and oscillatory wall shear stress. They found that BAV was associated with more eccentric flow and that the presence of aortic stenosis led to higher wall shear stresses and oscillatory shear index in the greater curvature of the AA, which is the typical site of dilation and thinning. Atkins et al. [27] applied typical BAV or TAV wall shear stress to porcine aortic tissue and found increases in matrix metalloproteinase activity in tissue exposed to BAV flow profiles, demonstrating that hemodynamics can affect aortic wall remodeling. Advances in imaging technologies and computational methods [28] make patient-specific modeling of flow dynamics a possibility for risk stratification of TAA outcomes.

Cell phenotype

SMCs surrounding the AA region come from different embryonic origins. In the aortic valve SMCs derive from the second heart field, in the AA SMCs derive from the neural crest, and in the descending aorta (DA) SMCs derive from the somatic mesoderm [29]. Recent work shows that SMCs from the second heart field and the neural crest overlap within the AA and occupy spatially distinct regions of the media [5]. Trigueros-Motos et al. [30] showed that embryonic origin causes differential expression of homeobox genes that may be related to differences in disease susceptibility between the AA and DA. Cheung et al. [31] differentiated human pluripotent stem cells into embryonic-origin specific SMCs to model

origin dependent disease susceptibility. Granata et al. [32] then used this differentiation protocol to create SMCs to model MFS. Although there is controversy over how well SMCs in a tissue culture dish recapitulate characteristics of SMCs in the aortic wall, in vitro models are needed to dissect molecular mechanisms of the disease.

SMC contractile phenotype has been implicated in TAA development. Mutations in *ACTA2*, *MYH11*, *PRKG1*, *MYLK*, and *FLNA* are associated with TAA and are critical for SMC contraction or relaxation. SMC contraction may act as sensor for the surrounding mechanical environment [33]. Abnormal SMC mechanosensing has been implicated in TAA progression in a variety of genetically-linked diseases [34–38]. Altered SMC phenotype has also been described in TAA associated with BAV. RNA [39], micro-RNA [40], and secreted proteins [41] are differentially expressed in BAV compared to TAV tissue and alterations in the TGF- β pathway are implicated.

Mutations in TGF- β related genes lead to TAA [2], highlighting the importance of the chemical signaling environment. In studies with MFS mouse models and in a small clinical trial, improper stimulation of TGF- β through the angiotensin 1 receptor (AT1r) correlated with TAA development. This observation led to a large clinical trial for MFS patients comparing losartan (an AT1r antagonist) to common β -blocker therapy. Losartan did not limit aortic dilation over the three-year clinical trial period [42]. Subsequent studies in MFS mice showed that losartan has additional effects beyond TGF- β inhibition and that specific TGF- β inhibition either exacerbated or mitigated TAA formation depending on when treatment was initiated [43]. These results highlight interrelationships among chemical signaling pathways and how bio-chemo-mechanical factors may evolve with disease progression.

A progenitor cell population has been identified in the AA adventitia that may contribute to TAA pathogenesis. These progenitor cells can differentiate into macrophages [44] and SMCs [45]. There is also evidence that these progenitor cells derive from differentiated SMCs [46]. SMCs are remarkably plastic and the direct transition from a contractile to a migratory, phagocytic phenotype has recently been recorded through time lapse imaging [47]. SMCs can be converted to ECs by passing through an intermediate vascular progenitor state during in vitro reprogramming [48]. As we learn more about cells in the aortic wall, our strict definitions of SMCs, ECs, macrophages, and progenitor cells are continually expanding and evolving. Cell type transitions and cell phenotype changes may both play a role in TAA formation.

Inflammation

While abdominal aortic aneurysms have long been associated with inflammation, there has been less investigation of inflammation in TAA. Sulkava et al. [49] recently compared gene expression of normal AA and TAA samples from patients without genetic disorders and found that many of the inflammation-related signaling pathways were upregulated in TAA samples. Their results are consistent with earlier reports of an increased number of inflammatory cells within the media of TAA samples [50]. Using a mouse model of TAA, Jia et al. [51] found that macrophage infiltration followed SMC apoptosis and was linked to increased ER stress. They found that ER stress was induced by mechanical stretch in

isolated SMCs, suggesting that alterations in the mechanical environment start the signaling cascade that brings inflammatory cells to the aortic wall in TAA. Wu et al. [36] found that the NLRP3-caspase 1 inflammatory cascade is involved in SMC contractile protein degradation and TAA formation in mice, directly linking inflammation to SMC phenotype and aortic biomechanics.

Angiotensin II (Ang II) infusion in mice promotes inflammation and leads to abdominal and thoracic aneurysms. After 28 days of continuous Ang II infusion, AA diameter is increased 25% and elastic fiber fragmentation and macrophage infiltration are evident in the wall [52]. Although Ang II infusion in hypercholesterolemic mice (*Apoe*^{-/-} or *Ldlr*^{-/-}) is often used for TAA models, high cholesterol is not necessary for TAA development. Bersi et al. [53] examined multiple aortic regions in the Ang II infused *Apoe*^{-/-} mouse model. They found that mechanical metrics (such as energy storage and wall stress) correlated most strongly with inflammatory metrics (such as CD45⁺ cells) in the thoracic region, suggesting an important interplay between solid mechanics and the recruitment of inflammatory cells in TAA. Trachet et al. [54] found an increase in single elastic laminae ruptures in Ang II infused *Apoe*^{-/-} AA, which may facilitate the progressive enlargement of focal dissections and ultimate failure.

Matrix composition

In the large arteries, matrix proteins surrounding the SMCs provide the bulk of the mechanical stiffness and strength. Elastic fibers provide resiliency and resistance to deformation at low pressure, while collagen fibers provide strength and resistance to deformation at high pressure. The inner portion of the arterial wall is called the intima and consists of a single layer of ECs on top of a basement membrane. The middle portion of the wall is called the media and consists of concentric layers of SMCs surrounded by elastic laminae made up of elastic fibers. A thin layer of collagen fibers resides between the SMCs and their adjacent elastic laminae [55]. The outer portion of the wall is called the adventitia and consists mostly of collagen fibers and fibroblasts. Numerous matrix gene mutations are associated with TAA. For collagen fibers these include *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, and *LOX*. For elastic fibers these include *EFEMP2*, *ELN*, *EMILIN1*, *FBN1*, *FBN2*, *LOX*, and *MFAP5* [2]. *LOX* is listed for collagen and elastic fibers because it encodes lysyl oxidase, the enzyme that catalyzes crosslinking of both collagen and elastin.

Mutations in the proteoglycan, biglycan (*BGN*), are also associated with TAA [56]. Biglycan contributes to normal collagen fiber formation and has been associated with elastic fibers. Additionally, proteoglycan and glycosaminoglycan deposits have been described within the media of TAA samples [57]. Computational modeling suggests that these deposits may facilitate delamination of the medial layers and encourage aortic dissection [58].

It seems obvious that genetic mutations that affect the mechanical integrity of the aortic wall lead to TAA, however the association is complicated. For example, *FBN1* mutations cause MFS which leads to TAA. TAA tissue from MFS patients is characterized by elastic fiber fragmentation, as well as altered SMC phenotype [59], and TGF-beta dysregulation [60], indicating that all three components: bio-, chemo-, and mechanical play a role in TAA

pathogenesis. Additionally, mice with genetic knockout of *Lox* [61] or *Efemp2* [62] have highly fragmented elastic fibers in the AA and the DA, but only the AA dilates. There must be a contribution of changes in the mechanical behavior of the AA due to the genetic matrix mutations, as well as contributions from other bio-chemo-mechanical factors in the AA that cause a high propensity of aneurysms, dissections, and rupture in this vascular location.

Figure 1 summarizes bio-chemo-mechanical changes observed in the AA for a mouse model of TAA associated with CTDs. The mouse (SMKO) has a SMC-specific deletion of *Efemp2*, which encodes fibulin-4. Fibulin-4 is necessary for the proper assembly of elastic fibers during development. SMKO mice develop TAA that is characterized by elastic fiber fragmentation [63], alterations in SMC phenotype and contractility [34], and changes in solid mechanical behavior of the wall [64]. Although fluid mechanics in SMKO AA have not been quantified, the geometric changes, including increases in diameter, length, and branching angles of the connecting arteries will likely cause changes in the flow profile and resulting wall shear stresses.

Multifactorial studies

Many studies have focused on characterizing the role of individual factors, i.e. stiffness, shear stress, SMC phenotype, TGF- β signaling, or individual gene mutations in TAAs. There are a few examples of studies that investigate multiple factors. For example, Bersi et al. [53] quantify solid mechanics, matrix composition, and inflammation in four different aortic regions in the Ang II infused *Apoe*^{-/-} mouse model. They conclude that the sensitivity and response of each aortic region to Ang II infusion varies, driving disparate effects from aneurysm formation to fibrosis. Yamashiro et al. [34] quantify solid mechanics, matrix composition, and SMC phenotype in SMKO mice. They suggest that abnormal SMC mechanosensing due to the loss of elastic fiber connections leads to TAA development. Atkins et al. [27] study fluid mechanics, matrix composition, and chemical signaling using a FSI model and in vitro experiments on porcine aortic tissue. They determine that alterations in wall shear stress can drive aortic medial degeneration and subsequent aneurysm formation.

Integrating the results of different experiments into a comprehensive prediction of how the AA will respond to perturbations in the bio-chemo-mechanical environment will require multifactorial computational models. Current TAA computational models focus on at most two of the factors discussed in this review. Examples include microstructurally-based models that incorporate collagen or elastin fiber structure in the solid mechanics predictions [19, 65], FSI simulations that include geometry, solid mechanical properties, and hemodynamics specific to TAA [66], and growth and remodeling models that predict solid mechanics based on changes in matrix parameters and SMC contractility [64]. Solid mechanics with growth and remodeling has been coupled to fluid dynamics simulations [67] or to an agent based model with biological and chemical responses to various signaling molecules [68], but these multifactorial models have not been applied to TAAs.

Conclusions

The AA is characterized by a unique bio-chemo-mechanical environment that may play a role in its susceptibility to TAA and the risk of dissection and rupture. Individual biological, chemical, or mechanical factors cannot explain the heterogeneity of TAA disease, the vascular location of aneurysm formation, or predict failure risk. Examples of solid mechanics, fluid mechanics, cell phenotype, and matrix composition factors involved in TAA are summarized in Table 1. Future work should include multifactorial experimental and computational studies that define relative contributions of and interactions between factors to predict disease progression and interventional outcomes. To accomplish these studies, expertise will be needed across engineering and biology specialties including, but not limited to solid mechanics, fluid mechanics, imaging, computational modeling, cell biology, matrix biology, and immunology. Multifactorial experiments and modeling may help define more effective, broad treatment strategies for TAA. For example, it may be beneficial to reduce blood pressure to reduce wall stress, as well as inhibit ER stress pathways to prevent SMC apoptosis.

Acknowledgments

This work was supported by National Institutes of Health grants HL115560 and HL106305. Yoshito Yamashiro, Hiromi Yanagisawa, Jungsil Kim, and Lien Tran are gratefully acknowledged for providing the histological and morphological images of SMKO AA in Figures 1B and D.

References

- *Of special interest
- **Of outstanding interest
- 1. Ramanath VS, Oh JK, Sundt TM 3rd, Eagle KA. Acute aortic syndromes and thoracic aortic aneurysm. *Mayo Clin Proc.* 2009; 84(5):465–81. [PubMed: 19411444]
- *2. Brownstein AJ, Ziganshin BA, Kuivaniemi H, Body SC, Bale AE, Elefteriades JA. Genes Associated with Thoracic Aortic Aneurysm and Dissection: An Update and Clinical Implications. *Aorta (Stamford).* 2017; 5(1):11–20. This brief review summarizes genes associated with TAA and presents a simplified schematic for the AA diameter at which surgical intervention is suggested for each causal gene. The schematic is a good illustration of the heterogeneity of TAA presentation and the main metric (aneurysm size) used to determine timing of interventional strategies. [PubMed: 28868310]
- 3. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation.* 2010; 121(13):e266–369. [PubMed: 20233780]
- 4. Saikrishnan N, Mirabella L, Yoganathan AP. Bicuspid aortic valves are associated with increased wall and turbulence shear stress levels compared to trileaflet aortic valves. *Biomech Model Mechanobiol.* 2015; 14(3):577–88. [PubMed: 25262451]
- **5. Sawada H, Rateri DL, Moorleggen JJ, Majesky MW, Daugherty A. Smooth Muscle Cells Derived From Second Heart Field and Cardiac Neural Crest Reside in Spatially Distinct Domains in the

Media of the Ascending Aorta-Brief Report. *Arterioscler Thromb Vasc Biol.* 2017; 37(9):1722–1726. It has long been known that there are boundaries between SMCs deriving from the second heart field in the aortic valve and the neural crest in the AA. This brief report shows that there is more mixing of SMCs across axial boundaries than previously thought and that there is a distinct transmural separation of SMCs from different origins in the AA. [PubMed: 28663257]

- *6. Humphrey JD, Schwartz MA, Tellides G, Milewicz DM. Role of mechanotransduction in vascular biology: focus on thoracic aortic aneurysms and dissections. *Circ Res.* 2015; 116(8):1448–61. This review summarizes multi-scale mechanobiology of the aortic wall as related to TAA. Genetic defects in matrix, integrin, or SMC contractility genes are known to cause TAA. The authors present the hypothesis that altered mechanosensing and mechanoregulation are common factors linking different genetic mutations to TAA pathology. [PubMed: 25858068]
7. Bell V, Mitchell WA, Sigurdsson S, Westenberg JJ, Gotal JD, Torjesen AA, Aspelund T, Launer LJ, de Roos A, Gudnason V, et al. Longitudinal and circumferential strain of the proximal aorta. *J Am Heart Assoc.* 2014; 3(6):e001536. [PubMed: 25523153]
8. Guo X, Kono Y, Mattrey R, Kassab GS. Morphometry and strain distribution of the C57BL/6 mouse aorta. *American Journal of Physiology - Heart & Circulatory Physiology.* 2002; 283(5):H1829–37. [PubMed: 12384460]
- **9. Bellini C, Bersi MR, Caulk AW, Ferruzzi J, Milewicz DM, Ramirez F, Rifkin DB, Tellides G, Yanagisawa H, Humphrey JD. Comparison of 10 murine models reveals a distinct biomechanical phenotype in thoracic aortic aneurysms. *J R Soc Interface.* 2017; 14(130) This manuscript collates biaxial mechanical data from 10 different mouse models of TAA tested in a consistent fashion. The authors find that increases in intrinsic circumferential material stiffness correlate with aneurysmal dilation.
10. Singh SD, Xu XY, Pepper JR, Izgi C, Treasure T, Mohiaddin RH. Effects of aortic root motion on wall stress in the Marfan aorta before and after personalised aortic root support (PEARS) surgery. *J Biomech.* 2016; 49(10):2076–2084. [PubMed: 27255604]
11. Ichikawa K, Sakuragi S, Nishihara T, Tsuji M, Mori A, Yokohama F, Wada T, Hasegawa D, Kawamoto K, Tanakaya M, et al. Influence of arterial stiffness on cardiovascular outcome in patients without high blood pressure. *Heart.* 2017
- **12. Prakash A, Adlakha H, Rabideau N, Hass CJ, Morris SA, Geva T, Gauvreau K, Singh MN, Lacro RV. Segmental Aortic Stiffness in Children and Young Adults With Connective Tissue Disorders: Relationships With Age, Aortic Size, Rate of Dilation, and Surgical Root Replacement. *Circulation.* 2015; 132(7):595–602. Retrospective analysis of MRI data from young patients with CTD that causes TAA was performed to compare aortic stiffness measurements to aortic dilation, prevalence of dissection and deaths, and surgical interventions. Higher aortic stiffness is associated with higher rates of dilation and surgical root replacement. The authors also find that vertebral artery tortuosity is a novel metric that correlates with aortic root replacement. [PubMed: 26115544]
13. Azadani AN, Chitsaz S, Mannion A, Mookhoek A, Wisneski A, Guccione JM, Hope MD, Ge L, Tseng EE. Biomechanical properties of human ascending thoracic aortic aneurysms. *Ann Thorac Surg.* 2013; 96(1):50–8. [PubMed: 23731613]
14. Lee JJ, Galatioto J, Rao S, Ramirez F, Costa KD. Losartan Attenuates Degradation of Aorta and Lung Tissue Micromechanics in a Mouse Model of Severe Marfan Syndrome. *Ann Biomed Eng.* 2016; 44(10):2994–3006. [PubMed: 27090893]
15. Chung J, Lachapelle K, Wener E, Cartier R, De Varennes B, Fraser R, Leask RL. Energy loss, a novel biomechanical parameter, correlates with aortic aneurysm size and histopathologic findings. *J Thorac Cardiovasc Surg.* 2014; 148(3):1082–8. discussion 1088–9. [PubMed: 25129601]
- *16. Kim J, Staiculescu MC, Cocciolone AJ, Yanagisawa H, Mecham RP, Wagenseil JE. Crosslinked elastic fibers are necessary for low energy loss in the ascending aorta. *J Biomech.* 2017; 61:199–207. Circumferential mechanical properties of the AA from three different newborn mouse models with severe defects in elastic fibers are compared. The authors find few differences in modulus values across groups, highlighting the adaptability of the developing AA. AAs with elastic fiber defects have large increases in energy loss with cyclic loading compared to control confirming the role of elastic fibers in providing reversible elasticity to the AA wall. [PubMed: 28778385]

17. Duprey A, Trabelsi O, Vola M, Favre JP, Avril S. Biaxial rupture properties of ascending thoracic aortic aneurysms. *Acta Biomater.* 2016; 42:273–285. [PubMed: 27345137]
- *18. Sommer G, Sherifova S, Oberwalder PJ, Dapunt OE, Ursomanno PA, DeAnda A, Griffith BE, Holzapfel GA. Mechanical strength of aneurysmatic and dissected human thoracic aortas at different shear loading modes. *J Biomech.* 2016; 49(12):2374–82. Most previous studies of TAA failure focus on uniaxial tensile tests. This study performs triaxial shear failure tests to better predict TAA failure under physiologic loading conditions. The authors find that TAA tissue has anisotropic failure behavior with significant differences between TAA failure stresses from patients with different disease causes (i.e. CTDs). [PubMed: 26970889]
19. Witzenburg CM, Dhome RY, Shah SB, Korenczuk CE, Wagner HP, Alford PW, Barocas VH. Failure of the Porcine Ascending Aorta: Multidirectional Experiments and a Unifying Microstructural Model. *J Biomech Eng.* 2017; 139(3)
20. Shahmansouri N, Alreshidan M, Emmott A, Lachapelle K, Cartier R, Leask RL, Mongrain R. Evaluating ascending aortic aneurysm tissue toughness: Dependence on collagen and elastin contents. *J Mech Behav Biomed Mater.* 2016; 64:262–71. [PubMed: 27526037]
21. Davis FM, Luo Y, Avril S, Duprey A, Lu J. Local mechanical properties of human ascending thoracic aneurysms. *J Mech Behav Biomed Mater.* 2016; 61:235–249. [PubMed: 27077532]
22. Sassani SG, Tsangaris S, Sokolis DP. Layer- and region-specific material characterization of ascending thoracic aortic aneurysms by microstructure-based models. *J Biomech.* 2015; 48(14): 3757–65. [PubMed: 26476765]
23. von Spiczak J, Crelier G, Giese D, Kozerke S, Maintz D, Bunck AC. Quantitative Analysis of Vortical Blood Flow in the Thoracic Aorta Using 4D Phase Contrast MRI. *PLoS One.* 2015; 10(9):e0139025. [PubMed: 26418327]
24. Francois CJ, Markl M, Schiebler ML, Niespodzany E, Landgraf BR, Schlensak C, Frydrychowicz A. Four-dimensional, flow-sensitive magnetic resonance imaging of blood flow patterns in thoracic aortic dissections. *J Thorac Cardiovasc Surg.* 2013; 145(5):1359–66. [PubMed: 22841438]
- **25. Cao K, Atkins SK, McNally A, Liu J, Sucusky P. Simulations of morphotype-dependent hemodynamics in non-dilated bicuspid aortic valve aortas. *J Biomech.* 2017; 50:63–70. While differences in hemodynamics have been demonstrated in dilated AA for BAV patients, it is unclear whether the changes are due to BAV geometry or the dilated AA geometry. This computational study simulates flow through the aortic valve with various BAV morphotypes and the normal TAV using the same AA geometry for each case. The authors find hemodynamic abnormalities in BAV cases that correlate with sites of AA dilation. [PubMed: 27855987]
- *26. Youssefi P, Gomez A, He T, Anderson L, Bunce N, Sharma R, Figueroa CA, Jahangiri M. Patient-specific computational fluid dynamics-assessment of aortic hemodynamics in a spectrum of aortic valve pathologies. *J Thorac Cardiovasc Surg.* 2017; 153(1):8–20 e3. Patient-specific computational fluid dynamics shows highly eccentric and helical flow in BAV cases. The BAV flow profiles cause high wall shear stress and lower oscillatory shear index in the greater curvature of the AA, which is the region prone to dilation. This study demonstrates that noninvasive hemodynamic measurements may prove useful for managing TAA treatment. [PubMed: 27847162]
27. Atkins SK, Cao K, Rajamannan NM, Sucusky P. Bicuspid aortic valve hemodynamics induces abnormal medial remodeling in the convexity of porcine ascending aortas. *Biomech Model Mechanobiol.* 2014; 13(6):1209–25. [PubMed: 24599392]
28. Lee JJ, D'Ancona G, Amaducci A, Follis F, Pilato M, Pasta S. Role of computational modeling in thoracic aortic pathology: a review. *J Card Surg.* 2014; 29(5):653–62. [PubMed: 25080972]
29. Majesky MW. Developmental basis of vascular smooth muscle diversity. *Arterioscler Thromb Vasc Biol.* 2007; 27(6):1248–58. [PubMed: 17379839]
30. Trigueros-Motos L, Gonzalez-Granado JM, Cheung C, Fernandez P, Sanchez-Cabo F, Dopazo A, Sinha S, Andres V. Embryological-origin-dependent differences in homeobox expression in adult aorta: role in regional phenotypic variability and regulation of NF-kappaB activity. *Arterioscler Thromb Vasc Biol.* 2013; 33(6):1248–56. [PubMed: 23448971]

31. Cheung C, Bernardo AS, Pedersen RA, Sinha S. Directed differentiation of embryonic origin-specific vascular smooth muscle subtypes from human pluripotent stem cells. *Nat Protoc.* 2014; 9(4):929–38. [PubMed: 24675733]
- *32. Granata A, Serrano F, Bernard WG, McNamara M, Low L, Sastry P, Sinha S. An iPSC-derived vascular model of Marfan syndrome identifies key mediators of smooth muscle cell death. *Nat Genet.* 2017; 49(1):97–109. Human dermal fibroblasts from MFS patients were used to generate iPSCs and then differentiated into embryonic-origin specific SMCs. MFS-iPSCs recapitulated traits seen in MFS AA including fibrillin-1 accumulation, matrix degradation, SMC contraction and apoptosis, and TGF- β dysregulation. The authors find that neural-crest derived SMCs, such as those found in the AA, are the most severely affected by MFS mutations. The authors confirm previous interventions that ameliorate disease traits and identify novel interventions that may be used for future disease treatment. [PubMed: 27893734]
33. Karimi A, Milewicz DM. Structure of the Elastin-Contractile Units in the Thoracic Aorta and How Genes That Cause Thoracic Aortic Aneurysms and Dissections Disrupt This Structure. *Can J Cardiol.* 2016; 32(1):26–34. [PubMed: 26724508]
34. Yamashiro Y, Papke CL, Kim J, Ringuette LJ, Zhang QJ, Liu ZP, Mirzaei H, Wagenseil JE, Davis EC, Yanagisawa H. Abnormal mechanosensing and cofilin activation promote the progression of ascending aortic aneurysms in mice. *Sci Signal.* 2015; 8(399):ra105. [PubMed: 26486174]
35. Kuang SQ, Medina-Martinez O, Guo DC, Gong L, Regalado ES, Reynolds CL, Boileau C, Jondeau G, Prakash SK, Kwartler CS, et al. FOXE3 mutations predispose to thoracic aortic aneurysms and dissections. *J Clin Invest.* 2016; 126(3):948–61. [PubMed: 26854927]
36. Wu D, Ren P, Zheng Y, Zhang L, Xu G, Xie W, Lloyd EE, Zhang S, Zhang Q, Curci JA, et al. NLRP3 (Nucleotide Oligomerization Domain-Like Receptor Family, Pyrin Domain Containing 3)-Caspase-1 Inflammasome Degrades Contractile Proteins: Implications for Aortic Biomechanical Dysfunction and Aneurysm and Dissection Formation. *Arterioscler Thromb Vasc Biol.* 2017; 37(4):694–706. [PubMed: 28153878]
37. Huang J, Wang T, Wright AC, Yang J, Zhou S, Li L, Yang J, Small A, Parmacek MS. Myocardin is required for maintenance of vascular and visceral smooth muscle homeostasis during postnatal development. *Proc Natl Acad Sci U S A.* 2015; 112(14):4447–52. [PubMed: 25805819]
38. Crosas-Molist E, Meirelles T, Lopez-Luque J, Serra-Peinado C, Selva J, Caja L, Gorbenko Del Blanco D, Uriarte JJ, Bertran E, Mendizabal Y, et al. Vascular smooth muscle cell phenotypic changes in patients with Marfan syndrome. *Arterioscler Thromb Vasc Biol.* 2015; 35(4):960–72. [PubMed: 25593132]
39. Forte A, Della Corte A, Grossi M, Bancone C, Provenzano R, Finicelli M, De Feo M, De Santo LS, Nappi G, Cotrufo M, et al. Early cell changes and TGFbeta pathway alterations in the aortopathy associated with bicuspid aortic valve stenosis. *Clin Sci (Lond).* 2013; 124(2):97–108. [PubMed: 22857993]
40. Albinsson S, Della Corte A, Alajbegovic A, Krawczyk KK, Bancone C, Galderisi U, Cipollaro M, De Feo M, Forte A. Patients with bicuspid and tricuspid aortic valve exhibit distinct regional microrna signatures in mildly dilated ascending aorta. *Heart Vessels.* 2017; 32(6):750–767. [PubMed: 28102444]
41. Rocchiccioli S, Cecchetti A, Panesi P, Farneti PA, Mariani M, Ucciferri N, Citti L, Andreassi MG, Foffa I. Hypothesis-free secretome analysis of thoracic aortic aneurysm reinforces the central role of TGF-beta cascade in patients with bicuspid aortic valve. *J Cardiol.* 2017; 69(3):570–576. [PubMed: 27298013]
42. Milleron O, Arnoult F, Ropers J, Aegerter P, Detaint D, Delorme G, Attias D, Tubach F, Dupuis-Girod S, Plauchu H, et al. Marfan Sartan: a randomized, double-blind, placebo-controlled trial. *Eur Heart J.* 2015; 36(32):2160–6. [PubMed: 25935877]
- **43. Cook JR, Clayton NP, Carta L, Galatioto J, Chiu E, Smaldone S, Nelson CA, Cheng SH, Wentworth BM, Ramirez F. Dimorphic effects of transforming growth factor-beta signaling during aortic aneurysm progression in mice suggest a combinatorial therapy for Marfan syndrome. *Arterioscler Thromb Vasc Biol.* 2015; 35(4):911–7. Using a MFS mouse model, the authors show that losartan acts through multiple pathways to inhibit aneurysm growth, not just through TGF- β as previously hypothesized. The authors also show that specific TGF- β inhibition

can either exacerbate or attenuate aneurysm growth depending on the timing of the intervention. [PubMed: 25614286]

44. Psaltis PJ, Puranik AS, Spoon DB, Chue CD, Hoffman SJ, Witt TA, Delacroix S, Kleppe LS, Mueske CS, Pan S, et al. Characterization of a resident population of adventitial macrophage progenitor cells in postnatal vasculature. *Circ Res.* 2014; 115(3):364–75. [PubMed: 24906644]
45. Kramann R, Goettsch C, Wongboonsin J, Iwata H, Schneider RK, Kuppe C, Kaesler N, Chang-Panesso M, Machado FG, Gratwohl S, et al. Adventitial MSC-like Cells Are Progenitors of Vascular Smooth Muscle Cells and Drive Vascular Calcification in Chronic Kidney Disease. *Cell Stem Cell.* 2016; 19(5):628–642. [PubMed: 27618218]
46. Majesky MW, Horita H, Ostriker A, Lu S, Regan JN, Bagchi A, Dong XR, Pocobutt J, Nemenoff RA, Weiser-Evans MC. Differentiated Smooth Muscle Cells Generate a Subpopulation of Resident Vascular Progenitor Cells in the Adventitia Regulated by Klf4. *Circ Res.* 2017; 120(2):296–311. [PubMed: 27834190]
- *47. Sandison ME, Dempster J, McCarron JG. The transition of smooth muscle cells from a contractile to a migratory, phagocytic phenotype: direct demonstration of phenotypic modulation. *J Physiol.* 2016; 594(21):6189–6209. SMC phenotype transition has been observed both in vivo and in vitro, however the timing and existence of a transition depends on the markers used to define SMC phenotype and many SMC markers are expressed by other cell types. The authors in this study used time-lapse microscopy to track the migratory and phagocytic behavior of freshly isolated SMCs in culture over time. They find that SMCs become motile and display macrophage-like behavior after a few days in culture. [PubMed: 27393389]
48. Hong X, Margariti A, Le Bras A, Jacquet L, Kong W, Hu Y, Xu Q. Transdifferentiated Human Vascular Smooth Muscle Cells are a New Potential Cell Source for Endothelial Regeneration. *Sci Rep.* 2017; 7(1):5590. [PubMed: 28717251]
49. Sulkava M, Raitoharju E, Mennander A, Levula M, Seppala I, Lyytikainen LP, Jarvinen O, Illig T, Klopp N, Mononen N, et al. Differentially expressed genes and canonical pathways in the ascending thoracic aortic aneurysm - The Tampere Vascular Study. *Sci Rep.* 2017; 7(1):12127. [PubMed: 28935963]
50. He R, Guo DC, Estrera AL, Safi HJ, Huynh TT, Yin Z, Cao SN, Lin J, Kurian T, Buja LM, et al. Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. *J Thorac Cardiovasc Surg.* 2006; 131(3):671–8. [PubMed: 16515922]
- *51. Jia LX, Zhang WM, Zhang HJ, Li TT, Wang YL, Qin YW, Gu H, Du J. Mechanical stretch-induced endoplasmic reticulum stress, apoptosis and inflammation contribute to thoracic aortic aneurysm and dissection. *J Pathol.* 2015; 236(3):373–83. The authors administer BAPN, a lysyl oxidase inhibitor to 3 week old C57BL6 mice for 4 weeks which causes TAA in the AA. The TAA ruptures in about 50% of the treated mice. The authors find significant SMC apoptosis in the TAA wall that is caused by ER stress due to increased mechanical stretch of the SMCs. Blocking ER stress in CHOP deficient mice decreases the incidence of TAA and subsequent rupture. [PubMed: 25788370]
52. Rateri DL, Davis FM, Balakrishnan A, Howatt DA, Moorlegghen JJ, O'Connor WN, Charnigo R, Cassis LA, Daugherty A. Angiotensin II induces region-specific medial disruption during evolution of ascending aortic aneurysms. *Am J Pathol.* 2014; 184(9):2586–95. [PubMed: 25038458]
53. Bersi MR, Khosravi R, Wujciak AJ, Harrison DG, Humphrey JD. Differential cell-matrix mechanoadaptations and inflammation drive regional propensities to aortic fibrosis, aneurysm or dissection in hypertension. *J R Soc Interface.* 2017; 14(136)
54. Trachet B, Piersigilli A, Fraga-Silva RA, Aslanidou L, Sordet-Dessimoz J, Astolfo A, Stampanoni MF, Segers P, Stergiopoulos N. Ascending Aortic Aneurysm in Angiotensin II-Infused Mice: Formation, Progression, and the Role of Focal Dissections. *Arterioscler Thromb Vasc Biol.* 2016; 36(4):673–81. [PubMed: 26891740]
55. O'Connell MK, Murthy S, Phan S, Xu C, Buchanan J, Spilker R, Dalman RL, Zarins CK, Denk W, Taylor CA. The three-dimensional micro- and nanostructure of the aortic medial lamellar unit measured using 3D confocal and electron microscopy imaging. *Matrix Biol.* 2008; 27(3):171–81. [PubMed: 18248974]

56. Meester JA, Vandeweyer G, Pintelon I, Lammens M, Van Hoorick L, De Belder S, Waitzman K, Young L, Markham LW, Vogt J, et al. Loss-of-function mutations in the X-linked biglycan gene cause a severe syndromic form of thoracic aortic aneurysms and dissections. *Genet Med*. 2017; 19(4):386–395. [PubMed: 27632686]
57. Jain D, Dietz HC, Oswald GL, Maleszewski JJ, Halushka MK. Causes and histopathology of ascending aortic disease in children and young adults. *Cardiovasc Pathol*. 2011; 20(1):15–25. [PubMed: 19926309]
- *58. Roccabianca S, Ateshian GA, Humphrey JD. Biomechanical roles of medial pooling of glycosaminoglycans in thoracic aortic dissection. *Biomech Model Mechanobiol*. 2014; 13(1):13–25. Finite element simulations show that medial deposits of glycosaminoglycans and proteoglycans in the TAA wall can lead to significant stress concentrations and Donnan swelling pressures that may facilitate delamination of the medial layers and initiate dissection. [PubMed: 23494585]
59. Dale M, Fitzgerald MP, Liu Z, Meisinger T, Karpisek A, Purcell LN, Carson JS, Harding P, Lang H, Koutakis P, et al. Premature aortic smooth muscle cell differentiation contributes to matrix dysregulation in Marfan Syndrome. *PLoS One*. 2017; 12(10):e0186603. [PubMed: 29040313]
60. Verstraeten A, Alaerts M, Van Laer L, Loeys B. Marfan Syndrome and Related Disorders: 25 Years of Gene Discovery. *Hum Mutat*. 2016; 37(6):524–31. [PubMed: 26919284]
61. Staiculescu MC, Kim J, Mecham RP, Wagenseil J. Mechanical behavior and matrisome gene expression in aneurysm-prone thoracic aorta of newborn lysyl oxidase knockout mice. *Am J Physiol Heart Circ Physiol*. 2017 ajpheart 00712 2016.
62. Kim J, Procknow JD, Yanagisawa H, Wagenseil JE. Differences in genetic signaling, and not mechanical properties of the wall, are linked to ascending aortic aneurysms in fibulin-4 knockout mice. *Am J Physiol Heart Circ Physiol*. 2015; 309(1):H103–13. [PubMed: 25934097]
63. Huang J, Davis EC, Chapman SL, Budatha M, Marmorstein LY, Word RA, Yanagisawa H. Fibulin-4 deficiency results in ascending aortic aneurysms: a potential link between abnormal smooth muscle cell phenotype and aneurysm progression. *Circ Res*. 2010; 106(3):583–92. [PubMed: 20019329]
64. Le VP, Yamashiro Y, Yanagisawa H, Wagenseil JE. Measuring, reversing, and modeling the mechanical changes due to the absence of Fibulin-4 in mouse arteries. *Biomech Model Mechanobiol*. 2014; 13(5):1081–95. [PubMed: 24526456]
- *65. Thunes JR, Pal S, Fortunato RN, Phillippi JA, Gleason TG, Vorp DA, Maiti S. A structural finite element model for lamellar unit of aortic media indicates heterogeneous stress field after collagen recruitment. *J Biomech*. 2016; 49(9):1562–1569. The authors develop a structural finite element model for a single medial layer of the aorta consisting of SMCs, the adjacent elastic lamellae, and collagen fibers. They incorporate collagen fiber architecture measured from TAV and BAV patients. The model predicts localized stress concentrations in the non-fibrous matrix due to collagen fiber disruptions at high stretch. [PubMed: 27113538]
66. Yeh HH, Rabkin SW, Grecov D. Hemodynamic assessments of the ascending thoracic aortic aneurysm using fluid-structure interaction approach. *Med Biol Eng Comput*. 2017
67. Wu J, Shadden SC. Coupled Simulation of Hemodynamics and Vascular Growth and Remodeling in a Subject-Specific Geometry. *Ann Biomed Eng*. 2015; 43(7):1543–54. [PubMed: 25731141]
- *68. Keshavarzian M, Meyer CA, Hayenga HN. Mechanobiological model of arterial growth and remodeling. *Biomech Model Mechanobiol*. 2017 The authors present a coupled agent-based model (ABM) and finite element analysis (FEA) to study bio-chemo-mechanical factors in blood vessel remodeling. The ABM incorporates 25 rules dictating cellular apoptosis, proliferation, and production of matrix and signaling molecules. The authors predict vessel remodeling in response to changes in blood pressure.

Highlights

- Most thoracic aortic aneurysms (TAAs) occur in the ascending aorta (AA).
- Bio-chemo-mechanical factors likely contribute to TAA susceptibility in the AA.
- Factors include solid and fluid mechanics, cell phenotype, and matrix composition.
- Multifactorial studies are needed to better understand and treat TAA.

Figure 1. Bio-chemo-mechanical factors in a mouse model of thoracic aortic aneurysm (TAA) Mice (SMKO) with a smooth muscle specific knockout of *Efemp2*, which encodes fibulin-4, have alterations in solid mechanics, possibly fluid mechanics, cell phenotype, and matrix composition that may contribute to TAA development, progression, and failure. SMKO AA has altered circumferential stretch-stress behavior compared to WT and increased stiffness at high stretch ratios (A) [64]. Fluid mechanics have not been quantified in SMKO AA, but are likely affected by the geometric differences compared to WT (B). Yellow latex was injected into the arterial tree for contrast and the heart was removed. The AA, major branches, and DA are visible. SMKO SMCs have increased cofilin dephosphorylation which leads to actin cytoskeletal remodeling and altered contractility (C) [34]. SMKO AA has fragmented elastic fibers and increased proteoglycans compared to wild-type (WT) (D). The lumen is at the top of each image. Harts stains elastic fibers black, while alcian blue stains proteoglycans blue.

Table 1

Examples of factors associated with solid mechanics, fluid mechanics, cell phenotype, and matrix composition that may contribute toward thoracic aortic aneurysm (TAA) development, progression, and failure in the ascending aorta (AA).

Examples of bio-chemo-mechanical factor in TAAs.			
<i>Solid mechanics</i>	<i>Fluid mechanics</i>	<i>Cell phenotype</i>	<i>Matrix composition</i>
Axial stretch	Flow profile	SMC embryonic origins	Elastic fiber defects
Stiffness	Vortex characteristics	SMC contractile phenotype	Collagen fiber defects
Energy loss	Peak shear stress	TGF- β signaling	Proteoglycan deposits
Failure behavior	Oscillatory shear stress	Progenitor cells	
		Inflammatory cells	