

Biomechanics and Pathobiology of Aortic Aneurysms

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Abstract Biomechanical weakening of the aorta leads to aneurysm formation and/or dissection and total biomechanical failure results in rupture, which is often fatal. The most common aneurysm is the abdominal aortic aneurysm (AAA) whereas thoracic aortic aneurysms (TAA) involve the ascending or descending segments of the aorta. Biomechanical strength of the aorta is maintained in part via balance between the integrity of the aortic medial and adventitial extracellular matrix and the health of the mural cells. From a biomechanical perspective, aneurysms rupture or dissect when wall stresses locally exceed the wall strength. Pathobiologic mechanisms, pre-disposing disorders and variability of patient demographic characteristics can weaken the aortic wall while increased blood pressure and dilatation increase the stress acting on it, leading to further aneurysm expansion. Thoracic and abdominal aortic aneurysms arise from very different pathophysiologies that ultimately result in a final common outcome of matrix degeneration and biomechanical failure. Therefore, the patient-specific knowledge of both wall stress and wall strength distributions for a given aneurysm will greatly improve the ability to identify those aortic aneurysms that are at highest risk of rupture. Towards this end, the biomechanics of AAA has been studied extensively by many groups whereas TAA biomechanics has not been fully considered. This chapter articulates the state-of-the-art

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of aortic biomechanics, including the modeling of tensile strength and wall stress distributions and the biological mechanisms which influence them. The potential clinical utility of these biomechanical estimates in predicting AAA rupture is also discussed.

1 Introduction

Aortic aneurysm is a consequence of biomechanical weakening of the vessel that leads to a local enlargement of the aorta over years but can rupture suddenly, often without warning. Thus, aortic rupture is a catastrophic failure of the vessel that is responsible for high mortality and morbidity. The most common aneurysm is the abdominal aortic aneurysm (AAA) whereas thoracic aortic aneurysms (TAA) involve the ascending or descending segments of the aorta. Dissection is another pathology in which the aortic wall dissects, thereby permitting the blood to enter the wall and causing enlargement. Biomechanical strength of the aorta is maintained in part via balance between the integrity of the aortic medial and adventitial extracellular matrix (ECM) and the health of the mural cells; namely, the medial smooth muscle cells and adventitial fibroblasts. This state of balance is known as tissue homeostasis and is essential for proper functioning of the aorta.

The diagnosis of an aortic aneurysm occurs principally via radiologic imaging of the aorta. Current clinical practice dictates that replacement of the aneurysmal aorta should be performed when the aneurysm size reaches 5.0–5.5 cm in maximum diameter for both TAAs [1] and AAAs [2–4]. However, rupture or dissection can occur at diameters <5.0 mm in 0–23% cases (Table 1) [5–9]. This wide discrepancy in rupture or dissection occurrence may be due to variability in the pathology of the aortic disease, which can be influenced by patient demographics, co-morbidities or pre-disposing conditions such as connective tissue disorders. Furthermore, studies reporting rates of rupture are limited by lack of information regarding the diagnosis criteria and post-mortem studies [7, 10] and are likely unreliable due to diameter measurement discrepancies [5]. Clearly, a patient-specific approach would be desirable for more reliable rupture or dissection risk predictions to improve clinical management, and tailoring a prognosis and treatment course unique to the patient.

From a biomechanical perspective, aneurysms rupture or dissect when wall stresses locally exceeds the wall strength. Pathobiologic mechanisms, pre-disposing disorders and variability of patient demographic characteristics tend to weaken the aneurysm wall [11–13] while increased blood pressure and aneurysmal enlargement increase the stress acting on it [14, 15], leading to further aneurysmal expansion. This cycle continues as the aneurysm enlarges eventually ruptures or dissects, unless repaired or the patient succumbs to other causes.

The earliest predictions of wall stress used the law of Laplace (Eq. 1) as the theoretical basis for using the “maximum diameter” as the criterion for predicting AAA rupture potential. This law states that wall tension (T) increases in proportion

Table 1 Adapted from Darling et al. [7]; Vorp and Vande Geest [236]

Size, cm	N ruptured	N unruptured	Total	% Ruptured
≤5.0	34	231	265	12.8
>5.0	78	116	194	40.0
No size recorded	6	8	14	43.0
Total	118	355	473	24.9

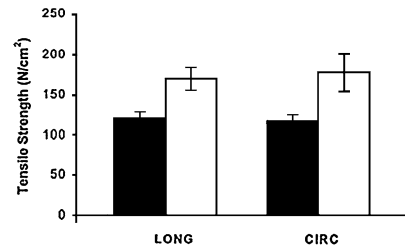
to an increase in the intraluminal pressure (P), an increase in diameter D(R) or a decrease in wall thickness (t).

$$T = (P \times D)/2t \quad (1)$$

The law of Laplace has two major fallacies for its application in biomechanics. First, the aorta is not a simple cylindrical or spherical shape of uniform radius of curvature for which the law of Laplace is valid. Rather, the geometry of the aortic wall is complex, containing a greater and lesser curvature, and these vary spatially [16, 17]. Therefore, the maximum diameter criterion to predict rupture risk ignores the important roles of vessel wall topography and geometry. This notion is supported by studies which demonstrated that stress on the wall is dependent on wall shape unique to each aneurysm [15, 16, 18]. Secondly, rupture predictions based on only the wall stress are not sufficient because a region of the aneurysmal wall that is under elevated wall stress may also have higher wall strength, thus equalizing its rupture potential. The wall strength will have spatial variance within a given aneurysm and also from patient-to-patient [19–21]. The rupture potential is highest in the location of peak ratio of wall stress to wall strength. However, risk analysis for rupture based upon the maximum diameter criterion is improved when a measurement of peak wall stress is also considered [22–24]. Ruptured AAAs demonstrated higher peak stress compared to diameter-matched electively repaired AAAs [12]. Clearly, the ability to noninvasively predict the locally acting wall stress and wall strength of an aortic aneurysm on a patient-specific basis will provide a more accurate diagnostic tool for evaluating the high risk of failure of an aortic aneurysm. Preliminary efforts toward this end have been reported [18, 25–28].

Although the in vivo wall strength distribution of an aneurysm can only be estimated [29], biomechanical experimental testing has been performed to assess ex vivo the biomechanical behavior of the aneurysmal and non-aneurysmal human aorta. Several studies have found that aneurysmal tissue is substantially weaker and stiffer than normal aorta [11, 12, 26, 29–31]. The aorta displays anisotropic biomechanical strength that is spatially dependent in both ascending [32–34] and abdominal [20, 31] segments. For both aneurysmal and non-aneurysmal aorta, the longitudinal segments were stiffer than segments measured in the circumferential orientation (Fig. 1) [32, 33]. Perhaps the most important piece of biomechanical data is the finding that tensile strength does not appear to be related to aneurysm diameter [33]. Hence, aortic diameter is not the only determinant of either wall strength or wall stress [15], and rupture risk prediction criteria that account solely for aortic diameters do not offer a complete picture of the true risk for

Fig. 1 Tensile strength of human thoracic aortic aneurysms (*black bars*) in the longitudinal (LONG) and circumferential (CIRC) orientations and non-aneurysmal controls (*white bars*). Bars present mean \pm SEM. (Adapted from Fig. 2 of Vorp et al. [33])



aortic failure. Other criteria have been proposed for rupture prediction models such as rate of aneurysm growth [3, 35, 36], stiffness [37] intraluminal thrombus (ILT) thickness in AAA [38], wall tension [8] and peak AAA wall stress [22–24]. However, all these were empirical approaches and have their limitations and could potentially lead to sometimes fatal errors in the decision pertaining to clinical management of AAA and TAA. Using a concept of the Rupture Potential Index (RPI) proposed and preliminarily applied by Vorp et al. [26–28] demonstrated for AAA that this new index may hold promise for a patient-specific diagnostic assessment. The RPI, which is the ratio of acting wall stress to the wall strength at a particular point on the aneurysm wall, was found to be higher in AAA that ruptured compared to those that did not rupture. Currently, there is only one model to assess the RPI of AAAs that has been used recently [28, 39]. Indeed, significant differentiation of rupture risk by RPI was found for aneurysm diameter ranging between 55 and 75 mm of asymptomatic and symptomatic/ruptured AAAs where the maximum diameter criterion failed to adequately predict risk [28].

Thoracic and abdominal aortic aneurysms are thought to arise from different, very distinct pathophysiologies. However, both pathologies culminate to a final common pathway of matrix degeneration and biomechanical failure. Aneurysms of the thoracic aorta are generally non-inflammatory in nature and are related to connective tissue disorders such as Marfan, Ehlers-Danlos or Loeys-Dietz syndrome, the presence of a congenital defect such as the bicuspid aortic valve (BAV) or other familial aortic disease. TAAs and dissections can also arise from non-genetic pathologies including Takayasu's arteritis [40], giant cell arteritis [41], or tuberculous mycotic infection [42] and these conditions involve an inflammatory component. Aneurysms arising from these causes are less common than those of a genetic basis.

Matrix metalloproteinases (MMPs) are over-expressed in aortic aneurysms [43–46] specifically in TAAs [47–50] MMPs control degradation of elastin and collagen [51] and rupture or dissection occurs when the physiologic forces exerted on the vessel wall exceed its strength. Although AAAs exhibit marked inflammatory changes and associated atherosclerosis [52–59] there is a lack of evidence of an inflammatory component in TAAs [60–62]. This non-inflammatory phenomena is uniformly consistent with aortopathies of the ascending aorta, of which, key effector proteins inciting the phenotype have been identified for the Marfan (*fibrillin-1*) [63], Loeys-Dietz (*TGF- β R*) [64], and Ehlers-Danlos-vascular type

(*Type III collagen*) [65] syndromes and familial forms of TAAs, including mutations in genes that regulate SMC contractility (α -smooth muscle actin (SMA) (*ACTA2*) and smooth muscle myosin heavy chain (*SM-MHC*) [66, 67]). The presence of a BAV also predisposes the patient to development of TAA and/or dissection in addition to aortic stenosis or insufficiency. [44, 45, 68–72]. The incidence of BAV overlaps with α -SMA and *TGF- β R* mutations at a frequency of 2.5–3% [73] but no gene or pathway responsible for inciting TAAs in BAV patients has been identified.

Common histopathological evidence for many incidences of TAAs include non-inflammatory smooth muscle cell loss, fragmentation of the elastin fibers, mucoid degeneration, and accumulation of proteoglycans within areas of cell depletion. These phenomena are collectively termed “cystic medial degeneration” or CMD and are observed within the medial layer of the aortic wall [45, 48, 60–62, 74, 75]. Development of AAAs often includes a contribution from inflammatory cells as increased MMP production by macrophages and occurrence of ILT which are generally absent in TAAs. The differing pathobiologies involved in aneurysm formation in the thoracic and abdominal aortas likely results in variations in the mechanical stresses and wall weakening associated with each type of aneurysm with patient-to-patient nuances. Hence, the clinical recommendation for patient management will depend upon understanding, with patient specificity, the role of biomechanics in diagnosis, counseling, monitoring and treating patients at risk for and presenting with, aortic aneurysm and determining their relative risk for rupture.

This chapter will detail the relative biological mechanisms that contribute to aneurysm formation in both the thoracic aorta and abdominal aorta and their role in vessel wall biomechanics, which ultimately leads to aneurysm formation and potential rupture of the aorta through weakened strength and increased stress.

2 Biological Mechanisms that Impact Mechanical Properties of the Aneurysmal Thoracic Aorta

2.1 Marfan Syndrome

Marfan syndrome (MFS) is a hereditary connective tissue disorder that is autosomal dominant and manifests in several organs including those of the cardiovascular, ocular and skeletal systems. Patients with MFS display a definitive body habitus, namely a tall stature and wing span that exceeds the height, arachnodactyle, craniofacial defects, pectus excavatum or carinatum. Ectopia lentis may occur in up to 80% of patients, usually bilaterally. MFS has widespread clinical presentation but the most dangerous and often lethal manifestation of the disorder is acute aortic dissection.

Aortic dissection often occurs after a period of progressive aortic dilation and involves weakening of the vessel wall. In MFS, this weakening results at least in

part due to degeneration of the minute architecture of the extracellular matrix (ECM). In 1991, mutations in the fibrillin-1 (*fbn1*) were identified as the cause of MFS [63]. Fibrillins are ECM proteins that comprise microfibrils, which are the key connectors between elastin and collagen to local cells in the microenvironment. These microfibrils are essential for not only the microarchitecture of the tissue, but also provide substantial biomechanical support. Similar to fibrillins, a related protein family, the latent TGF- β -binding proteins (LTBPs) participate in both structure of the matrix and also function as signaling molecules to direct cell behavior. LTBPs directly interact with TGF- β to sequester the growth factor within the tissue microenvironment and thus regulate the bioavailability. When bound to LTBPs, TGF- β isoforms cannot interact with their receptors and therefore, signaling activity is attenuated. LTBPs retain TGFs within the matrix, keeping them at the ready to be released in their active state and capable of receptor binding. Fibrillins are similar in structure to LTBPs. Both are cysteine-rich with multiple epidermal growth factor (EGF)-like domains that bind calcium [76]. An 8-cysteine module, which is distinct only to fibrillins and LTBPs may be critical for microfibril assembly [77] and also be responsible for interactions with TGF- β [78–79].

Fibrillins interact with TGF- β s as the microfibrils of the ECM. These microfibrils self-assemble and interact with integrins on the cell surface and other matrix molecules within the microenvironment. Fibrillins can be viewed as a physical tether between local cells and their matrix and contain the known integrin-interacting sequence RGD to support cell adhesion [80–82]. The amino acid sequence RGD serves as code for cell adhesion to matrix molecules and provides a means for direct cell–matrix interactions. Such interactions are essential for integrity of the matrix and the biomechanical strength of the tissue. In the case of the aorta, the elastic laminae are connected to the endothelial cells on the intimal side and the SMCs of the medial layer. Fibrillin-based microfibrils provide this connectivity between matrix and cells which contributes to stability of the tissue. Mice lacking these connections displayed increased elastin degradation and alterations in SMC phenotype in an apparent attempted repair mechanism to sustain loss of matrix. These defenses also include an increase in the MMPs that are induced as part of the remodeling process, but unfortunately mediate further degeneration of the matrix and contribute to weakening of the vessel. When cells are no longer physically linked to their matrix, they cannot sense the ongoing needs of the matrix for homeostasis. Cell–matrix interactions are a constant dynamic dialogue and exchange of information. Loss of cell–matrix connections is itself a signal to rebuild because the cell senses a matrix deficit. However, loss of cell-ECM connections is also a trigger for apoptosis which is a self-initiated program of induced cell death. SMC apoptosis is a characteristic of aortic diseases and vessel weakening and in the case of MFS, may stem from improperly formed fibrillin-based microfibrils.

The fibrillin microfibrils elicit their structural contribution to matrix homeostasis by providing a template for tropoelastin deposition. The microfibril network provides elasticity in elastin-based and non-elastin tissues. Normal organization of

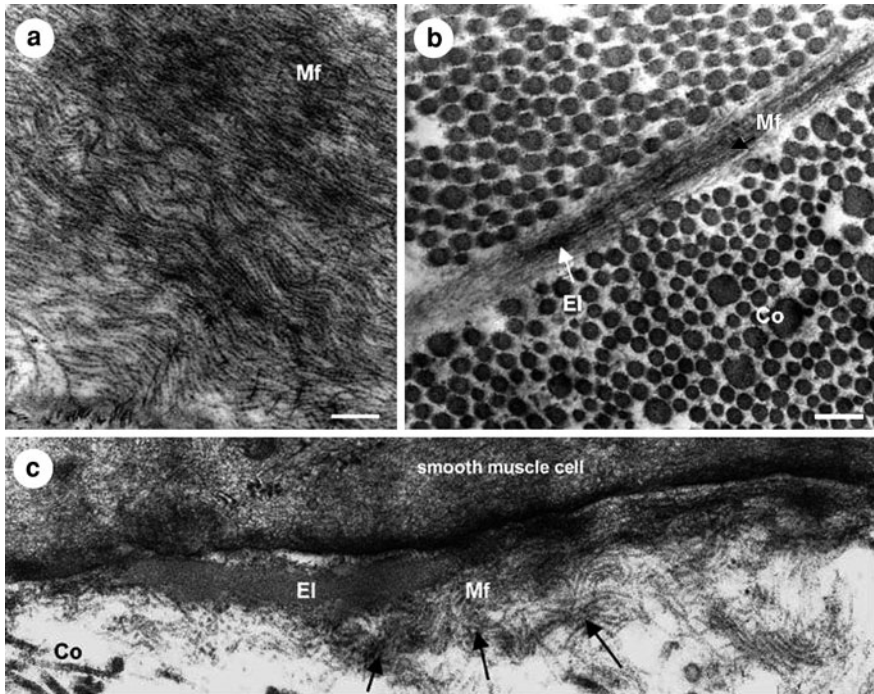


Fig. 2 Fibrillin microfibrils in (a) lobster aorta and mouse aorta (b, c). Mf=microfibrillar mantle; El=elastin; Co=collagen fibrils. Scale bar is 400 μm . (Reproduced from Fig. 1, Kielty et al. [83])

the microfibrils involves self-assembly of the fibrillin in moderately tight bundles of fibers that are oriented parallel to each other. The strength of the microfibrils is spatially dictated and controlled not only by the cells within the tissue, but also the forces upon which the tissue is subjected to. For this reason, microfibrils are often found within tissues that need to withstand considerable mechanical stress such as bone, and blood vessel, serving as anchors for various connective tissues (Fig. 2) [83]. In the MFS patient, mutations in fibrillin result in reductions in synthesis and deposition of fibrillin within the ECM and improper assembly of the microfibril bundles. These defects in fibrillin expression and organization are likely to impact the dual function of fibrillin as a regulator of TGF- β signaling and a biomechanical support for the aorta.

There are over 600 mutations of the Fbn1 gene. The majority of the mutations are point mutations, with some being nonsense or missense mutations. Substitutions of cysteine residues that alter the disulfide bonds within the EGF or 8-Cys modules are the most frequent mutations, while other common mutations involve the calcium binding region. These alterations affect the organization of the fibrillin into microfibril bundles and substantially impact their ability to bind TGF- β , interact with the cell surface and orient properly to guide elastin deposition in the matrix. These shortcomings will ultimately contribute to reduced and possible

failure of vessel biomechanical strength and result in a lethal rupture of the ascending aorta in MFS patients. A mouse model of MFS, the *Fbn1* knockout support the theory that fibrillin-rich microfibrils significantly contribute to the overall biomechanical strength of the aorta. *Fbn1*^{-/-} mice die within one year of birth due to aortic dissection and rupture. Although elastin fibers appear normal at birth, aneurysm initiates within 2 weeks of birth and continues to enlarge with time [84]. There is elastin degradation and disorganization along with considerable loss of fibrillin-1 [85]. SMCs adopt a synthetic phenotype in attempt to repair the insufficient ECM. These phenomena progress to elastin breakdown initiating from the adventitia and moving inward to the media. Aortic dilatation, aneurysm, dissection and rupture then coalesce. Microfibrils work together with elastin to provide biomechanical support to the aorta [86]. Fibrillin deficiency is related to increased aortic stiffness and decreased compliance, possibly due to a compensatory role for collagen to endure the bulk of load bearing in the absence of adequate fibrillin and elastin. Fibrillin works together with elastin to regulate the pressure-diameter relationship of the aortic wall. The biomechanical function of fibrillin-1 microfibrils is dependent upon its proper expression, assembly and incorporation. Details of the molecular assembly of fibrillin 1 into complex microfibrils are not completely understood. However, recombinant approaches have allowed the investigation of various domains on fibrillin molecular assembly into the higher-order microfibrils. Inter-molecular cross-linking is known to be driven by tissue transglutaminase to form dimers with disulfide bonds and furin processing appears to accelerate but is not essential for this event. However, it remains to be seen if these biochemical manipulations occur in vivo to maintain aortic biomechanics. The vital role of fibrillin-1 in aortic homeostasis targets this protein as a focus of extensive research for eventual therapeutic intervention for the care of MFS patients.

Mutations in fibrillin that impair its TGF- β -binding role lead to increases in free TGF- β and excessive signaling of this pathway. This led investigators to hypothesize that TGF- β played a role in aortic dilation in MFS patients. TGF- β neutralizing antibodies prevent elastin breakdown in *fbn*^{-/-} mice but such a therapy lacks clinical feasibility. Losartan, an angiotensin (Ang) II inhibitor also antagonizes TGF- β signaling. As a currently FDA-approved drug, losartan is widely successful medication used to treat hypertension. While blood pressure control is commonly sought in patients with MFS and aortic aneurysm, a means to attenuate or reverse matrix damage in the vessel wall and maintenance of biomechanical stability of the aorta to prevent rupture is necessary. Treatment of *fbn*^{-/-} mice with losartan effectively prevented matrix degradation in the ascending aorta and mice were phenotypically and histologically indistinguishable from wild-type mice [85]. This treatment was also effective in preventing aortic root dilatation in children [87]. Losartan may prevent dilation through two mechanisms: (1) decrease in the absolute blood pressure or rate of change in blood pressure reduces the effect of hemodynamics on the already compromised aortic wall due to fibrillin mutations and/or (2) inhibition of TGF- β signaling through regulation of the Ang II type I receptor (AT1). How TGF- β signaling regulates matrix homeostasis

remains unclear but may be due to altered SMC phenotype and synthesis of new matrix proteins in effort to remodel a matrix damaged by degradation. Furthermore, since TGF- β s are important for growth and development, it will be important to include tissue targeting strategies in any therapeutic drug design in order to limit the potential deleterious side effects of TGF- β on normal development and renal function [87, 88].

MFS patients present clinically with manifestations of this connective tissue disorder in several organ systems. A multitude of mutations in fibrillin have been identified that may contribute to the diseases. However, fundamentally, the microfibrils of the ECM are composed of fibrillin and when improperly synthesized, assembled or maintained, alterations in biomechanical stability and growth factor signaling through TGF- β are significantly altered. These mechanisms contribute to degradation of the ECM through elastolysis and SMC loss and culminate in reduced biomechanical strength, progressive weakening of the vessel wall, aortic aneurysm, dissection and the highly-fatal rupture. However, to our knowledge, no *ex vivo* mechanical testing has been conducted on the ascending aorta of the MFS patient population. There have been some reports that used noninvasive ultrasonography to demonstrate that MFS patients have increased stiffness of the infrarenal aorta and decreased strain, despite normal aortic diameters [89]. *Ex vivo* mechanical testing has been limited to mouse models of MFS. Increased stiffness was reported in carotid arteries and aortae of *fbn1*^{-/-} mice and elastin and fibrillin were shown to provide the primary biomechanical strength of the tissue [86, 90]. Efforts to further understand the role of these biological mechanisms on the individual efforts of each matrix molecule on the overall biomechanical strength of the vessel itself should be pursued in depth in order to develop better treatments for patients with MFS.

2.2 *Loeys-Dietz Syndrome*

Loeys-Dietz syndrome (LDS) is an autosomal dominant disorder linked to mutations in the TGF- β receptors (TGFBR1 and TGFBR2) [64]. In addition to a pre-disposition for TAA, LDS patients exhibit other manifestations of this connective tissue disorder such as craniosynostosis, bifid uvula, cleft palate and translucent skin [91]. The histopathologic observations of the aorta in LDS patients are consistent with those of other TAAs including CMD, increased collagen deposition, elastin fragmentation and lack of an inflammatory response [92]. Interestingly, the mutations in TGFBRs result in excessive TGF- β signaling rather than inhibited signaling. This leads to effects similar to those observed for MFS and underscores the importance of TGF- β s in regulating vascular tissue homeostasis. In LDS patients, contrary to expectation, increased collagen deposition was observed, accompanied by elevated connective tissue growth factor (CTGF) expression and nuclear Smad2 localization [64, 91] which are all clear indicators of enhanced TGF- β signaling. CTGF is directly regulated by TGF- β via the Smad2

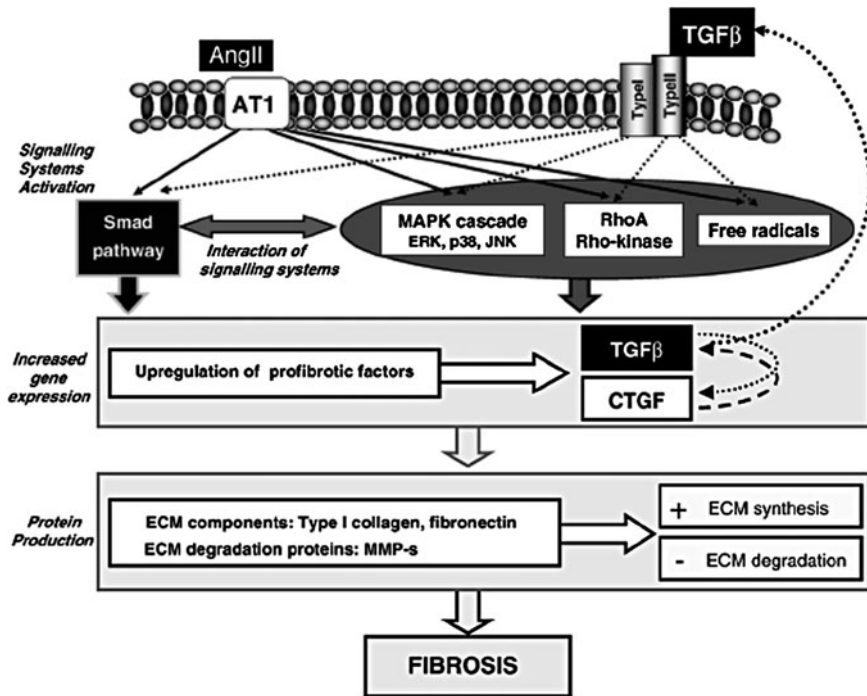


Fig. 3 Pathways of vascular fibrosis involving Ang II and TGF- β . (Figure 3 from Ruiz-Ortega et al. [94])

pathway and promotes proliferation and ECM production by fibroblasts and SMCs. The up-regulation of CTGF could propagate excessive TGF- β signaling via attenuation of the inhibitory Smad7, a key component of the TGF- β feedback loop [93]. CTGF has also been shown to regulate TGF- β responses and inhibition of CTGF can reduce TGF- β -induced collagen synthesis, while elevated levels of CTGF directly contribute to ECM accumulation (Fig. 3) [94]. As tissue homeostasis relies on a balance between organized matrix deposition and matrix degradation, TGF- β also elicits control over the remodeling process by activating inhibitors of tissue proteases such as plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitors of the MMPs (TIMPs). These observations are counter-intuitive since aneurysm development is well known to include over-production of the ECM degenerative MMPs and calls into question the relative role of MMPs as instigators of aneurysm formation. Perhaps the causal agents lie upstream in the signaling cascade and initiate a faulty remodeling process which results in an improperly formed ECM, lacking sufficient biomechanical integrity. MMPs are essential for normal remodeling, evidenced in other tissues such as the skeletal system where ECM fragments are stimulators of new, organized matrix deposition. These apparently synergistic effects of TGF- β and CTGF create a fibrosis-like state of the aortic ECM in LDS patients, where biomechanical integrity is

compromised. It has been well-established that both TGF- β and CTGF are potent fibrotic agents in many tissues; however the challenge that remains is devising an intervention at the molecular level to prevent these signaling events that cause impaired collagen deposition. CTGF, as a down-stream modulator of TGF- β -mediated fibrosis is an attractive target for therapeutic intervention to prevent collagen accumulation and matrix disorganization.

Fibrosis occurs as a result of tissue defense to an assault or injury and represents a poorly repaired tissue, lacking adequate biomechanical properties. Often there is excessive insoluble collagen with improperly formed cross-links or poorly organized into fibrils. More collagen does not translate to increased strength. However, unlike fibrosis, this accumulated collagen in TAA patients occurs in the absence of an inflammatory response. Contrary to MFS, there have been no studies measuring the biomechanical strength of the aorta in LDS patients. However, given the disruption of the TGF- β signaling cascade, it is reasonable to hypothesize, that dysregulation of collagen synthesis and factors that regulate matrix remodeling such as MMPs and inhibitors of tissue proteases will significantly impact the biomechanical integrity of the matrix and the vessel wall as a whole. The direct contributions of each pathway or mechanism on the biomechanical strength will likely be determined through a combination of animal models and targeted interrogation of particular molecules in the signaling cascade, complemented by analysis of the biomechanical properties of the aneurysmal aorta. Within any given tissue niche, the cell senses the needs of the matrix and responds in kind to remodel, repair, or regenerate and disruptions upstream can have devastating effects that contribute to the pathogenesis of the connective tissues. To avoid surgical intervention, medical therapies should target correction of the upstream events (i.e., TGF- β signaling) to prevent the deleterious effects of an improperly organized and maintained ECM on aortic biomechanics.

In the LDS patient, medical intervention with Ang II receptor inhibitors to combat the effects of increased TGF- β signaling in LDS patients may show similar to promise as treated MFS patients, but to date, no conclusive efficacy studies have been performed.

2.3 Ehlers-Danlos Syndrome

In patients with Ehlers-Danlos syndrome (EDS), the predilection for vascular abnormalities is rupture or dissection of the first-order branch arteries but aortic dissection and rupture do also occur [70]. EDS patients show clinical manifestation of the disorder as hyperextensibility of the skin which is thin and translucent, hypermobility of joints, extensive bruising, rupture of the arteries, intestines and uterus. The leading cause of death for EDS patients is rupture or dissection of thoracic or abdominal medium-large vessels and this often occurs when the patient age is in the fifties. Clinical management is very difficult in these patients because the vascular tissue is extremely fragile and is not easily sutured. Therefore,

surgical intervention often leads to further complications and increases the risk for aortic catastrophe [70]. Expert opinion promotes regular monitoring of EDS patients by CT or MR angiography of the vasculature but there are no well-established guidelines for elective intervention [70]. The EDS patient is extremely difficult to treat due to the high risk of operative treatment and the lack of understanding of the appropriate mechanism to target for medical intervention.

Of the at least 12 known types of EDS with various genetic bases, there are 6 types that are associated with thoracic aortic disease [95]. Over 70 mutations have been linked to EDS and patients displaying the vascular effects of EDS (type IV) are known to have a mutation in the gene encoding type III procollagen [65, 96]. Mutations in type V alpha 1 procollagen have also been reported for EDS patients with arterial rupture [97].

Type III collagen, along with Type I collagen is a predominant form of collagen in the aortic media and is synthesized by aortic SMCs [98, 99]. The effects of Col3a1 mutation has been difficult to analyze due to lack of a successful animal model. Mutations achieved through targeted ablation of Col3a1 showed aortic dissection and bruising of the skin, however only 5% of homozygous mice survived at weaning and most died within 48 h of birth. Recently, a new mouse model with spontaneous mutation of the Col3a1 gene was identified serendipitously whilst investigating the role of Mro in sexual development [100]. These mice died of aortic dissection of the descending thoracic and abdominal aorta with no evidence of inflammation. While there was no difference in overall collagen gene expression, histological analysis of collagen deposition showed an overall decrease in collagen content in the aortic adventitia. Transmission electron microscopy displayed disrupted collagen as well as elastin fibers (Fig. 4). The investigators also provided evidence of normal TGF- β signaling as well as lack of hypertension in col3a1-mutated mice. This model should prove useful in future investigations of the role of Type III collagen in the microarchitecture of the aorta. Since the adventitia has long been recognized as providing substantial biomechanical support for the aorta, disruption in Col3a1 may abrogate this role of the adventitia in EDS IV patients. Improperly formed collagen fibrils probably provide less strength against hemodynamic forces and lead to dissection, rather than aneurysm. The mouse model described by Smith et al. [100] also brings to light a putative role for Type III collagen in maintaining the layers of SMCs and the collagen/elastin matrix within the aorta. Evidence of shearing between layers was observed with infiltration of red blood cells. This is primary evidence for impending dissection. Therefore, the biomechanical contribution of Type III collagen may be to protect inter-layer strength and mutations in this key ECM protein may place the patient at risk for rupture by aortic dissection. While Type I collagen is thought to provide most of the tensile strength of the aorta and organize as thicker fibers, Type III collagen is found as thinner fibers in close association with elastin where it can participate in recoil capabilities [101]. A point mutation was identified in a patient with EDS IV, located in one of the Gly-X-Y backbone sequences of the alpha chain [102]. The mutation causes the Gly to become a Glu and given that Gly is required for the triple-helical structure of the collagen fiber, this mutation

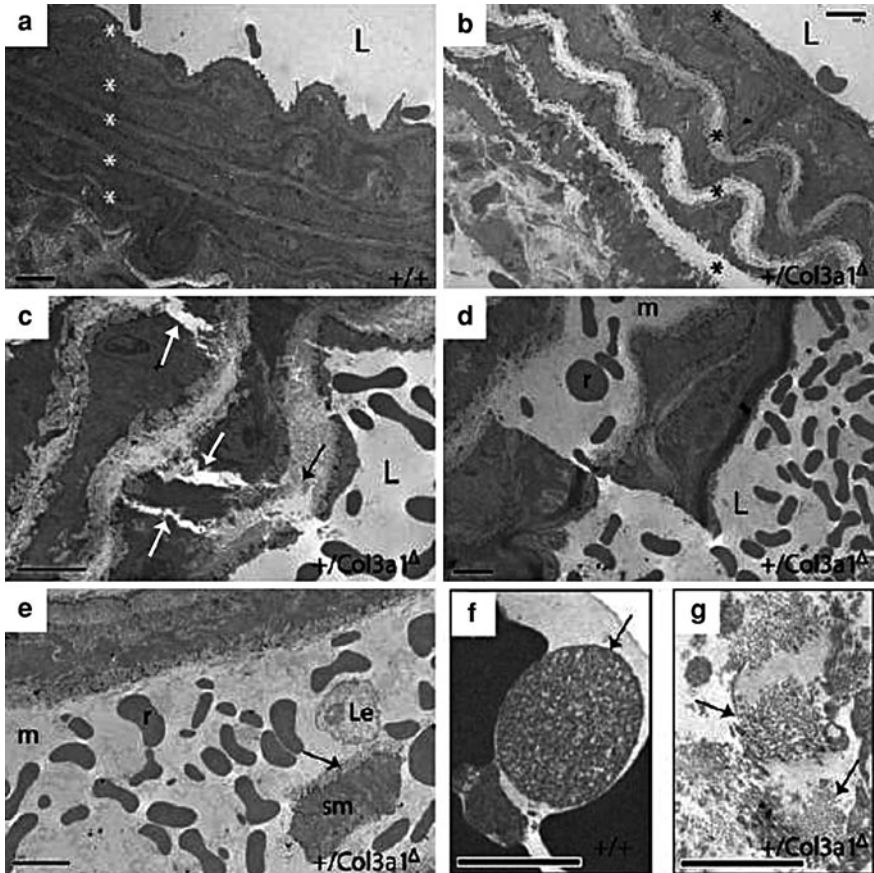
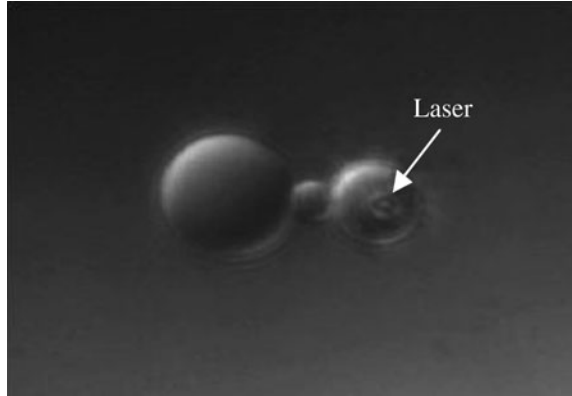


Fig. 4 Transmission electron microscopy of aortas from $+/\text{Col3a1}^{\Delta}$ mice display abnormalities in matrix architecture. **a** Normal $+/\text{Col3a1}^{\Delta}$ mice show regular continuous elastin (*) while there is reduced density of elastin (*) in $+/\text{Col3a1}^{\Delta}$ mice (**b**). The elastin lamellae is discontinuous (*black arrows*) and dissection through the media layer is also noted in $+/\text{Col3a1}^{\Delta}$ mice (*white arrows*) (**c**). There is evidence of erythrocyte infiltration within the medial layer in (**d**) and (**e**) and the elastin lamellae (*arrow*). Collagen fiber abnormalities are evident as shown (**f**) and (**g**) (*arrows*). L=lumen; m=media; r=erythrocytes; sm=smooth muscle; Le=leukocyte. Scale bar=5 μm for **a–e** and 2 μm for **f, g**. (Figure 4 from Smith et al. [100])

de-stabilizes the collagen within the aorta and likely compromises its biomechanical integrity.

Collagen fiber strength is dependent on its cross-links formed between adjacent helical domains. The mechanical properties can be altered when cross-linking is modified either chemically or physically. The enzyme lysyl oxidase (Lox) catalyzes formation of lysine or hydroxylysine cross-links. Lox expression parallels that of Type I and III collagens [103–105]. Enzymatic activity of Lox is dependent on copper for the transfer of electrons to and from oxygen for delamination of peptidyl lysyl groups on collagen and elastin [106]. Furthermore, variations in

Fig. 5 Demonstrate of using optical tweezers to measure force of stretching a single collagen molecular. Such technology will be useful for characterizing the biomechanical properties of collagen fibrils. (Figure 1 from Sun et al. [110])



copper metabolism have long been linked to EDS type IX which has clinical manifestations including bladder diverticula, skin hyperelasticity and skeletal abnormalities [107]. In patients with impaired copper metabolism, a reduction in *Lox* expression and decreased collagen cross-linking in cultured skin fibroblasts was reported. Inactivation of *Lox* has also been linked to aortic aneurysm formation and death in a mouse model [108]. Mutations in Type III collagen that alter collagen fiber assembly may also negatively impact the cross-linking by *Lox* by directly altering the sites for cross-link formation which are critical to the biomechanical function of the collagen fibers.

There is also an established link between EDS patients and mutations in TGFBRs, accompanied by elevated TGF- β signaling, similar to LDS patients. It is also thought that reduced expression of Type III collagen may be compensated for by enhanced TGF- β in an ineffective attempt to rebuild a deficient matrix. It has also been proposed that cellular response to TGF- β within the aortic wall differ by cell type as reviewed recently by Jones et al. [109]. During the process of aneurysm formation or other forms of vascular injury, the relative proportion of SMCs, fibroblasts and myofibroblasts changes and the phenotype of SMCs is also altered toward the undifferentiated, synthetic state. It is important to understand the molecular nuances of TGF- β signaling in the normal and aneurysmal aorta in order to ascertain the role of these pathways on the overall tissue homeostasis. Balanced interplay between cells and matrix ultimately drives maintenance of adequate biomechanical strength to support the efforts of the heart to deliver blood throughout all body tissues. There are clues in the biochemical pathways, but the real knowledge of tissue homeostasis lies with biomechanical analysis of the tissue itself.

As with MFS and LDS patients, to date, the biomechanical strength of ascending aorta from EDS patients has not been investigated using *ex vivo* approaches. The work of Sun et al. [110] using optical tweezers offers another strategy to quantify the strength of individual collagen fibers from native tissue or those produced by culture cells *in vitro* (Fig. 5). These analyses could allow the interrogation of mutated forms of collagen produced recombinantly to determine the role of particular collagens and collagen structure on the biomechanical

strength of the aorta and the causal role of mutations in EDS. Understanding the metabolism of collagen cross-linking and the impact of improper collagen assembly on the overall biomechanical strength of the aorta will improve the clinical management and treatment of patients with EDS who are at increased risk for complications during surgical intervention. Strategies to derive medicinal therapies for EDS patients might include focus on targeted repair of collagen cross-linking and/or assembly to improve the biomechanical strength of the aorta and prevent dissection or rupture in these patients.

2.4 Bicuspid Aortic Valve

BAV is the most common cardiac malformation and occurs in 1–2% of the general population with a gender bias of 2:1, males versus females [72]. The presence of a BAV pre-disposes the patient to formation of TAA and aortic dissection and usually requires careful surveillance and often surgical intervention for the associated co-morbidities of aortic insufficiency or stenosis in addition to ascending aortic replacement due to TAA or dissection. These phenomena that transpire in the BAV patients arise from an unknown pathway that is thought to stem from effects of altered hemodynamics through the BAV and/or due to an inherent defect in the wall of the ascending aorta which contributes to loss of biomechanical strength and leads to dilatation and aneurysm formation. The causal pathway of aneurysm formation in BAV patients appears to be distinct from patients with a morphologically normal aortic valve, known as tricuspid aortic valve (TAV). Within our clinical database, we confirm a remarkable bimodal age distribution for TAAs with a mean age of 51 for patients with BAV compared to a mean age of 68 for patients with TAV. This same bimodal age distribution was noted among patients with Stanford type A aortic dissection [111]. Strikingly, over 40% of patients undergoing replacement of the ascending aorta for aneurysm or dissection at large thoracic aortic surgical centers have BAV. BAV patients have uniformly larger diameter aortic roots and ascending aortas compared to age- and sex-matched controls [112]. The aortic roots of BAV patients, even in the absence of aneurysmal disease or valvular stenosis, have abnormal elasticity [113, 114]. This inherent aortopathy present with the BAV syndrome and the consequent aortic aneurysm formation greatly increases the risk of aortic dissection and sudden death in these patients [69].

Although linkage analysis shows evidence of genetic basis for BAV [70, 115, 116] and mutations in Notch 1 have been associated with calcification of the aortic valve and development of aortic stenosis [117], no gene or pathway to date has clearly defined a cause of the aortic pathologies occurring in patients with BAV. TAAs of the BAV patients display similar histopathology as those of connective tissue disorders discussed above. These included CMD, non-inflammatory SMC apoptosis, accumulation of proteoglycans, increased MMP activity and extensive elastin fragmentation. As with other TAAs, those occurring in BAV patients

involve matrix degradation which results in a weakened biomechanical response, incapable of withstanding hemodynamic forces and as a result, aneurysm occurs and places the patient at increased risk for dissection and rupture.

Unlike the other connective tissue disorders, no gene has been identified for BAV, so there is considerably less known on the potential mechanism of TAA formation in BAV patients. The incidence of BAV overlaps with α -SMA and TGF- β R mutations at a frequency of 2.5–3% [73] but no gene or pathway responsible for inciting TAAs in BAV patients has been identified. A role for reactive oxygen species (ROS) in the development of TAAs in BAV patients has been reported by Phillippi and Gleason [118, 119] ROS have been implicated in the development of TAAs in non-BAV patients as well [120, 121], but the mechanism inciting TAAs remains elusive. Recent work from Phillippi and Gleason has focused on the role of the ascending aortic SMCs in maintenance of the aortic ECM. It was shown by gene array that several isoforms of a family of stress response proteins called metallothioneins (MTs) were substantially down-regulated in the ascending aorta of aneurysmal patients with BAV relative to normal non-aneurysmal patients and aneurysmal patients with TAV [119]. MTs are a superfamily of intracellular cysteine-rich proteins of low (<7 kD) molecular weight, with high metal binding and redox capabilities. MTs appear to be primarily stress response proteins and are transcriptionally activated under conditions of reactive oxygen species, hypoxia, UV irradiation and heavy metal exposure. The mechanism of action for MT has not been delineated. Many studies suggest that MT plays a role in the homeostasis of essential metals such as zinc [122] and cadmium (Cd) [123], detoxification of metals, and protection against oxidative stress [124–127]. MT-/- mice are non-lethal and studies have demonstrated that MT is not required for proper growth or development, however the absence of MT-1 or -2 increased Cd-induced lethality and hepatotoxicity, and overexpression of MTs provided protection from Cd-induced death [128]. MT has been implicated in the pathogenesis of multiple diseases including oxidative stress-induced cardiac dysfunction [129]. MT was also shown to rescue hypoxia-inducible factor 1-alpha (HIF-1 α) activity and increase vascular endothelial growth factor (Vegf) expression in a mouse model of diabetic cardiomyopathy [130]. HIF-1 α has been extensively characterized as a key player in processes of ECM degradation during neoangiogenesis in cancer progression [131–133] and in normal cells [134, 135]. Induction of Vegf in the presence of ROS was also dramatically reduced in primary SMCs from BAV patients [118]. However, MT has not yet been shown to play a direct role in ECM homeostasis. As part of the overall oxidative stress response and an upstream regulator of HIF-1 α and Vegf, MT could elicit downstream effects that are proponents of ECM degradation.

In a mouse model of Marfan syndrome, Fbn1^{C1039G/+} mice developed TAAs [136] with reduced expression of superoxide dismutase (SOD) and increased expression of iNOS, NADPH oxidase (NOX) and Xanthine oxidase (XO) [137]. Elevated levels of homocysteine and protein carbonyl content, accompanied by a decrease in total antioxidant capacity, were found in the serum of Marfan patients [121]. Homocysteine is thought to affect MMP/TIMP ratios by modulating Nitric

oxide (NO) availability [138, 139], causing increased deposition of collagen and degradation of elastin leading ultimately to altered vessel biomechanics evidenced by reduced aortic flow velocity [140]. Oxidative stress has also been implicated in the pathogenesis of AAAs [141]. Increased expression of the NOX subunit p22^{phox} in TAAs co-localized with MMP activity in the aortic media [120]. These data support a causal role for NOX activity in sub-clinical pathogenesis of BAV aortas. Mice deficient in Nox1 or NOX subunit p47^{phox} were protected from angiotensin II-induced aneurysm and dissection, potentially through modulation of MMP/TIMP ratios [142, 143]. ROS appear to be associated with impaired vasomotor function [137].

A theoretical cause of TAAs is that the BAV elicits undue biomechanical stress on the aortic wall. This is substantiated by reports that altered hemodynamics cause aortic wall weakening and spatially dependent expression of matrix proteins [144–146]. Evidence against a hemodynamic cause for TAAs in BAV patients arises from the clinical observation that BAV patients who have undergone aortic valve replacement prior to TAA development remain at increased risk for ongoing aortic dilatation [147] which is discordant with the degree of aortic stenosis or insufficiency [112, 114]. Patients with aneurysm or dissection of the ascending aorta, including those with BAV, exhibit evidence of ECM degeneration, such as elastin fragmentation and increased collagen deposition [45, 48, 60–62, 74, 75, 118] as do NOX-1-deficient animals [148, 149]. The increase in collagen matrix deposition [45, 47, 118, 150, 151] in BAV-TAAs as a putative result of ROS [142] may serve as a compensatory mechanism to counter the MMP/TIMP imbalance [152, 153]. Endothelial nitric oxide synthase (eNOS)-deficient mice demonstrate a 32–41% incidence of BAV [154, 155]. Polymorphisms of eNOS are linked to AAAs [156–158] and intracranial aneurysms [159–163] and reduced eNOS is observed in the aortic endothelium of BAV patients [164] and linked to experimental (elastase perfusion) [165] and age-related AAAs [166] but has not been characterized for TAAs. There is mounting evidence for a role of ROS in disrupted ECM homeostasis but a defined molecular mechanism has yet to be established. ROS is known to impact the SMC phenotype [167, 168], shifting them towards a de-differentiated state which increases ECM matrix synthesis [169] and is associated with TAAs of various origins [66, 67, 73, 170–173] and thus could modulate tissue biomechanical strength.

The BAV aorta is pathologically similar to those of the other connective tissue disorders but the mechanisms inciting the final common pathway of ECM degeneration and biomechanical failure appear to be distinct. Like LDS, collagen expression is elevated in TAAs of BAV patients [118]. Collagen is radically affected by the presence of ROS and the lucid SMC phenotype takes preference toward de-differentiation in TAAs [173] and is strongly influenced by oxidative stress [167, 168]. The inability of SMCs of BAV patients to adequately sense and cope with oxidative stress appears to negatively impact matrix deposition and orientation. Collagen fibers appear more disorganized in TAAs of BAV patients [174]. In agreement with the observations of increased collagen deposition and disorganization, preliminary results the authors' laboratories of *ex vivo*

biomechanical testing of freshly-harvested TAA specimens demonstrated increased tensile strength and decreased delamination strength of BAV specimens when compared to aortas of healthy individuals [175–178].

These observations support a pivotal role of the SMCs in maintaining the aortic ECM. The aortic SMCs, presence of excess ROS, and the cells' ability to manage oxidative stress warrants further investigation pertaining to their role in overall ECM homeostasis and biomechanical integrity of the vessel wall. Improved treatment of BAV patients will likely come from drawing connections between SMC response to ROS in the form of cell viability and phenotypic modulations and the impact of these behaviors on ECM deposition, organization and biomechanical integrity.

2.5 Other Familial Thoracic Aortic Aneurysms

There are many instances of familial TAA where there is no connective tissue disorder present, nor incidence of BAV but there is heritability of aortic diseases within families. Linkage analysis has documented genetic loci that are implicated in familial aortic disease but no gene or pathway inciting ECM degeneration has been identified to date. In some patients, mutations in fibrillin-1 are similar to that of Marfan syndrome but lacking clinical manifestations in other organ systems [73, 179]. Expert surgical opinion suggests that these patients follow strict surveillance similar to that recommended for MFS patients [70]. The fundamental mechanism of failure is likely similar to that of other TAAs and include ECM degradation. As mutated genes and faulty pathways are identified in these patients, the impact of their dysfunction on ECM homeostasis and biomechanical integrity can be investigated.

3 Biological Mechanisms that Impact Mechanical Properties of the Aneurysmal Abdominal Aorta

During AAA formation and enlargement, the biomechanics of the aortic wall change dramatically [11, 26, 30, 31, 180–182] due to loss of ECM integrity which is spatially variable [21, 31, 183–185] (Fig. 6). Several studies demonstrated that the tensile strength decreases as the aneurysm expands [11, 26] and wall strength and stiffness are spatially variable [21, 29, 31]. The evidence supports the notion that local factors such as wall stress and/or hypoxia negatively influence the biomechanical strength of the vessel wall by promoting localized ECM degradation that is known to occur in AAAs [30, 186, 187]. Portions of AAAs were found to be stiffer, contain less elastin and collagen when compared to normal aorta. It is now well accepted that AAAs arise and progress up to failure when stress in the

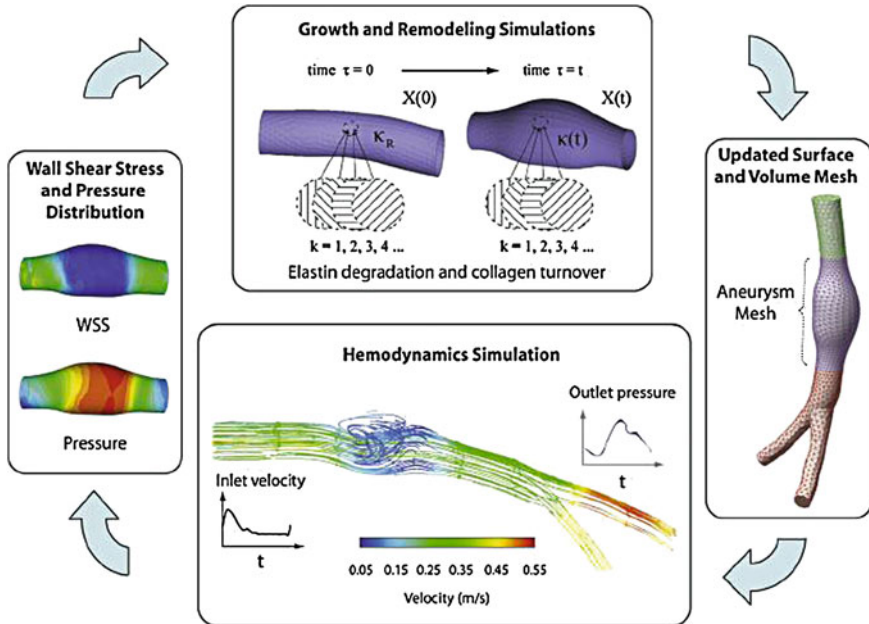


Fig. 6 Relationship between hemodynamics and growth and remodeling simulations of blood vessels. (Reproduced from Fig. 1, Sheidaei et al. [185])

aneurysm wall exceeds the strength of vessel wall. However, little is known of the biological mechanisms driving ECM degeneration in AAAs but two areas under close scrutiny are stress-mediated and strain-mediated wall weakening and hypoxia-mediated disruption of ECM homeostasis.

3.1 Stress/Strain-Mediated Formation of AAAs

Mechanical forces or deformations are considered to be paramount to maintenance of microstructure in normal tissue under physiological conditions. Elastin concentration was found to decrease with the diameter in the non-aneurysmal and aneurysmal aorta [188]. Variations in aortic wall stress are supported by the law of Laplace which indicates that vascular wall stress is directly proportional to its diameter. Hence, areas of dilatation may occur in response to spatial changes in wall stress [183]. The observation of focal saccular outpouchings, also known as “blebs” within the walls of AAAs are speculated to be sites of higher risk for rupture since these represent areas of stress concentration [189]. The latter is very important in practice because rupture of the material is commonly expected to start at the location of stress concentration. These blebs were also characterized by decreased collagen and elastin when compared to neighboring sites within the

AAA [190]. Mechanical forces are known to influence ECM production by SMCs [191, 192], endothelial cells [193] and other cells [194]. These combined data on spatial variability in ECM content and cell response to stress support the fact that stress concentration leads to disrupted ECM homeostasis, resulting in weakening of the aortic wall. In atherosclerosis, the occurrence of lesions at branch in artery is also correlated with the stress concentration. Similar mechanisms may contribute to formation and/or progression of TAA since ECM proteins were found to be differentially expressed on the greater and lesser curve of the ascending aorta [195].

Some of the major known contributors to ECM degradation are the MMPs. Elevated MMPs have been identified in both TAAs and AAAs and are influenced locally by stress [43, 153], aneurysm size [196] and growth rate [197]. MMPs, and other proteolytic enzymes such as tPA and urokinase plasminogen activator are enhanced by mechanical stress [153]. Macrophages also play a dominant role in increasing MMP production as part of the inflammatory response that occurs with AAA [21, 198]. Macrophages are centralized to areas of atherosclerotic plaques and elevated MMP production is observed in these zones of decreased mechanical strength [199, 200]. These studies suggest that macrophages may play a key role in reducing the strength of AAA via stress-mediated expression of proteolytic enzymes. The local SMCs and/or fibroblasts and especially the macrophages appear to “sense” the mechanical stimulation and respond by increasing production of proteolytic enzymes. Elevated levels of MMPs then work to degrade the ECM and thus weaken the biomechanical integrity of the aortic wall, leading to aneurysm formation and risk for rupture. The molecular signaling mechanisms by which mechanical stimulation promotes increased MMP expression remain elusive but likely involves a complex network of intracellular signaling pathways connected to cytoskeletal proteins that are indirectly tethered to the ECM. Some recent studies have targeted the Jnk and MAPK pathways as mediators of MMP regulation in AAA [201, 202].

Therefore, locally acting forces (and therefore wall stresses) play an important role in the pathophysiology of aneurysmal disease. Specifically, local ECM degeneration of the aneurysmal wall, which could result in a compromised structural integrity of the AAA wall, appears to coincide with areas of increased wall stress. These studies support the idea of spatial variation of wall strength that could result in increased risk for rupture in defined locations that vary patient-to-patient.

3.2 Hypoxia-Mediated Wall Weakening

Another powerful modulator of ECM deposition is hypoxia. As discussed in the TAA sections above, hypoxia and ROS disrupt the normal balance of ECM synthesis and degradation by directly influencing production of ECM protein and regulatory proteins. Hypoxia has been shown to both increase [203–205] and

decrease [206, 207] production of collagen by SMCs. These observations suggest that local hypoxia contribute to aneurysm wall weakening through inhibition of ECM synthesis. Expression of MMPs as well as their release of elastase [208] and cytokines [209] is also greatly enhanced in macrophages under hypoxic conditions [210]. The hypoxic state may be caused by the presence of ILT [21, 211]. As a consequence, the mural cells within these zones likely respond to this environment. A greater number of macrophages were found within [212] and in the vicinity [198] of the ILT along with many other inflammatory cells when compared to adjacent locations within the AAA. These areas displayed reduced elastin and increased MMPs. These collective data point to a role for hypoxia in stimulating ECM degradation and thus, negatively influence the biomechanical integrity of the aorta wall, consequently leading to AAA formation in these patients.

3.3 Genetic Causes of Abdominal Aortic Aneurysm

There have been extensive efforts made to identify genetic causes of AAA and a genetic basis for aneurysm growth. A recent systematic review of the literature by Saratzis et al. summarized a majority of these studies as of the year 2011 [213]. Most of the genetic studies center on the matrix-regulating proteins (MMPs, TIMPs), factors related to the inflammatory (interleukins, C reactive protein) and wound healing responses (TGF- β s, platelet-activating factor, plasminogen activator inhibitor 1 (PAI-1), osteopontin and osteoprotegerin (OPG)). The majority of studies investigating the role of these proteins in AAA formation demonstrated alterations in gene or protein expression and identified gene polymorphisms causing these changes in expression. However, most analyses failed to demonstrate a direct association between gene polymorphisms and AAA formation or growth. A few polymorphisms were found to be associated with development (MMP-3, [214] MMP-9, [215] TIMP-1 and -2 [216–218] the β -chemokine receptors, CCR5 [219] and CCR2 [220] angiotensin converting enzyme [221] methylene tetra hydro folate reductase (MTHFR) [222–224] and potentially endothelial nitric oxide synthase (eNOS), although the sample size was relatively small [225]) or growth (PAI-1 [226], and an OPG-regulating factor called peroxisome proliferator-activated receptor gamma (PPARG) [227]).

Another recent review by Krishna et al. discussed the genetic and epigenetic causes of AAA [228] and was in agreement with Saratzis et al. for which there is a general lack of genetic polymorphisms strongly correlated with AAA. The “Aneurysm Consortium” has undertaken large Genome-Wide Association Studies (GWAS) to analyze variance in diseased patients and controls [229]. From this work, there was a strong correlation of chromosome 9p21.3 locus performed with respect to AAAs and was originally identified from seven different populations [230]. A more recent study demonstrated that this association remained despite removing other AAA risk factors such as smoking, coronary heart disease, family history and dyslipidemia [231]. This chromosomal region is thought to be

non-coding DNA, consisting of repetitive DNA of retrotransposons which are transient genetic elements that move across the genome. Among these are a long interspersed nuclear elements 1 (LINE-1) which can invade a variety of genes and result in multiple phenotypic outcomes. A recent study evaluated several polymorphisms of 9p21.3 and their association with AAA. Only two polymorphisms were found to be significantly associated with two open reading frames (ORFs), providing evidence that LINE-1 elements may be involved in a genetic cause of AAA [232]. However, further larger studies are needed to confirm this association. The Aneurysm Consortium also identified a single nucleotide polymorphism (SNP) on 9p21 which was previously shown to be associated with heart disease and recently with AAA [230]. Neighboring genes to this particular SNP code for proteins related to cell proliferation, apoptosis and senescence [229] and could be related to SMC phenotype.

Gene products which have been shown to be altered in AAA and may or may not have had polymorphisms identified include MMP-2,3,7, 9, TIMP-3, inducible nitric oxide synthase (iNOS), eNOS, interferon-gamma (INF- γ), tumor necrosis factor (TNF)- α , intercellular adhesion molecule (ICAM)-1, IL-6, TGF- β RII, platelet-derived growth factor (PDGF)-A, estrogen receptor (ER)- α/β , c-fos, 5-lipoxygenase (5-LO), extracellular superoxide dismutase (EC-SOD), fatty acid desaturase (Fads)-2, MTHFR and p53 [228]. Several epigenetic changes such as histone modifications and DNA methylation can alter expression of these genes, and therefore cause the variation observed in AAA relative to normal patients. These epigenetic alterations can stem from known AAA-related risk factors such as smoking, ageing and inflammation. Among these, smoking is the most prevalent risk factor for AAA, and over 80% of patients developing AAA have a history of smoking [233].

4 Biomechanics of AAA and TAA

4.1 *Methods for Measuring and Modeling Aortic Biomechanics*

Aneurysm rupture can be seen as a mechanical failure of the degenerated aortic wall that occurs when the wall stress acting on the aneurysmal wall exceeds the wall strength. Therefore, the knowledge of both wall stress and wall strength distributions for a given aneurysm will greatly improve the ability to identify those aortic aneurysms that are at highest risk of rupture. Towards this end, the biomechanics of AAA has been studied extensively by many groups whereas TAA biomechanics has not been fully considered. This section provides the state-of-the-art of AAA biomechanics, including the modeling of tensile strength and wall stress distributions and factors which influence them. Then the potential clinical utility of these estimates in predicting AAA rupture will be also presented. A summary of recent advances in TAA biomechanics is also articulated.

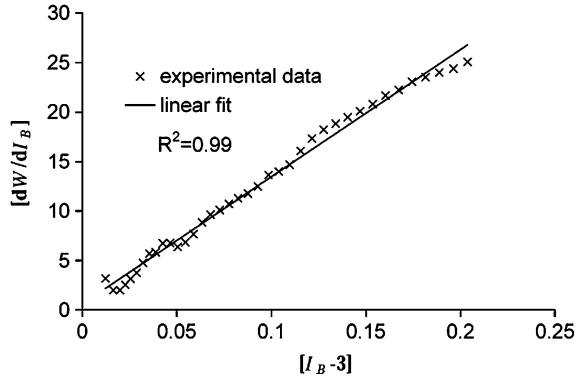
4.2 Analysis of Biomechanical Strength and Wall Stress In vivo

4.2.1 AAA Wall Strength

Given the general recognition of the importance of wall mechanics in the natural history of AAAs (e.g., [183, 234–236]), there have been numerous studies of AAA biomechanical properties. Noninvasive diagnostic techniques such as ultrasound and computer tomography have long been used to understand AAAs wall mechanics. Indeed, early studies focused on gross measurement of structural stiffness [37, 237–239] or vessel compliance [240, 241], including the effect of ILT [242]. Although these investigations were useful for clinical correlations, the AAA wall strength was not evaluated by these approaches.

Vessel wall strength has not yet been measured in vivo due to the deficiency of current experimental techniques. However, researchers have easily assessed AAA wall strength performing ex vivo experimental testing on excised normal and pathological aortic tissue. Early ex vivo studies on the biomechanical properties of AAAs focused on understanding the effect of extracellular derangement observed in aneurysms [186, 187]. Reported uniaxial sub-failure tensile data for eight human AAAs and eight age-matched controls (all axially oriented specimens) revealed a stiffer AAA wall compared to that of the normal aorta [30]. Similar findings demonstrated that the aneurysmal aorta in the circumferential direction was stiffer than the axial direction, and that posterior portions were less stiff than anterior or lateral portions, suggesting a stiffness variation around the lesion [31]. These findings were corroborated by Vallabhaneni et al. [243] suggesting a correlation between strength and variation in MMP production, and Ragahvan et al. [244] reporting spatial variation of wall thickness and tensile strength in an excised AAA. Variation in AAA wall strength from point-to-point in a given aneurysm or from patient-to-patient support the fact that evaluation of AAA wall stress alone is insufficient to predict rupture and that AAA wall strength cannot be assumed to be constant on aneurysms. Vorp et al. widely investigated AAA wall mechanics, reporting measurements of AAA wall strength [26], and formulating both microstructure-based [11] and hyperelastic, continuum-mechanics-based models for the AAA wall mechanics [181]. In particular, the latter study reports uniaxial tensile tests on 69 freshly-excised human AAA specimens oriented along either the circumferential and longitudinal directions. They also quantified experimental data with a strain energy function of the form $W = \alpha(I_B - 3) + \beta(I_B - 3)^2$ where $I_B = \text{tr} \mathbf{B} = \text{tr}(\mathbf{F} \cdot \mathbf{F}^T)$ and \mathbf{F} is the deformation gradient, and α and β are the model parameters indicative of the mechanical properties in longitudinal or circumferential directions (Fig. 7). This continuum-based constitutive model is appropriate for wall stress prediction [183] since it can be easily implemented in finite element analysis compared to microstructure-based models. To investigate the association of aortic wall weakening with AAA rupture, ex vivo tensile tests on freshly-excised wall tissue specimens from patient who suffered AAA rupture prior to surgery were compared to specimen tissues from elective repaired, asymptomatic

Fig. 7 The experimentally determined relationship between the first derivative of strain energy function and the first invariant of the stretch tensor for a representative AAA specimen. Linear regression resulted in a highly correlated fit ($R^2=0.99$), indicating a linear relationship between the two. (From Fig. 1, Raghavan and Vorp [14])



AAA [12]. The tensile strength of the ruptured AAA tissue was found to be significantly lower than that for the elective AAA tissue (Fig. 8). This data suggests that AAA rupture is associated with significant aneurysm wall weakening, supporting the idea that wall strength needs to be carefully considered on a patient-specific basis in order to accurately predict rupture potential of individual aneurysms.

Uniaxial testing is not sufficient for highlighting the multi-axial biomechanical response of vessel in vivo; therefore, normal and pathological abdominal aorta tissue specimens have been tested in a biaxial testing device [245] to obtain more appropriate constitutive relation of aortic tissue and to investigate any apparent anisotropy of the aorta. The high non-linear responses found on 26 AAA tissue samples and 8 aged-matched abdominal aorta samples were described well by a two-dimensional phenomenological Tong-Fung (1976) strain energy function. These results confirmed the general observation that AAAs are indeed stiffer and more anisotropic (i.e., stiffer in circumferential direction) than the normal aorta. Comparison between strain energy functions derived from uniaxial testing [14] and biaxial testing [246] provided evidence for remarkable differences in mechanical response of the tissue between the two models, demonstrating the importance of correct model choice in biomechanical simulations (Fig. 9).

There has been less attention to the influence of biomechanical properties of ILT that often lines AAAs. Di Martino [180] first reported uniaxial testing on 21 samples of thrombus obtained from 6 patients generating support for the idea that thrombus may be “mechanically protective” by providing stress shielding or a cushioning effect for AAA wall. The most comprehensive study of the biomechanical properties of ILT from human AAAs [247] revealed that the behavior is mildly non-linear over large strain, nearly isotropic [29] and inhomogeneous since portions of tissue from the luminal region were found to be stiffer and stronger when compared to middle region (Fig. 10).

Although these mentioned studies established that AAA biomechanical properties changes with aneurysm formation and that these properties are spatially variable, little progress has been made to provide methodology to noninvasively

Fig. 8 Difference in tensile strength of ruptured and electively repaired AAA wall specimens. (From Fig. 10, Vorp [183])

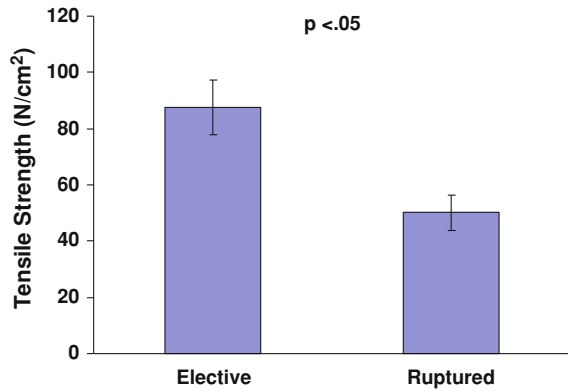


Fig. 9 The strain energy of the averaged isotropic relation [12] and the averaged anisotropic constitutive relation [218] for AAA versus equibiaxial strain (E). (From Fig. 2, Vorp [183])

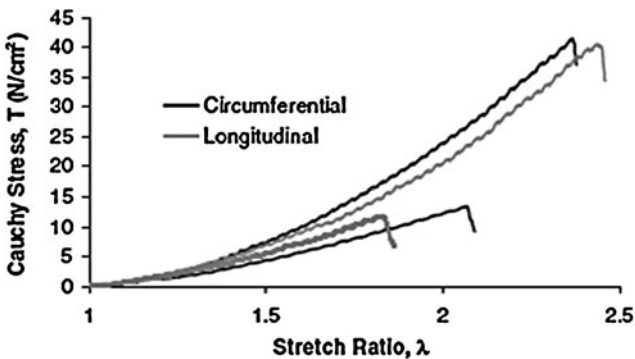
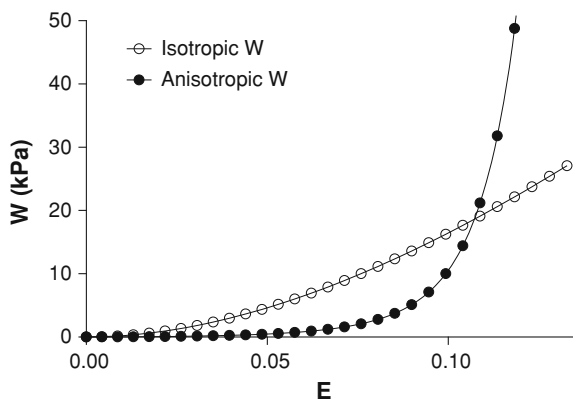


Fig. 10 Typical set of stress-stretch curves for ILT samples taken from the luminal region (*upper set of curves*) and the medial region (*lower set of curves*). All data were obtained from the same ILT (same patient). (From Fig. 3, Vorp [183])

Fig. 11 Predicted versus measured strength for the statistical model of wall strength. The *dash line* represents the line of unity. (From Fig. 3A, Vande Geest et al. [20, 29])

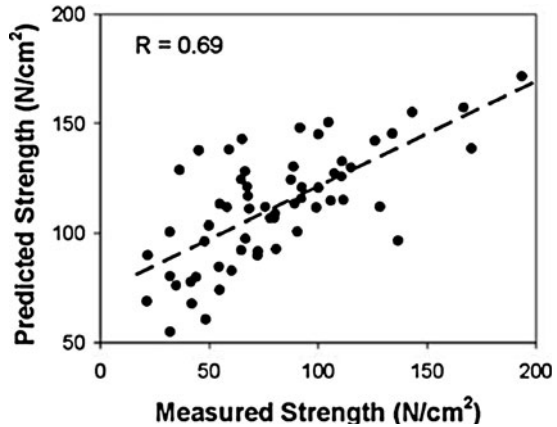
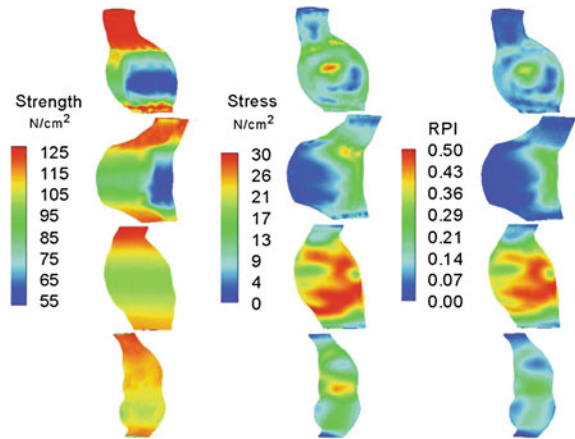


Fig. 12 Demonstrative application of the statistical model of wall strength (Eq. 3 in [20], left), wall stress (*middle*), and rupture potential index (*right*) for four representative AAAs. (From Fig. 4, Vande Geest et al. [20, 29])



predict the local wall strength distribution in a given AAA. A statistical-multi-factorial mathematical model is currently the only model for assessing the AAA wall strength with a noninvasively approach. Specifically, multiple linear regression techniques were used to derive a statistical model for the prediction of AAA wall strength based on experimental measurements and measurable pertinent predictors, including local AAA diameter, local ILT thickness, patient age and gender, and patient family history of AAA disease [see the excellent work by Vande Geest [20] for more on this statistical model]. The predictability and example applications of such a model are shown in Figs. 11 and 12 [20]. In this study, the concept of RPI, which is defined as the locally acting wall stress divided by the local wall strength, was also introduced to define the propensity to rupture of a given AAA.

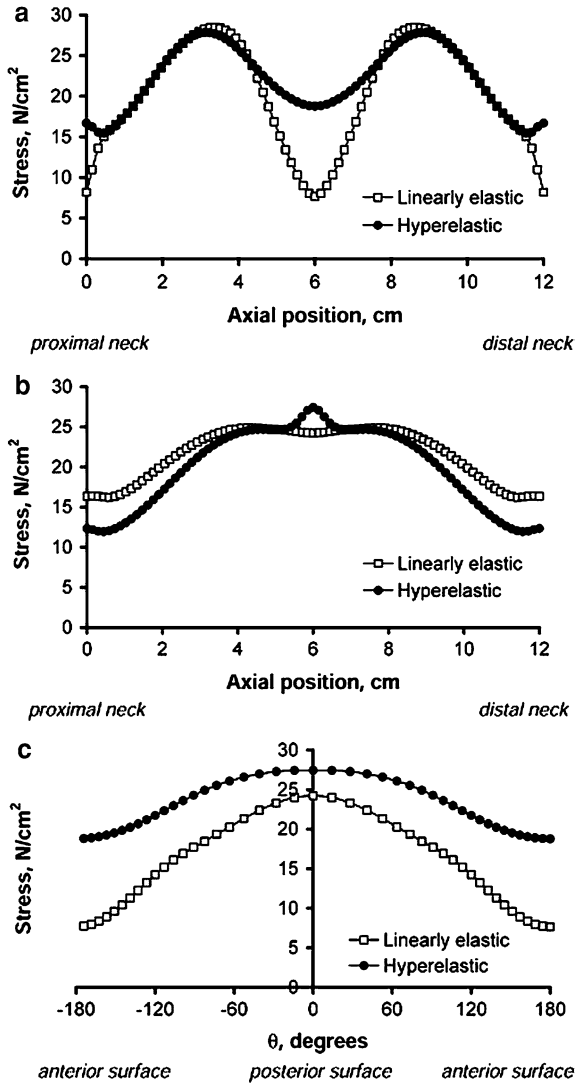
4.2.2 AAA Wall Stress

In recent years, there has been an increasing effort to develop appropriate finite element (FE) models to assess the wall stress in dictating the fate of aneurysm failure. Early stress analyses have assumed idealized geometries, and are based on law of Laplace [248–250], axisymmetric membrane theory [16] or linear elastic material behavior [251, 252]. Moreover, Inzoli et al. [251] were the first group to introduce an important, but controversial, concept: that ILT may act to reduce AAA wall stress by a shielding effect. However, these models are inappropriate to describe the inherent non-linearity of the aorta under large deformations and fail to demonstrate the likely importance of blebs which, in turn, cause stress concentration (Fig. 13). The best models available utilize patient-specific geometries and treat the aneurysmal wall as a non-linear elastic, isotropic, homogenous body [22, 23, 253] (Fig. 14). From these studies, the stress magnitude and distribution were found to be dependent on either the shape of the AAA bulge as well as aneurysm diameter. These findings strengthen the argument for which aneurysm with the same diameter may not necessarily have the same propensity to failure.

To accurately mimic the physiological mechanical behavior of the normal and pathological aorta, the proper utilization of the constitutive material models implemented in FE models needs to be evaluated. This was accomplished by Vorp et al. who investigated the influence of constitutive-model material parameters [13, 181] and tissue anisotropy [246] on wall stress prediction. They performed a parametrical analysis by changing the α and β material parameters of the constitutive material model described by Raghavan et al. [181], on several FE stress analyses of hypothetical 3D asymmetric AAAs. The maximum variation of material parameters led to less than 5% in the predicted wall stress, and this suggests that the differences in AAA wall stress from patient-to-patient are driven more by the differences in surface geometry than in material properties. In a similar way, FE analyses on two non-ruptured and one-ruptured AAAs modeled with both isotropic [14] and anisotropic [29] wall constitutive relation demonstrated that an anisotropic material model provides a better prediction of the stress distribution in AAAs compared to an isotropic model. The most advanced FE models also consider the presence of ILT contained in most AAAs. Indeed, the incorporation of thrombus into computational stress analysis models the profound influence on the magnitude and distribution of stress acting on the AAA wall, and this should be considered for accurate wall stress estimations (Fig. 15). Recently, the statistical model for predicting wall strength and rupture potential index proposed by Vande Geest et al. [182] were implemented in FE analysis [28] and compared with the maximum diameter criterion to evaluate their reliability in AAA rupture prediction. The strength model reported by Vande Geest was misused by the authors (the local normalized diameter that was used was not as specified by the original model), and it is unclear how this affected their results.

There has been increasing interest in fluid–structure interaction (FSI) modeling of AAAs, yet most studies assume the non-aneurysmal and aneurysmal aorta, and ILT as linear elastic, homogeneous, isotropic, nearly incompressible body

Fig. 13 Comparison of stresses computed for a 3D asymmetric AAA model using the hyperelastic constitutive model [12] with those using a linearized elasticity model along anterior surface (a), along posterior surface (b), and around mid-section (c). Note the substantial error involved with using the theory of linearized elasticity. (From Fig. 7, Raghavan and Vorp [14])



[254–256]. While these studies have been important to demonstrate that the pressure field in AAAs is relatively constant [257, 258], the effect of shear stress was neglected. Perhaps, the most important sophisticated FSI model to date is that by Rissland et al. [259], incorporating ILT, wall calcification, and anisotropic tissue properties. Experimental biaxial data of AAAs [29] were fitted with the Holzapfel orthotropic material formulations [260] which models vessel wall as fiber-reinforced composite material. Calcified plaques surrounding AAAs were assumed to behave as stiff isotropic materials whereas the ILT was modeled as linearly elastic. Later, Xenos et al. [39] validated this FSI methodology to assess

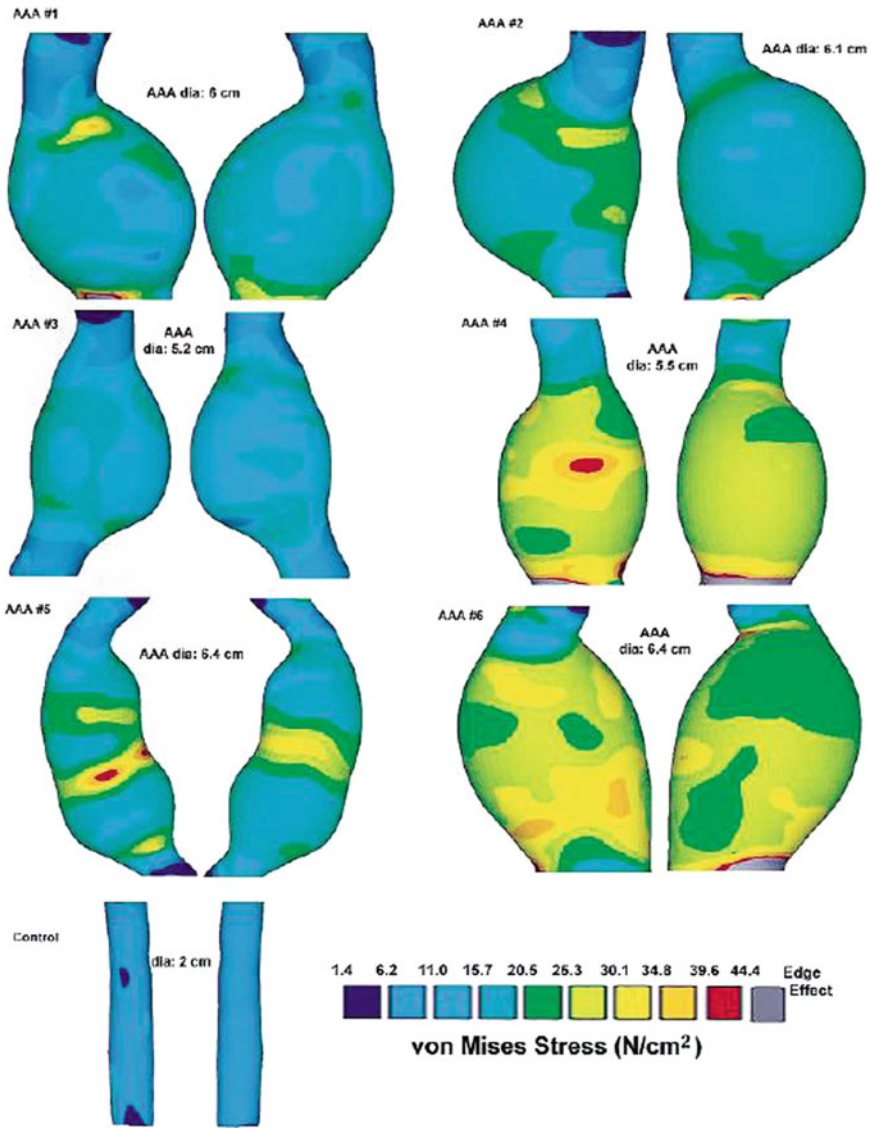


Fig. 14 The distribution of von Mises stress on the posterior and anterior abdominal aortic walls of the control subject and the patients with abdominal aortic aneurysms. Grey regions are those with artificially high stress concentrations because of edge effects. The individual color scales give the stress magnitude. In all cases, *blue* represents the lowest stress magnitude, and *red* represents the highest stress magnitude. Note the comparatively lower range of stress in the control aorta. (From Fig. 4, Raghavan et al. [181])

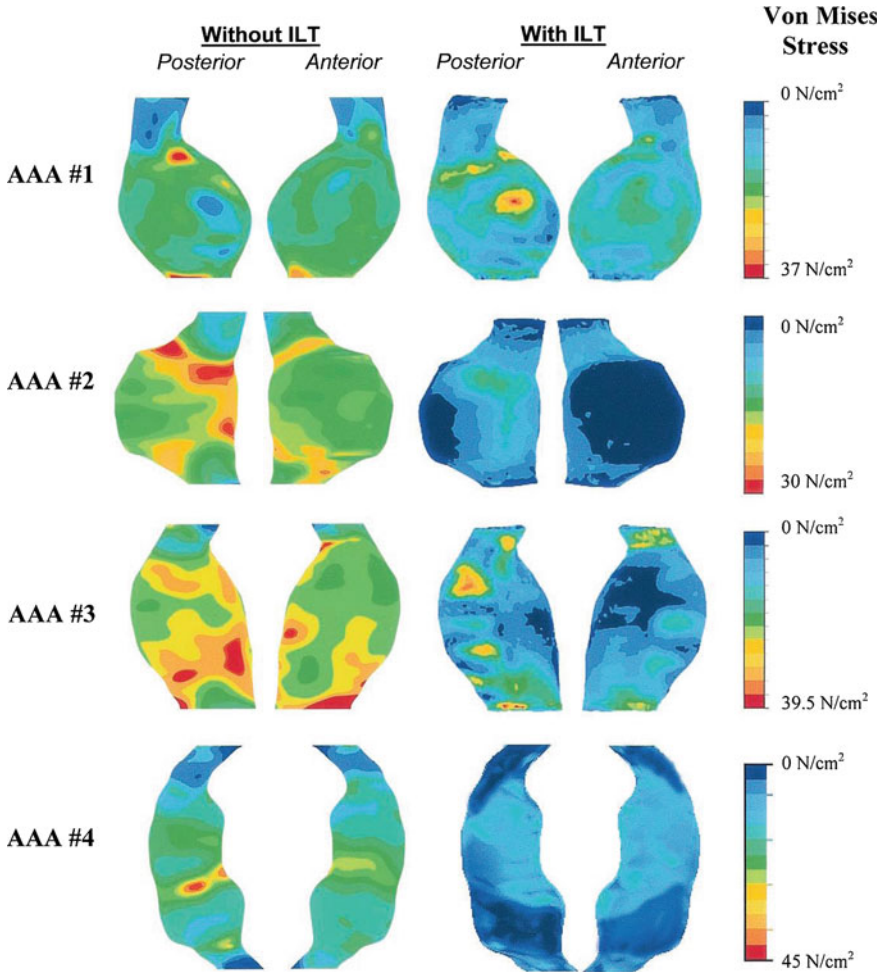


Fig. 15 Comparison of 3D wall stress distribution between AAA models with and without ILT. Individual color scales (*right*) indicate von Mises stress for each AAA. Both posterior and anterior views are shown for each case. (From Fig. 4, Wang et al. [19])

rupture propensity on cases of ruptured AAA using the wall strength model and RPI proposed by Vande Geest et al. [182] (Fig. 16).

These studies have demonstrated that computational models have potential to improve the predictions of rupture potential. It should be also noted that many investigators report the Von Mises stress to assess the maximum stress, inducing to AAA failure. However, Von Mises stress has its importance in the fracture mechanics of ductile materials, which yield due to excessive shear stresses. The aorta has a nonlinearly elastic behavior, not exhibiting yielding, where failure is governed by maximum normal stress [261–263]. Therefore, this issue of a most appropriate failure criterion must be addressed in future investigations.

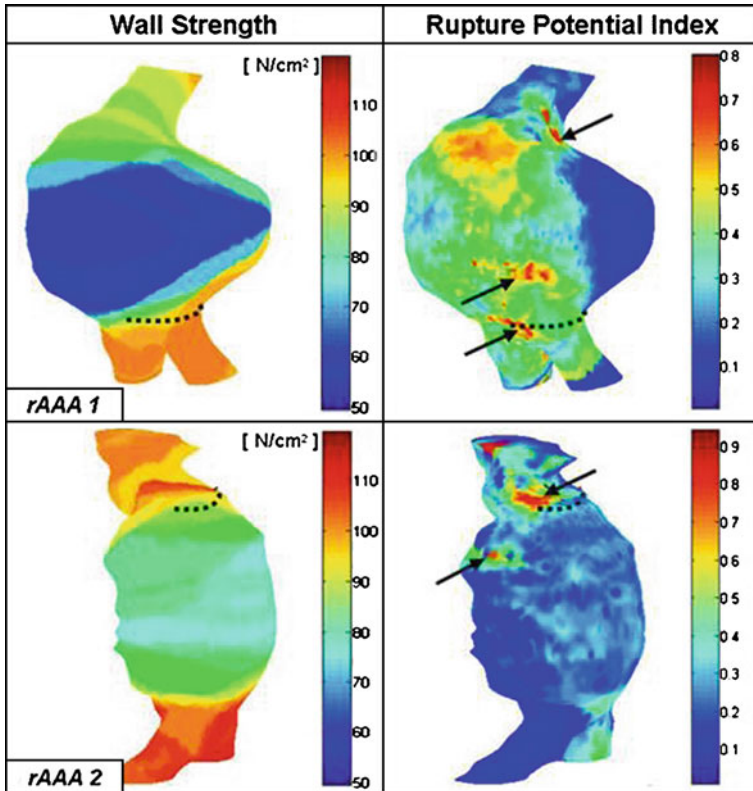


Fig. 16 Wall strength mapping and the corresponding rupture potential index, for the ruptured AAA cases. Multiple distinct regions of high RPI are observed, with at least one that coincides with the actual location of rupture. The RPI for both cases is close to unity indicating a very high risk of rupture, with a higher RPI (0.95) for the smaller rAAA. (from Fig. 6, Xenos et al. [39])

4.2.3 TAA Wall Strength and Wall Stress

Despite the aforementioned importance of wall strength in the mechanics underlying the aortic failure, there has been less attention to that of thoracic aortic aneurysm. This pathology is also particularly lethal although the relatively rare incidence. Similar to AAA, aneurysm involving the ascending and descending aortic segments can rupture. However, a more common pathology is dissection where an intimal tear, often circumferential in origin, permits blood to enter the aortic wall splitting the media and progressively separating the medial plane along the axial direction of the aorta. From a biomechanical viewpoint, the dissection represents a separation of the elastic layers of the degenerated aortic wall that occurs when the hemodynamic loads exerted on the aneurysmal wall exceed bonding forces that normally hold the layers together. Clinical hemodynamic

disturbances that render the aorta susceptible to the onset of dissection are principally elevated maximum systolic and mean aortic blood pressure [264].

Early studies reported experimental data for normal descending and mid-thoracic aorta from uniaxial tensile tests [261, 265] and inflation tests [261, 266]. These studies indicated that wall strength is dependent on the anatomic site of the vessel and that tensile failure behavior is perhaps anisotropic. Early wall strength measurements of ascending thoracic aortic aneurysm (ATAA) revealed biomechanical characteristics similar to those of the abdominal aorta. Ex vivo studies by our laboratory on thirty aneurysmal aortic tissue specimens oriented in both the longitudinal and circumferential direction demonstrated that tensile strength in ATAA is 30% lower than non-aneurysmal ascending aorta, suggesting higher risk of rupture in patients with ATAA [33]. Additionally, tissue stiffness of ATAA wall was found to be higher than normal aorta and particularly, the longitudinal direction was stiffer than the axial direction. Later, Iliopoulos et al. [32] reported lower longitudinal tensile strength with aneurysm enlargement. The low wall strength in longitudinal direction found in these investigations may be responsible for aortic dissection in ATAAs.

As found for AAAs, the ATAA wall strength and stiffness vary spatially. Ex vivo tensile testing data revealed uniform ATAA tissue strength and stiffness along the circumferential direction whereas, in the longitudinal direction the anterior region was the weakest and least stiff part of the aneurysm, and this can be associated with the clinical evidences of preferential ATAA bulging in the anterior region [267]. Tensile wall strength data associated with abnormal valve morphology revealed that ATAA tissues excised from patients with bicuspid aortic valve are stiffer than those from those patients with tricuspid aortic valve [34]. However, these findings are limited by a relatively small sample size ($n = 6$). Only one study reported media splitting testing measurements to understand the dissection properties of thoracic aorta [268]. By infusing liquid into media, a bleb was created and thus the propagation of the liquid was monitored to explore the mechanics of dissection.

Although FE methodology has been applied extensively in the prediction of wall stress for AAAs, it has not been given the same degree of importance in the investigation of wall stress in ATAAs. Therefore, computational modeling of ATAAs is very limited and recent. In the earliest study, the ATAA was modeled as an axisymmetric dilation in a cylindrical aorta as an isotropic, nonlinear, hyperelastic material behavior [269]. As the aneurysm grows, the longitudinal stress in the bulb of the aneurysm is the only stress that was found to increase significantly and thus is likely to cause rupture or dissection. The influence of the aortic root movement on the aortic wall stress as related to aortic dissection was also investigated in a single-layered, linear elastic, isotropic, homogeneous ATAA model [270]. The aortic root motion determined a direct impact on the longitudinal stress that was found to increase critically in the ascending aorta above the sinotubular junction. This may explain why the intima tears circumferentially and aortic dissections occur more often in this orientation. FSI analyses of descending dissecting aneurysms were reported by several groups [271–273]. Recently, a FSI

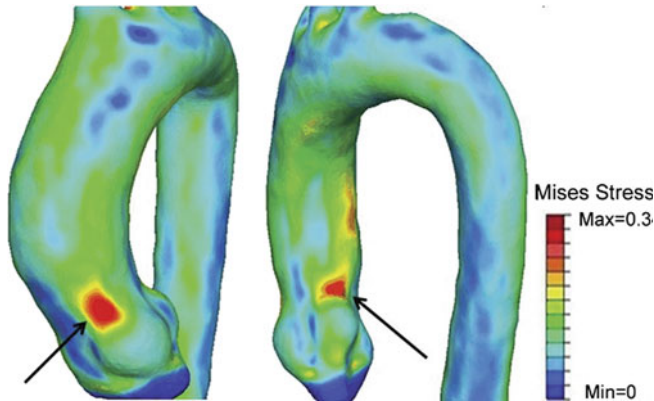


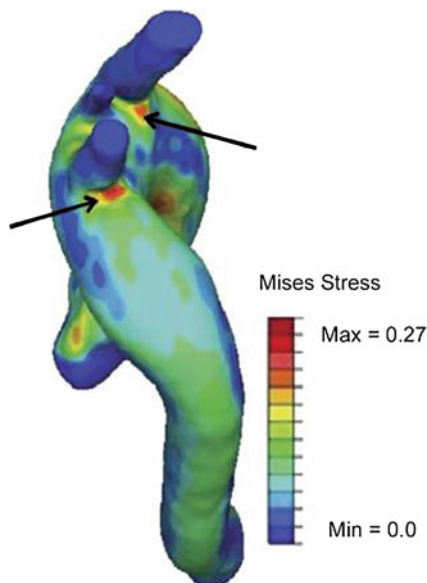
Fig. 17 Three-dimensional wall stress distribution for the normal ascending aorta. Stress in mega-pascals (MPa) is mapped, with the highest stress in *red* and lowest stress in *blue*. The *black arrows* indicate maxima of stress on the (a) convex and (b) concave side of the ascending aorta. (From Fig. 3, Nathan et al. [274])

analysis of an idealized three-layered descending aorta under turbulent pulsatile flow revealed that the media layer exhibited a larger wall stress compared with the intimal and adventitial layers, and thus the high stress due to elastic properties mismatch in the aortic wall is a risk factor for tearing in aortic dissections [272]. The most sophisticated FE model of an ATAA has been presented recently by Nathan et al. [274]. For the purpose of understanding the pathogenesis of aortic dissection, the authors developed a patient-specific model of an ATAA, though their assumptions of homogeneous, incompressible, isotropic, linear elastic properties and uniform thickness are limitations of this work (Figs. 17 and 18). Their results suggested that peak systolic pressure induces localized high wall stress above the sino-tubular junction and at the ostia of the left subclavian artery that may account for the development of type A and type B aortic dissection, respectively.

5 Using Aortic Biomechanical Data to Transform Clinical Care

All of the criteria that have been proposed to treat AAA and ATAA are based on empirical data with less emphasis on sound physical principles. The current gold standard for surgical intervention for a patient is based primarily on the maximum orthogonal diameter of the vessel, namely the “maximum diameter criterion”, which is 5.0–5.5 cm for both TAAs and AAAs. Nevertheless, this criterion can be improved as it has resulted in a rupture rate of 1% per year for patients under observation [2, 275]. Areas of peak wall stress were found to overlap with sites of rupture [39] and locations of deficient extracellular matrix [30, 186]. Efforts to

Fig. 18 Three-dimensional wall stress distribution for the normal thoracic aorta. Stress in mega-pascals (MPa) is mapped, with the highest stress in *red* and the lowest stress in *blue*. The *black arrows* indicate maxima of stress distal to left subclavian and innominate arteries. (From Fig. 4, Nathan et al. [274])



refine surgical recommendations and predict relative risk for rupture in a patient-specific manner have included consideration of wall stiffness [37], ILT thickness [38], wall tension [8], peak wall stress [22–24] and growth rate [276]. Serum biomarkers of elastolysis also offer promising non-invasive methods and correlated with disease progression but are not of sufficient predicative value. However, all of these approaches have their own limitations, and may lead to errors in decisions pertaining to clinical management of aortic aneurysm.

In this section, we have emphasized the importance of both the wall stress and the wall strength and that these physical parameters derived from failure mechanics principles may be translated in a novel improved criterion to identify those aneurysms that are at highest risk of rupture or dissection. Toward this end, the RPI, which is defined as the locally acting wall stress divided by the local wall strength, appears to be currently the most promising approach. This model relies on the relatively well-established methods for estimating wall strength stress and the evolving field on noninvasive techniques for modeling wall stress.

Despite the great efforts over the past 20–30 years in identifying not only the pathology of aneurysm, but also the significant advances in discovering genetic causes for several forms of ATAAs and the risk factors for AAA, the current risk prediction models are unreliable. Current improvements on this model which incorporate wall stress and wall strength are not yet ready for clinical translation, and the potential future success of these ideas is dependent on the development of novel noninvasive imaging technologies to measure wall strength. One promising technique is 4-dimensional MR that has recently been demonstrated to evaluate systolic flow patterns in the ascending aorta of aneurysmal patients and healthy volunteers [144]. This study shows in dramatic fashion the disrupted flow in BAV

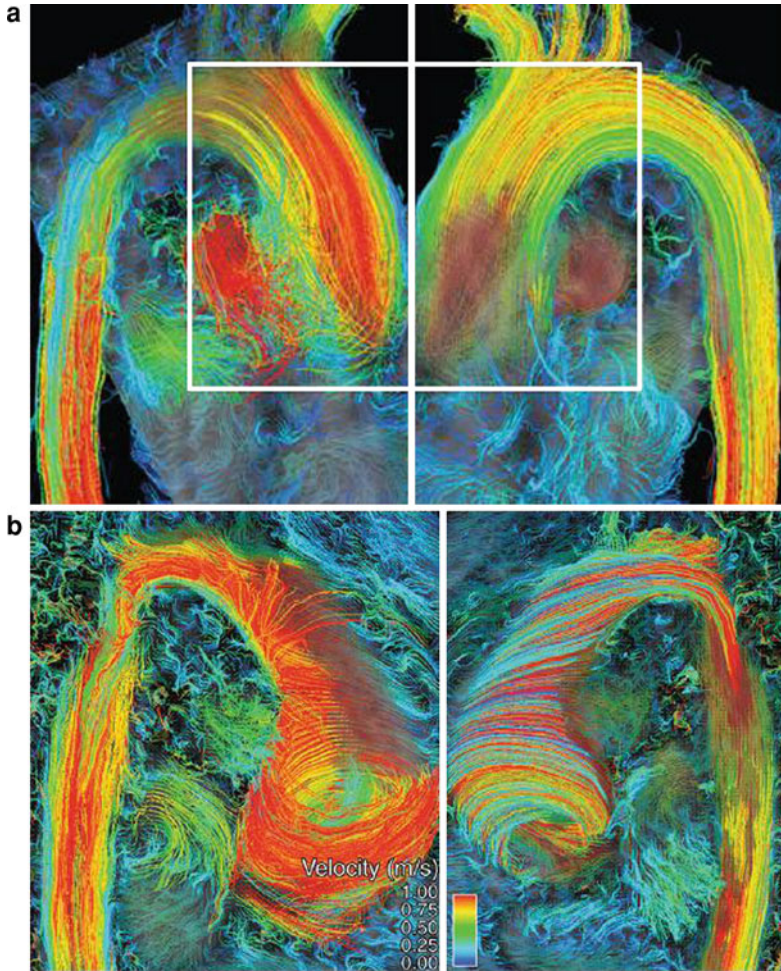


Fig. 19 Use of 4-dimensional flow magnetic resonance (MR) to characterize blood flow velocity in the human ascending aorta. **a** Smooth trajectory of normal systolic flow in a non-aneurysmal patient with tricuspid aortic valve. **b** Disrupted, turbulent and helical flow in a patient with an ascending aortic aneurysm and the abnormal bicuspid aortic valve. (Figure 1a and 2c, d from Hope et al. [144])

patients in a nested helical pattern and could be used to not only estimate local wall shear stress but also model wall strength (Fig. 19).

Our understanding of aortic diseases continues to advance as new partnerships between surgeons, biologists, engineers and mathematicians are established. The future of clinical care for aneurysmal patients lies at the intersection of these fields. In summary, the puzzle of how to care for patients with aneurysm will ideally incorporate knowledge of the biological pathways inciting matrix degradation, an understanding of the biomechanical contributions of the individual molecular

entities comprising the matrix, the matrix as a whole and a thorough quantification of both wall strength and stress. The missing pieces lie in developing the enabling noninvasive technologies to measure wall stress and strain, refinement of the mathematical models and establishing links between the clinical manifestations and the biological mechanisms inciting them.

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