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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.

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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 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 (*FBN1*), a matrix protein that also interacts with TGF-β. Mutations in *FBN1* 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

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.			
Solid mechanics	Fluid mechanics	Cell phenotype	Matrix composition
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	

calculated from the unloaded state for mouse AA range from 1.1 to 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 to 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