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Biomechanical roles of medial pooling of glycosaminoglycans in thoracic aortic dissection

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Abstract

Spontaneous dissection of the human thoracic aorta is responsible for significant morbidity and mortality, yet this devastating biomechanical failure process remains poorly understood. In this paper, we present finite element simulations that support a new hypothesis for the initiation of aortic dissections that is motivated by extensive histopathological observations. Specifically, our parametric simulations show that the pooling of glycosaminoglycans/proteoglycans that is singularly characteristic of the compromised thoracic aorta in aneurysms and dissections can lead to significant stress concentrations and intra-lamellar Donnan swelling pressures. We submit that these localized increases in intramural stress may be sufficient both to disrupt the normal cell-matrix interactions that are fundamental to aortic homeostasis and to delaminate the layered microstructure of the aortic wall and thereby initiate dissection. Hence, pathologic pooling of glycosaminoglycans/proteoglycans within the medial layer of the thoracic aortic should be considered as a possible target for clinical intervention.

Keywords

Osmotic (Donnan) swelling pressure; Stress concentration; Wall stress; Proteoglycan; TGF-beta

1 Introduction

Similar to other types of aneurysms and arterial dissections, the natural history of thoracic aortic aneurysms and dissections (TAADs) depends strongly on the mechanics and associated mechanobiology (Milewicz et al. 2008; Ruddy et al. 2008; El-Hamamsy and Yacoub 2009; Elefteriades and Farkas 2010). Indeed, one of the primary targets of non-surgical clinical care has long been the control of blood pressure to moderate aortic wall stress and thus the likelihood of dissection or rupture (Roberts 1982; Kroner et al. 2011); for example, current clinical guidelines for patients harboring a thoracic aneurysm recommend against extreme exertion, including weight lifting, in an attempt to moderate wall stress

(Mayerick et al. 2010). Nevertheless, there has been disproportionately less attention to the biomechanics of TAADs compared to that for abdominal aortic and cerebral aneurysms (cf. Lasheras 2007; Humphrey and Taylor 2008).

Prior studies of the biomechanics of thoracic aortic dissections have progressed along four lines. First, Prokop et al. (1970) and later Roach and colleagues (e.g., Tam et al. 1998) focused on the intramural (blood) pressure needed to propagate an existing intramural defect and thus create a false lumen within the aortic wall. They found that pressures needed to be on the order of 67 kPa (i.e., ~500 mmHg) to dissect the wall under static conditions, but only on the order of 25 kPa (~190 mmHg) under pulsatile conditions. Second, MacLean et al. (1999) performed complementary steady-state radial tensile tests on excised aortic samples and similarly found failure stresses on the order of 61 kPa. It is important to note that all of these studies used healthy animal thoracic aortas. In contrast, Holzapfel and colleagues reported experimental and computational results on the propagation of a dissection in healthy human abdominal aortas during in vitro mode I tearing tests (Sommer et al. 2006; Gasser and Holzapfel 2006). Among other findings, they reported that the “energy of dissection” was on the order of 5–8 mJ/cm² and anisotropic (with axial values greater than circumferential). Pasta et al. (2012) performed similar tearing tests, albeit more appropriately on healthy and diseased thoracic human aortas. They reported that delamination strength is lower in the inner than the outer media (consistent with the findings on healthy canine thoracic aorta; Van Baardwijk and Roach 1987) and that aortic disease lowers this strength further (~30%). Third, numerous groups used either in vitro flow loops or computational fluid dynamic models to estimate blood flow and pressure within an existing false lumen (Tsai et al. 2008; Karmonik et al. 2011; Tse et al. 2011). One of the key findings is that diastolic pressures can increase within a false lumen in the absence of a reentry tear or if the reentry tear is blocked by an intramural thrombus; such increases are only on the order of 1–2.5 kPa (~8 to 19 mmHg), however, relative to normal diastolic pressures on the order of 11 kPa (~80 mmHg). Each of these three lines of investigation provides insight into the propagation of a dissection, but not the initiation event or associated intralamellar delamination that likely precedes and facilitates the propagation. A fourth line of investigation employed finite element analyses to compute wall stresses in the ascending aorta and aortic arch in an attempt to identify reasons for the initiation of TAADs (Beller et al. 2008; Khanafer and Berguer 2009; Nathan et al. 2011). These studies are limited, however, by the inappropriate assumptions of spatially uniform, linearly elastic, homogeneous, and isotropic material behavior, the neglect of residual stresses which tend to homogenize the normal transmural distribution of stress, and the lack of attention to the underlying histopathology (cf. Humphrey 2002).

In contrast, we explore computationally a new hypothesis that a localized pooling of glycosaminoglycans/proteoglycans (GAGs/PGs) within the media of a compromised thoracic aorta can render this region vulnerable to dissection (Humphrey 2013). Briefly, TAADs share three distinguishing histopathologic characteristics with abdominal aortic and cerebral aneurysms: loss of competent elastic fibers, loss of functional smooth muscle cells, and extensive remodeling of collagen. Yet, among these three different types of aneurysms, thoracic aortic aneurysms alone exhibit extensive accumulations of GAGs/PGs and they alone tend to dissect (Milewicz et al. 2008; Collins et al. 2008; Borges et al. 2009; Maleszewski et al. 2009; Jain et al. 2011). There is, therefore, strong motivation from prior histopathologic observations as well as mechanical studies on other tissues, especially cartilage which is rich in GAGs/PGs, to explore the biomechanical consequences of accumulated GAGs/PGs in TAADs. Indeed, the parametric simulations presented herein suggest that a loss of tensile strength due to the localized loss of competent elastic fibers, collagen fibers, and smooth muscle cells (cf. Fig. 1 in Homme et al. 2006, Fig. 2 in Borges et al. 2008, and Fig. 1 in Borges et al. 2009 for histological evidence), a concentration of

stress around the associated pools of GAGs/PGs, and a localized increase in swelling (Donnan) pressure due to the accumulation of negatively charged GAGs/PGs could either initiate or contribute to an intra-lamellar delamination. We submit further that this unique combination of local changes in wall mechanics could subsequently contribute to the propagation of a dissection that either creates a false lumen (i.e., connects with the lumen via an intimal tear) or leads to a rupture of the wall (i.e., crosses the adventitial layer), which would also depend on the structural integrity of the adventitia that depends largely on fibrillar collagen.

2 Theoretical background and framework

Dissections occur most frequently in the ascending aorta, but in the proximal descending aorta as well (Milewicz et al. 2008; Lindsay and Dietz 2011). Although we focus on the latter, our results should hold for both regions because of structural and mechanical similarities between these two regions of the thoracic aorta. The normal human thoracic aorta is ~1.7 to 2.0 mm thick and consists of three primary layers (Iliopoulos et al. 2009): the innermost layer, or intima, occupies ~5% of the wall and probably confers little overall load-bearing capability; the middle layer, or media, occupies ~77% of the wall and likely bears most of the hemodynamically induced loads during a cardiac cycle; the outermost layer, or adventitia, occupies the remaining ~18% of the wall and is thought to serve as a protective sheath during marked, acute increases in blood pressure (Lindeman et al. 2010). The thoracic aorta also remodels with aging, and in particular, the intimal layer tends to thicken due to an accumulation of disorganized collagen and thereby to carry more load (Weisbecker et al. 2012). Regardless of age, however, dissections appear to originate and initially propagate primarily within the media (MacLean et al. 1999; Bode-Janisch et al. 2012); thus, we focused on stresses within this layer and employed a homogenized model of its nonlinearly elastic and anisotropic mechanical behavior under finite deformations. Specifically, we used a “four-fiber family” constitutive model that describes well the mechanical behavior of the human abdominal aorta under normal conditions as well as during aging and the development of aneurysms (Ferruzzi et al. 2011). Associated best-fit model parameters for the human descending thoracic aorta were determined herein via nonlinear regression of data reported by Garcia-Herrera et al. (2012) on its biaxial mechanical behavior, as detailed below.

The media of the normal human ascending aorta consists of ~70 lamellar units, each of which consists of paired, parallel layers of elastic laminae and embedded smooth muscle cells, adhesion molecules, collagens, and GAGs/PGs (Dingemans et al. 2000). These “medial lamellar units” are approximately 15 microns thick and tend to support a nearly constant tension (~2 N/m) under normal conditions (cf. Humphrey 2002). Overall, the non-diseased medial layer consists of, in middle age, approximately 23% elastin, 30% collagen, 43% smooth muscle, and 4% GAGs/PGs by dry weight (Iliopoulos et al. 2009; Wight 2008). It appears that localization of GAGs as well as elastin to the media contributes to the existence of residual stresses in healthy arteries (Azeloglu et al. 2008), which in turn tend to homogenize the transmural distribution of tensile stresses (Humphrey 2002). This latter finding motivated a fundamental hypothesis in arterial mechanobiology that, under normal conditions, vascular cells tend to establish, maintain, and restore local homeostatic stresses via a continuous turnover of cells and matrix (Humphrey 2008). It appears, however, that TAADs result from a dysregulated mechanical homeostasis (Jones et al. 2009; Lindsay and Dietz 2011), which may be both a cause and consequence of perturbations in the mechanical state of stress from homeostatic.

Given the apparent uniformity in both lamellar tension and transmural stress in the normal aortic media, we focused on a representative local portion of the media that was initially

subjected to nearly uniform and equibiaxial in-plane circumferential and axial stresses plus an out-of-plane compressive radial stress (cf. Humphrey 2002). Under normotensive conditions in a young healthy person (~90 mmHg blood pressure), the in-plane stresses are on the order of 100 kPa, whereas the out-of-plane stress (dictated primarily by boundary conditions, particularly luminal blood pressure) is on the order of -6 kPa (ranging from -12 kPa at the intima to ~0 at the adventitia if untethered). As noted by Maleszewski et al. (2009), pooled GAGs/PGs tend to occupy “cystic spaces” (Fig. 1 top right; from Maleszewski et al. 2009) on the order of 200–500 microns $\times$ 200–1,000 microns in Marfan syndrome and 20–50 microns $\times$ 100–200 microns in Loeys–Dietz syndrome, two heritable disorders with a high propensity for aortic dissection (Jain et al. 2011). Hence, most pools of GAGs/PGs encompass two to twenty or more medial lamellar units, which supports our modeling of this condition at the continuum level as a localized inclusion (GAGs/PGs) within a prestressed continua (normal wall), each described by individual material properties. In particular, the GAGs/PGs were endowed with a modest tensile stiffness by using a modified neo-Hookean constitutive relation, but more importantly, they were endowed with a significant compressive stiffness and swelling potential by allowing a Donnan osmotic pressure (see below). Briefly, the Donnan effect explains thermodynamically how equilibrium and electro-neutrality can be maintained in a biological tissue while gradients or jumps persist in mobile ions (e.g., Na^+ within the interstitial fluid) due to a region of the tissue having fixed molecules that are charged (e.g., negative charges due to SO_3^- or COO^- groups within GAGs; Alberts et al. 2002). In turn, these ionic gradients or jumps alter the regional distribution of interstitial water and, as in the case of GAGs/PGs, cause a swelling pressure within the region containing the fixed charges (Tinoco et al. 2002). A pilot finite element study revealed marked changes in the distribution of intramural stress when modeling the particular case represented by the histology shown in Fig. 1, but because of the considerable variability in the size and shape of these pools of GAGs/PGs (e.g., Collins et al. 2008; Milewicz et al. 2008; Maleszewski et al. 2009; Jain et al. 2011), we explored parametrically the potential mechanical consequences of different, but otherwise idealized (spheroidal) centrally located, pools of GAGs/PGs on the local stress field within the media. To simplify the computations and the interpretation of the results, we first considered a local rectangular domain 10 mm $\times$ 10 mm $\times$ 1.7 mm subjected to far-field uniform tensile circumferential and axial Cauchy stresses of 100 kPa and a compressive radial Cauchy stress of -6 kPa. Moreover, because of the inherent geometric symmetry, the final model consisted of one-fourth of the overall domain and similarly one-fourth of the GAG/PG inclusion (Fig. 1).

3 Computational methods

Histological observations reveal two primary directions within the media about which the collagen fibers are distributed (Schriebl et al. 2012b). Although such findings are often used to motivate a two-fiber family constitutive model (Holzapfel et al. 2000), we prefer a four-fiber family model that can also capture phenomenologically the net effects of the fiber distributions and the yet unquantified effects of lateral cross-links and physical entanglements. This model is defined by a strain energy function W of the form

$$W = \frac{c}{2} (I_c - 3) + \sum_{k=1}^4 \frac{c_1^k}{4c_2^k} \left(\exp \left[c_2^k \left((\lambda^k)^2 - 1 \right)^2 \right] - 1 \right) \quad (1)$$

where c , c_1^k , and c_2^k are material parameters, I_c is the first invariant of the right Cauchy–Green tensor $\mathbf{C}$ (i.e., $\text{tr } \mathbf{C}$), and λ^k is the stretch ratio of a fiber that was oriented in direction $\mathbf{M}^k = [0, \sin \alpha_0^k, \cos \alpha_0^k]$ in an appropriate reference configuration (i.e., $\lambda^k = \sqrt{\mathbf{M}^k \cdot \mathbf{C} \mathbf{M}^k}$).

We let $\alpha_0^1=0^\circ$ (axial family), $\alpha_0^2=90^\circ$ (circumferential family), and $\alpha_0^{3,4}=\pm\alpha_0$ (symmetric diagonal family), the last of which is thus a free parameter. That this four-fiber family model describes diverse human aortic stress-strain data well in a least squares sense is demonstrated by Ferruzzi et al. (2011) and Roccabianca et al. (2013). Best-fit values of the 8 model parameters were determined herein via a nonlinear regression of biaxial data that were recreated from the constitutive relations and parameters given in Garcia-Herrera et al. (2012) for the descending thoracic aorta of both young (20–35 years old) and older (45–60 years old) human subjects (see Table 1). Noting that these 8 parameters (c , c_1^1 , c_2^1 , c_1^2 , c_2^2 , $c_1^{3,4}$, and α_0) reflect the stiffness of the elastin-dominated matrix (first parameter), axial effects of oriented families of collagen fibers (next two parameters), circumferential effects of oriented families of collagen fibers (next two parameters), and two families of symmetric diagonal collagen fibers (next three parameters, including the angle of this family relative to axial), Table 1 reveals that the best-fit value for the elastin-dominated parameter was slightly lower for the older subjects and that contributions by the diagonal collagen fiber families tended to dominate the other two collagen families in this description, both consistent with data. Finally, note that histological observations suggest that the elastin and collagen fibers merely “terminate” at the edge of a GAG/PG pool (Homme et al. 2006; Borges et al. 2008), without remodeling around the edge; hence, we assumed homogeneous properties outside the inclusion.

GAGs/PGs are thought to confer little tensile stiffness to the aortic wall. Their mechanical behavior was modeled using a modified neo-Hookean relation, namely a strain energy function W of the form

$$W=\mu((I_c-3)/2-\ln(\det \mathbf{F})) \quad (2)$$

where $\mathbf{F}$ is the deformation gradient tensor and μ is a shear modulus, the value of which was studied parametrically. These two constitutive relations were incorporated within a finite element model of a rectangular portion of the media (10 mm $\times$ 10 mm $\times$ 1.7 mm), including a single centrally located GAG/PG inclusion (cf. Fig. 1). The final model was constructed of 75,168 linear hexahedral elements using a commercial mesh generation code (Cubit, v. 13.2) and the open source finite element code FEBio (v. 1.4.2) developed at the University of Utah (Maas et al. 2012). Preliminary studies comparing solutions for models containing 62,500, 75,000, 87,500, and 100,000 elements suggested that a 75,000 element model yielded convergent solutions.

The analysis was then performed via four sequential loading steps: a displacement-driven problem to impose initial equibiaxial circumferential and axial stresses of 100 kPa, a radial compression to superimpose a –6 kPa radial stress, an osmotic loading to increase the fixed charge density of the normal arterial wall from 0 mEq/l to its baseline value of –50 mEq/l (Porterfield et al. 1968), and an osmotic loading of the inclusion to 0 (for a void) –80, or –160 mEq/l depending on the simulation. The one exception to this general strategy was the initial loading of the media to biaxial stresses of 240 kPa (circumferential) and 150 kPa (axial) for the case of elevated blood pressure (radial stress of –10 kPa). In both cases, these target values of in-plane normal stresses were first computed from a standard thick-walled cylindrical model of the arterial wall including residual stresses (Roccabianca et al. 2013).

4 Computational results

4.1 Salient effects of a GAG/PG pool

Histopathology reveals that pools of GAGs/PGs within the thoracic aorta have diverse shapes and sizes. Nevertheless, preliminary computational studies suggested that overall

mechanical consequences of a spheroidal GAG/PG inclusion on the local stress field tended to be qualitatively similar regardless of aspect ratio or size. Figure 2 shows representative features of the stress field that resulted from the presence of a small (0.0022 mm^3), asymmetric (defined by the parameters $c/a = 2.303$ and $b/a = 1.00$; cf. Fig. 1) inclusion endowed with uniform material properties (neo-Hookean shear modulus = 0.5 kPa) and fixed charge density (-80 mEq/l , recalling that the normal baseline value is -50 mEq/l). The dimensions of the inclusion in this example were chosen to model the particular shape represented by the histology shown in Fig. 1. Note the highly localized increase in the hoop (i.e., circumferential) and axial stresses around the periphery of the inclusion (i.e., stress concentrations) as well as the highly focal increase in the radial stress just in front of the tip of the inclusion along its major axis. In particular, this marked increase in radial stress included a transition from the far-field uniform state of compression to a highly focal state of tension. Because peak values of stress tended to localize within common regions near the maximum dimensions of the inclusion (denoted R1 to R4 in Fig. 2), we focus on such regions below.

4.2 Size and shape of a GAG/PG pool

Figure 3 shows the effect of the shape of an inclusion (parameterized via c/a and b/a as shown in Fig. 1) given the same volume (0.028 mm^3), uniform material properties (shear modulus = 0.5 kPa), and fixed charge density (-80 mEq/l). The values for volume (given by $a = b = 150$, $c = 300$ microns) were chosen to reflect dimensions of the pools of GAGs/PGs found in Marfan syndrome (Maleszewski et al. 2009). Results are plotted as the peak value of radial, hoop, axial, or in-plane shear stress observed within any of the four predetermined regions of interest (R1–R4). A spherical inclusion (c/a and $b/a = 1$) resulted in an ~ 3.5 -fold increase in hoop and axial stress, which increased to ~ 5.5 -fold in the more asymmetric inclusions. Although failure criteria have not been established for the thoracic aorta, diverse studies suggest that abdominal aortic aneurysms may fail (rupture) at peak in-plane normal stresses on the order of 450 kPa (Fillinger et al. 2002). The most asymmetric inclusions considered herein (c/a and $b/a \sim 4.3$) resulted in local values on that order.

More dramatically, however, Fig. 3 shows further that GAG/PG inclusions caused the radial stress to transition from compressive (-6 kPa) to tensile in regions just in front of the tip of the inclusion, the degree of which increased with increasing asymmetry of the inclusion. For example, the peak tensile radial stress reached $\sim 60 \text{ kPa}$ in region R3 in the most asymmetric inclusions considered. Recall, therefore, that MacLean et al. (1999) found that elastic lamellae within healthy aorta separated and the media failed under the action of applied radial stresses on the order of 61 kPa under static conditions, consistent with related findings by Prokop et al. (1970) and Tam et al. (1998) who used intramural pressurization to determine failure thresholds. Figure 4 shows further that a 4-fold change in the volume of the inclusion (from 0.014 to 0.028 to 0.056 mm^3) altered both the degree of the stress concentrations and the magnitude of the radial stress, although shape appeared to play a more important role as might be expected. Regardless, given that measured radial failure stresses have been reported to be even lower under dynamic loading ($\sim 25 \text{ kPa}$; Prokop et al. 1970) and that diseased aortas may fail at yet lower values (30% lower; Pasta et al. 2012), the current computations clearly suggest that pooled GAGs/PGs could locally increase the tensile radial stresses to well within the reported failure regimes.

4.3 Aortic properties

It should be noted that the slight material anisotropy of the normal media, as captured by the four-fiber family constitutive relation (Eq. 1), rendered results in Figs. 2, 3 and 4 slightly different for equal geometric asymmetries described by the parameters c/a and b/a . It is well known that aging can result in significant overall stiffening of the arterial wall as well as

changes in anisotropy (Garcia-Herrera et al. 2012). Because TAADs present in young and old individuals are alike, we repeated the simulations of Figs. 2, 3 and 4 for normal medial properties for individuals aged 45–60 years of age rather than the originally selected 20–35 years of age. Albeit not shown, effects of age on perturbations in the stress field due to a GAG/PG inclusion were generally modest. The most dramatic difference in results was in the peak tensile radial stress for the most asymmetric inclusion ($c/a \sim 4.3$), wherein increased age increased this value from ~65 to 77 kPa.

4.4 Elevated blood pressure

As noted earlier, one of the primary non-surgical clinical treatments for TAADs is control of blood pressure. Indeed, the potential deleterious effects of elevated blood pressure is reflected in the warning to individuals with a thoracic aneurysms to avoid weight training wherein blood pressures can rise over 200 mmHg (Mayerick et al. 2010). Figure 5 compares effects of a GAG/PG inclusion on local wall stresses under normal (90 mmHg) and elevated (220 mmHg) static blood pressures for a young otherwise healthy subject. As it can be seen, elevated blood pressure dramatically increased the predicted local peak stresses, with tensile in-plane stresses approaching 1 MPa (relative to baseline values of 240 kPa hoop stresses and 150 kPa axial stresses) and tensile radial stresses approaching 100 kPa (relative to a baseline ~10 kPa radial stress), both well above apparent failure thresholds (e.g., the aforementioned 450 and 60 kPa, respectively). These simulations are thus consistent with clinical observations that acutely elevated blood pressure, particularly during strenuous activity or emotional stress, could contribute significantly to an increased risk of dissection.

4.5 GAG properties

Notwithstanding ubiquitous findings of accumulations of GAGs/PGs in TAADs, there has not been any attention to the related biomechanics, including the lack of measurement of physicochemical properties of aortic GAGs/PGs in humans. Hence, based on the most relevant data (Porterfield et al. 1968; Chahine et al. 2005; Azeloglu et al. 2008), we performed parametric studies to investigate the potential role of inclusion stiffness (e.g., a neo-Hookean shear modulus of 0 kPa for a void and from 0.05 to 5.0 kPa for a GAG/PG pool) and fixed charge density (0 mEq/l for a void and from –50 mEq/l at baseline to –160 mEq/l). Figure 6 suggests that, over the range studied, the value of the GAG/PG stiffness had little effect on the predicted stress concentrations, whereas the value of the fixed charge density (i.e., Donnan swelling potential) had a dramatic effect, particularly on the value of the peak tensile radial stress just in front of the tip of the inclusion. For example, “increasing” the fixed charge density from –50 to –160 mEq/l increased the peak radial stress from ~50 to ~100 kPa, again well above the reported values at which intra-lamellar delamination can be expected (MacLean et al. 1999).

5 Discussion

The importance of heritable disorders in TAADs—especially Marfan syndrome, familial TAADs, and Ehlers–Danlos syndrome—has appropriately focused attention on the affected glycoproteins and proteins: fibrillin-1, alpha smooth muscle alpha actin and beta myosin, and collagen III, respectively. The structural integrity of the aortic wall clearly depends on the presence, organization, strength, and interactions of each of these constituents, but others as well. Whereas the concentration of GAGs/PGs is low in the normal thoracic aorta (~2 to 5% by dry weight; Wight 2008), histopathology consistently reveals significant increases in GAGs/PGs in many arterial injuries and diseases, including hypertension and atherosclerosis (Reynertson et al. 1986; Rasmussen et al. 1995; Yang et al. 2010). Of more importance herein, however, localized pooling of GAGs/PGs is a singular characteristic histopathologic feature of TAADs (Collins et al. 2008; Milewicz et al. 2008; Borges et al. 2009;

Maleszewski et al. 2009; Grond-Ginsbach et al. 2010; Guo et al. 2011; Jain et al. 2011; Bode-Janisch et al. 2012).

We thus focused on a new hypothesis that the pooling of GAGs/PGs may contribute to an initial delamination within the media due to a combined localized loss of tensile strength, genesis of stress concentrations, and increased Donnan swelling pressures, which in turn could promote dissections in the thoracic aorta (Humphrey 2013). Note, therefore, that it has long been assumed by most that dissections (and the associated false lumens) arise following an intimal tear that propagates into the media under the action of blood pressure (e.g., Roberts 1982; Tse et al. 2011). We agree with Matt et al. (2010), however, that “it is uncertain whether the initiating event is a primary rupture of the intima with secondary dissection of the media.” Indeed, new insight into the origin and time course of dissections has recently been gleaned from mouse models of dissecting aneurysms. Chronic subcutaneous infusion of angiotensin-II in athero-prone (ApoE^{-/-}) mice yields dissecting suprarenal abdominal aortic aneurysms within a period of weeks (Saraff et al. 2003). Among the many findings, the first observable change within the wall is the accumulation of macrophages in the media, which via the production of diverse cytokines and proteases appears to initiate a local weakening of the media and possible delamination that could initiate a dissection independent of an initial intimal tear (Schrieffl et al. 2012a). There can similarly be an intramural infiltration of inflammatory cells in human TAADs (He et al. 2008), although this is thought to be less prominent (Lindsay and Dietz 2011). Nevertheless, histopathologic data from both humans and animal models consistently reveal localized regions distant from the luminal surface that appear both to be weakened due to the loss of elastic fibers, functional smooth muscle, and collagen fibers and to be filled with GAGs/PGs (Lesauskaite et al. 2001; Homme et al. 2006; Borges et al. 2008, 2009; Collins et al. 2008; Milewicz et al. 2008; Maleszewski et al. 2009).

Our initial simulations revealed that even a localized replacement of tensile-bearing constituents (e.g., elastic fibers, smooth muscle, and collagen) with a material having an equivalent fixed charge density (-50 mEq/l) but a lower tensile stiffness (comparable to that of GAGs/PGs) could result in a weak inclusion and associated marked stress concentrations. That is, relative to the far-field in-plane stresses, which were not affected by the simulated local pooling of a non-tensile-bearing material, stress concentrations ranged from ~ 3.5 to 5.0 , with the largest values occurring at near the tip of the inclusion for the more asymmetric geometries. These simulations allowed us to separate purely mechanical from electrochemomechanical effects. Yet, the GAGs/PGs of interest are highly negatively charged, thus the more important simulations focused on this aspect of the overall mechanics. Given the lack of data on the electrochemistry of GAGs/PGs in TAADs, we selected parameter values that represented reasonable ranges of fixed charge density based on data that are available for the aorta (Porterfield et al. 1968; Azeloglu et al. 2008) as well as comparable experimental information on solutions of chondroitin sulfate (Chahine et al. 2005). For values of fixed charge density ranging from -50 to -160 mEq/l, our simulations suggested that a Donnan swelling pressure could increase the in-plane stress concentrations, but even more so could increase the tensile radial stress locally, with values ranging from 40 to 100 kPa (relative to baseline values of -6 kPa). Given that the more asymmetric inclusions tended to result in the highest values of tensile radial stress, note that most histopathologic images of pools of GAGs/PGs in diseased thoracic aorta reveal complex shapes, including multiple coalescing pools (e.g., see Figure 1 in Jain et al. 2011) or even “finger-like” projections into the compromised media (e.g., see Figure 1 in Maleszewski et al. 2009). Hence, the present findings likely represent conservative estimates. Indeed, recall that the vast majority of the most relevant experimental findings on radial failure stresses also likely represent only estimates because of the common use of healthy rather than diseased aortas. That is, values of radial failure stress of 65 kPa for static loading and 25 kPa

for dynamic loading of healthy animal aortas (Prokop et al. 1970; Van Baardwijk and Roach 1987; MacLean et al. 1999) should probably be lowered based on the report that dissection stresses are ~30% lower in diseased than healthy human aorta (Pasta et al. 2012). That is, given that the aorta is always under dynamic loading, it is possible that diseased vessels could delaminate at radial stresses on the order of 0.7×25 kPa, or 17.5 kPa. The present static simulations suggest that stress concentrations and Donnan swelling pressures could easily yield intra-lamellar radial stresses on this order and consequently that pooled GAGs/PGs could contribute to the increased inter-lamellar separation distances seen in compromised aortas (Guo et al. 2011; Jain et al. 2011) and help initiate intra-lamellar delaminations that could ultimately lead to dissections. In particular, Donnan swelling pressures could be similar to or well greater than the blood pressures that have been calculated by computational fluid dynamics to exist within an already established false lumen (i.e., intramural dissection)—see Tsai et al. (2008) or Karmonik et al. (2011). We submit, therefore, that a dissection need not initiate from an intimal tear and associated exposure of the media to blood pressure. Rather, GAG/PG-induced swelling pressures and intra-lamellar stress concentrations may well contribute significantly to the initiation and subsequent propagation of a thoracic medial dissection.

A corollary to these findings, of course, is that even less marked accumulations of GAGs/PGs could possibly, via either a mass effect or an increased Donnan swelling pressure, perturb direct smooth muscle—extracellular matrix interactions by separating the elastic laminae. Such perturbations, in turn, could alter mechanosensitive cell signaling and possibly disrupt matrix homeostasis or cell survival, or both. Indeed, such perturbations in matrix-controlled cell signaling could be consistent with similar suggestions by Bunton et al. (2001) and Milewicz et al. (2008), which were motivated by different aspects of the disease (i.e., increased proteolytic activity and loss of smooth muscle cell function). There is a need, therefore, to consider both mechanical (e.g., intralamellar delamination) and mechanobiological (cell signaling) effects of pooled GAGs/PGs, which could elicit many changes in wall homeostasis.

Before concluding, we emphasize that this is but an initial mechanical study; there is a need for both more data and further analyses to determine the precise biochemomechanical consequences of accumulated GAGs/PGs in thoracic aortic disease. Toward this end, note that some of the pooled GAGs/PGs may be either abnormal or degraded (Borges et al. 2009, which may alter their biological and physicochemical properties. In particular, degradation products from GAGs/PGs can elicit diverse changes in cell signaling (Stern et al. 2006; Ricard-Blum and Ballut 2011), which in turn could affect the development or repair of the accumulated GAGs/PGs or the remodeling of nearby tissue; thus, there is a need to consider the associated biochemomechanical effects as well. In addition, note that Elkin et al. (2011) report that the degradation of chondroitin sulfate in brain tissue can reduce its fixed charge density by ~20%, whereas Wheaton et al. (2004) reported that osteoarthritis (presumably via the degradation of PGs) can reduce the fixed charge density in cartilage by 20–40%. Clearly, there is a pressing need for specific information on aortic values of fixed charge density and how they may change with disease. Such changes may also affect the mechanical properties of the pooled GAGs/PGs, including viscoelastic properties. We did not consider effects of dynamic loading or the possible effects of viscoelasticity herein, both of which merit careful study, particularly because Prokop et al. (1970) showed that failure stresses are lower under dynamic loading.

6 Conclusion

The ultimate fate of TAADs, namely catastrophic rupture of the wall, depends primarily upon the mechanics—failure occurs when wall stress exceeds wall strength. Biomechanics

should thus play an increasingly important role in understanding these lesions and improving interventional strategies. In this paper, we presented novel computational findings that support a new hypothesis that focuses attention on possible biomechanical, electrochemical, and mechanobiological roles of pooled GAGs/PGs in separating the elastic laminae that define the medial lamellar units. Similar roles of inclusions (i.e., microcalcifications) have been implicated in rendering atherosclerotic plaques vulnerable to rupture (Vengrenyuk et al. 2006), hence highlighting the general need for increased attention to local mechanical failure mechanisms in vascular mechanics. We did not consider the mechanics associated with the subsequent process of dissection (i.e., propagation of the initial delamination), however, or the eventual causes of an intimal tear versus a transmural rupture. There is, therefore, a need for much more study of many aspects of the biochemomechanics of TAADs. Nevertheless, we expect that GAG/PG-induced stress concentrations and Donnan swelling pressures within the aortic wall will likely contribute to the subsequent tearing or rupture as well. Whether our overall hypothesis will contribute to understanding non-traumatic dissections of other arteries (e.g., cervical, intracranial, renal, coronary, and carotid; Grond-Ginsbach et al. 2010; Stevic et al. 2011) or a common mouse model of dissecting aneurysms (Saraff et al. 2003) remains to be seen, but comparisons of histopathological features and the biochemomechanics of different types of dissections may provide further insight into mechanisms responsible for each particular situation.

We also did not address the likely location of the intimal tear that is typically diagnostic for the presence of a dissection or associated false lumen within the wall. It is observed, for example, that many dissection-associated false lumens originate just distal to the aortic valve in the ascending aorta or just distal to the left subclavian artery in the descending aorta (Milewicz et al. 2008). Of particular note, these two sites demarcate transitions between smooth muscle cells of different embryonic lineages: from those derived from the second cardiac field to those derived from the neural crest and from those derived from the neural crest to those derived from the mesoderm, respectively (Majesky et al. 2011). There is similarly a need to understand better the possible biological and mechanical consequences of these transition regions, including different TGF- β signaling, effects of angiotensin-II, and so forth. We suggest, however, that the common occurrence of an intimal tear at these unique sites of cellular transition need not imply that the initiating delamination occurred at that site. Rather, the present results are consistent with the hypothesis that the initial delamination can originate at other sites and then propagate distally or proximally until communicating with the lumen at preferred sites of biomechanical discontinuity, which would again focus mechanical analysis on local effects. This possibility and others must be investigated carefully, however.

Finally, we did not address the possible cause of the initial pooling of the GAGs/PGs. As noted in Humphrey (2013), this pooling could be consistent with the growing awareness of the importance of the dysregulation of transforming growth factor-beta (TGF- β) in TAADs (Jones et al. 2009; Inamoto et al. 2010; Lindsay and Dietz 2011; Halushka 2012). In particular, vascular smooth muscle cells can increase their production of GAGs/PGs in response to increased TGF- β activity, particularly in cases of disease or injury (Rasmussen et al. 1995; Wight 2008; Yang et al. 2010). Indeed, Nataatmadja et al. (2006) specifically reported that overexpression of TGF- β in Marfan syndrome associates with a significant increase in hyaluronan, a high molecular weight GAG that can influence extracellular matrix organization as well as cellular apoptosis, migration, and differentiation. Hyaluronan also colocalizes with versican, a chondroitin sulfate-rich PG that is highly charged (Wight 2008), and could contribute a Donnan swelling pressure. Nataatmadja and colleagues even suggested further that increased hyaluronan could “limit tissue repair and ... contribute to aneurysm development.” There is clearly a need to consider possible connections between

dysregulated TGF- β and the excessive production and accumulation of GAGs/PGs, although other mechanisms may similarly be operative.

In conclusion, it is widely recognized, even among basic life scientists and clinicians, that mechanics plays fundamental roles in the natural history of TAADs (Milewicz et al. 2008; Ruddy et al. 2008; El-Hamamsy and Yacoub 2009; Elefteriades and Farkas 2010). There is clearly a need to understand better the mechanical consequences of altered fibrillin-1 in Marfan syndrome, altered smooth muscle in familial TAADs, and altered collagen III in Ehlers–Danlos syndrome, as well as possible mechanical consequences of altered fibulin-4,5 (which contribute to elastogenesis), collagen V and biglycan (which contribute to collagen fibrillogenesis), and collagen cross-linking as revealed by recent rodent models. Nevertheless, albeit not considered before in aortic mechanics, the present computational simulations strongly suggest that there is also a need to understand the perhaps fundamental role of charged glycosaminoglycans and proteoglycans in TAADs.

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Fig. 1.

Final quarter-symmetric finite element model (75,168 hexahedral elements) of the overall $10 \text{ mm} \times 10 \text{ mm} \times 1.7 \text{ mm}$ rectangular slab of the aortic media with a central GAG/PG inclusion. Shown, too, are dimensions for the three axes of the inclusion (a , b , and c , as, for example, $a = 0.061 \text{ mm}$, $b = 0.061 \text{ mm}$, and $c = 0.14 \text{ mm}$ in this case), values of which were studied parametrically. The GAG/PG inclusion was endowed with a modified neo-Hookean material behavior, whereas the media was endowed with a nonlinearly elastic and anisotropic behavior described by a four-fiber family constitutive model. The fixed charge density of the GAG inclusion was studied parametrically from 0 to -160 mEq/l , where the fixed charge density of the non-affected aortic media was maintained at -50 mEq/l . Note that the quarter-symmetric model is $5 \text{ mm} \times 5 \text{ mm} \times 1.7 \text{ mm}$

Fig. 2.

For qualitative purposes, shown is a grayscale representation of multi-axial stresses in and near the GAG/PG inclusion for an illustrative case. Specifically, this inclusion was defined by a volume of 0.0022 mm^3 , dimensions $c/a = 2.303$, $b/a = 1.00$, a neo-Hookean shear modulus of 0.5 kPa , and a fixed charge density of -80 mEq/l . The *scale bar* represents well the stresses on the right face in this oblique view; additional *shading* of the left face helps to visually convey the three-dimensionality of the computational domain (cf. Fig. 1, which includes similar shading). Focusing on the right face, note the hoop and axial stress concentrations as well as the transition of the radial stress from a low compressive value in the far field to a high tensile value near the tip of the inclusion. For quantitative results in the four regions of interest (R1–R4), see Figs. 3, 4, 5 and 6

Fig. 3.

Calculated peak values of stress within any of the four primary regions of interest (R1–R4, see Fig. 2) as functions of the inclusion geometry (b/a varies while $c/a = 1.0$ and c/a varies while $b/a = 1.0$; see Fig. 2), with an inclusion volume of 0.028 mm^3 , shear modulus of 0.5 kPa , and fixed charge density of -80 mEq/l . Values of stress are shown for radial (*closed square*), hoop (*closed diamond*), and axial (*closed triangle*) directions as well as for the in-plane shear stress (*closed circle*). The *open symbols* represent far-field “prestress” values (radial = -6 kPa , hoop and axial = 100 kPa , and shear = 0 kPa)

Fig. 4.

Peak values of stress in any region of interest R1–R4 for 3 different inclusion volumes: 0.028 mm³ (*closed square*), 0.056 mm³ (*closed diamond*), 0.014 mm³ (*closed triangle*). Values are also given for different inclusion geometries (c/a varies while $b/a = 1.00$). The *open circles* represent the far-field prestresses (radial = -6 kPa, hoop and axial = 100 kPa, and shear = 0 kPa)

Fig. 5.

Comparison of peak values of stress in regions R1–R4 for a normal blood pressure of 90 mmHg (*closed square*) and an elevated blood pressure of 220 mmHg due to exercise (*closed diamond*) for a young healthy individual. Peak values of stress are shown for different inclusion geometries (b/a varies while $c/a = 1.00$). The *open symbols* represent the far-field prestresses: *open squares* correspond to a normal blood pressure (radial = -6 kPa, hoop and axial = 100 kPa, and shear = 0 kPa), and *open diamonds* correspond to the case of extreme exercise (radial = -10 kPa, hoop = 240 kPa, axial = 150 kPa, and shear = 0 kPa)

Fig. 6.

Peak values of stress in regions R1–R4 as a function of the fixed charged density of the GAG inclusion and its shear modulus: 0.05 kPa shown by *closed squares*, 0.5 kPa shown by *closed diamonds*, and 5.0 kPa shown by *closed triangles*. The *closed circles* represent the peak stresses due to a pure geometric effect (i.e., a void defined by a zero shear modulus and zero fixed charged density). The *open circles* represent the far-field prestresses (radial = –6 kPa, hoop and axial = 100 kPa, and shear = 0 kPa)

Table 1

Best-fit values of model parameters for the four-fiber family description of biaxial data from Garcia-Herrera et al. (2012) for the human descending thoracic aorta

Age range	c (kPa)	c_1^1 (kPa)	c_2^1	c_1^2 (kPa)	c_2^2	$c_1^{3,4}$ (kPa)	$c_2^{3,4}$	α_0 (deg)
20–35 years old	37.20	5.16E–06	4.61E–06	3.20E–05	1.68E–05	28.16	3.48	43.88
45–60 years old	24.66	2.32E–05	1.33E–05	3.22E–05	7.57E–06	90.10	5.33	42.19

The lower value of the elastin-related parameter c and the higher values of the diagonal collagen fiber-related parameters $c_1^{3,4}$ and $c_2^{3,4}$ for the older subjects are both consistent with expected effects of aging