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Effect of Aneurysm on Biomechanical Properties of “Radially-oriented” Collagen Fibers in Human Ascending Thoracic Aortic Media

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Abstract

We recently reported a mechanistic model to link micro-architectural information to the delamination strength (S_d) of human ascending thoracic aorta (ATA). That analysis demonstrated that the number density (N) and failure energy (U_f) of the radially-oriented collagen fibers contribute to the S_d of both aneurysmal (ATAA) and non-aneurysmal (CTRL-ATA) aortic tissue. Among the set of ATAA samples, we studied specimens from patients displaying bicuspid (BAV) and tricuspid aortic valve (TAV) morphologic phenotypes. Results from our prior work were based on the assumption that the U_f was independent of dissection direction. In the current study, we excluded that assumption and hypothesized that U_f correlates with the S_d of ATAA. To test the hypothesis, we used previously-reported experimentally-determined S_d measurements and N of radially-oriented collagen fibers as input in our validated mechanistic model to calculate U_f for BAV-ATAA, TAV-ATAA and CTRL-ATA tissue specimens. The results of our analysis revealed that U_f is significantly lower for both BAV-ATAA and TAV-ATAA compared to CTRL-ATA cases, and does not differ between BAV-ATAA and TAV-ATAA. Furthermore, we found that U_f is consistent between circumferential-radial and longitudinal-radial planes in either of BAV-

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CONFLICT OF INTEREST STATEMENT

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ATAA, TAV-ATAA or CTRL-ATA specimens. These findings employ a novel mechanistic model to increase our understanding of the putative interrelationship between biomechanical properties, extracellular matrix biology, and failure energy of aortic dissection.

Keywords

human ascending thoracic aortic aneurysm; radially-oriented collagen; micro-architecture; multi-photon microscopy; dissection; fiber bridge failure energy

1 INTRODUCTION

Ascending aortic disease manifesting as aneurysm or dissection is a major health concern (Jondeau and Boileau, 2012; Lu *et al.*, 2012; Matsushita *et al.*, 2012; Takigawa *et al.*, 2012). Aortic dissection (AoD) usually begins with an intimal tear in the thoracic aorta permitting entry of blood in the wall. This tear eventually splits the media and creates a false lumen, which in turn can re-enter the true lumen anywhere along the course of AoD or exit through the adventitia causing complete rupture (Lu *et al.*, 2012; Matsushita *et al.*, 2012). The occurrence of AoD is typically 5 to 30 cases per million of the population annually and the mortality rate during first 24 to 48 hours in patients not treated surgically is 74% (Davies *et al.*, 2002; Knipp *et al.*, 2007). AoDs which involve the ascending thoracic aorta (ATA) are considered a cardiovascular emergency with an extraordinarily high lethality (Masuda *et al.*, 1991).

From a biomechanics standpoint, a possible mechanism for AoD is the occurrence of mechanical inter-laminar stresses, arising from entry of blood into the arterial wall, in excess of the delamination strength (S_d) between the aortic wall layers. S_d may be influenced by local micro-architectural features of load bearing components of the wall tissue, mainly characterized by the transmural content and orientation of both elastin and collagen fibers. As dissection typically propagates in an inter-laminar manner, S_d may be specifically affected by the inter-laminar elastin and collagen fibers and especially those fibers that are radially (RAD)-oriented. The latter contribute to the adhesive cell-extracellular matrix forces that hold the aortic layers together. Therefore, in the degenerated ascending thoracic aortic aneurysm (ATAA) wall, the forces developed by hemodynamics may exceed the forces holding the mural layers together (Pasta *et al.*, 2012), likely inducing spontaneous tears in the weakened aorta.

We recently presented a collagen fiber bridge failure model that related the S_d of human non-aneurysmal ascending thoracic aorta (CTRL-ATA), as obtained from the previously reported peel tests by Pasta *et al.* (2012), to the biomechanical properties of RAD-oriented collagen fibers acting as inter-laminar bridges across a propagating experimental dissection (Pal *et al.*, 2014a). Our model made use of micrographs captured using state-of-the-art multi-photon microscopy analysis in the longitudinal-radial (Z-RAD) and circumferential-radial (Θ -RAD) planes of human CTRL-ATA tissue, which exhibited the presence of RAD-oriented collagen fibers that may act as fiber bridges (Tsamis *et al.*, 2013). The previous analysis showed that the number density (N) and failure energy (U_f) of the RAD-oriented collagen fibers control the S_d of the aortic wall. A similar study on bicuspid aortic valve

(BAV)-ATAA and tricuspid aortic valve (TAV)-ATAA specimens provided attention support for an important role of collagen fiber bridges on determining S_d (Pal *et al.*, 2014b).

Here, we hypothesized that U_f is a key biomechanical parameter correlating with predictable changes in S_d of ATAA. To test the hypothesis, we used the S_d results from Pasta *et al.* (2012) and the N from Pal *et al.* (2014b) as input in the validated mechanistic models of Pal *et al.* (2014a) and (2014b) to calculate the U_f of a representative collagen fiber bridge for both CTRL-ATA and ATAA tissue specimens. Among the set of ATAA samples, we considered both BAV and TAV phenotypes. The results of our analysis revealed that U_f is significantly lower for ATAA specimens compared to CTRL-ATA specimens, and does not differ between BAV-ATAA and TAV-ATAA. We also found that U_f does not change between Θ -RAD and Z-RAD planes in either ATAA or CTRL-ATA specimens.

2 METHODS

2.1 Human Aorta Specimens

All human ATA specimens were gathered from our previous experimental study (Pasta *et al.*, 2012) according to guidelines of our Institutional Review Board and Center for Organ Recovery and Education. For information about specimen collection, processing and storage, the reader is referred to the original study by Pasta *et al.* (2012). For information about imaging and analysis of a subset of experimentally-dissected ATA specimens, the reader is referred to the studies by Tsamis *et al.* (2013) and Pal *et al.* (2014b), respectively.

2.2 Theoretical Model of Peel Test

The analytical model for peel test developed by Pal *et al.* (2014a) relied on the first law of thermodynamics, requiring the energy expended for propagation of a dissection to be supplied by a concomitant reduction in the potential energy of the system. Equating these two quantities for the case of steady state dissection propagation, we expressed the S_d for a T-peel test (Figure 1) in terms of N and U_f as

$$S_d \approx NU_f/2 \quad (1)$$

In this expression, we assumed that the energy required for a unit area of non-fibrous extracellular matrix to fail G_{matrix} is negligible compared to that of the collagen fibers. Rearranging the terms of Equation 1, we express the U_f as

$$U_f = 2S_d/N \quad (2)$$

N in this expression was evaluated from the image-based analysis within a small zone of $\pm 5\mu\text{m}$ from the delaminated medial plane as outlined in Pal *et al.* (2014b), while S_d was extracted from experiments reported in Pasta *et al.* (2012). The peel force, at which the dissection starts to propagate, was taken as the S_d of the specimen (see Figure 2 for an example).

A schematic flowchart presented in Figure 3 depicts the summary of experimental and analytical procedures undertaken to estimate U_f . To perform an assessment of the parameters N and U_f among BAV-ATAA, TAV-ATAA and CTRL-ATA and in directions Z and Θ , detailed statistical analysis was performed as described in the following section.

2.3 Statistical Analysis

Student's unpaired t-test ($p < 0.05$) was performed using SigmaPlot software (SYSTAT Software, Chicago, Ill) to determine significant differences in N among groups (BAV-ATAA $n=7$, TAV-ATAA $n=4$, CTRL-ATA $n=4$) in the media of the Θ -RAD and Z-RAD planes. One-way ANOVA ($p < 0.05$) followed by Tukey post-hoc test (unequal samples) was performed using the same statistics software to determine significant differences in the predicted U_f among the three aortic phenotypes in the Θ -RAD and Z-RAD planes. Data are presented as mean $\pm$ standard error mean. Linear regression analysis was also performed to study correlations with patient demographic data (i.e. ATAA diameter and patient age) but did not reveal statistically significant results (data not shown).

3 RESULTS

3.1 Number Density of RAD-oriented Collagen Fiber Bridges among ATA Phenotypes

Statistical results revealed that N was not significantly different among CTRL-ATA, BAV-ATAA and TAV-ATAA in either Θ -RAD or Z-RAD medial planes (Figure 4). Nevertheless, there was anisotropic distribution of RAD-oriented collagen fiber bridges in the media layer of CTRL-ATA, while this anisotropy was not observed in the media layer of ATAA. In particular, in the media of CTRL-ATA, N was significantly higher in the Z-RAD plane when compared to Θ -RAD plane. However, in the media of either BAV-ATAA or TAV-ATAA, N was equivalent between the Θ -RAD and Z-RAD planes.

3.2 Failure Energy per RAD-oriented Collagen Fiber Bridge among ATA Phenotypes

The values of U_f for three ATA phenotypes and for both Z and Θ strips were calculated according to Equation 2 (also see Figure 3) and are presented in Table 1. Our statistical analysis revealed that U_f was lower in BAV-ATAA compared to CTRL-ATA in either Z-RAD or Θ -RAD plane, and was lower in TAV-ATAA compared to CTRL-ATA in the Θ -RAD plane (Figure 5). Also, it was found that U_f did not change between the Θ -RAD and Z-RAD planes for all three ATA phenotypes considered in this report.

4 DISCUSSION

4.1 Number Density of RAD-oriented Collagen Fiber Bridges Associates with Anisotropic Delamination Properties in CTRL-ATA

Our multi-photon microscopic studies demonstrated that in the media of CTRL-ATA, N was significantly higher in the Z-RAD plane when compared with the Θ -RAD plane. Borges *et al.* also demonstrated the presence of a network of small inter-laminar collagen fibers in CTRL-ATA (de Figueiredo Borges *et al.*, 2008; Nakashima *et al.*, 1990; Sariola *et al.*, 1986). However, the amount of inter-laminar collagen fibers was not compared between Z-RAD and Θ -RAD planes. The increased N in the media of the Z-RAD plane of CTRL-ATA

tissue that we observed in our study may contribute to improved resistance to delamination in this plane for CTRL-ATA, as predicted by Equation 2 for same U_f for both Z-RAD and Θ -RAD planes, and in accordance with the higher S_d determined by Pasta *et al.* (2012) in the Z-strips than in the Θ -strips of CTRL-ATA tissue. Conversely, the reduced N in the media of the Θ -RAD plane of CTRL-ATA tissue may compromise the ability of Θ -strips to withstand RAD loads.

Our analysis also reveals that the anisotropy of N in the media of CTRL-ATA was not appreciated in the media of ATAA. The similar N that we found between the Θ -RAD and Z-RAD planes in the media of either BAV-ATAA or TAV-ATAA supports the notion of similar S_d between Z-strips and Θ -strips in either type of ATAA. Indeed, Pasta *et al.* (2012) reported isotropic S_d for both BAV-ATAA and TAV-ATAA.

A particularly interesting finding of our study is that N remained unchanged among CTRL-ATA, BAV-ATAA and TAV-ATAA in the media of either Θ -RAD or Z-RAD planes. Sariola *et al.* (1986) showed that the inter-laminar collagen deposition was more concentrated in specimens of pathological ATA dissection when compared with CTRL-ATA, which is not in agreement with our finding using experimentally-dissected tissue. Also, other studies have suggested that the overall collagen content is increased in thoracic aortic dissections (de Figueiredo Borges *et al.*, 2008; Wang *et al.*, 2006). In addition, co-morbid abnormalities can have an effect on the orientation and/or content of collagen fibers. For example, in presence of cystic medial degeneration, dissected specimens contained collagen fibers which were found to be organized as thick bundles within the media having Z-orientation (Sariola *et al.*, 1986). Despite the finding of elevated type-I collagen mRNA levels in BAV-ATAA when compared to CTRL-ATA (Phillippi *et al.*, 2010), Pichamuthu *et al.* (2013) observed that the total collagen content is maintained between BAV-ATAA and TAV-ATAA. These data are suggestive of altered turnover of collagen in BAV-TAA vs TAV-ATA and consistent with reports from our group (Phillippi *et al.*, 2014) and others (Wagsater *et al.*, 2013). Conversely, no change in collagen content was reported in ATAA of patients with Marfan syndrome (Lindeman *et al.*, 2010) or in BAV-ATAA (Fedak *et al.*, 2003) when compared with CTRL-ATA tissue. Yet, the above studies mentioned in this paragraph except for Sariola *et al.* (1986) did not account for the effect of disease on the RAD-oriented collagen fiber bridges. This information in the literature together with our collective data provoke the need for additional studies to further quantify changes of inter-laminar or RAD-oriented collagen fiber bridges in pathologically dissected ATA tissue and the biological pathways that incite these architectural changes.

4.2 Collagen Fiber Bridge Failure Energy Does Not Depend on Orientation of Dissection Propagation

Aside from N , another critical parameter revealed by our model is U_f , the energy required for each collagen fiber bridge to fail. Failure of a fiber bridge encompasses three separate modes: Fracture of the collagen fiber (Figure 1-c, **Mode 1**, in Pal *et al.* (2014b)), pull out of fiber from non-fibrous extracellular matrix (Figure 1-c, **Mode 2**, in Pal *et al.* (2014b)), and/or a combination of these two cases (Figure 1-c, **Mode 3**, in Pal *et al.* (2014b)). U_f can be estimated from the area under the experimental load vs. displacement curve for a single

collagen fiber until complete failure (Figure 3-d in Pal *et al.* (2014a)). This parameter incorporates information about the biomechanical failure behavior of a representative collagen fiber bridge, from the onset of its elongation from its undeformed state to its complete failure, and thus is expected to correlate with the altered histochemical state of the arterial wall due to disease, aging, gender etc. However, the direction of dissection propagation should not alter U_f , as fiber pull out direction is always orthogonal to the delamination plane. Figure 5 indeed shows that U_f is statistically similar for both Z and Θ peeling experiments for BAV-ATAA, TAV-ATAA and CTRL-ATA tissues. This fact indirectly validates our modeling approach and establishes U_f as a key parameter for the quantification of dissection behavior of arterial walls requiring further investigation.

4.3 Failure Energy per RAD-oriented Collagen Fiber Bridge in ATA is Lower in Aneurysmal Patients

Our analysis predicted that U_f was higher in CTRL-ATA compared to BAV-ATAA in either Z-RAD or Θ -RAD plane, and was higher in CTRL-ATA compared to TAV-ATAA in the Θ -RAD plane. The higher U_f in CTRL-ATA may indicate a favorable biomechanical state for the collagen fiber bridges when compared with ATAA, and thus would contribute to improved resistance to delamination. Furthermore, U_f did not change between BAV-ATAA and TAV-ATAA in either Θ -RAD or Z-RAD planes, indicating that the aneurysm in ATA has a stronger influence on U_f than the aortic valve phenotype. However, the fact that the U_f of only BAV-ATAA was significantly different in the Z-RAD plane makes this a notable difference in BAV-ATAA vs. TAV-ATAA. This might influence the S_d as reported by Pasta *et al.* (2012) to be lower in BAV-ATAA than TAV-ATAA. The reduced U_f in both BAV-ATAA and TAV-ATAA when compared with CTRL-ATA explains the reduced S_d of ATAA measured by Pasta *et al.* (2012), and might represent a consequence of cystic medial degeneration occurring in BAV-ATAA and TAV-ATAA alike, despite the probable alternative upstream effector molecules that initiate this final common pathway of aneurysm formation in both phenotypes (Phillippi *et al.*, 2010; Phillippi *et al.*, 2014; Phillippi *et al.*, 2009).

4.4 Limitations

We note that our analysis used S_d from experimentally-dissected CTRL-ATA and ATAA tissues (Pasta *et al.*, 2012). Pathologically dissected tissues may exhibit local remodeling in the vicinity of the inter-laminar dissection plane (Sariola *et al.*, 1986) and associated changes in N and/or U_f . Our biomechanical analysis relies on the local failure response of a single RAD-oriented collagen fiber bridge based on the parameter U_f , and subsequent homogenization on the dissection plane accounting for parameter N . Thus our modeling approach still remains valid in the face of local changes in the biomechanical state of a tissue. This fact is demonstrated by the validity of our model for CTRL-ATA, BAV-ATAA and TAV-ATAA specimens exhibiting different local arrangement and properties of collagen fibers. We expect that our model will be valid even for the case of pathologically dissected tissues, and extract valuable information about the role of different biomechanical parameters.

Another limitation of our analysis is that we utilized results from delamination tests (Pasta *et al.*, 2012) and subsequent multi-photon microscopy imaging analysis of collagen fiber micro-architecture (Tsamis *et al.*, 2013) which were non-specific to Θ location of the aortic wall. In a region-specific analysis by Sokolis *et al.* (2012) it was reported that collagen fibers formed bundles about Z-axis in the sub-intimal layers of the right-lateral region of TAV-ATAA. Della Corte *et al.* (2008) also reported that collagen content was spatially-dependent in BAV-ATAA. But the authors did not report if the amount of specifically the RAD-oriented collagen fiber bridges was spatially-dependent.

4.5 Conclusions

We conclude that the N of CTRL-ATA is significantly higher in the Z-RAD plane when compared with the Θ -RAD plane. This architectural profile may explain the anisotropic S_d of the CTRL-ATA tissues reported by Pasta *et al.* (2012). Also, our analytical results reveal that U_f does not depend on the direction of loading and dissection propagation. However, we demonstrate that U_f exhibits a decrease in ATAA compared to CTRL-ATA specimens. Moreover, the aneurysm in ATA has more influence on U_f than the aortic valve phenotype. We further conclude that collagen fiber bridge failure is biomechanically favorable in the ATAA compared with CTRL-ATA due to reduced energy requirement in the former, and thus explains the reduced S_d of ATAA measured by Pasta *et al.* (2012). Since U_f was found to be decreased in the presence of aneurysm, one would expect that the former could be correlated with biochemical changes within the degenerated ATAA wall (de Figueiredo Borges *et al.*, 2008). Collectively, we purport that our analysis may give rise to a future investigation, in which biomarkers specific to the modes of failure of a collagen fiber bridge could be clinically identified and measured. In this way, we aspire to ultimately provide insight into the pathophysiology of aortic dissection, improve risk assessment for aortic catastrophe and help guide clinical decision-making and care of patients with aortic disease.

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Figure 1. Schematic representation of (a) artificial dissection of human ATA, (b) arrangement of collagen fibers along dissection/fracture plane. P , peel force; Δ , separation.

Figure 2.

Schematic representation of typical peel force-separation response. The peel force attains its maximum once the dissection starts propagating, and remains essentially constant thereafter. S_d , delamination strength; P , peel force; Δ , separation.

Figure 3.

A flow-chart showing the procedures to estimate the fiber bridge failure energy U_f . The delamination strength and the number density of fiber bridges (# of bridges/unit length) are denoted as S_d and N , respectively.

Figure 4.

Results of statistical analysis to determine the significant differences ($p < 0.05$) in the number density of radially-oriented collagen fiber bridges (# of bridges/mm) among the three aortic phenotypes in the media of the Θ -RAD and Z-RAD planes. Results are presented as mean $\pm$ standard error of the mean. † indicates significant differences. The number density of radially-oriented collagen fiber bridges in the media of CTRL-ATA is significantly lower in the Θ -RAD plane compared to ZRAD plane. The number density of radially-oriented collagen fiber bridges in the media of either BAV-ATAA or TAV-ATAA is the same between the Θ -RAD and ZRAD planes.

Figure 5.

Results of statistical analysis to determine the significant differences ($p < 0.05$) in the predicted failure energy per radially-oriented collagen fiber bridge [mN×mm/mm] among the three aortic phenotypes in the Θ -RAD and Z-RAD planes. Results are presented as mean $\pm$ standard error of the mean. †, ‡ and * indicate significant differences. The failure energy per radially-oriented collagen fiber bridge in CTRLATA is higher compared to BAV-ATAA in either Z-RAD or Θ -RAD plane, and is higher compared to TAV-ATAA in the Θ -RAD plane. The failure energy of a single radially-oriented collagen fiber bridge does not change between the Θ -RAD and ZRAD planes in either aneurysmal or non-aneurysmal specimens.

Table 1

Predicted failure energy per radially-oriented collagen fiber bridge [mN×mm/mm] in the Z-RAD and Θ-RAD planes in the investigated aortic tissue samples.

Predicted failure energy per radially-oriented collagen fiber bridge [mN×mm/mm]		Z-RAD plane	Θ-RAD plane
CTRL-ATA	Patient #1	17.0	24.3
	Patient #2	32.0	21.3
	Patient #3	26.2	31.5
	Patient #4	19.7	41.7
	Mean ± S.D.	23.7 ± 6.7	29.7 ± 9.1
BAV-ATAA	Patient #1	11.5	9.3
	Patient #2	15.9	7.2
	Patient #3	17.7	18.3
	Patient #4	16.0	25.5
	Patient #5	11.5	25.0
	Patient #6	15.1	15.7
	Patient #7	17.7	12.6
	Mean ± S.D.	15.0 ± 2.6	16.2 ± 7.2
TAV-ATAA	Patient #1	15.6	17.1
	Patient #2	23.6	16.6
	Patient #3	15.5	27.4
	Patient #4	13.8	16.2
	Mean ± S.D.	17.1 ± 4.4	19.3 ± 5.4

S.D., standard deviation; BAV, bicuspid aortic valve; TAV, tricuspid aortic valve; CTRL, control non-aneurysmal with TAV; ATA, ascending thoracic aorta; ATAA, ascending thoracic aortic aneurysm; Z, longitudinal; Θ, circumferential; RAD, radial.