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Original Article

Local mechanical and structural properties of healthy and diseased human ascending aorta tissue

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Abstract

Objective: This study investigates the mechanics and histology of healthy and dilated human ascending aortas (AA). The regional variation in mechanical response and tissue structure were compared. **Methods:** Rings of human AA from healthy (n=5), dilated tricuspid aortic valve (TAV, n=5), and dilated bicuspid aortic valve (BAV, n=6) patients were mechanically tested. Each aortic ring was sectioned into quadrants—anterior, posterior, medial (inner curvature) and lateral (outer curvature). Low- and high-stress elastic moduli were calculated from the equibiaxial stress strain curve to determine the local mechanical properties. Histological analysis was used to quantify the percent composition of elastin, collagen, and smooth muscle cells. **Results:** BAV tissue was thinnest and contained the largest percent composition of collagen. Both TAV and BAV tissue had significantly less elastin than healthy tissue. At low strain in the circumferential direction, TAV tissue was on average the least stiff. The elastic modulus was dependent on quadrant and tissue type but not direction (isotropic). Generally, the lateral quadrant tissue was the stiffest and the medial quadrant the least stiff. There were no apparent local variations in the tissue histology. **Conclusions:** Local variations in tissue thickness and mechanical properties were evident in all samples analyzed and may be linked to the type of aortic valve present.

Keywords: Aorta; Bicuspid; Mechanics; Hemodynamics; Elastic modulus

1. Introduction

The biomechanics within the ascending aorta (AA) characterize the pressure and flow for the entire vascular system. It is uniquely constructed to withstand the large fluid and tissue stresses created in the left ventricle outflow tract. The structured medial layer, which consists mostly of elastic plates, interspersed collagen, and smooth muscle cells (SMCs), is responsible for the majority of the structural and functional properties of the AA [1–3].

Dilation is the most frequent condition requiring surgical treatment of the AA [4]. Dilation is believed to be caused by a degeneration of the AA medial layer, which can lead to aneurysm formation, dissection, or rupture of the AA and is a common cause of aortic valve insufficiency [5]. Concomitant dilation with valve disease implicates hemodynamic forces in the pathogenesis. Fluid and tissue stresses are believed to be capable of altering vascular cell phenotype, which leads to extracellular matrix degradation, apoptosis, and infiltration of inflammatory cells [6–8]. It has been suggested that asymmetric medial degeneration is caused by hemodynamic stress asymmetry in valve patients [9,10]. In bicuspid aortic

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valve patients, (BAV), clinical imaging has been used to suggest abnormal elastic properties of the aortic root when compared to healthy controls [11–13]. It is ultimately the biomechanic properties of the tissue that will determine the fate of a dilated AA.

There is limited data on the mechanical properties of dilated AA tissue and almost none on healthy ascending aortas. Most studies have used numerical modeling to identify tissue stresses and made the assumption that uniform (homogeneous) remodeling occurs and therefore uniform wall properties exist with no directional dependence (isotropic) [14–16]. The validity of tissue isotropy has been contested [17–19]. In abdominal aortic aneurysms, Thubrikar et al. [20] have shown that regional variations of the mechanical properties exist. In general, very little work has been done on the homogeneity of the mechanical properties of human vascular tissue, and no work has been published on the local nature of human AA tissue mechanical properties.

In this study, we hypothesized that focal AA tissue remodeling and, therefore, nonuniform biomechanical properties would be present in human dilated AA. We analyzed the local properties of pathologic human dilated AA tissue from both tricuspid and bicuspid aortic valve patients and compared the findings with the properties of healthy aortas. Biaxial tensile tests were conducted to obtain the mechanical behaviour of the tissue and the content of elastin, collagen, and SMCs were evaluated from histological sections.

2. Methods

2.1. Patient group

All tissue specimens were obtained with ethical approval following the guidelines of the Tri-Council Policy Statement. Pathologic AA tissue was acquired from patients with ascending aortic aneurysm scheduled for ascending aorta resection surgery at the Montreal Heart Institute (MHI), Table 1. Healthy AA tissue was obtained at autopsy from both the MHI and the University Health Network Toronto General Hospital.

2.2. Biaxial tensile tests

Over an 8-month period, a total of 16 ascending aortic rings were obtained for mechanical analysis when they became available. The samples were grouped as healthy (healthy, n=5), dilated tricuspid (TAV, n=5), and dilated bicuspid (BAV, n=6) aortic valve patients. All samples consisted of a tubular section of the AA (Fig. 1). The tissue was obtained from 10 men and 6 women with ages ranging from 30 to 74 years (58±11 years).

For each test, the intact specimen was photographed and grossly examined. The presence of any remarkable features (such as atherosclerotic lesions) was noted. Four measurements of the diameter were made at the proximal, middle, and distal section of the excised aortic ring with a hand held digital caliper (ABS Digimatic, Mitutoyo USA). Special care was taken to not distort the excised geometry when taking the diameter measurements. In all cases, the maximum diameter was used. The tissue was then placed in Krebs–Ringer physiological saline solution in a closed container and refrigerated at 4°C until mechanical testing could be performed (within 24 h). Representative tissue samples of the medial (inner curvature), anterior, lateral (outer curvature), and posterior quadrants were obtained using dissection scissors. The tissue was cut into square 1.5×1.5 cm samples with the edges aligned with the circumferential and axial directions of the aorta (Fig. 1). The thickness of the samples was recorded using a Mitutoyo (Litematic VL-50A, Mitutoyo USA) constant force thickness indicator (±0.0001 mm) at

Table 1
Patient characteristics grouped by tissue type

Patient valve function category	Age	Sex	Diameter (mm)	Known risk factors and comorbidities	Valve function
Healthy	74	F	32.2	None	Normal
Healthy	30	F	26	CAD	Normal
Healthy	55	M	28	CAD	Normal
Healthy	71	F	30	Mitral valve prosthesis	Normal
Healthy	37	M	23	None	Normal
TAV	46	M	58	HT, DLP, CAD, AAE	Incomp.
TAV	68	F	66	HT	Normal
TAV	52	M	63	HT, DLP, smoker, CAD	Incomp.
TAV	51	M	48	None	Incomp./stenosis
TAV	66	F	60	HT, smoker	Incomp.
BAV	58	M	49.6	AAA, HT	Incomp.
BAV	71	M	58	HT	Stenosis
BAV	53	F	53	HT, CAD, smoker	Stenosis
BAV	64	M	66	Diabetic, CAD	Stenosis
BAV	60	M	55	None	Stenosis
BAV	44	M	48	Smoker	Stenosis

HT indicates hypertensive; CAD, coronary artery disease; DLP, dyslipoproteinemia; AAE, annuloaortic ectasia; AAA, abdominal aortic aneurysm; Incomp., incompetent.

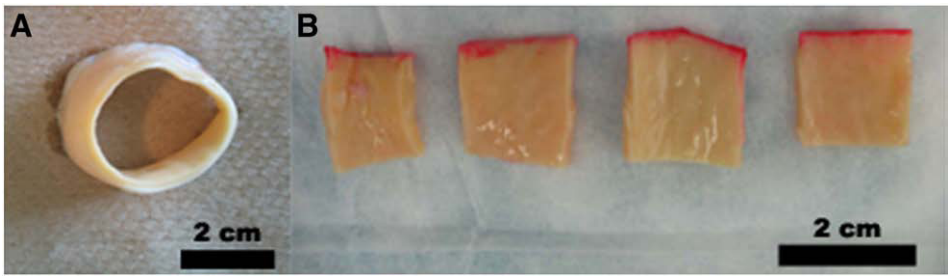

Fig. 1. (A) Gross photograph of a 42-year-old male healthy human AA segment. (B) Subsequent processing for obtaining sample pieces from each quadrant. Red India ink was used to stain the proximal edge of each sample.

5 locations in the tissue. Three measurements were taken of each of the circumferential and axial lengths. The average value of the dimensions was used in all calculations.

The specimens were subjected to tensile testing using the EnduraTEC *elf* 3200 biaxial tensile tester system supplied with WinTest software (Bose Corporation, Minnesota, USA). The tissue was attached to the tester with 3-0 (0.2 mm diameter) silk sutures with pledgets used for reinforcement and floated in a saline bath at room temperature. The tensile test was equibiaxial with a constant strain rate of 0.1 mm/s. The tissue was subjected to 13 loading and unloading cycles with a displacement of 5 mm. The first 10 cycles served to precondition the tissue. The final three cycles were considered the experimental runs; only the data following preconditioning is reproducible [21]. A final stretch resulting in a 12-mm displacement was then applied to bring the tissue to failure.

2.3. Mechanical variables

For the statistical analyses, elastic moduli were fit to the final stretch stress–strain curves in both the low- and high-stress regions. This was done for tissue from each quadrant of a given sample to investigate local properties. The low stress elastic moduli (E_L) is associated with the elastin content of the tissue, and the high stress or strain hardening region elastic moduli (E_H) is related to both the elastin and collagen content of the tissue. These two regions were identified as the linear regions in the loading curve, similar to the technique used by Vorp et al. [16] in the investigation of aortic aneurysms.

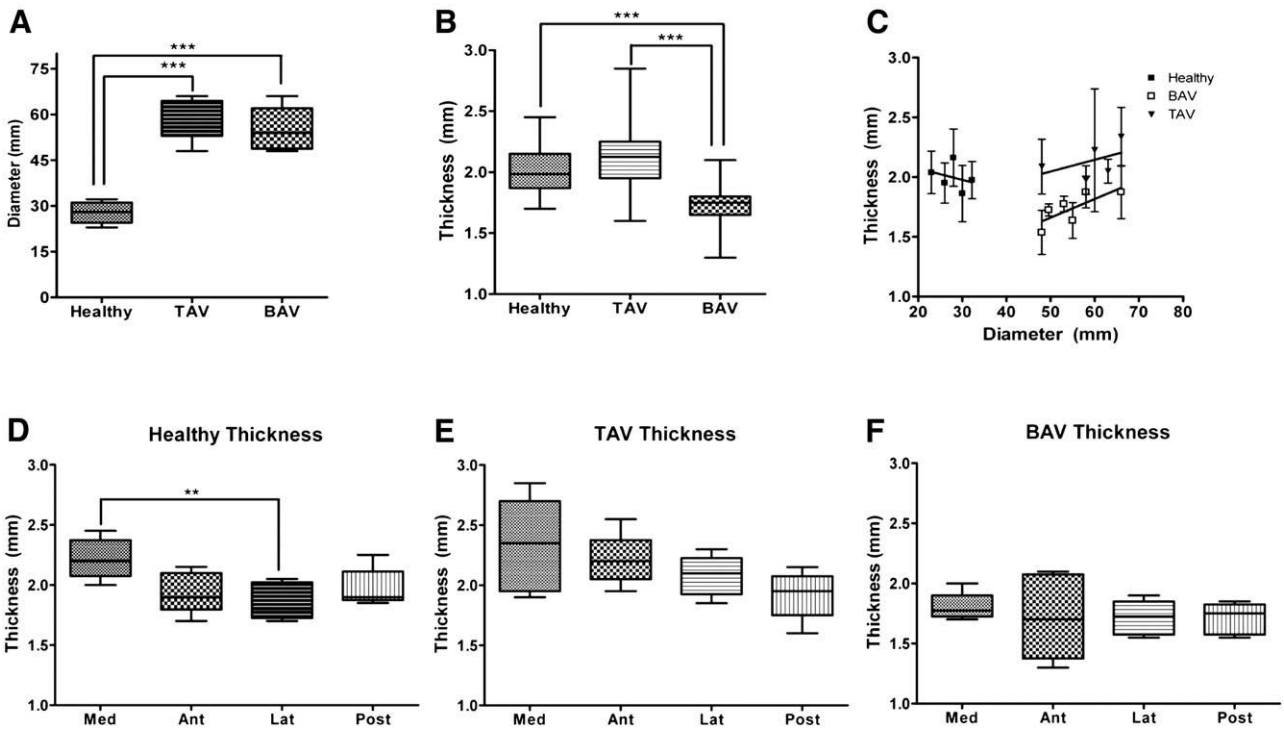

Fig. 2. Diameter and thickness data from the biomechanical study. (A) AA diameter. (B) Wall thickness. (C) There was no apparent correlation between the diameter and thickness. Regional variation in tissue thickness in healthy (D), TAV (E), and BAV samples (F). MED indicates medial; ANT, anterior; LAT, lateral; POST, posterior quadrants. Asterisks denote significant difference: *$P<.05$; **$P<.01$; ***$P<.001$.

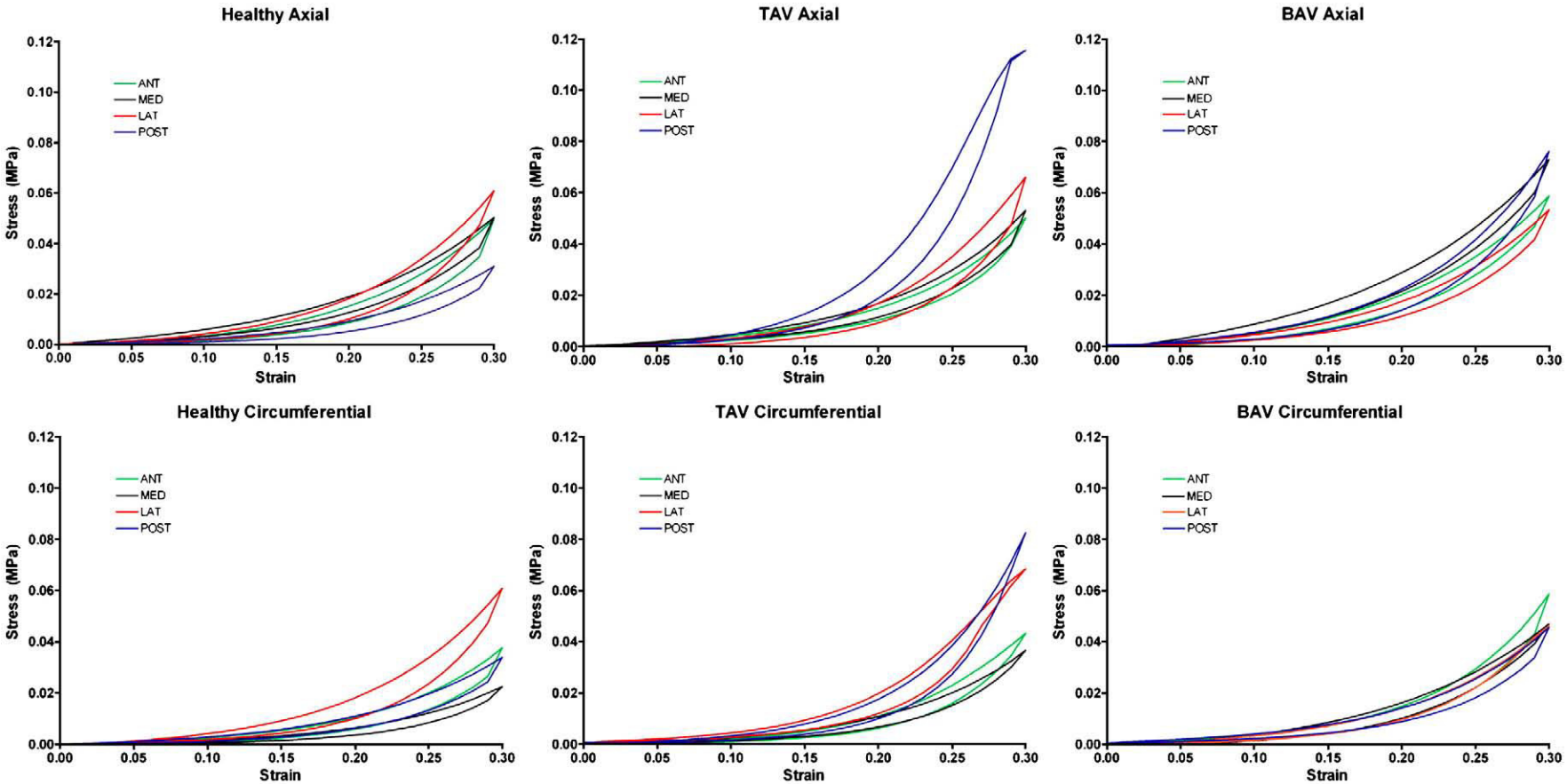

Fig. 3. Mean engineering stress–strain curves for human AA grouped by tissue type, direction, and location.

The anisotropic index (A.I.) was used to quantify the directional dependency of the mechanical properties of the tissue. This variable compares the difference in slopes between the axial and circumferential directions. Tissue with no directional dependence (isotropic) has an A.I. that approaches zero. The A.I. was calculated for the low- and high-stress regions of the stress–strain curves using an equation similar to that of Lee et al. [22] [Eq. (1)].

$$A.I. = \frac{E_A - E_C}{\frac{1}{2}(E_A + E_C)} \quad (1)$$

where E_A and E_C are the slopes in the axial and circumferential direction, respectively.

2.4. Histological analyses

In addition to the mechanical testing, sections were taken for histological analysis. Representative sections of the 4 quadrants were taken from the aortic rings and fixed with 4% neutral buffered formalin solution. The fixed tissue was paraffin-embedded, cut into thin sections (~3 μm), mounted onto microscope slides, and stained with Movat Pentachrome stain to distinguish between the different components. The components of interest were elastin, collagen, and SMCs. For each sample, histological slides from each quadrant were examined with a Leitz Diaplan upright microscope through a 40× objective. Digitized images were taken with a Leica DC 300 digital camera (Leica Microsystems, Montreal, QC, Canada). A semi-quantization of the tissue composition was obtained using a color detection program written in MATLAB. For each patient, areas of known content were used to set the color threshold for each component. Replicate readings were taken for statistical purposes.

2.5. Statistical analyses

Statistical analyses were carried out using GraphPad Prism version 4.01 (GraphPad Software, San Diego, CA, USA). All statistics are presented as mean values±S.D. Both one- and two-way analysis of variance (ANOVA) were used. Bonferroni's multiple comparisons posttest were used to identify which groups were different, with $P<.05$ considered statistically significant.

3. Results

3.1. Sample population

There were no differences in age between the healthy and pathological TAV and BAV groups (53.4±19.7 vs. 56.6±9.8 vs. 58.3±9.3 years, respectively; $P=.833$, one-way ANOVA). The maximum excised diameter of healthy aortas (2.8±0.4 cm) was significantly less than TAV (5.9±0.6 cm) and BAV (5.4±0.7 cm) patients ($P<.001$, one-way ANOVA, Bonferroni's multiple comparison test). There was no statistical difference in the maximum aortic diameter between the TAV and BAV dilated groups (Fig. 2A).

Dilated BAV tissue was significantly thinner than healthy and TAV tissue ($P=.001$, one-way ANOVA, Bonferroni's posttest) (Fig. 2B). There was no significant correlation between the mean thickness and maximal diameter (Fig. 2C).

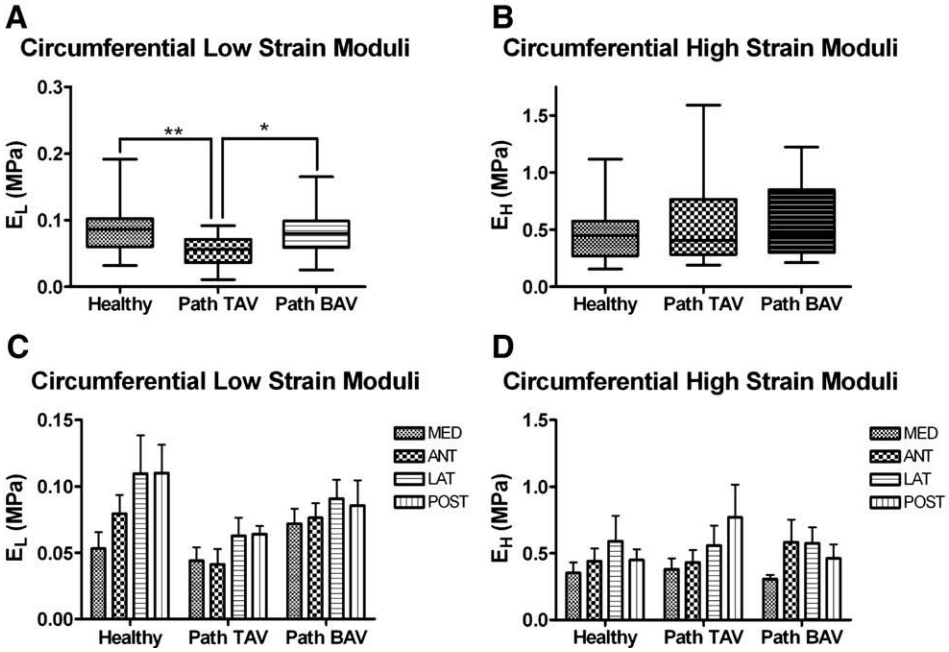

Fig. 4. Circumferential low (A) and high-strain slope (B) comparisons in healthy ($n=5$), TAV ($n=5$), and BAV ($n=6$) samples. The local variation in circumferential low (C) and high (D) elastic moduli. Asterisks denote significant difference: *$P<.05$; **$P<.01$; ***$P<.001$.

Table 2
Failure location as a fraction of the samples tested

	Medial	Anterior	Lateral	Posterior
Healthy	3/5	4/5	0/5	0/5
TAV	4/5	2/5	2/5	1/5
BAV	5/6	3/6	2/6	3/6

Only the healthy tissue showed any significant regional variation in tissue thickness (P=.018, one way ANOVA). In healthy tissue, the medial quadrant (inner curvature) was significantly thicker (P<.01, Bonferroni's posttest) than the lateral quadrant (outer curvature) (Fig. 2D). There was significant variance in the thickness of bicuspid tissue (P=.040, Bartlett's test for equal variance), with the anterior quadrant having a very large coefficient of variability (18.5%).

3.2. Mechanical response

Average engineering stress–strain curves were plotted to visualize the mechanical response of the tissue, Fig. 3. All tissue demonstrated a characteristic nonlinear viscoelastic response.

The low and high strain moduli (E_L and E_H respectively) obtained from the individual stress–strain curves were used for statistical comparison of the mechanical response, Fig. 4. Only the low strain moduli (E_L) in the circumferential direction showed any significant difference between tissue types (P=.005, one-way ANOVA), with TAV samples demonstrating a significantly lower slope than healthy or BAV samples (P<.01 and P<.05, respectively, one-way ANOVA, Bonferroni's multiple comparison test) (Fig. 4A).

The circumferential E_L was also dependent on the quadrant in addition to tissue type (P=.032 and P=.004 respectively, two-way ANOVA). The lateral wall was most often the stiffest quadrant and the medial, the least stiff in all groups. This pattern is evident in both the low and high elastic moduli (Fig. 4C and D) and axial E_L and E_H (data not shown).

In Fig. 3, it appears that a different average stresses is experienced in the axial and circumferential direction at the same strain. Although the average A.I. values were positive (suggesting that the axial direction was stiffer than the circumferential direction) for all tissue types and almost all the quadrants, only a few of the means were actually significantly different from 0 (t tests, P>.05). There was no difference between the low and high stress A.I. values, demonstrating that the biaxial response was consistently isotropic at both low and high strains.

To expose any general trends, the occurrence of failure was also noted for each of the clinical samples tested. Not all samples ruptured by our maximal extension (12 mm, 80% strain) (Table 2); however, when the tissue did rupture, it was always due to axial loading. Generally, regardless of the tissue type, when failure occurred, it was most often in the medial and anterior quadrants. In healthy tissue, no samples from the lateral (outer curvature) or posterior quadrants failed.

3.3. Histology

Significant differences in tissue content were detected between tissue types (Fig. 5). The content of elastin, collagen, and SMC were dependent on tissue type (P=.004, P=.0007, and P=.0001, respectively, one-way ANOVA). Healthy tissue contained more percent composition of elastin than TAV and BAV tissue (P<.01 and P<.001 respectively, Bonferroni's multiple comparison test). The content of collagen was significantly higher in BAV samples than Healthy or TAV samples (P<.01 and P<.01, Bonferroni's multiple comparison test). TAV aortic tissue contained less SMC than either healthy or BAV tissue (P<.001 and P<.001, Bonferroni's multiple comparison test). No significant regional variation in the tissue composition was found in any tissue type.

4. Discussion

The complex hemodynamics created in the left ventricle outflow tract has been hypothesized to cause local tissue remodeling that may lead to aortic dilation. Although histological evidence has suggested an asymmetry in medial

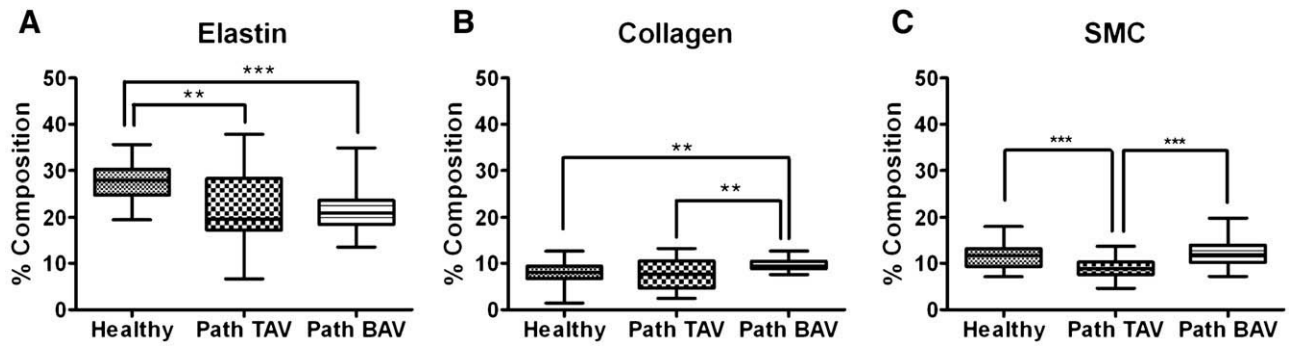

Fig. 5. Tissue content comparisons grouped by tissue type. Asterisk denote significant difference: **P<.01; ***P<.001.

degeneration exists in dilated samples [9,10], the local tissue mechanical properties have not been investigated. Our data support the hypothesis that there is some variation in local tissue mechanical properties in the human AA. Furthermore, the variation is dependent on the type of aortic valve present.

4.1. Tissue type

Despite similar maximum diameters, the tissue thickness of BAV samples was significantly thinner than dilated TAV samples (Fig. 2). There was no discernable correlation between the average excised tissue thickness and maximum excised diameter. Thinning of the aorta wall with increasing diameter has been well documented in abdominal aneurysms [23] but debated in nondissecting ascending aortic aneurysms [8]. Our results suggest that the mean thickness of the tissue in the dilated region of TAV patients is not significantly different than healthy aortas. To preserve thickness after dilation, the vessel wall must actually increase in volume due to tissue incompressibility [8]. Intimal thickening in the presence of medial thinning may preserve wall thickness. Tang et al. [8] found a reduction in the medial thickness in TAV-dilated patients was compensated for by intimal thickening. Using biopsy samples, the authors deduced that the intima mass must greatly increase, and adventitial and medial mass may have also increased to preserve wall thickness. No mention of the valve type was given in this work. In a larger sample size histological study, Bauer et al. [24] reported no significant difference in medial thickness between BAV and TAV samples. Given our finding that overall wall thickness in BAV patients is less than the other groups, we speculate that the ability of the intima and adventitia to remodel with dilation may be impaired in BAV patients.

When comparing the overall thickness results with the overall mechanical properties, it is evident that tissue thickness alone cannot explain the reduction in stiffness at low strain. Despite a similar tissue thickness, the TAV samples were significantly less stiff than the healthy samples, Fig. 4. The BAV samples were significantly thinner than the healthy samples but maintained similar mechanical properties. These results suggest that tissue composition also plays a role in the low-strain mechanical response when comparing between tissue type.

There were significant variations in the histological composition of the three tissue groups. The contribution of SMCs in the passive mechanical response is believed to be minimal, and therefore, the variation in SMC content between the tissue types is unlikely to have had an affect our mechanical results [25,26]. Healthy samples contained a higher percentage of elastin than the dilated tissue samples. The results of our small sample population are similar to Fedak et al. [27] who found no significant difference in the amount of elastin in the aorta between BAV and TAV patients. The mechanical response of the lower part of the stress–strain curve has been attributed mainly to elastin [28,29]. It is likely that the mechanical effect of the decreased elastin content in BAV tissue is compensated for by thinning of the media. In the TAV samples, the thickness was similar to the healthy samples, and therefore, the reduction in elastin is noticeable in the mechanical response. There was also an overall percent increase in collagen in our BAV samples. The recruitment of collagen fibers is believed to dominate the mechanical response at high strains [28]. Although BAV samples did have on average the highest stiffness (and collagen content) at high strains, there was no significant difference in mechanical properties; however, the data were highly variable.

Magnetic resonance and echocardiographic images have been used to infer the mechanical properties of the aortic root in stenotic and nonstenotic BAV patients [11–13]. These studies have concluded that there is an impairment of the elastic properties of the aorta in BAV patients. The results are based on diameter or area measurements of the aortic root and peripheral blood pressure measurements. The elastic indexes calculated are difficult to distinguish if they are a secondary response to blood pressure changes or intrinsic elastic properties or both [30]. This is evident in the recent study of Yap et al. [13] where the aortic root distensibility and aortic strain were shown to be similar in BAV aortic stenosis patients and control patients, yet the aortic stiffness index was significantly greater in BAV patients. Our results show no difference in the elastic modulus of BAV and healthy patients, suggesting that the in vivo results may reflect the difference in pressure in these patients rather than tissue mechanics. It is also important to note that in vivo measurements of elasticity are indirect and do not account for local variations in tissue structure. Our results show that there are local variations in the tissue mechanics.

There have been conflicting reports on the directional dependence of the mechanical response of aortic tissue. Zhou and Fung [19] reported that thoracic aorta tissue of dogs was anisotropic in both the low and high stress region. Okamoto et al. [17] described human AA tissue as “somewhat anisotropic,” whereas others have found the tissue to be mainly isotropic [29]. Our data suggest that at a strain rate of 0.1 mm/s, human ascending aortic tissue shows no directional dependence under equibiaxial loading. However, it is interesting to note that when failure occurred, it was predominately due to axial loading. This observation is consistent with clinical reports that the majority of aortic dissections occur with a transverse tear [31], possibly due to increased stress caused by the downward motion of the aortic root during the cardiac cycle [32].

4.2. Regional variation

We expected to see regional variability in the thickness, composition, and mechanical properties of the dilated samples corresponding with a change in hemodynamics caused by valve disease. Surprisingly, the only significant regional variation in thickness was seen in healthy tissue,

with the medial quadrant (inner curvature) significantly thicker than the lateral quadrant (outer curvature). This suggests that a natural variation in tissue thickness exists around the circumference of the human AA. A similar pattern of thickness variation was evident in TAV dilated tissue. No pattern was evident in BAV tissue. If hemodynamic remodeling is responsible for the change in thickness pattern, the orientation of the BAV would be important. BAV orientation was not considered in this study and could be the cause of the considerably higher variability seen in the local BAV tissue thickness. Recently, Schaefer et al. have shown that BAV orientation has an impact on the Valsalva diameter and stiffness index measured from echocardiograph data [33].

The histological analysis did not show any significant regional variation in tissue composition. Medial degeneration has been reported to be most severe in the posterior lateral wall [9,10]. In this study, only two locations on the vessel wall were analyzed (noncoronary vs. right coronary wall), and degeneration was determined by a grading scheme coupled with more detailed analysis on the state of the elastic fibers and smooth muscle cells. The overall percent composition was not reported.

Despite a lack of discernable variation in regional tissue composition, there were differences in the regional biomechanics. The location had a significant influence on the circumferential E_L. The pattern of variation was similar to the regional changes in thickness, with the thickest quadrant (medial) being the least stiff and the thinnest quadrants (lateral and posterior) being the stiffest. This was most evident in the healthy tissue. A similar trend was seen in the high-strain circumferential elastic modulus; however, this was not found to be significant. In the axial direction, the lateral wall was again relatively stiff, but no significance was evident.

Clinically, dissections most frequently occur on the lateral wall [31]. Increased stiffness of the lateral wall would make it more likely to reach its ultimate stress first. Moreover, the fluid and tissue dynamics of the ascending aorta would be expected to create higher stresses on the lateral wall than the medial wall. In our study, we have imposed the same strain on all quadrants, which is unlikely to occur in vivo [32].

Under our imposed equibiaxial loading, failure most often occurred in the medial and anterior quadrants. The medial quadrant was less stiff and thicker than the lateral wall yet failed more frequently. This suggests that the aortic wall at the inner curvature has a lower rupture stress than the other quadrants. Stress is related to the inverse of thickness, so a thinner wall will experience more stress at a defined load than a thicker wall, as was seen in the biaxial tests (Fig. 2). If the tissue properties were indeed homogenous, it would be expected that the thinner walled section would fail first as it would reach its rupture stress first. It is therefore surprising that the thicker medial quadrant frequently failed (Table 2) and suggests the mechanical properties at high strain are not uniform around the aorta. This may be an artifact of dissecting the aorta from the pulmonary artery. In vivo, the aorta and pulmonary trunk are connected by periadventital tissue. It may not be necessary for the medial wall of the ascending aorta to be mechanically strong because of this built-in support. Similarly, lower hemodynamic stresses experienced on the medial wall may promote this weakness.

4.3. Limitations

The data presented are limited by the small sample size. More work is needed to confirm these observations, and it is possible that regional significance would be achieved with larger sample sizes. The small sample size also made it necessary to neglect the affect of age, degree of insufficiency, and other clinical factors. The diameter and thickness measurements were performed on the excised tissue and may vary from the in vivo dimensions. In the biomechanics study, a single strain rate has been investigated and the change in tissue thickness during testing ignored. In vivo, the strain cycle is considerably different which could have a significant effect on the mechanical response. Moreover, only the passive nature of the tissue has been captured under equibiaxial loading.

In this study, the tissue experienced large deformations, and thus, the response was nonlinear. The use of nonlinear modeling rather than linear local moduli may better capture the mechanical response. Also, large variations in the organization and structure of tissue were seen within a clinical sample in the histological analyses. A quantitative approach, such as the use of biochemical analyses, would provide a more sensitive analysis. Despite these limitations, the data do show a valve dependency and local dependency of the morphology and mechanical properties.

5. Conclusions

Local variations exist in human AA thickness and mechanical properties. These differences may be due to the anatomy of the AA and its attachment to the pulmonary trunk. In general, the lateral quadrant (outer curvature) is the stiffest, and the medial quadrant (inner curvature), the most elastic. The data also show thinning of BAV aortic tissue occurs, while TAV aortic tissue is more capable of preserving normal thickness despite an increase in diameter. BAV disease is not limited to the leaflets and does significantly affect the AA. The passive mechanical properties of dilated BAV AA tissue are significantly different than dilated TAV AA tissue. This implies that BAV patients with dilated ascending aorta may represent a higher risk of rupture than those with TAV, and this perhaps should be taken in consideration in surgical decision making.

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