Chapter 11
Mechanical Properties of Ascending Thoracic Aortic Aneurysm (ATAA): Association with Valve Morphology

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Abstract Type A aortic dissection (AoD) of an ascending thoracic aortic aneurysm (ATAA) is a life-threatening cardiovascular emergency with a high potential for death. AoD represents a devastating separation of elastic aortic layers occurring when the hemodynamic loads on the diseased wall exceed the adhesive strength between layers. The goal of this study was to evaluate and compare the dissection properties of non-aneurysmal and aneurysmal human ascending thoracic aortas from patients with bicuspid aortic valve (BAV) and normal tricuspid aortic valve (TAV) morphologies using biomechanical delamination testing. Following complete delamination of ATAA tissue samples, tensile tests were performed on each delaminated half for comparison of their tensile strengths. Results evinced that the aneurysmal aortas with BAV and TAV have lower delamination properties than non-aneurysmal aorta, and that ATAA with BAV has lower S_d than TAV, suggesting an apparent propensity of AoD.

11.1 Introduction

One of the most common lethal complications of an ascending thoracic aortic aneurysm (ATAA) is the aortic dissection (AoD), causing significant mortality

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despite advances in diagnostics and surgical management (Bonnichsen et al., 2011). The exact prevalence of AoD is difficult to determine, and most estimates are based on necropsy studies with evidence in 1–3 % of all cases. The incidence of AoD is believed to be 5–30 cases per 1 million people per year, typically presenting in elderly patients, and in males more frequently than females (ratio 3 : 1). AoD occurs more typically in elderly patients in the presence of a tricuspid aortic valve (TAV) and in relatively younger patients if a bicuspid aortic valve (BAV) is present. During the first 24 to 48 hours, the mortality in patients not treated surgically is as high as 74 % (Knipp et al., 2007). Even among patients treated with emergent aortic reconstruction, operative mortality averages 24 % worldwide as reported by the International Registry of Acute Aortic Dissection (Rampoldi et al., 2007).

Type A ascending aortic dissections originate with an intimal tear typically occurring near the sinotubular junction where the wall stresses are believed to be elevated (Coady et al., 1999). The intimal tear allows blood to enter the aortic wall, splitting the media and progressively separating the medial plane along the longitudinal direction of the aorta. This creates a new 'false lumen' which runs parallel to the true lumen. The false lumen can reenter the true lumen anywhere along the course of the AoD or exit through the adventitia resulting in frank rupture. As the dissection extends distally, its propagation and re-entry follows unpredictable courses that can result in life threatening ischemia of the heart, brain, abdominal viscera, spinal cord and extremities (Johansson, 1995). There are several risk factors predisposing patients to AoD. Among these are severe hypertension, connective tissue disorders such as the Marfan and Ehlers-Danlos syndromes, and bicuspid aortic valve (BAV). The congenital malformation, bicuspid aortic valve is distinctly associated with the development of ascending aortic dilatation imparting a marked risk of AoD (Cripe et al., 2004) and occurs in 1 to 2 % of the population, making it the most common congenital heart malformation (Bonderman et al., 1999; Ward, 2000). In the clinical practice of ATAA reported by Gleason (2005), over 40 % of patients undergoing elective surgical replacement of the ascending aorta indeed have BAV. Additionally, older necropsy studies shown a risk of fatal dissecting aneurysm in BAV patients nine times higher than patients with tricuspid aortic valve (TAV) (Edwards et al., 1978; Larson and Edwards, 1984). The histopathologic analyses of AoD and aneurysms appear strikingly different from those of abdominal aortic aneurysms (AAA). Thoracic aneurysms have distinct histopathologic characteristics classified as cystic medial degeneration, which is non-inflammatory and in stark contradistinction to AAAs showing inflammatory characteristics (Davies, 1998; El-Hamamsy and Yacoub, 2009).

From a biomechanical point-of-view, the AoD of ATAAs involves a separation (i.e. a delamination) of the elastic layers of the degenerated aortic wall that occurs when the hemodynamic loads exerted on the aneurysmal wall exceed adhesive forces that normally hold the mural layers together.

The purpose of this work was therefore to quantify the biomechanical properties of ATAA samples relative to non-aneurysmal human ascending aorta and to distinguish specific differences in the biomechanical properties of ATAAs from BAV and TAV patients. This was achieved performing biomechanical delamination tests, followed by tensile tests on the delaminated halves to show the distinct strengths of the

outer and inner aortic walls of the artificially created 'false lumen' for evaluating the propensity of either intimal flap propagation or frank disruption. SEM investigations was also performed to examine the failure modality of AoD.

11.2 Material and Methods

11.2.1 Human Aortic Tissue Specimens

All human ascending thoracic aorta tissue specimens were obtained after informed consent following guidelines of our Institutional Review Board and Center for Organ Recovery and Education. Segments of non-aneurysmal aorta (control) were collected from organ donor subjects whereas non-dissected ATAAs were collected from patients undergoing elective ascending aortic replacement at the University of Pittsburgh Medical Center. A total of 31 aortic segments (7 controls and 24 ATAAs) with age range of 41–79 yr, aortic diameter of 40–68 mm and gender comprised of 24 males and 7 females were analyzed. The aneurysmal groups were composed of 16 BAV and 8 TAV segments, respectively. All non-aneurysmal segments were collected from individuals with TAV. The aortic samples were tested within 48 hours of harvest after storing at 4 °C in a calcium-free and glucose-free 0.9 % physiological saline solution (Raghavan et al., 1996).

11.2.2 Biomechanical Testing

The harvested aortic segments were cut into long, thin, rectangular (approximately 30 × 6 mm) strips with their long axis in either longitudinal (LONG) or circumferential (CIRC) orientation with respect to that of the aorta. Generally, the same aortic segment was used to obtain strips of both orientations for direct comparison. To create an initial delamination plane, a delaminating incision was made with the aid of a surgical scalpel between elastic lamellae of each specimen, parallel with the plane of the aortic wall and 8–12 mm in length (Fig. 11.1).

Since the initial incision was made manually, there naturally was a moderate variation in terms of the exact location of the incision plane with respect to the center of the media or to the external or internal elastic lamina. However, the artificial delamination plane was reproducible. The dimension of each specimen (i.e., the width, thickness and length) were measured at three different locations using a dial caliper and then averaged and recorded before testing. The two free flaps of each delaminated half of the ATAA specimen were mounted between the grips of an Instron tensile system (model 5542) with a 5 N load cell. To avoid slipping of the specimen in the pneumatic grips, surfalloy jaw faces with gritty, sandpaper-like surfaces were used. During testing, the mounted specimens were submerged in 0.9 % physiological saline solution in a BioPuls bath under controlled temperature of 37 °C.

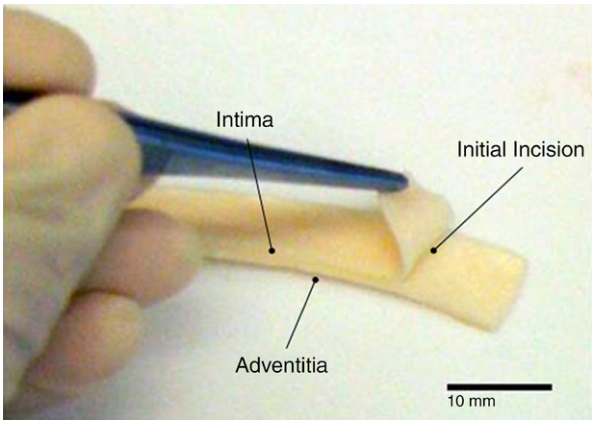

Fig. 11.1 Photography of a representative specimen for a delamination test showing the through-thickness incision for creating the initial dissection plane. Taken from Pasta et al. (2011)

A constant crosshead speed of 1 mm/min was used to pull apart the two free flaps of the tissue specimen whereas the applied load and resulting displacement were recorded continuously using the Instron-packaged software (Bluehill v.2). The two delaminated halves resulting from each delamination test (i.e., the one between the intimal surface and the delaminated plane (INT-DEL), and the one between the adventitial surface and the delaminated plane (ADV-DEL)) were stretched to failure in the uniaxial tensile testing system to evaluate the tensile strength of each. None of specimens failed for technical reason during biomechanical testing.

11.2.3 Data Analysis

'Delamination curves' were generated from each test, and consisted of a plot of the 'peel tension' (T_{peel}, defined as the applied force normalized by the width of the specimen) as function of the elongation (displacement). The mean value of T_{peel} after the initial peak was taken as the delamination strength S_{d} of the specimen. The S_{d} values calculated for multiple LONG and CIRC specimens tested for a given patient were taken as the overall $S_{\text{d,LONG}}$ and $S_{\text{d,CIRC}}$ for that specific patient. For the tensile tests, we utilized the approach published previously by our laboratory (Raghavan et al., 1996). In short, the Cauchy stress T was calculated as the applied force normalized by the deformed cross-sectional area, and stretch was calculated as the deformed length normalized by the original length of each specimen. The tensile strength S_{T} was taken as the peak value of stress attained prior to complete specimen failure.

One-way ANOVA, followed by Holm-Sidak post-hoc test for all pair-wise comparisons, was performed using SigmaPlot software (SYSTAT Software Inc., Chicago, Ill) to determine significance among groups. Level of statistical significance was set as $p = 0.05$. Data are shown as mean $\pm$ SEM.

11.2.4 SEM Imaging

Changes of tissue microstructure due to the propagation of the dissection were investigated observing the surfaces of delaminated halves of specimens from each group at SEM. The aortic tissues were fixed in 2.5 % glutaraldehyde for one hour, dehydrated in a graded series of ethanol/water solutions, dried, and then sputter coated with gold. The orientation of each specimen inside the microscope was aligned to that of the dissection propagation before imaging.

11.3 Results

Figure 11.2 shows representative delamination curves for three separate LONG and CIRC strips cut from an ATAA of a 56 yr old male patient with BAV and aortic diameter of 46 mm. The initial 'ramp' phase of the loading curve corresponds to stretching of the peel arms whereas the jagged plateau region shows the slow and controlled propagation of the AoD. In delamination testing, the oscillation is typical and is often referred in the rubber mechanics literature as unstable or 'stick-slip' tearing; i.e., the delamination does not propagate at a steady rate, but is arrested and re-initiated at irregular intervals.

A comparison of S_d between non-aneurysmal and ATAA with BAV and TAV in both LONG and CIRC directions was performed (Fig. 11.3). A significant difference was observed for the S_d (i.e. the resistance to AoD) in both LONG and CIRC directions of the non-aneurysmal aorta ($S_{d,LONG} = 149.0 \pm 7.6$ and $S_{d,CIRC} = 126.0 \pm 6.6$, $n = 7$) with respect to that of BAV ATAAs ($S_{d,LONG} = 100.0 \pm 4.1$ and $S_{d,CIRC} = 88.4 \pm 4.1$, $n = 16$) and with respect to that of TAV ATAAs ($S_{d,LONG} = 116.8 \pm 6.1$ and $S_{d,CIRC} = 109.1 \pm 5.2$, $n = 8$). Furthermore, the significant difference between LONG and CIRC strengths for the non-aneurysmal group indicates anisotropic (i.e., directionally-dependent) dissection properties of the human ascending thoracic aorta. However, the aneurysmal aorta displays isotropic dissection properties since both BAV and TAV groups are not statistically difference in LONG and CIRC orientations. The S_d of BAV ATAAs was significantly lower than TAV ATAAs in both orientations.

Patient age or aneurysm diameter could affect the delamination strength of the aneurysmal aorta. To determine if the difference in S_d between groups was age-dependent, the S_d data for the non-aneurysmal and BAV groups as a function of the patient age were fit by linear regression to calculate two new sets of extrapolated S_d for non-aneurysmal (non-aneurysmal$_{extr}$) and BAV (BAV$_{extr,\ age}$), respectively, at the ages of each of the TAV patients, see Fig. 11.4(A). To assess if the difference in S_d between aneurysmal groups was diameter-dependent, the S_d data for the BAV group as a function of the aneurysm diameter were fit by linear regression to obtain a new set of extrapolated S_d for BAV (BAV$_{extr,\ dia}$) at the aneurysm diameter of each of the TAV patients, see Fig. 11.4(B). For the latter analysis, the comparison was performed only between aneurysmal groups since the S_d can not be extrapolated for

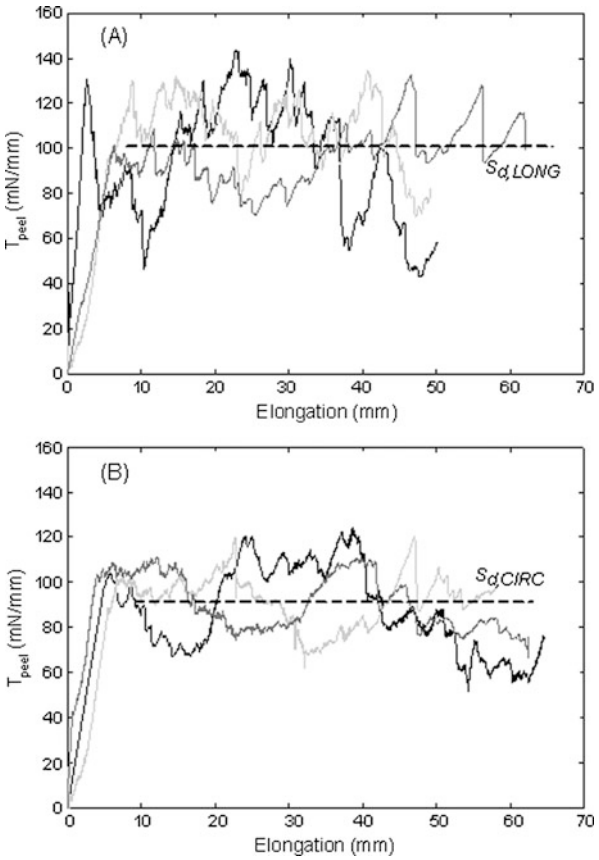

Fig. 11.2 Delamination profiles for (**A**) three LONG and (**B**) three CIRC strips cut from the same BAV aneurysm. The *dashed lines* represent the average of the mean values of T_{peel} for all LONG and CIRC strips and were taken as the S_d in LONG and CIRC directions for the patient, respectively. Taken from Pasta et al. (2011)

the non-aneurysmal aorta as a function of aortic diameter. Results suggest that even with corrections of age or aneurysm diameter the S_d of TAV ATAAs still remains higher than that of BAV_{ext}, see Figs. 11.4(A) and 11.4(B).

A comparison of S_T of non-aneurysmal and aneurysmal tissues for both INT-DEL and ADV-DEL halves following the delamination tests in LONG and CIRC orientations was performed, see Figs. 11.5(A) and 11.5(B). In all cases, the S_T of the CIRC strips was found to be higher than that of LONG specimens, and the INT-DEL half is significantly weaker than the ADV-DEL half. It should be also noted that the ultimate tensile strength of BAV ATAAs is higher than that of TAV ATAAs, though not significantly different. This trend is opposite of that observed for the delamination testing.

SEM imaging of the dissected surfaces for the healthy aorta reveals that the delamination in the LONG direction creates a remarkably 'rougher' surface compared to the surfaces from CIRC specimens (Fig. 11.6(A)). Similar failure surfaces were found for both BAV and TAV ATAAs; however, they appeared rougher than those of normal aorta (Fig. 11.6(A)). At high magnification, a 'fiber bridging' failure modality, which occurs when the dissection switches from one fiber/matrix interface to

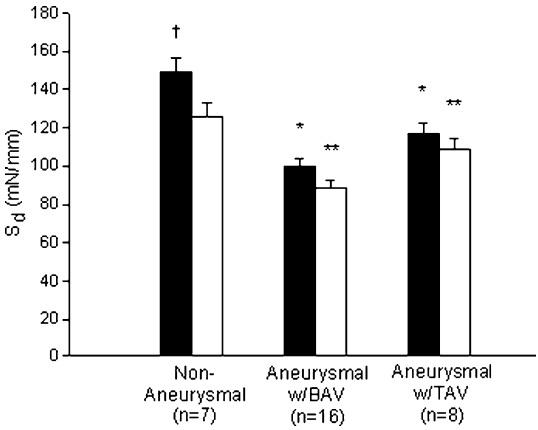

Fig. 11.3 Delamination strength in both LONG (■) and CIRC (□) orientations. * significantly different from LONG non-aneurysmal aorta ($p < 0.05$); ** significantly different from CIRC non-aneurysmal aorta ($p < 0.05$); † significantly different from CIRC non-aneurysmal aorta ($p < 0.05$). Taken from Pasta et al. (2011)

another and leaves behind the unbroken fibers to bridge the delamination, was observed for both non-diseased and aneurysmal aorta (Fig. 11.6(B)).

11.4 Discussion

The present investigation was performed to evaluate the delamination properties of the human ascending aorta to improve our understanding of the mechanics underlying aortic dissection in patients with ATAAs, and to compare these properties in patients with BAV and TAV. The mechanical integrity of the outer versus inner half of the dissected aorta was also explored to assess the relative probability of exit through the adventitia (frank disruption) versus propagation of the dissection flap, respectively, after the onset of AoD. Finally, the failure mechanisms during dissection were optically investigated. Our findings suggest that the propensity of AoD is greater in thoracic aneurysms compared to non-aneurysmal aorta, and is intrinsically greater for BAV ATAAs than those of TAV ATAAs. To our knowledge, these results have never been reported. Similar dissection properties for the human abdominal aorta were reported by Sommer et al. (2008).

The delamination curves (see Fig. 11.2) show an oscillation of T_{peel} about a mean 'plateau' value similar to the results found for tearing tests of the pig descending aorta (Purslow, 1983) and peeling tests of the human abdominal aorta (Sommer et al., 2008). Therefore, AoDs do not propagate at steady rates but arrest and re-initiate at somewhat regular intervals. The force necessary to drive the AoD appears to vary widely from a minimum at delamination arrest to a maximum at delamination initiation. This failure modality is mainly supported by the observation of a large amount of broken elastin fibers on the dissected tissue surfaces (see Fig. 11.6(B)) and is consistent with a fiber bridging failure modality (Gregory and Spearing, 2004). In this manner, the elastin fibers between halves may experience high stretch values during delamination testing with a consequent increase in the T_{peel} magnitude. Their subsequent failure induces a rapid decrease

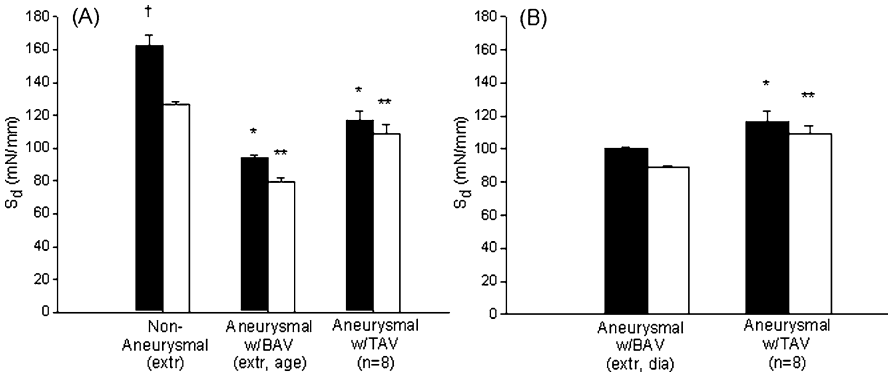

Fig. 11.4 (**A**) Delamination strength of aneurysmal aorta with BAV ($BAV_{extr,\ age}$) extrapolated (calculated) at the ages of each of the TAV patients in both LONG (■) and CIRC (□) directions for $n = 8$ specimens. ⋆ significantly different from LONG non-aneurysmal aorta ($p < 0.05$); ⋆⋆ significantly different from CIRC non-aneurysmal aorta ($p < 0.05$); † significantly different from CIRC non-aneurysmal aorta ($p < 0.05$); (**B**) delamination strength of aneurysmal aorta with BAV ($BAV_{ext,\ dia}$) extrapolated at the aneurysm diameter of each of the TAV patients in both LONG (■) and CIRC (□) directions for $n = 8$ specimens. ⋆ significantly different from LONG aneurysmal aorta with BAV_{ext} ($p < 0.05$); ⋆⋆ significantly different from CIRC aneurysmal aorta with BAV_{ext} ($p < 0.05$). Taken from Pasta et al. (2011)

in T_{peel} due to the reduced resistance to delamination, and this process repeats in intervals as the delamination propagates. Delamination was observed during the testing to propagate entirely within the medial layer of the aortic tissue specimens.

The significantly lower resistance to AoD of either type of aneurysm compared to that of healthy aorta (see Fig. 11.3) evinces that patients with ATAAs are more prone to AoD. Similar findings on the tensile strength of ATAAs were reported by our group and suggest that the propensity of rupture in thoracic aneurysm is 30 % higher than that of the non-aneurysmal ascending aorta (Vorp et al., 2003). Lower LONG tensile strength with aneurysm enlargement was also reported. This work suggests that a lower LONG tensile strength may be a cause of AoD in ATAAs (Iliopoulos et al., 2009). The fact that we found a $S_{d,CIRC}$ significantly lower than the $S_{d,LONG}$ is consistent with the notion that the pathogenesis of AoD is initiated by a transverse intimal tear on most of tear morphology seen clinically (Coady et al., 1999). Anisotropic dissection properties of the non-aneurysmal human ascending thoracic aorta are deduced by the significant difference of S_d in LONG and CIRC orientations (see Fig. 11.3). In contrast, aneurysmal disease leads to isotropic behavior of the aorta most likely due to a more disorganized microstructure, see Fig. 11.3. The most relevant finding is the difference in delamination propensity among BAV ATAAs compared to TAV ATAAs (Fig. 11.3), suggesting a greater propensity of AoD among BAV individuals. Furthermore, our deduction that age and aneurysm diameter are not key factors for AoD in patients with thoracic aneurysms (see Figs. 11.4(A) and (B), respectively) suggests that the higher propensity of aortic dissection in patients with BAV is related to lower delamination resistance that may

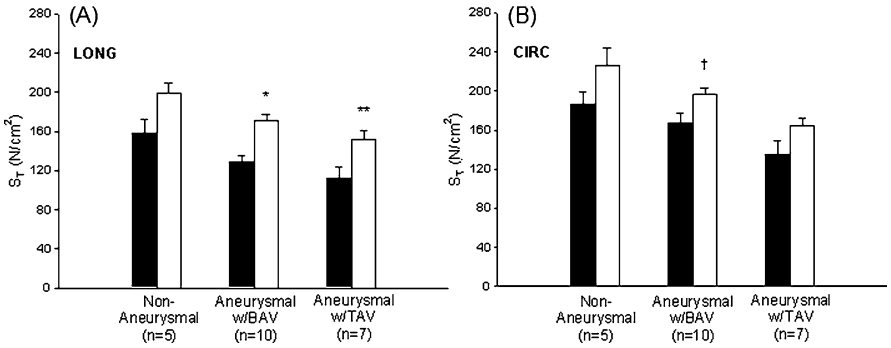

Fig. 11.5 (**A**) Tensile strength in LONG and (**B**) CIRC directions for INT-DEL halves (■) and ADV-DEL halves (□). * significantly different from INT-DEL LONG BAV ATAA ($p < 0.001$); ** significantly different from INT-DEL LONG BAV ATAA ($p = 0.016$); † significantly different from INT-DEL CIRC TAV ATAA ($p = 0.024$). Taken from Pasta et al. (2011)

be caused by predisposing structural disorders. A deficit in the smooth muscle cell response to the oxidative stress could be responsible for example of the inherent lower S_d in BAV tissues (Phillippi et al., 2009, 2010).

Our results demonstrate a weaker S_T of the intimal half of the aortic wall (i.e. the INT-DEL half; see Figs. 11.5(A) and (B)), imparting an apparent risk of the propagation of AoD. Exit through the outer residual layer (i.e. the ADV-DEL half) causing frank aortic disruption is less common than dissection propagation, and this may be explained by the relatively stronger S_T of the adventitial half of the aortic wall in this study. These results are consistent to the disparate strengths of healthy arterial layers found in the literature (Holzapfel et al., 2007).

Anisotropic dissection properties of the non-aneurysmal ascending aorta are consistent with SEM imaging results. Indeed, the elastin and collagen fibers are oriented mainly in the circumferential direction in the non-aneurysmal aortic wall and, as a result, may provide a greater strength to AoD in LONG direction. For the non-aneurysmal aorta, the creation of a rougher dissection surface may explain both higher mean and variance in S_d of LONG strips compared to those oriented in CIRC direction, see Fig. 11.2. The dissection in LONG direction frequently crosses the elastic layers while that in CIRC strips propagate mainly between adjacent elastic laminae (Fig. 11.6(A)) resulting in a 'flat' broken surface as found by Sommer et al. (2008) for the non-aneurysmal human abdominal aorta. Moreover, the fracture surfaces of both BAV and TAV ATAAs appear rougher than those for normal aorta (see Fig. 11.6(A)), likely due to the more disorganized microstructure caused by the disease. Disorganization of elastin and collagen fibers due to aneurysm appears to impact the mechanical properties of ATAAs. For the healthy aorta, the formation of a rougher surface may clarify the non-significant difference in S_d between the LONG and CIRC directions, suggesting isotropic dissection properties.

These results are limited by the fact that delamination testing does not accurately model the spontaneous initiation of AoD that occurs in vivo. Other models

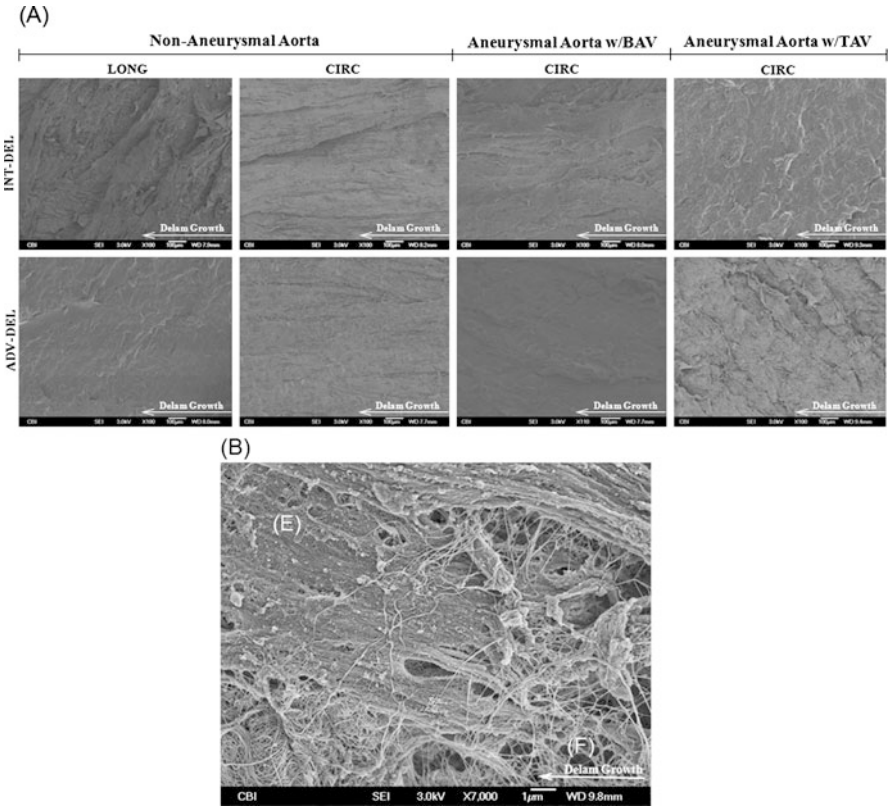

Fig. 11.6 (**A**) Representative SEM images of fracture surfaces of the non-aneurysmal and ATAA with BAV and TAV in LONG and CIRC direction; (**B**) high magnification image of a CIRC TAV ATAA for the INT-DEL half showing bundles of broken elastin fibers (**F**) existing between elastic sheets (**E**). The fibers act like a 'bridge' between halves in a fracture modality called 'fiber bridging' in delamination testing. Taken from Pasta et al. (2011)

of AoD have been described (Tiessen and Roach, 1993), but the onset of dissection was typically forced in these studies by injecting liquid with a syringe into the media to separate the aortic lamellae. Additionally, the stresses that lead to AoD are likely multi-factorial and could be composed of stresses due to blood pressure, shear stresses due to the blood flow field, torsion due to heart motion or propagation of the pressure pulse, etc. However, the purpose of this investigation was not to simulate these forces, but rather to measure the resistance of the tissue to stresses induced by delamination (i.e., bonding forces between the mural layers of the aortic wall, or the delamination strength). Future work could be to investigate correlation not observed in this investigation between tissue strength and aortic diseases as the aortic stenosis and regurgitation.

11.5 Conclusion

Thoracic aneurysms with BAV and TAV both have significantly altered biomechanical properties compared to normal ascending aorta, thus imparting their propensity of AoD. Moreover, BAV ATAAs have lower delamination strength than TAV ATAAs, rendering an apparently greater risk of AoD for BAV than TAV patients.

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