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Wall Stress And Geometry Of The Thoracic Aorta In Patients With Aortic Valve Disease

Short Title: Aortic wall stress and valve disease

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Abstract

Background: Aortic valve disease increases velocity and changes the way blood enters the aorta. Over time, the biomechanical environment can cause aortic remodelling. We hypothesised that aortic geometry and wall stress would be different in patients with aortic valve disease compared to controls.

Methods: We examined 40 patients with aortic sclerosis (n=10), mild (n=10), moderate (n=10) and severe (n=10) aortic stenosis, and also 10 control cases. The thoracic aorta of each case was reconstructed into a three-dimensional model from computed tomography. We measured geometric parameters and used finite element analysis to compute aortic wall stress. Statistical analyses were performed to test our hypothesis.

Results: Aortic wall stress was significantly associated with tortuosity of the descending aorta ($r=0.35$, $p=0.01$), arch radius ($r=0.49$, $p<0.01$), ascending aortic diameter ($r=0.59$, $p<0.01$) and aortic centreline length ($r=0.39$, $p<0.01$). Wall stress was highest in patients with severe stenosis ($p=0.02$), although elevations in wall stress were also noted in subjects with mild stenosis ($p=0.02$), and aortic sclerosis ($p=0.02$) compared to controls. Similar trends were observed when we corrected for difference in blood pressure. Total centreline tortuosity was higher in patients with severe aortic stenosis compared to controls ($p=0.04$), as was descending aorta tortuosity ($p=0.04$).

Conclusions: Aortic geometry is associated with aortic wall stress. Patients with aortic valve disease have higher aortic wall stress than control cases, and those with severe aortic stenosis have more tortuous aortas. However, increases in geometric measures and wall stress are not stepwise with increasing disease severity.

Abstract word count=244

Aortic valve disease changes the haemodynamics in the aorta, with changes in peak velocity typically measured with ultrasound [1]. Aortic dilation is often seen in cases of aortic stenosis [2, 3] however it is currently unknown if this is due to the increase in velocity and potential increase in mechanical stresses and can cause aortic dilatation. The peak velocity of blood ejected through the valve can be increased more than 4 fold and this jet can also become more eccentric and helical, and have vortical flow formation [4]. As such, the haemodynamic profile entering the ascending aorta changes markedly in the presence of valve disease with abnormal impingement of blood on the ascending aorta wall and disturbed haemodynamics in the arch and descending aorta. This results in an elevated and axisymmetric shear stress pattern [4]. Over time, these biomechanical factors influence aortic remodelling and induce geometric changes in the aorta. Consequently, the change in geometry will also change the mechanical stresses acting on the aortic wall with elevated wall stress contributing to the development of aneurysm or dissection [5] and further geometric changes. It is therefore important to understand the biomechanical environment of the thoracic aorta in patients with aortic valve disease. This is now possible with advanced non-invasive imaging and engineering techniques.

We hypothesised that the geometry of the aorta would be significantly different and the stresses within the aortic wall would be higher in patients with aortic valve disease compared to controls. To test this, we examined patients with a range of aortic valve disease (sclerosis, mild, moderate and severe stenosis), measuring geometric parameters and calculating aortic wall stress in each case. We then used statistical tests to investigate differences and associations.

PATIENTS AND METHODS

Study group and Imaging

Ethical approval was granted by the local ethics committee. Fifty subjects were included from a recent clinical trial [6], with 10 subjects randomly selected from each of the trial's

groups. Of the 40 patients included, 10 had aortic sclerosis, 10 mild, 10 moderate and 10 with severe aortic stenosis. A further 10 were controls with no aortic valve disease. All subjects were >50 years old and had a tri-leaflet aortic valve. There were no cases with any connective tissue disorder (e.g. Marfans or Ehlers Danlos syndrome). In the original study [6], patients were grouped using peak jet velocity according to clinical guidelines [7]: mild, 2.0-3.0 m/s; moderate, 3.1–4.0 m/s; severe, >4 m/s. Aortic sclerosis was defined as a thickened aortic valve on echocardiography but with peak jet velocity <2 m/s. Controls were cases with velocity <2 m/s and no signs of aortic valve thickening. All patients underwent full clinical assessment, which included recording of routine clinical parameters listed in Table 1. In addition, we calculated the Society of Thoracic Surgery (STS) Risk Score for each case. Non-enhanced low dose (230 kV, 50 mAs) attenuation-correction computed tomography (CT) imaging was performed on a hybrid scanner (Biograph mCT, Siemens Medical Systems, Germany), with further details previously reported [6].

3D Reconstructions

CT datasets were imported in DICOM format into Mimics (v18, Materialise, Belgium). Segmentation began at the sinotubular junction and ended at the diaphragm level of the descending thoracic aorta. The aorta was semi-automatically segmented using pixel intensity and manual editing. We omitted the supra-aortic branches from the reconstructions as they were not clearly visible on the non-contrast CT. The three-dimensional (3D) geometry was exported to 3-matic (v8, Materialise, Belgium) where the surfaces of the model were conservatively smoothed to remove any artefacts from the reconstruction process. As the exact aortic wall thickness cannot be determined from CT and as men have thicker aortic walls than women [8], we used a uniform thickness of 2.32 mm for male cases and 2.11 mm for females. These measurements are average data of 98 men and 98 women imaged with magnetic resonance imaging (MRI) [8].

Geometric Measurements

The 3D reconstructions were used to determine several geometric measurements within Mimics. Firstly, the centreline of the each aorta was created and the total tortuosity of the centreline measured. The centreline is line that connects the centre point of the aorta on each axial CT slice. This centreline was then divided into two sections using the apex of the arch, with tortuosity of the ascending and descending aorta determined. The arch angle was measured from the right, along the inner surface of the arch. The arch radius was found by inscribing a circle to the inner curvature of the centreline and recording the radius. Finally, the maximum ascending aortic diameter was quantified using a measurement perpendicular to the centreline. An illustration of these measurements is shown in Figure 1. We also categorised each aorta as Type 1 or 2 depending on the location of the supra-aortic branches. As described in Nathan et al. [5], aortas where the left subclavian artery originates from the top of the outer curvature of the arch are classed as Type 1, whereas, in Type 2 aortas, the left subclavian originates from below the outer arch curvature.

Finite Element Analysis Details

In 3-matic (v10, Materialise, Belgium), a surface mesh was created with a maximum element edge length of 1 mm. We converted the surface mesh to shell elements and imported the meshes into ABAQUS (v6.14, Dassault Systemes, USA) for analysis. A mesh independence study demonstrated that further mesh refinement beyond that used throughout the study had negligible impact on wall stress (<1%). Therefore a typical computational mesh consisted of about 80,000 shell elements with an example shown in Figure 1.

As the aorta is internally pressurised at the time of imaging, we approached the problem as a statically determinate geometry, which eliminates the need for patient-specific material properties [9, 10]. Using this method we can assume the wall to have arbitrary material properties as they do not impact the resulting wall stress, so long as the material is stiff enough to ensure no deformation and the pressure loading is applied in a single loading procedure. Therefore, we assumed the wall was a linearly elastic material with Young's

modulus, *E*=200 MPa and Poisson's ratio, *v*=0.49. The model was physically constrained at the aortic root and the distal region of the descending aorta to simulate tethering to the heart and the abdominal aorta. Patient-specific blood pressure was measured at the time of imaging and assigned as a pressure loading on the internal surface of the aorta. However, we also simulated wall stress using a standardised blood pressure of 120 mmHg across the entire cohort. This was to correct for any potential differences in blood pressure between the groups.

Data Analysis

Continuous data is presented as mean ± standard deviation (range) and the 99th percentile of peak von Mises wall stress was used as a reproducible measure of wall stress [11]. Relationships were investigated using t-tests, ANOVA, Chi-squared, Pearson's or Spearman's Rank correlation tests (depending on normality of data determined using the Shapiro-Wilk test) and also using multiple regression. We used $p<0.05$ to determine significance.

RESULTS

Cohort Characteristics

Table 1 presents the cohort characteristics. Subjects were 73.8±8.2 (54-90) years and consisted of more males than females (31 vs. 19). Mean blood pressure was 146±18 (109-193) mmHg and body mass index (BMI) was 26.8±3.7 (19.9-40.0) kg/m^2. Although there were differences in age between groups ($p<0.01$), they were matched for comorbidities with no significant difference in STS Risk Score ($p=0.20$). Age can change aortic morphology [12], however in our cohort there were no correlations between age and any geometric measures (Figure 2).

Geometric Analyses and Wall Stress in the Cohort

Ascending aortic diameter was 36.1±4.8 (28.1-56.6) mm. Total centreline tortuosity was 0.53±0.06 (0.43-0.67), ascending aortic tortuosity was 0.12±0.04 (0.06-0.23) and descending aortic tortuosity was 0.15±0.04 (0.07-0.27). The mean arch angle was 113±16° (45-151°) and arch radius was 46.8±6.3 (34.9-62.3) mm. The cohort consisted of 23 Type 1 and 27 Type 2 aortas. Aortic diameter (37.5±5.4 vs 34.5±3.4 mm, p=0.03) and total tortuosity (0.55±0.05 vs 0.51±0.07, p<0.01) was higher in Type 2 aortas. There was no difference in age (p=0.61), ascending tortuosity (p=0.35), descending tortuosity (p=0.95) and arch radius (p=0.10) between Type 1 and 2 aortas.

Peak wall stress was 0.29±0.07 MPa (0.17–0.50 MPa). As we assumed females to have thinner aortic walls, women had higher wall stress (0.32±0.08 vs 0.27±0.06 MPa, p<0.01). As shown in Figure 2, age (r=0.41, p<0.01) and blood pressure (r=0.51, p<0.01) were significantly associated with patient-specific wall stress, but not when we used 120 mmHg blood pressure in the simulations (age, p=0.07; blood pressure, p=0.95). When cases were grouped by age (irrespective of disease), those over 80 years (n=13) had higher wall stress than 70-79 year olds (n=23) (0.34±0.07 vs 0.29±0.07 MPa, p=0.05) and those <69 years (n=14) (0.34±0.07 vs 0.26±0.06 MPa, p<0.01). However, when we simulated wall stress at 120 mmHg, there were no significant differences between any age groups (>80 y vs. 70-79 y, p=0.76; >80 y vs. <69 y, p=0.13; 70-79 y vs. <69 y, p=0.20). Wall stress was associated with peak jet velocity at both patient-specific blood pressure (r=0.28, p=0.05) and 120 mmHg (r=0.31, p=0.03). Wall stress was similar in both Type 1 and 2 aortas (0.31±0.08 vs 0.28±0.07 MPa, p=0.19) but there were several strong associations between geometry and wall stress (Figure 2). Notably, wall stress was correlated with descending tortuosity (r=0.35, p=0.01), arch radius (r=0.49, p<0.01), diameter (r=0.59, p<0.01) and aortic centreline length (r=0.39, p<0.01).

Using multiple regression, we found that gender (p=0.04) and blood pressure (p<0.001) influence patient-specific wall stress, independent of all geometric measures (tortuosity, arch angle, arch radius and centreline length) age and aortic valve disease. Gender remained

significant (p=0.01) when we tested for wall stress at 120 mmHg, but blood pressure, unsurprisingly, was no longer significant (p=0.91). Strong effects of gender are expected here as females have thinner aortic walls and therefore will have higher wall stress. However, at 120 mmHg, there was no difference between men and women, despite the difference in wall thickness (p=0.30). Increases in diameter indicate geometric remodelling and we determined that arch angle (p<0.01) and arch radius (p<0.001) both influence diameter independent of other geometric measures, sex, age, blood pressure, peak velocity, wall stress and aortic valve disease. Therefore, aortas with more acute arch angles and larger arch radius are more likely to have larger ascending aortic diameters.

Aortic Geometry and Valve Disease

Total aortic centreline tortuosity (Figure 3A) was higher in patients with severe aortic stenosis compared to controls (0.57±0.04 vs 0.52±0.05, p=0.04) and when compared to moderate stenosis (0.50±0.06, p=0.01). Descending tortuosity (Figure 3B) was higher in the severe stenosis group compared to controls (0.17±0.03 vs 0.13±0.04, p=0.04). However, we did not find a stepwise increase in tortuosity with increasing valve disease. Also, there was also no difference in geometry across groups (Table 1).

Wall Stress and Aortic Valve Disease

When we consider all patients together compared to controls, wall stress was on average 25% (12-33%) higher (0.31±0.07 vs 0.25±0.03, p<0.01). Compared to controls, values were numerically highest in patients with severe stenosis (0.33±0.09, p=0.02), with wall stress also higher in subjects with mild stenosis (0.31±0.07, p=0.02), and aortic sclerosis (0.31±0.08, p=0.02) (Figure 4A). The findings were largely unchanged when we simulated at 120 mmHg blood pressure and found patients to have higher wall stress than controls (0.25±0.06 vs 0.21±0.02, p<0.01). Compared to controls, wall stress was higher in the severe stenosis (0.28±0.09, p=0.04) and sclerosis groups (0.25±0.03, p<0.01), though not patients with mild stenosis (0.24±0.05, p=0.07) (Figure 4B). Figure 5 shows wall stress

contours in patients who experienced different levels of wall stress (high, mean, low) in each of the five study groups.

COMMENT

Aortic valve disease changes the haemodynamic profile entering the ascending aorta and increases blood velocity. Over time, this mechanical environment contributes to aortic remodelling as the vessel wall responds to the changing biomechanics. Our aim here was to investigate the biomechanics of the aorta in the presence of aortic valve disease and determine if these patients have significantly different aortic geometries and elevated wall stress, compared to controls. By understanding the wall stresses in the thoracic aorta in the presence of aortic valve disease, further insight into the systemic aspects of cardiovascular disease can be provided. As patients with valve disease may have valve replacement surgery, it is important to have a thorough understanding of the biomechanical environment into which the valve will be implanted. Therefore, future work investigating cases with valve replacement and follow-up imaging would be worthwhile to determine if aortic remodelling continues once the jet velocity is reduced through valve repair.

We found patients with aortic valve disease experience significantly higher wall stress than controls, and that the descending aorta was 22% more tortuous in disease groups compared to controls. As geometry is a key element in wall stress, it is likely that the increased velocities entering the aorta due to valve disease cause biomechanically-stimulated remodelling, and in turn, increased wall stress. Indeed, we found peak velocity to be associated with wall stress, especially when we calculated wall stress using uniform blood pressure across all subjects (Figure 2). Ha et al. [13] investigated the effect of aortic valve angle on blood ejecting into the aorta and showed that the rotational direction and strength of helical flow varies substantially. Higher helical velocities and rotational flow will influence subsequent morphological changes in the ascending aorta such as dilation [14]. It is the helical flow patterns in the ascending aorta that is thought to play a key role in the incidence of ascending aortic dilation in BAV [15]. Furthermore, aortic valve orientation is also

associated with both morphology and dissection [16]. Therefore, as the high velocity helical flow travels through the ascending aorta and aortic arch, it will continue to rotate and travel along the descending aorta, further contributing to the remodelling process (increasing tortuosity of the descending aorta and likelihood of aortic disease development), and also resulting in the associated increases in wall stress. In our study we found that the tortuosity was significantly increased in the descending aorta but not the ascending aorta, which further suggests that the high velocity helical blood flow passing through the ascending aorta of patients with aortic stenosis, begins to cause remodelling where the flow decelerates into the descending aorta, distal to the supra-aortic branches. Conversely, in the aortic sclerosis cases where the jet velocity is similar to controls, it could be the shape of the flow rather than the velocity magnitude that causes tortuosity changes. These geometric changes are a continuous process occurring over long time periods and will require serial follow-up imaging to fully understand.

Inherited valve disease also influences wall stress in the thoracic aorta. It is generally accepted that bicuspid aortic valve (BAV) cases are more likely to have aortic disease [17-19] and may be associated with alterations in the structure of the aorta. Nathan et al. [20] showed that thoracic aortic wall stress was higher in patients with BAV (n=20) compared to those with tricuspid aortic valve (TAV) (n=20), although the difference was not significant (0.51±0.07 vs 0.45±0.10 MPa, p=0.15). However there were no BAV patients in the present analysis, only TAV, and there is limited data on the link between aortic pathology and stenosis of TAV. Boudoulas et al. [21] showed a strong association between valvular aortic stenosis, coronary atherosclerosis and aneurysmal dilatation of the ascending aorta, recommending that aortic stenosis be considered as a cluster of diseases; “the aortic stenosis complex”. In this current study, we have found that TAV patients with aortic valve disease have elevated aortic wall stress, which could contribute to the development of aortic disease, especially aortic dilation and dissection. Indeed, it is believed that the initial event in the development of aortic stenosis is endothelial damage from mechanical stresses enabling

infiltration of lipids and the recruitment of inflammatory cells into the valve [22]. Similar mechanisms are involved in the early stages of atherosclerosis and therefore aortic disease. Patients with aortic stenosis have disturbed high velocity flow entering the ascending aorta and here we show that these cases also have elevated wall stress throughout the thoracic aorta which is likely driving geometric remodelling and contributing to overall pathology.

There are several strengths to our study, one of which is that we computed the patient-specific wall stress without requiring patient-specific material properties [9, 10]. Not only does this eliminate uncertainty of patient-specific material data, but also reduces the simulation time (e.g. typical simulation time was about 10 s on a workstation with an Intel Core i7-6400 CPU and 64 Gb RAM). Therefore, with further work, the methods we show here could be automated to fit into the clinical workflow and could be a useful tool for further clinical insight into the systemic nature of valve disease and to better understand this complex disease [21]. This could be particularly useful for developing management plans and pre-surgical guidance.

However, this work is not without limitations. Specifically, the use of a uniform wall thickness in our modelling reduces fidelity. As CT cannot accurately distinguish aortic wall thickness, uniform wall thickness is a common assumption in aortic wall stress analyses. We used data (2.32 and 2.11 mm) from MRI measurements [8] which are similar to average measurements of Okamoto et al. of 2.5 mm [23]. In a study of thoracic aortas by Nathan et al. [20] they used a considerably lower value of 1.7 mm and did not vary wall thickness based on gender or apply patient-specific blood pressure values. The implications of a thicker aortic wall are lower wall stresses. Recently we reported our new method of merging MRI and CT to create aortic aneurysm reconstructions with patient-specific wall thickness [9, 10]. A similar method would be useful here. Also, although we randomly selected cases from larger groups [6], our control cases were slightly younger than the original control group (70±8 vs. 66±7 y).

Therefore, in our study there is a difference in age between groups (p=0.01), whereas in the original trial they were well matched (p=0.73). However, as we show no association between age and any measure of geometry (Figure 2), we believe that age is not an influential factor here and younger control cases does not negatively impact our findings. This is further supported by the use of aortas with uniform wall thickness where the only parameters affecting wall stress are geometry and blood pressure. We eliminated the effects of varying blood pressure by applying 120 mmHg to all cases (Figure 4B), and therefore the only influential factor is geometry, which in our cohort does not significantly change with age, but does with aortic valve disease. We also found no difference in STS Risk Score between groups (p=0.20), demonstrating that the small age difference between groups does not translate into any differences in comorbidity that may have confounded our observations. Finally, we have no measured flow profile data for our cohort (only peak jet velocity) and without contrast-enhanced CT we cannot distinguish the orientation of the valve, with both valve orientation [13] and flow pattern entering the ascending aorta [4, 14, 15] recognised as important.

Conclusion

In conclusion, we have shown the associations between thoracic aortic geometry and wall stress in a cohort of fifty subjects. We show that wall stress was significantly associated with descending aorta tortuosity, arch radius, ascending aorta diameter, aortic centreline length and peak jet velocity.

We found that patients with aortic valve disease, in particular those with severe aortic stenosis, have significantly higher thoracic aortic wall stress and more aortic tortuosity than controls. However, there is not a stepwise increase in wall stress or geometric factors with increasing severity of aortic valve disease.

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Table 1: Patient characteristics. Data shows mean ± standard deviation or percentage of total cohort. P value is from ANOVA.

			Aortic Stenosis			
	Controls	Sclerosis	Mild	Moderate	Severe	*p*
Number	10	10	10	10	10	
Age (y)	66.2±6.8	74.2±5.7	74.4±9.8	75.8±7.3	78.3±7. 1	0.01
Male sex (%)	60	70	60	80	40	0.84
Systolic BP (mmHg)	139±9.5	148±24.6	151.8±14.7	144. 1±11.3	144.1±24.6	0.57
BMI (kg/m^3)	25.7±2.9	26.7±6.2	27.5±2.2	27.5±3.6	26.6±2.3	0.80
Ischaemic heart disease (%)	20	40	40	40	20	0.83
Cardiovascular disease (%)	20	40	40	60	20	0.54
Ex or current smoker (%)	50	50	50	30	50	0.95
Diabetes mellitus (%)	10	10	10	0	20	0.74
CKD stage, ≥3 (%)	10	30	10	30	30	0.70
STS Score* (%)	0.99±0.44	1.26±0.77	1.72±1.51	1.42±0 .54	2.03±1.24	0.20
Creatinine (mg/dL)	76.1±21.5	91±22.1	88.9±30.8	98.4 ±21.3	89.5±38.4	0.50
Total cholesterol (mg/dL)	5.18±0.84	5.0±1.4	6.17±1. 4	4.06±0.1	5.3±1.5	0.01
HDL cholesterol (mg/dL)	1.53±0.42	1.36±0.44	1.36±0. 28	1.28±0.32	1.39±0.37	0.59
LDL cholesterol (mg/dL)	2.88±0.94	2.87±1.22	3.89±1. 12	1.95±0.72	3.09±1.32	0.01
Triglycerides (mg/dL)	1.56±1.0	1.68±0.64	2.03±0.98	1.91±0.69	1.84±1.45	0.86
Betablockers (%)	30	40	40	50	50	0.83

Statin therapy (%)	30	50	30	90	60	0.31
ACE inhibitor therapy (%)	40	60	60	30	30	0.72
Peak jet velocity (m/s)	1.35±0.2	1.66±0.17	2.51±0.21	3.39±0.28	4.76±0.56	<0.001
Total tortuosity	0.52±0.05	0.55±0.07	0.53±0.06	0.50±0.06	0.57±0.04	0.14
Ascending tortuosity	0.12±0.4	0.11±0.04	0.12±0.03	0.13±0.03	0.14±0.04	0.54
Descending tortuosity	0.13±0.04	0.16±0.06	0.16±0.02	0.15±0.03	0.17±0.03	0.24
Ascending diameter (mm)	34.3±4.2	36.6±3.6	35.9±3.9	35.8±2.8	37.9±8.0	0.57
Arch angle (degree)	110±14	111±12	117±13	118±16	107±25	0.52
Arch radius (mm)	45.5±6.6	50.7±7.4	45.4±5.8	45.2±6.7	47.4±4.1	0.24
BP wall stress (MPa)	0.25±0.03	0.31±0.08	0.31±0.07	0.26±0.07	0.33±0.09	0.06
120 mmHg wall stress (MPa)	0.21±0.02	0.25±0.03	0.24±0.05	0.24±0.05	0.28±0.09	0.06

*****Society of Thoracic Surgery (STS) Score presents the risk of mortality from aortic valve repair

Figure Legends

Figure 1. Example control aorta showing (A) 3D reconstruction, (B) geometrical measurements and (C) computational mesh of finite elements.

Figure 2: All correlations between variables for the entire cohort. Rows (A-G) show geometry relationships. Panels on the right show wall stress with age (H), blood pressure (I) and peak jet velocity (K). Correlation coefficients (r) and p-values are shown for each relationship.

Figure 3: (A) Total centreline tortuosity and (B) descending aortic centreline tortuosity for each group.

Figure 4: 99^{th} percentile of peak wall stress for each group under (A) patient-specific and (B) standardised 120 mmHg blood pressure conditions.

Figure 5: 99^{th} percentile of peak von Mises wall stress contours at patient-specific blood pressure in cases from each group. Top row: cases with highest wall stress. Middle row: cases closest to the mean wall stress (see Table 1). Bottom row: cases with the lowest wall stress in the group. Colour bar refers to all cases and all units are MPa. Cases are not to size scale.