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# Accepted Manuscript

Patient-Specific Computational Fluid Dynamics – Assessment of Aortic Hemodynamics in a Spectrum of Aortic Valve Pathologies

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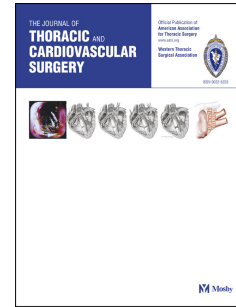
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1 **Patient-Specific Computational Fluid Dynamics – Assessment of**  
2 **Aortic Hemodynamics in a Spectrum of Aortic Valve Pathologies**

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35

36 **Disclosures**

37 None.

38

39 **ABSTRACT**

40

41 **Objectives:** The complexity of aortic disease is not fully exposed by aortic dimensions alone,  
42 and morbidity or mortality can occur before intervention thresholds are met. Patient-specific  
43 computational fluid dynamics (CFD) was used to assess effect of different aortic valve  
44 morphologies on velocity profiles, flow patterns, helicity, wall shear stress (WSS) and  
45 oscillatory shear index (OSI) in the thoracic aorta.

46 **Methods:** 45 subjects were divided into 5 groups: Volunteers, AR-TAV, AS-TAV, AS-  
47 BAV(RL), AS-BAV(RN), where AR=aortic regurgitation, AS=aortic stenosis,  
48 TAV=tricuspid aortic valve, BAV=bicuspid aortic valve, RL=right-left cusp fusion,  
49 RN=right-non cusp fusion. Subjects underwent magnetic resonance angiography, with phase-  
50 contrast MRI at the sino-tubular junction to define patient-specific inflow velocity profiles.  
51 Hemodynamic recordings were used alongside MRI angiographic data to run patient-specific  
52 CFD.

53 **Results:** BAV groups had larger mid-ascending aorta diameters ( $p<0.05$ ). Ascending aorta  
54 flow was more eccentric in BAV ( $\text{Flow}_{\text{asymmetry}}=78.9\pm 6.5\%$  for AS-BAV(RN), compared to  
55  $4.7\pm 2.1\%$  for Volunteers,  $p<0.05$ ). Helicity was higher in AS-BAV(RL) ( $p<0.05$ ). Mean  
56 WSS was elevated in AS groups, highest in AS-BAV(RN) ( $37.1\pm 4.0 \text{ dyn/cm}^2$ , compared to  
57  $9.8\pm 5.4$  for Volunteers,  $p<0.05$ ). The greater curvature of the ascending aorta experienced  
58 highest WSS and lowest OSI in AS patients, most significant in AS-BAV(RN) ( $p<0.05$ ).

59 **Conclusions:** BAV displays eccentric flow with high helicity. Presence of AS, particularly in  
60 BAV-RN led to higher WSS and lower OSI in the greater curvature of the ascending aorta.

61 Patient-specific CFD provides non-invasive functional assessment of the thoracic aorta, and  
62 may enable development of a personalized approach to diagnosis and management of aortic  
63 disease beyond traditional guidelines.

64

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66

67

**68 Abbreviations**

- 69 CFD = Computational fluid dynamics
- 70 WSS = Wall shear stress
- 71 OSI = Oscillatory shear index
- 72 BAV = Bicuspid aortic valve
- 73 TAV = Tricuspid aortic valve
- 74 AS = Aortic stenosis
- 75 AR = Aortic regurgitation
- 76 AV = Aortic valve
- 77 CMR = Cardiovascular magnetic resonance
- 78 HFI = Helical flow index

79

80 **Central Message**

81 Patient-specific CFD reveals high WSS and lower OSI in the greater curvature of BAV  
82 aortas, with highly eccentric and helical flow.

83

84

85



## 86 **Perspective Statement**

87 In patients with AV disease and aortic aneurysm, morbidity or mortality can occur before size  
88 criteria for intervention are met. Patient-specific CFD provides non-invasive functional and  
89 hemodynamic assessment of the thoracic aorta. With validation it may enable development of  
90 an individualized approach to diagnosis and management of aortic disease beyond traditional  
91 guidelines.

92

93

## 94 INTRODUCTION

95 For many years, treatment guidelines and intervention criteria have concentrated on  
96 traditional echocardiographic measurements for the aortic valve (AV).<sup>1, 2</sup> Furthermore, size  
97 remains the principal decision-making index for treatment of the thoracic aorta.<sup>3, 4</sup> However,  
98 there is growing evidence that hemodynamics play an important role in aneurysm formation,  
99 with effects on endothelial homeostasis, smooth muscle response, and fibroblast function.<sup>5, 6</sup>

100 Flow characteristics are highly variable in the thoracic aorta, where the inflow velocity  
101 profile is largely dependent on the morphology of the AV. Bicuspid aortic valve (BAV) is the  
102 most common congenital cardiac abnormality with an estimated prevalence of 1-2%, as well  
103 as a morbidity and mortality accounting for more than that of all other congenital cardiac  
104 diseases combined.<sup>7</sup> BAV is often associated with aneurysms of the ascending aorta or aortic  
105 root. This dilatation can lead to eventual dissection or rupture.<sup>8</sup>

106 Disease processes such as aneurysm formation and atherosclerosis are greatly affected by  
107 hemodynamic factors in the vascular system.<sup>9-12</sup> Spatial velocity gradients together with  
108 blood viscosity result in wall shear stresses on the endothelium. Wall shear stress (WSS)  
109 refers to the force per unit area exerted by a moving fluid in the direction of the local tangent  
110 of the luminal surface.<sup>13</sup> Lower WSS has been observed in those carotid arteries with higher  
111 levels of plaque formation.<sup>14</sup> In contrast, high wall shear stress has been associated with  
112 aneurysm formation in the cerebral arteries.<sup>15</sup> Oscillatory shear index (OSI) is a metric that  
113 quantifies the changes in direction and magnitude of WSS and has been associated with  
114 vasculopathy.<sup>16</sup> It ranges between 0 (in uni-directional steady flow) and 0.5 (perfectly  
115 oscillating back-and-forth velocities over the cardiac cycle). Flow in the thoracic aorta has a

116 significant helical component due to a combination of factors such as ventricular twist and  
117 torsion,<sup>17</sup> mechanics of the AV and aortic root, and the curved morphology of the aortic  
118 arch.<sup>18</sup> This helical flow has been related to both plaque deposition<sup>19</sup> and aneurysm  
119 formation.<sup>20</sup> These hemodynamic and biomechanical parameters can be measured non-  
120 invasively using computational fluid dynamics (CFD).

121 In this study, we aimed to use patient-specific CFD to assess the effect of different AV  
122 morphologies on velocity profiles, flow patterns and helicity, wall shear stress and oscillatory  
123 shear index in the thoracic aorta.

124

125

## 126 **METHODS**

### 127 **Study Population**

128 45 subjects were studied. They were divided into the following 5 groups: Volunteers –  
129 healthy volunteers with tricuspid aortic valves (n=5); AR-TAV – aortic regurgitation  
130 tricuspid aortic valves (n=10); AS-TAV – aortic stenosis tricuspid aortic valves (n=10); AS-  
131 BAV(RL) – aortic stenosis bicuspid aortic valves with fusion of right and left coronary cusps  
132 (n=10); AS-BAV(RN) – aortic stenosis bicuspid aortic valves with fusion of right and non-  
133 coronary cusps (n=10). Diagnosis of AS or AR was based on trans-thoracic  
134 echocardiographic data. AS was defined as aortic  $V_{max} > 4$  m/s, mean pressure gradient  $> 40$   
135 mmHg, AV area  $< 1.0$  cm<sup>2</sup>, or AV area index  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>. AR was defined as jet width  
136  $> 65\%$  of left ventricular outflow tract, vena contracta  $\geq 0.6$  cm, regurgitant volume  $> 60$   
137 ml/beat, or effective regurgitant orifice  $\geq 0.3$  cm<sup>2</sup>.<sup>1</sup> Patients with coarctation were excluded.  
138 The study was approved by the local ethical committee (St. George's University of London,  
139 equivalent to IRB), and informed consent was gained from all healthy volunteers and  
140 patients.

141

### 142 **Imaging**

143 Patients underwent standard of care Cardiac Magnetic Resonance (CMR) imaging and  
144 Magnetic Resonance Angiography (MRA) to image the entire thoracic aorta, including the  
145 head and neck vessels.

146 Time-resolved, velocity encoded 2D anatomic and through-plane PC-MRI (flow MRI) was  
147 performed on a plane orthogonal to the ascending aorta at the sino-tubular junction. Heart  
148 rates amongst subjects ranged between 50-95 bpm during which 30 images were  
149 reconstructed. Cine sequences were performed for assessment of valve morphology. Velocity  
150 sensitivity was set between 150 to 500 cm/s depending on the degree of AS. Average scan  
151 times were 20 minutes. Supine bilateral upper blood pressure (BP) assessment was performed  
152 using a Dinamap system (GE Healthcare, Waukesha, WI). See Appendix A for details of the  
153 MRI imaging techniques.

154

### 155 **Computational Fluid Dynamics**

156 Three-dimensional geometric models of the thoracic aorta were reconstructed from the MRA  
157 data using custom software (<http://www.crimson.software/>).<sup>21</sup> A tetrahedral mesh was created  
158 by discretising the geometric model of the aorta to produce anisotropic meshes consisting of  
159 approximately 2.5 to 5.5 million elements. Blood flow simulations were carried out using a  
160 stabilized finite element formulation to solve equations enforcing conservation of mass  
161 (continuity) and balance of linear momentum (Navier-Stokes) for the flow of an  
162 incompressible Newtonian fluid with density  $\rho = 1.06 \text{ g/cm}^3$  and dynamic viscosity  $\mu = 0.04$   
163 Poise.<sup>22</sup> The validated in-house code CRIMSON was used for this process  
164 (<http://www.crimson.software/>).<sup>21</sup>

165 The flow-MRI data was used to define the patient-specific inflow velocity profile. An in-  
166 house software written in *Matlab* (*The Mathworks Inc., Massachusetts, USA*) was used to

167 extract velocity profiles from the flow-MR images and map them to the inlet face of the  
168 aortic model.

169 The outflow boundary conditions were carried out in a patient-specific manner using blood  
170 pressure recordings and cardiac output measurements from the flow-MRI data. A coupled-  
171 multi-domain formulation was utilized whereby 3-element Windkessel models (comprising  
172 of a proximal resistance ( $R_p$ ), compliance (C), and a distal resistance ( $R_d$ )) were coupled to  
173 each outflow branch (e.g., innominate artery, left common carotid artery, left subclavian  
174 artery, and descending aorta) (Appendix B).<sup>23</sup>

175

#### 176 **Quantification of Hemodynamic Indices**

177 Velocity maps (2D) and velocity profiles (3D) were extracted from the PC-MRI data above  
178 the AV (see figure 1). Flow asymmetry ( $Flow_{asymmetry}$ ) was acquired by measuring the  
179 distance between the centroid of the top 15% of peak systolic velocities ( $V_{max}^{15\%}$ ) and the  
180 geometric centroid of the inlet plane, as a percentage of the equivalent radius of the inlet  
181 plane. A  $Flow_{asymmetry}$  of 0% means flow is central to the axis of the vessel, and a  
182  $Flow_{asymmetry}$  of 100% means flow is completely eccentric and at the periphery of the lumen  
183 (see figure 1).

184 Aortic 3D velocity streamlines were calculated from temporally resolved 3D velocity data for  
185 the entire thoracic aorta, and colour coded by blood velocity magnitude. Helicity is a metric  
186 that represents the extent to which corkscrew-like motion occurs, and is governed by velocity

187 and vorticity. Helical Flow Index (HFI) was calculated to quantitatively measure the degree  
188 of helicity according to Hardman et al.<sup>16</sup>

189 WSS and OSI were obtained for the entire thoracic aorta, with further in-depth sub-analysis  
190 in the ascending aorta. In order to look for asymmetry and differences in WSS and OSI on  
191 different sides of the aorta, the ascending aorta was divided into 8 anatomical sectors  
192 (anterior (A), right-anterior (RA), right (R), right-posterior (RP), posterior (P), left-posterior  
193 (LP), left (L), and left-anterior (LA) sectors; see figure 2).

194 The results were visualised using the open-source software ParaView (Kitware, Inc., Clifton  
195 Park, NY). Further details on how HFI, WSS and OSI were calculated are included in  
196 Appendix C.

197

## 198 **Statistical Analysis**

199 Data is presented as mean  $\pm$  standard deviation. For each group, data was tested for Gaussian  
200 distribution using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used  
201 to test for difference in results between groups. If this revealed  $p < 0.05$ , multiple  
202 comparisons were carried out between all groups using independent-sample  $t$  tests. A  $p$  value  
203  $< 0.01$  was considered significant following Bonferroni correction to adjust for multiple  
204 comparisons. All statistical analysis was carried out using SPSS (version 21, IBM).

## 205 **RESULTS**

### 206 **Patient Demographics**

207 The degree of AS or AR met the severity criteria described above in all patients except for  
208 the Volunteers group, who were chosen for their normal functioning AVs. The demographics  
209 and aortic dimensions for the 5 groups are displayed in Table 1. Both BAV groups had larger  
210 mid-ascending aortic diameters compared to Volunteers ( $p < 0.01$ ).

211

### 212 **Velocity Patterns**

213 Figure 3 depicts 2D velocity maps and 3D velocity profiles above the AV for a representative  
214 subject from each of the 5 groups. When AS is present, the 3D velocity profiles are very  
215 peaked and narrow, compared to the broader velocity profiles of Volunteers and AR-TAV.  
216 BAV patients show high velocity in the periphery of the lumen, whereas TAV patients  
217 display more central velocity jets. BAV patients had  $\text{Flow}_{\text{asymmetry}}$  almost twice the magnitude  
218 of the TAV patients, indicating blood flow was much more eccentric and asymmetrical (table  
219 1).

220

### 221 **Helicity**

222 The Volunteers group show laminar flow patterns with relatively uniform parallel 3D  
223 velocity streamlines indicating undisrupted flow (figure 4). AS-TAV and AR-TAV show a  
224 slightly higher degree of helical flow compared to the Volunteers group. BAV patients



225 display the most degree of cork-screw like helical flow and high velocity jets travelling in a  
226 spiral manner around the ascending aorta and arch. Helicity of blood flow in the ascending  
227 aorta was assessed by the Helical Flow Index (HFI), which at peak systole was significantly  
228 higher in the AS-BAV(RL) group (see table 1).

229

### 230 **Wall Shear Stress**

231 Figure 5 shows cycle-averaged, or mean WSS (MWSS) maps throughout the thoracic aorta  
232 for each of the 5 groups. The 3 groups with AS show high levels of MWSS in the ascending  
233 aorta, predominantly affecting the greater curvature. Volunteers and AR-TAV show lower  
234 levels of MWSS. Table 1 shows the values of MWSS averaged over the ascending aorta  
235 ( $MWSS^{Asc\ Aorta}$ ).  $MWSS^{Asc\ Aorta}$  was similar in Volunteers and AR-TAV. AS-BAV(RN)  
236 showed the highest  $MWSS^{Asc\ Aorta}$  at  $37.1 \pm 4.0$  dyn/cm<sup>2</sup>.

237 For each subject, the ascending aorta was divided into 8 sectors circumferentially. WSS  
238 averaged for each sector at each time point was plotted against time over the cardiac cycle  
239 (figure 6). For Volunteers and AR-TAV, WSS plots are low in magnitude and the curves  
240 remain close together throughout the cardiac cycle, indicating relatively symmetrical and  
241 uniform WSS distribution around the ascending aorta. In contrast, the 3 AS groups (AS-  
242 BAV(RL), AS-BAV(RN) and AS-TAV), show higher WSS plots in the first one-third of the  
243 cardiac cycle (corresponding to systole). The sectors displaying high WSS are the right-  
244 anterior (RA) and right (R) sectors for the BAV patients, and the anterior (A), right-anterior  
245 (RA), and right (R) sectors for the TAV aortic stenosis patients. This indicates significantly  
246 asymmetrical WSS distribution.

247 The 3-dimensional radar plots shown in figure 7 reveal an asymmetrical distribution of  
248 MWSS around the circumference of the ascending aorta in the 3 AS groups. When  
249 comparing between groups, MWSS in the anterior (A), right-anterior (RA) and right (R)  
250 sectors for AS-BAV(RN) is statistically higher when compared to Volunteers and AR-TAV  
251 ( $p < 0.01$ ). MWSS in the right-anterior (RA) sector for AS-BAV(RL) is higher when  
252 compared to Volunteers (but only achieving  $p < 0.05$ ).

253

254

### 255 **Oscillatory Shear Index**

256 Ascending aorta oscillatory shear index ( $OSI^{Asc\ Aorta}$ ) is lower in AS-BAV(RN) ( $OSI^{Asc\ Aorta} =$   
257  $0.13 \pm 0.02$ , compared to  $0.18 \pm 0.03$  for AS-BAV(RL),  $0.19 \pm 0.02$  for AS-TAV,  $0.21 \pm 0.04$   
258 for AR-TAV, and  $0.18 \pm 0.04$  for Volunteers). Only the Volunteers showed symmetrical OSI  
259 values in the ascending aorta. Both bicuspid groups showed relatively lower OSI levels in the  
260 right-anterior (RA) sectors. For AS-BAV(RN), this was statistically significant for the  
261 anterior (A), right-anterior (RA) and right (R) sectors when compared to Volunteers ( $p <$   
262  $0.01$ ). The tricuspid patients (AS-TAV and AR-TAV) have higher OSI levels on the left side  
263 of the aorta, with a significantly higher OSI in the left-anterior (LA) sector for AS-TAV when  
264 compared to AS-BAV(RN) ( $p < 0.01$ ) (see figure 7).

265

266

## 267 **DISCUSSION**

268 The results from this study show that the presence of BAV was associated with eccentric  
269 blood flow patterns and high helicity. AS, whether bicuspid or tricuspid, led to higher WSS  
270 levels in the ascending aorta, with the WSS distribution being asymmetrical and highest in  
271 AS-BAV(RN). OSI was also asymmetrically distributed, with the lowest levels found in  
272 patients with AS-BAV(RN). These findings corresponded with larger mid-ascending aorta  
273 diameters in BAV patients.

274

### 275 **Implications for Management Guidelines**

276 The results of this study question whether a patient-specific functional assessment of the  
277 thoracic aorta should be undertaken instead of size measurements alone. Guidelines of  
278 intervention on the aorta consist of maximal aortic diameter as the principal management  
279 criteria, with treatment recommended at smaller diameters in the presence of risk factors such  
280 as connective tissue disorders or family history of dissection.<sup>3</sup> These criteria have remained  
281 largely unchanged for many years. However despite these guidelines, there is still an  
282 incidence of rupture or dissection when the aorta is below these size criteria. Elefteriades et  
283 al. have shown the yearly risk of rupture, dissection or death to be 4.4%, 4.7%, 7.3% and  
284 12.1% for aortic sizes 4, 5, 6 and 7 cm respectively.<sup>24</sup> This shows that there remains a small  
285 but significant incremental risk of aortic events for those patients with aortic size below  
286 current intervention criteria.

287 These findings also provide new insights into the adequacy of traditional long-standing  
288 indices of valve assessment. Maximum aortic velocity, pressure gradients, valve area,  
289 regurgitant volumes and vena contracta are some of the established echocardiographic indices  
290 used to assess AV function.<sup>2</sup> Whilst some of these hemodynamic indices relate to symptoms  
291 and signs of aortic valve pathology, and assess its effect on the left ventricle, they do not help  
292 in the assessment of aortic valve-related aortopathy. There is as of yet no robust functional  
293 assessment of the effect of the AV on the aorta, both in terms of flow changes and  
294 mechanical stresses. Evidence shows a strong association between BAV and aneurysm of the  
295 ascending aorta, with a risk of subsequent dissection or rupture.<sup>8</sup> Yet the decision of when to  
296 intervene surgically on this group of patients can be difficult. The degree of aortic dilatation  
297 can be highly variable, and management guidelines are supported by limited evidence. It is  
298 not uncommon to be presented with a BAV patient who has an intermediate severity of valve  
299 dysfunction and a moderate degree of aortic dilatation. This patient may not fulfil current  
300 criteria for surgical intervention on the AV or the aorta, however assessment of some of the  
301 functional indices outlined in this study may help decision making.

302

### 303 **Valve Morphology & Hemodynamics**

304 Wall shear stress was higher in the presence of AS, whether BAV or TAV. MWSS was  
305 highest in the right-non fusion BAV patients. The WSS distribution was highly asymmetrical,  
306 with the right-anterior (RA) and right (R) sectors experiencing the highest levels of WSS.  
307 These sectors correlate with the convexity (greater curvature) of the ascending aorta. It was  
308 interesting to note that both BAV groups had significantly larger mid-ascending aorta

309 diameters compared to Volunteers. These trends are in keeping with earlier CFD studies,<sup>25, 26</sup>  
310 although our results are based on larger patient numbers, less hemodynamic assumptions, and  
311 more patient-specific parameters. 4D flow MRI studies by Mahadevia et al. also found WSS  
312 to be higher in sectors corresponding to the greater curvature of the ascending aorta in  
313 patients with BAV.<sup>27</sup> Meierhofer et al. also used 4D flow MRI and measured WSS to be up to  
314  $7.5 \text{ dyn/cm}^2$  ( $0.75 \text{ N/m}^2$ ) in the ascending aorta of healthy tricuspid valve patients,<sup>28</sup>  
315 corresponding to  $9.8 \pm 5.4 \text{ dyn/cm}^2$  measured in our study. WSS measurements for BAV  
316 patients in their study were higher than TAV patients, but were not as high as the levels seen  
317 in our study. This may be due to lack of aortic stenosis or insufficiency in their BAV patients.

318 Our results also correlate well with the findings of Della Corte et al. who found that medial  
319 degeneration was more severe in the greater curvature of BAV aortas.<sup>29</sup> Type I and III  
320 collagen were reduced in this area. Smooth muscle cell apoptosis was seen to be increased in  
321 the greater curvature of BAV aortas even before significant dilatation had occurred.<sup>30</sup>

322 Oscillatory shear index throughout the ascending aorta was lower in the right-non BAV  
323 group. When comparing the 8 sectors, lower OSI was seen in the A, RA and R sectors.  
324 Higher OSI has been associated with increased atherosclerotic plaque formation, and an  
325 increase in vessel wall thickness.<sup>31</sup> It may be postulated that this lower OSI seen in AS-  
326 BAV(RN) may be protective from atherosclerotic plaques, or perhaps to even cause thinning  
327 of the wall. The 3 sectors which demonstrated lower OSI were those corresponding to the  
328 greater curvature of the ascending aorta, typically the site of wall thinning.<sup>29</sup> Further work in  
329 this area may lend additional insights into the mechanisms of aortopathy.

330 As the morphology of the AV changed relative to healthy volunteers, blood flow helicity  
331 increased. There was a step-wise increase in helicity from Volunteer → TAV (AS or AR) →  
332 AS-BAV(RN) → AS-BAV(RL). This may be related to the asymmetrical flow seen in BAV  
333 patients. Helicity has been shown to play an important role in plaque deposition<sup>19</sup> and  
334 aneurysm formation.<sup>20</sup> High helicity has been linked with high WSS, in part due to the non-  
335 axial velocity component as well as its link with disrupted flow.<sup>32, 33</sup> This trend was also seen  
336 in our results.

337 This work has been focused on hemodynamic indices in the aorta and their correlation to  
338 known vasculopathies. Pressure, on the other hand, is the most important contributor to  
339 tensile stress, the key determinant in aneurysm rupture when wall stress exceeds wall  
340 strength. WSS acts in the direction of the vessel wall and is governed by velocity. It is a  
341 smaller quantity compared to tensile stress<sup>34</sup> and the tensile strength<sup>35</sup> of the aortic wall  
342 (Pascals for WSS compared to hundreds of kiloPascals for tensile stress), however interacts  
343 with the vessel wall via different mechanisms. Tensile stress could be estimated by Finite  
344 Element Modelling of the aorta using appropriate constitutive models to describe the  
345 characteristics of the wall.

346

### 347 **Future Application of CFD**

348 Current assessment of patients with aortopathy is largely limited to surveillance of aortic size  
349 by CT or MRA. There remains a lack of information regarding each patient's aortic wall  
350 biomechanics and flow patterns. Indices such as WSS and OSI have been shown to be  
351 associated with aneurysm formation/rupture<sup>15</sup> and vasculopathy.<sup>16</sup> This study found WSS to

352 be highest and OSI to be lowest in the greater curvature of the ascending aorta of bicuspid  
353 patients, the site of typical dilatation and thinning.<sup>29</sup> Further investigations should include  
354 longitudinal studies to assess the correlation between the proposed hemodynamic indices and  
355 aortopathy events, as well as the effect of these indices on proteomic changes, gene  
356 expression, and inflammatory changes in the aortic wall. Knowledge of these parameters may  
357 then help highlight those patients at higher risk of aortic complications, and help guide timing  
358 of surgical intervention.

359 4D flow MRI can also be used to assess some of these hemodynamic parameters, however  
360 due to lower spatial and temporal resolution, underestimation of WSS is a recognised  
361 problem.<sup>36</sup> Furthermore, 4D flow MRI has a longer acquisition time which may be  
362 inconvenient for the patient. The MRA and PC-MRI image acquisition required to carry out  
363 CFD is of significantly shorter duration.

364 CFD is a non-invasive approach to quantify biomechanics and hemodynamics in assessment  
365 of aortic pathology. Future development and incorporation of CFD algorithms and tools into  
366 imaging modality systems may give clinicians access to each patient's individual aortic flow  
367 dynamics and biomechanics.

368

### 369 **Limitations**

370 The results from this study have not been adjusted for patient characteristics such as age.  
371 Future studies should contain different AV morphology groups such as aortic regurgitation  
372 BAV, and even mixed AV disease groups (mixed AS and AR). Furthermore, a comparison of

373 BAV morphologies with different degrees of stenosis or regurgitation should be made to  
374 assess hemodynamic parameters in bicuspid patients with less than severe AS or AR.

375 Computations were performed under the assumption of rigid walls. Increasing compliance  
376 and elasticity causes a small reduction in WSS, so our results may have over-estimated WSS  
377 in all 5 groups. As the aorta dilates, its compliance and elasticity reduce, and it becomes  
378 stiffer and more rigid. This makes it more susceptible to higher shear stresses, and increases  
379 the risk of rupture or dissection.<sup>37</sup> The 2 bicuspid groups in this study had significantly larger  
380 aortas, and it may be suggested that the aortic wall may have been stiffer than the smaller  
381 diameter tricuspid groups. Therefore, WSS would have been proportionally more over-  
382 estimated in the TAV groups. Thus the actual differences in WSS between BAV and TAV  
383 groups could have been even higher than that seen in this study. In future studies, fluid-  
384 structure interaction analysis that takes into account the elasticity of the aortic wall will be  
385 performed.

386

387

## 388 **CONCLUSIONS**

389 The outcomes in aortic hemodynamics from this study may relate to a potential explanation  
390 for the increased incidence of aortopathy in BAV patients, and indeed to some degree of post-  
391 stenotic dilatation seen in some TAV aortic stenosis patients. Our results show that there are  
392 increased velocity jets found at the periphery of the aorta in BAV patients. Velocity  
393 streamlines show that these narrow jets impact on the greater curvature of the ascending



394 aorta, and subsequently spiral around the ascending aorta and arch. They cause increased wall  
395 shear stress and reduced oscillatory shear index at the greater curvature, corresponding to  
396 larger mid-ascending aorta diameters. These findings provide a possible mechanistic link  
397 between aortic valve morphology and aortopathy. CFD is a non-invasive functional  
398 assessment of the thoracic aorta, and may enable development of an improved personalized  
399 approach to the diagnosis and management of aortic disease beyond traditional guidelines.

400

401

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405

406

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521



## 522 **Figure Legends**

523

524 **Central Picture.** Mean wall shear stress (MWSS) map of right-non fusion BAV patient.

525

526 **Figure 1.** (a) 2D velocity map above the AV showing areas of different velocity represented  
527 by colour; (b) 3D velocity profile showing a warped geometric representation of the velocity  
528 pattern; (c) and (d) velocity map and velocity profile showing  $V_{\max}^{15\%}$  (the top 15% of  
529 velocities at peak systole) in red dots. The yellow sphere is the centroid of the whole plane,  
530 whereas the blue sphere is the centroid of  $V_{\max}^{15\%}$ .  $\text{Flow}_{\text{asymmetry}}$  is calculated by dividing  
531 distance  $x$  by distance  $y$  as a percentage.

532

533 **Figure 2.** The ascending aorta is divided into 8 anatomical segments for sub-analysis of  
534 hemodynamic parameters. A = anterior; RA = right-anterior; R = right; RP = right-posterior;  
535 P = posterior; LP = left-posterior; L = left; LA = left-anterior. RCA = right coronary artery;  
536 LCA = left coronary artery.

537

538 **Figure 3.** (a) schematic diagram of AV morphology in the 5 study groups; (b) 2D velocity  
539 maps above the AV at peak systole; (c) 3D velocity profiles above the AV at peak systole;  
540 (d) 3D schematic of the location of the top 15% of velocity at peak systole ( $V_{\max}^{15\%}$ ), as  
541 shown in red; (e) 2D map of the location of  $V_{\max}^{15\%}$  (white circle = centroid of inflow,  
542 yellow circle = centroid of  $V_{\max}^{15\%}$ ). RCA = right coronary artery, LCA = left coronary

543 artery.

544

545 **Figure 4.** 3D velocity streamlines showing trajectory of velocity during peak systole for  
546 example patients from the 5 study groups. Higher velocity jets are represented by red colour.

547

548 **Figure 5.** Mean wall shear stress (MWSS) maps for example patients from the 5 study  
549 groups. The MWSS maps look at the thoracic aorta from 2 different views. Red colour  
550 represents areas of high WSS.

551

552 **Figure 6.** Wall shear stress (WSS) plots throughout the cardiac cycle for example patients  
553 from each of the 5 groups. Each line represents one of the 8 anatomical sectors of the  
554 ascending aorta. Abbreviations as in figure 2

555

556 **Figure 7. (a)** Plots of mean wall shear stress (MWSS) for each of the 8 sectors of the  
557 ascending aorta. Error bars represent standard deviations of MWSS. **(b)** Radial graphs of  
558 oscillatory shear index (OSI) for each of the 8 sectors of the ascending aorta. \* indicates  
559 statistically significant differences for AS-BAV(RN) cohorts in comparison with AR-TAV  
560 and AR-TAV ( $p < 0.01$ ).  $\phi$  represents statistically significant differences for AS-TAV cohorts  
561 in comparison with AS-BAV(RN) ( $p < 0.01$ ).  $\psi$  represents differences for AS-BAV(RL)  
562 cohorts in comparison with AR-TAV ( $p < 0.05$ ). Abbreviations as in figure 2.

563

565 **Video Legend (online supplementary content)**

566 **Video 1.** Wall shear stress (WSS) maps throughout the cardiac cycle for example patients  
567 from the 5 study groups. The WSS maps look at the thoracic aorta from 2 different views.  
568 Red colour represents areas of high WSS. AR-TAV = aortic regurgitation tricuspid aortic  
569 valve; AS-TAV = aortic stenosis tricuspid aortic valve; AS-BAV(RL) = aortic stenosis  
570 bicuspid aortic valve with right left cusp fusion; AS-BAV(RN) = aortic stenosis bicuspid  
571 aortic valve right non cusp fusion.

572

573

574

575 **TABLE 1. Demographics, aortic dimensions and hemodynamic indices in the 5 study**  
 576 **groups**

577

	Volunteers	AR-TAV	AS-TAV	AS-BAV(RL)	AS-BAV(RN)
Demographics					
n	5	10	10	10	10
Male, n (%)	5 (100)	4 (40)	2 (20)	3 (30)	8 (80)
Age	31.3±3.1	54.0±10.8	78.0±1.4*	63.5±7.5*	64.0±8.6
Hypertension	1 (20)	3 (30)	5 (50)	4 (40)	4 (40)
B-Blockers	1 (20)	2 (20)	4 (40)	3 (30)	3 (30)
ACEi / ARBs	1 (20)	2 (20)	5 (50)	3 (30)	4 (40)
Aortic Dimensions (mm)					
SOV diameter	28.8±1.3	33.9±1.9	34.4±2.8	32.2±2.4	35.6±5.1
STJ diameter	22.8±0.9	29.7±1.6	26.3±2.2	29.9±2.7	31.8±2.0
MAA diameter	23.5±1.0	32.4±2.4	32.0±4.3	37.2±4.4*	39.9±2.4*
Hemodynamic Indices					
Flow <sup>asymmetry</sup> (%)	4.7±2.1	23.2±5.3	41.1±9.8	72.6±17.2	78.9±6.5†
HFI <sup>systole</sup>	0.24±0.02	0.28±0.06	0.26±0.04	0.39±0.04*	0.28±0.03
MWSS <sup>Asc Aorta</sup> (dyn/cm <sup>2</sup> )	9.8±5.4	17.4±8.8	35.0±20.1	27.3±10.0	37.1±4.0*
OSI <sup>Asc Aorta</sup>	0.18±0.04	0.21±0.04	0.19±0.02	0.18±0.03	0.13±0.02

578

579

580 All continuous data are given as mean ± standard deviation. AR-TAV = aortic regurgitation

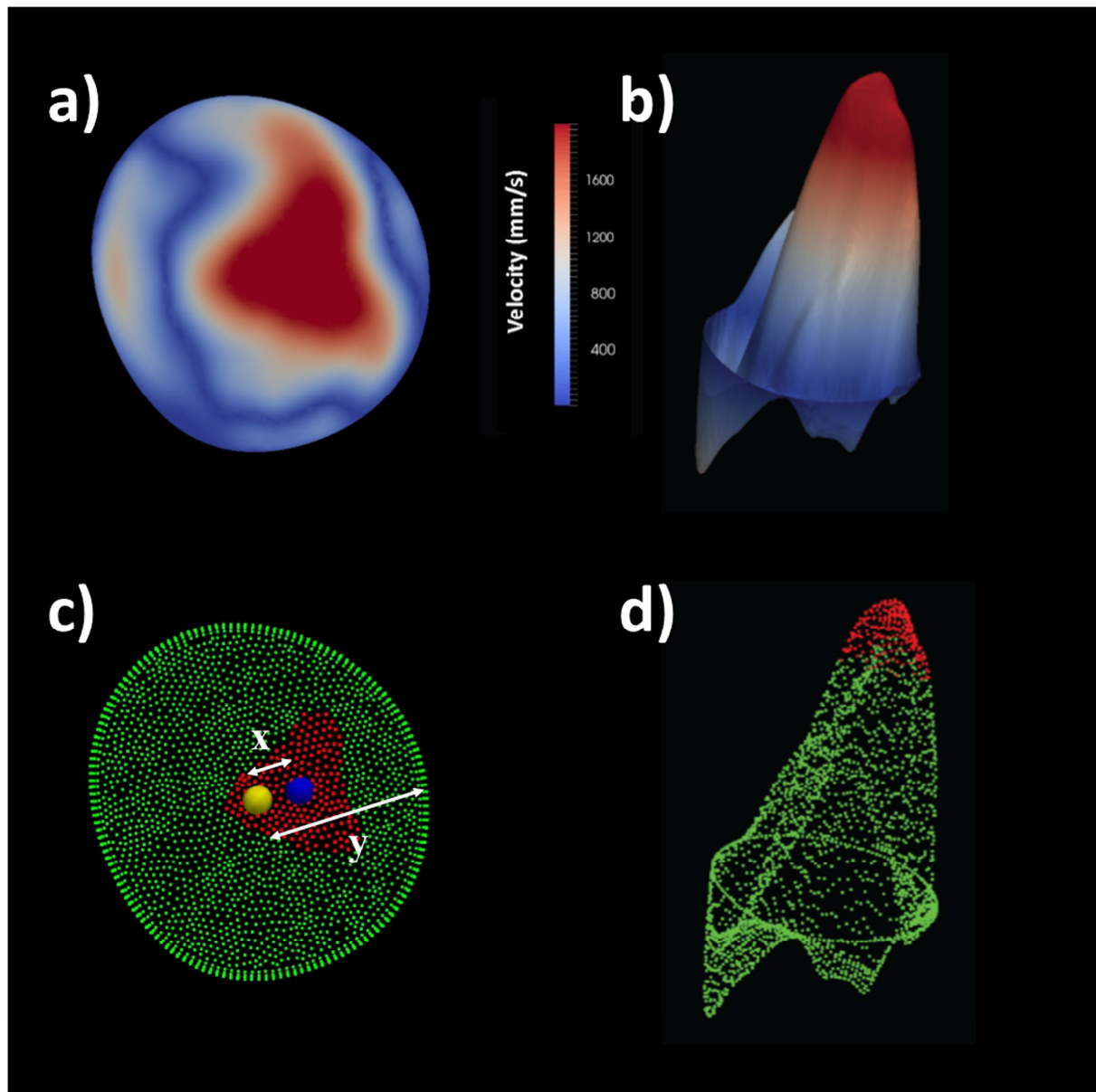
581 tricuspid aortic valve; AS-TAV = aortic stenosis tricuspid aortic valve; AS-BAV(RL) =

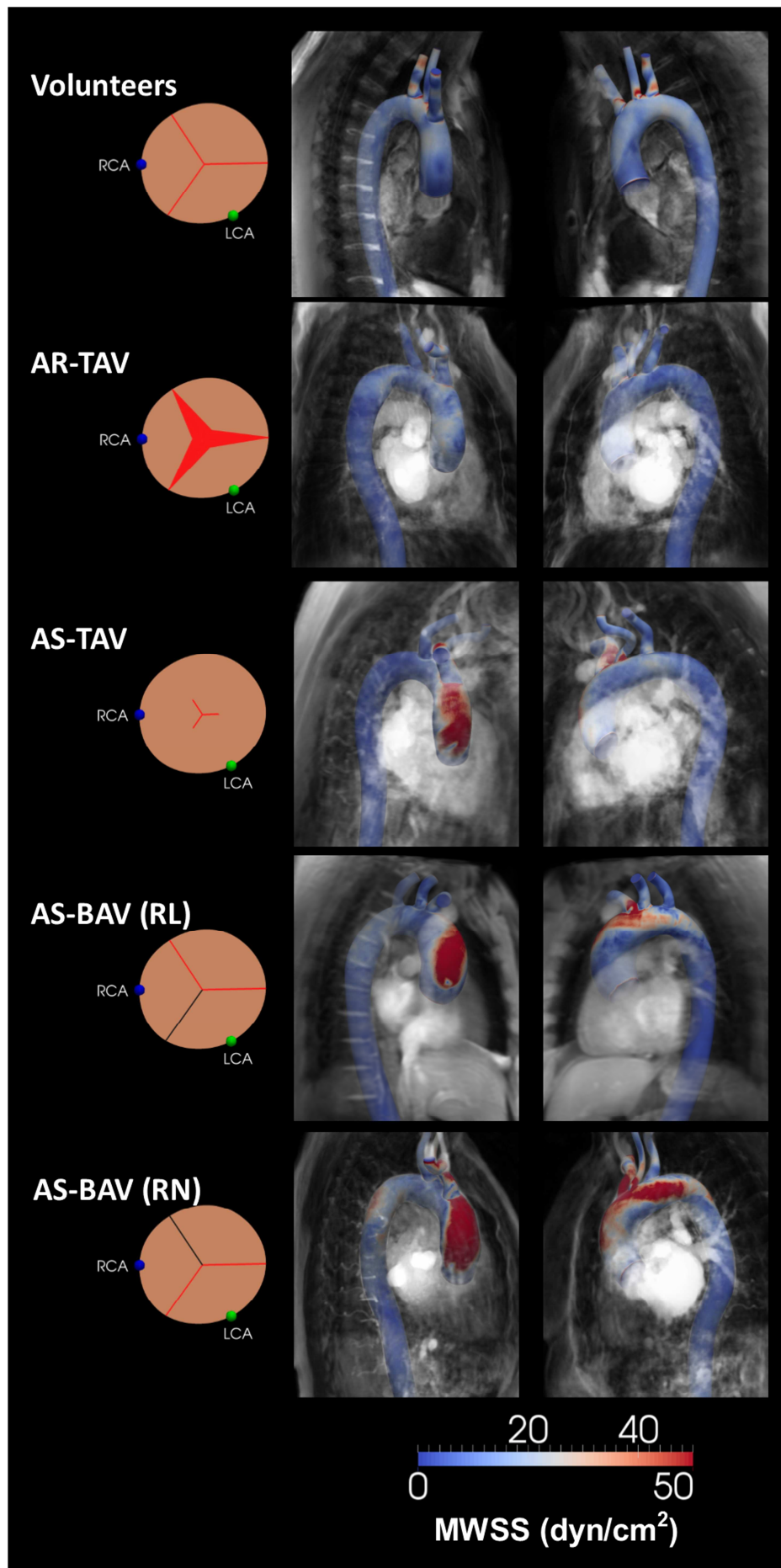
582 aortic stenosis bicuspid aortic valve with right left cusp fusion; AS-BAV(RN) = aortic

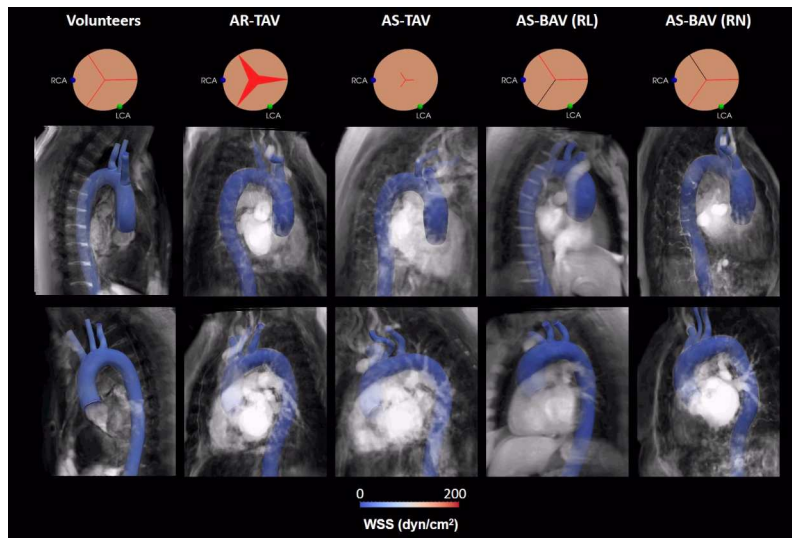
583 stenosis bicuspid aortic valve right non cusp fusion; STJ = sinotubular junction; SOV =

584 sinuses of Valsalva; MAA = mid-ascending aorta; HFI = helical flow index; MWSS = mean  
585 wall shear stress; OSI = oscillatory shear index; ACEi = angiotensin converting enzyme  
586 inhibitor; ARBs = angiotensin II receptor blockers. \* denotes significant difference after  
587 ANOVA and independent-sample t-test ( $p < 0.01$ ) between the marked group and Volunteers.  
588 † denotes significant difference between the marked group and Volunteers, AS-TAV and  
589 AR-TAV.

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## Appendix A

### MRI Imaging Parameters

Patients underwent standard of care Cardiac Magnetic Resonance (CMR) imaging and Magnetic Resonance Angiography (MRA) to image the entire thoracic aorta, including the head and neck vessels. Gadolinium (0.3 ml/kg; gadodiamide, Omniscan®, GE Healthcare, Waukesha, WI) was infused with a breath-held 3D fast gradient echo sequence using a Philips Achieva 3T scanner (Philips Medical Systems, Eindhoven, Netherlands). Acquired slice thickness was 1.0-2.0 mm, with 56–80 sagittal slices per volume. A  $344 \times 344$  acquisition matrix was used with a field of view (FoV) of  $35 \text{ cm} \times 35 \text{ cm}$  (reconstructed to slices with a spatial resolution of  $0.49 \text{ mm} \times 0.49 \text{ mm}$ , and resampled to a slice thickness of 1.00 mm). Other parameters included a repetition time (TR) of 3.9 ms, echo time (TE) of 1.4 ms, and a flip angle of  $27^\circ$ .

Time-resolved, velocity encoded 2D anatomic and through-plane PC-MRI (flow MRI) was performed on a plane orthogonal to the ascending aorta at the sino-tubular junction. Heart rates amongst subjects ranged between 50-95 bpm during which 30 images were reconstructed. Imaging parameters included TR, TE, and flip angle of 4.1-4.2 ms, 2.4-2.5 ms, and  $15^\circ$ , respectively. The FoV was  $30\text{-}35 \text{ cm} \times 30\text{-}35 \text{ cm}$  with an acquisition matrix of  $152\text{-}170 \times 120\text{-}150$ , and a slice thickness of 10 mm, resulting in a voxel size of  $2.3 \text{ mm} \times 2.4 \text{ mm} \times 10 \text{ mm}$  (resampled at  $1.37 \text{ mm} \times 1.36 \text{ mm} \times 10 \text{ mm}$ ). Data acquisition was carried out within a single breath-hold and gated to the cardiac cycle. Cine sequences were performed for assessment of valve morphology. Velocity sensitivity was set between 150 to 500 cm/s depending on the degree of AS. Average scan times were 20 minutes.

## APPENDIX B

### Outflow Boundary Conditions

Patient-specific outflow boundary conditions were prescribed at each outlet in the innominate artery, left common carotid artery, left subclavian artery and descending aorta. Upper limb blood pressure was measured after each study using an automated sphygmomanometer cuff with participants in the supine position. A 3 element Windkessel RCR model<sup>1, 2</sup> was superimposed on each outlet. The Windkessel model represents the arterial tree beyond the model outlet in an intuitive and physiological manner comprising of a proximal resistance ( $R_p$ ), compliance ( $C$ ), and a distal resistance ( $R_d$ ) for each outlet.

$R_T$  is the total resistance in the vascular system. These values were calculated in the following patient-specific manner:

$$R_{total} = \frac{P}{Q}$$

where  $P$  = patient's mean arterial pressure,  $Q$  = flow, as derived from the PC-MRI inlet velocity profile.

$$R_{total} = \left( \sum_i \frac{1}{R_i} \right)^{-1}$$

and  $R_i$  is the total resistance for each individual outlet.

$$R_i = R_p + R_d$$

for each individual outlet, where  $R_p$  is proximal resistance, and  $R_d$  is the distal resistance.  $R_i$  is calculated using the following relationship:

$$\frac{R_{total}}{R_i} = \frac{A_i}{A_T}$$

where  $A_i$  is the cross-sectional area of the individual outlet, and  $A_T$  is the total cross-sectional area of all outlets in the model. We assumed the ratio of proximal to total resistance:

$$\frac{R_p}{(R_p + R_d)} = 0.056$$

3

Similarly,  $C_T$  is the total compliance in the vascular system.

$$C_T = \sum_i C_i$$

and

$$\frac{C_i}{C_T} = \frac{A_i}{A_T}$$

Therefore the flow and compliance at each outlet is proportional to the outlet's area.

**Windkessel Parameters****Table 2.** Values of the lumped parameter Windkessel boundary conditions for an example patient from each of the 5 groups.

Group	Outlet	Windkessel Parameters		
		$R_p$	$R_d$	C
Volunteers	Brachiocephalic Artery	1.36	9.23	48.3
	Left Common Carotid Artery	2.46	15.3	29.2
	Left Subclavian Artery	1.74	11.3	39.3
	Descending Aorta	0.25	2.14	208
AR-TAV	Brachiocephalic Artery	0.41	9.79	22.68
	Left Common Carotid Artery	2.08	39.57	5.61
	Left Subclavian Artery	1.18	24.31	9.13
	Descending Aorta	0.10	2.79	79.58
AS-TAV	Brachiocephalic Artery	0.48	4.91	36.22
	Left Common Carotid Artery	1.73	14.81	12.00
	Left Subclavian Artery	1.65	14.19	12.52
	Descending Aorta	0.19	2.23	79.85
AS-BAV(RL)	Brachiocephalic Artery	0.79	18.2	28.2
	Left Common Carotid Artery	1.15	24.9	20.5
	Left Subclavian Artery	1.29	27.6	18.6
	Descending Aorta	0.17	4.69	109
AS-BAV(RN)	Brachiocephalic Artery	0.67	5.61	49.28
	Left Common Carotid Artery	2.38	16.49	16.77
	Left Subclavian Artery	2.00	14.22	19.45
	Descending Aorta	0.20	2.01	137.90

$R_p$  = proximal resistance;  $R_d$  = distal resistance; C = capacitance. The units of resistance are  $10^3$  dynes s /  $cm^5$ . The units of capacitance are  $10^{-6}$   $cm^5$  / dynes.

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## APPENDIX C

### Haemodynamic Indices

#### Helical Flow Index

Aortic 3D velocity streamlines were calculated from temporally resolved velocity data for the entire thoracic aorta, and colour coded to represent blood velocity. Helicity is a metric that represents the extent to which corkscrew-like motion occurs, and is governed by velocity and vorticity.<sup>1</sup> Helical Flow Index (HFI) was calculated to quantitatively measure the degree of helicity.  $HFI_p$  is the helical flow index for each pathline (velocity streamline), calculated over the particle trajectory:

$$HFI_p = \frac{1}{N_j} \sum_i^{N_j} \psi_i$$

Here,  $\psi_i$  is the dimensionless normalised helicity, calculated as the cosine of the angle between velocity and vorticity vectors at each point of the pathline.  $N_j$  is the number of 0.5mm steps,  $i = 1, \dots, N_j$ , along the fluid particle pathline  $j$ . Steady Poiseuille flow gives a value of  $\psi_i = 0$ , whereas values of  $|\psi| = 1$  occur when flow is purely helical.<sup>1,2</sup>  $HFI_{systole}$  is the average  $HFI_p$  over all pathlines during peak systole.

#### Wall Shear Stress

WSS expresses the force per unit area exerted by a flowing fluid on a surface of the lumen in the direction of the local tangent. In a complex 3D geometry such as the aorta, wall shear stress  $\overline{WSS}$  can be obtained as follows:

$$\overline{WSS} = \mu(\nabla\vec{u} + \nabla\vec{u}^T)\vec{n}$$

where  $\mu$  is the blood viscosity,  $\nabla\vec{u}$  is the gradient of the velocity field,  $\nabla\vec{u}^T$  is the transpose of the gradient of the velocity field, and  $\vec{n}$  is the unit normal vector to the vessel wall.

### Oscillatory Shear Index

In pulsatile flow, the temporal variation in WSS direction can be expressed in terms of the OSI:

$$OSI = \frac{1}{2} \left( 1 - \frac{|\int_0^T WSS_z dt|}{\int_0^T |WSS_z| dt} \right)$$

1

where an OSI value of zero indicates unidirectional flow throughout the pulsatile cycle, and a value of 0.5 indicates that flow oscillates forward and backward for the same period of time during the cycle (i.e. disturbed flow). OSI essentially measures the degree of disturbed flow at the vessel wall,<sup>1</sup> and has been shown to be associated with vasculopathy.<sup>1</sup>

### References

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