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Hemodynamics alteration in patient-specific dilated ascending thoracic aortas with tricuspid and bicuspid aortic valves

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Abstract

In this paper, we evaluate computationally the influence of blood flow eccentricity and valve phenotype (bicuspid (BAV) and tricuspid (TAV) aortic valve) on hemodynamics in ascending thoracic aortic aneurysm (ATAA) patients. 5 TAV ATAA, 5 BAV ATAA (ascending aorta diameter > 35 mm) and 2 healthy subjects underwent 4D flow MRI. The 3D velocity profiles obtained from 4D flow MRI were given as input boundary conditions to a computational fluid dynamics analysis (CFD) model. After performing the CFD analyses, we verified that the obtained time-averaged velocity profiles and flow eccentricity were in good agreement with 4D flow MRI. Then we used the CFD analyses to evaluate the time-averaged wall shear stress (TAWSS) and the local normalized helicity (LNH). We found that the flow eccentricities at the aortic root were not significantly different ($p > 0.05$) between TAV and BAV phenotypes. TAWSS ($R^2 = 0.697$, $p = 0.025$) and absolute LNH ($R^2 = 0.964$, $p < 0.001$) are in good correlation with flow eccentricity. We conclude that eccentricity at the aortic root is a major determinant of hemodynamics patterns in ATAA patients regardless of the aortic valve phenotype.

Key words: Aneurysm, 4D flow MRI, Computational Fluid Dynamics, Biomechanics, Tricuspid and Bicuspid aortic Valve

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1 Introduction

2 Ascending thoracic aortic aneurysms (ATAAs) are life-threatening pathologies characterized by pro-
3 gressive vessel dilation. It is associated with smooth muscle cell dysfunction, occasional localized
4 inflammatory infiltrates, and severe maladaptive extracellular matrix remodeling together predisposes
5 the arterial wall to dissection and rupture leading to premature death (Lavall et al., 2012; Azadani
6 et al., 2013; Real et al., 2014; Lasheras, 2007; Pasta et al., 2012). Among the etiology of ATAAs, in-
7 dividuals with a BAV are more vulnerable to ATAA than normal TAV. Recent studies have shown that
8 deficient TAVs also contribute to ATAA progression (Muraru et al., 2016). ATAAs progression is the
9 result of multifactorial effects including genetics or epigenetics expressions, biomechanical (Farzaneh
10 et al., 2018) and altered hemodynamics patterns (Girdauskas et al., 2011).

11 4D PCMRI (phase-contrast magnetic resonance imaging) also called 4D flow MRI has been com-
12 monly used to understand aortic hemodynamics (Simao et al., 2017; Bakhshinejad et al., 2017;
13 Biglino et al., 2015). Retrograde flows and recirculations were frequently found in BAV subjects
14 using 4D flow MRI and it was shown that they occur at earlier age compared to TAVs (Barker et al.,
15 2010, 2012). Moreover, hemodynamics alterations in BAV usually differ with valve fusion alterations
16 (Bissell et al., 2013). Among hemodynamics alterations, the impact on the wall shear stress (WSS)
17 distribution in the ascending aorta (AA) of BAV patients without concomitant valve or vessel dis-
18 ease is significant compared with TAV subjects (Meierhofer et al., 2012). WSS responsive pathways
19 are known to regulate endothelial function and vessel integrity (Baeyens et al., 2016). In coronary
20 or carotid arteries, the endothelial cells exposed to high, unidirectional wall shear stress maintain a
21 quiescent phenotype, while those exposed to low and/or directional varying WSS are activated, dis-

22 playing a pro-inflammatory phenotype (Kwak et al., 2014). Although studies related to ATAAs are
23 scarcer, there is enough evidence to highlight essential roles of WSS in ATAA progression (Liu et al.,
24 2014; Condemi et al., 2019; Guzzardi et al., 2015). Helicity of the flow also contributes to aneurysm
25 progression (Youssefi et al., 2018; Pirola et al., 2018). Blood flow in the aorta possesses a significant
26 helical component due to the complex aortic morphology (Morbiducci et al., 2013) and the helic-
27 ity of the flow patterns can be altered in BAV patients (Garcia et al., 2017) and in ATAA patients
28 (Frydrychowicz et al., 2012).

29 CFD is an appropriate computational method to simulate blood flows in the aorta (Yu et al., 2016;
30 Chen et al., 2017; Bakhshinejad et al., 2017). Most of the simulation studies that have been published
31 in the literature on this topic used idealized inlet boundary conditions rather than patient specific ve-
32 locity maps (Pasta et al., 2013; Stevens et al., 2017). Hence there is a need to explore more accurately
33 hemodynamics alterations related to TAVs and BAVs using CFD. The combination of 4D flow MRI
34 and CFD presents a promising method to address this need (Callaghan et al., 2015; Romarowski et al.,
35 2018).

36 Therefore, the main goal of this study is to characterize the effect of valve phenotype on the hemo-
37 dynamics descriptors, namely time-averaged WSS and helicity, in the dilated ascending aortic region
38 using CFD with inflow boundary conditions derived from 4D flow MRI. As hemodynamics calcula-
39 tions need to be accurate, a secondary goal was to verify the accuracy of the calculations by assessing
40 the agreement between the CFD simulations and the 4D flow MRI measurements.

41 **2 Methods**

42 *2.1 Data acquisition*

43 4D flow MRI data-sets obtained from 3T MR scanner (Magnetom Prisma, Siemens, Erlangen) were
44 used to assess blood flows in the ascending thoracic aorta (ATA) from 12 subjects (Tab. 1). The
45 protocol was approved by the Institutional Review Board of the University Hospital Center of Saint-
46 Etienne and an informed consent was obtained from the participants. The axial cross sectional images
47 at predefined anatomic levels were used for measuring the ATA maximum diameter. We measured
48 outer to outer diameter knowing that there is no convention about measuring the luminal or outer to
49 outer diameter of the aorta (Boehm et al., 2015). The discussion regarding the patient characteristics
50 are given in Section B in the supplementary materials.

51 All the patients were assessed for the presence of functional valvular defects by standard transthoracic
52 echocardiography. The echocardiographic exam relies on three parameters, namely the peak velocity,
53 the mean pressure gradient and the aortic valve area. The first two parameters are directly calculated
54 from Doppler, whereas the aortic valve area is derived from measurement of the left ventricular out-
55 flow tract (LVOT) diameter, LVOT time-velocity integral (TVI) and aortic TVI using the continuity
56 equation.

57 *2.2 Numerical simulation*

58 The reconstructed patient-specific geometry from 4D flow MRI data, including the ATA starting from
59 sinotubular junction (STJ), aortic arch with branches (brachiocephalic artery (BCA), left common

60 carotid artery (LCC) & left subclavian artery (LSUB)) and the descending aorta, was imported in An-
 61 sys Fluent (ANSYS, Academic research, Release 17.2) and meshed with tetrahedral cells for further
 62 analysis. Details regarding the methodology are given in Section A in the supplementary materials.

63 2.3 Estimation of flow parameters

The flow eccentricity was calculated as follows (Condemi et al., 2019),

$$Flow_{eccentricity} = \frac{\sqrt{\sum_j (C_j - C_j^{vel})^2}}{D} \quad j = x, y, z; \quad (1)$$

64 Where C_j , C_j^{vel} and D are the coordinates of the lumen center (Fig. S1 in the supplementary materi-
 65 als), center of velocity and diameter, respectively.

The center of velocity C_j^{vel} was calculated as the average position of lumen pixels (r_i), weighted by
 the velocity information (v_i) as given in Eq. 2 (Sigovan et al., 2011)

$$C_j^{vel} = \frac{\sum_i r_{i,j} |v_i|}{\sum_i |v_i|} \quad i = \text{lumen pixels } (x, y, z), \quad j = x, y, z; \quad (2)$$

66 Flow eccentricity equal to 0 indicates that the flow is centrally distributed along the length of the
 67 vessel and 1 indicates that the flow is fully eccentric.

The local normalized helicity (LNH) corresponds to the local value of the cosine of the angle between
 the velocity V and vorticity ω (Garcia et al., 2017)

$$LNH = \frac{V \cdot \omega}{|V| |\omega|} \quad (3)$$

68 LNH varies between -1 (left-handed rotation) and 1 (right-handed rotation) with 0 indicating a sym-
69 metrical flow (Manuel et al., 2009; Condemi et al., 2017). [An optimal LNH threshold detecting dif-](#)
70 [ferences between patients and the healthy group is set as 0.6 based on the study conducted by Garcia](#)
71 [et al. \(2017\)](#). At each threshold the percentage of the total volume occupied by the isosurface volume
72 was assessed.. For example, the % volume of absolute $LNH \geq 0.6$ was calculated from the iso-surface
73 volume ($\% \text{ volume of absolute } LNH \geq 0.6 = \text{volume of absolute } LNH \geq 0.6 / \text{Total volume} \times 100$).

The TAWSS value was calculated such as (Condemi et al., 2019),

$$TAWSS = \frac{1}{T} \int_0^T WSS \, dt \quad (4)$$

74 where T is the period of the cardiac cycle and WSS is the instantaneous wall shear stress. The %
75 surface area with $TAWSS \leq 1 \text{ Pa}$ was derived, being defined as the surface area with $TAWSS \leq 1 \text{ Pa}$
76 /Total surface area $\times 100$.

77 2.4 Statistical analyses

78 The statistical analysis was performed with SPSS 17 (IBM SPSS software, Chicago). A Bland Altman
79 analysis was performed to evaluate the agreement between the CFD simulation and the 4D flow
80 MRI measured flow eccentricity. A 2-tailed independent samples t-test was conducted to evaluate
81 the significant differences between TAV and BAV ATAAs. The deduced parameters namely flow
82 eccentricity, TAWSS and absolute LNH in the ATA between TAV and BAV were compared using an
83 independent-sample t-test. A pre-determined level of significance equal to 95% and p-values < 0.05
84 were considered as significant.

85 **3 Results**

86 *3.1 Comparison between CFD-calculated vs. 4D flow MRI- measured velocities and flows*

87 In order to ensure that the velocity profiles obtained from 4D flow MRI at different time frames
88 throughout the cardiac cycle are correctly estimated by CFD, we have compared the time-averaged
89 velocity profiles from CFD simulations with the 4D flow MRI. Agreement between the 4D flow MRI
90 and CFD profiles should be satisfied as the former was used to assign boundary conditions of the
91 latter. However, interpolation was required to assign the boundary conditions at the correct times as
92 time steps of the CFD analysis did not coincide with the times at which the MRI data were acquired.
93 The time-averaged velocity profiles obtained from 4D flow MRI and CFD are shown in Fig. 1.

94 Flow eccentricity calculated near the dilated region (section 2-2' i.e largest diameter in the dilated
95 region shown in Fig. S2) from 4D flow MRI during the systolic phase was compared with the CFD
96 simulations using Bland-Altman plot. The estimated bias was -0.01085, standard deviation of bias
97 was 0.0353, the 95% limits of agreement varied from -0.080 (blue dotted line) to 0.058 (red dashed
98 line) and the continuous brown line represents the mean (Fig. 2). All data points remained in the
99 95% limit band (average difference ± 1.96 standard deviation of the difference), indicating the good
100 agreement between the 4D flow MRI measurements and the CFD simulation quantitatively.

101 *3.2 Streamlines*

102 The streamlines obtained from the simulations at peak systole for different cases are shown in Fig 3.
103 The streamline contours for both BAV and TAV ATAA patients showed that the flow starts detaching

104 from the aortic wall and a vortex is formed near the dilated ATA region. In healthy subjects the flow is
105 found to be laminar and evenly distributed through the cross-section of the aorta near the ATA region.

106 3.3 TAWSS

107 TAWSS was obtained for TAV ATAA, BAV ATAA and healthy subjects (Figs. 4, 5, & 6). Both TAV
108 ATAA and BAV ATAA patients exhibited low TAWSS (i.e ≤ 1 Pa) in the ATA region. The surface
109 area of the ATA with TAWSS ≥ 3 Pa and ≤ 1 Pa were evaluated (Tab. 2). Irrespectively of the valve
110 phenotype, all patients, except patient 4, have large surface area (i.e varying between 70% and 99%)
111 with low TAWSS (i.e ≤ 1 Pa). High TAWSS (i.e ≥ 3 Pa) were found only in small regions ($\leq 1\%$
112 surface area) of the ATA in 8 out of 10 patients, whereas patient 6 and 8 have 8% and 7% of the
113 surface area with TAWSS ≥ 3 Pa. Healthy subjects have surface area $\geq 25\%$ with high TAWSS (≥ 3
114 Pa) and $\approx 20\%$ surface area with low TAWSS ($\leq 1\%$).

115 3.4 Helicity

116 The LNH magnitude was extracted for all patients and healthy subjects (Figs. 4, 5, & 6). It was ob-
117 served that large absolute LNH values were more prominent in ATAA patients than healthy subjects.
118 In ATAA patients the % volume with absolute LNH ≥ 0.6 is > 2 and absolute LNH ≤ 0.4 varies
119 between 80 and 95. In healthy subjects, more than 98% volume has an absolute LNH below 0.4 and
120 less than 1% volume has absolute LNH ≥ 0.6 (Tab. 2).

121 3.5 Correlation between flow eccentricity and hemodynamics descriptors

122 A significant correlation is obtained between flow eccentricity at section 2-2' = ascending aortic
123 region with maximum diameter and flow eccentricity at section 1-1' = sinotubular junction - also
124 referred as aortic inlet in this paper. Hence, we also studied correlation between flow eccentricity at
125 section 2-2' and WSS, TAWSS and LNH biomarkers. Figure 7 summarizes the independent associa-
126 tions between parameters such as flow eccentricity at section 1-1', % surface area with TAWSS ≤ 1
127 Pa, % volume with absolute LNH ≥ 0.6 , maximal ATAA diameter and inlet angle with flow eccen-
128 tricity at section 2-2'. Strong and significant correlations exist between flow eccentricity at section
129 1-1' ($R^2 = 0.655$, $p = 0.040$), % surface area with TAWSS ≤ 1 Pa ($R^2 = 0.697$, $p = 0.025$), % volume
130 with absolute LNH ≥ 0.6 ($R^2 = 0.964$, $P < 0.001$), maximal ATAA diameter ($R^2 = 0.664$, $p = 0.036$)
131 with flow eccentricity at section 2-2'. But there is no significant relationship between the inlet angle
132 ($R^2 = 0.261$, $p = 0.467$) and the flow eccentricity at section 2-2'.

133 3.6 Correlation between maximum ATAA diameter and hemodynamics descriptors

134 A significant correlation was found between the diameter and hemodynamics descriptors namely
135 TAWSS and helicity (Fig. 8). For instance, regarding the % of surface area with TAWSS ≤ 1 Pa
136 significance is valued at $R^2 = 0.688$, $p = 0.028$ and for the % of volume with absolute LNH ≥ 0.6
137 significance is valued at $R^2 = 0.650$, $p = 0.045$. The increase in maximal ATAA diameter affects the
138 hemodynamics descriptors for both TAV ATAA and BAV ATAA patients.

139 3.7 Significance of differences in hemodynamics descriptors between TAV and BAV ATAA patients

140 Hemodynamics descriptors, namely flow eccentricity, TAWSS and helicity in TAV and BAV groups
141 were compared using 2-tailed independent samples t-test . Results are reported in Tab. 1. The data
142 are presented as mean \pm standard deviation (max,min). The parameters such as flow eccentricity at
143 section 1-1' (p = 0.268), flow eccentricity at section 2-2' (p = 0.575), % surface area with TAWSS
144 ≥ 3 Pa (p = 0.282), % surface area with TAWSS ≤ 1 Pa (p = 0.483), % volume with absolute LNH
145 ≥ 0.6 (p = 0.367) and % volume with absolute LNH ≤ 0.4 (p = 0.235) have a p-value > 0.05 . The
146 significance > 0.05 shows that the hemodynamics descriptors obtained from TAV and BAV patient
147 were not significantly different.

148 4 Discussion

149 This study showed that flow eccentricity at the aortic root is a major determinant of hemodynamics
150 alterations in ATAAs, such as low TAWSS and elevated absolute LNH values are independent of the
151 aortic valve phenotype. The flow eccentricity at the aortic root indicates a dysfunction of the aortic
152 valve and is frequent with BAV phenotype. But the relation between eccentricity downstream and
153 WSS, TAWSS & LNH biomarkers remains to be elucidated, especially how the enlargement of aortic
154 diameter in aneurysms participates to increase the flow disturbance caused by eccentricity at the aortic
155 root.

156 Our CFD simulations are time resolved and provide estimations of the velocity maps at different
157 timeframes. Only after running the simulations, at the post-processing stage, we eventually compute

158 time averaged metrics to compare the groups of subjects. The time-averaged velocities obtained from
159 CFD analyses were validated against MRI data justifying the significance of time-averaged metrics
160 derived from CFD analyses.

161 Among studies related to BAV and TAV patients, Hope et al. (2011) and Pasta et al. (2013) compared
162 the blood flow patterns between TAV and BAV in patients harbouring ATAA. One of the two was
163 based on 4D flow MRI to measure *in vivo* 3D blood flow velocities in the aorta, finding abnormal
164 eccentric flow and asymmetric WSS for both BAV and TAV patients (Hope et al., 2011). The other
165 study was based on CFD simulations, showing a slight difference in the helical flow patterns between
166 TAV and BAV ATAA patients (Pasta et al., 2013) but they did not consider patient specific velocity
167 patterns. Our study proposed a framework combining 4D flow MRI and CFD to compute ATAA
168 hemodynamics.

169 We found that blood flow disturbance near the dilated region generates vortices in TAV and BAV
170 ATAAs and not in the healthy subjects (Weigang et al., 2008; Sigovan et al., 2011; Pasta et al., 2013;
171 Numata et al., 2016). The flow disturbance refers here to the existence of retrograde flows and recir-
172 culation areas (Chiu and Chien, 2011). The vortices manifest with flow eccentricity and non-uniform
173 distribution of WSS, potentially causing accumulation of atherogenic particles at the endothelial sur-
174 face (Deng et al., 2008; Ethier, 2002; Tarbell, 2003; Chiu and Chien, 2011).

175 As we assumed rigid and impermeable walls (Torii et al., 2009; Steinman, 2012), we focused our
176 analysis on TAWSS values only, not on temporal variations of WSS. TAWSS contours of both TAV
177 and BAV ATAAs show large areas with TAWSS lower than 1 Pa. In healthy subjects the area fraction
178 occupied by $TAWSS \leq 1$ Pa and ≥ 3 Pa was significantly lower. The increase in flow eccentricity

179 near the dilated region induces a decrease of the TAWSS magnitude. More surface is occupied by
180 low TAWSS in TAV and BAV ATAAs. Commonly TAWSS in healthy arteries is between 1 and 7
181 Pa (Nordgaard et al., 2010). Low TAWSS (i.e. ≤ 1 Pa) in a large area fraction of the aortic vessel
182 indicates possible endothelial dysfunction and progress in vascular disease (Nordgaard et al., 2010;
183 Papadopoulos et al., 2016; Numata et al., 2016). If the TAWSS is larger than 7 Pa, endothelial damage
184 can also be induced but the mechanisms of this damage have not yet been fully elucidated (Fukumoto
185 et al., 2008). TAWSS also shows good correlation with maximal ATAA diameter. With increased
186 ATAA diameter, the percentage of area with low TAWSS increases.

187 LNH contours show that both TAV ATAA and BAV ATAA have large volumes with elevated absolute
188 LNH (i.e. ≥ 0.6) compared to healthy subjects. These results are in agreement with previous studies
189 where elevated helicity was found in ATAA patients (Lorenz et al., 2014; Garcia et al., 2017). It was
190 observed that the % volume of absolute LNH ≥ 0.6 had a significant correlation with flow eccentricity
191 and maximal ATAA diameter. Eventhough there are many studies indicating the role of helicity in the
192 development of cardiovascular diseases (Kilner et al., 1993; Caro et al., 1996; Stonebridge et al., 1996;
193 Morbiducci et al., 2007; Liu et al., 2009, 2014), it is yet unclear how these hemodynamics alterations
194 affect wall remodeling in ATAAs (Gataulin et al., 2015; Ha et al., 2016).

195 The correlation analysis between the aortic valve phenotype and the hemodynamics descriptors shows
196 that TAV and BAV ATAA patients have no significant difference in terms of blood flow patterns and
197 hemodynamics descriptors (refer Tab. 1). Patients with both aortic valve phenotypes have shown more
198 region with low TAWSS, elevated absolute LNH and pronounced flow eccentricity near the dilated
199 ATA region. Irrespective of the aortic valve phenotype the alteration in hemodynamics parameters
200 was due to flow eccentricity patterns.

201 Basically the aortic valve condition should be classified based on:

202 1) the morphological condition (phenotype) which relates to the natural feature of the valve (BAV or
203 TAV)

204 2) the functional condition which relates to the behaviour of the valve during the cardiac cycle. It can
205 be quantified in terms of hemodynamics descriptor, namely the flow eccentricity

206 In the present work we have shown that both BAV and TAV can have similar functional conditions.
207 This may explain why it is very difficult to establish correlations between the valve phenotype and
208 the aneurysm rupture risk (Agnese et al., 2019; Forsell et al., 2014; Kjellqvist et al., 2013; Ikonomidis
209 et al., 2007; Corte et al., 2008).

210 In our 5 BAV patients, only two of them presented a mild degree of AR, the rest had BAV phenotypes
211 without any gradient or AR degree. Accordingly, the functional status of the aortic valve seems to in-
212 fluence the ATA flow patterns. This was also previously demonstrated for AS, with good correlations
213 between the AS degree and ATAA flow patterns (Farag et al., 2018). Moreover, almost 50% of BAV
214 patients never develop ATAA and keep normal functions during the entire lifetime without treatment
215 (Pedersen et al., 2019). Reciprocally, diseased tri-leaflet aortic valves can acquire abnormal opening
216 just like bi-leaflet valves inducing eccentric flows at the aortic root. Therefore, the aortic valve func-
217 tional condition (characterized by flow eccentricity at the aortic root) rather than the phenotype is a
218 major factor in determining hemodynamics alterations in the ATA (Fig. 3).

219 There are some limitations in this study. The sample size was limited to 10 patients and 2 healthy
220 subjects. [Ooij et al. \(2017\)](#) found significant differences in peak systolic WSS between a large group
221 of BAV (n = 136) and TAV (n = 213) with no AS. In the present study we could not find any differences

222 between TAWSS in BAV and TAV. It may be due to the small sample size and/or the fact that averaging
223 out WSS patterns over time is not accurate enough to detect differences.

224 CFD simulations were based on the assumption of rigid and impermeable walls. The comparison
225 between the CFD and 4D flow MRI time-averaged velocity maps shows some differences in some pa-
226 tients. This may be induced by the interpolation effects, but also due to outlet boundary conditions and
227 the rigid wall assumption. These assumptions are usually reasonable for flow and WSS predictions
228 in finite segments of large arteries (Steinman, 2012) although they may induce errors in evaluating
229 temporal variations of WSS. The velocity distribution obtained from 4D flow MRI was used as inlet
230 boundary condition for the simulation. As 4D flow MRI datasets are noisy, this can be transmitted
231 to the computational predictions. However these datasets permit to assign patient-specific boundary
232 conditions to the model, which is essential for modelling hemodynamics computationally.

233 5 Conclusions

234 This study demonstrated that the flow eccentricity at the aortic root influences the blood flow patterns
235 in ATAA patients independently of the aortic valve phenotype. Flow eccentricity values across the
236 dilated region have significant correlation with TAWSS, absolute LNH and maximal ATAA diameter,
237 however they have no correlation with the inlet angle. Knowing the critical role of flow eccentricity in
238 hemodynamics alterations, it will be important to determine how it interacts with other critical factors
239 of ATAA such as aortic wall remodeling and smooth muscle cell differentiation.

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244 **6 Conflict of interest**

245 There is no conflict of interest.

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FIGURE CAPTIONS

- 441
- 442 Fig.1 Time-averaged velocity profiles obtained from 4D flow MRI and CFD at the inlet. The dorsal
443 (D), ventral (V), anterior (A) and posterior (P) regions are defined according to Fig. S1 in the
444 supplementary materials.
- 445 Fig.2 Bland-Altman plot showing 4D flow MRI vs CFD $Flow_{eccentricity}$ obtained from time-averaged
446 velocity profiles near the ATA region.
- 447 Fig.3 Streamlines of blood velocity at peak systole for TAV ATAA, BAV ATAA and healthy subjects.
- 448 Fig.4 TAWSS and LNH distribution in the ATA region for TAV ATAA patients.
- 449 Fig.5 TAWSS and LNH distribution in the ATA region for BAV ATAA patients.
- 450 Fig.6 TAWSS and LNH distribution in the ATA region for healthy subjects.
- 451 Fig.7 Correlation between the flow eccentricity near the dilated region and other significant parameters
452 (hemodynamics and morphology).
- 453 Fig.8 Correlation between the maximum ATAA diameter and hemodynamics parameters.

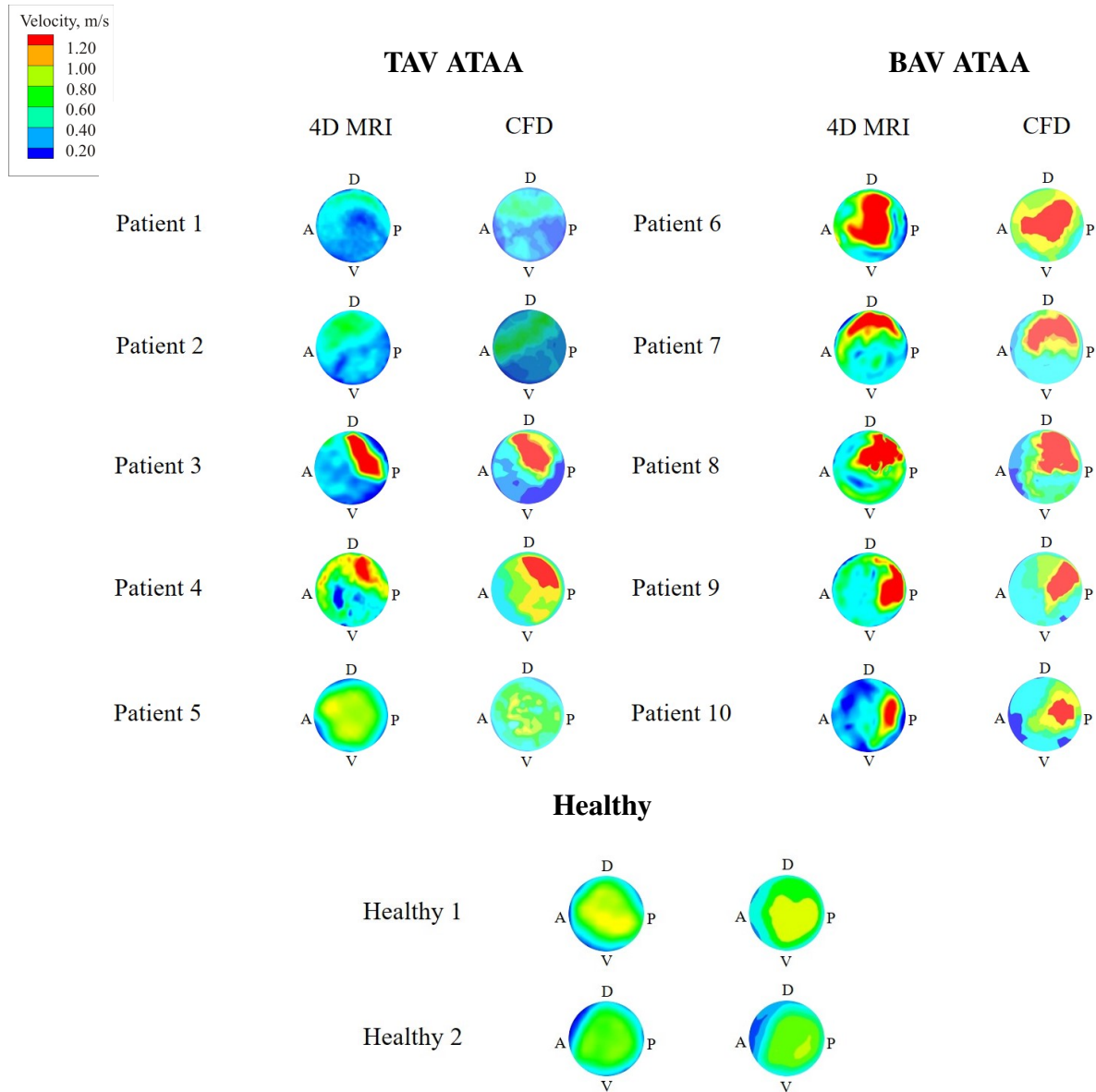


Fig. 1. Time-averaged velocity profiles obtained from 4D flow MRI and CFD at the inlet. The dorsal (D), ventral (V), anterior (A) and posterior (P) regions are defined according to Fig. S1 in the supplementary materials

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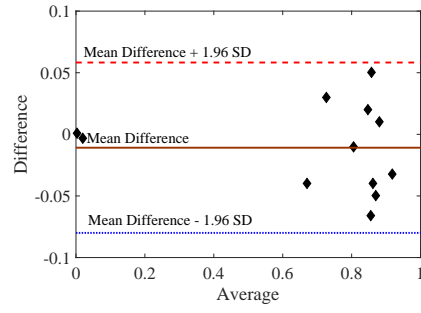


Fig. 2. Bland-Altman plot showing 4D flow MRI vs CFD $Flow_{eccentricity}$ obtained from time-averaged velocity profiles near the ATA region.

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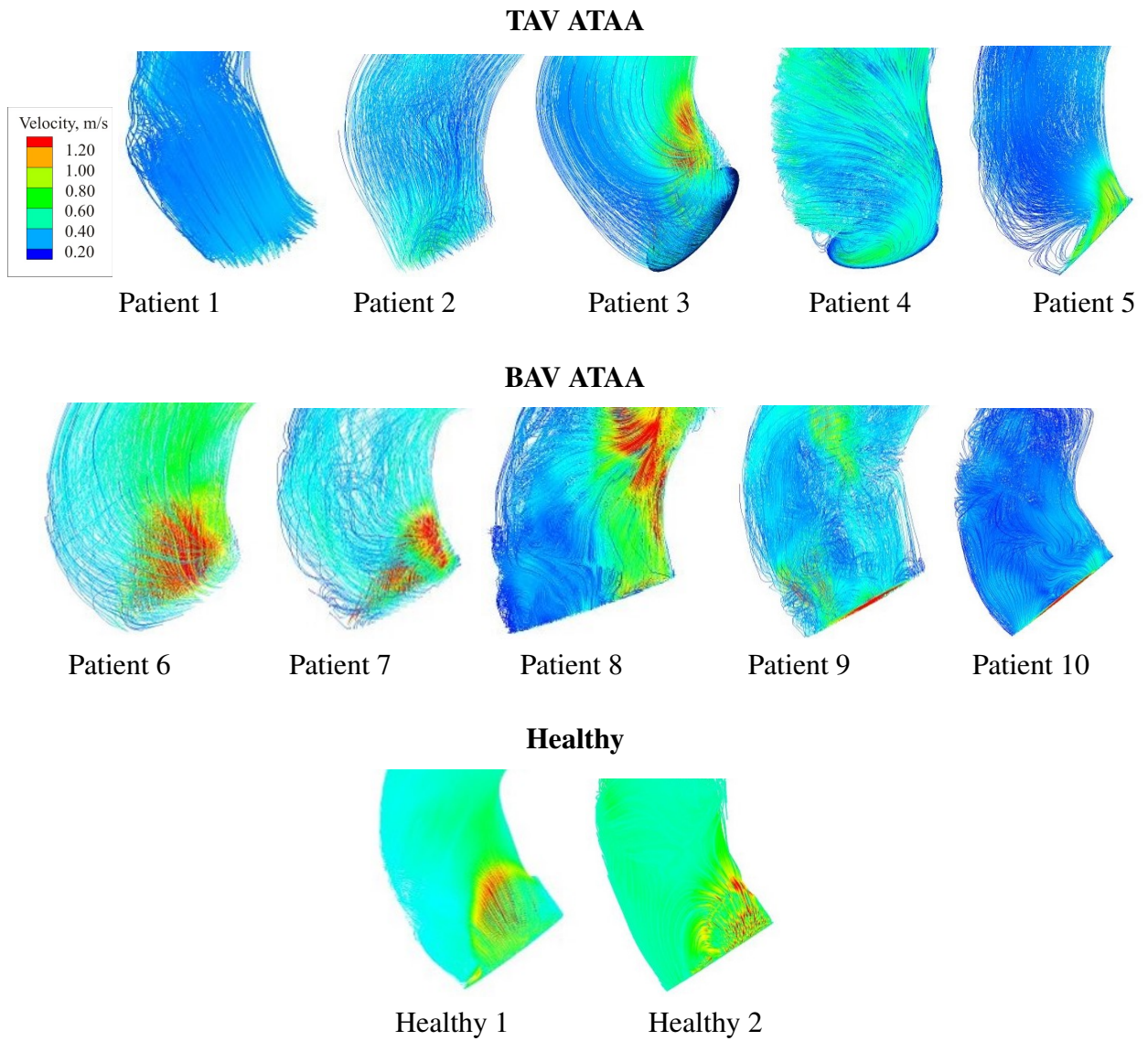


Fig. 3. Streamlines of blood velocity at peak systole for TAV ATAA, BAV ATAA and healthy subjects.

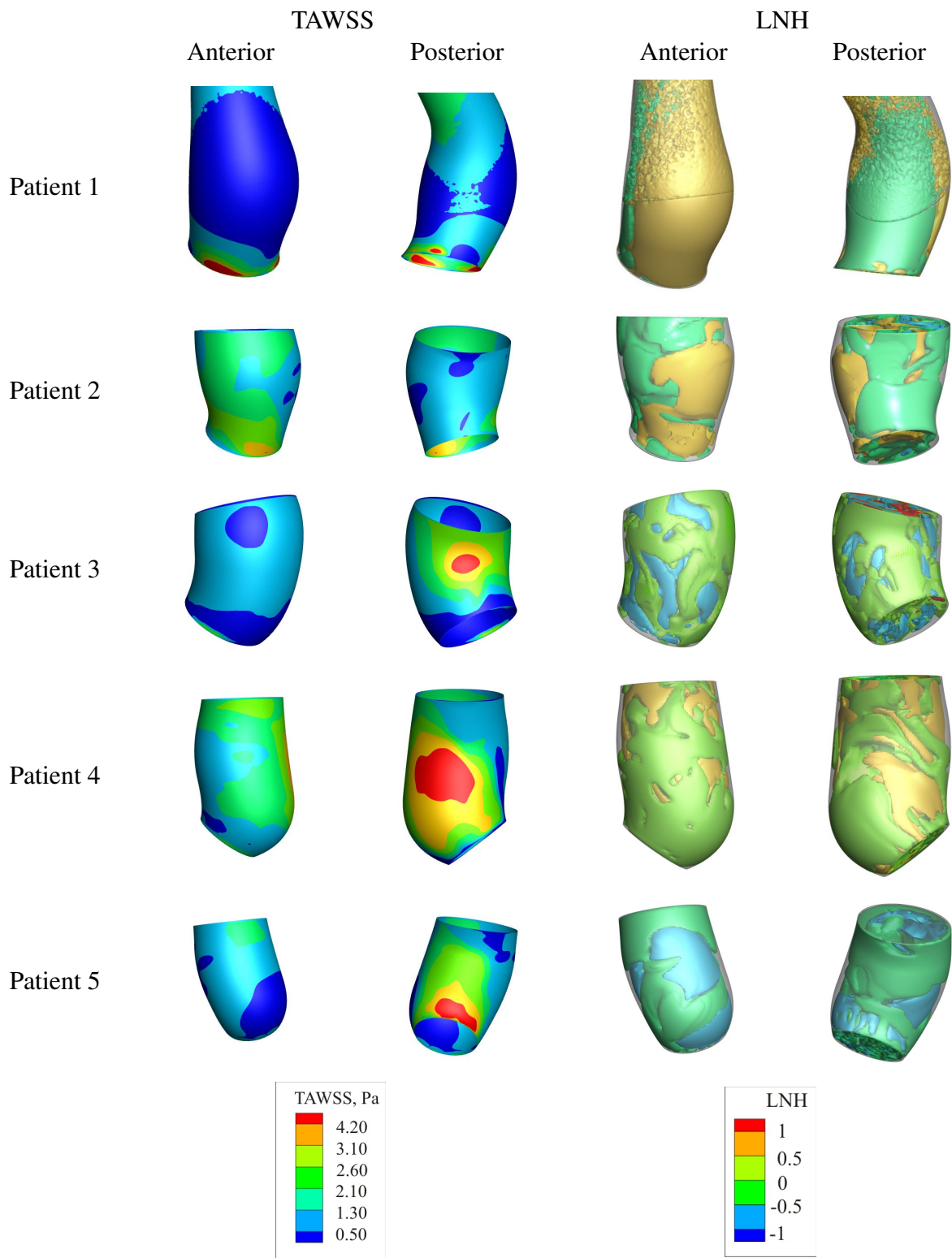


Fig. 4. TAWSS and LNH distribution in the ATA region for TAV ATAA patients.

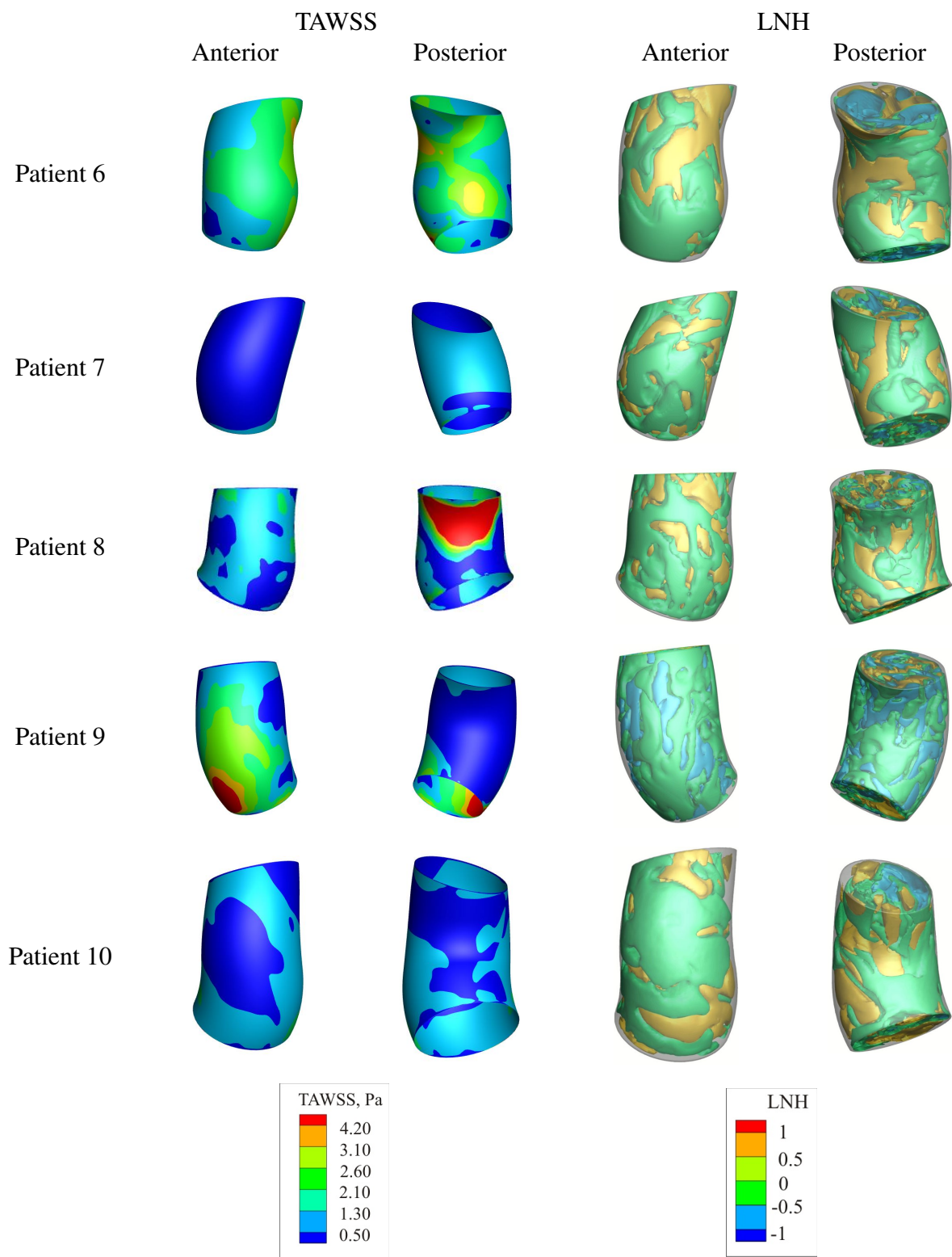


Fig. 5. TAWSS and LNH distribution in the ATA region for BAV ATAA patients.

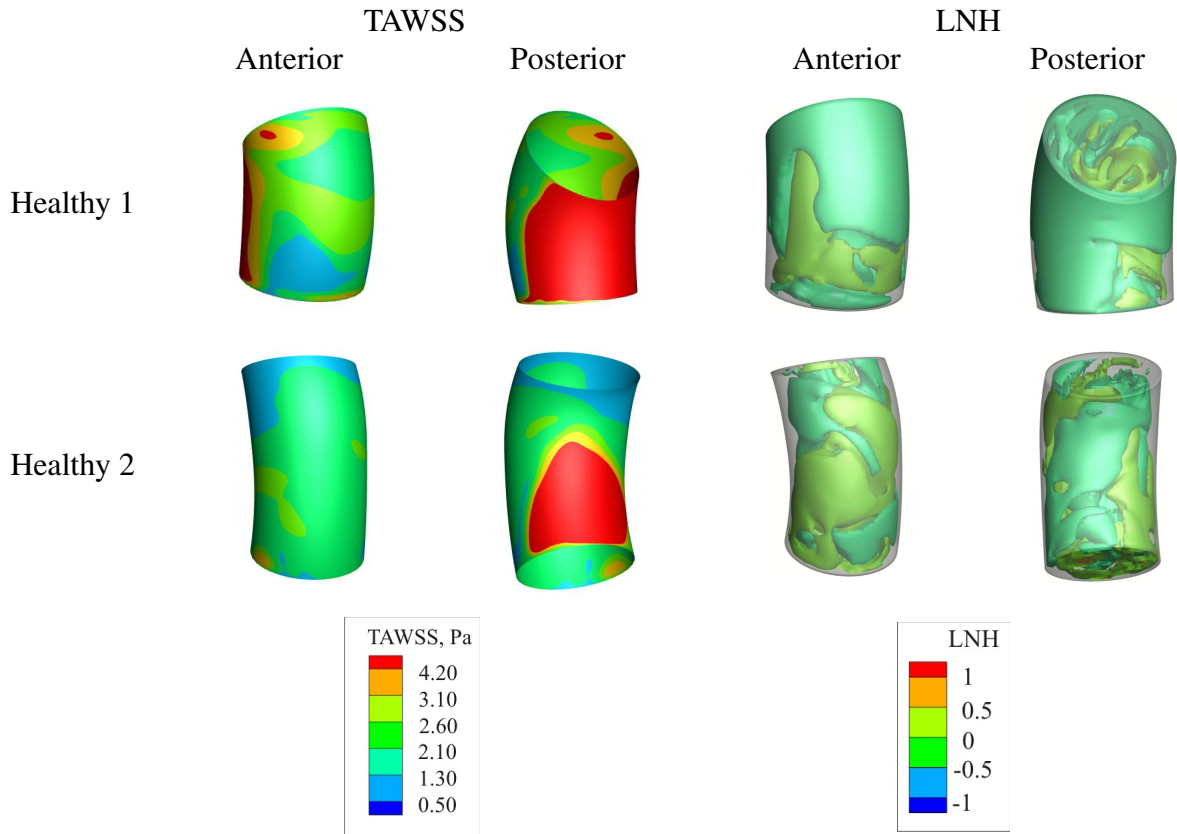


Fig. 6. TAWSS and LNH distribution in the ATA region for healthy subjects.

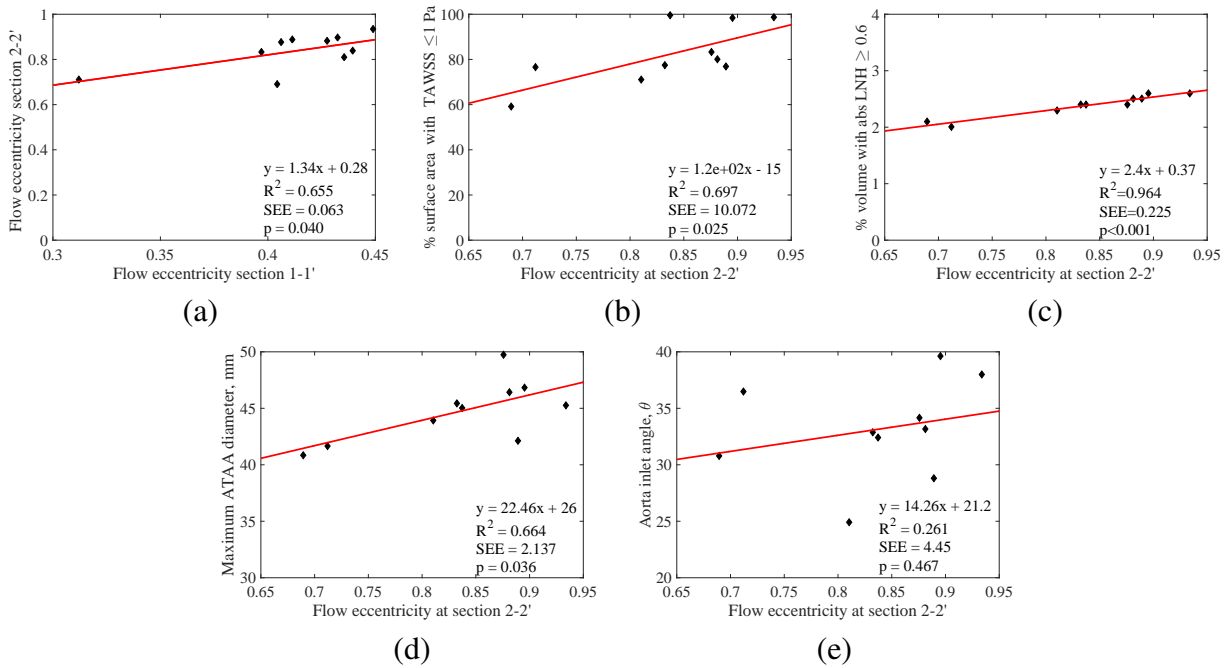


Fig. 7. Correlation between the flow eccentricity near the dilated region and other significant parameters (hemodynamics and morphology)

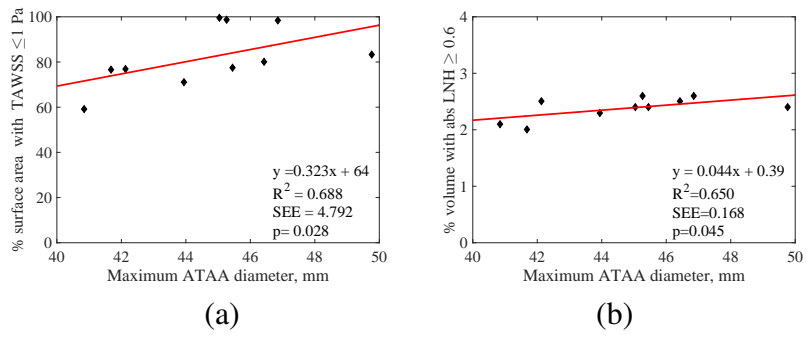


Fig. 8. Correlation between the maximum ATAA diameter and hemodynamic parameters

459

TABLE CAPTIONS

460 Tab.1 Test of significance for TAV ATAA versus BAV ATAA patient characteristics and hemodynamics
461 descriptors.

462 Tab.2 Percentage of TAWSS area and absolute LNH volume for TAV ATAA, BAV ATAA patients and
463 healthy subjects.

Table 1

Test of significance for TAV ATAA versus BAV ATAA patient characteristics and hemodynamics descriptors.

	Parameters	TAV ATAA	BAV ATAA	Sig (2-tailed) TAV ATAA vs BAV ATAA
Patient characteristics	Age, Years	59.60 ± 11.63	58.20 ± 5.59	0.817
	Weight, Kg	75.40 ± 18.63	73.20 ± 11.38	0.829
	Height, m	1.67 ± 0.13	1.66 ± 0.03	0.779
	BSA	1.85 ± 0.26	1.83 ± 0.14	0.855
	Maximum ATAA diameter, mm	43.94 ± 3.66	45.55 ± 1.14	0.393
	Inlet angle, θ	33.65 ± 3.84	32.59 ± 5.21	0.725
Hemodynamics parameters	Flow eccentricity at section 1-1'	0.39 ± 0.05	0.43 ± 0.01	0.268
	Flow eccentricity at section 2-2'	0.82 ± 0.11	0.85 ± 0.03	0.575
	% Surface area with TAWSS \geq 3 Pa	0.33 ± 0.49	3.08 ± 4.05	0.282
	% Surface area with TAWSS \leq 1 Pa	78.96 ± 14.19	85.28 ± 12.95	0.483
	% Volume with absolute LNH \geq 0.6	2.02 ± 1.96	1.11 ± 0.53	0.367
	% Volume with absolute LNH \leq 0.4	88.50 ± 6.72	93.38 ± 5.21	0.235

Table 2

Percentage of TAWSS area and absolute LNH volume for TAV ATAA, BAV ATAA patients and healthy subjects.

		% surface area with TAWSS		% volume with absolute LNH	
		≥ 3 Pa	≤ 1 Pa	≥ 0.6	≤ 0.4
TAV ATAA	Patient 1	0.10	98.7	2.10	90.4
	Patient 2	0.12	76.8	2.60	89.4
	Patient 3	0.10	83.4	2.10	91.5
	Patient 4	1.20	59.3	3.10	80.9
	Patient 5	0.15	76.6	5.50	82.3
BAV ATAA	Patient 6	8.00	71.0	3.10	85.0
	Patient 7	0.15	99.7	2.40	91.9
	Patient 8	7.00	80.0	2.10	93.8
	Patient 9	0.15	77.4	2.80	94.2
	Patient 10	0.10	98.3	2.10	93.2
Healthy	Healthy 1	28.5	20.5	0.50	98.6
	Healthy 2	27.3	20.1	0.40	98.7

464 7 Supplementary Materials

465 A Materials and Methodology

466 A.1 4D flow MRI Data acquisition

467 4D flow MRI datasets consists of magnitude data representing the patients aortic anatomy and phase
468 data representing the velocities along V_x , V_y & V_z (Fig. S3) obtained throughout the cardiac cycle
469 thus providing a dynamic imaging of the blood flow. 4D flow MRI data acquisition requires efficient
470 scan times which synchronizes between cardiac and respiratory movements (Stankovic et al., 2014)
471 in order to obtain good images. The ECG gating and the imaging parameters for 4D flow MRI data
472 acquisition are as follows: spatial resolution = $2.4 \times 2.4 \times 2.4 \text{ mm}^3$, field of view (FOV) = $380 \times$
473 285 mm^2 , velocity encoding (VENC) = 200 cm/s, Bandwidth (BW) = 496 Hz/Pixel, Flip angle = 7° ,
474 echo time (TE) / repetition time (TR) = 2.19 / 37.9 and phase duration (Temporal resolution) = 37.9
475 ms.

476 A.2 Pre-procssing of 4D flow MRI data

477 The data obtained from 4D flow MRI may have some artifacts that can degrade the image quality and
478 flow measurements hence appropriate correction strategies are to be employed in order to be used in
479 the simulation (Stankovic et al., 2014). 4D flow MRI datasets were analyzed using the Velocity Map-
480 ping Tool (Tool for preprocessing & converting of 4D Flow MRI data- Freiburg University, Germany
481 & Northwestern University, USA) in combination with MATLAB (MathWorks Inc. R2015b). This

482 tool helps us to apply the eddy-current correction, noise filter to improve the quality of the image and
483 the pre-processed data were imported into 3D visualization software (Enlight, CEI, Inc.), to obtain
484 dynamic visualization and extraction of velocity profiles (Fig. S3).

485 *A.3 3D Velocity profile extraction*

486 Enlight is a commercial tool used to extract the 3D velocity profiles from the 4D flow MRI mea-
487 sured data. 2D analysis cross-sectional plane were introduced (i.e ascending aorta and apico-aortic
488 branches such as brachiocephalic artery (BCA), left common carotid artery (LCC) & left subclavian
489 artery (LSUB)) on the pre-processed image obtained from velocity mapping tool (Fig. S3). On these
490 planes, the 3D blood flow velocity vector field were projected for each individual cardiac time-frame.
491 The magnitude and velocity vectors obtained from these planes were post processed using Matlab.
492 The obtained patient-specific velocity maps and flow rate waveforms were given as input boundary
493 conditions to the CFD simulation.

494 *A.4 Aorta reconstruction and meshing*

495 The 3D aorta model was reconstructed from the 4D flow MRI data using a semi-automatic segmenta-
496 tion in the CRIMSON (Cardiovascular Integrated Modelling and SimulatiON) tool where a center-
497 line was positioned along the entire length of the aorta starting from the aortic root to the descending
498 aorta. The analysis planes were automatically distributed along the center-line after manually select-
499 ing the points along the center-line and they were oriented normal to the aorta. These analysis planes
500 were useful for tracking the cross section of the aorta at the respective points. The reconstructed

501 patient-specific geometry, including the ascending thoracic aorta, aortic arch with branches and the
502 descending aorta, was imported in Ansys-Fluent (ANSYS, Academic research, Release 17.2) and
503 meshed with 1.5-6.2 millions of tetrahedral elements (Fig. S3). A convergence analysis was carried
504 out to obtain mesh independent analyses.

505 *A.5 CFD analysis and simulation setup*

506 The finite volume method (FVM) was used to solve the governing equations of the fluid motion under
507 unsteady flow conditions in Ansys Fluent. The blood flow was assumed to be laminar, non-Newtonian
508 and incompressible with a density of 1050 kg/m^3 . The details regarding the model and the parameters
509 used in this simulation can be obtained from Jayendiran et al. (2020).

510 Patient-specific 4D flow MRI data were used to define the inflow velocity profile. Pixel-based time-
511 varying velocities were obtained from these phase-contrast flow maps. The 3D velocity profiles (V_x ,
512 V_y & V_z) were extracted from these phase-contrast flow maps by using an in-house Matlab code
513 (MathWorks Inc. R2015b) and mapped onto the inlet face of the aorta (Fig. S4). Therefore, every
514 voxel of the aorta inlet section was assigned a velocity vector whose direction and magnitude was
515 determined from the PC-MRI data. The patient-specific flow rate obtained from 4D flow MRI was
516 assigned at the outlet sections of the apico-aortic branches (BCA, LCC, LSUB) (Morbiducci et al.,
517 2013; Youssefi et al., 2017) as outflow boundary conditions (Fig. S4). A multiscale approach was
518 implemented to describe the hemodynamics at the descending aorta outlet by coupling the 3D domain
519 with a reduced order model (i.e three element Windkessel model). The three-element Windkessel
520 model was assigned to represent the targeted physiological blood pressure measured from the patients
521 during the 4D flow MRI data acquisition (Fig. S4). Given a target diastolic and systolic pressure

522 (measured from the patients during the 4D flow MRI data acquisition), the value of the impedance
523 (Z), the distal resistance (R) and the capacitor (C) were adjusted in an iterative manner so that the
524 predicted flow distributions in each vascular region were within 3% of 4D flow MRI measurements.
525 The outlet boundary meshes were extended 20 times the length of their diameter for sufficient pressure
526 recovery. The aortic walls were assumed to be rigid, impermeable and with no-slip.

527 The solution of Navier-Stokes equations was obtained with Ansys Fluent v17.2 using the Semi-
528 Implicit Method for Pressure-Linked Equations (SIMPLE), a second-order interpolation scheme and
529 a second-order upwind interpolation. A second order implicit time advanced scheme was used as
530 transient-time solver and a time step size Δt of 1 ms was chosen. This time step size is fine enough to
531 capture the time-dependent flow parameters accurately and to ensure that the convergence is reached
532 with the assigned maximum number of iterations per time step. The appropriate time step size was
533 evaluated as follows (Ansys Fluent):

$$\Delta t \approx \frac{\textit{Typical cell size}}{\textit{Characteristic flow velocity}} \quad (\text{A.1})$$

534 The convergence of the solution was assessed for relative residual errors below 10^{-3} . A residual
535 plot for the transient flow simulation is shown in Fig. S5. The initial guess and the time step size
536 were chosen in such a way that the residuals reduce by around three orders of magnitude within one
537 time step and stabilizes after the few iterations providing accurate resolution of transient behavior. To
538 ensure fully developed flow and to avoid unsteady state solution due to initial transient conditions, the
539 simulation was performed for three cardiac cycles and the last cycle was used for post-processing.

540 **B Patient characteristics**

541 The patient-specific aortic geometry was reconstructed using 4D flow MRI and the maximum ATA di-
542 ameter was measured for each subject. In order to optimize measurement accuracy, the ATA diameter
543 was measured several times from 4D MRI data sets and uncertainty in the measurements was esti-
544 mated. We performed 10 multiple measurements for each subject. Details regarding the uncertainty
545 analysis and the estimation of maximum ATA diameter can be found in Jayendiran et al. (2020).

546 The inlet angle θ was measured using a horizontal plane placed at the aortic root and the inclination
547 made by the aortic inlet with respect to the horizontal plane gave us the θ (Fig. S4). The measurement
548 of this angle was introduced in Condemi et al. (2019).

549 The comparison of patient characteristics in TAV and BAV groups are reported in Tab. 1. The param-
550 eters such as age ($p = 0.817$), weight ($p = 0.829$), height ($p = 0.779$), Body Surface Area (BSA) ($p =$
551 0.855), maximum ATAA diameter ($p = 0.393$) and inlet angle ($p = 0.725$) all have a p -value > 0.05 . In
552 this study the significance ($p > 0.05$) value shows that the TAV and BAV patient characteristics were
553 not significantly different. In the TAV group, two patients presented mild degree of aortic regurgita-
554 tion (AR) and only one a mild degree of aortic stenosis (AS) (mean gradient = 10 mmHg). In the BAV
555 group only two patients presented a mild degree of AR (Tab. S1 in the supplementary materials).