Orientation effects of bicuspid aortic valve with mild/severe aortic stenosis on aortic hemodynamics: a parametric study

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Abstract
While bicuspid aortic valve (BAV) shows different phenotypes associated with aortic aneurysm and valvular dysfunction due to aortic stenosis (AS), hemodynamics in patients with stenotic BAVs remains poorly understood. Here we address a study of the effects of valve phenotypes on aortic hemodynamics in different configurations of AS using an image-based subject-specific left ventricle (LV)-aorta integrated computational model. The model was built up by combining both MRI images and realistic motions of aortic valve, mitral valve, and LV apex as well as its contraction and dilatation of a healthy subject. Physiological boundary conditions were given based on a parameter-adjusted 0-1D cardiovascular model. Symmetrical BAV models with mild and severe stenosis were constructed with the orientation angle varying every 15° from 0° to 165° with regards to mitral valve while within a planar disc and the orientation effects on aortic hemodynamics were systematically investigated. Our results revealed that systolic jets in aorta were dominated by a combination of valve orientation and AS. Furthermore the hemodynamic indices of maximum wall shear stress (WSS), oscillatory shear index (OSI), and axial energy loss also demonstrated a feature of phenotype-and stenosis-dependency, pointing to the importance of taking into account the valve configuration in clinical decision-making on BAV patients.

Keywords: Bicuspid aortic valve, Aortic stenosis, Hemodynamics, Orientation, Phenotype

1. Introduction

Bicuspid aortic valve (BAV) is a congenital heart disease affecting 1.3% of the annual newborns (Verma and Siu, 2014). Due to its high incidence of aortopathy such as aortic aneurysm or aortic dissection and valvular dysfunction such as aortic stenosis (AS) and insufficiency in later stage (Fazel, et al., 2008; Sabet, et al., 1999; Sievers and Sievers, 2011), it has been increasingly attracting clinician’s attention. While normal tricuspid aortic valve (TAV) is composed of almost equal-sized three leaflets named right-coronary, left-coronary and non-coronary cusps according to their anatomical location, BAV is composed of two equal or unequal-sized leaflets, resulting from the fusion of any two leaflets.
Owing to its asymmetric feature and the combination of fusing leaflets, BAVs have been classified into several phenotypes (Russo, et al., 2008; Sievers and Schmidtke, 2007; Sievers, et al., 2016; Sun, et al., 2017). One well-recognized classification was by Sievers, et al., 2016, in which BAVs were classified according to the existence and the number of raphes (the mark of fusion) and the combination of fusing leaflets. Among these phenotypes, the number of patients is significantly unbalanced. Of all the BAV patients, the right-left coronary (RL) fusion is the most major phenotype (approximately 70-80%), which is followed by right-noncoronary (RN) fusion (10-20%) and some minor phenotypes such as left-noncoronary fusion and BAV with equal-sized leaflets.

BAV phenotypes are reported to be associated with the location and the progression of aortic aneurysms. Russo et al. 2008 found that the BAV patients with RL fusion turned out to suffer from aneurysm at aortic root as well as degeneration of ascending aorta at younger age than those with RN fusion. Schaefer, et al. 2007 clarified that the RL-BAV was associated with larger dimension of the sinus of Valsalva with stiffer wall and smaller diameter of aortic arch. Sun, et al., 2017 employed a robust and simple criterion named dichotomous classification, in which BAVs were categorized into two types based on its orientation, to investigate the association between BAV and aortopathy. They found that the BAVs with orifice locating between right and left-coronary ostia were more likely to trigger off the aortopathy or valvular dysfunction. Such phenotype-dependent aortopathy in BAV patients is considered due to the genetic and hemodynamic factors (Verma and Siu, 2014).

Within this context, in recent years, researchers have been studying the aortic hemodynamics in BAV patients through 4D phase-contrast MRI and computational fluid dynamics (CFD) and revealed some findings on several hemodynamic traits. Hope et al 2010, 2011 observed several key features specific to BAV patients based on MRI visualization in terms of helical and eccentric systolic jets as well as asymmetrically elevated wall shear stress (WSS). MRI studies further found out that the BAV phenotype determined the systolic jet direction (Barker, et al., 2014; Rodriguez-Palomares, et al., 2018). Moreover, helicity density or energy dissipation in the BAV patients was calculated based on MRI visualization to differentiate BAV flow features and to quantify the risk of valvular diseases (Garcia, et al., 2017; Barker, et al., 2014). On the other hand, Faggiano, et al., 2013 computationally quantified the WSS and helical flow with aortic models of TAV and BAV, reporting a higher helical feature in BAV patients than normal TAV case. Cao, et al., 2017 used an aortic valve-aorta FSI model to investigate phenotype-dependent hemodynamic characteristics and pointed out that WSS and its directionality were more dependent on valve phenotypes than flow eccentricity or skewness. However, the hemodynamic effects of BAV’s orientation with various degree of AS has not been investigated even though both BAV geometries and incidence of AS are observed to be highly patient-specific in BAV patients (Sabet, et al., 1999).

In this study, we aim at making an investigation on the orientation effects of BAVs on aortic hemodynamics under mild and/or severe AS conditions through a parametric study with various valve angles to quantify the corresponding hemodynamic traits and its implication for clinical decision-making on BAV patients.

2. Methods
2.1 Image-based LV-aorta modeling

The process of model construction is illustrated in Fig. 1. A 4D-MRI dataset of a healthy subject, 72 year-old man with normal tricuspid aortic valve (TAV), was employed to construct a subject-specific model. The information of subject is summarized in Table 1. The images were taken in Northwestern University, USA. The dataset contains 25 phases for a complete cardiac cycle and consists of (1) slices of short axis image, (2) 2, 3 and 4-chamber image, (3) the aortic valve images for left ventricle (LV) and (4) slices of sagittal plane image for aorta. Three-dimensional geometry of LV and aorta was reconstructed on an open-source software, 3D slicer (www.slicer.org) based on slices of short axis image of LV and sagittal image of aorta. From each geometry, long axes, short axes and centerlines are extracted in two mutually perpendicular views with Rhinoceros 3D (Robert McNeel & Associates, USA). The skeleton model of LV and aorta was then separately created using an in-house mesh generation code. Here we assumed aorta had rigid wall, i.e., images at single phase were used for aorta but at all the phases for LV. The motion of aortic and mitral annulus as well as apex were also obtained from 2-and 3-chamber images and taken into account in the model to reproduce systolic/diastolic dynamics of LV (Cheng-Baron, et al., 2010).

The geometrical connection of LV and aorta was achieved by coordinate transformation. Every image includes the information of its spatial orientation (two vectors forming column and row of the image), which facilitates precise
determination of the angle and orientation between the two models. Here, the two vectors in the column \( \mathbf{r} = (r_1, r_2, r_3)^T \)

Fig. 1 Schematic description of the model construction. The aorta model was created based on the geometrical outlines taken from sagittal images. The LV model was created based on geometrical outlines and dynamic motion of the apex, aortic annulus, and mitral annulus. The LV outline was extracted from the slices of short-axis image while location of the apex and heart valves were determined based on combination of the 2- and 3-chamber images and 3-chamber image, respectively. The separately constructed models were then combined with adapting interfaces accordingly. The characters a and b indicate the inlet and outlet of the aorta, respectively, between which PPI and PELI were calculated (For PPI and PELI, see Section 2.5). AV, aortic valve; MV, mitral valve.

<table>
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<th>Table 1 Subject’s characteristics.</th>
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<td>Age</td>
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<td>Sex</td>
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<td>Height [m]</td>
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<td>Weight [kg]</td>
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<td>Heart rate [bpm]</td>
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<tr>
<td>Stroke volume [ml]</td>
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<tr>
<td>Aortic valve annulus area [cm²]</td>
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<td>Ascending aortic diameter [cm]</td>
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and row \( \mathbf{s} = (s_1, s_2, s_3)^T \) direction of the LV short axis image were used to transform LV from local coordinate system, which corresponds to the 3-chamber view of LV, to the patient’s coordinate system, where the aorta was reconstructed. Suppose \( \mathbf{p} = (x, y, z) \) and \( \mathbf{p}' = (x', y', z') \) are a grid point of LV before and after transformation, since the components of two vectors are written in the patient coordinate system, \( \mathbf{p}' \) is transformed by
\[
\mathbf{p} = \begin{pmatrix}
  x' \\
  y' \\
  z'
\end{pmatrix} = \begin{pmatrix}
  r_1 \\
  r_2 \\
  r_3
\end{pmatrix} + \begin{pmatrix}
  s_1' \\
  s_2' \\
  s_3'
\end{pmatrix} \begin{pmatrix}
  t_1 \\
  t_2 \\
  t_3
\end{pmatrix},
\]

where
\[
\mathbf{t} = (t_1, t_2, t_3)^T, \quad \mathbf{s}' = (s_1', s_2', s_3')^T.
\]

Note that the vector \( s' \) is introduced to ensure the orthogonality of the vectors. Being adjusted spatial location of aortic valve, LV and aorta were geometrically connected. Herein, we introduced the transient interface between LV and aorta to ensure smooth transition from the left ventricular outflow tract (LVOT) to the aorta. This is achieved by linearly interpolating the displacement of aortic grid points from aortic valve (image-based displacement) to distal ascending aorta (zero displacement) at all the time instants assuming the continuity of the motion. The smoothing spline interpolation was used for temporally interpolating moving points (Graham, 1983).

### 2.2 Computational fluid dynamic modeling

Blood flow was assumed to be an incompressible Newtonian fluid governed by three-dimensional, unsteady, incompressible Navier-Stokes equation and equation of continuity. A finite volume in-house solver for multi-block, overset meshes was employed to derive the flow field (Liu, et al., 1999; Liu, 2009). Here the pseudo-compressibility was introduced for reasonable derivation of pressure field. Computational conditions are summarized in Table 2. Reynolds number and Strouhal number were computed from diameter of the aortic valve, mean velocity through the aortic valve, and cardiac cycle. Through the grid dependency study, the total node number of 344365 is found to be able to balance both accuracy and computational time. The temporal resolution is 1000 steps for a cardiac cycle. The residual error at ascending aortic flow once went up from 0.3% (second cycle) to 1.7% (third cycle) but gradually decreased and finally dropped to 0.11% (10th cycle). Therefore, the outcomes of 10th cycle were used for discussion. The computations were parallelized with 12 threads (Intel (R) Core (TM) i7-5930K CPU, 6 cores, 3.50GHz), which cost us up to 5 days to compute 10 cardiac cycles. The results were visualized with Paraview (www.paraview.org), an open-source software.

### 2.3 Cardiac valve modeling

Aortic and mitral valves were designed as a planar disc, precluding the effects of the leaflets (Nakamura, et al., 2002). The opening region was regarded as free flow area while no-slip condition was imposed on the remaining region covered by leaflets. The defined valve orifice was illustrated in Fig. 2. We defined two kinds of BAV models: mild AS and severe AS (Fig. 2A). The stenosis rate was defined by the following equation:

\[
\text{Stenosis rate} = \left(1 - \frac{A_{\text{orifice}}}{A_{\text{annulus}}} \right) \times 100 \text{ [%]},
\]

where \( A_{\text{orifice}} \) and \( A_{\text{annulus}} \) denote the total annulus area of the aortic valve and the area of orifice, respectively. The resulting stenosis rate was 54% for the mild case and 76% for the severe case. BAVs with different orientations were made by mapping the condition of defined BAV annulus to another annulus with the defined annulus inclined by certain angle (Fig. 2B). Note that the valve orientation was defined based on the angle between the symmetrical lines of the opening orifice of mitral and aortic valves. For instance, a BAV opening perpendicular to the mitral valve was named 90° model.

We prepared BAVs with twelve kinds of orientation with equally distributed valve angle for each AS model (Fig. 2C). The angle was defined every 15°. We gave the correspondence with the pathological valve phenotypes (Fig. 2C). The mapped orifice did not have rigorously the same opening area as seen in Fig. 2B due to the limited resolution of the grid. However, the error of the orifice area was within 1% and the difference of the computed flow rate through the
valve at peak systole was approximately 1% in all the models, indicating the minor effects of the difference of the opening area on the computation.

<table>
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<tr>
<th>Table 2 Computational parameters.</th>
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<td>Reference length [cm]</td>
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<td>Reference velocity [cm/s]</td>
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<td>Cardiac period [s]</td>
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Fig. 2 The method for aortic valve modeling and prepared valve models. The two aortic valves with symmetrical orifice but different degree of AS (54%, mild; 76%, severe) were designed. Valve orientation is defined as the angle between symmetrical lines of the orifice of aortic and mitral valve (A). The valve orifice of the 0° case was then inclined and mapped on the original mesh (red mesh) to create BAV with various valve orientation. An example of the case of 30° with mild stenosis is illustrated as an example (B). In this manner, 24 cases of the orientation were prepared with varying the orientation every 15° for both stenosis models (C). Assuming the three commissures of aortic valve form an equilateral triangle, pathological phenotypes of right-left coronary (RL), right-noncoronary (RN) and left-noncoronary (LN) fusions are analogous to 120°, 60° and 0° models, respectively.
Fig. 3 The volume change of the LV and pressure boundary conditions applied on the mild (54%) (A) and severe (76%) (B) stenotic cases. The systolic and diastolic phase were determined according to volume change of the LV.

2.4 0-1D model-based boundary conditions

To impose physiological boundary conditions, we applied 0-1D model-based boundary conditions; specifically, the MRI-based 0-1D model was introduced. To the population-averaged 0-1D model (Liang, et al., 2009), we applied some subject-specific parameters derived from MRI and the geometrical model. The applied parameters were (1) the left ventricular volume and its temporal variation, (2) the timing of opening and closure of aortic and mitral valve and (3) the duration and timing of atrial and ventricular contraction, and (4) length and radius of the aorta. Due to the limited information from MRI, the parameters of other arteries and peripheral circulation, such as geometry of carotid artery or peripheral resistance, were not reflected and kept population-averaged value. The defined AS were also reflected in the pressure difference of the aortic valve $\Delta p_{av}$ calculated by the following equation (Garcia, et al. (2006); Liang, et al., 2009):

$$\Delta p_{av} = \frac{1}{2} \rho \frac{Q_{av}^2}{EOA} \left( \frac{1}{A_{ao}} - \frac{1}{AOA} \right)^2 + 2\pi \rho \frac{\partial Q_{av}}{\partial t} \left( \frac{1}{EOA} - \frac{1}{A_{ao}} \right)^{0.5},$$

where $\rho$ is density of the blood; $t$ is time; $Q_{av}$ represents flow rate through the aortic valve; $EOA$ and $A_{ao}$ are the effective orifice area of the aortic valve and the area of the ascending aorta. In the equation, the first and second terms represent the pressure difference caused by convective inertia and local inertia, respectively (Garcia, et al. (2006)). $EOA$ is known to be less than the actual geometrical orifice (aortic valve annulus area), but here we used the geometric orifice since the BAV model employed in this study is ideal and hence no information of systolic flow jet characteristics. The employed area of aortic valve annulus and ascending aorta are presented in Table 1.

Figure 3 shows the computed pressure waveforms of left atrium (LA), LV and ascending aorta (AA) as well as LV volume curves. The peak pressure differences across the aortic valve were 25mmHg and 56mmHg for the mild and severe cases, respectively, which were within physiological range. For the three dimensional LV computational model, these pressure waveforms were imposed uniformly on the corresponding region at the beginning of every time step and the inflow and outflow of the LV were initiated by pressure difference of the LA-LV and LV-AA. The profiles of intraventricular flow velocity and local pressure were computed in the three dimensional CFD solver. For aorta, outflow of three branches at aortic arch was imposed while periodic-averaged pressure was imposed at the outlet of descending aorta.

2.5 Hemodynamic indices

Computed blood flow was evaluated in terms of velocity profile, WSS, WSS directionality, and energy loss. To evaluate the WSS directionality, oscillatory shear index (OSI) was computed as

$$OSI = \frac{\int_{0}^{T} \left( \frac{\partial V}{\partial t} \right)^2 dt}{\int_{0}^{T} \left( \frac{\partial V}{\partial t} \right)^2 + \left( \frac{\partial V}{\partial x} \right)^2 + \left( \frac{\partial V}{\partial y} \right)^2 + \left( \frac{\partial V}{\partial z} \right)^2}$$

where $\partial V/\partial t$ is time derivative of velocity and $\partial V/\partial x$, $\partial V/\partial y$, and $\partial V/\partial z$ are spatial derivatives of velocity.
OSI = \frac{1}{2} \left( 1 - \frac{|\mathbf{r}_{\text{mean}}|}{|\mathbf{r}|_{\text{mean}}} \right), \quad (4)

where

|\mathbf{r}_{\text{mean}}| = \frac{1}{T} \int_{0}^{T} |\mathbf{r}(x, t)| dt, \quad |\mathbf{r}|_{\text{mean}} = \frac{1}{T} \int_{0}^{T} |\mathbf{r}(x, t)| dt.

To evaluate the energy loss throughout the aorta, the recently proposed novel indices, pulsatile power index (PPI) and pulsatile energy loss index (PELI) (Liu, et al., 2012; Sughimoto, et al., 2014) were computed. PPI and PELI are defined as

\begin{align}
\text{PPI} &= \frac{1}{2} \left( 1 - \frac{\beta_{A}^\tau}{\bar{\beta}_A} \right), \quad \text{PELI} = 2(\text{PPI}_{\text{outlet}} - \text{PPI}_{\text{inlet}}). \quad (5)
\end{align}

where

\begin{align*}
P_{Axi} &= \int (p + \frac{1}{2} \rho |\mathbf{V}|^2)(\mathbf{V} \cdot \mathbf{n}_{Axi}) d\mathbf{A} \\
\bar{P}_{Axi} &= \frac{1}{T} \int_{0}^{T} P_{Axi} dt \\
\bar{P}_{Axi} &= \frac{1}{T} \int_{0}^{T} |P_{Axi}| dt
\end{align*}

\begin{align*}
Q' &= \int (\mathbf{V} \cdot \mathbf{n}_{Axi}) d\mathbf{A}, \quad \bar{\beta}_A = \frac{\bar{P}_{Axi}}{Q'_{\text{max}}} \\
Q'_{\text{max}} &= \text{Max}(Q')
\end{align*}

Here, \( p, \mathbf{V} \) and \( Q \) represent blood pressure, velocity vector, and volumetric flow rate at a certain cross-section \( A \) of aorta with normal vector \( \mathbf{n}_{Axi} \), respectively. \( \xi \) represents the direction normal to the cross-section. Note that PPI was computed throughout the region between the inlet (aortic valve) and outlet of the aorta (a, b in Fig. 1) and hence PELI is the difference of PPI between the inlet and outlet. As seen in the definition, PPI is not capable of capturing the effects of the flow in the cross-sectional direction such as secondary flow. Thus we computed the axis work ratio (AWR), which is calculated by

\begin{align}
\text{AWR} &= \frac{\bar{P}_{Axi}}{\bar{P}_{\text{total}}} \quad (6)
\end{align}

where

\begin{align*}
\bar{P}_{\text{total}} &= \bar{P}_{Axi} + \bar{P}_{Ayi} + \bar{P}_{Azi}.
\end{align*}

In the preceding equation, \( \bar{P}_{Ai} \) \((i=\xi, \eta, \zeta)\) is already defined in Eq. 5. The subscripts \( \eta, \zeta \) were further defined in each cross-section and forms orthogonal system; \( \xi \) is the normal direction while the others are two in-plane directions. Therefore, AWR represents the ratio of the work done by blood flow in the axis direction to the total work; lower AWR means secondary flow-dominant energy consumption. To grasp global secondary flow features, \( \text{mAWR} \) was also computed as

\begin{align}
\text{mAWR} &= \frac{1}{D_{\text{out}}} \int_{0}^{D_{\text{out}}} \text{AWR}_{\xi} d\xi, \quad (7)
\end{align}

where \( D_{\text{out}} \) denotes the distance from the inlet to the outlet of the aorta.
3. Results
3.1 Instantaneous characteristics of the systolic jet and maximum WSS

Figure 4 illustrates the streamlines of the representative 6 models for each stenosis case at systole. Clearly, severe stenotic BAVs showed stronger systolic jets in all the valve angles compared to mild BAVs. The systolic jets migrated toward right-lateral wall of the ascending aorta while complicated vortical flows were observed around. At a valve angle close to 90°, the systolic jet obviously became more intense, migrating further downstream. Furthermore, due to the severe stenosis, additional effect of valve angle emerged as well as the different strength of jets. The severe stenotic BAVs (76%) with higher valve angle (90°-150°) enhanced the earlier impingement of the jets at proximal aortic root, leading to a breakdown and hence a narrower systolic jet at distal aortic arch, whereas mild stenotic BAVs (54%) showed almost equivalent jet width over all the valve angles (right-anterior view of Fig. 4). This characteristic is mostly prominent in the 90° model, in which the systolic jet split into three parts at aortic root.

The maximum WSS at peak systole in the ascending aorta and its axial and circumferential location via valve angle were plotted in Fig. 5 based on the analogy to physiological phenotypes (Fig. 2C). Consistent with the trend of systolic jets, the WSS reached its maximum value at the valve angle of 90° in two cases (Fig. 5A) while a sharper elevation of maximum WSS in the severe case was observed with an increase of 73.8% compared to the 0° model and of 46.3% in the mild case. On the other hand, the location of maximal WSS showed different characteristics between two cases. The maximum WSS location of the mild case turned out to move to distal aortic wall at 90°, similar with the trend seen in Fig. 5A, while the WSS in the severe case was observed to move to distal aortic wall at 0°. The circumferential location of both cases was displaced to right-lateral location at 90° but then returned to the anterior position at 180°. Despite of the same trend, the overall variation of the circumferential location was smaller in the severe stenotic case than that in the mild case (84° in the mild case, 72° in the severe case; Fig. 6C).

3.2 Evaluation with periodic-averaged indices: mean WSS and OSI

To evaluate the stenosis dependency of local hemodynamic traits, mean WSSs and OSIs were averaged throughout the ascending aorta, with the aortic wall divided into four portions (Fig. 6): left-anterior, left-posterior, right-anterior and right-posterior walls. The mean WSS was observed to elevate at right-anterior wall, where the impingement of systolic jet occurred in all the cases. Although we can clearly distinguish the local hemodynamic conditions, no marked differences were detected between two cases.

On the other hand, OSIs showed marked difference between two cases. In the mild stenosis, the OSIs elevated at the left portion of the aortic wall, where large vortices were formed due to the migration of the strong systolic jet toward the right-anterior wall (Fig. 4). Although the same flow features were observed, severe stenosis obviously led to an increase in OSIs at the right-posterior wall but a reduction at the left-anterior wall at smaller angles of 0°-75°.

A close-up view of the OSIs at root section and distal ascending section were further given in the same manner as in Figs. 6, 7. At the root section, the higher OSI portion is dependent on valve angle. For example, in the 54% stenosis case, the left-posterior aspect marked the largest OSI at 45° (RN-fusion) while the right-posterior aspect around 135°-165°. The same trends are seen in the severe cases. At the distal ascending portion, the OSI is observed to be independent of valve angle in the mild stenosis case: the left wall marked higher OSI consistently. However, in the severe stenosis case, the elevated OSIs were detected at the right-posterior aspect in the smaller angle of 0°-75°. This is identical to the remarkable increase of OSIs at right posterior aspect in the mid-ascending aorta.

3.3 Quantification of energy dissipation in terms of PPI, PELI and AWR

While the distributions of PPI and AWR along aortic axis were given for all the cases, the indices at a single axial position, where their variations among different valve angles reached the maximum values, were identified and the indices therein were plotted with respect to the valve angle (Fig. 8). It is seen that the major variation caused by valve angle occurred at middle ascending aorta, i.e., the blocked region in Fig. 8. Note that the severe stenosis cases showed remarkable variation of PPI and AWR throughout the aorta due to the large flow separation.
As a result, the PPIs showed highly phenotype-dependent distribution in the mild stenosis case: the highest PPIs were found in RL fusion whereas the PPIs around RN fusion were smallest (75°). AWR was almost equivalent among three phenotypes but tended to become higher between phenotypes. Both stenosis cases were compared in terms of PELI and mAWR as well as the mild stenosis case (Fig. 9). Both PELI and mAWR showed larger variations in the severe stenosis case; the differences between maximum and minimum values of PPI are 0.036 and 0.127 for the mild and severe stenosis case, respectively while those of mAWR are 0.018 and 0.024. Furthermore, phenotype-dependent characteristics were detected: PELIs of the severe stenosis case were mostly smaller than those of the mild cases except for middle valve angle (75°-120°, around RL fusion). On the contrary, mAWRs of the severe case turned out to be lower than the mild case, particularly in the case of LN and RN fusions but became relatively larger at the valve angle of 90° with RL to LN fusions.

4. Discussion
4.1 Effects of valve orientation on aortic hemodynamics in severe AS

Here we give an extensive discussion on the effects of valve orientation on aortic hemodynamics in different levels of AS. Our results demonstrated that the severe AS brought different outcomes in terms of local maximum WSS, OSIs, and energy dissipation compared to mild AS.

Fig. 4 Streamlines of the representative models of mild (54%) and severe (76%) AS at peak-systole from anterior (upper) and right-anterior (lower) views. Valve orifices are also shown by the contour of the velocity magnitude.
The extreme case with angle of 90° obviously resulted in the highest WSS and an intense systolic jet irrespective to the degree of stenosis likely due to the geometrical association between BAV orientation and aortic curvature. As shown in Fig. 4, the BAV is aligned with the curvature of ascending aorta at the angle of 90°, which can enhance the centrifugal force on the jet and hence lead to an accelerated inflow along the outer curvature of ascending aorta as well as higher WSSs with the local maximum WSS migrated to distal wall. As reported in an experimental study by Haya and Tavoularis, (2016), the orientation of prosthetic aortic valve had a defect in inducing more viscous stresses in the sinus flow, indicating that this alignment between BAV and AA curvature may even make things worse. This indicates the importance of taking consideration of the anatomic or geometric association between BAV orientation and aortic characteristics of torsion, curvature and skewness, in discussing the BAV orientation-induced WSSs and jet traits.

In severe stenotic condition, the axial position of local maximum WSS at ascending aorta was distributed irregularly with respect to the valve angle while the variation of circumferential position was reduced. This was likely attributed to the stronger systolic jet. Combined with the centrifugal force, the systolic jet formed a unique shape after impingement (Fig. 4), leading to a complicated flow distribution. At the same time, the severe AS could contribute to the axial component of the jet. Thus the circumferential position was observed to be less affected by the valve orientation. These results point to the importance of the balance between the effects of stenosis and valve angle: critical severe stenosis may impose further burden on the aortic wall in addition to the orientation-dependent hemodynamic event.

Fig. 5 Peak-systolic maximal WSS in the ascending aorta (A) and its axial (B) and circumferential (C) position in the two stenotic cases. The definition of the each position is illustrated on the aortic model and the corresponding positions were marked on the (B) and (C). The angle was classified according to the analogy to the physiological phenotypes (see Fig. 2). RN, right-noncoronary fusion; RL, right-leftcoronary fusion; LN, left-noncoronary fusion; AV, aortic valve; Br, branch; Conv, convex; Ant, anterior.
Fig. 6 Local mean absolute WSS and OSI averaged throughout the ascending aorta in two stenotic cases. The ascending aortic wall was divided into four portions (left-anterior, LA; left-posterior, LP; right-anterior, RA; right-posterior, RP) and their spatial averages throughout the ascending aorta were plotted separately. The classification of the angle and abbreviation are as noted in Fig. 5.

Fig. 7 Local mean absolute OSI at proximal and distal ascending aortas in two stenotic cases. The ascending aortic wall was divided into four portions (left-anterior, left-posterior, right-anterior, and right-posterior) and their spatial averages throughout the ascending aorta were plotted separately. The classification of the angle and abbreviation are as noted in Fig. 5.
Fig. 8 PPI and AWR in 54% stenotic cases at middle ascending aorta (blocked region), in which marked discrepancy among different valve models was detected.

![Image of 3D model]

![Graph showing PPI and AWR distribution]

The further burden caused by the stronger systolic jet resulted in increasing OSIs at right-posterior portion of distal ascending aorta in the smaller valve angle (0°-75°). Cao, et al., 2017 performed a CFD-based analysis in a similar setting as we had here and found that the circumferential distribution of OSIs at proximal aorta was strongly phenotype-dependent while those at distal aorta was insensitive with some eccentric elevation at aortic concave in all

![Graph showing PELI and mAWR distribution]

Fig. 9 PELI and mAWR distributions via angles.

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the phenotypes. Their findings coincide with our results with mild stenosis but do not with severe stenosis. This may be attributed to the larger vortices due to the stenotic systolic jet. In addition, aortic geometry may also play a crucial role in increasing OSIs because such trend were not seen in the model with larger angles of 105°-165°, which is symmetrical to these models about the centerline of the aortic valve. Local elevation of OSI at right-posterior section of the distal ascending portion may be associated with development of aortic diseases. For example, this region is close to the frequent site of the aortic dissection (Ma et al. 2016). Thus, this AS-induced OSI elevation may lead to damaging endothelial cells and hence initiation of adverse events such as the aortic dissection.

The energy dissipation measured by PPI, AWR and PELI were also affected by severely stenosed condition. While mild stenosis caused phenotype-specific local energy dissipation at ascending aorta, where systolic jet impingement occurred, and smaller variation of global energy dissipation with respect to valve angle, severe stenosis caused highly phenotype-specific energy dissipation both locally and globally. In the severe stenotic case, since systolic jet reached up to aortic arch or even to descending aorta, the characteristics of jet was reflected in the whole aorta, which makes it difficult to quantify the local difference of PPI and AWR in the severe case. In this respect, PELI and mAWR seems to be able to provide reliable information on energy loss.

Plots of PELI and mAWR (Fig. 9) suggest that the contribution of axial flow-based energy dissipation (i.e. flow oscillation or reversal) and secondary flow-based dissipation are dependent on the valve phenotypes in severe stenotic cases. For example, the LN and RN fusion type is associated with lower axial flow-based energy loss in the severe case but larger secondary flow-based energy loss. On the contrary, RL fusion type is associated with higher axial flow-based energy loss and lower secondary flow-based dissipation. Although the local PPI showed similar trend as PELI’s, the local AWR did not exhibit such phenotype-dependency, which implies severe stenosis enhance the global energy loss and its phenotype-dependency in terms of the types of the energy loss.

The energy loss in the BAV patients was addressed by Barker, et al., 2014. They quantified viscous energy loss of systolic jet and elucidated that BAV initiated larger energy loss, which in turn increase burden on LV and hence lead to LV abnormality. Therefore the quantification of energy loss is clinically meaningful to predict disease of LV. Recent study evaluated axial and circumferential WSS separately in the aorta of BAV patients and found that BAV-RL and -RN types were characterized by axial and circumferential-dominant WSS, respectively (Rodriguez-Palomares, et al., 2018). This finding agrees with the outcome of present study, highlighting the reliability of our results. Our computed results with patient-specific models demonstrated that even mild stenotic BAV-RL/-RN showed axial flow-/secondary flow- based energy loss. Such patient-specific geometry (eccentricity of valve or aortic shape) can also be the factors that determine the types of energy loss to some extent.

4.2 Clinical implication

Our study demonstrated orientation of the valve opening affected the aortic hemodynamics using an image-based computational model. This method can be applicable to patient-specific modeling for the patients with BAVs to predict the speed to develop aortopathy and timing for its surgical intervention. The bicuspid aortic valve does not only cause the aortic dilatation but also cause the aortic valve insufficiency. For example, aortic root dilatation is associated with BAV-RL type and aortic regurgitation (Wojnarski, et al., (2018)). BAV-RL type is also associated with elevated WSS at aortic root (Rodriguez-Palomares, et al., 2018). In our study, the severe stenotic BAV showed much larger and more proximally elevated WSS around 90° case (from RN type to RL type). Therefore, aortic regurgitation is more likely to occur among the patients with stenotic BAV-RL and BAV-RN types, which may affect workload of the left ventricle. Similarly, BAV-RN type demonstrated elevated OSI in the part of the wall only in the stenotic case. They suggests the severity of the valve stenosis may influence the timing of surgical intervention as well as hemodynamics in the aorta since these hemodynamic characteristics may be linked to degeneration of the endothelial cells of aorta and altered wall stress, which is internal force on aortic wall and associated with aortic dissection (Barker, et al., 2018).

The 90° type of stenotic BAV may bring worse outcome such as ascending aortic aneurysm or valvular dysfunction due to elevated WSS and remarkably larger axial energy loss despite comparatively low secondary-flow based energy loss. Pathologically, BAV fusion phenotypes do not strictly adhere to the fact that RL is 120 degrees in orientation to the mitral valve (nor is the RN always 60 degrees to the mitral valve). Thus, if a patient has an orientation of ~90 degrees to the mitral valve, this may represent a particularly important phenotypic orientation to
4.3 Limitation

The valve leaflets motion were not taken into account. In the patients with severe AS, the leaflets are calcified and hence become stiffer, which may contribute to orient systolic jet toward unexpected direction. In addition, only one aortic geometry was analyzed; some of the flow features observed may be attributed to the aortic geometry specific to the subject involved although no aneurysms or valvular disease were found. The effects of aortic geometry should be quantified for future application. Also, this model did not include the aortic valve regurgitation that is more common in the realistic bicuspid aortic valve and can influence the left ventricular overload and amount of the systolic jet.

5. Conclusion

Effects of valve orientation on aortic hemodynamics in terms of systolic jet, WSS, OSI and energy loss indices were investigated systematically in different severity of AS. We found that a combination between valve orientation and AS plays a crucial role in affecting the BAV-induced aortic hemodynamics: (1) systolic jets and WSS distributions are altered significantly by larger orientation angles greater than $90^\circ$ with severe stenosis; (2) OSIs at right-posterior aspect of ascending aorta are more sensitive to valve orientation; and (3) energy loss in terms of axial and secondary flow throughout aorta arch is largely affected by valve orientation. Our results therefore indicate that it would be of great importance to take consideration of the feature of phenotype-and stenosis-dependency associated with valve configuration in clinical decision-making on BAV patients.

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