Valvular Heart Disease

Bicuspid Aortic Cusp Fusion Morphology Alters Aortic Three-Dimensional Outflow Patterns, Wall Shear Stress, and Expression of Aortopathy

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Background—Aortic 3-dimensional blood flow was analyzed to investigate altered ascending aorta (AAo) hemodynamics in bicuspid aortic valve (BAV) patients and its association with differences in cusp fusion patterns (right-left, RL versus right-noncoronary, RN) and expression of aortopathy.

Methods and Results—Four-dimensional flow MRI measured in vivo 3-dimensional blood flow in the aorta of 75 subjects: BAV patients with aortic dilatation stratified by leaflet fusion pattern (n=15 RL-BAV, mid AAo diameter=39.9±4.4 mm; n=15 RN-BAV, 39.6±7.2 mm); aorta size controls with tricuspid aortic valves (n=30, 41.0±4.4 mm); healthy volunteers (n=15, 24.9±3.0 mm). Aortopathy type (0–3), systolic flow angle, flow displacement, and regional wall shear stress were determined for all subjects. Eccentric outflow jet patterns in BAV patients resulted in elevated regional wall shear stress (P<0.0125) at the right-anterior walls for RL-BAV and right-posterior walls for RN-BAV in comparison with aorta size controls. Dilatation of the aortic root only (type 1) or involving the entire AAo and arch (type 3) was found in the majority of RN-BAV patients (87%) but was mostly absent for RL-BAV patients (87% type 2). Differences in aortopathy type between RL-BAV and RN-BAV patients were associated with altered flow displacement in the proximal and mid AAo for type 1 (42%–81% decrease versus type 2) and distal AAo for type 3 (33%–39% increase versus type 2).

Conclusions—The presence and type of BAV fusion was associated with changes in regional wall shear stress distribution, systolic flow eccentricity, and expression of BAV aortopathy. Hemodynamic markers suggest a physiological mechanism by which the valve morphology phenotype can influence phenotypes of BAV aortopathy. (Circulation. 2014;129:673-682.)

Key words: aortic diseases ▫ bicuspid aortic valve ▫ hemodynamics ▫ magnetic resonance imaging

Congenital bicuspid aortic valve (BAV) is the most common congenital cardiovascular abnormality and occurs with an incidence of 1% to 2% of the population. This entity is associated with significant morbidity and mortality including valvular stenosis, valvular regurgitation, aortic dilation, aneurysm, and dissection. The most common distinct morphologies have been identified based on fusion patterns between the right and left coronary leaflet (RL, frequency ≈80%), the right and noncoronary leaflet (RN, ≈17%), and the less commonly left and noncoronary leaflet (≈2%) fusion patterns. Additionally, BAV fusion patterns have been shown to be significant as a potential predictive factor in the location and rate of development of aortic complications. Although studies have linked genetics to the development of aortopathy in patients with BAV, the role of valve-related alterations in aortic hemodynamics and their impact on the underlying aortopathy is a reoccurring topic of debate. Studies based on flow-sensitive MRI and, more recently, four-dimensional (4D) flow MRI, provide evidence that the modified hemodynamic environments associated with BAV can cause altered wall shear stress (WSS) in the ascending aorta, which may trigger maladaptive vascular remodeling.

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Studies have shown that BAV with the RL cusp fusion pattern is strongly associated with asymmetrically elevated WSS in the ascending aorta. Recent studies in individual cases and larger cohorts have provided evidence that differences in the BAV phenotype for RL and the less common RN cusp fusion patterns can impact aortic blood flow and WSS. In addition, recent studies have shown that the type of valvular dysfunction and BAV aortopathy differ significantly between the RL- and RN-BAV phenotypes. Thus, the investigation of
the relationship between valve fusion pattern, changes in aortic hemodynamics, and phenotype of BAV aortopathy may shed new light on the search for a mechanistic link between BAV and differences in the development of aortic pathology.

The aim of this study was therefore to evaluate the impact of different BAV cusp pattern fusion (RL and RN) on quantitative measures of aortic hemodynamics (WSS, flow angle, and flow asymmetry). Results were compared with young healthy volunteers and a dilated aorta control group matched for aortic size. We hypothesize that differences in BAV cusp morphology are associated with significant changes in aortic hemodynamics and are associated with a fusion pattern–specific phenotypic expression of aortopathy. Furthermore, we hypothesize that less technically involved analysis methods such as flow angle and flow displacement have the potential to provide quantitative measures of changes in regional ascending aortic hemodynamics that are associated with different types of aortic pathologies and BAV cusp fusion morphologies.

Methods

Study Population

Patients referred for MRI to assess aortic valve morphology and function were divided into 3 groups: RL-BAV patients (n=15), RN-BAV patients (n=15), and patients with tricuspid aortic valves and aortic dilatation (n=30) to serve as aorta size–matched controls for BAV patients. Aortic dilatation was defined as a sinus of Valsalva diameter >40 mm or mid ascending aorta diameter >40 mm. Healthy young volunteers (n=15) with morphologically normal tricuspid aortic valves and no history of cardiovascular abnormalities were also included. Demographic characteristics are summarized in the Table. The study was approved by the Institutional Review Board of Northwestern University. Informed consent was obtained from all healthy volunteers. Patients were included in accordance with an institutional review board protocol which permitted retrospective chart review. Informed consent was obtained from all healthy volunteers.

Magnetic Resonance Imaging

All participants underwent cardiac MRI at 1.5T or 3T (Magnetom, Siemens Medical Systems, Germany). All subjects underwent a standard-of-care thoracic cardiovascular MRI, including ECG-gated time-resolved cine cardiac MRI for the evaluation of cardiac function and valve morphology and contrast-enhanced MR angiography, as well as, for the quantification of aortic dimensions. To assess valve morphology, breath held, ECG-gated time-resolved (2-dimensional cine) steady-state free precession imaging was performed in a 2-dimensional imaging plane that was carefully positioned orthogonal to the aortic root at the level of the aortic valve.

For the assessment of aortic blood flow, time-resolved 3-dimensional (3D) phase-contrast MRI with 3-directional velocity encoding (4D flow MRI) was used to measure 3D blood flow velocities with full volumetric coverage of the thoracic aorta. Four-dimensional flow MRI was acquired during free breathing by using respiratory and prospective ECG gating in a sagittal oblique 3D volume of the thoracic aorta as described previously. Pulse sequence parameters were as follows: flip angle, 15°; spatial resolution, 1.7 to 3.7 mm by 1.8 to 2.6 mm by 2.2 to 3.7 mm; temporal resolution, 36.8 to 43.2 ms; total acquisition time, 8 to 15 minutes depending on heart rate and navigator efficiency; velocity sensitivity, 100 to 300 cm/s.

Data Analysis: Valve Morphology, Aortic Diameter

Valve morphology, aortic sinus of Valsalva and mid ascending aorta diameters, and severity of stenosis or regurgitation were determined by an experienced radiologist using standard-of-care imaging as described above. Two-dimensional cine steady-state free precession was used to assess valve morphology. Contrast-enhanced MR angiography was used to assess aortic diameter. Aortic dimensions were measured both at the sinus of Valsalva and mid ascending aorta at the level of the pulmonary artery.

Phenotypes of BAV Aortopathy

An experienced cardiac radiologist analyzed the MR angiography images for different types of aortopathy. Similar to Fazel et al and Kang et al, different phenotypes of aortopathy were defined: type 0, normal aorta; type 1, dilated aortic root; type 2, aortic enlargement involving the tubular portion of the ascending aorta; and type 3, diffuse involvement of both the entire ascending aorta and the transverse aortic arch (see Figure 1A). An aortic segment (root, ascending aorta, transverse arch) was considered dilated if a diameter >40 mm was found.

Data Analysis: 4D Flow MRI

Data preprocessing included noise filtering and correction for eddy currents, Maxwell terms, and velocity aliasing, as previously described by Bock et al. A 3D phase-contrast MR angiogram was derived from 4D flow data and used to manually position 3 analysis planes in 3D visualization software (EnSight, CEI, Apex, NC) at defined anatomic landmarks in the ascending aorta (Figure 1), directly distal to the sinotubular junction (S1), at the midpoint between the sinotubular junction and the origin of the brachiocephalic trunk (S2), and proximal to the origin of the brachiocephalic trunk (S3). Aortic 3D blood flow was visualized by using 3D streamlines at peak flow systole and color coded to represent blood flow velocity (Figure 2).

For each analysis plane, the aortic lumen contours were manually delineated for all time frames with the use of custom-built software programmed in Matlab (The Mathworks) to quantify systolic valve flow angle, outflow asymmetry, and regional WSS. As shown in Figure 1, valve flow angle was calculated as the angle between the mean flow vector (Q) and a normal unit vector (n) orthogonal to the analysis plane. A visualization of outflow asymmetry was created by mapping the location of the upper 15% of peak systolic velocities on a segmental aortic lumen map (schematically illustrated in Figure 1B). In addition, and similar to the strategy reported by Sigovan et al, the flow displacement distance d (in millimeters) from the vessel centroid to the velocity-weighted centroid was extracted as a quantitative marker to represent outflow asymmetry.

WSS was derived from the velocity data for each analysis plane by directly interpolating the local velocity derivative on the lumen contour by using b-splines as described by Papathanasopoulou et al and Stalder et al. For each plane, regional systolic WSS was calculated at 8 standardized angular segments of the aortic wall (L, left; R, right; A, anterior; P, posterior; LA, left anterior; RA, right anterior; LP, left posterior; RP, right posterior; see Figure 3 for details). For each analysis plane and each segment, systolic WSS was averaged over peak flow systole and 3 subsequent time points. Circumferentially averaged WSS was calculated as the mean over all eight segments.

Statistical Analysis

All continuous data are presented as mean±standard deviation. In addition, median and interquartile ranges were calculated. For each group (healthy volunteers, aorta size–matched controls, RL-BAV, RN-BAV), a Shapiro-Wilk test was used to determine if parameters were normally distributed. To compare hemodynamic parameters between the 4 groups, 1-way analysis of variance (Gaussian distribution) or Kruskal-Wallis (non-Gaussian distribution) was used. If these tests determined that a hemodynamic parameter was significantly different between groups (P<0.05), multiple comparisons for all groups were performed by the use of independent-sample t tests (Gaussian distribution) or Mann-Whitney tests (non-Gaussian distribution). Bonferroni correction was used to adjust for multiple comparisons and differences were considered significant for P<0.0125. Differences between categorical variables were assessed by using the Fisher exact test. All analysis was performed using Matlab (version R2011a, The Mathworks) and SPSS (version 21, IBM).
Results

Study Cohort

The degree of aortic valve stenosis or aortic insufficiency did not exceed moderate in all patients. The majority of patients had none or mild (70/75, 93%) stenosis or insufficiency (65/75, 87%). Patients with tricuspid valves were matched to aortic size for RL-BAV and RN-BAV patients (Table). Sex distribution was similar in all groups (Fisher exact test). Typical images for the different aortic valve morphologies are shown in Figure 2. Four-dimensional flow MRI and hemodynamic analysis was successfully performed in all subjects and a complete set of flow metrics (WSS, flow angle, flow displacement) was obtained in all study participants.

Phenotypes of BAV Aortopathy

Among the phenotypes of aortopathy, type 2 was the most common in our BAV patients and aorta size controls (47% [28/60]), followed by type 1 (30% [18/60]) and type 3 (23% [14/60]). Although all types 1 to 3 were frequently found in tricuspid aorta size controls, RL- and RN-BAV phenotypes were associated with different types of aortopathy. Noticeably, the majority (87%) of RL-BAV patients presented type 2 aortopathy, whereas RN-BAV patients demonstrated much higher

Table. Descriptive Statistics of Patient Demographics, Aortic Dimensions, and Hemodynamic Parameters at the 3 Analysis Planes S1 (Sinotubular Junction), S2 (MAA), and S3 (Distal Ascending Aorta)

<table>
<thead>
<tr>
<th></th>
<th>Tricuspid Valve</th>
<th>Bicuspid Valve</th>
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<tbody>
<tr>
<td></td>
<td>Healthy Volunteers</td>
<td>Aorta Size Controls</td>
</tr>
<tr>
<td>Female, n</td>
<td>15 (5)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Age</td>
<td>32.6±7.6 (31.0, 7.5)</td>
<td>59.2±12.5 (58.5, 16.2)</td>
</tr>
<tr>
<td>MAA diameter, mm</td>
<td>24.9±3.0 (25.0, 4.9)</td>
<td>41.0±4.4 (42.0, 5.8)</td>
</tr>
<tr>
<td>SOV diameter, mm</td>
<td>—</td>
<td>42.3±4.6 (42.0, 5.0)</td>
</tr>
<tr>
<td>Aortopathy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 0</td>
<td>15 (100)</td>
<td>—</td>
</tr>
<tr>
<td>Type 1</td>
<td>0</td>
<td>9 (30)</td>
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<tr>
<td>Type 2</td>
<td>0</td>
<td>13 (43)</td>
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<tr>
<td>Type 3</td>
<td>0</td>
<td>8 (27)</td>
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<tr>
<td>Systolic WSS, N/m²</td>
<td></td>
<td></td>
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<tr>
<td>S1</td>
<td>0.60±0.15* (0.61, 0.15)</td>
<td>0.41±0.16 (0.38, 0.24)</td>
</tr>
<tr>
<td>S2</td>
<td>0.56±0.14* (0.63, 0.22)</td>
<td>0.30±0.14 (0.28, 0.18)</td>
</tr>
<tr>
<td>S3</td>
<td>0.55±0.16† (0.52, 0.23)</td>
<td>0.32±0.16 (0.31, 0.22)</td>
</tr>
<tr>
<td>Valve flow angle, °</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>6.3±3.5† (4.5, 5.5)</td>
<td>18.0±10.8 (16.1, 12.7)</td>
</tr>
<tr>
<td>S2</td>
<td>8.4±4.8† (7.4, 6.5)</td>
<td>19.6±12.4 (17.9, 16.6)</td>
</tr>
<tr>
<td>S3</td>
<td>13.1±8.1 (12.7, 12.2)</td>
<td>11.0±7.0 (9.1, 9.2)</td>
</tr>
<tr>
<td>Flow displacement, d, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>1.8±1.5† (1.4, 0.7)</td>
<td>3.9±2.3 (3.2, 4.0)</td>
</tr>
<tr>
<td>S2</td>
<td>1.2±0.5* (1.2, 0.7)</td>
<td>4.3±2.7 (3.9, 4.0)</td>
</tr>
<tr>
<td>S3</td>
<td>1.3±0.5† (1.3, 0.7)</td>
<td>2.5±2.4 (1.6, 0.6)</td>
</tr>
</tbody>
</table>

All continuous data are presented as mean±standard deviation (median, interquartile range). BAV indicates bicuspid aortic valve; MAA, mid ascending aortic; RL, right and left coronary leaflet; RN, right and noncoronary leaflet; and SOV, sinus of Valsalva.

*Independent-sample t test; denotes significant differences compared with aorta size–matched controls (P<0.0125 after Bonferroni correction).

†Mann-Whitney test; denotes significant differences compared with aorta size–matched controls (P<0.0125 after Bonferroni correction).
prevalence of type 1 (53%) and type 3 (34%), which were only found in 2 RL-BAV patients (Table).

3D Blood Flow Visualization
Healthy volunteers (Figure 2A) showed uniform velocity distributions with cohesive streamlines indicating flow generally parallel to the vessel walls. In contrast, highly eccentric outflow jet patterns were found in BAV patients and resulted in different flow impingement zones at the AAo wall (yellow arrows in Figure 2C and 2D, right anterior wall for RL-BAV, right-posterior wall for RN-BAV).

Ascending Aortic WSS
Systolic WSS distribution in the ascending aorta showed distinct differences between valve morphologies (Figure 3). Comparisons between groups revealed significant differences (Kruskal-Wallis and analysis of variance; range, \( P=1.0E-6 \) to \( P=0.010 \)) for all but 1 segment (S1, left anterior, \( P=0.051 \)). Subsequent groupwise testing showed significantly increased and highly asymmetrical WSS at the level of the sinotubular junction for both BAV cohorts in comparison with aorta size controls. The location of significantly increased WSS was different for RL-BAV (Figure 3, S1, increase in regional WSS for RA, R, RP segments) and RN-BAV (Figure 3, S1, increase in regional WSS for RP, P segments) reflecting changes in localized outflow jets for different BAV cusp fusion patterns. Further downstream at the mid and distal ascending aorta (Figure 3, S2 and S3), significantly increased WSS (\( P<0.001 \)) was seen in 63% to 100% of segments, with RN-BAV showing the most regions of increased WSS magnitude, in agreement with the increased incidence of type 3 aortopathy in this cohort.

Flow Angle and Outflow Asymmetry
Figure 4 illustrates the magnitude and location of the top 15% of velocities at the sinotubular junction (S1) for all patient groups. Most healthy volunteers showed centrally distributed peak systolic velocities (Figure 4A). In contrast, peak velocities were concentrated toward the outer aortic walls in BAV patients. Consistent with differences in regionally increased WSS in Figure 3, RN-BAV showed eccentric systolic outflow distributed along the right-posterior aortic wall (Figure 4D), whereas RL-BAV demonstrated flow jets directed more toward the right-anterior wall in all subjects (Figure 4C). Aorta size controls (Figure 4B) showed less outflow asymmetry with more central locations of the top 15% velocities.

The Table summarizes differences in flow angle and flow displacement \( d \) for all groups and all 3 analysis plane locations S1 to S3. Note that flow displacements provided a better discrimination between groups. At the sinotubular junction, significantly increased flow displacement (\( P<0.0125 \)) was found for both BAV groups (RL-BAV, 7.6±2.6 mm; RN-BAV, 6.7±2.6 mm) in comparison with aorta size–matched controls (3.9±2.3 mm) indicating the sensitivity to valve morphology–induced changes in 3D aortic outflow.27

Ascending Aorta Hemodynamics and Phenotypes of BAV Aortopathy
Figure 5 summarizes the distribution of flow angle and flow displacement \( d \) for BAV patients as a function of their
phenotypes of BAV aortopathy. Flow displacement was most sensitive to differences in aortopathy phenotype. Note that the involvement of the distal ascending aorta (type 3) was found with increased frequency in RN-BAV, whereas RL-BAV mostly demonstrated type 2 aortopathy. Flow displacement in patients with type 3 aortopathy (mostly RN-BAV) was predominantly increased in the mid and distal AAo (difference=18%/39%/33% for S1/S2/S3 in comparison with type 2) indicating enhanced outflow asymmetry in comparison with patients who have the type 2 aortopathy phenotype (mostly RL-BAV). Moreover, type 1 aortopathy was more frequent for RN-BAV and led to reduced displacement in comparison with type 2 (difference=81%/42%/16% for S1/S2/S3), which was most prominent in the proximal and mid AAo. Interestingly, circumferentially averaged peak systolic WSS did not show similar differences between aortopathy phenotypes for type 1 (maximum difference=11%), whereas the differences for type 3 versus type 1 were similar for all slices S1 to S3 (27%–30%). These findings indicate the potential value of other metrics of hemodynamics, such as flow displacement to identify potential mechanisms leading to the different expression of aortopathy in our BAV cohort.

Discussion
The findings of this study show that the presence of BAV and the type of cusp fusion pattern were accompanied
by changes in systolic outflow as quantified by flow displacement, flow angles, and regional WSS. In addition, we observed that altered aortic hemodynamic markers were associated with the predominant expression of aortopathy phenotype (type 2 for RL-BAV versus type 1 and 3 in RN-BAV) in our cohort.

**BAV Aortopathy and Hemodynamics: Implications for BAV Management**

These findings represent important new insights regarding the current recommendations of aortic diameter to influence the timing and extent of surgical aortopathy management in BAV patients. The decision of how to medically manage these

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**Figure 3.** Segmental systolic wall shear stress (WSS) measurements at the sinotubular junction (analysis plane S1), the mid ascending aorta (S2), and the distal ascending aorta (S3). The individual data points represent mean systolic WSS for patients with bicuspid aortic valves (C and D), aorta size–matched controls (B), and healthy volunteers (A) across 8 anatomic locations (A, anterior; LA, left anterior; L, left; LP, left posterior; P, posterior; RP, right posterior; R, right; RA, right anterior). Error bars represent the standard deviation of interindividual WSS variation. * indicates statistically significant differences for RL-BAV and RN-BAV cohorts in comparison with aorta size–matched controls (P<0.0125 after Bonferroni correction). BAV indicates bicuspid aortic valve; RL, right and left coronary leaflet; and RN, right and noncoronary leaflet.

**Figure 4.** Flow profile asymmetry maps schematically illustrating flow eccentricity by using the locations of the upper 15% of systolic velocities for all participants within each cohort at the sinotubular junction (analysis plane S1). RN-BAV patients showed outflow asymmetry toward the right posterior wall in comparison with RL-BAV patients, whose flow profile was directed more toward the right-anterior wall. (A, anterior; L, left; P, posterior; R, right). Note that each subject’s profile map was normalized to their sinotubular junction diameter. BAV indicates bicuspid aortic valve; RL, right and left coronary leaflet; and RN, right and noncoronary leaflet.
patients or when to operate in BAV aortopathy is difficult. Many times the degree and location of aortic dilatation is highly variable and current guidelines are supported by limited evidence. Medical management recommendations are currently based on the limited evidence in patients who have Marfan syndrome and do not address the duration of medical therapy or how to monitor for long-term physiological responses to medical therapy. When an individual is referred for surgery, the decision to resect aortic tissues in BAV aortopathy is difficult, because the degree of aortic dilatation can be highly variable with respect to location on the aorta and the degree of enlargement. We recently published results of a large survey of cardiac surgeons and found that operative approaches and management of BAV aortopathy is highly variable and not consistent with current guidelines. Hemodynamic alterations as measured by 4D flow MRI may aid in surgical decisions with respect to the operative management of BAV aortopathy. For example, our data indicate that patients with RN cusp fusion patterns exhibit different hemodynamics and aortopathy than subjects with RL morphology. Four-dimensional flow MRI may thus be used to determine which regional areas of the aorta are most prone to developing complications and should therefore be resected. These initial data suggest that hemodynamic alterations and the aortopathy phenotype can have variable patterns that could be important for clinical surgical management decisions.

We recognize that further studies will be needed to correlate our 4D flow MRI data with histological morphology and clinical outcomes to further direct medical and surgical management. Novel imaging metrics such as outflow asymmetry, once validated with clinical outcomes, may be capable of shaping decisions with respect to the timing and extent of aortic replacement in this diverse group of patients with BAV.

Aortic Hemodynamics: Association With BAV Fusion Pattern and Aortopathy Phenotype

Regional WSS and flow displacement revealed significant differences between patient cohorts with differing fusion patterns. Of all the metrics assessed, flow displacement was most sensitive to differences in BAV aortopathy phenotype and may represent a novel and highly feasible noninvasive metric for the quantification of regional hemodynamic abnormalities in patients with bicuspid aortic valve disease.
These changes in aortic hemodynamics point to a potential explanation for the increased incidence of type 1 and type 3 aortopathy in our RN-BAV patients in comparison with most RL-BAV patients presenting with type 2 aortopathy. The distribution of the type of aortopathy in our cohort was similar to findings in a recent study by Kang et al.\(^\text{18}\) We speculate that the differences in geometry and orientation of the aortic valve in RL-BAV versus RN-BAV patients resulted in altered outflow patterns (as shown in Figure 2) that can lead to changes in regional WSS and flow profile asymmetry and flow displacement, as well. In contrast, neither healthy volunteers nor aorta size–matched controls showed such an obvious elevation in WSS or flow displacement at any single anatomic location across the aortic wall.

Specifically, RL-BAV patients demonstrate high-velocity flow profiles (upper 15% of systolic velocities) directed toward the posterior-right-anterior wall (Figure 4). For RN-BAV patients, the current study showed that the high-velocity RN-BAV flow distribution was mostly contained within the right-posterior aorta and did not deviate toward the anterior wall. These findings suggest that RN-BAV flow follows a trajectory that reflects off or follows the inner curvature of the aorta to eventually impinge along the right or right-posterior wall at variable heights.\(^\text{16}\) Moreover, differences in flow displacement directly corresponded to the anatomic regions affected by different aortopathy phenotypes. Type 3 (involvement of the distal ascending aorta and transverse arch) resulted in flow displacement that was predominantly altered in the distal AAo in comparison with aortopathy types 2 and 1, which excluded the distal ascending aorta. In contrast, patients with type 1 (dilation of the aortic root) exhibited highest differences in proximal AAo locations at the sinotubular junction and mid AAo. These findings provide evidence for a direct mechanistic link between BAV cusp fusion morphology and expression of aortopathy phenotype via a hemodynamic measure.

WSS in the younger trileaflet healthy volunteers was similar in magnitude to the BAV cohorts. In contrast, patients with tricuspid aortic valves and dilated aorta (aorta size controls) had significantly reduced WSS in comparison with the younger healthy volunteers in most segments (67%). Although BAV and aortic dilatation resulted in an eccentric increase of WSS (even in comparison with younger healthy controls), the presence of dilatation aorta alone (with normal tricuspid valves) led to an opposite effect on WSS, indicating the importance of cusp fusion morphology.

**3D Blood Flow Visualization and WSS: Comparison With Previous Studies**

Three-dimensional visualization of in vivo aortic 3D blood flow velocities as measured by 4D flow MRI can help to depict differences in aortic outflow between different aortic valve morphologies and provides a visual illustration of the underlying mechanisms for the development of aortopathy.\(^\text{10,12,15,16}\) It should be noted that higher velocities in the descending aorta, as seen in Figure 2, are a common finding. As previously reported by Hope et al.,\(^\text{30}\) peak velocities that are initially high in the AAo show a significant slowing in the transverse aortic arch and subsequently increase when reaching the descending aorta owing to a reduction in vessel diameter. The presentation and analysis of the data, however, remain semiquantitative and are potentially subject to observer variability. Recent studies have thus shifted focus to the quantification of AAo WSS, which can be directly derived from the 4D flow data, and has been implicated in the development of aortopathy.\(^\text{12,15,16}\) Previous reports by Hope et al,\(^\text{12}\) Meierhofer et al,\(^\text{13}\) Bissell et al,\(^\text{17}\) and our own study\(^\text{16}\) demonstrated significantly elevated WSS in the AAo.

The magnitude of circumferentially averaged WSS in this study (RL-BAV, 0.6 N/m²; aorta size–matched controls, 0.3–0.4 N/m²; healthy tricuspid volunteers, 0.6 N/m²) were similar to those previously reported by Barker et al\(^\text{16}\) (RL-BAV, 0.8±0.2 N/m²; age- and size–matched controls, 0.4±0.2 N/m²; healthy tricuspid volunteers, 0.4±0.1 N/m²) and Meierhofer et al\(^\text{13}\) (BAV, median 0.6 N/m², range 0.4–1.0 N/m²; controls, median 0.5 N/m², range 0.4–0.7 N/m²), but much lower than those by Hope et al\(^\text{12}\) (RL-BAV with helical flow, 1.56 N/m²; RL-BAV with normal flow, 1.15 N/m²; healthy tricuspid volunteers, 0.85 N/m²). This discrepancy is based on differences in methodology. Although Hope et al reported a WSS maximum from all wall segments, other studies calculated systolic WSS as an average over multiple systolic time points and averaged along the wall segment.\(^\text{12,16}\)

Similar to previous findings, both BAV subgroups had significantly elevated WSS measured compared with aorta size–matched controls.\(^\text{12,16}\) The finding of reduced regional WSS in aorta size controls is in excellent agreement with a recent study that reported similar findings in a cohort of n=33 patients with tricuspid aortic valve and aortic dilatation in comparison with control groups.\(^\text{29}\) Noticeably, the extent and eccentricity of asymmetrically elevated systolic WSS in RL-BAV was similar to previous findings by Barker et al,\(^\text{16}\) Hope et al,\(^\text{12}\) and Bissell et al.\(^\text{17}\)

**Alternative Metrics of Aortic Hemodynamics**

Given the time constraint and technical complexity involved with WSS quantification, many studies have explored simpler metrics as potential prognostic indicators to identify alterations in aortic hemodynamics in patients with bicuspid aortic valves.\(^\text{24,31,32}\) For example, restricted cusp opening angle was recently shown to differentiate BAV patients from healthy volunteers (BAV fused leaflet, 62±5°; healthy tricuspid volunteers, 75 ±3°; \(P<0.001\)) and was strongly correlated with ascending aortic diameters and growth rate (\(P<0.001\)).\(^\text{31}\) Systolic left ventricle outflow jet angle, or the angle between the experimental flow vector and theoretical axis of left ventricular outflow, was another such measure that differentiated BAV patients from healthy tricuspid volunteers (BAV, 17.54±0.87°; healthy volunteers, 10.01±1.29°; \(P<0.01\)) and correlated with aortic dilatation in BAV patients (\(P<0.05\)).\(^\text{32}\) Sigovan et al modified den Reijer et al’s approach to develop 2 metrics: flow angle and flow displacement.\(^\text{24,32}\) Similar to our findings, Sigovan et al found that flow displacement was the most sensitive marker and was significantly elevated in patients with marked eccentric flow in comparison with the mild eccentric cohort (0.18±0.03 versus 0.12±0.05, \(P<0.04\)).
Study Limitations
A limitation of this study is the lack of longitudinal outcomes that underlines the feasibility character of our study. Future studies would benefit from a greater number of patients within each cohort and the inclusion of additional congenital valve abnormality phenotypes, such as those with equal-sized valves (true BAV without raphe) or unicuspid valves. Although aorta size controls were carefully selected to match aortic dilatation on the BAV cohort, differences in age remain. It should be noted that the results presented in this article have not been adjusted for age or other differences in patient characteristics. However, because aortic dilatation occurs at a much younger age in BAV patients, it was not possible to match the BAV and control cohorts for age, and covariate adjustment may thus not appropriately reflect age-related effects. Further studies are warranted to systematically investigate the combined influence of age and type of valve abnormality on the metrics of aortic hemodynamics. Another limitation is that healthy volunteers were not age matched to the other 3 cohorts. This issue may be addressed by recruiting older participants to serve as healthy volunteers.

WSS quantification is a time-consuming and technically complex analysis. Future investigation and use of measures such as outflow asymmetry and flow displacement may offer a novel index that is easier to obtain and has the potential to be automated. Additional studies are needed to systematically investigate the relationships between different measures of altered aortic blood flow and their association with the development of aortopathy. Most importantly, longitudinal studies are required to link altered hemodynamics and the progression of aortic disease with medical management and surgical resection strategies.

Conclusion
Our study shows that the presence and type of BAV fusion was associated with changes in regional WSS distribution, systolic outflow asymmetry, and the expression of BAV aortopathy. Of the parameters measured, flow displacement was most sensitive to differences in BAV aortopathy phenotype and may represent a new and easily accessible metric for the quantification of hemodynamic abnormalities in aortic valve disease. Future longitudinal studies are warranted to evaluate the impact of BAV valve morphology and the associated hemodynamic alterations in determining the risk for aortopathy development and progression.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

The findings of this study show that the presence of bicuspid aortic valve and type of cusp fusion pattern were accompanied by changes in systolic outflow as quantified by flow displacement, flow angles, and regional wall shear stress. Altered aortic hemodynamics were clearly associated with the predominant expression of the aortopathy phenotype (aortic region affected by dilatation) which was different for the right-left in comparison with the less common right-noncoronary cusp fusion morphology. These findings represent new insights regarding the current guidelines using maximal aortic diameter to influence timing and extent of surgical resection. The decision to resect aortic tissues in bicuspid aortic valve aortopathy is difficult, because the degree of aortic dilatation can be highly variable with respect to location on the aorta and the degree of enlargement. The findings of this study indicate that 4-dimensional flow MRI may be used to determine which regional areas of the aorta are most prone to developing aortopathy, and different aortic resection may be indicated in patients with right-left versus right-noncoronary fusion patterns. However, our data also indicate that hemodynamic alterations and the aortopathy phenotype can have variable patterns that could be important for clinical surgical management decisions for the individual patient. Novel metrics of aortic hemodynamics such as flow displacement may be capable of shaping these decisions with respect to the timing and extent of aortic replacement in this diverse group of patients with bicuspid aortic valve.
Bicuspid Aortic Cusp Fusion Morphology Alters Aortic Three-Dimensional Outflow Patterns, Wall Shear Stress, and Expression of Aortopathy
Riti Mahadevia, Alex J. Barker, Susanne Schnell, Pegah Entezari, Preeti Kansal, Paul W.M. Fedak, S. Chris Malaisrie, Patrick McCarthy, Jeremy Collins, James Carr and Michael Markl

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